Special Edition 2013

THE STORY OF Immunization

South Dakota medicine

SPECIAL EDITION

The Journal of the South Dakota State Medical Association

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A special thanks to Avera Health, Sanofi Pasteur, Inc., Sanford Health and the South Dakota Department of Health for their contributions which have made this special issue possible.

Vaccinations – Maintaining The Safety Net

By Robert L. Allison, MD, FACP
SDSMA President

The origin of viral infectious disease is shrouded in the mists of time. Many examples throughout history give evidence of their longevity. The mummy of Ramses V is seen to have the scars of smallpox. Chinese inoculation was thought to have occurred as early as 1000 BCE.

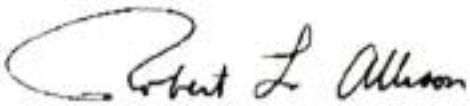
The modern desire to prevent infection goes back centuries. Edward Jenner (1749-1823) is often cited as the physician that pioneered this work. The story goes that Jenner overheard a milkmaid state that she would never get smallpox because she had gotten cowpox. The word vaccine comes from Latin – "vaccines." The word literally means "of or from cows." Eight-year-old James Phipps was inoculated as his first successful patient.

Every physician today appreciates the work involved in containing infectious diseases. Primary care physicians place vaccinations as the penultimate therapy when addressing health care maintenance. Recent public confusion and the denial of the value of vaccinations has become a struggle to remedy. The success stories, such as the eradication of epidemics of smallpox and the scourge of polio, are lost in the recent memory of the public.

As a physician, I urge you to educate your patients and the public by committing to the values of vaccination.

I would like to thank the staff of the South Dakota State Medical Association for undertaking our fifth special edition of *South Dakota Medicine*; the collaborative efforts of the South Dakota Department of Health and the contributing physicians make this special edition one of our best yet.

Sincerely,



South Dakota physicians,

Childhood immunization is rightly recognized as one of the most significant public health accomplishments of the 20th century and a major contributing factor to the increased lifespan today's Americans enjoy. Prior to vaccination, infectious diseases were widespread and caused considerable disability and death. In 1920 there were 469,924 measles cases, including more than 7,500 deaths, in the U.S. South Dakota alone reported 11,000 measles cases in 1934. Now, thanks to readily available vaccine and school entry requirements for measles vaccination, the state has reported just eight cases since 1991.

Immunizations have made measles and other once common childhood diseases very rare in South Dakota. Where parents once worried about their children dying from polio or losing their eyesight or hearing from rubella, today's parents have ready access to vaccines to protect their children.

Vaccines have been so effective some parents no longer see such diseases as a threat and choose to delay vaccination for their children while some avoid it altogether. Fortunately, South Dakota's immunization laws are strong and effective, particularly for the school entry population and providers, schools and parents do a great job getting kids immunized for school entry. This strong support translates into very high coverage levels by the time kids enter kindergarten.

Unfortunately, coverage is not so good for either preschoolers or adolescents. Our challenge is to increase the focus on age-appropriate immunizations for all kids, based on the recommended schedule from the Advisory Committee on Immunization Practices (ACIP). We must work to assure infants, preschoolers, kindergarten students, and adolescents all get the vaccines they need when they need them, and not assume school entry coverage is enough.

As the state's public health agency, the Department of Health places a high priority on maintaining a strong immunization program and the high vaccination coverage levels needed to protect our citizens from the threat of vaccine-preventable diseases. The department is proud to count South Dakota's physicians as vital partners in this effort and we are committed to working with you to assure our children get the vaccines they need.

We are pleased to be a part of this special issue of *South Dakota Medicine* and hope it will be a valuable resource for physicians in your efforts to educate parents about the importance of vaccination.

Doneen B. Hollingsworth
Secretary of Health

FOREWORD

What a joy it is to provide remarks for this unique compilation of immunization articles from such passionate and outstanding authors. This publication paints the big picture of immunization on the canvas that I have been working on for more than 30 years, beginning when I was a family medicine resident. My focus on immunization continued while practicing in community health centers, which led to organizing a grassroots immunization coalition in Saint Paul, Minnesota, and directing several walk-in immunization clinics in the years following the measles epidemic of 1989 through 1991. Today, I serve as executive director of the Immunization Action Coalition (IAC), now the largest immunization education organization in the nation.

To tell the story of how this compilation came to be is to tell the story of how coalitions are shaping immunization today. The idea of forming a "coalition" of contributing authors for this collection of articles grew out of the success of the ad hoc coalition of immunization professionals who came together early in 2012 to defeat two bills in the South Dakota Legislature. The bills aimed to expand immunization exemptions by permitting parents to exempt their children from state vaccination requirements based on the parents' personal or holistic health care beliefs. When news of the introduction of this dangerous legislation became known, people representing nurses groups, medical organizations, hospitals, rural health and public health came together to discuss what could be done. The coalition effort led by the South Dakota Department of Health and the South Dakota State Medical Association succeeded, and the legislation was overwhelmingly voted down in committee.

Based on their experience in South Dakota, members of that ad hoc coalition realized the need for and the power of broad collaborative immunization efforts with defined goals. As a result, in this 2013 special edition of *South Dakota Medicine*, guest editor Wendell Hoffman, MD, patient safety officer at Sanford Health – Sioux Falls Region and clinical professor of internal medicine at Sanford School of Medicine of the University of South Dakota, has brought together a stellar group of prominent experts to make the "case for vaccines."

Immunization coalitions are not new. They date back to the 1970s when former First Lady of Arkansas Betty Bumpers and former First Lady Rosalyn Carter became the dream team of immunization coalition building and urged governors' wives from states across the nation to speak out on the importance of vaccinating their states' children. Coalitions have been forming ever since in response to compelling events. For example, a large number of coalitions arose subsequent to the nation's measles epidemic of 1989 through 1991, an epidemic that sickened more than 55,000 and killed 123 people – 80 percent of them children or teens. Ninety percent of those who died were unvaccinated.[1]

Coalitions and Recent Legislation in Other States

Attempts to add personal belief exemptions or to loosen the legal criteria for personal belief exemptions in state legislatures occurred during 2012 in seven states in addition to South Dakota: Kansas, Massachusetts, Minnesota, Mississippi, New Jersey, New York and West Virginia. Coalitions of individuals, organizations and public health departments played major roles in speaking to legislators about the risks of children not receiving recommended vaccines. As a result, none of these bills has been enacted to date.

State immunization coalitions also have been powerful forces at legislatures in supporting the enactment of laws that add administrative obstacles to obtaining personal belief exemptions. For example, in Washington and California, previous laws allowed parents to exempt their children from vaccination by simply signing a form at their child's school. The laws did not require parents to consult a health care provider about their decision. Vaccine-preventable disease rates have been climbing in both states. Coalitions of health care professionals in both states have succeeded in changing the laws so that it is no longer as convenient for parents to obtain personal belief exemptions.

Current Status of Immunization Coalitions in the U.S.

Today, there are more than 200 immunization coalitions in the U.S. From an IAC survey in March 2012, we learned they are located in 44 states and the District of Columbia. Of the coalitions that responded, 33 were state

coalitions; approximately 110 were city, county, or multicounty coalitions; and 11 were national.

The majority of coalitions target all age groups, but some coalitions focus on very young children and some on older adults. Other coalitions promote vaccination to prevent specific diseases such as influenza, hepatitis B or meningococcal disease. Many disease-specific immunization coalitions began when parents experienced the tragic loss of a child to a disease that might have been prevented by a vaccination. Motivated by their loss, these parents did not want another person to lose a loved one as they had lost theirs. Examples of these coalitions include Families Fighting Flu, National Meningitis Association and Meningitis Angels.

In most coalitions, member organizations represent public health, private practices, medical or nursing professional societies, hospitals, schools, and vaccine companies, among others. About half of coalitions report they are entirely made up of volunteers and have no paid staff. Often it is a health department staff person who coordinates the coalition's meetings and activities. Some coalitions have part-time staff, amounting to at most the full-time equivalent of 1.5 persons. Only 15 coalitions in the survey reported having two or more staff.

When queried about their coalition activities, most coalitions reported engaging in educational projects (97 percent). When asked about advocacy activities, 45 percent answered "none," and 77 percent said "none" when asked about lobbying activities. These low rates of advocacy and lobbying apply mostly to local coalitions that have no paid staff. State and national coalitions often engage in advocacy and lobbying.

Impact of the 2013 Special Edition of *South Dakota Medicine*

This wonderful compendium of articles on such a broad range of immunization topics is unique in my experience. Outside of the foundational texbook *Vaccines*, one would be hard-pressed to find the contributions of so many immunization experts and leaders in one publication. In this busy world, I believe that other readers will appreciate, as much as I do, the option of reading chapters in any order. There is no need to go cover to cover, just choose the chapter of most interest to you at any point in time, and enjoy. For this reason, this publication should be kept at hand by anyone involved in providing immunization services. Physicians-in-training will especially benefit from the technical knowledge and real-world experiences these articles present, both of which are needed if we are to realize our continuing goal of increasing immunization rates.

Deborah L. Wexler, MD
Executive Director, Immunization Action Coalition

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About the Immunization Action Coalition (IAC)

The IAC was started in 1990 as a Saint Paul, Minnesota, grassroots coalition comprising my community health center, local and state public health departments, several private medical practices, and the Children's Hospital of Saint Paul. Our driving mission was to make sure healthcare professionals were following the Centers for Disease Control and Prevention's recommendations to provide hepatitis B vaccination to the new Southeast Asian refugee children whose families were settling in our city.

Within months of beginning our educational efforts, we learned that not only were these children missing their hepatitis B vaccinations, they were also lacking routinely recommended vaccinations such as measles, mumps and rubella (MMR) and diphtheria, pertussis and tetanus (DTP). Three Hmong children died of measles during the 1990 measles epidemic in our city. The mission of our coalition expanded to make sure all children, teens and adults received all routinely recommended vaccines. We helped bring vaccination services to Women, Infants, and Children (WIC) clinics located in public housing facilities throughout the city to make sure that even children who were not visiting doctors' offices would have access to lifesaving vaccines.

Today, IAC's two main websites, www.immunize.org and www.vaccineinformation.org, are visited by more than 20,000 people each day. Every year, more than 4 million copies of immunization education materials for healthcare professionals and their patients are downloaded from immunize.org, including Vaccine Information Statements in more than 30 languages.

PREFACE

A Time Of Ignorance, a Time of Pathos, a Time Of Change

By Gregory A. Poland, MD, MACP, FIDSA and
Caroline M. Poland, MA, LCAC, NCC

There is no other medical maneuver that we attempt to deliver to every single living human being, multiple times throughout the lifespan, other than vaccines. It is unprecedented in human history and has tremendously benefited individuals, families, communities and nations. On the strength of vaccines, smallpox has been eliminated as a human scourge, and other diseases reduced in incidence by well over 99 percent in the U.S. That is the importance and power of vaccines and the prevention of infectious diseases which otherwise cause untold human misery, morbidity and mortality. Here's a quick "face validity" test of the above statement – when's the last time you saw a case of smallpox? Of polio? Of measles? Of rubella? Of Hib meningitis? Of tetanus? Of diphtheria? In every case, the answer is "I've never seen one," or for some diseases in the latter part of the list, "I can't think of when the last case I saw might have been – maybe when I was a resident."

And yet, vaccines are popularly maligned in our culture – with vaccine-hesitant and vaccine-resistant individuals, groups and communities.[1,2] Surprisingly, these groups include physicians and nurses. These are individuals who should know better, but – and this is the point – don't. Therein lies the crux of the issue. The public (and many providers) are simply ignorant of the morbidity and mortality of vaccine-preventable infections, and the safety and efficacy of vaccines to prevent those diseases. This has led to pathos throughout the system among providers, patients, public health officials, politicians and payers. The consequences of the resulting inadequate vaccine coverage rates are considerable and easily seen in the resurgence of measles, mumps and pertussis in our communities.

The traditional approach physicians and scientists have taken is to marshal the data and provide the facts and figures. That is necessary, but – in our culture and for many patients – insufficient. We have developed a model we call "preferred cognitive styles" useful in creating patient-centric educational materials and discussions wherein the health care provider seeks to understand (using the framework of motivational interviewing) the patient's concerns and preferred cognitive style of decision making.[3] Like the story of "Tyler" in this special edition of *South Dakota Medicine*, one of us has written of the influenza-preventable death of a patient resistant to the usual entreaties for influenza vaccination.[4] The author has received many comments regarding how this article, and the story it tells, has motivated many to be more reflective in educating their patients about the need for influenza vaccine specifically, and vaccines generally. The article points out, as Rachel Cunningham and Julie Boom articulate in their article in this issue, "Telling Stories of Vaccine-Preventable Diseases: Why it Works," how people make decisions. The point is that new models of delivering information customized to a given individual that is useful to their decision-making style will be imperative to reach high population coverage levels of vaccines. Partnering with peers in psychology and counseling is critical to these advances as the field of mental health and counseling uses a number of techniques and "languages of change" that increase the likelihood that the patient will make healthy decisions and behavior changes. We believe that some of these techniques are critical to fundamentally changing how we educate and how we approach discussions of vaccine acceptance.[5]

As an example, a whole-person approach may be useful in integrating the fields together. Because the mental and physical health of the patient is so tightly entwined, we believe that it is crucial for both areas of health to be addressed in health decision making and overall practice. Because those in the health care profession often are the "first line of defense" when it comes to an individual's overall health, it is critical that health care workers not only

work closely with mental health professionals, but also develop some level of comfort and competence in some of the tools from the field (i.e., motivational interviewing). A specific example may be that using the ideas behind cognitive behavioral therapy (CBT) may prove to be highly beneficial in addressing vaccine hesitant or resistant patients. CBT is predicated on the theory that an individual's thoughts, feelings and behaviors are linked. With this understanding, thoughts provoke feelings, and these feelings influence behavior. Behavior may then impact feelings, and the cycle continues. In the CBT model, if a change in behavior is the goal, the thought and feelings behind that behavior must be identified, addressed and challenged. The critical aspect is that in order to effect a change in health habits or decision making, a change in attitude about that behavior must be made explicit and challenged before the actual behavior can be changed.

In previously published work, we provided an example of how CBT might relate to decision making about vaccines: "Perhaps an individual is exposed repeatedly through the media to the Wakefield hypothesis that measles, mumps and rubella vaccine (MMR) causes autism. A follow-on thought might be, 'MMR vaccine causes autism and why don't the experts tell the truth about the vaccine?' This may lead to a feeling such as, 'I don't trust what I am being told and I don't want to harm my child.' This thought and feeling would then predictably lead to a behavioral decision such as 'I'm not giving my child that vaccine.'" Further details of this model we have called the "Preferred Cognitive Style and Decision-Making Model" are available.[3,5]

For clinicians, this special edition is a gem, concentrating not on data specific to each vaccine (which one can find easily and in many places), but concentrating on perhaps less familiar foundational aspects of vaccinology and vaccine delivery such as the history and science of vaccinology, current controversies, vaccines and the fear of autism, becoming an immunization champion, disparities in vaccine delivery, safe handling and storage of vaccines, new vaccines in the pipeline and other important topics. This information is difficult to find in one place, and certainly not available through any other single resource that we know of.

We live, in the case of vaccines, in a time of ignorance, a time of pathos and, yet, a time of change. The changes coming from advances in immunology, the new biology, communication, and wisdom will result in sickness, disabilities, and deaths prevented. Such changes will require that all health care professionals be well educated in the science of vaccinology and the psychology of health decision making, and, in turn, use that knowledge to educate those they are privileged to care for. The stakes are high, the rewards great, the goal clear, and the path beckoning.

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Healthcare Personnel Vaccination Recommendations[1]

Vaccine	Recommendations in brief
Hepatitis B	Give 3-dose series (dose #1 now, #2 in 1 month, #3 approximately 5 months after #2). Give IM. Obtain anti-HBs serologic testing 1–2 months after dose #3.
Influenza	Give 1 dose of influenza vaccine annually. Give inactivated injectable influenza vaccine intramuscularly or live attenuated influenza vaccine (LAIV) intranasally.
MMR	For healthcare personnel (HCP) born in 1957 or later without serologic evidence of immunity or prior vaccination, give 2 doses of MMR, 4 weeks apart. For HCP born prior to 1957, see below. Give SC.
Varicella (chickenpox)	For HCP who have no serologic proof of immunity, prior vaccination, or history of varicella disease, give 2 doses of varicella vaccine, 4 weeks apart. Give SC.
Tetanus, diphtheria, pertussis	Give a one-time dose of Tdap as soon as feasible to all HCP who have not received Tdap previously. Give Td boosters every 10 years thereafter. Give IM.
Meningococcal	Give 1 dose to microbiologists who are routinely exposed to isolates of *N. meningitidis*. Give IM or SC.

Hepatitis A, typhoid, and polio vaccines are not routinely recommended for HCP who may have on-the-job exposure to fecal material.

Hepatitis B

Healthcare personnel (HCP) who perform tasks that may involve exposure to blood or body fluids should receive a 3-dose series of hepatitis B vaccine at 0-, 1-, and 6-month intervals. Test for hepatitis B surface antibody (anti-HBs) to document immunity 1–2 months after dose #3.

- If anti-HBs is at least 10 mIU/mL (positive), the patient is immune. No further serologic testing or vaccination is recommended.
- If anti-HBs is less than 10 mIU/mL (negative), the patient is unprotected from hepatitis B virus (HBV) infection; revaccinate with a 3-dose series. Retest anti-HBs 1–2 months after dose #3.
  - If anti-HBs is positive, the patient is immune. No further testing or vaccination is recommended.
  - If anti-HBs is negative after 6 doses of vaccine, patient is a non-responder.

For non-responders: HCP who are non-responders should be considered susceptible to HBV and should be counseled regarding precautions to prevent HBV infection and the need to obtain HBIG prophylaxis for any known or probable parenteral exposure to hepatitis B surface antigen (HBsAg)-positive blood.[2] It is also possible that non-responders are persons who are HBsAg positive. Testing should be considered. HCP found to be HBsAg positive should be counseled and medically evaluated.

Note: Anti-HBs testing is not recommended routinely for previously vaccinated HCP who were not tested 1–2 months after their original vaccine series. These HCP should be tested for anti-HBs when they have an exposure to blood or body fluids. If found to be anti-HBs negative, the HCP should be treated as if susceptible.[1]

Influenza

All HCP, including physicians, nurses, paramedics, emergency medical technicians, employees of nursing homes and chronic care facilities, students in these professions, and volunteers, should receive annual vaccination against influenza. Live attenuated influenza vaccine (LAIV) may only be given to non-pregnant healthy HCP age 49 years and younger. Inactivated injectable influenza vaccine (TIV) is preferred over LAIV for HCP who are in close contact with severely immunosuppressed persons (e.g., stem cell transplant patients) when patients require protective isolation.

Measles, Mumps, Rubella (MMR)

HCP who work in medical facilities should be immune to measles, mumps, and rubella.

- HCP born in 1957 or later can be considered immune to measles, mumps, or rubella only if they have documentation of (a) laboratory confirmation of disease or immunity or (b) appropriate vaccination against measles, mumps, and rubella (i.e., 2 doses of live measles and mumps vaccines given on or after the first birthday and separated by 28 days or more, and at least 1 dose of live rubella vaccine). HCP with 2 documented doses of MMR are not recommended to be serologically tested for immunity; but if they are tested and results are negative or equivocal for measles, mumps, and/or rubella, these HCP should be considered to have presumptive evidence of immunity to measles, mumps, and/or rubella and are not in need of additional MMR doses.
- Although birth before 1957 generally is considered acceptable evidence of measles, mumps, and rubella immunity, healthcare facilities should consider recommending 2 doses of MMR vaccine routinely to unvaccinated HCP born before 1957 who do not have laboratory evidence of disease or immunity to measles and/or mumps, and should consider one dose of MMR for HCP with no laboratory evidence of disease or immunity to rubella. For these same HCP who do not have evidence of immunity, healthcare facilities should recommend 2 doses of MMR vaccine during an outbreak of measles or mumps and 1 dose during an outbreak of rubella.

Varicella

It is recommended that all HCP be immune to varicella. Evidence of immunity in HCP includes documentation of 2 doses of varicella vaccine given at least 28 days apart, history of varicella or herpes zoster based on physician diagnosis, laboratory evidence of immunity, or laboratory confirmation of disease.

Tetanus/Diphtheria/Pertussis (Td/Tdap)

All HCPs who have not or are unsure if they have previously received a dose of Tdap should receive a one-time dose of Tdap as soon as feasible, without regard to the interval since the previous dose of Td. Then, they should receive Td boosters every 10 years thereafter.

Meningococcal

Vaccination is recommended for microbiologists who are routinely exposed to isolates of *N. meningitidis*. Use of MCV4 is preferred for persons age 55 years or younger; give IM. Use MPSV4 only if there is a permanent contraindication or precaution to MCV4. Use of MPSV4 (not MCV4) is recommended for HCP older than age 55; give SC.

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1. CDC. Immunization of Health-Care Personnel: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*, 2011; 60(RR-7).
2. See Table 3 in "Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis," *MMWR*, 2001; 50(RR-11).

For additional specific ACIP recommendations, refer to the official ACIP statements published in *MMWR*. To obtain copies, visit CDC's website at www.cdc.gov/vaccines/pubs/ACIP-list.htm; or visit the Immunization Action Coalition (IAC) website at www.immunize.org/acip.

Adapted from the Michigan Department of Community Health.

Technical content reviewed by the Centers for Disease Control and Prevention.

www.immunize.org/catg.d/p3017.pdf • Item #P3017 (7/12)

CHAPTER 1

The Case for Vaccines

By Wendell W. Hoffman, MD, FACP
Guest Editor

Abstract:
The case for vaccines is one which has been made through scientific advancement and public health implementation, resulting in one of the most significant historical achievements for mankind. This includes the elimination of endemic smallpox, polio, measles and rubella from the U.S. This exhilarating accomplishment was sobered with the threat of smallpox through biological attack following September 11, 2001. While the unthinkable return of that vaccine-preventable disease never materialized, other vaccine-preventable disease, such as pertussis, have markedly increased in many states because of never-established or waning immunity. Drivers of these current threats come both from the anti-vaccine movement, through legislative efforts to expand childhood immunization exemptions and the medical establishment itself through lack of immunization prioritization in adolescent and adult populations. Therefore, the case for vaccines needs to be made both externally and internally through sound science, sound logic and sound ethics. Most powerfully, however, the case for vaccines is told through stories of real people who have suffered or died from these preventable diseases.

A Sobering Background

The fall of 2001 found our nation in a very tense situation following September 11. Anthrax cases had been appearing for several weeks on and after September 18 in Florida, New York City, Washington, D.C., and New Jersey. Locally, many of us were asked to help provide consultation to state emergency planners and on October 12, 2001, then-Governor Bill Janklow convened an urgent conference at the capital in Pierre, South Dakota. There, several hundred gathered to make terror related preparations, including the possibility of a biological attack. Just three days later it became personal, when our own Senator Tom Daschle's office received an anthrax laden letter opened by one of his aides.[1] More than just spores were delivered in that envelope, indeed a message, which began with the chilling and ominous words, "You cannot stop us. We have this anthrax. You die now. Are you afraid?" South Dakota had momentarily become an international bull's-eye.

In the several years following September 11, a top 10 list of possible biological weapons was frequently discussed. Many bio-terrorism experts had smallpox as the No. 2 potential threat behind anthrax, even though the last case of smallpox had occurred in 1977 in Somalia, and the world was finally declared free of this plague in 1980. It was known, however, that the former Soviet Union had stored the virus in a laboratory in Siberia, one of two labs in the world with the virus; the other is at the Centers for Disease Control and Prevention (CDC). In a post-September 11 climate, rumors abounded that some of these stocks had been removed by disaffected scientists who had departed this lab and were willing to sell to the highest nefarious bidder.

Because of this perceived threat, a national smallpox vaccination program was announced on December 13, 2002 by President George W. Bush, and plans ensued with smallpox vaccine being made available in 2003 to the states for distribution and administration.[2,3] Groups of health care personnel from across South Dakota volunteered to receive the vaccine, so that if an event involving the unthinkable should come, we could initially respond. Preparation like this was more than sobering – more like dread – for the idea of responding to a first wave of smallpox victims and to assist with a much broader vaccination endeavor taxed not the imagination, but the unimaginable. This was the only approach available which might prevent millions of deaths

from the worst vaccine-preventable disease in history. On February 20, 2003, after word came from the South Dakota Department of Health (SDDOH), I made my way along with 30 other colleagues from my system (including seven other physicians) to the designated SDDOH vaccine center. There we received for the first time since we were infants, the most famous of all vaccines, Vaccinia, via the equally famous and rather anciently practiced bifurcated needle ("scarification") technique.

Why did this plan go forward? Because the world knew that smallpox had been a monster, and under the threat of return, it would have been unconscionable not to prepare to offer our population the proven protection afforded by this historic vaccine. The case against smallpox had been made long ago through discovery and widespread public health implementation over time, an effort which eventually engaged the entire world and resulted in the elimination of that monster.[4] The effort that South Dakota put forth was exemplary, and in fact led the nation with a 9.8 per 10,000 vaccination rate and 62 of 66 counties being represented. In South Dakota, 736 people stepped forward with a 96 percent vaccine "take" being achieved. This total was made up of 432 hospital staff from 51 hospitals, along with 82 emergency medical service providers, 80 volunteer nurses, 67 SDDOH personnel and 34 highway patrol officers. Nationally 37,450 individuals were vaccinated by June 24, 2003.[5] Thankfully, however, the case against smallpox never had to be remade.

The Three Laws

Fast forward to another February day, nine years later when I was asked again to help make the case for vaccines, this time more broadly, on behalf of the South Dakota State Medical Association (SDSMA) before the House Health and Human Services Committee of the South Dakota State Legislature during the 2012 session. The issue flowed, not from a threatened attack from without, but from a friendly challenge from within, represented by HB 1175 and HB 1259.[6,7] Both of these measures would have promoted laws permitting philosophical exemptions ("further exemptions") and/or conscientious objections ("personal beliefs") to school immunization requirements established by the SDDOH. These exemptions and objections, going beyond medical reasons, encompassed the concepts of "religious doctrine, holistic health care, autonomous parental rights and personal beliefs." After hearing from both sides, HB 1175 was defeated by a 9-3 vote, and HB 1259 was defeated by a 9-4 vote. An emerging worldwide debate had just been played out on our local stage.

This was my first direct encounter on this scale, with what some have called the "anti-vaccine movement," and I came away with the conviction that there was much more that we in the health care community needed to do to make the case for vaccines. I was struck, for instance, by the notion of the term "philosophical" in describing personal belief exemptions in order to avoid vaccines either full or in part. The definition of the word "philosophy" literally means "the love of wisdom," and I wondered how wisdom rightly formed could support efforts to poke holes in or in even tear down one of the most important public health protective barriers which has ever been constructed over time.

According to the CDC, "during the 20th century, life expectancy at birth among U.S. residents increased by 62 percent, from 47.3 years in 1900 to 76.8 in 2000, and unprecedented improvements in population health status were observed at every stage of life."[8] Among the top 10 reasons for this profound progress in the well being of the general public has been the development and implementation of immunizations, which have markedly reduced some of the great scourges of mankind, and in the smallpox example, completely purged it from the planet. This progress was then again restated by the CDC in 2011, citing vaccine-preventable diseases as one of the 10 great public health achievements of the first decade of this century worldwide.[9] The arguments made to the Health and Human Services Committee that day to establish the case for vaccines were discussed in light of these great public health achievements, and have led to this special edition on immunization. To a growing chorus, led by experts such as Gregory Poland, MD, of the Mayo Vaccine Research Group and editor-in-chief of the journal *Vaccine*, we add our voice. Dr. Poland's recent article, "The Clinician's Guide to the Anti-vaccinationist's Galaxy," is representative of an emerging counter-balance aimed at the presuppositions of a dangerous trend.[10] In this same spirit, the South Dakota contribution began with another metaphor: the defense of a "fence."

Having spent five summers as a teenager working on various farms 45 miles west of Sioux Falls, I became acquainted with what is the *Law of Fences*. Repairing or building fences taught me what every farmer or rancher in our state knows: *Before you tear down a fence you must first ask why it was constructed in the first place*. The overarching point to the legislators that day was that before you consider tearing down the fence of sound vaccine policy, a wall of defense built over the centuries against some of the worst menaces to mankind, you must implicitly reject several crucial "laws." The violation of three fundamental laws in fact would be necessary to accept the premises of these perhaps well-intentioned, but ultimately misguided exemptions to

immunization. A "law" by definition includes contributions from knowledge, common sense and obligation. In this sense, good law looks more like an "ideal" and is based on reliable and reproducible knowing, joining with the rules of common sense and driven by obligation. Conversely, bad law looks more like an "agenda" and embodies contradiction despite that which is demonstrably known, internally consistent and for the common good. To persuade our fellow citizens regarding the *why* of vaccines will require sound science, sound logic and sound ethics.

The Law of Sound Science

The first law to be violated is that of the Law of Sound Science, which is *a call to reliable knowledge*. A twofold challenge was put forth to the legislators and went something like this: "Your eyes are not deceiving you when you notice that smallpox, polio, measles and rubella have been eliminated endemically from the U.S. as of 1949, 1979, 2000 and 2004, respectively.[11-14] Your ears are also not deceiving you when you hear from other states that when sound vaccine policy is relaxed through expanded exemptions, vaccination rates decrease. As a result, old threats like pertussis, which have not been eliminated endemically, return with a vengeance, resulting in the deaths of young children."[15-17]

The science that brought these astounding achievements is the rigorously applied knowledge concerning the safety, efficacy and effectiveness of vaccines in our populations. At the core of this knowledge is the randomized controlled trial (RCT) which is rooted in the scientific method which is further rooted in how human reason can more objectively trust what it observes, including differentiating causation from coincidence. The RCT seeks "the truth" regarding a drug, a gene, a procedure or in this case, a vaccine, by controlling to the greatest extent the various biases of human reason, thus the classic formulation of the "prospective, randomized, placebo controlled trial." The RCT has been the gold standard of determining the veracity of medical therapy since the 1940s, when the first RCT demonstrated that patients with tuberculosis did better with the antibiotic streptomycin than with bed rest alone.[18] To ignore this law of sound science, as it has pertained to vaccine-preventable disease, is therefore to throw out the engine which has powered so many of the "miracles of modern medicine" in the 20th and 21st centuries.

The Law of Sound Logic

The second is the Law of Sound Logic which is *a call to internal consistency*. This form of thinking uses the old logic of common sense, also known as classical or Aristoltean logic.[19] It is what we use in everyday discussion and debate, and is characterized by three principles: clear and unambiguous terms, true as opposed to false presuppositions, and conclusions which logically follow from those presuppositions. In the current matter, to be logically consistent, those who question the science of vaccine development need to also question other science-driven public health measures. The most powerful example of this is clean municipal water. This progress, which has also greatly benefited humankind in terms of life expectancy, is the envy of developing countries, but has been simply accepted carte blanche in "developed" countries like the U.S. The Environmental Protection Agency (EPA), for instance, monitors nearly 90 "contaminants" in U.S. municipal water supplies and deems them acceptable and not harmful to human beings as long as they fall below the "maximum contaminant level" (MCL).[20] These regulated contaminants include microorganisms, disinfectants, disinfection by-products, inorganic chemicals, organic chemicals and radionuclides. If one adds to this list the "unregulated contaminants," the number increases by 30.[21]

The science used to establish the MCLs for these contaminants and the regulatory industry, which holds municipalities to the highest standard of water safety, has been de facto embraced by the public. This is why by and large there is no "anti-water" movement. It is highly unlikely, therefore, given the trust in this area of science and regulation, that we would ever see anyone going out to the Big Sioux or Missouri rivers to obtain a glass of dirty water and then drinking it to be holistic and naturally building up their immune system. The inconsistency, it seems, is that since I can no longer see the dirty water from my faucet, I have accepted without question the science that brought that clean glass of water to my lips. How is it then, that since I don't see the dirty plague (e.g., polio, measles, rubella, etc), I feel free to question the science that brought the absence of that plague?

The Law of Sound Ethics

The third law is the Law of Sound Ethics, which is *a call to mutual obligation*. This law is a part of what one writer called the "Tao," or the first things that we can't not know.[22-24] The Tao is foundational to all ethical systems, in all times, in all places, and in this situation, the prior two laws. It states that I am obliged as a member of the community which I have greatly benefitted from, to act in the best interest of those in that community. Central to this is what some have called the "global ethic," which is founded on the golden rule and its several expressions.[25,26] "So in everything, do to others

what you would have them do to you" (Jesus)[27] or, "Do not do unto others as you would not have them do unto you" (Confucius).[28] These imply that if I know that either an action to do the wrong thing or an inaction to do the right thing will place others around me in harm's way, I have the obligation to exercise the positive action and to avoid the negative action. Vaccines have been so successful, precisely because of what has resulted from this obligation – what the vaccine industry calls "herd immunity" – where entire families, communities, states, and nations have joined together, with each individual acting in the best interest of the whole (the herd), so that the whole can protect the individual, particularly the most vulnerable in its midst.

A Story to Tell…to Ourselves

So much for the arguments put forward that February morning, but the case for immunization cannot be made by one person on one date before one legislature in one state. Rather, the case is more like a story which needs to be told by many voices on many occasions and in many settings. With the CDC listing some 27 diseases as "vaccine preventable," ranging from anthrax to yellow fever, our planet has witnessed the unfolding of a truly remarkable narrative, which is breathtaking in its scope and well worth the telling.[29] This account of immunization encompasses the micro in the form of the "molecular," with an astounding probe inwardly into the intricacies of a spectacular immune system and how it has been enjoined to reject an enemy without the direct consequences of that enemy. And this story also encompasses the macro in the form of the "human" with an astounding reach outwardly into the intricacies of public health, ethics, industry, health care delivery and politics, to achieve the common good.

The Story of Immunization: A Special Edition of South Dakota Medicine attempts to tell this story through a coalition of experts joining together from frontline, industry, academia and public health. This notion of coalition building in support of vaccines has been championed by Deborah Wexler, MD, and colleagues of the Immunization Action Coalition.[30] Our particular collaboration comes from in-state and out-of-state authors including the three major health systems within South Dakota. It is an effort, therefore, that to our knowledge may be unique in the annals of immunization education. But before we move to tell this story, we need to remind ourselves that this case needs to be made not just to the anti-vaccine movement and those wooed by it, but also to our own colleagues within the medical establishment. Again, the classics are instructive. In the *Art of Rhetoric*, Aristotle observed that the ability to persuade depended on three things: *logos* (the content of the persuasion), *pathos* (the passion of the persuader) and *ethos* (the integrity of the persuader).[31] While all three play important roles, Aristotle noticed in the Greek Academy that one clearly rose to the surface, that of ethos, for without it, the other two are completely undermined. It is true to this day, for only some may be able to put together a cogent argument and only some may be able to passionately move an audience. But all of us can be persuaders characterized by our own integrity. Therefore, in the matter of sound vaccine policy, we first and foremost must live up to the laws of sound science, sound logic and sound ethics – and persuade each other.

As to sound science, we need to continue a relentless pursuit of the best evidence regarding the safety and efficacy of immunizations, and not shy away from internal debate when challenged, so that the knowledge backing our claims to the public is everything it should be. Such a challenge has been put forth by Michael Osterholm, Ph.D and colleagues from the Centers for Infectious Disease & Research Policy with two new recently published reports.[32,33] These meta-analyses review the extensive evidence (12,000 studies) regarding influenza vaccination, attempting in their effort to apply the strictest of criteria for efficacy/effectiveness. The authors propose, in summary, that:

> The currently licensed influenza vaccines can provide moderate protection against virologically confirmed influenza, but such protection is greatly reduced or absent in some seasons. Further even though TIV (trivalent inactivated vaccine) provided some protection for healthy adults 18 to 65 years of age, there is a paucity of evidence for protection in adults 65 years of age and older. Evidence is also limited to determine the efficacy and effectiveness of TIV in children aged 2 to 17 years. Live attenuated influenza vaccines (LAIVs) have consistently shown highest efficacy in young children (from 6 months to 7 years old), while evidence of protection is not available for individuals from 8 to 59 years of age.

While providing a stinging critique of the evidence, the reports do not advocate an abandonment of current influenza vaccines, but rather call for "novel-antigen game-changing seasonal and pandemic influenza vaccines that have superior efficacy and effectiveness compared with current vaccines." These reports will no doubt provoke significant debate within the vaccine community, for their perspective has significant implications. As these reports are very much in the public domain, we await the exchange.

Provocations like this are not new to scientific inquiry but rather are a part of its great legacy and strength, for if we have learned anything, the soundest of science is as much a journey as it is a destination, and so is never afraid of the truth bend in the road, following wherever it leads. Provocations like this also illustrate that the soundest of science is not afraid of perspective, also a part of scientific inquiry which includes vigorous deliberation, so that the biases of human reason can be tested, revealed, filtered and refined. This kind of Aristoltean arguing, which the public is largely unaware of, is healthy and humbling. In the end, we all must stand before the bar of reliable knowing, which states two fundamentals: 1) not all science is sound science and 2) sound science is never pure science.

Second, the logic argument stares us just as equally in the face as the knowledge one does, for it is inconsistent on the one hand to state that vaccines "work" but then fail to encourage and operationalize every patient encounter to make them available to those who need them. Witness, for instance, the significant under-vaccination rates in the U.S. characteristic of adolescence and adulthood.[34] Once again pertussis comes to mind, an endemic disease no longer lurking just behind the curtain but taking full stage with declared outbreaks in "a majority of states" per the CDC.[35] Witness also the less than robust attempts by many health care systems to protect patients from health care workers infected with pertussis or influenza. It is inconsistent, on the one hand, to be places which actively treat pertussis, influenza, and their consequences while at the same time are places which actively facilitate transmission of these microbes. The protection of the most vulnerable in our midst through high rates (CDC calls for 90 percent in the case of influenza) of health care worker vaccination should be the goal. Internal consistency must inform all of our decisions and policies, lest our integrity suffers before the public in our primary obligation to *do no harm*.

Lastly, the ethical argument cuts much more deeply for us than for the general public, for the irrevocable claim on health care goes beyond a simple summons to mutual obligation but rather is more like a covenant that lifts up this highest of all professions, binding us to the privilege and solemn responsibility of caring for our fellow human beings. As such, sound ethics is the designated driver of science and logic rather than just another passenger. The health care industry is currently in the midst of a massive test of this human covenant, given the dangerous and unsustainable situation that we have all contributed to. This dilemma is best contrasted from two leaders, a warning from Steven Nissen, MD, chair of Cardiovascular Medicine at Cleveland Clinic, "When medicine became a business we lost our moral compass,"[36] and a call from Dennis Cortese, MD, former chief executive officer and president of the Mayo Clinic, "to align providers' incentives with value rather than volume."[37]

"Business," per Nisssen, a transformed and therefore potentially subversive term to our industry, must embrace what business guru Jim Collins reminded the social sectors of "why business thinking is not the answer," with the statement, "In business, money is both an input (a resource for achieving greatness) *and* an output (a measure of greatness).[38] In the social sectors, money is *only* an input and not a measure of greatness." This would comport well with the traditional meaning of business relative to health care, what Sir William Osler stated long ago, "Our fellow creatures cannot be dealt with as corn and coal."[39] "Value," per Cortese, an overused and therefore potentially emptied term within our industry, is increasingly being expressed in patient-centered formulaic models such as, "patient outcomes divided by total cost per patient over time."[40] These equations of value return the patient to the center and reflect the new science of the art of medicine. This in fact represents a knowledge revolution, calling medicine back into its "right mind," back to the reason for health care's existence – *the patient*.[41,42,43] The well-being of the patient is optimally achieved through the prevention of disease rather than just its management.

To move us from a disease management-driven system to a preventive health-driven system is the clarion call of 21st century medical delivery. *To prevent us from moving* from the business of care to just another business of commodity is the clarion call of 21st century medical ethics. At the crossroads of business and value are vaccine-preventable diseases called the "cornerstone of public health" by the National Conference of State Legislators.[44] According to the Healthy People 2020 initiative, "Vaccines are among the most *cost-effective* clinical preventive services and are a *core component of any preventive services* package. Childhood immunization programs provide a very high return on investment. For example, each birth cohort vaccinated with the routine immunization schedule saves 33,000 lives, prevents 14 million cases of disease, reduces direct health care costs by $9.9 billion and saves $33.4 billion in indirect costs." (italics mine). Therefore, vaccine-preventable disease simultaneously satisfies both the basest definition of the business of medicine with an extraordinary return on investment, as well as the loftiest definition of patient centered value, the prevention of morbidity and mortality. Vaccine promotion and availability appears to play a

prominent feature in the Affordable Care Act of 2010, but the story of this massive shift in American health care delivery is barely into chapter 1. As science, logic, and ethics do seem to find their way into our laws, let us argue for the best law possible, indeed a Law that supersedes all laws.

The Story of Immunization: A Special Edition of South Dakota Medicine continues to make this argument, a case for this cornerstone at these crossroads. I offer my profound thanks to our compelling author contributors, without which there would be no case to make, and to the SDDOH, the SDSMA and its journal *South Dakota Medicine* and our corporate sponsors, without which there would be no vehicle to make this case. In particular, I would like to thank our wonderful editor-in-chief, Keith Hansen, MD, who has provided wise leadership and unwavering support to this novice guest editor. Indeed I have been very humbled by this opportunity.

The Closing Argument

There is one more thing to say – a very potent closing argument. The best case for vaccines is made through story, for it is perhaps the most powerful of the right brain aptitudes, far more powerful than any RCT in terms of driving improvement.[45] In making our case, therefore, we begin with a real case of vaccine-preventable disease, which collapses the argument of all of the laws mentioned in this article into a real person. In chapter 2 of this special edition, listen to the riveting account of a remarkable boy named Tyler, as chronicled by his physician Joe Segeleon, MD, who met him at the peak of the H1N1 influenza pandemic in 2009.[46] Listen also to Tyler's parents who reflecting on this special edition said, "You have captured the essence of the immunization debate. Had immunizations been readily available that year, Tyler might be here today, but we will never know. We will challenge anyone in the gamble they take in not getting immunized…This is good for all the medical profession and families to experience…so that hopefully, one day they will not be in the same situation. Immunizations are very important, even if it only saves one life."[47] To Tyler's parents, Renee and Tim Newville, we express gratitude, as a purveyor of words, which is difficult to put into words. Thank you for your permission and the honor to dedicate *The Story of Immunization: A Special Edition of South Dakota Medicine* to the memory of Tyler Newville and to all whom he represents.

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CHAPTER 2

Tyler

By Joseph E. Segeleon, MD

"What's your name?"
"Tyler."
"What school do you go to?"
"Patrick Henry."

In any other context this would have been a very ordinary conversation. It remains one I frequently replay. It was the only conversation I had with Tyler Newville. It was at the beginning of a 10-hour span that ended with the death of a very special young man.

In the fall of 2009, we were acutely aware of a worldwide pandemic caused by the H1N1 virus, the first of its kind in 41 years. As a pediatric intensivist with 18 years of experience, I had come to understand the danger of diseases that were once viewed as common infections. I had seen varicella deaths, trained in the era prior to *Haemophilus influenzae* type b vaccination, and seen the morbidity associated with seasonal influenza. However, the H1N1 pandemic felt different than in years past. Newspapers described the deaths of previously healthy young adults that were occurring not just in the "third world," but also in modern cities with state of the art intensive care units. Pediatric intensive care colleagues from other parts of the U.S. would describe cases of morbidity and mortality in healthy children, and in Sioux Falls we were feeling fortunate that we had not shared this experience.

Early on the morning of November 20, I received a phone call from one of the community pediatricians. She was sending a child by ambulance to the children's hospital with a complaint of respiratory distress and increased work of breathing. The pediatrician, a seasoned, highly competent colleague, told me the kid looked sick, and we agreed that

direct admission to the pediatric intensive care unit (PICU) was in order. At approximately 9 am, a local ambulance crew brought Tyler into the PICU. He was pale, and his accentuated work of breathing was obvious to all. We had already donned the necessary apparel of gloves, masks, and gowns prior to his arrival, and the assembled team consisted of nurses, a respiratory therapist, and me.

This is what we do. We are a team. There was a determination and resolve on the faces of those in the room; we were ready to help this boy and his family. As I spoke to him, I did what is customary in my exam, and let my hand rest upon his foot. Over the years I have done this to be less threatening to young children, and it also provides a very good indication of cardiac function. Tyler's feet were ice cold. In fact, I could feel no pulses in his feet and his legs were cold up to the knees, his arms to the elbows. A normal capillary refill time is less than 2 seconds. Tyler's time was greater than 8 seconds. A quick assessment revealed tachycardia, hypotension, pulse oximetry in the 70s in spite of oxygen, and significant work of breathing, all of which forced a collective acknowledgement throughout the room – this kid was really sick.

In a short period of time and with very little conversation we began his resuscitation. Every member had a role. There was a singular purpose to our effort. Watching an ICU team work can be inspiring. From a family's perspective it frequently is alarmingly insightful, for they can tell by the speed at which things are done, the determination on the team members' faces, the lack of humor, and the overwhelming and unwavering tension of effort that their child is very sick.

Shortly after Tyler arrived, I spoke to his mom. I introduced myself, told her we were going to breathe for him, put catheters in his veins and arteries and resuscitate him. I told her he could die. The lack of time to prepare for this type of conversation is brutally cruel. Parents are fearful, sometimes incapable of comprehension, and above all they are hopeful. A unique aspect of my job is that I meet people at the worst time of their lives and ask them for their trust. It is one of the most powerful aspects of the job. Strangers forge bonds of intimacy that are forever captured in those moments of despair. Understanding this emotion separates nurses, therapists, and physicians in the ICU from other health specialties. It is not for everyone.

The early resuscitation phase entailed endotracheal intubation, placement of foley catheter, nasogastric tube, central venous catheters and an arterial catheter. Early data was ominous; it confirmed the gravity of his illness that we had gleaned from the clinical exam. The chest X-ray revealed "extensive consolidation in the left lower lung and right upper lobe and perihilar region." Initial blood work revealed a blood gas with a pH of 7.17, a prothrombin time of 23.4, elevated creatinine, albumin of 1.2, mixed venous saturation of 19 percent and most alarming, a white blood cell count of 0.6. Our rapid test for influenza came back positive confirming what was already obvious to all in the room – we were facing a case of H1N1 in a previously healthy child. Sioux Falls would not remain unscathed by the H1N1 epidemic.

Resuscitations have a pattern. Early aggressive volume, rapid airway control, and appropriate vasoactive agents will in most cases yield success. For Tyler, the first hour was met with success. Feet began to warm, and urine outflow was established, but the lungs continued to worsen as evidenced by worsening hypoxemia in spite of ventilator manipulations and poor blood pressure response despite vasoactive agents. After initial improvement, things deteriorated consistently, and multiple attempts at improvement failed. A phenomenon in septic shock is heralded by capillary leak. In spite of aggressive and large amounts of volume instilled (in this case well over 200 ml/kg), the blood pressure did not improve and end organ damage continued. Tyler had massive capillary leak which was clinically manifested by anasarca and worsening pulmonary status. Therapies included dopamine, norepinephrine, epinephrine, hydrocortisone, calcium, sodium bicarbonate, broad spectrum antibiotics and multiple blood products.

As the day progressed, it became apparent that our therapies were not having the desired effect. He suffered from vascular paralysis, and temporary elevations in blood pressure with volume boluses were achieved for only brief periods of time in spite of escalating vasoactive agents to maximal levels. Having failed conventional ventilation, we had begun high frequency oscillator as a rescue therapy. I called one of my partners and she took over the other patients in the PICU so I, as well as the entire team, could spend all of our time with Tyler. We were losing. It was evident on our faces. We were resolved to do all that we could, but the Newville family could see it as they stayed in the room and watched our struggle. Objective data confirmed things were worsening. Creatinine was rising. Protrombin time was now 65.2; platelet count was 17,000. Tyler was becoming progressively cyanotic and end organ damage was readily apparent. We were witnessing what the influenza literature calls "cytokine storm." Storm indeed,

for Tyler, like many susceptible patients in a pandemic who are without immune protection, it can have a devastating effect.

As day turned into early evening it became clear that Tyler was not going to survive this disease. Phone calls to colleagues in Minneapolis were met with empathy but not much in the way of altering advice. A transfer for Extracorporeal Membrane Oxygenation (ECMO) was discussed but survival on ECMO was not likely and transfer in this condition was impossible. Nine hours after arrival in the PICU, Tyler had an 8-minute episode of cardiac arrest. In the last hour of his life, we were unable to maintain a blood pressure beyond a few minutes, in spite of extraordinary doses of vasoactive agents, calcium and hydrocortisone. The ICU room looked like a MASH unit. There was equipment everywhere, opened access kits, overflowing garbage cans and IV pumps full of medications stacked on top of each other on every pole. The oscillator was running at full tilt, the IV pumps blinking in sequence, my team covered in sweat, gowns bloodied, masks damp – all remnants of a determination so powerful it was palpable. There comes a time in situations like this where everyone, including the family, knows that survival is not possible. It is a profound moment.

Tyler died of primary H1N1 pneumonia and irreversible shock with possible methicillin-resistant staphylococcus aureus (MRSA) superinfection. He died 10 hours after his arrival to the PICU. A team of dedicated individuals stayed at his side the entire time and struggled to save his life. We were not successful. His death was met with tears, exhaustion, and the alarming notion that we were battling something more powerful than all of our equipment and modern day resources. For me, it was a tremendous sense of loss.

A short time after his death, while Christmas shopping, I ran into Tyler's parents. You would think after doing this so long that I would have a prepared response, some comforting words. I had none. Tyler's mom and I hugged. I'm not sure who was hugging whom, but that moment stays with me today.

This special issue on immunization contains information that will appeal to a variety of individuals in various specialties. As you read the chapters to follow and apply them to your practice, I hope you think of Tyler. Let us not do so in remembrance of his death, but rather in honor of his life.

Need help responding to vaccine-hesitant parents?

Science-based materials are available from these respected organizations

American Academy of Pediatrics (AAP)

Healthcare providers can find numerous resources on the AAP's website to help with parents and caregivers who have questions about vaccinating their child at www.aap.org/immunization/families/deciding.html, including:

- "Why immunize?" www.aap.org/immunization/families/whyimmunize.html
- "Are Vaccines Safe?" www.aap.org/immunization/families/safety.html
- "Evaluating Web Information" www.aap.org/immunization/families/evaluatingwebinfo.html
- "Misconceptions and Frequently Asked Questions" www.aap.org/immunization/families/faq.html
- When parents cannot be convinced, consider using AAP's Refusal to Vaccinate form at www.aap.org/immunization/pediatricians/pdf/RefusaltoVaccinate.pdf.

California Immunization Coalition

The California Immunization Coalition (CIC) has developed several excellent provider pieces that discuss common questions many parents may have regarding vaccines for their children. These include

- "Responding to Parents' Top 10 Concerns" http://immunizeca.org/documents/IMM-917_web.pdf
- "Talking with Parents About Vaccine Safety" http://immunizeca.org/documents/IMM-915_web.pdf
- "Alternate Vaccine Schedules: Helping Parents Separate Fact From Fear" http://immunizeca.org/documents/IMM-988.pdf

Centers for Disease Control and Prevention (CDC)

Among CDC's many online immunization resources is the "Parent's Guide to Childhood Immunization," a 64-page booklet that can be ordered or printed at www.cdc.gov/vaccines/pubs/parents-guide.

Other CDC materials, designed to help healthcare providers work with hesitant parents, include the following:

- "If you choose not to vaccinate your child, understand the risks and responsibilities" www.cdc.gov/vaccines/spec-grps/hcp/conv-materials.htm#understand
- "Parents who question vaccines" www.cdc.gov/vaccines/spec-grps/parents.html#question
- "Common questions parents ask about infant immunizations" www.cdc.gov/vaccines/spec-grps/infants/parent-questions.htm
- "Talking with parents about vaccines for infants" www.cdc.gov/vaccines/spec-grps/hcp/conv-materials.html#talkpvi

Every Child by Two (ECBT)

Created by Every Child by Two, www.vaccinateyourbaby.org focuses on answering parents' commonly asked questions about vaccines. It features video clips and links to current vaccine news stories.

Immunization Action Coalition (IAC)

IAC's Talking about Vaccines web section provides healthcare professionals with top vaccination resources from trusted sources such as CDC, AAP, IAC, VEC, and many more. Visit www.immunize.org/concerns. IAC has developed several patient handouts for vaccine-hesitant parents. These include:

- "Clear Answers & Smart Advice About Your Baby's Shots," an excerpt from the popular book "Baby 411" by Dr. Ari Brown www.immunize.org/catg.d/p3058.pdf
- "Reliable Sources of Immunization Information: Where to go to find answers?" www.immunize.org/catg.d/p4012.pdf
- "Vaccines Work!" www.immunize.org/catg.d/p4037.pdf

Institute for Vaccine Safety, Johns Hopkins University

The Institute for Vaccine Safety collects vaccine-specific safety information. Of particular interest is its "Components of Vaccines" section, which contains tables specifying the contents of various vaccines: www.vaccinesafety.edu/components.htm.

Vaccine Education Center (VEC) Children's Hospital of Philadelphia

- Tear sheets—offered in tear-off pads of 50, intended for physicians to hand out to patients. Useful titles for hesitant parents include "Aluminum in Vaccines," "The Facts About Childhood Vaccines," "Thimerosal," "Too Many Vaccines?," "Vaccine Ingredients," and "Vaccines and Autism."
- Videos—"Vaccines: Separating Fact from Fear" and "Vaccines and Your Baby" come in DVD format.

Materials can be viewed or printed at http://vaccine.chop.edu/resources. Tear-off pads and DVDs, as well as other VEC materials, can be ordered at nominal cost.

For parents with concerns about vaccines and autism

AAP has issued a statement that can be printed at www.aap.org/advocacy/releases/autismparentfacts.htm. Parents may wish to investigate further at www.aap.org/healthtopics/Autism.cfm. IAC also recommends these books:

- *Autism's False Prophets: Bad Science, Risky Medicine, and the Search for a Cure*, by Paul A. Offit, MD
- *Unstrange Minds: Remapping the World of Autism*, by Roy Richard Grinker, PhD

And, here are two well-researched handouts from IAC:

- "MMR Vaccine Does Not Cause Autism: Examine the Evidence!" www.immunize.org/catg.d/p4026.pdf
- "Evidence shows vaccines unrelated to autism" www.immunize.org/catg.d/p4028.pdf

Technical content reviewed by the Centers for Disease Control and Prevention, Mar 2011

www.immunize.org/catg.d/p2070.pdf • Item #P2070 (5/11)

Immunization Action Coalition • 1573 Selby Ave. • St. Paul, MN 55104 • (651) 647-9009 • www.vaccineinformation.org • www.immunize.org

CHAPTER 3

Telling Stories of Vaccine-Preventable Diseases: Why it Works

By Rachel M. Cunningham, MPH and Julie A. Boom, MD

Abstract:
In this paper, we explore the benefits of storytelling in health communication and, in particular, immunization education. During the mid-20th century polio epidemic, both personal stories and scientific information abounded in the media. However, as rates of vaccine-preventable diseases declined, narratives about the dangers of such diseases faded as did the public fear of them. Meanwhile, anti-vaccine advocates flooded the media and Internet with stories of injured children and tied those injuries, such as autism, to vaccines. Medical experts often counter anti-vaccine concerns with scientific information which can fail to persuade parents. Furthermore, evidence suggests that many people misunderstand quantitative information resulting in a misinterpretation of risk. Compared to scientific information, stories relate life lessons and values. They are effective because they are memorable and relatable. Evidence also suggests that storytelling can effectively improve health knowledge and behaviors. Inspired by *In Harm's Way – True Stories of Uninsured Texas Children* by the Children's Defense Fund and *Faces of Influenza* by the American Lung Association, we published *Vaccine-Preventable Disease: The Forgotten Story*, a collection of photographs and personal stories of families affected by vaccine-preventable diseases. We have found that the stories included in our booklet capture all the benefits of storytelling. Given the many benefits of storytelling, providers should strive to include stories along with medical facts in their daily practice.

What is Storytelling?

Storytelling is one of the oldest and most meaningful forms of human communication. We utilize stories to communicate experiences, life lessons and values. At a minimum, a story contains the facts of a situation. But, stories also reveal the feelings and meaning that surround the factual information. A story relates to the listener what happened, how it felt and why it happened.[1] In addition, stories are thoughtful, reflective and reveal an important human element to the reader.[2]

Despite the ubiquitous nature of stories, they are not commonly used by health care providers. Traditional medical training focuses primarily on objectivity and evidence-based practices.[3] Subsequently, most health care providers rely on statistical evidence only and do not include anecdotal information, such as stories, in their health communication. In fact, storytelling is thought by some to be the antithesis to good science, as it is less analytical and more imaginative. However, good science and medical practice require imagination in many aspects – generating interesting research questions, making tough clinical decisions and managing complex patient care.[4] While statistical evidence appeals to logic and reason, it fails to fully demonstrate the entirety of a person's risk for disease. Storytelling can bridge the gap between logic and emotion by shifting the focus from the hypothetical to reality.[5] A Hassidic proverb states, "Give people a fact or an idea and you enlighten their minds; give them a story and you touch their souls."[6] While statistical evidence contains uncertainty and a theoretical risk, stories can transform theoretical odds and risk into more understandable images and possibilities.[2,7,8]

A Paradigm Shift

Over the last 60 years, immunization communication has undergone a paradigm shift. During the 1940s and 1950s, the U.S. experienced a nationwide polio epidemic. The campaign to battle the polio epidemic was successful in uniting a nation against a disease. Every day the media was

filed with personal stories of children affected by polio. We even had a president who shared his own battle with polio in the media and served as the face of the campaign. At the same time, science had never been so visible to the public. The country held its breath as a vaccine was developed and underwent clinical trials. Hundreds of thousands flocked to receive the first polio vaccine, and the creators of the vaccines, Jonas Salk and Albert Sabin, became national celebrities. During this time, both personal narratives and scientific information about polio abounded in the media. However, as rates of vaccine-preventable diseases declined due to the ongoing development of new vaccines, narratives about the dangers of such diseases faded so that only a generation or two after the eradication of polio in the U.S., the public fear of such diseases also seems to have disappeared.

As both the narratives about vaccine-preventable diseases and the diseases themselves disappeared, a new phenomenon began to occur. The scientific community acquired overwhelming amounts of robust data demonstrating the safety, efficacy and necessity of vaccines, yet lost the personal message of why immunizations are important. As a result, instead of being a society that understood the dangers of vaccine-preventable diseases, we became a society who gradually developed the false belief that since the diseases were no longer visible, the vaccines are no longer important.[9,10] Not only was the importance of vaccines questioned but many became quick to blame vaccines for other health issues, such as autism. As a result, we have seen vaccines tried in the court of public opinion with celebrities and the news media vilifying them. In spite of the lack of scientific evidence supporting their belief that vaccines are harmful, anti-vaccine advocates have flooded the media and Internet with stories of injured children, and they have tied those injuries to vaccines. In a commentary in *Pediatrics*, Parikh described this phenomenon: "anti-vaccine groups… have shared the heartbreak when they learned that their children were autistic and tied vaccines to it. People, logical or not, do not forget this kind of emotional prowess. On the other hand, our medical and scientific experts counter with accurate evidence and citation of studies, which do not resonate with many parents. Thus, we have had a failure to persuade."[11] Attention-grabbing, emotionally-charged stories are powerfully persuasive; listeners may disregard robust statistical evidence in favor of the story's message even though the story doesn't correctly represent reality.[7,12,13] A well-known example of this phenomenon is what occurred when Jenny McCarthy shared her personal story about her son's diagnosis with autism.

In 2007, Jenny McCarthy appeared on the *Oprah Winfrey Show* and shared the story of her son, Evan. This was the beginning of Jenny's fight against vaccines and the first time she publically blamed vaccines for her son's autism. In clear, concise language she described her son's vaccination and sudden descent into autism. "Right before Evan's MMR shot, I said to the doctor, 'I have a very bad feeling about this shot. This is the autism shot, isn't it?' And he said, 'No, that is ridiculous. It is a mother's desperate attempt to blame something,' and he swore at me, and then the nurse gave him the shot. And I remember going, Oh, God, no! And soon thereafter I noticed a change. The soul was gone from his eyes." Oprah then followed with a statement from the Centers for Disease Control and Prevention (CDC), which said there was no science to support the connection between vaccines and autism. Jenny's response – "At home, Evan is my science."[14] Following her *Oprah* appearance, Jenny appeared on *Larry King Live, Good Morning America* and several other television shows in which she repeatedly shared her son's story. In just a few words she communicated a message that resonated with many parents despite its medical inaccuracies. Undoubtedly, Jenny and other vaccine-concerned parents realized the power of a story.

Why Should Health Care Providers Utilize Storytelling?

In a culture that is over-saturated with technology and multi-media, storytelling instead provides listeners with a personal interaction and experience that is memorable.[5] This is best demonstrated by the media's use of narratives to enhance a factual story. For example, Olympic media coverage not only includes footage of the various events but also incorporates in-depth personal stories of the athletes. This human interest angle allows viewers to understand athletes' memorable journeys including their trials, tribulations, sacrifices and emotions. As a result, athletes become endeared to viewers in a much more real and personal way than they would simply watching brief segments of athletic competition. For years afterward, viewers will remember the award-winning moment as well as the personal story of the athlete.

In addition to being memorable, stories are relatable and provide visual imagery that allows listeners to transport themselves into the storyteller's experience.[2] The listener develops a relationship with the storyteller that allows him or her to engage in the story and live vicariously through the storyteller. For example, in the best-selling *Harry Potter* book series, J.K. Rowling effectively used strong visual imagery to send her readers into Harry's world. Readers young and old became friends of Harry's and experienced Harry's trials and tribulations as he grew and the series

progressed. When listeners are transported into a story, they become more receptive to the story's theme and message. This is also true in health risk communication. For parents who are resistant to vaccines and fail to recognize their importance as a preventive tool, a powerful story may allow the parent to step into the life of another parent whose child has been affected by a vaccine-preventable disease. Through a vicarious experience, parents understand that vaccine-preventable diseases are serious and unimmunized or under-immunized children are susceptible to them.[5,8,13,15,16]

Stories are also universal and can transcend all educational levels. Storytelling is an intuitive form of communication that humans learn from birth. Beginning in early childhood, parents tell their children stories to share memories, teach lessons and communicate values. As a result, humans learn to process this type of social information very early in life without education, training or literacy.[2,13,16] What pre-school child doesn't love to hear their parents tell the story of their birth? Children often ask to hear these family stories over and over again. Through family storytelling, we learn how to receive a story as well as to share stories ourselves.

Stories can also be made culturally relevant, particularly to cultures with strong oral traditions.[1] African-American and in particular Native American cultures are known for their oral traditions. In both cultures, the position of storyteller is a highly valued one. These cultures not only recognize the role of storytelling in healing but also its role in preserving cultural history and educating future generations about the past. In these cultures, stories often serve to communicate cultural values and norms.[6,17] Research has demonstrated that stories might be more effective in health communication in cultures with strong oral traditions, especially when the listener identifies with the storyteller and perceives him or her as sharing similar cultural values.[18] For example, Kreuter et al. found that video stories of African-American breast cancer survivors were more likeable and memorable to African-American women than an informational video. Moreover, the women who viewed these video stories were less resistant to the health information, had higher cancer fear scores and a higher intent to get a mammogram.[19]

Pitfalls of Relying on Statistical Evidence in Health Communication

As health care becomes increasingly focused on evidence-based practice, providers would do well to incorporate storytelling into their patient interactions in order to provide medical knowledge in a concise and understandable way.[2,7] Many providers communicate health information with statistical data; however, evidence suggests that many people misunderstand quantitative information about risk such as probabilities, percentages and prevalence. As a result, they may be unable to correctly perceive their risk of illness. Several studies have shown that when given basic probabilities and risk reduction data, few people are able to correctly apply that information.[20] In a study conducted by Lipkus et al. researchers found that even among highly educated participants, only 60 percent were able to solve a basic probability concept and fewer than 20 percent correctly answered all three numeracy questions.[21] As stated in *Time* magazine, "…You would think we'd get pretty good at distinguishing the risks likeliest to do us in from the ones that are statistical long shots. But you would be wrong. We agonize over avian flu, which to date has killed precisely no one in the U.S., but have to be cajoled into getting vaccinated for the common flu, which contributes to the deaths of 36,000 Americans each year."[22] Clearly, many of us fail to comprehend statistical health information in our everyday lives and, as a result, may underestimate our risk of disease.

Examples of Storytelling in Health Risk Communication

Recently, several studies have examined the effect of storytelling on health behavior change. Ricketts et al. found that including stories in safety and health behavior messaging about unintentional injuries resulted in improved safety behaviors among adults assembling child swing sets. Compared with participants who received traditional safety communications that did not include stories, safety behavior was 19 percent better in those who received story-based safety messages.[8] Mazor et al. found that using patient stories in education about anticoagulant medication resulted in improved knowledge compared with education that only used statistical information.[7] Although proven helpful in some areas of health education and behavior change, evidence regarding effectiveness of stories in immunization interventions is limited. A study assessed the impact of a narrative intervention on human papillomavirus (HPV) vaccination among college women, comparing the effect of three interventions using narratives delivered by peers, medical experts or a combination of both. Participants who received the combined peer-medical expert narrative intervention were twice as likely to get vaccinated as the control group. Interestingly, both the peer-only and medical expert-only narrative interventions had no significant effect on increasing vaccination.[23] De Wit et al. compared the effects of narratives to statistical information among men who have sex with men and are at increased risk for hepatitis B. The narratives were found to be more effective at increasing both risk perception and intention to vaccinate.[24]

Storytelling in health communication can be combined with powerful visual imagery to create an even more profound effect. Two examples are *In Harm's Way – True Stories of Uninsured Texas Children* by the Children's Defense Fund and *Faces of Influenza* by the American Lung Association. *In Harm's Way* is a booklet targeting policy-makers and elected officials that shares the personal stories of 16 uninsured Texans who were impacted by the confusing and oftentimes impractical eligibility process of the Texas Children's Health Insurance Program (CHIP) and Medicaid system.[25] *Faces of Influenza* is a multi-media campaign that shares photos and stories of people, some of whom have been affected by influenza and others who are advocates for influenza vaccination such as police officers, physicians, celebrities, school teachers, pregnant women and families living with chronic illnesses. The campaign aims to remind all Americans that anyone can be affected by influenza and reinforces the recommendation that all persons 6 months of age and older receive an annual influenza vaccine.[26] Both of these educational tools demonstrate thoughtful approaches to storytelling in health communication. The stories from *In Harm's Way* clearly yet succinctly communicate the impracticalities of the Texas CHIP and Medicaid eligibility process and subsequent impact on children who relied on CHIP and Medicaid for health insurance coverage. While the booklet also contained factual information, the inclusion of personal stories appealed to the emotional side of the reader despite the political nature of the topic.[25] Similarly, the strong visual imagery from the photos in the *Faces of Influenza* campaign captures the viewer's attention. While some of the "faces" are of families who have been personally affected by influenza, many of them are national health leaders or persons with a special interest in preventing influenza.[26] The compelling nature of these stories led us to realize that the medical community was missing this important element in its immunization communication.

Vaccine-Preventable Disease: The Forgotten Story

Understanding the power of a personal story, we, along with many others in the medical community, recognized the need to incorporate personal stories back into the immunization education message. We knew that there were many parents whose children had been affected by a vaccine-preventable disease who could share medically accurate stories that would be as persuasive and thought-provoking as Jenny McCathy's story about her son, Evan. As a result, we aimed to provide an outlet for parents to communicate the importance of immunization to other parents.

Inspired by *Faces of Influenza* and *In Harm's Way*, we began to collect photographs and personal stories of families affected by vaccine-preventable diseases culminating in the publication of our booklet, *Vaccine-Preventable Disease: The Forgotten Story* in 2009. In this booklet, we focus on each family's story rather than the scientific medical facts. We have found that the stories included in *Vaccine-Preventable Disease: The Forgotten Story* capture all the benefits of story-telling. Simply written and brief, the stories are memorable. The accompanying photograph with each story provides a captivating visual image of the affected family and transports the reader into that family's experience. Because the story is told from the parent's perspective, other parents reading it can easily identify with the storyteller and engage in the story, and they can develop a more realistic view of the risks of vaccine-preventable diseases.[27]

A recurrent theme in the feedback we have received is that the book effectively shares real stories from real families and allows parents to understand that vaccine-preventable diseases can happen to them. Other responses include, "This put real patients with the diseases in front of the parents," "It allows parents to see themselves in possible scenarios that actually happened to real parents", and "It provides the parents with a personal experience of one of these rare but dangerous diseases." Another reader also stated, "It gives parents a snapshot of what can happen when you don't vaccinate."[28]

The booklet also provided an outlet for healing and comfort to families affected by vaccine-preventable diseases. These stories represent a vulnerable period of time for the families and sharing their stories created a sense of purpose and allowed them to turn their experiences into something productive.[29] The families were also able to make meaning of these experiences and subsequently share that meaning with others.[4] Greg Williams is father to Nicolis Williams, and Nicolis Williams died from meningococcal meningitis and is featured in the video "Facing Meningitis." Greg Williams illustrated this aspect of storytelling when he stated that participating in this video project "helped our family heal in so many ways. (G. Williams, father to Nicolis Williams, personal communication, February 2012)."[30] Several of the families who participated in this book are immunization advocates who have dedicated their lives to educating others about the importance of immunization.

The following stories from our book illustrate the effectiveness of using compelling stories to highlight a medical message.

Figure 1. Gary and Denise Palmer with a photo of their daughter, Breanne, who died from influenza at 15 months of age. Her story is featured on page 27 of *Vaccine-Preventable Disease: The Forgotten Story*.

Breanne Palmer – Influenza

When Gary and Denise Palmer traveled to Maryland for Christmas vacation with their 15-month-old daughter, Breanne, she caught the flu. After she got a fever, they consulted a local pediatrician. When she began vomiting and her fever reached 105.5°F, they called 911. At the hospital, the doctors said the influenza virus was attacking Breanne's heart and brainstem, resulting in extensive brain damage. Two days before Christmas in 2003, Breanne died. Had she received a flu vaccine, Denise and Gary strongly believe Breanne might still be alive today.

Figure 2. Abby Wold, meningococcal meningitis survivor and double amputee. Her story is featured on page 53 of *Vaccine-Preventable Disease: The Forgotten Story*.

Abby Wold – Meningococcal Meningitis

A few days before she was to begin basic training for the U.S. Army, Abby Wold contracted meningococcal meningitis. The struggle to survive this vaccine-preventable disease changed her life forever. Abby's illness began with vomiting and excruciating muscle pain which eventually left her unable to walk. When she arrived at the hospital, she was placed in a coma and put on a ventilator as her organs began to fail. Over the next couple months, Abby lost both of her legs below the knee and two fingertips. Since then, Abby has continued to face health issues such as chronic kidney problems, adrenal failure and severe headaches. Abby is often surprised by the lack of awareness surrounding meningitis. "I meet so many parents who never knew about meningitis and are astonished that there is a vaccine to prevent it," Abby says. "The truth of the matter is that vaccines save lives."

While *Vaccine-Preventable Disease: The Forgotten Story* effectively uses storytelling to communicate the importance of immunization, we realize that the book does not stand alone. In a survey to physicians using the book, we found that most use the book in conjunction with other immunization materials including handouts, vaccine information statements (VISs), and other vaccine books, as well as personal conversations with the parent. Most respondents (77 percent) indicated that they use a combination of written and verbal information alongside the book.[28]

Special Considerations

While storytelling in and of itself is an intuitive form of communication that we use every day, soliciting stories from people about a vulnerable period of their life is difficult and requires a generous measure of sensitivity. Because storytelling in health risk communication often involves tragic or painful experiences, the potential storyteller should be approached carefully and respectfully. Moreover, because medical stories disclose patient health information, all efforts to solicit stories from patients should comply with standards set forth by the Health Insurance Portability and Accountability Act (HIPAA). It is also important for the person and/or family sharing their story to be advocates with a clear message. The story and underlying message should be able to stand on its own, be easily understandable and be free from complicated medical details. Lastly, consent should be collected from each storyteller if personally identifiable information is to be used.

Conclusion

Storytelling is one of the most common forms of communication and can be a powerful adjunct when used by health care providers to relay health information to patients. Stories have the unique ability to transform confusing, medical information into understandable, memorable

messages. A powerful story allows a parent to step into the shoes of another parent and provides visual imagery that can trigger a positive health behavior. Evidence demonstrates that storytelling can improve health behaviors and knowledge.

With increased emphasis on evidence-based practices, stories can be used to personalize medical information and motivate patients into taking the best steps to protect their health. Given the many benefits of storytelling, providers should reflect on their personal and professional backgrounds and strive to include stories along with medical facts in their daily practice.

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CHAPTER 4

The State of Immunization 2013: We Are The World

By Anne Schuchat, MD

Abstract:
Most vaccine-preventable diseases in the U.S. are at record low levels, and immunization coverage among toddlers and teenagers is high or increasing. However, importations of measles virus from other countries, resurgences of pertussis and mumps, and the 2009 pandemic of influenza A H1N1 are reminders that Americans remain vulnerable to vaccine-preventable diseases and that sustained support for public health and clinician efforts is needed. Geographic areas with high rates of exemptions from vaccinations required for school attendance place communities at risk for disease outbreaks. There has been much progress internationally in reducing the toll of vaccine-preventable diseases, through public-private partnerships like the Global Alliance for Vaccines and Immunizations (GAVI). Paralytic poliomyelitis is on the verge of eradication, with wild virus transmission continuing in only three countries – Nigeria, Afghanistan and Pakistan. Intensified efforts in those countries are critical. The Decade of Vaccines Collaboration offers an opportunity to strengthen immunization in every community and country.

"We are the world, we are the children"
Michael Jackson and Lionel Richie, Recorded by United Support of Artists (USA) for Africa, 1985

"Life or death for a young child too often depends on whether he was born in a country where vaccines are available"
Nelson Mandela

Introduction

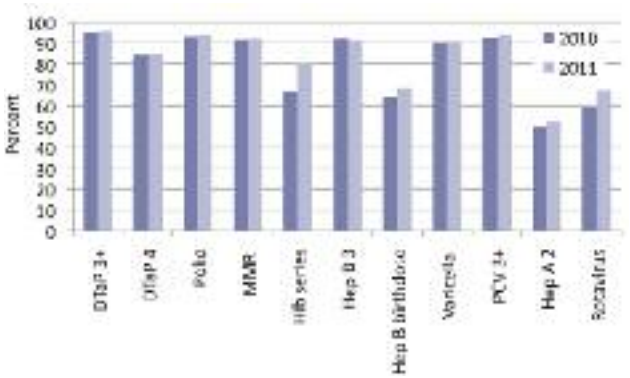
Michael Jackson may have more in common with vaccine-preventable diseases and immunization than you think. He was dramatic and unforgettable; his music and humanitarianism were going viral globally before the Internet; and he suffered a tragic early death – one that was preventable. There are few illnesses as dramatic as meningococcal meningitis or paralytic poliomyelitis. Measles and influenza transmission patterns represent the ultimate in global spread. And each child who dies from a disease vaccination could have prevented represents a collective tragedy. Benjamin Franklin, after refusing to have his 4-year-old son inoculated and then losing him to smallpox, wrote of the sadness of the regret that compounded his grief .[1]

Whether immunization today lives up to the best or worst of Michael Jackson's legacy can be debated. However, when it comes to infectious diseases and the vaccines that can prevent them, Jackson's "We are the World" anthem holds true: each individual and every single country is inextricably interconnected with the rest of the world. Viruses and bacteria don't respect borders; they are literally a plane ride away. In response to these age-old threats, public-private partnerships are now bringing innovation and life-saving assistance to the poorest communities around the world. While most vaccine-preventable diseases are on the run, special challenges of the 21st century do require attention.

State of Immunization in the U.S.

The state of immunization in the U.S. in 2013 is strong but also threatened, partly due to that strength. Most vaccine-preventable diseases are at extremely low levels, reflecting the high immunization coverage that has been achieved or sustained, particularly among young children[2,3] (Table 1).

Figure 1. Estimated Percent Vaccination Coverage Among Children Aged 19 to 35 Months by Selected Vaccines and Dosages and Year of Survey

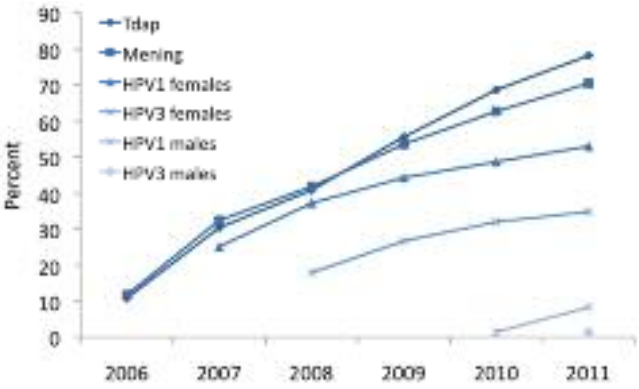


National Immunization Survey, 2010 and 2011. Data from reference 4. Diphtheria-tetanus-acellular pertussis vaccine (Dtap), measles-mumps-rubella vaccine (MMR), Haemophilus influenzae type b conjugate vaccine (Hib), hepatitis B vaccine (Hep B), pneumococcal conjugate vaccine (PCV).

The latest national immunization survey confirmed that in 2011, all pediatric vaccinations had higher or similar levels of coverage among toddlers as were reported in 2010, with significant increases for rotavirus, hepatitis A, the birth dose of hepatitis B, and the complete series of *Haemophilus influenzae* type b (Figure 1).[4] Immunizing one's children remains a social norm in the U.S.; less than 1 percent of toddlers receives no vaccines at all.[4]

Vaccination coverage continues to increase among teenagers, with notable increases for meningococcal conjugate and tetanus, diphtheria and acellular pertussis (Tdap) vaccines received by 13 to 17-year-olds[5] (Figure 2). The 2011 National Immunization Survey revealed that coverage of Tdap vaccines among 13 to 15 year olds has already achieved the Healthy People 2020 target of 80 percent. Unfortunately, minimal increases in coverage between 2010 and 2011 were evident for human papillomavirus (HPV) vaccination of teenage girls, and the gap between Tdap or meningococcal conjugate vaccination and HPV vaccination in most states is growing. Among females, the coverage gap between Tdap or meningococcal conjugate vaccine and coverage with at least one dose of HPV was 25.3 percentage points nationally.[5] The strong recommendation by a clinician remains the greatest predictor of whether someone will receive an immunization, and avoiding missed opportunities (e.g., when another vaccine is being offered) is an important strategy to raise HPV immunization coverage among teenagers.

Figure 2. Estimated Percent Vaccination Coverage Among Adolescents Aged 13 to 17 Years for Tdap, Mening Conjugate, and Greater Than or Equal to 1 and 3 doses HPV Vaccines



National Immunization Survey – Teen, U.S., 2006-2011. Data from reference 5. Tetanus-diphtheria-acellular pertussis (Tdap), meningococcal ACYW-135 conjugate (Mening), human papillomavirus vaccine (HPV)

The U.S. has achieved and sustained the elimination of indigenously circulating measles and rubella, but measles importations continue to occur from regions where measles still circulates or causes large outbreaks. In 2011, the U.S. experienced the greatest number of measles cases in 15 years[6] as a result of importations, many of which came from Europe, where countries such as France had large outbreaks. American travelers as well as international visitors brought the virus back to several communities. Fortunately, rates are down again at the time of this writing in 2012, but each importation requires a rapid public health response to trace contacts and make sure that high coverage prevents the re-establishment of local transmission.

Vaccines introduced into routine use in the U.S. during the past decade, such as rotavirus and 13-valent pneumococcal conjugate vaccine, are already showing impressive impact on disease reduction. Rotavirus vaccination has reduced hospitalizations and emergency visits for gastroenteritis among children less than 5 years old, with evidence of substantial herd immunity.[7,8] Within two years of vaccine introduction, the 13-valent pneumococcal conjugate vaccine has already reduced invasive disease caused by the six types not included in the 7-valent vaccine among children less than 2 years of age, and early reports suggest vaccine-type disease reduction among adults as well, according to the Centers for Disease Control and Prevention (CDC) and Active Bacterial Core surveillance Emerging Infections Program Network. Newer vaccine recommendations, such as a second dose of varicella vaccination for children, are also having effects, with a more than 70 percent reduction in varicella incidence since the second dose policy went into effect.[9]

Not all diseases are quiescent, and the past five years have seen large outbreaks of mumps in selected areas,[10] and record high levels of pertussis occurred during 2012.[11] Outbreaks of measles have been associated with international travel that permitted virus importation from abroad; disease in the U.S. spread primarily among children who

were not vaccinated due to the personal beliefs of their parents.[6] The influenza A H1N1 pandemic of 2009 was a reminder of the unpredictable nature of influenza viruses as well as the critical importance of maintaining a strong public health infrastructure capable of detecting and responding to emergent threats. One legacy of the pandemic has been improving rates of seasonal influenza vaccine coverage among children and pregnant women.[12,13] While influenza vaccine coverage is not as high as we see for other routine childhood vaccines, about 50 percent of children under 19 years of age have received influenza vaccination in the past two seasons, significantly higher than the rates in 2008 and before.

Recent pertussis outbreaks around the country have underscored the critical role that public health infrastructure plays in protecting communities. State and local health departments conducted communication campaigns and organized emergency immunization clinics in affected areas. They disseminated updated diagnosis and treatment recommendations to clinicians, and public health laboratories at the state and national level ran pertussis diagnostic tests and provided training to laboratory staff on appropriate methods for confirming pertussis including newer polymerase chain reaction testing. Epidemiologic studies assessed vaccine effectiveness and provided support to clinical practices regarding appropriate vaccine storage and handling. The Advisory Committee on Immunization Practices updated vaccine recommendations to address expanded ages and improved approaches to protect the youngest infants through vaccinating women late in pregnancy. Public health also handled interim guidance for vaccine use during a temporary shortage of an acellular pertussis-containing combination vaccine in frequent use among infants and toddlers. These vital public health activities supplement the key role that clinicians and parents play in protecting children from vaccine-preventable diseases, and illustrate the importance of public-private partnerships and core infrastructure support to national, state and local programs.

State of Immunization in the World

Polio The world is on the verge of eradicating polio. There have been fewer cases reported from fewer places in 2012 than ever before.[14] India has gone more than two years without transmission, and only three countries – Nigeria, Afghanistan and Pakistan – have never interrupted transmission. In May 2012, the World Health Assembly declared eradication of polio a global public health emergency – intensification of the eradication effort now is essential to sustain the Indian success and maximize the chances to achieve this historic goal. Thus far, smallpox is the only human disease that has been globally eradicated – but the prospects for success with polio have never been better. Successful eradication of polio will not only mean a world free of paralyzing polio everywhere forever, but also a stronger national and global capacity for tackling other health and community challenges. The laboratory and surveillance investments, public health work force and management practices, and social and community mobilization that have been cornerstones to interrupting polio transmission in nearly all countries of the world can be the foundation for other public goals. For example, India followed their historic interruption of polio transmission with large scale measles immunization campaigns, as well as strengthening and expanding their routine immunization systems to incorporate *Haemophilus influenza* type b- (Hib) and hepatitis B-containing pentavalent vaccine. Countries within the Pan American Health Organization region followed polio elimination by taking on regional elimination of measles and rubella and accelerating introduction of numerous newer vaccines. Many countries have broadened national and subnational immunization days initiated for polio campaigns to permit delivery of other health interventions, including other vaccinations, insecticide treated bed nets, vitamin A, and deworming medications, reflecting national or local priorities.

New and Underutilized Vaccine Introduction New vaccines against leading causes of child mortality – pneumococcal pneumonia and rotavirus diarrhea – are being introduced in the poorest countries of the world through the support of the Global Alliance for Vaccines and Immunization (GAVI). GAVI support for low income countries is credited with preventing 5 million premature deaths from vaccine-preventable diseases during its first decade. Current programs are aimed to prevent an additional 4 million early deaths through vaccinations given from 2011 through 2015. Programs are accelerating uptake of pneumococcal and rotavirus vaccines, in addition to supporting measles, measles-rubella, meningococcal A conjugate and yellow fever vaccine campaigns. GAVI has also opened windows for countries to apply for national introduction of HPV vaccination of girls, aimed to prevent cervical cancers associated with selected types of that virus. GAVI funds country efforts to strengthen health systems in support of achieving immunization goals. GAVI also aims to shape vaccine markets and strengthen country ownership as evidenced in co-financing by national governments, aimed to achieve sustainability of development and vaccine introduction assistance. More information can be found by visiting www.gavialliance.org.

Table 1. Comparison of 20th Century Annual Morbidity and Current Morbidity of Vaccine-preventable Diseases.

Disease	20th Century Annual Morbidity†	2011 Reported Cases††	Percent Decrease
Smallpox	29,005	0	100%
Diphtheria	21,053	0	100%
Measles	530,217	222	> 99%
Mumps	162,344	404	> 99%
Pertussis	200,752	18,719	91%
Polio (paralytic)	16,316	0	100%
Rubella	47,745	4	> 99%
Congenital Rubella Syndrome	152	0	100%
Tetanus	580	36	94%
Haemophilus influenzae	20,000	14*	> 99%

†Source: JAMA (Reference 2).
† † Source: CDC (Reference 3).
* *Haemophilus influenzae* type b (Hib) less than 5 years of age. An additional 14 cases of Hib are estimated to have occurred among the 226 reports of Hi (less than 5 years of age) with unknown serotype.

The Haiti Earthquake and Emergency Immunization Efforts

Natural disasters and other emergencies continue to require immunization responses. Public health workers in post-earthquake Haiti, fresh from tackling the devastation caused by the introduction of cholera to that island's population, implemented urgent vaccination campaigns against measles, rubella and polio. Without such efforts, Haiti would be particularly vulnerable to measles importations, which continue to occur across the Americas. A prime source could be France – where uncontrolled spread of that virus led to over 15,000 cases in 2011. Fifty years after the U.S. began measles vaccination, measles has essentially been eliminated from the Americas, and all but one other region has established targets for measles elimination. Attitudes, rather than access, that are pervasive in some communities in Europe may now represent the greatest threat to global measles elimination.

Haiti's cholera epidemic also put the spotlight on the potential value of oral cholera vaccination as part of control of that disease. Pilot programs introduced oral cholera vaccine in two areas within Haiti during 2012 and the Pan American Health Organization, World Health Organization (WHO) and others are re-evaluating the role of oral cholera vaccine in cholera control programs. Vaccine supply has been a key barrier, but discussions have been ongoing about establishment of stockpiles to be directed to urgent areas. Critical attention to provision of clean water and improved sanitation is always needed in addressing epidemic and endemic cholera, but WHO prequalification of oral cholera vaccine formulations opens the door for vaccines to play more of a role in the context of public health emergencies.

Challenges for our Time

Although national immunization coverage data for the U.S. reflect high levels of community support for immunization, beneath the national or state averages remain pockets of under-immunization. In the 1980s and early 1990s, so-called pockets of need reflected limited access to affordable vaccination by the poorest children in many cities.[15] Children were being seen by physicians or clinics but providers were missing opportunities to vaccinate them. The Vaccines for Children Program (VFC) implemented in 1994 greatly reduced financial and access barriers for uninsured and other vulnerable children. The program led to increases in immunization rates, reductions in racial and ethnic disparities in coverage and introduction of many new or improved vaccines to the routine childhood and adolescent immunization schedules. However, in 2012, pockets of under-immunization in the U.S. often reflect very different forces.[16] Parents in some communities have increasingly voiced concerns about the number and timing of recommended vaccines, in addition to raising questions about specific vaccines or vaccine ingredients, such as measles, mumps and rubella vaccine (MMR) and thimerosal. Some of these concerns date back to a discredited article published in *The Lancet* in 1998, which was subsequently retracted, in which Wakefield and colleagues posited a link between MMR and autism. Investigations in Britain have now identified fraudulent information was included in this report, and Wakefield's medical license was taken away. Parental concerns, often vague and uncertain, have to some extent persisted, although national coverage levels remained high in the U.S. even though they dropped in the U.K.

Pediatricians and family physicians cite a growing burden on office visits to fully address parental concerns. Communication research suggests gaps in provider-patient encounters with parents who are hesitant about specific vaccines or immunization in general, and who clamor for individualized attention to their concerns. The CDC has conducted a series of research efforts to better understand factors underpinning vaccine acceptance, and to develop tools and strategies to support clinicians in their conversations with parents about vaccines. Some academic

researchers and innovative public-private partnerships are carrying out intervention studies to learn more about the most effective approaches to strengthening provider-patient communication around vaccines. A variety of tools for clinicians and the public are available at www.cdc.gov/vaccines/conversations.

One indicator of vaccine acceptance is the proportion of school children whose parents request exemptions from vaccination requirements. Investigators have shown that geographic areas with higher rates of exemptions are at increased risk of pertussis and measles.[16,17] In addition, researchers have shown that the easier it is to obtain an exemption, the higher the rates of exemptions. The CDC has issued minimum standards for how states or cities track vaccination and exemptions at kindergarten entry, and reports for the 2011-12 school year show wide state-to-state variation in exemptions.[18]

The explosion of sources of information and misinformation is another challenge for parents trying to make good choices for their children's health. While parents consistently rate their child's clinician as the most important influence on their decisions about vaccination, the Internet and social media have expanded the other influences on an individual's decision-making beyond friends, family and traditional media. These new technologies provide exciting opportunities for targeted and interactive communication strategies, but also produce a cacophony of opinions. Ideally, reliable and validated sources of information rise to the top of trusted sites, but rumors can take on a life of their own, permitting them to persist even if they have been scientifically discredited.

Opportunities for the Decade

In 2010, philanthropist Bill Gates used the World Economic Forum at Davos to propose a Decade of Vaccines and announce his commitment to donate at least $10 billion toward support of an ambitious agenda. In May 2012, the World Health Assembly endorsed the Global Vaccine Action Plan, which spelled out goals and strategies to improve vaccine development, delivery, access and public support. Each country is encouraged to develop multiyear plans and to strengthen community engagement, the quality of immunization services and reduce inequities in immunization coverage. The research and development community is urged to take advantage of new scientific tools, incorporate multidisciplinary approaches and bring user needs and researcher targets closer together. The current decade could very easily see the first vaccine licensed for malaria and has already brought forward proof of principle results for dengue vaccines. The six strategic objectives included in the Global Vaccine Action Plan are: 1) All countries commit to immunization as a priority; 2) Individuals and communities understand the value of vaccines and demand immunization as both their right and responsibility; 3) The benefits of immunization are extended equitably to all people; 4) Strong immunization systems are an integral part of a well-functioning health system; 5) Immunization programs have sustainable access to predictable financing, quality supply and innovative technologies; and 6) Country, regional, and global research and development innovations maximize the benefits of immunization. More information can be found by visiting http://apps.who.int/gb/ebwha/pdf_files/WHA65/A65_22-en.pdf.

The U.S. Department of Health and Human Services (HHS) recently released its Global Health Strategy for 2011 through 2015. More information about the Global Health Strategy can be found at www.globalhealth.gov/global-programs-and-initiatives/global-health-strategy/index.html. The Global Health Strategy's three goals are to protect and promote the health and well-being of Americans through global health action; to provide leadership and technical expertise in science, policy, programs, and practice to improve global health; and to advance U.S. interests in international diplomacy, development and security through global health action.

HHS also has released the National Vaccine Plan and an accompanying implementation plan, found at www.hhs.gov/nvpo/vacc_plan/. The National Vaccine Plan reflects roles for the federal government, state and local government and private and community stakeholders, including private industry, the health care sector, community-based groups and the public. The Patient Protection and Affordable Care Act of 2010 included several key provisions that should strengthen immunization services and access, including requirements that new or updated insurance plans include first dollar coverage for all CDC Advisory Committee on Immunization Practices (ACIP) recommended vaccines (with no copays or deductibles) when vaccines are provided by an in-network provider. Many of the health information technology investments of the past few years have advanced the quality and completeness of immunization data organized in electronic health records and immunization registries, as well as improving the interoperability of these systems through incentive payments from the Center for Medicare and Medicaid Services' (CMS) Meaningful Use program. While these developments provide a framework upon which to build, the efforts of state and local governments as

well as health care organizations and consumers will be critical to assuring improved individual and community immunization efforts.

Conclusion

The *We Are the World* album raised public attention to a humanitarian crisis – famine in Afria – to unforeseen heights and raised extraordinary sums of money to bring relief to that problem. Unfortunately, recent drought and famine in the Horn of Africa remind us that extreme human suffering continues. The series of global fiscal crises and U.S. economic challenges remind us how interconnected we still are. The universality of the *We are the World* message rings true for protecting people, especially children, from infectious disease threats like vaccine-preventable diseases. The concept of herd immunity means that each of us can play a role in protecting the most vulnerable, since vaccines protect an individual but can also reduce a person's risk of spreading an infection to those unable to be directly protected by vaccines.

In a world where smallpox has already been banished to the history books, where polio flickers on the verge of extinction, and where vaccines against leading childhood killers like pneumonia and diarrhea are already being adopted by the poorest countries, there is much success to celebrate. But unfortunately, lifesaving technology is not the only thing with worldwide distribution options. Microbes have perfected techniques for rapid and efficient global spread. The same world which can successfully eradicate a human disease is one where pandemics will continue to happen, where a new virus like SARS may be only a plane ride away. Ten years ago, the SARS corona virus managed to cripple hospitals from Taipei to Toronto; tomorrow the next influenza pandemic could do the same if our vigilance lapses. These realities are why there is no place for complacency. Vaccine interventions continue to represent a best buy in public health, but sustaining the infrastructure to assure vaccines reach people everywhere is essential to our communities' health. Strong immunization systems in the U.S. reflect the best of public-private partnerships and can strengthen the level of trust and respect between parents and the doctors, nurses, pharmacists, public health professionals and others who attend to our patients and communities. We may not all be rock stars like Michael Jackson, but we can try to treat everyone's children as though they were our own.

There can be no keener revelation of a society's soul than the way in which it treats its children.

Nelson Mandela

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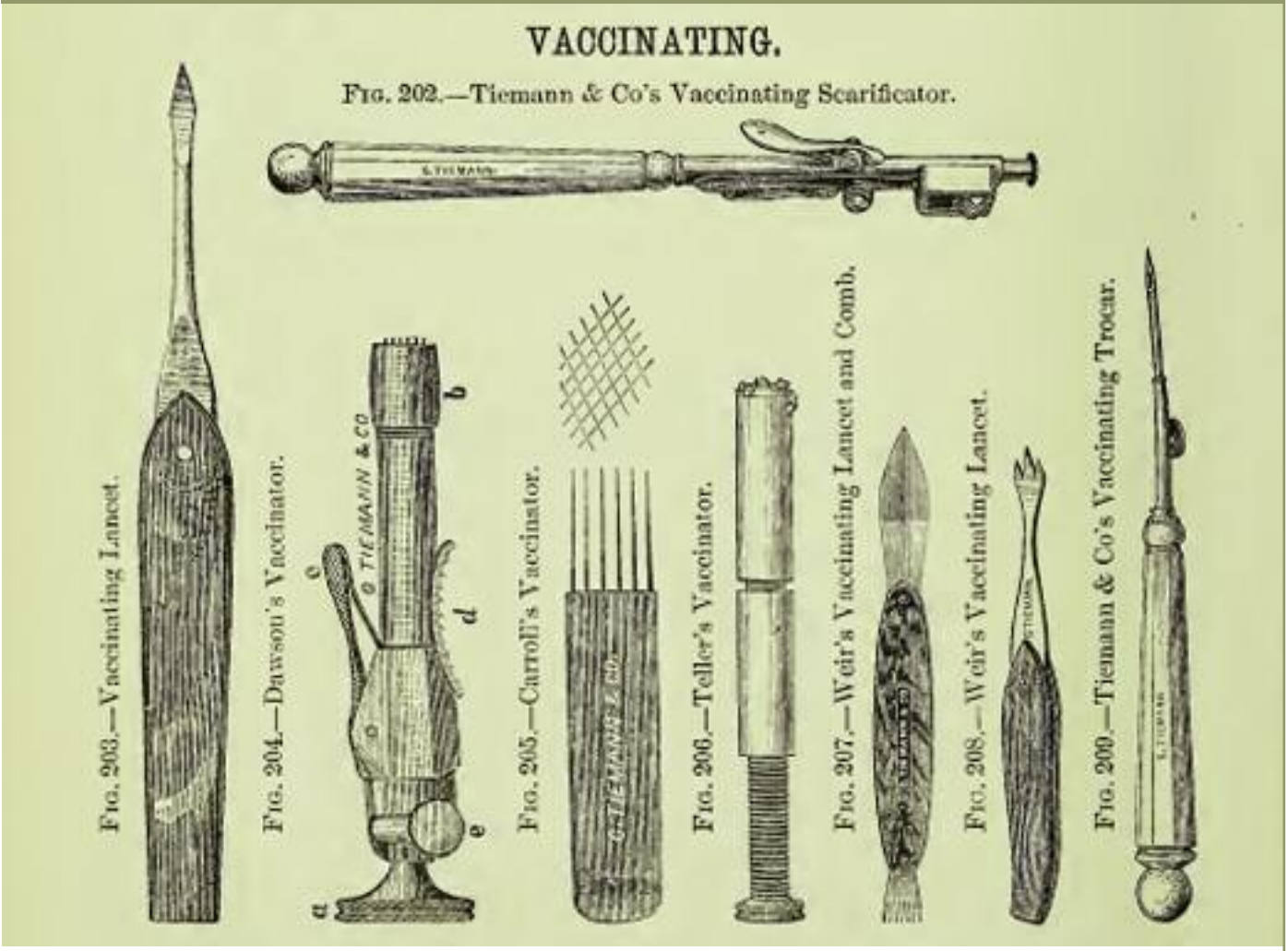

CHAPTER 5

A Brief History of Vaccines: Smallpox to the Present

By Jennifer L. Hsu, MD

Abstract:
Modern vaccine history began in the late 18th century with the discovery of smallpox immunization by Edward Jenner. This pivotal step led to substantial progress in prevention of infectious diseases with inactivated vaccines for multiple infectious diseases, including typhoid, plague and cholera. Each advance produced significant decreases in infection-associated morbidity and mortality, thus shaping our modern cultures. As knowledge of microbiology and immunology grew through the 20th century, techniques were developed for cell culture of viruses. This allowed for rapid advances in prevention of polio, varicella, influenza and others. Finally, recent research has led to development of alternative vaccine strategies through use of vectored antigens, pathogen subunits (purified proteins or polysaccharides) or genetically engineered antigens. As the science of vaccinology continues to rapidly evolve, knowledge of the past creates added emphasis on the importance of developing safe and effective strategies for infectious disease prevention in the 21st century.

Introduction

To most Americans, paralysis from poliomyelitis, birth defects from rubella, and sterility from mumps represent obscure diseases with only historical relevance. However, just a century ago, infant and child mortality in the U.S. was 20 percent, primarily due to infectious diseases.[1] Humankind suffered for centuries with epidemic disease resulting in war, social upheaval and economic crisis. Compared to this long history, vaccination is a relatively recent strategy for disease prevention among large populations. In just over 200 years, vaccination has had a major impact on global health, including eradication of naturally occurring smallpox and reduction of poliomyelitis by 99 percent.[2] Experts have argued that with the exception of safe drinking water supplies, no other single health intervention has had such a major impact on mortality reduction and population growth.[3]

A Short History of Smallpox

> "Smallpox was always present, filling the churchyard with corpses, tormenting with constant fear all whom it had not yet stricken, leaving those whose lives it spared the hideous traces of its power, turning the babe into a changeling at which the mother shuddered, and making the eyes and cheeks of the betrothed maiden objects of horror to the lover."[4]
>
> – Macauley, 1800

For centuries, smallpox was one of most lethal diseases known to man. Initially appearing in African agricultural settlements around 10,000 B.C., smallpox likely spread to Egypt via traveling merchants in the last millennium B.C.[5] Egyptian mummies have provided the earliest known skin lesions consistent with smallpox. From Egypt, infection spread through wars, resulting in epidemics in Greece, where in 430 B.C. Thucydides made the first recorded observation that those who survived the disease were later immune.[6] Arab expansion, the Crusades and the discovery of the New World all promoted further spread of this lethal disease.

Smallpox inspired great dread, earning monikers such as "the most terrible of all the ministers of death" and "the speckled monster."[4] The clinical course was commonly known as the sudden appearance of high fever, rigors, cephalgia and dorsal-lumbar pain, as well as nausea and vomiting. Two to four days later, the fever resolved and maculopapular skin lesions evolved into vesicles and pustules and then scabs. The case fatality rate varied 20 percent to 60 percent, and survivors were often left with blindness and disfiguring scars.[5]

Immunity in survivors of smallpox was common knowledge. As early as 1000 A.D., unverified texts have suggested that the Chinese powdered scabs of smallpox lesions to be inhaled by healthy persons. This practice of inoculation, or variolation, became commonplace, spreading to Europe in the 18th century via traveling merchants from Turkey.[7] English royalty later adopted the practice further increasing its popularity. Although a small fraction of variolated persons died or acquired additional infections from the donor, including syphilis and tuberculosis, case-fatality rates were 10 times lower than with naturally occurring smallpox.[5] Thus, the practice of variolation spread further to the American colonies. Notably, George Washington even variolated the Continental Army to avoid spread of smallpox from immune English troops to vulnerable American soldiers.[3]

The Cowpox – Smallpox Connection

Anecdotes of people previously infected with cowpox, a zoonotic pathogen, later avoiding smallpox infection abounded in rural 18th century England. Benjamin Jesty, an English farmer, acquired cowpox as a young man. When an outbreak of smallpox occurred in his locale in 1774, he sought protection for his family. Using a needle, he transferred material from cowpox lesions on cow udders to the skin of his family in hopes of preventing smallpox. His wife and two sons did not acquire the infection despite exposure to multiple epidemics.[8] Additionally, his two sons were later variolated and did not develop any evidence of smallpox. Although ridiculed at the time for injecting his family with an animal disease, Jesty's strategy created the first known immunization against smallpox.[8]

Edward Jenner's Discovery

Working as an apothecary apprentice in rural England, Edward Jenner learned of the protection from smallpox occurring after cowpox exposure. He published the first studies of inoculation against smallpox in 1798, drawing attention to the merits of 'vaccination.' The term 'vaccination,' from the Latin for cow ("vacca") replaced 'variolation."[9] Jenner faced significant opposition regarding the exposure of humans to animal fluids; however, he persisted, predicting in 1801 "the annihilation of smallpox – the most dreadful scourge of the human race – will be the final result of this practice."[7]

During the first half of the 19th century, the vaccine was maintained through person-to-person, specifically arm-to-arm passage. Jenner and others soon realized that the protection afforded from vaccination was short-lived. This led to the discovery that serial passage decreased fitness of the cowpox strains. In 1836, Dr. Edward Ballard reported the importance of passing the lymph (vesicle fluid) back through calves to regain strength. Calves were deliberately

infected with cowpox to enhance the strength of the virus and later used to mass produce sufficient supplies of lymph for vaccination.[7] Additionally, concerns for secondary infection transmission, including syphilis, remained with arm-to-arm transmission. Based on Robert Koch's recommendations, German scientists began using glycerin to kill bacteria and preserve lymph.[3] Glycerinated calves' lymph became the standard for vaccination by the end of the 1890s. Jenner's work was made famous by the rapid development and spread of vaccination against smallpox. Prior to his death in 1823, there was a near 50 percent decrease in smallpox in England and spread of vaccination throughout the world.[9] Not only did Jenner contribute to future eradication of smallpox, but he popularized the idea of deliberate strategies to protect against infectious disease, giving rise to the era of vaccine development.

Pasteur and Development of Attenuated Vaccines

Important vaccine concepts had been developing for 40 years, including attenuation and modification through passage, as well as the need to replace person-to-person vaccination with safer, more standardized methods.[3] The first major advance in vaccine science after Jenner's smallpox vaccine came in the late 1870s with Louis Pasteur's observations on chicken cholera, now known as *Pasteurella multocida*. Pasteur observed that chickens inoculated with cultures left out over a prolonged period did not become ill. These same chickens were later inoculated with fresh culture material and again did not develop infection, suggesting protective immunity developed after exposure to the aged culture.[10] This observation led Pasteur to attenuate bacteria through exposure to adverse conditions, including high temperatures, oxygen and chemicals. Although Pasteur incorrectly attributed the finding to depletion of necessary growth factors for the organism, the practical results were a landmark finding.[11] This discovery led to the modern concept of vaccination with the actual disease-causing agent and laboratory-developed materials.

Building on the knowledge of attenuated vaccines, Pasteur and colleagues developed a practical method of rabies vaccination. Rabbit spinal cords infected with rabies showed rapidly decreased virulence when exposed to dry air. Dogs injected with this avirulent material resisted later inoculations with active virus. Carrying this strategy forward, the first patient, Joseph Meister, was vaccinated in 1885 after suffering numerous bites from an infected dog.[12] He, too, resisted infection. This treatment aroused great interest, as well as criticism due to objections against injecting deadly pathogens into humans. With the spread of rabies vaccination, many more patients were saved from rabies than were infected and ultimately, Pasteur was heroized for his discovery.[13]

Live Versus Inactivated Vaccines

Vaccine development remained empirical in the late 19th and early 20th centuries as knowledge of immunology was in its infancy. After Pasteur's vaccines, Daniel Elmer Salmon and Theobald Smith published work on their killed hog cholera 'virus' vaccine, now known as *Salmonella*, in 1886.[13] Injection with killed, or inactivated, bacteria resulted in protective immunity among pigeons. At the end of the 19th century, vaccine development rapidly expanded with inactivated vaccines against typhoid, plague and cholera. In parallel, understanding of human immunity was increasing. Elie Metchnikoff popularized the theory of cellular immunity in 1884.[3] Shortly thereafter, Paul Ehrlich published on his receptor theory of immunity in 1897, which eventually led to development of anti-toxins against pathogens such as diphtheria. Understanding of the antigen-antibody relationship followed these innovations, setting the stage for anti-toxin development in the 20th century. At the conclusion of the 19th century, the knowledge of human immunity was burgeoning along with vaccine science. Five human vaccines were in use: two live virus vaccines (smallpox and rabies) and three killed bacterial vaccines (typhoid, cholera and plague.)[11] Using the techniques of Pasteur, these vaccines created a framework for more refined vaccines in the early 20th century.

The Advent of Cell Culture

In the first half of the 20th century, vaccine science continued to grow with development of diphtheria and tetanus anti-toxins. From this advance, came the term 'immunization' as patients were inoculated with rabbit 'immune serum.' Additionally, vaccines against tuberculosis, Bacille Calmette-Guérin (BCG), yellow fever, typhus, influenza A and pertussis were developed. Work on combination vaccines was also completed with development of diphtheria, tetanus and pertussis in 1948. These developments paralleled rapid improvements in the understanding of microbiology, as identification of the correct pathogen was a fundamental obstacle in early vaccine development.

A monumental achievement in vaccine science came in 1949 with propagation of viruses through cell culture. Previously, anti-viral vaccines were only cultured through live animals, such as cows or rabbits. Hugh and Mary Maitland were the first to propagate viruses in cell culture. They developed flask tissue culture in 1928 where vaccinia virus was grown in minced chicken kidneys.[3] Shortly thereafter, in 1931, Goodpasture introduced the chorioallantoic membranes of a fertile hen's egg as a culture medium for sterile passage viruses. Passage in cell culture became the primary means of attenuating viruses. However, cell culture

also allowed intentional selection of mutants by isolation of single clones and incubation at temperatures below the normal host temperature.[10] From these early studies, John Enders, Thomas Weller and Fred Robbins were later able to expand tissue culture to achieve viral growth in explanted human muscle and skin cells. They were the first to successfully cultivate human poliovirus in monolayer cell cultures, a finding that led to a flood of new vaccines. This opened the door to the current era of vaccine development.[3]

Polio: Development of Live Virus Vaccines

Prior to the 20th century, virtually all children were infected with poliovirus while still protected by maternal antibodies. Improved sanitation practices of the late 18th and early 19th centuries led to an increase in the average age of exposure. Without maternal antibodies present in the older children, large epidemics ensued.[14] The causative agent, poliovirus, was identified in 1909. Development of tissue culture for propagation of poliovirus around the time of World War II was the first step in development of a vaccine. Using these new cell culture techniques, Hilary Koprowski developed a live polio vaccine in 1950 using a variant virus strain grown in mice.[3] In 1955, Jonas Salk developed the first inactivated, or killed, vaccine against polio, which contained all three serotypes of poliovirus, inactivated by formaldehyde. The search for effective prevention against polio was widely publicized. Salk's clinical trial included 1.8 million children and declared the vaccine to be safe and effective. Inactivated poliovirus vaccine (IPV) was immediately licensed. However, the haste to produce vaccine led to the Cutter Incident. Vaccine produced by Cutter Laboratories was found to have live poliovirus. Among the 120,000 primarily first- and second-grade children receiving vaccine from these lots, 40,000 developed abortive polio (headache, stiff neck, fever and muscle weakness); 51 were permanently paralyzed and five died.[15] Cutter's vaccine also spurred a polio epidemic in the U.S. It was a disaster in U.S. pharmaceutical history.

Despite the tragedy associated with initial use of IPV, work continued on a live vaccine. Researchers believed that live vaccine would induce longer protection through induction of gastrointestinal immunity. Albert Sabin's oral, or live, vaccine (OPV) was licensed in the U.S. in 1960. This became the preferred vaccine in the U.S. and Europe through the late 1990s when the only remaining polio cases were vaccine-associated. With international focus on elimination of polio, IPV has returned as the recommended vaccination strategy to avoid spread of live vaccine strains.

The initial work on live virus vaccines in the World War II era led to creation of multiple modern-day vaccines. In the 1960s, vaccine research rapidly advanced with development of three live attenuated virus vaccines: measles, mumps, and rubella, all of which were constructed by passage through cell culture. The primary goal was maintenance of immunogenicity while reducing virulence.[10] Research on live, attenuated vaccine production has since continued with more recent production of varicella, influenza and rotavirus vaccines. Live attenuated vaccines remain among the most powerful for disease prevention. However, their use has been complicated by genetic instability and residual virulence. Given these issues, molecular techniques, including reassortment, recombination and deletion mutants have been implemented in viral vaccine research for creation of safer, more effective vaccines.[16]

Development of Other Vaccine Strategies

During the 1970s and 1980s, there was heightened focus on use of bacterial proteins and polysaccharides for induction of immunity. Previous attempts with use of a whole-cell pertussis vaccine failed due to a variety of adverse reactions, resulting in an increase in the worldwide incidence of pertussis. This in turn led Japanese researchers to develop an acellular pertussis vaccine based on two of the main protective antigens of *Bordetella pertussis*, toxin and filamentous hemagglutinin.[3] It was first licensed in Japan in 1981 and later in the U.S. in 1996.

Similarly, interest developed in use of bacterial capsular polysaccharides for induction of immunity. Oswald Avery and Walther Goebel devised the use of protein conjugation to enhance immunogenicity of polysaccharides as early as 1931. However, this knowledge was not applied until years later with development of polysaccharide vaccines including meningococcus, pneumococcus and *Haemophilus influenzae* type b.[11] From work associated with these vaccines, it was discovered that the polysaccharides induced poor B cell memory and failed to produce functional antibodies in young children. Thus, capsular polysaccharides were linked to carrier proteins, such as diphtheria or tetanus toxoids. This enhanced immunogenicity, yielding modern day vaccines and subsequent drastic reductions in incidence of meningococcal, pneumococcal and *Haemophilus influenzae* type b infections.

The early 1980s also saw the initial implementation of genetic engineering for vaccine creation, first with development of the hepatitis B vaccine by Maurice Hilleman and colleagues. It had been previously discovered that hepatitis B surface antigen (HBsAg) isolated from infected persons was non-infectious, but promoted protective immunity. The initial vaccine licensed in 1981 was derived from human plasma. However, new concerns about human immunodeficiency (HIV) virus arrived at the same time, prompting avoidance of products associated with human

blood. This obstacle stimulated creation of the first recombinant vaccine, which was licensed in 1986. The gene for HBsAg was cloned in yeast and mammalian cells. The antigen could then be adsorbed on an alum adjuvant, thus avoiding any potential contamination from human blood.[3] Recombinant protein technology was also used to develop vaccines for Lyme disease (now withdrawn due to lack of demand) and more recently human papillomavirus (HPV).

Vaccines of the Present and Future

Older methods of vaccine creation, including attenuation and use of whole viruses, continue to yield effective new vaccines. However, modern vaccine science is focused on technologies that afford greater safety with continued immunogenicity. These techniques include using vectored antigens, pathogen subunits (purified proteins or polysaccharides) or genetically engineered antigens. Vectors are nonpathogenic viruses and bacteria into which genes can be inserted and expressed. This strategy is currently used more than any strategy in vaccinology because of the potential for use in difficult-to-target pathogens, such as intracellular organisms.[16]

Vaccine technology is also growing in terms of developing additional adjuvants, combination vaccines and new routes of administration. Historically, alum salts were the only acceptable adjuvants for vaccines. However, the search continues for new adjuvants to induce immune responses to poorly immunogenic proteins. Work is ongoing with incorporation of antigens and adjuvants into nanoparticles and nanoemulsions to utilize antigen-presenting cells on mucosal surfaces.[16] With limitations on the number of traditional injection sites for vaccines, work is also underway to develop combination vaccine products and/or new routes of administration. The newest route is intradermal where antigen-presenting Langerhans cells traffic antigen to nearby lymph nodes, leading to development of systemic immunity. A prime example of this technique is the recently released intradermal influenza vaccine where a microneedle penetrates only the epidermis and produces equivalent immune response to the intramuscular injection.[16]

Looking forward, vaccine science continues to grow. Historically, vaccination has been focused on infants and children, but increasingly, need for adolescent and adult vaccination is being recognized. Future incorporations into vaccine schedules may include group B streptococcus, meningococcus, Herpes simplex and cytomegalovirus.[10] The threat of bioterrorism continues to spur research on anthrax, plague and smallpox. Lastly, there is increasing interest in use of active immunization to treat a variety of noninfectious diseases including cancer and autoimmune diseases such as multiple sclerosis and type I diabetes mellitus.[10]

Conclusion

For many modern global citizens, the history of plagues and epidemics is just that – history. However, the story of infection prevention through vaccination is an important one. In just over 200 years, vaccines have transformed global health like no other medical intervention. Life expectancies have greatly increased and societies have been shaped through vaccination in the prevention of infectious diseases. Knowing this background places continued emphasis on the importance of developing safe, protective and cost-effective vaccinations to extend control of infectious diseases in the 21st century.

"Those who cannot remember the past are doomed to repeat it."
– George Santayana, 1905

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CHAPTER 6

The Science of Vaccination: Establishing Safety and Efficacy

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Abstract:
Vaccination remains a critically important public health tool. It has been responsible for drastically reducing the occurrence of diseases that were once responsible for invoking extreme fear and anxiety. As a consequence, vaccines themselves, and not the diseases they help prevent, have now become the focus of fear and anxiety for many. This review describes the various activities and systems that are in place to ensure that modern vaccines continue to be safe and effective. A better understanding of existing safeguards may help bolster public confidence in immunization.

Background

Immunization has been called one of the 10 great public health achievements of the 20th century and is considered "one of the greatest tools in the public health arsenal."[1,2] These distinctions are understandable given the dramatic decreases in morbidity that have been observed following the introduction of several vaccines that have been universally recommended for children in the U.S. Using estimated pre-vaccine case counts as a baseline, reports of at least eight vaccine-preventable diseases have declined greater than 98 percent as of 2010 (Table).[3,4] Unfortunately, however, vaccines have become the victims of their own success.[5] Public health experts have commented, "In the absence of visible diseases, parents' recognition of the health threat posed by them will wane, and so will the public's appreciation of vaccines."[6] Indeed, worries about vaccine safety have supplanted worries about the illnesses that vaccines help prevent.[7] Health care professionals have grown accustomed to parents questioning the value of vaccines as a result of information from "alternate" sources such as alternative medicine practitioners, anti-vaccine organizations and the Internet, mistrust of the pharmaceutical industry, failure to understand the risk-benefit profile of vaccines and failure to appreciate the potential severity of vaccine-preventable diseases.[8]

Complicating the ability to placate concerns about vaccine safety are several blemishes to the otherwise exemplary track record of vaccines with respect to their safety and effectiveness. In 1901, diphtheria antitoxin, which was prepared from horse serum contaminated with tetanus bacilli, resulted in 20 children becoming ill and 14 deaths in St. Louis, Missouri.[9,10] In the same year, nine children died after receiving contaminated smallpox vaccine in Camden, New Jersey.[10] In 1955, enthusiasm around the declaration of the development of a safe and effective vaccine against polio was tempered months later by what would eventually be known as the Cutter Incident.[11] After five cases of polio following immunization with the new vaccine surfaced, investigators discovered that one of five manufacturers of the vaccine, Cutter Laboratories, inadvertently failed to adequately inactivate the poliovirus used to produce two lots of the vaccine. Among children receiving vaccine from these lots, 40,000 developed mild polio illness, 51 were permanently paralyzed and five died.[11] Also tragic is that the impact of the Cutter Incident was not confined to just vaccine recipients; over 100 people in the children's families or communities were paralyzed and five died.[11]

If there is any silver lining associated with the above events, it is the tighter controls that have been put into place to ensure that vaccines and other biologic products are safe and effective. In response to the use of tainted diphtheria antitoxin and contaminated smallpox vaccine in 1901, the Biologics Control Act was passed in 1902. The Biologics Control Act is considered to be the first modern law

Table. Annual Pre-vaccine Morbidity and 2010 Morbidity for 10 Vaccine-preventable Diseases – U.S.

Disease	Annual Pre-vaccine Cases, US[4,a]	2010 Reported Cases, US[3]	Percent Decline
Diphtheria	21,053	0	100
Polio (paralytic)	16,316	0	100
Smallpox	29,005	0	100
Hib[b] (less than 5 years of age)	20,000	23	>99
Measles	530,217	63	>99
Rubella	47,745	5	>99
Varicella	4,085,120	15,427	>99
Mumps	162,344	2612	>98
Tetanus	580	26	>95
Pertussis	200,752	27,550	>86

[a] Estimated annual average
[b] Invasive *Haemophilus influenzae* type b (Hib) disease

intended to ensure the quality of biologicals, including vaccines.[10,12,13] Four years later, the Food and Drug Act was passed, which ultimately led to the creation of the U.S. Food and Drug Administration (FDA).[10,13] In response to the Cutter Incident, the Division of Biologics Standards (DBS) was established to manage vaccine safety and regulation. DBS was later transferred to the FDA and renamed the Bureau of Biologics.

After the Bureau of Biologics became part of the agency, the FDA has continued to undergo multiple changes in its organizational structure and responsibilities.[9] These changes eventually culminated in the establishment of the FDA's Center for Biologics Evaluation and Research (CBER). CBER is the branch of the FDA charged with regulating biological products for human use. Specifically, CBER is responsible for ensuring that licensed vaccines are safe, pure and effective.[14] Its powers are derived from Section 351 of the Public Health Service Act and the Federal Food, Drug and Cosmetic Act (FDCA).[14]

Determining Safety

The Code of Federal Regulations Title 21, Section 600.3 defines safety as the "relative freedom from harmful effect to persons affected directly or indirectly by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time."[15] "Relative" is the operative term in this definition. Vaccines, which are often intended for use in young healthy populations to help prevent disease, are essentially held to a higher standard of safety compared to drugs, which are often used to treat conditions in persons who are already ill.[16] Even within the realm of vaccines, safety remains a relative concept and what might be considered an acceptable risk-benefit profile for a vaccine can be influenced by several factors:[17]

The risk of the disease that the vaccine is intended to prevent versus risk of adverse events associated with vaccine (such as the use of a smallpox vaccine when the disease has been eradicated);

Existing vaccine options and the risk of adverse events associated with each (for example, inactivated versus live, attenuated poliovirus vaccine); and

The population for which the vaccine is intended for use (for example, young, healthy adults versus older adults with comorbid conditions).

Determining Efficacy

Although safety is often a primary concern when vaccination is the topic of discussion, another important concern is whether vaccines are able to accomplish what they are intended to do – prevent disease. Before addressing this topic, it is helpful to make a distinction between efficacy and effectiveness. Effectiveness refers to the ability of a vaccine to prevent disease under "real world" conditions, whereas efficacy refers to the ability of a vaccine to prevent disease in a controlled setting (e.g., in the context of a clinical trial).[18] The gold standard for gaining insight into the effectiveness of a new vaccine remains the clinical efficacy study.[19] In such a study, the primary outcome of interest is prevention of the disease that is the target of the vaccine. Such trials are characteristically randomized controlled trials, a design that helps ensure that any differences in study groups are attributable primarily to the intervention(s).[18] Efficacy studies may be necessary when a vaccine is the first of its kind or when no acceptable immune correlate of protection exists.[20] Although considered ideal for establishing the ability of a vaccine to protect against disease, efficacy trials, which can be time-consuming and resource-intensive, may not be practical in certain situations, such as when the incidence of the targeted disease is low or there are limited options to address a current unmet medical need. In such instances, the FDA may approve a vaccine based on its impact on a surrogate endpoint, for example, certain levels of immune response that is predictive of protection against the targeted disease.[20]

Pre-licensure (Pre-approval) Vaccine Assessments

From a regulatory perspective, the timeline for development of a novel vaccine can be divided into two main stages: the period before the investigational new drug (IND) application is filed and the period after the IND is filed.[12,17] During the pre-IND period, exploratory research and preclinical trials are performed. In the exploratory stage, "bench" research may provide insight into which antigens make good vaccine candidates. These antigens are often derived from viruses or bacteria that cause the disease that the vaccine will be targeted to prevent.[12] Antigens (i.e., vaccine candidates) that show promise become the subject of preclinical trials, which may involve testing of the candidate in tissue culture, cell culture or animals to evaluate its safety and ability to induce an immune response.[12] If these trials are successful, the sponsor (for example, the manufacturer) can consider the next step in vaccine development – testing in human beings.[12,21]

The IND stage is when the FDA becomes involved in vaccine development. Before vaccine trials in human beings can begin, the sponsor must provide the FDA with information about the manufacturing and testing processes used during the vaccine's development. In addition, the manufacturer must provide the results of tests that were performed to determine the vaccine candidate's safety and immunogenicity. Proposed studies in human subjects need to be presented in sufficient detail in a clinical protocol. (Of note, the protocol must eventually be approved by an institutional review board which, in addition to the FDA, will help ensure that the welfare of human subjects is protected). Finally, information regarding the qualifications of clinical investigators must be provided to make certain that persons overseeing clinical trials have the skills to do so responsibly. All this information is packaged in the IND application, which must be submitted to the FDA before trials involving humans can begin. The FDA has 30 calendar days to review the application.[21]

As a general rule, clinical trials are conducted in three phases. Phase 1 trials tend to be small (less than 100 persons). Because children are subject to additional or unknown risks through participation in research, Phase 1 clinical trials are often conducted in adults, even when the vaccine is ultimately intended for use in children.[12,22] Phase 1 trials provide the first opportunity to describe the safety profile of the vaccine candidate in humans.[12,23] These trials can also help determine the type and magnitude of the immune response the vaccine candidate can generate.[12]

Phase 2 trials are larger than Phase 1 trials; these studies may involve up to several hundred participants who might have been selected because of their risk for the disease that has been targeted for prevention.[12,23] During Phase 2 trials, there is continued evaluation of the safety and immunogenicity of the vaccine candidate.[12] In addition, there are often attempts to determine the dose and vaccine delivery schedule that results in the optimal risk-benefit profile.[12,23] Phase 3 trials are even larger and can involve thousands of people.[12,23] Participants in these trials often represent the primary population in which the vaccine is intended for use.[12] The objectives of Phase 3 trials include the continued assessment of safety, including the identification of adverse events that occur too infrequently to be captured by earlier, smaller studies.[12,23] In addition, Phase 3 trials provide additional opportunities to evaluate the immunogenicity of the vaccine candidate. Phase 3 trials are also sometimes used to determine if the vaccine candidate actually helps protect against the disease that it is designed to prevent.[12]

During vaccine development, the FDA requires sponsors to submit a Development Safety Update Report (DSUR). This report serves to ensure the FDA that sponsors are exercising due diligence with respect to monitoring the evolving safety profile of the vaccine. To this end, the DSUR is a comprehensive summary of relevant safety data collected on the vaccine during each reporting period, which usually spans one year.[24] The reporting period defines the safety information that should be included in the DSUR. The DSUR is not intended to be used as a mechanism to first notify the FDA of significant new safety findings.[24] Rather, sponsors are obligated to expeditiously report any unexpected vaccine-related serious adverse event (SAE) that occurs during the course of the clinical trials. An adverse event is considered serious if it is life-threatening, results in death, hospitalization or prolongation of hospitalization, is a congenital anomaly, results in persistent or significant disability or incapacity, or requires intervention to prevent permanent impairment or damage. The FDA must be notified of an unexpected SAE "no later than 15 calendar days" of the sponsor being informed of the event. For an unexpected fatal or life-threatening experience, the FDA must be notified "no later than seven calendar days" of the sponsor being informed.[15]

Moving from Vaccine Development to Approval for Use

Once the clinical development program for a vaccine has been successfully completed, the sponsor can file a biologics license application (BLA). In the BLA, the sponsor must provide safety, immunogenicity, and, if applicable, efficacy data resulting from the studies that were conducted during

the clinical development program.[25] In addition, the facility that will be used to manufacture the vaccine is inspected as part of the application process; this "pre-approval inspection" is performed to ensure that the facility is in compliance with FDA rules and regulations and the vaccine was developed according to current good manufacturing practices (CGMPs).[14,26] The FDA has 10 months to review the BLA.[27] Upon licensure, the vaccine is approved for use in the persons for whom it is indicated.[28]

The Roles of the FDA and Manufacturers in Post-licensure (Post-approval) Vaccine Assessments

Monitoring vaccine safety and effectiveness does not end with licensure. After a vaccine is approved for use, it will be administered to increasing numbers of people, which serves as an additional opportunity to identify adverse events that were too rare to be captured during pre-licensure clinical trials.[28,29] As a result, the FDA sometimes calls for sponsors to conduct Phase 4 (post-approval) studies.[19,28,29] These studies are known as post-marketing requirements (PMRs) if the studies are required by statute or regulation, or post-marketing commitments (PMCs) if the studies are not required by statute or regulation but sponsors have agreed to conduct them.[30] PMRs or PMCs may be active, controlled studies (resembling the design of many Phase 2 or Phase 3 pre-licensure trials) or observational cohort studies.[19] Whatever the design, PMRs and PMCs are typically large-scale, involving thousands to tens of thousands of vaccine recipients.[19]

Though not all newly approved vaccines may be subject to PMRs or PMCs, the FDA requires all to be routinely evaluated through pharmacovigilance, which encompasses all "scientific and data gathering activities relating to the detection, assessment and understanding of adverse events."[29] Effective pharmacovigilance begins with trained health care professionals exercising due diligence with regard to obtaining complete information for reported adverse events, especially those that are deemed serious. After adverse event reports are received, efforts to detect and assess "safety signals" take place. Safety signals represent concerns that arise when the number of adverse event reports for a vaccine exceeds what would be expected for that vaccine or vaccines in that same class. These signals can be generated from post-marketing data, pre-clinical data and reports of adverse events following use of similar vaccines. Even an isolated report can represent a safety signal, particularly if the report describes either a medical condition that is rare in the first place or the recurrence of an adverse event following a repeat dose of vaccine.[29]

Safety signals indicate the need for further investigation to determine if a safety risk indeed exists and if specific action is warranted. Investigation activities often begin with a careful review of spontaneous reports previously captured by the sponsor's database of adverse events or other databases, such as the Vaccine Adverse Events Reporting System (VAERS) to search for more cases. If additional cases are found, the FDA recommends that sponsors perform a case series and summarize clinical findings associated with the events to help characterize the safety concern and identify risk factors associated with the adverse event. To better understand the safety risk associated with the vaccine, pharmacoepidemiologic studies (i.e., systematic studies of the effects of the vaccine in large numbers of people) may be performed.[29]

Findings resulting from pharmacovigilance activities conducted over the course of one year are presented to the FDA in what is known as the Periodic Safety Update Report (PSUR). The PSUR is a comprehensive summary of safety data associated with a marketed vaccine. Through preparation of this document, sponsors and the FDA can identify new safety signals associated with the marketed vaccine or changes in its risk-benefit profile. In addition, development of the PSUR can inform risk management activities and provide insight into the effectiveness of previously implemented risk mitigation measures.[31] Taken together, the DSUR described previously and the PSUR provide an opportunity to communicate safety information during the earliest stages of a vaccine's clinical development program and throughout its post-approval period.[32]

Other post-approval activities aimed at assessing vaccine safety rely on the use of pregnancy registries. When women of child-bearing age are part of the population for which a novel vaccine is recommended, enhanced safety surveillance may be performed through such registries.[19] Vaccine manufacturers maintain pregnancy registries for several vaccines (hepatitis B vaccine, human papillomavirus [HPV] vaccine, influenza vaccine, meningococcal conjugate vaccine, rubella vaccine, tetanus, diphtheria, and acellular pertussis [Tdap] vaccine and varicella vaccine).[19,33] Through these registries, pregnancy outcomes following exposure to certain vaccines can be captured.

Beyond the activities designed to continuously monitor the safety of vaccines after they are administered, there are manufacturing checks in place that help ensure the quality of vaccines prior to their use in humans. Because vaccine production depends on living organisms, it is more challenging to maintain sterility and potency compared to

drugs. To address these challenges, the FDA mandates that manufacturers perform lot-release testing. Lot-release testing is intended to detect the presence of microbial contaminants, assess toxicity, verify that the vaccine induces specific antibodies after vaccination (using small animal models), ensure the vaccine's potency and purity, detect the presence of fever-causing substances, and ensure adequate inactivation of potentially harmful agents.[14] To further ensure vaccine safety, manufacturing facilities undergo inspections at least every two years (or annually for facilities that produce influenza vaccine). These inspections assess whether vaccines are manufactured and tested according to accepted protocols and applicable regulations. Manufacturers that are found to be noncompliant with CGMPs can have their licenses suspended or revoked, depending on the violations discovered.[14]

The Role of the CDC in Post-licensure (Post-approval) Vaccine Assessments

In addition to the roles that the FDA and manufacturers play to maintain the public's confidence in the safety and effectiveness of vaccines, the Centers for Disease Control and Prevention (CDC) performs key functions when it comes to monitoring vaccines. Together with the FDA, the CDC co-manages VAERS. Created in 1990 following passage of the National Childhood Vaccine Injury Act, VAERS is the "nation's frontline vaccine safety surveillance program."[34] It collects information regarding adverse events following use of U.S.-licensed vaccines. Adverse events following vaccination can be submitted by anyone, including health care providers, patients, caregivers and manufacturers. VAERS casts a wide net; any adverse event following vaccination that is of concern to a health care provider, patient or family member can be reported to VAERS, even if the relationship between the event and vaccination is not clear. As such, VAERS has the potential to identify rare adverse events that cannot be detected during clinical trials.[34] To help ensure serious adverse events are captured by VAERS, legislation requires health care professionals to report specific events following use of certain vaccines (listed in a Vaccine Injury Table) and any event considered a contraindication to future doses of the vaccine.[7,35] Information collected by VAERS includes demographic information about the patient, details about the adverse event (such as symptoms, onset, duration, treatment and outcome), details about the vaccine(s) administered prior to the event (type, manufacturer, lot number and date administered), and whether the patient had any pre-existing conditions at the time of the event.[36] Any personal identifying information captured by VAERS is kept confidential. The preferred method of reporting events is through a secure website at https://vaers.hhs.gov/esub/step1. Completed paper forms can be faxed or mailed.[34]

Given the volume and type of information collected through VAERS, the system has the ability to identify safety signals associated with licensed vaccines. An example of one important safety signal that was detected by VAERS occurred in 1999. In this year, an unexpected number of intussusceptions were reported to VAERS following use of the earliest rotavirus vaccine. Further investigation into this safety signal ultimately led to the withdrawal of the vaccine.[37] More recent examples of safety signals detected by VAERS include increased reports of syncope following vaccination in adolescents, especially girls receiving HPV vaccine,[38] and increased reports of febrile seizure following use of influenza vaccine in children younger than age 5.[39] Further investigation into the former signal led to findings that underscored previous recommendations to implement an observation period following vaccination; investigation into the latter resulted in clarifying the risk of febrile seizures associated with separate and concomitant use of influenza and pneumococcal conjugate vaccines during the 2010-2011 influenza season.[38,39] Of note, estimates of febrile seizure risk did not alter the risk-benefit profiles associated with these vaccines; accordingly, there were no changes in recommendations regarding their use.[38-40]

VAERS also plays a role beyond detecting safety signals; it affords an opportunity to provide reassuring information about vaccine safety. During the 2009 H1N1 pandemic, health officials were able to monitor and affirm the safety of the vaccines that were developed in response, especially with respect to Guillain-Barré syndrome (GBS).[41] This was critical to securing public confidence in the 2009 vaccination campaign given the GBS risk associated with the vaccine developed in response to the 1976 swine flu epidemic.[42] In addition, analysis of VAERS data made it possible to document the reduction in episodes of fever and seizures following use of acellular pertussis-containing vaccines compared to whole-cell formulations.[43]

Despite the ability of VAERS to capture a large number of adverse event reports following vaccination, the system has several limitations. As a passive reporting system, it is subject to under-reporting. It is also subject to stimulated, or "over-reporting," as might occur when the media brings attention to a particular safety concern reported to be associated with a vaccine. Because reports may be submitted with incomplete or missing information (such as contact information), follow-up may be impossible, leading to the

inability to verify data. In addition, VAERS does not allow the opportunity to calculate adverse event rates since it does not collect information on the number of vaccine doses administered. Of note, VAERS was not designed to assess whether a causal relationship exists between an adverse event and a vaccine. In fact, adverse events reported to VAERS may have some cause other than vaccination.[7,34,43]

Though VAERS cannot assess causal relationships between vaccines and adverse events, the Vaccine Safety Datalink (VSD) project allows investigators to assess the strength of association between an adverse event and a vaccine. Like VAERS, the VSD project has been in existence since 1990. It is a collaboration between the CDC and 10 managed care organizations (MCOs). The VSD project draws on information collected through a large database that contains administrative data captured by each MCO site. Examples of data gathered by each MCO site include type of vaccine administered, vaccination date, concurrent vaccinations, medical outcomes (e.g., outpatient, inpatient and urgent care visits), birth data and census data. Through the VSD project, investigators can conduct robust planned or ad hoc studies of vaccine safety. Planned studies often seek to address questions or concerns that arise from a review of medical literature, changes in the immunization schedule or the introduction of new vaccines. Ad hoc studies are often spurred by the need to investigate safety signals detected by VAERS.[7,44]

Rapid Cycle Analysis (RCA) is one aspect of the VSD project that bears particular mention. Launched in 2005, RCA is a means to conduct, in near real-time, active surveillance for adverse events that occur after vaccination. RCA covers approximately 9 million MCO members annually (3 percent of the U.S. population). Through the use of data updated weekly (and contain no personal identifiers), investigators can determine the rates of adverse events that occur in vaccinated MCO members compared to the rates that occur in unvaccinated members. If RCA suggests that there is relationship between an adverse event and vaccination, investigators will perform additional investigation, such as formal epidemiologic studies to confirm or refute findings. Vaccines that are the focus of RCA include newly licensed vaccines, meningococcal conjugate vaccine, rotavirus vaccine, measles, mumps, rubella (MMR) vaccine, varicella vaccine, Tdap vaccine, HPV vaccine and seasonal influenza vaccines.[45]

The Clinical Immunization Safety Assessment (CISA) Network is yet another CDC-sponsored collaborative project that helps promote vaccine safety. CISA was established in 2001 and is comprised of the CDC's Immunization Safety Office and six medical research centers (Boston University Medical Center, Columbia University Medical Center, Johns Hopkins University, Northern California Kaiser Permanente, Stanford University and Vanderbilt University) that have staff who possess expertise in a variety of medical specialties and subspecialties, epidemiology, biostatistics, health economics and genetics.[7,46] In addition, America's Health Insurance Plans are members of CISA.[46]

The mission of CISA is to enhance understanding of which factors, especially genetic factors, might predispose vaccine recipients to adverse events, to develop evidence-based recommendations to help mitigate the occurrence of vaccine-related adverse events, and to help improve public confidence in vaccines.[46] Through CISA, health care providers can refer patients with a history of rare and serious adverse events following immunization for consultation.[7,46] Such cases are discussed during monthly conference calls in which experts from the six medical centers listed above participate. Using expert opinion, information from the medical literature and VAERS data, call participants make an assessment and develop a plan which is provided to the referring health care provider as appropriate.[46] In addition, select referral patients may be asked to submit clinical samples for inclusion in the CISA Vaccine Safety BioRepository. These clinical samples may be used to support future genetic or immunologic studies of vaccine safety.[7]

The 2011 Institute of Medicine Report

Following passage of the National Childhood Vaccine Injury Prevention Act in 1986, the Institute of Medicine (IOM) has been charged on multiple occasions with assessing adverse events following the use of vaccines covered by the Vaccine Injury Compensation Program (VICP), a program that compensates people for injuries believed to be caused by particular vaccines. In 2009, the IOM convened a committee to review the literature to determine the causal relationship between certain adverse events (including ones for which people sought claims from VICP – successfully or not) and eight vaccines covered by VICP (varicella zoster vaccine, influenza vaccines, hepatitis B vaccine, HPV vaccine, MMR vaccine, hepatitis A vaccine, meningococcal vaccine and tetanus-containing vaccines that do not carry the whole-cell pertussis component).[2,5] Members of the IOM committee were experts from a variety of fields, including medicine, immunology, immunotoxicology, epidemiology, biostatistics and law.[7] The IOM committee reviewed thousands of research articles in consideration of

158 vaccine-adverse event pairs before concluding that few adverse events are caused by the vaccines that were studied.[2,5]

When making its causality assessments, the IOM committee based its decisions on the weight of epidemiologic evidence and mechanistic evidence derived from biological and clinical studies. Weights were based on the strengths and weaknesses of the research articles that were reviewed. What follows is a summary of the IOM's conclusions for four causality categories:[2]

1. Evidence Convincingly Supports a Causal Relationship
   - Varicella vaccine and disseminated varicella infection, vaccine strain viral reactivation;
   - MMR vaccine and measles inclusion body encephalitis (in persons who are immunocompromised), febrile seizures;
   - MMR, varicella zoster, influenza, hepatitis B, meningococcal, tetanus-containing vaccines and anaphylaxis; and
   - Injection of vaccine (regardless of antigen) and syncope, deltoid bursitis.
2. Evidence Favors Acceptance of a Causal Relationship
   - HPV vaccine and anaphylaxis;
   - MMR vaccine and transient arthralgia (female adults and children); and
   - Trivalent inactivated influenza vaccine (TIV) and oculorespiratory syndrome.
3. Evidence Favors Rejection of a Causal Relationship
   - MMR vaccine and autism or type I diabetes;
   - Diphtheria, tetanus and acellular pertussis vaccine and type I diabetes; and
   - TIV and exacerbation of asthma or reactive airway disease episodes in children and adults.
4. Evidence Inadequate to Accept or Reject a Causal Relationship
   - For the majority (135 of 158) of vaccine-adverse event pairs, the evidence is inadequate to accept or reject a causal relationship.

Conclusions

Per the CDC, the U.S. currently has the safest, most effective vaccine supply in history.[47] The ability to confidently make this claim is the result of the many systems that are in place to ensure that vaccines are developed with a high regard for safety, and, once approved for use, are closely and continuously monitored to make certain they perform as desired. The successful execution of these activities requires participation by many parties that must work collaboratively – the public at large, health care professionals, regulators, policy makers, legislators and vaccine manufacturers. With everyone's continued commitment to establishing the safety and effectiveness of vaccines, this important public health tool can continue to live up to the medical dictum of *primum non nocere* ("First, do no harm").

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CHAPTER 7

Current Controversies in Childhood Vaccination

By Maria Carrillo-Marquez, MD and Lisa White, MD

Abstract:

As pediatric practitioners, one of the contemporary challenges in providing medical care for children is the increasing proportion of vaccination refusal. This occurs in spite of the demonstrated individual and collective benefit and cost effectiveness of vaccination. Controversies regarding vaccine components and side effects have misled parents to believe that vaccines might be harmful based on inaccurate data from the Internet, celebrities, as well as misinterpreted and frankly bad science. This belief of vaccines being harmful has led to fear and decreased immunization rates in spite of sound scientific evidence supporting the safety of vaccines and their lack of association with autism, developmental disabilities or other medical disorders. Some parents also believe in alternative ways to avoid disease, often adhering to practices that have little foundation in the best of empiric science.

It is not a coincidence that recent outbreaks of vaccine-preventable diseases, including measles and pertussis (whooping cough), have occurred in areas where vaccination has declined largely due to exemptors. This article intends to review some of the common vaccine myths and controversies and to serve as a resource to provide accurate information and references for busy practitioners and the families that we serve.

Introduction

Immunizations are one of the most important and successful public health interventions in history.[1] Along with clean water and safe food, eradication of epidemic infectious diseases through vaccination is one of the major contributing factors to improved life expectancy in the U.S. over the 20th century.

In the U.S., thanks to a progressive, national universal immunization program, four diseases that once killed thousands of children have been eliminated: (i.e., endemic disease no longer occurs) smallpox (1949), polio (1979), measles (2000) and rubella (2004). Other infectious diseases and their impact have been dramatically reduced through vaccination; among these are diphtheria, tetanus, mumps, pertussis (whooping cough), hepatitis A, hepatitis B, varicella (chickenpox) and invasive *Haemophilus influenzae* type b and *Streptococcus pneumoniae*.[2]

According to researchers at the Pediatric Academic Society (PAS), childhood vaccinations in the U.S. prevent about 10.5 million cases of infectious illness and 33,000 deaths per year.[3] Childhood immunizations are one of the most cost-effective components of our public health system.[4,5] Routine immunization has prevented hundreds of thousands of deaths and has saved tens of billions of dollars. According to the Centers for Disease Control and Prevention (CDC), every $1 spent on vaccination saves the public $6.30 in medical costs from having to treat unvaccinated diseased individuals.

Despite these compelling statistics, people wonder about how well vaccines work. Vaccines are highly effective in preventing disease ranging from 90 to 100 percent efficacy. Furthermore, when children who have been vaccinated contract a disease, despite being vaccinated against it, they usually have milder symptoms with less serious complications than an unvaccinated child who gets the same disease.[6] But no matter how good vaccines are at preventing disease, no matter how much they have reduced disease over the years, and no matter how many lives they have saved, if we are unable to answer parental concerns regarding vaccine safety, vaccination rates will continue to decline

and we will continue to see increased rates of vaccine-preventable diseases. We review nine broad categories of controversy in this paper, covering individual immunity, immunization schedule, herd immunity, adverse effects, vaccine ingredients, allergies, direct causation of infection, long term adverse effects and immune system overload.

Individual Immunity

It is important to understand how vaccines work. The message to parents on the immunity question is simply that vaccines contain the same "germs" that cause disease that have been either killed or weakened to the point that they can't cause disease. When a child is vaccinated, the vaccine stimulates his or her immune system to produce antibodies that confer protection against the disease. Another common immunity question in this area is whether natural immunity is superior to immunity from vaccination. Although in some cases immunity from natural infection could be longer lasting, this means that the child has to get sick before becoming immune.[7] It is important to realize that vaccine preventable diseases and their complications are not benign conditions, and some can actually be fatal and can occur even to healthy children.

Immunization Schedule

Some parents frequently express concern about the number of shots that children receive. The reason why most vaccines require multiple doses is that inactivated vaccines contain a fixed amount of disease antigen (virus or bacteria) that builds immunity in phases by boosting with each dose to a protective level whereas in the case of live vaccines, the antigen in the vaccine reproduces itself and spreads throughout the body. A single dose, therefore, produces satisfactory immunity in most children. However, because not all children respond to the first dose, a second is given to assure immunity.

The science behind the number of vaccines necessary for immune protection in children is reflected in the current immunization schedule established by the Advisory Committee on Immunization Practices (ACIP) whose members have expertise in vaccinology, immunology, pediatrics, internal medicine, nursing, family medicine, virology, public health, infectious diseases, and/or preventive medicine, as well as consumer representation who provide perspectives on the social and community aspects of vaccination. Other federal agencies with responsibility for immunization programs in the U.S. and representatives of liaison organizations that bring related immunization expertise are included.

To this extent, ACIP determines the timing and combination of various vaccines used at each age through rigorous review of data on large groups of children, to ensure that there are no interactions between vaccines and that the combinations result in adequate protective immunity. While in the recent past there have been some advocates for flexible or alternative immunization schedules, they have not been studied and thus there is no data to support their safety and effectiveness. Potential harms from "spacing out" vaccines include an increased duration of susceptibility to disease, assuming equivalent efficacy despite the lack of data and the discomfort of more shots over time.

Herd Immunity

There is another common misconception that vaccines can be avoided by having a healthy life style. Although a healthy diet and exercise are good habits for your health, they cannot substitute for vaccines, and even healthy children can get infections and severe complications from vaccine-preventable illnesses. Also, there is the benefit conferred by the healthy vaccinated child to the vaccinated but still at risk child. This is because vaccines protect people from disease in two ways. First, vaccine administration results in immunity to the recipient. However, this is not a perfect system because not all healthy individuals respond optimally to all vaccines, leaving some susceptible to disease despite immunization. Another caveat is that due to age or medical reasons, not all individuals can be immunized. Examples include infants who will not be fully protected until they have completed a series of immunizations and children with cancer who are undergoing chemotherapy who cannot be vaccinated or, if vaccinated, will not respond well. These special groups must therefore rely on a second, indirect form of protection termed community immunity (or herd immunity).[7] Herd immunity refers to the phenomenon whereby if enough individuals in a community are immunized, diseases cannot spread.

The implications of herd immunity cannot be overstated because it only takes a small number of unimmunized individuals in a community to facilitate the spread of disease and to decrease the effects of herd immunity. Consider that in the late 1980s, pockets of unimmunized children in the U.S. led to a resurgence of measles that caused 11,000 hospitalizations and 123 deaths.[8] More recently in 2008, the largest outbreak of measles in over a decade in the U.S. occurred. The difference in 2008 is that the outbreak was a direct consequence of purposeful refusal to vaccinate, in contrast to prior outbreaks where issues like programmatic deficiencies or increased disease importation

from other countries played a major role.[9, 10] In other words, recent outbreaks have occurred because individuals who should have been immunized were intentionally not immunized. These outbreaks, therefore, represent a threat to return to a situation where measles and other vaccine-preventable diseases are again endemic in the U.S. In situations like this, transmission has affected not only the index patient's siblings, but also schoolmates and children who had also been in the doctors' office at the same time. Quarantine has been needed for unimmunized children whose parents refused immunization or were too young to be vaccinated. These recent outbreaks illustrate how diseases can spread when children are unimmunized and how others will be affected by the individual decision of refusing immunization. If we become lax about vaccinations, we will unfortunately see these now uncommon or eliminated vaccine-preventable diseases again.

Adverse Reactions

While vaccines are safe, and although some children can experience adverse reactions, they are mostly local and self-limited. Minor reactions include redness, pain at site of injection, which occurs, depending on the study, in 5 to 25 percent; fever in 10 to 25 percent; prolonged crying in 0.001 percent (diphtheria, tetanus and acellular pertussis vaccine) to 2 percent (*Haemophilus influenza* type b); vomiting in 2 to 5 percent and headache in 5 to 50 percent. Moderate reactions like febrile seizures have been estimated to occur in one in 1,000 to one in 14,000 children. Severe adverse effects including anaphylactic reactions (life threatening allergic reactions) are rare (less than one in 1 million). The risk of encephalitis/encephalopathy with measles vaccine is one in 3 million; however, the risk of encephalitis from measles infection is one in 1,000.

Vaccine Ingredients

Arguably the most important of the controversies covered herein and which fills the most pages of debate regarding both the fears of direct adverse effect and allergic response to immunization surrounds the question, "So, what is in vaccines?" All vaccines contain the disease antigen as mentioned above. Some vaccines also contain adjuvants, which are substances that help vaccines produce a stronger immune response. In addition, some vaccines come in multiple dose vials which often contain a preservative to prevent contamination – thimerosol is an example. Also, since vaccine antigens are grown on growth media, substances such as yeast may be present in small quantities. Chemicals such as formaldehyde can be used during the production of vaccines which are removed from the final product during purification. Tiny traces of them, however, too small to have a clinical effect, can remain. In the same category, stabilizers help to maintain antigenic reaction following production of the vaccines. Lastly, diluents are liquids – usually saline or sterile water – used to reconstitute a powdered vaccine given as a single dose.[11]

In many of these examples, vaccine ingredients could be toxic . . . *at much higher doses*. But at a very low dose, even a highly toxic substance can be safe. We might not be aware of it, but we are exposed to small amounts of these same "toxic" substances every day. A more detailed account of the more controversial constituents is enumerated below.

Mercury, which is a component of thimerosol, was previously used to prevent viral contamination in multi-dose vials beginning in the 1940s. Mercury occurs in a number of forms in the environment and the most hazardous for children is methyl mercury, although inorganic mercury is also a potential concern. Methyl mercury is toxic to the developing brain, and therefore considered a neurotoxin at designated concentrations.[12] Most people are exposed to methyl mercury from fish, such as tuna, swordfish and shark. Freshwater fish from contaminated lakes, rivers and estuaries can also bioaccumulate very high levels of methyl mercury, which are passed on to humans who eat the fish. Other sources of mercury include coal burning, incineration, chlorine manufacturing and mining, as well as some natural sources. Inorganic mercury exposure primarily comes from dental amalgam fillings. Infants can be exposed via breast milk, although in general, the metals found in breast milk are usually at lower levels than are found in maternal blood making prenatal trans-placental exposure a much greater concern.[13]

Mercury in vaccines is metabolized or degraded to ethylmercury and thiosalicylate. Much of the initial study of mercury toxicity involved methylmercury, and various agencies developed guidelines for safe exposure to methylmercury, including the U.S. Environmental Protection Agency (EPA),[14] U.S. Agency for Toxic Substances and Disease Registry[15] and the Food and Drug Administration (FDA).[16] These agencies found that mercury exposure from vaccines was less than the recommended level of exposure. However, there was discussion about the metabolism to ethylmercury as compared to known data regarding methylmercury, so many government agencies agreed that elimination of all mercury-containing products from vaccines was most prudent until additional studies could definitely support or refute any relationship of ethylmercury to neurotoxicity.[17] Elimination of thimerosol from

vaccines became standard in 2000.[18] The exception to date is multi-dose influenza vaccine. Most recently, data became available through CDC-sponsored case-controlled studies analyzing the effects of ethylmercury on neurodevelopmental outcomes, and a causal relationship was not found. [19]

Aluminum is present in certain vaccines as an adjuvant, which often allow for lesser quantities of vaccine antigen and fewer needed doses. Aluminum is formulated as a salt to achieve this response. Aluminum hydroxide, aluminum phosphate and aluminum potassium sulfate have been used to improve the immune system's response to vaccines for decades.[20] It is also present in the water, air and the food (pancake mixes, baking powder, processed cheeses, corn bread) which we are exposed to daily. Aluminum is also present in vaccines that prevent hepatitis A, hepatitis B, diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, human papillomavirus and pneumococcus.

During the first six months of life, infants could receive about 4 milligrams total of aluminum from vaccines. During the same period, babies will also receive about 10 milligrams of aluminum in breast milk, about 40 milligrams in milk-based infant formula and three times that, or 120 milligrams, in soy-based formula.[21] Aluminum that enters the body is very quickly eliminated. Although all of the aluminum present in vaccines enters the bloodstream, less than 1 percent of aluminum present in food is absorbed through the intestines into the blood.[22] Either way, most of the aluminum in the bloodstream is immediately bound by a protein called transferrin, which carries aluminum to the kidneys where it is eliminated from the body. Half of the aluminum in vaccines or in food is eliminated in less than 24 hours.[23] The total body burden of aluminum in food and vaccines combined has been studied and found to be below risk, except for a transient period following immunization, when the flux of aluminum into the bloodstream is briefly elevated. Since half of the aluminum in vaccines or in food is eliminated in less than 24 hours, the relative risk of toxicity from vaccines is felt to be negligible.[24]

Formaldehyde has been safely used in the manufacturing of some vaccines. It inactivates viruses so that they don't cause direct infection (attenuation of influenza virus to make influenza vaccine) and detoxifies bacterial toxins, such as the toxin used to make diphtheria vaccine. Formaldehyde is diluted to negligible levels during the manufacturing process. The average amount of formaldehyde to which a young infant could be exposed to at one time through vaccines is considered to be safe. Formaldehyde is also produced naturally in the body during amino acid metabolism. It is also found in the environment, such as a preservative in labs and in many household products and furnishings such as carpets, upholstery, cosmetics, paint, and felt-tip markers. Even some over-the-counter health products such as antihistamines, cough drops and mouthwash contain formaldehyde.[25] The body metabolizes formaldehyde regardless of its source.[26] In comparison, the amount of formaldehyde produced by the body is at least 10 to 50 times higher than that given in vaccines.[27] For instance, a 2-month-old, 11-pound baby has 1 mg of formaldehyde in his or her blood (10 times more than contained in vaccines). People most at risk for toxic exposure to formaldehyde are those in industries whereby formaldehyde is used in significant quantity, especially when fumes are inhaled. There is no evidence linking cancer to infrequent exposure to tiny amounts of formaldehyde via injection as occurs with vaccines.

Finally, antifreeze is a popular myth that needs to be debunked, for no vaccine contains, or has ever contained, even a molecule of antifreeze. If you search the web, however, you can easily find a dozen websites that persist in claiming that vaccines contain antifreeze. The manufacturer product information details confirm the lack of antifreeze in vaccines.

Allergies

Are there substances in vaccines to which my child can be allergic? Some antibiotics are used during the manufacturing process to prevent bacterial contamination within the medium that vaccines are grown. The amount of antibiotic used is undetectable and thought to be non-immunogenic. Examples of antibiotics used during vaccine manufacture include neomycin, polymyxin B, streptomycin and gentamicin. No severe allergies to neomycin have been found.

Antibiotics known to have the most allergenic potential, such as penicillin, cephalosporins and sulfa-containing drugs are not used in the processing of vaccines. The preparation of recombinant hepatitis B vaccines and HPV vaccines involves using cellular cultures of *Saccharomyces cerevisiae*, otherwise known as baker's yeast. People allergic to bread are allergic to the wheat, not to the yeast. Those with sensitivities to yeast proteins were studied, and, despite some descriptions of possible or probable anaphylaxis, there were no reported cases of death in these patients, according to the Vaccine Adverse Event Reporting System (VAERS).[28] Egg proteins are used in the manufacturing of influenza and yellow fever vaccines, but awareness for patients with egg allergy continues to be well-described and therefore a preventable issue for adverse reactions to

vaccines. Influenza virus has to grow on cells, in this case in eggs, which are present in the vaccine only in trace amounts. It is estimated that one in 200 people suffer from egg protein allergy. Within the past year, the ACIP has significantly relaxed the precautions related to egg allergy as an exclusion for vaccination.

Stabilizers added to vaccines include sugars such as sucrose and lactose, amino acids such as glycine or the monosodium salt of glutamic acid, and proteins such as human serum albumin or gelatin. Collagen from pigs' skin is used as a stabilizing agent, which allows small amounts of live vaccines to distribute evenly through the vial. These stabilizers help to protect the vaccine from adverse conditions during manufacturing, which helps to maintain the immunogenicity of the vaccine. The allergic potential of these stabilizers is reported, but rare. The incidence of severe allergic reactions to the gelatin used in influenza and rabies vaccines has been reported as one case per 2 million doses.[29]

Direct Causation of Infection

As vaccines contain antigens, parents question if a child can actually get the disease from a vaccine. The answer is almost never. With inactivated (killed) vaccines, it isn't possible. A dead virus or bacteria, or part of a virus or bacteria, can't cause disease. With live vaccines, some children get what appears to be a mild case of the disease (for example what looks like a measles or chickenpox rash, but with only a few spots). A vaccine causing full-blown disease would be extremely unlikely. One exception historically was the live oral polio vaccine, which could very rarely mutate and actually cause a case of polio. This was a rare but tragic side effect of this otherwise effective vaccine. Oral polio vaccine is no longer used in the U.S., and the preferred polio vaccine is an inactivated polio vaccine.

Long Term Adverse Effects

In 50 years of experience in vaccine administration, there is no evidence that vaccines cause any long term problems. Every vaccine is continually monitored for safety, and the VAERS was established for ongoing post licensure reporting of adverse events and is accessible to anybody (parents, patients, physicians, nurses). The system has helped in identifying adverse events that were too rare to be detected during the licensure process and due to public health concerns resulted in discontinuation of the vaccine. An example is the first rotavirus vaccine, which was licensed in 1998. Within a year, monitoring systems revealed intussusceptions were occurring in children who got the vaccine, slightly more often than it would have been expected to occur by chance. This was too uncommon to have been detected during clinical trials, and was only apparent after millions of children had been vaccinated. Once the problem was detected, the vaccine was immediately taken off the market.

Immune System Overload

With now more vaccines available than in the past, parents worry about "overwhelming" their child's immune system. Although there may not be consensus over exactly how many germs a baby's immune system can handle at a time, it is considerably more than they will ever get from the recommended vaccine schedules. From the day a baby is born, his or her immune system is busy dealing with the thousands of germs they are exposed to as part of daily life, which is the immune system's function.

In Summary

In a sense, immunizations have become victims of their own success. Because some vaccine-preventable diseases have been eliminated or have become very rare due to our national large scale immunization program, parents have the erroneous perception that these diseases are not a threat anymore. In spite of the parents' intention to do the best for their children, they have been victims too, led to believe that vaccines might be harmful based on misinformation.[30-34] This belief has led to fear and decreased immunization rates in spite of sound scientific evidence supporting the safety of vaccines and their lack of association with autism, developmental disabilities or other medical disorders. Some parents also believe in alternative ways to avoid disease, often adhering to practices that have little foundation in empiric science. The ultimate victims are the children, who in some cases have suffered disabilities or lost their lives to diseases that could have been easily prevented.[35] Ironically, their voices seem to be part of a forgotten story and they do not receive a fraction of media attention that anti-vaccine movements receive. Failure to vaccinate has severe consequences on affected individuals, public health and generates significant additional cost. Continuing to educate ourselves and the public on the safety and efficacy of vaccines would be a decisive factor in improving vaccination rates to continue to protect all the individuals in our community from vaccine-preventable diseases.

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CHAPTER 8

Roots of Vaccine Hesitancy

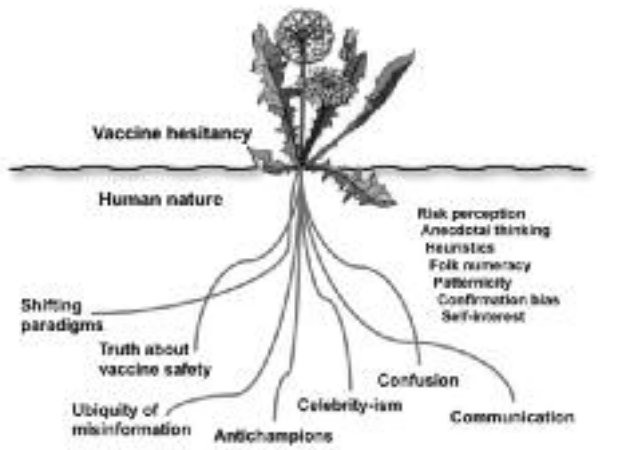
By Gary S. Marshall, MD

Introduction

It's paradoxical. Vaccines are among the safest products on the market, yet some parents refuse to have their children immunized for fear of serious adverse events. The routine childhood immunization schedule has delivered many dreaded diseases to the pages of history books, yet many people believe that vaccines are ineffective or unnecessary. Parents want to do what's best for their children, but they put them in harm's way by intentionally leaving them vulnerable to diseases that can be prevented. What is going on here?

The roots of vaccine hesitancy run deep and are grounded in human nature (Figure). Before exploring this, let's set the record straight. First, immunization is one of the most effective public health interventions ever devised – ever.[1,2] Through immunization programs, three diseases (polio, rubella, and measles) have been eliminated from the U.S. and one (smallpox) has been eradicated from the face of the earth (a second disease, rinderpest, also has been eradicated with the help of vaccines, but this is a disease of cattle, not humans[3]). Polio is on its way out.[4] Diphtheria, tetanus, pertussis, mumps, hepatitis A, varicella – you name it – all dramatically impacted by immunization programs.[5] Most of today's medical students and residents have never seen a case of *Haemophilus influenzae* type b meningitis. All of this has happened with unprecedented cost-effectiveness.[6] In fact, childhood immunizations return a huge bang for the buck. According to a 2001 analysis, which looked at the effect of diphtheria, tetanus and acellular pertussis vaccine (DTaP), *Haemophilus influenzae* type b vaccine (Hib), inactivated polio vaccine (IPV), measles, mumps and rubella vaccine (MMR), hepatitis B vaccine (HepB) and varicella vaccine (VAR), every $1 spent on childhood immunization returns $5 in direct medical costs and an additional $11 in societal costs.[7]

Figure. Roots of Vaccine Hesitancy



Second, various concerns (even outlandish ones) about vaccines have been raised, systematically addressed and dismissed by evidence.[8] To the extent that it is scientifically possible to certify, vaccines do not cause autism, overload the immune system, bring about sudden infant death syndrome (SIDS), transmit dangerous adventitious agents, exacerbate multiple sclerosis, predispose to allergies, trigger autoimmune diseases or lead to brain damage.

Given that vaccines are safe, effective, and important, why are people hesitant to use them?

Shifting Paradigms: From Fear of Disease to Fear of Vaccination

One reason is that people only take on risk, however small, if the perceived risk is outweighed by the perceived benefit. It is difficult to perceive benefit when the diseases themselves are no longer prevalent. Our parents viscerally understood that these diseases were dangerous, because they saw children hospitalized, paralyzed or killed, and they embraced the vaccines for this reason. Today, embracing vaccines takes a small leap of faith – understanding that, while the diseases are no longer as common in the U.S., they are lurking just a plane flight away.

In 1952, over 20,000 cases of polio occurred in the U.S.[9] There was a dramatic decline in cases after 1954, the year the (inactivated) Salk vaccine was licensed, which

continued through the 1960s when the (live, attenuated oral) Sabin vaccine replaced the Salk vaccine (the Sabin vaccine offered the ease of oral administration and the possibility that horizontal spread of vaccine virus would protect unimmunized people). By 1973, there were fewer than 20 cases of polio in the U.S., but the number of cases did not fall to zero. In fact, between 1980 and 1998, 152 cases of polio were reported – 144 of them associated with the vaccine itself (the other cases were either imported or of indeterminate origin).[10] Whereas natural poliovirus was no longer circulating, the Sabin vaccine was still being given to children, spreading to others, and, on rare occasion, causing polio. The risk of vaccine-associated polio was very small – one case for every 750,000 first doses distributed. Nevertheless, that risk was not justifiable in a country that had no natural disease. That is why, in the year 2000, the enhanced-potency inactivated vaccine replaced the live vaccine in the routine childhood schedule.

Here's the point: in a few very short decades, the polio paradigm had shifted from fear of the disease to fear (or, rather, cautious re-evaluation) of the vaccine that was being used to prevent the disease. The echoes of this paradigm shift can be heard today, as parents wonder why they should take on any risk at all given that the diseases are, seemingly, nowhere to be found.

What Does "Safe" Mean?

Are vaccines safe? If "safe" meant "harmless," the answer would be "no." Minor side effects like sore arms and low-grade fevers are common. Yet when compared to the seriousness of disease, such minor reactions are clearly tolerable. In this context, "safe" might more appropriately be taken to mean "being preserved from danger." The stakes are high when considering what about vaccines is safe and what is unsafe, because vaccines, unlike medicines, are given to individuals who are perfectly healthy.

While it is true that serious adverse events do occur, they are very rare. Table 1 lists selected serious adverse events linked to particular routinely used vaccines. The question is, once we establish a link between a vaccine and a serious adverse event, what do we do with the information? Do we stop using the vaccine? Do we modify the recommendations in some way? The answer lies in a unique combination of the seriousness of the adverse event, whether it is reversible, how often it occurs, whether or not alternatives are available and how high the imperative is to prevent the disease. In the case of rhesus rotavirus vaccine, tetravalent (RRV-TV), the first rotavirus vaccine (used from 1998 to 1999), intussusception was believed to be serious enough and occurred often enough after vaccination (one in 10,000 vaccinees) to prompt withdrawal of the vaccine from the market – despite the public health benefit of preventing rotavirus diarrhea. On the other hand, in the case of measles, mumps, rubella and varicella vaccine (MMRV), febrile seizures are benign enough (at least in the eyes of doctors) to have prompted only a minor change in the recommendations (no preference for MMRV over MMR plus VAR for the first dose) despite the frequency of this adverse event (one in 2,300 vaccinees). This illustrates how complex the decision-making can be around vaccine recommendations and adverse events.

To illustrate the point further, it is now known that the newer rotavirus vaccines, rotavirus vaccine, monovalent (RV1) and rotavirus vaccine, pentavalent (RV5), also may cause intussusception. In a study from Mexico and Brazil, the risk of intussusception attributable to RV1 was one in 51,000 to one in 68,000 vaccinated infants.[11] Data from Australia[12] suggest an increased

Table 1. Serious Adverse Events Associated with Vaccination

Vaccine	Adverse Event	Approximate Risk	Affect on Recommendations
Any vaccine	Anaphylaxis	1 in 1,000,000[a]	Severe allergy to vaccine or vaccine component contraindicates subsequent doses[b]
MMR	Immune thrombocytopenic purpura (ITP)	1 in 40,000[c]	Weigh risks and benefits in children with a history of ITP[d]
RRV-TV	Intussusception	1 in 10,000[e]	Stop using vaccine[f]
MMRV	Febrile seizures	1 in 2300[g]	MMRV no longer preferred over MMR plus VAR for first dose[h]

[a] Bohlke, K, Davis, R., Marcy, S., et al. (2003). Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics*, 112(4), 815-820.
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risk of intussusception after the first dose of both RV1 and RV5 (there is no evidence of increased risk from RV5 in the U.S.,[13,14] and the risk from RV1 has not be studied post-marketing because it is not widely used). Is this risk enough to stop the use of RV1 in Latin America? The answer is "no" when you consider the risks of vaccination in light of the benefits in disease prevention. The risk of hospitalization from rotavirus disease is 841 times higher than the risk of hospitalization from vaccine-associated intussusception, and the risk of death from rotavirus disease is 395 times higher.[15]

Table 2. Number of Subjects Needed to Assess Rare Adverse Events in Clinical Trials

Background rate of condition in the general population	Rate of condition in vaccinated population compared to background rate		
	2-fold higher	10-fold higher	100-fold higher
1 in 10,000	141,000†	5500	500
1 in 100,000	1,238,000	53,500	2500
1 in 1,000,000	12,951,500	532,500	23,500

†Number of subjects that would need to be enrolled in a clinical trial in order to detect the given increased risk of the condition in the vaccinated population, assuming a 5 percent risk of making a type-I error and a power of 90 percent.

Adapted from Evans, D., Cauchemez, S., Hayden, F. (2009). "Prepandemic" immunization for novel influenza viruses, "swine flu" vaccine, Guillain-Barré syndrome, and the detection of rare severe adverse events. *J Infect Dis*, 200, 321-328.

One other thing about safety – the more rare the adverse event, the more difficult it is to identify (Table 2). The mathematics behind this is staggering. Take, for example, a given condition that occurs at a rate of one in 100,000 people in the general population. In order to determine if a vaccine causes a 100-fold increased risk of that condition, 2,500 subjects would need to be enrolled in a clinical trial. However, in order to detect a two-fold increased risk, 1,238,000 subjects would need to be enrolled. Recognize that a study of "just" 2,500 subjects is a huge undertaking. This is where we must begin making tradeoffs between maximizing safety before licensure, that is, maximizing our ability to detect small risks and feasibility, keeping in mind that the longer we wait for more safety data, the more disease will continue to occur. Safety must be assured to a sufficient degree as to allow a vaccine to come to market after which careful, ongoing assessments for rare adverse events, which can only be detected after millions of people receive the vaccine, are conducted.

Misinformation, Antichampions, and Celebrity-ism

Fear of vaccines is nothing new. In the early 1800s, people were afraid to take the cowpox vaccine, which protected against smallpox, for fear that they would begin sprouting cow parts from their bodies.[16] Today, misinformation is ubiquitous. A Google search using the word "vaccines" conducted on July 22, 2012 yielded 37,100,000 "hits." The fifth hit was the home page of an organization called the National Vaccine Information Center at www.nvic.org. Two clicks into that page was a host of articles claiming that vaccines cause autism. Well-intentioned parents are likely to stumble upon those articles and, fearing autism, consider withholding vaccines from their children. This might be the right thing to do – if it were true that vaccines caused autism.

The problem is, they don't.[17] In fact, the Institute of Medicine,[18] the American Academy of Pediatrics,[19] the Centers for Disease Control and Prevention (CDC),[20] the World Health Organization,[21] autism advocacy groups like the Autism Science Foundation,[22] and even the U.S. Court of Federal Claims,[23] among other authoritative bodies, have said this loud and clear. Yet concerns about vaccines and autism persist, due in large part to the ubiquity of misinformation.

In addition, the arguments made by antivaccinationists are powerful and appeal to our deepest emotions. Take, for example, the claim that MMR causes autism, initially put forward by Wakefield in a 1998 *Lancet* paper.[24] That paper is now known to have been fraudulent.[25] Yet, many people still "believe in" Wakefield and his hypothesis. Why? Because antivaccinationists make emotive appeals, painting an "us versus them" picture, upholding the struggles of rank-breaking investigators as enlightened heros bent on exposing the truth that is being ignored by the "medical establishment."[26,27] Web 2.0 – defined by user participation, openness, and network effects – is likely to magnify the problem.[28]

And there's more. Celebrities have gotten into the act (no pun intended). Jenny McCarthy, for example, a popular model, actress, comedian and sympathetic mother, claims in television and newspaper interviews that vaccines caused her son's autism,[29] and for some reason people listen. People also listen to vaccine anti-champions – not celebrities per se, but authors and politicians who have achieved celebrity status because of their vocal anti-vaccine positions. Why are well-meaning parents so susceptible to misinformation and opinion? The answer has to do with human nature itself (see below).

Confusion and Communication

As if all of this were not confusing enough, there is the

sheer complexity of vaccine practice. In 1982, children in the U.S. received one series of shots (five diphtheria, tetanus, and pertussis vaccine followed by a Td booster), one oral series (four or five oral polio vaccines), and one MMR by 18 years of age – seven injections and a few sugar cubes. Today, the routine schedule prescribes over 50 immunizations and is so complex it has to be displayed on two pages.[30] This is enough to make a parent's head spin, let alone the fact that the recommendations can barely be contained in a 462-page book from the CDC.[31] There are vaccines for persons with particular risks, and particular risks of vaccines for certain persons. Shortages, labyrinthine guidelines and comprehensive regulations – these things characterize today's vaccination environment. Providers have less and less time while patients enter the exam room with increasingly sophisticated questions, demanding more sophisticated answers. Effectively communicating what parents and patients need to know during the vaccine encounter is difficult.[32]

Communicating the science of vaccinology to the general public is also difficult. Even the language we use is subject to misinterpretation (Table 3). Physicians, nurses and public health officials must work hard to hone their messages for maximum impact.

Human Nature

The soil in which vaccine hesitancy grows is the very nature of what it means to be human.

Risk Perception We are not very good at assessing risks and putting them into perspective. For example, we are terrified of sharks, despite the fact that dog bites[33] outnumber shark bites[34] by over 100,000 to one. Similarly, we are afraid to fly but not to drive, despite the fact that driving deaths outnumber commercial airline deaths by 14,000 to one.[35] In the case of vaccination, the risk of adverse events pales in comparison to the risk of injury from the natural disease. It's a good bet that 24,000 people will die from influenza this year;[36] yet no one is likely to die from influenza immunization.

Table 4. The Power of Box "a"

		Outcome (Adverse Event)	
		Yes	No
Exposure	Yes	a	b
(Vaccine)	No	c	d

Adapted from Offit, P. (2003). The power of 'box a.' *Expert Rev Vaccines*, 2(1), 89-91.

Anecdotal Thinking We are heavily influenced by anecdote, a phenomenon encapsulated by Dr. Paul Offit as the power of Box "a" (Table 4). We see an outcome of interest (e.g., autism) that occurs in a person with a given exposure (e.g., a vaccine), and we conclude (Box "a") that there must be a connection. However, one can only assess whether or not there is a connection by examining all of the other boxes ("b," "c" and "d") together with Box "a". What if, for example, the same outcome occurs with equal frequency among persons *not* exposed (Box "c")? Then, perhaps, there is no connection between the exposure and the outcome. Another version of anecdotal thinking is the logical fallacy summarized by the Latin phrase *post hoc ergo propter hoc*, or "after this, therefore because of this." The truth is, correlation does not necessarily mean causation. Yet we are hard-wired, perhaps through evolution,[37] to think this way.

To rise above anecdotal thinking, we (parents, patients, nurses and doctors) must think scientifically and probabilistically. How can we expect people to do this when as a nation we are failing miserably in science and math education?[38]

Heuristics Life is too complicated to draw a Venn diagram every time we need to make a decision. Therefore, we develop (subconsciously, if not consciously) "rules of thumb," or heuristics, to simplify things.[39] Take, for example, the "do no harm" heuristic, which amounts to the sense that a bad outcome is more tolerable if it occurs because of something I *do*, as opposed to something I *do not do*. If I refuse the influenza vaccine, I might get sick, but that is in a sense tolerable because it is an "act of nature" and "not my fault." On the other hand, if I take the flu shot and

Table 3. Language and Meaning

Expression	Technical meaning	Common interpretation
Biased	Having a systematic error that leads to the wrong conclusion	Not having an open mind
Not statistically significant	Findings are likely due to chance	Findings are not important
Statistically significant	Findings are not likely due to chance	Findings are important
Plausible	Theoretically possible	Worthy of belief
Adverse event	Temporally associated with vaccination	Side effect of vaccination

Adapted from Myers, M. (2009). In: Barrett, ADT, Stanberry, L. Vaccines for biodefense and emerging and neglected diseases. Maryland Heights, MO: Elsevier, Inc.

develop a serious reaction, that is harder to come to terms with, because the reaction was caused by my *action* rather than my *inaction*. The twist here is, of course, that *not taking* the flu shot is also an *action*.

Folk Numeracy We live in what Michael Shermer calls "Middle Land,"[40] having evolved in an environment where the size of things is between a speck of dust and an ocean, not between subatomic particles and galaxy clusters. Our intuitive sense of numbers is in this middle range, something referred to as "folk numeracy." We have trouble getting our minds around the very small and the very large, and we have a natural tendency to misperceive probabilities. Consider this: if 10 million pregnant women are given a shot today, 16,684 will have a spontaneous abortion within six weeks – if, that is, the shot is a placebo![41] You see, this is the background rate of pregnancy loss in the general population. If the shot were the influenza vaccine instead of a placebo, we would naturally blame the vaccine for pregnancy loss.

Patternicity and Confirmation Bias Our ancestors who could recognize patterns in nature had a survival advantage. They could make predictions about the world around them. We are highly evolved pattern-recognition machines, as Shermer puts it.[42] Sometimes, however, there really *is* no pattern, even though we perceive that one exists. We may hear about a girl who develops a demyelinating polyneuropathy and a woman who develops lupus after human papillomavirus (HPV) vaccination. The natural impulse is to believe that HPV vaccine must induce autoimmune disease – until we examine the evidence.[43] Will the scientific evidence be enough to convince us? Maybe not. We are dealing with thought patterns that are deeply rooted in the origin of our species!

Another tendency we humans have is to adopt a belief, then seek information (or interpret meaningless noise in such a way) that confirms our beliefs. This is called confirmation bias. In the above example, if we believe that HPV vaccine causes autoimmune diseases, then we are sure to see the "pattern" in the noise and interpret it as confirming our belief.

Misguided Self-interest Self-interest is rational and arguably also confers a survival advantage; however, if everyone is always out for themselves, everyone eventually loses. This is what is meant by the "tragedy of the commons."[44] It is within each herdsman's rational self-interest to add animals to his herd, and to let them graze freely on the commons. Overgrazing is of little consequence to him individually – until, of course, other herdsmen add animals to their own herds, acting in their own self-interest, such that soon the commons collapses and everyone is hurt. Parents and patients wonder why they should take on any personal risk, however small, from vaccination, since the diseases themselves are so rare and (seemingly) represent no threat to them personally. In this sense, self-interest leads to vaccine refusal. Unfortunately, like the herdsmen, if everyone takes this approach, everyone eventually is hurt, because the diseases, released from reigns of population immunity, return with a vengeance. The irony today is that vaccine refusal is rooted in risk avoidance, but it actually *increases* risk for everyone, *including* the vaccine refuser.[45,46,47]

Moving Forward

Vaccine hesitancy would have trouble taking root if we could "immunize" people against antiscience, creating, in essence, a generation of skeptics who when faced with the latest celebrity rant or sensationalistic Internet posting, could step back and say "what is the evidence." The challenge is converting natural anecdotal thinking to scientific thinking; heuristics to deductive reasoning; folk numeracy to statistical numeracy; patternicity to hypothesis testing; perception of risk to risk-benefit analysis; and the tragedy of the commons to the common good.

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CHAPTER 9

A Brief History of Autism, the Autism/Vaccine Hypothesis and a Review of the Genetic Basis of Autism Spectrum Disorders

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Abstract:
Autism spectrum disorders (ASD) represent a common spectrum of developmental disabilities, sharing deficits in social interactions, communication and restricted interests or repetitive behaviors with difficult transitions. In this article, we review the history of the identification and classification of autism and the origin of the now widely-debunked autism/vaccine hypothesis. The differences between syndromal (complex) and non-syndromal (essential) autism are described and illustrated with case descriptions where appropriate. Finally, the evidence that autism is fundamentally a genetic disease is discussed, including family studies, the role of DNA copy number variation and known single gene mutations.

Introduction

Autism spectrum disorders (ASD) comprise a common clinically heterogeneous group of neurocognitive conditions that include shared characteristics of impaired social relationships, impaired language and communication and repetitive behaviors or a narrow range of interests. The American Psychiatric Association's *Manual of Psychiatric Diseases, 4th edition (DSM-IV)* sets forth the behavioral criteria necessary for making a diagnosis of ASD.[1] Currently, three distinct subgroups are recognized within ASD: autistic disorder, Asperger syndrome and pervasive developmental disorder not otherwise specified (PDD-NOS). Just as the clinical manifestations of ASD are heterogeneous, so is its etiology. In this report, we discuss the history of the conditions comprising ASD, suggested environmental causes of ASD (including vaccines), and the evidence suggesting that autism is a predominantly complex genetically determined phenotype.

A Brief History: Unveiling the Autism Spectrum

In Siddhartha Mukherjee's Pulitzer Prize winning book, *The Emperor of All Maladies: A Biography of Cancer*, the author writes that cancer could only be unveiled once mankind lived long enough because "all other killers themselves have been killed."[2] So it is with autism spectrum disorders. As the infections that killed or disabled children in the past were eliminated through public health measures, antibiotics and vaccines, the neurobehavioral disorders have risen to a place of prominence in pediatrics. In fact, some question if we are in the midst of an autism epidemic and ironically blame the very vaccines that have helped unveil the disorder.

The word "autism" was coined by the Swiss psychiatrist Paul Eugen Bleuler in 1912 within the *American Journal of Insanity*.[3] The term is derived from the Greek *autos* meaning "self." Bleuler felt that this term described what he believed to be the childhood form of schizophrenia, a word that he also coined. In fact, Bleuler authored *The Textbook of Psychiatry* in 1916, which set the standard for many years. It wasn't until an Austrian-American physician by the name of Leo Kanner published his landmark article titled "Autistic Disturbances of Affective Contact" in the journal *The Nervous Child* in 1943 that 11 children with this disorder were described in the medical literature.[4] He described eight boys and three girls between the ages of 2 and 8 who displayed an extreme preference for solitude from birth onward, who had a mark need for sameness, persistent interests, repetitive behaviors, lack of imagination and language difficulties that included mutism, echolalia or

pronoun reversals. He distinguished this condition from childhood schizophrenia, noted a male predominance, commented that five of the 11 children had macrocephaly and described their parents as "intelligent folks who harbored an interest in science, literature or the arts with somewhat of a lesser interest in other people."[4] He would later describe the social awkwardness, a preference for routine and the presence of comorbid anxiety that is often seen in first degree relatives.[5] Since psychoanalytic theory was widely accepted at that time, it was only natural that Kanner felt that early infantile autism was due to cold, detached and rigid parents. He later coined the term "refrigerator mother" to describe their parenting. Dr. Kanner is considered the "father of child psychiatry" as he was the first to set up a child psychiatry department at Johns Hopkins and wrote *Child Psychiatry*, the first textbook on this topic in the English language.

In 1944, an Austrian pediatrician named Hans Asperger published an article in German describing four boys aged 6 to 11 with what he called "autistic psychopathy of childhood."[6] He too noticed that some of their parents had similar personality traits or were eccentric, and he considered this "constitutional basis" as providing a genetic link to autism. He was more positive in his approach to parents and felt that they had considerable potential in helping their children through treatment and education. He is credited with describing higher functioning forms of autism. In fact, one of his patients became a professor of astronomy and another became a Nobel Laureate in literature.[3] Lorna Wing, an English psychiatrist who had a daughter with characteristics similar to Asperger's patients, pointed out the similarities between Kanner's and Asperger's descriptions. It wasn't until Uta Frith's 1991 English translation of Asperger's original paper that psychiatrists in English-speaking countries began to make this diagnosis.[6]

Thirty-five years before Kanner's description of infantile autism, Austrian special educator Theodore Heller described a form of ASD that he called *dementia infantilis*. Between 1905 and 1930, he studied 28 children who developed in a normal fashion for the first two years of life, followed by symptoms of regression around ages 3 to 4 but no later than 10 years of age. Today we know this as childhood disintegrative disorder (CDD) or Heller syndrome. It is diagnosed when there are significant losses in at least two of the following developmental areas: language, social skills, motor skills, play behavior or bowel and bladder control. Because CDD is so rare (1.5 cases per 100,000 children), it was not added to the DSM until 1994. Much remains to be learned about its causes and treatments.[6] However, there is evidence to suggest that underlying genetic factors contribute to its degenerative course.[6]

Another Austrian born scientist, Bruno Bettelheim, Ph.D, immigrated to the U.S. after surviving the Dachau concentration camp. He became a professor of psychology and education at the University of Chicago and directed the Sonia Shankman Orthogenic School, a home that treated children thought to be emotionally disturbed. He became famous for his work seeking to interpret children's fairy tales to better understand childhood development. He also published an article in *Scientific American* in 1959 about a 9-year-old boy named Joey, which helped to introduce autism to the scientific world.[7] However, his work on autism became controversial because of his opinion that autism was caused by mothers who did not communicate properly with their children or withheld needed affection from them.[3] He popularized Kanner's earlier description of the "refrigerator mother" which was widely held in the 1960s and 1970s to be the cause of autistic behavior. Now that the neurologic basis of autism is increasingly understood, Bettelheim and his predecessors are considered to be controversial, and their ideas outdated.

Another psychologist, Bernard Rimland, Ph.D, challenged Bettelheim's psychoanalytic theory of autism. Rimland was a scientist and researcher in the fields of autism, attention-deficit/hyperactivity disorder, mental retardation and learning disorders. He stressed that autism had a neurologic basis and in 1964 published a now well-known book based upon this thesis. The foreword to the book was written by Kanner, indicating that he too was recognizing that a neurologic causation was the foundation of the disorder that he described.[3] In fact, in 1969 Kanner is reported to have said, "Parents, I acquit you."[6] Rimland himself had a son with autism who later became an artist. In 1965 in Teaneck, New Jersey, Rimland held a meeting with other parents of children with autism, which led to the formation of the Autism Society of America in that year. He also founded and directed the Autism Research Institute in 1967. Parents were happy not to be implicated in the cause of their child's autism and supported his efforts. Rimland was also concerned with what was perceived to be an increase in autism cases, and when he questioned vaccines as a possible causative link, he was placed in direct conflict with organized medicine.[3]

As the neurologic basis of autism became accepted, parents started to look at potential environmental causes for the disorder, while scientists, prompted by the observations of Kanner and Asperger that similar traits were observed in families, began to look at the genetic basis of the disease. Susan Folstein and Michael Rutter published the first twin study of autism in 1977.[8] Because identical twins arise from

a single fertilized ovum, they have the same genetic make-up, that is, in a very simple view, 100 percent of their DNA is identical. Fraternal twins, on the other hand, are derived from two different ova, which have been fertilized by different sperm. Although they share the same prenatal environment, fraternal twins are no more genetically similar than other pairs of siblings, and thus, approximately 50 percent of their DNA is identical. If autism has a genetic basis, one would expect that if one identical twin is autistic, his or her twin would have a much higher rate of also being autistic, a term known as concordance. The rate of concordance among fraternal twins, on the other hand, would be lower and closer to that of the general population. Folstein and Rutter evaluated 11 same-sex identical twin pairs and 10 same-sex fraternal twin pairs in which one or both twins had autism. Initially, they found that among identical twin pairs, four of 11 twin pairs were concordant (meaning that both twins had autism) yielding a concordance rate of 36 percent. The rate of concordance of fraternal twins in their study was zero percent.[8] When they used a less stringent criterion for autism in the same sample, they found the rate of concordance for identical twins rose to nine of the 11 pairs for a concordance rate of 82 percent. Using this same relaxed definition of autism, only one of the 10 fraternal twins was concordant for autism, yielding a concordance rate of 10 percent.[8] These findings indicated that genetic factors play an important causal role in autism. This study was extended and replicated by Anthony Bailey and colleagues in 1995, obtaining similar findings and drawing similar conclusions.[9] Since then, many additional studies have supported the finding that genetics contribute to the development of autism spectrum disorders.[10-14]

Parents, on the other hand, consistently reported that their children seemed to be progressing normally for the first year of life or so, but by 18 to 24 months began a developmentally downward spiral known as "autistic regression." To them, the progression from "neurologically normal" to "neurologically regressed" meant one thing – brain damage. Parents were intent on finding its cause. As they searched for environmental causes of brain damage, they looked at medical models that would do the same thing and settled on infections as causative. Ironically, according to Siddhartha Mukherjee's book, science took the same approach when examining the cause of cancer. Scientists knew that certain viral infections bore a causal relationship to certain cancers (Barr Epstein virus to Burkitt's lymphoma; human papillomavirus to cervical cancer, etc.) and they spent an enormous sum of research dollars in vain attempts to establish similar links for all cancers.[2] Meanwhile, parents knew that rubeola virus could cause encephalitis or subacute sclerosing panencephalitis, so why couldn't the rubeola vaccine, which was given at the same time that autistic regression occurred, cause autism?[3]

The anti-vaccine movement was not initiated by parents of children with autism. This movement was first launched at the time of the 1853 Vaccination Act in England, which mandated smallpox vaccination for the public in England. One of the anti-vaccine movement's leading proponents was Alfred Russel Wallace. Wallace was a co-discoverer of natural selection and was a famous explorer, biologist, anthropologist, geographer and naturalist. He published his own theory of evolution which stimulated Charles Darwin to publish his now-famous *The Origin of Species*. Wallace claimed that the smallpox vaccine was not safe, was dangerous and that compulsory vaccination was unethical.[3] To a certain extent, he was right. Since tissue culture had not been invented and viruses were unknown at that time, cowpox was transferred by arm-to-arm transfer, as were, inadvertently, hepatitis and syphilis. But Wallace also believed that the smallpox vaccine would upset what he perceived as the balance of nature, and would have disastrous results for human beings. He took on the medical establishment, encouraged some to avoid the smallpox vaccine, joined other famous scientists of the Victorian age to dismantle the compulsory vaccination act, and lent considerable discredit to vaccination in general. His disagreement with the well-known journal, *The Lancet*, previewed controversies to come in the next century.[3]

According to Offit, the anti-vaccine movement started in this country as a result of a one-hour TV documentary titled *DTP: Vaccine Roulette* shown on WRC-TV, an NBC affiliate in Washington, D.C., on April 19, 1982, linking the pertussis vaccine to severe reactions in children. Offit, as a pediatric infectious disease physician, has developed and tested one of the rotovirus vaccines, and has written extensively about vaccine development and safety. The documentary was produced by Lea Thompson and used video footage of severely disabled children to scare parents away from vaccinating their children against pertussis (whooping cough).[3] Wakefield added fuel to the vaccine-autism controversy with his 1998 article in *The Lancet* entitled "Ileal-lymphoid-nodular Hyperplasia, Non-specific Colitus and Pervasive Developmental Disorder in Children."[15,retracted] In the article, Wakefield described eight children whose first symptoms of autism appeared within one month after receiving the measles, mumps and rubella vaccine (MMR). All eight of these children were reported to have gastrointestinal symptoms and signs of lymphoid nodular hyperplasia on endoscopy. From these observations, Wakefield postulated that the MMR vaccine caused intestinal inflammation that led to translocation of usually

non-permeable peptides to the bloodstream and subsequently to the brain where they affected development. This study was never able to be replicated, but it did cause a flurry of research investigating any association between vaccines and autism. In 2001, the preservative thimerosal (ethylmercury) was removed from all children's vaccines in the U.S., even though there was no proof of a link between this preservative and autism. In 2004, the Institute of Medicine's Immunization Safety Review Committee released a report of their analysis of all published and unpublished epidemiological studies regarding the hypothesis that vaccines (MMR vaccine and thimerosal-containing vaccines) were causally associated with autism, and concluded they were not.[16] The prevalence of autism spectrum disorders in the U.S. has continued to rise in spite of taking thimerosal out of vaccines. In 2004, 10 of Wakefield's co-authors retracted their previous claims about the MMR vaccine, and in 2010 the medical journal *The Lancet* issued a full retraction of the 1998 article. Nevertheless, the vaccine/autism controversy has resulted in greater than 5,000 claims filed on behalf of children with autism spectrum disorder, seeking to link their condition to vaccination. After an eight-year process, the U.S. Federal Vaccine Compensation Court ruled in 2010 that autism was not an adverse reaction to the MMR vaccination, thimerosal or both.[17] This history and Wakefield's retracted study are extensively reviewed in Offits' books *Autism's False Prophets: Bad Science, Risky Medicine and the Search for a Cure* (2008) and *Deadly Choices: How the Anti-vaccine Movement Threatens Us All* (2011).

As the 21st century began, the rift between the public (parents of children with ASD and adults with ASD) and the scientific community appeared to be widening. However, history has taught us that if the scientific community wants to make meaningful progress in its research, it needs the support, advocacy and fund raising ability of public stakeholders (i.e., HIV/AIDS and the gay community, cancer and the public that has been touched by this disease). A positive sign appears to be Public Law 109-416 or the Combating Autism Act passed by Congress and signed by President George W. Bush in December 2006. It has dedicated nearly $1 billion over five years to the screening for early intervention services and education for autism spectrum disorders.[6] More importantly, the act is bringing parents and professionals to the table to address this important problem together. Researchers, meanwhile, continue to identify the genetic underpinnings of autism at a rapid pace.

The Genetic Basis of Autism

As described above, the heritability of ASD, a measure of the genetic component of a particular trait or phenotype such as height, is estimated to be as high as 90 percent.[10, 14, 18] However, until recently, the genetic basis for autism remained elusive. Recent rapid progress in uncovering the genetic etiology of ASD has changed the diagnostic landscape of the disorder. Autism can be separated into syndromal or complex autism, that is, autism that is associated with a particular syndrome, such as the Fragile X syndrome versus non-syndromal or essential autism. Here we describe four patients with known syndromal forms of autism, and with respect to non-syndromal autism, we review data from trio (patient, mother, father) and quartet (trio plus unaffected sibling) whole exome studies, and large cohort DNA copy number variant (CNV) studies.

Syndromal Autism

Syndromal or complex autism comprises approximately 20 percent of the ASD population. This may occur in association with chromosome disorders that are visible at the light microscope, such as deletion 22q13, or with chromosome disorders that are not visible at the light microscope but that can be detected by microarray-based technology, such as duplication 15q11q13.[19-21] Syndromal autism also can occur in the form of single gene disorders such as Rett syndrome, where mutations in the MECP2 gene account for 80 percent of typical cases.[22] Although not described below, syndromal forms of autism also occur in Angelman, Smith-Magenis, and Down syndromes, among other disorders caused by chromosomal abnormalities.[23] Similarly, autism occurs in several well-described single gene disorders, including but not limited to Fragile X syndrome, tuberous sclerosis complex, untreated phenylketonuria, and San Filippo, Cohen and Smith-Lemli-Optiz syndromes.[23] Referral for a medical genetics evaluation is appropriate for any child suspected of having an ASD, whether it be a syndromic form or a non-syndromic form.[24]

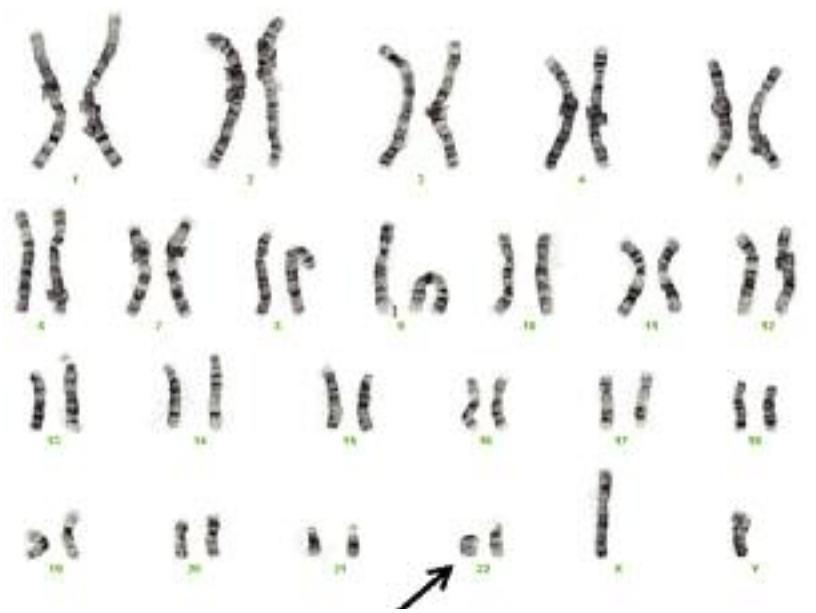
Patient 1 AC (initials have been chosen at random and do not reflect actual patient identifiers) was referred to the genetics clinic for concerns related to his autistic behavior. AC exhibited global developmental delay with absent speech. His parents reported little to absent interaction with his peers and a near absence of physical or eye contact with them. He did exhibit repetitive behaviors, including tracking power cords from beginning to end. Chromosome studies and Fragile X analysis were ordered. Fragile X testing was negative, but chromosome studies revealed an abnormal chromosome 22, which was in the form of a ring (Figure 1). The deleted region included band q13, which is a recognized cause of the autism-associated 22q13.3 microdeletion syndrome.[25] AC's parents were dismayed by the chromosome finding: they had sincerely believed that AC would

"outgrow" his behavior.

Children like AC with 22q13.3 microdeletion syndrome are characterized in part by developmental delay and profound expressive speech and language delay. Various dysmorphic craniofacial features may occur as well, including epicanthal folds, long eyelashes, supraorbital fullness, and an upturned nose with a blunt nasal tip, among others.[25] Also noted are two to three toe syndactyly and squared fingertips with nail abnormalities. AC exhibited no significant dysmorphic features, but his profound expressive speech and language delay were consistent with the described syndrome. He was referred for speech and occupational therapies, which are ongoing.

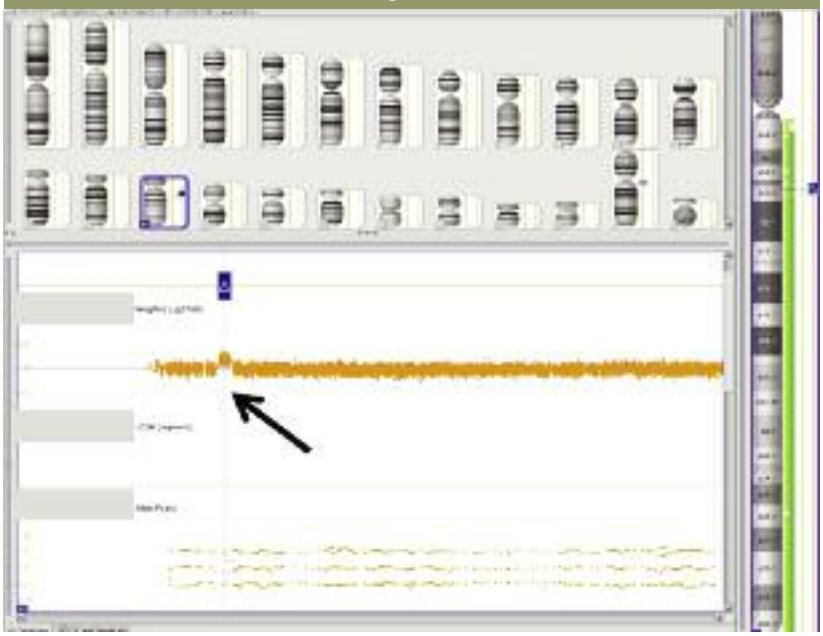
Patient 2 JL had been followed for many years in the genetics clinic for concerns related to her dysmorphic facial features, intellectual disability and autistic behaviors. No specific genetic diagnosis had been made, and chromosome and Fragile X studies were normal. At approximately age 20, she returned to clinic for a continuation of care visit, and microarray testing was suggested as a diagnostic option. (Microarray testing is based on the use of thousands to millions of small DNA probes placed on an array, also known as a chip, to scan the patient's genome for gains or losses of DNA that are too small to be observed at the level of the light microscope.[19]) JL's microarray result indicated that she had an approximately 1.7 megabase duplication on chromosome 15 involving bands q13.2 to q13.3 (Figure 2). This duplication, and its corresponding deletion, has been described as occurring in a subset of a large cohort comprised of patients originally referred for diagnoses ranging from developmental delay, intellectual disability, autism, dysmorphic features, or multiple congenital anomalies.[21] The subset identified as having DNA copy number changes for 15q13.2q13.3 was studied further, and those with duplications were found to have autism with associated expressive language delay and repetitive behaviors. Inheritance of DNA copy number changes for 15q13.2q13.3 from apparently unaffected parents has been

Figure 1.



G-band chromosome studies were performed for a patient with autistic behaviors and absent speech. A ring chromosome 22 was observed. Subsequent studies confirmed that the ring resulted in a deletion that was consistent with the described autism-associated 22q13.3 microdeletion syndrome[25] (karyogram at 100x magnification).

Figure 2.



Array studies were performed for a now-adult patient with dysmorphic facial features, intellectual disability and autistic behaviors. A 1.7 megabase duplication on chromosome 15 involving bands q13.2 to q13.3 was detected. This duplication contains more than 1 dozen genes, and there is increasing evidence that duplications in this region do contribute to developmental delay and autism spectrum disorders.[21] The opaque boxes in the lower panel mask patient identifiers.

reported, as have *de novo* gains and losses.[21] Parental studies were performed, and those indicated that JL's duplication was *de novo*; she continues to receive care from her parents and does not live independently.

Patients 3 and 4 Twins KM and NP were thought to be fraternal sisters because their placental configuration was diamniotic, dichorionic, indicating two separate placentas. However, both girls had disabilities. NP was the second born twin and presented to the neurology department at 3-and-a-half years of age with seizures. Her physical exam showed evidence of growth retardation (height much less than 5 percent and weight at the 5 percent); however, her head circumference was considered within the normal range (25 percent). NP showed poor eye contact, social aloofness, no communication intent, slightly increased tone with hyperactive deep tendon reflex (DTR), episodes of hyperventilation, and she had an anxious, serious appearance to her face. She was so unresponsive to verbal communication that she was initially thought to be deaf. Diagnostic testing included a normal Brainstem Auditory Evoked Response (BAER), MRI of the brain, high resolution chromosomes and Southern Blot test for the Fragile X syndrome. Her EEG showed bilateral temporal spike and wave activity consistent with a seizure disorder. She was started on anticonvulsants and referred to the developmental behavioral program with a suspected diagnosis of Rett syndrome. Over the next several months, both twins were evaluated. They looked somewhat alike, but KM was not as significantly growth retarded (height less than 5 percent and weight 25 percent) and her head circumference was normal (50 percent). KM's physical exam showed that she was more verbal, had better eye contact, demonstrated low muscle tone with hyperactive DTR's, was particular about what she wore, was more obsessive and hyperactive, and displayed tantrums when limits were set. While KM appeared to be similar to NP, she presented with more hyperactivity and disruptive behaviors and was not felt to meet criteria for Rett syndrome. At that time, the MECP2 gene had not been discovered. After the discovery of the gene and its role in Rett syndrome,[22, 26] gene sequencing became commercially available and NP was tested. She exhibited a heterozygous missense mutation in exon 4 which had been identified in other girls with Rett syndrome. KM was then tested and found to have the identical mutation. X chromosome inactivation studies showed that only 13 percent of KM's active X chromosomes contained the mutation, while 44 percent of NP's active X chromosomes contained the mutation, which explained the phenotypic differences.

Non-Syndromal Autism

So, what then, underlies autism when it is not associated with a specific syndrome? Non-syndromal, or essential, autism has a higher degree of heritability than syndromal autism, with both more affected relatives and a higher male to female patient ratio having been reported.[9,13,27] Numerous studies in recent years have identified DNA copy number variations (CNVs) and/or mutations in individual genes, which are implicated in or strongly associated with autism.[28-32] Although a complete review of all identified CNVs or gene mutations is beyond the scope of this report, we briefly review a subset of recent studies below.

Analysis of gain and loss of DNA (duplications and deletions, respectively) can be performed with light microscopy if the gain or loss is large enough. However, duplications and deletions are often simply too small to be seen at the microscope, though they may contain dozens or hundreds of genes.[19] Comparative genomic hybridization (CGH, also known as microarray analysis or array-CGH), allows the genome to be surveyed for gains and losses of DNA as small as 100 kilobases in size or perhaps smaller.[33] The technology has been employed in patients with autism as well as in matched but unaffected controls, and CGH has demonstrated that DNA duplications and deletions play a significant role in ASD.[34-37] Sanders and colleagues observed that *de novo* DNA copy number variations confer a significant risk for autism, and they suggested that more than 200 autism-susceptibility loci are present in the human genome.[36] This had been previously observed by Sebat and colleagues,[37] and work in this field of copy number variation research and the role of CNVs in autism continues apace.[38]

Mutations in individual genes are implicated as well. A recent study by Sanders et al. used a whole exome sequencing approach to examine mutations in the gene-coding portion of the genome (the exome). In their work, they sequenced the exomes of 238 patients with autism as well as sequencing the exomes of the parents of those patients (triad studies). Additionally, for 200 of those families, the researchers were able to sequence the exomes of an unaffected sibling (quartet studies). Their results revealed that novel point mutations occurred more frequently in affected individuals than in their unaffected siblings.[39] Furthermore, when they looked specifically at mutations in genes that are expressed in the brain, they observed a significant difference between patients with autism and their unaffected family members, concluding that nonsense and splice-site mutations have a significant impact on autism.[39] In particular, the researchers identified the gene *SCN2A*, which had previously been associated with epilepsy, as being implicated in autism.[39]

A concurrent study focused on triad cohorts. Neale and colleagues sequenced the exomes of 175 trios, and noted

that the mutation rate in patients with autism was "only modestly higher than the expected rate".[40] However, when they looked at the genes exhibiting the *de novo* mutations, they observed that the resulting proteins were members of interconnected networks. Two genes in particular, *CHD8* and *KATNAL2*, were identified as autism risk factors.[40] Furthermore, they suggested that polygenic models may explain a degree of the variability of the genetic foundation of autism, and concluded that *de novo* mutations likely contribute to some, but not all, cases of autism.[40]

Similarly, a study that included both triad and quartet analyses identified recurrent mutations in the genes *CHD8* and *NTNG1*, and *de novo* mutations in the genes *GRIN2B*, *LAMC3*, and *SCN1A*.[41] Like Neale and colleagues, O'Roak and colleagues observed that the mutations affected protein networks, specifically in the O'Roak study, the ß-catenin/chromatin remodeling network.[40-41] O'Roak and colleagues additionally observed both a paternal bias in mutation origin and a paternal age affect on the total mutation rate.[41]

These studies and numerous others are revealing that there is significant genetic heterogeneity in ASD.[39-41] The rapid pace of identification of contiguous gene regions and of individual genes associated with autism tells us that while we certainly cannot at this time identify the molecular or physical basis of each individual case of autism, we can safely conclude that autism occurs against a genetic background. Furthermore, while there is no single "autism gene," there are dozens, perhaps hundreds, of genes where mutations can occur resulting in the disorder.[38] Similarly, there is no "autism locus" in the genome. There instead are numerous regions where gains and losses of stretches of DNA can result in the phenotype we call autism.[34, 38]

Conclusion

Siddhartha Mukherjee concluded his book, *The Emperor of All Maladies: A Biography of Cancer* with the following quote: "Cancer at the *fin de siècle* (end of the century) as the oncologist Harold Burstein describes it, resides at the interface between society and science. It poses not one but two challenges. The first, the 'biological challenge' of cancer, involves harnessing the fantastic rise in scientific knowledge…to conquer this ancient and terrible illness. But the second, the 'social challenge,' is just as acute; it involves forcing ourselves to confront our customs, rituals and behaviors."[2] The challenges we face with autism are just as great and are likewise two-fold, residing at the interface between society and science. Once we understand the genetics of autism, we will need to face its epigenetics, which "unfortunately, are not customs or behaviors that lie at the peripheries of our society or selves, but ones that lie at their definitional cores; what we eat and drink, what we produce and exude into our environment, when we choose to reproduce and how we age."[2]

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CHAPTER 10

Becoming a Vaccine Champion: Evidence-based Interventions to Address the Challenges of Vaccination

By Erick Temoka, MD

Abstract:
The incidence, prevalence, morbidity and mortality rates of vaccine-preventable diseases have decreased drastically since the advent of modern vaccination by Edward Jenner at the end of the 18th century. In recent years, however, a growing number of parents have been refusing or delaying vaccination for their children for socio-economical, medical, religious and/or philosophical reasons. This has resulted in a loss of herd immunity that has caused a resurgence of many infectious diseases. This article describes evidence-based methods by which a pediatric clinic can become a vaccine champion by aiming at vaccination rates of 100 percent. This goal can be attained by a team effort that addresses the challenges of vaccination by using every visit as a chance to vaccinate, educate, address the fears and the concerns of the parents and provide articles and other written documentations on the benefits and side effects of vaccines. A standardized system that identifies and tracks patients who need vaccines is also essential to find those who are seldom brought to medical attention. A consistent and systematic use of these evidence-based methods by a dedicated staff is essential to attain vaccination rates close to 100 percent.

The incidence, prevalence, morbidity and mortality rates of vaccine-preventable diseases have decreased drastically since the advent of modern vaccination by Edward Jenner at the end of the 18th century. Nowadays, a newborn is more likely to survive infancy, grow strong, healthy and live a longer and more productive life. Indeed, most of the vaccine-preventable diseases that plagued humanity for centuries have seen their morbidity and mortality rates decline dramatically; Roush and Murphy[1] demonstrated significant decreases in morbidity rates of diphtheria (100 percent), measles (99.9 percent), paralytic poliomyelitis (100 percent), rubella (99.9 percent), congenital rubella syndrome (99.3 percent), smallpox (100 percent), mumps (95.9 percent), tetanus (92.9 percent) and pertussis (92.2 percent) and mortality from tetanus (99.2 percent) and pertussis (99.3 percent), directly related to vaccination.

In the 1980s, *Haemophilus influenzae* type b (Hib) was still the leading cause of bacterial meningitis and other invasive bacterial diseases among children less than 5 years of age. In the early 1990s, the introduction of the Hib conjugate vaccine caused a decline in Hib infections by 99 percent. *Streptococcus pneumoniae* then became the most common cause of meningitis and invasive bacterial infection in young children. Subsequently, the introduction of the 7-valent pneumococcal conjugate vaccine (PCV-7) in February 2000 caused a rapid decline in invasive pneumococcal diseases in children less than 5 years of age. This dramatic change was seen as early as 2001. Invasive pneumococcal diseases due to the seven serotypes declined from 80 cases per 100,000 populations to less than one case per 100,000 by 2007.

The effectiveness of vaccination is mainly due to two factors; first, the patient is immunized against the specific pathogen and the rate of asymptomatic carrier state is decreased; second, through herd immunity; if a large population is immunized, individuals for which vaccinations are contraindicated have a decreased chance of exposure to pathogens.

But vaccines may be victims of their own success. Most vaccine-preventable diseases have declined to historically low levels in the U.S. as a result of high vaccination rates among children under 5 years of age. Consequently, many young parents have no memory of the diseases that terrorized their parents and grandparents. Parents are increasingly refusing to vaccinate their children, deliberately delaying vaccination or using alternative immunization schedules. They are also more boldly questioning the safety of vaccines; some consider vaccines to be the culprits for autism and/or attention deficit hyperactivity disorder (ADHD); others are convinced that their children are more likely to acquire infectious diseases if they get vaccinated; other parents believe that the rate of decline in vaccine-preventable diseases was not due to vaccination but to other factors, like improved hygiene, sanitation and health care; others also claim that young infants and children should not be vaccinated because their bodies are still fragile and immature. The 2009 National Immunization Survey interview showed that in 2009, 25.8 percent of parents delayed vaccinations, 8.2 percent refused, 5.8 percent both refused and delayed, and only 60.2 percent neither refused nor delayed. Parental requests for alternative vaccination scheduling have also risen to up to 13 percent in recent years.

A major contribution to incomplete or delayed vaccination hinges on socioeconomic factors. Many parents go through hard times because of job loss, foreclosure, divorce and/or financial hardship; some parents are single, overworked and overwhelmed, not able to keep up with their children's well visits and vaccinations. When they lose their jobs and their health insurances, they often ignore that they could qualify for Medicaid and maintain their access to health care. Vaccination rate is hence influenced by poverty level. Although there is no difference in rate between children living under and above poverty level for vaccines such as measles, mumps and rubella (MMR), polio and hepatitis B provided under the Vaccines For Children program (VCF), the vaccination rate among children living below poverty lags behind the rate of children living at or above poverty for vaccines that require 4 doses to complete the series and newer vaccines. Black children have a lower vaccination rate for diphtheria, tetanus, acellular and pertussis (DTaP), Hib, pneumococcal conjungate vaccine (PVC) and rotavirus than white children, but the racial difference disappears after adjustment for poverty status, suggesting that the higher prevalence of poverty among black children could explain the lower coverage.[2]

At Avera St. Luke's Pediatrics, our goal is to exceed the Healthy People 2020 objectives and get as close as possible to the 100 percent coverage rate. Healthy People 2020 has set a vaccination coverage goal of 90 percent for one or more MMR, three or more hepatitis B, three or more inactivated polio virus vaccine (IPV), one or more varicella, four or more DTaP and four or more prevnar and the full Hib series. In our community, most children are brought to the clinic for sick visits. Parents are more likely to skip well visits because they tend to assume that after 2 years of age,

Table 1. National, South Dakota and Avera Pediatrics Vaccination Rates

Vaccination(s)	Avera Pediatrics Coverage (percent)	South Dakota Coverage (percent)	National Coverage (percent)
Diphteria, tetanus, acellular pertussis (DTaP #4)	98.2	95.2	95
Inactivated Poliovirus (IPV) #3	100	94.7	93.3
Measles/Mumps/Rubella	99.1	92.1	91.5
Haemophilus influenzae Type b	100	89.2	90.4
Pneumococcal	97.3	76.4	83.3
Hepatitis B	100	95.9	91.8
Varicella	100	91	90.4
Hepatitis A	82.3	33.1	49.1

children do not need to be seen by their provider if they appear healthy. For that reason, every sick visit is for us an opportunity to verify our patients' well visits and vaccination statuses.

I and my staff were honored to be named the Centers for Disease Control and Prevention (CDC) Childhood Immunization Champion in 2012 for the state of South Dakota, for the outstanding vaccination rates of our clinic. Table 1 compares our vaccination rates with the national and the South Dakota vaccination rates. In June 2012, an assessment by the South Dakota Department of Health (SDDOH) vaccine initiative of immunization rates for South Dakota clinics found our rate for 4 or more doses of DTaP vaccine to be 98.2 percent versus 95 percent for the national rate and 95.2 percent for the South Dakota rate. Our rate for 3 or more doses of IPV was 100 percent versus 93.3 percent and 94.7 percent for the national and the South Dakota rates, respectively. Our coverage for 1 or more dose of MMR was 99.1 percent versus 91.5 percent and 92.1 percent for national and South Dakota rates, respectively. Our rates for 3 or more doses of Hib vaccine were 100 percent versus 90.4 percent and 89.2 percent for the national and the South Dakota rates, respectively. Our rate for 4 or more dose of pneumococcal conjugated vaccine was 97.3 percent versus 83.3 percent and 76.4 percent for the national and the South Dakota rates, respectively. We had 100 percent coverage for 3 or more doses of Hepatitis B vaccine versus 91.8 percent and 95.9 percent for the national and the South Dakota coverage. For 2 or more doses of hepatitis A, we had 82.3 percent rate versus 49.7 percent and 33.1 percent for the national and the South Dakota rates; we had 100 percent rate for 1 or more doses of varicella vaccine (VAR) versus 90.4 percent and 91 percent for the national and the South Dakota rates. Over the past several years, we have consistently exceeded the Healthy People 2020 objectives. When audited by the SDDOH, our rate for the DTaP #4, polio3, MMR1, Hib3, HepB3, varicella1, prevnar4 series was 99 percent in 2010, 98 percent in 2011 and 98 percent in 2012.

We have attained these rates by using the following approaches which incorporate evidence-based practices. First, for all of our patients, there is a vaccination standing order that allows nurses to vaccinate independently from seeing the provider. One situation where this is particularly important is when patients are scheduled for nurse visits only for weight check or to get an influenza vaccine. Our nurses will typically verify their vaccination status and offer the vaccines when they are needed.

Our nurses also have the responsibility to use our electronic medical record reminder system to identify patients who are not up-to-date with their immunization. Our administrative assistant would then send up a letter and if no response, call up to three times to schedule an appointment for well visit and vaccination. Also, all of our families are provided with a summary of all visits with their vaccination records and dates of their future vaccinations, to give them a better awareness of their upcoming visits. Second, and beyond these standardization principles used for everyone, we plan and respond to those situations which are often more challenging. Broadly speaking, when it comes to dealing with vaccination, we have divided challenging families into two groups: the socio-economic group and the philosophical group.

The socio-economic group includes parents who have a hard time keeping up with their appointments, don't have reliable transportation means, relocate frequently, and are overwhelmed by their jobs, and their financial and/or family conditions. For all patients belonging to this group, the first intervention that increased vaccination rates was to make their access to the clinic very easy.[2] For instance, they can usually be seen the same day they make the appointment. This "walk-in visit" strategy includes a check of their vaccination status. If they have minor illnesses (diaper rash, mild upper respiratory infection, constipation, etc.), they will typically get their vaccinations during the walk-in visit encounter. We often convert post-surgical, post-hospitalization and follow up visits into well visits with vaccinations and parents are usually happy with this approach that reduces the number of clinic visits and their medical expenses.

Another evidence-based intervention is the patient reminder.[3] Our administrative assistant typically sends a letter to families to remind them of their upcoming visit, but more importantly, parents are called the day before the visit as a last reminder. In a nutshell, patients belonging to the socio-economic group are likely to skip their well visit and come only when they really need to, for medication refills, health concerns or when they are sick. Our job is to take advantage of these visits to vaccinate them and perform well visits.

A significant number of families who frequently miss their well visits and vaccinations are tracked when they call our office for medication refill or advice. Our policy is that if a family calls for a medication refill or advice and a well visit and/or vaccination is due, they need to schedule an appointment at the clinic. This is, in our experience, a very successful approach to track healthy children who would otherwise not be brought to medical attention by their parents. For instance, a mother who has not brought her child to the clinic for two years would call our clinic to inquire if her 3-year-olds' symptoms are consistent with allergy. Our approach would be to invite the mother to schedule an appointment for evaluation. During the visit, if the symptoms are trivial, we would just convert that into a well visit. If they are more serious, we would perform the well visit during the follow up visit, typically after one to two weeks.

Within the philosophical group, we have observed that there are two types of families with a stated opposition to vaccination: the "hesitants" and the "non-hesitants." When we encounter families that are opposed to vaccines, our approach is first of all to genuinely inform them that we will work with them regardless of their decision to immunize or not. Interestingly, many parents feel relieved by this statement as they often fear to be rejected or marginalized by their philosophical differences. We also inform them that although we strongly believe in vaccines, our job is not to force parents into endorsing them. It is merely to share our knowledge and experience, and thoroughly discuss the benefits and consequences of their decision to vaccinate or not. Ultimately, we want our parents to consciously decide to vaccinate their children after deeply weighing the pros and the cons. The level of trust usually increases exponentially when parents opposed to vaccination recognize that their provider is not going to force them into a procedure that they are not comfortable with.

In our practice, the overwhelming majority of parents who are opposed to vaccination are "hesitant." They know that some or all vaccines are probably beneficial to health but they are also concerned about the pain caused by the procedure, the number of shots per session, the ingredients in the vaccines, the young age of the children who are being vaccinated and the side effects. Providers should always ask parents the following questions: why are you opposed to vaccination? What are your specific concerns? Many times, the answer will be an easy fix. Some parents, for instance, refuse the influenza vaccine because they are concerned about thimerosal, a mercury-based preservative that they say causes autism. When informed that thimerosal-free influenza vaccines are available, they usually agree to proceed with the vaccination. When dealing with hesitant parents, if the provider is able to show that the pros outweigh the cons, they will usually accept to vaccinate. Many parents just seek reassurance from the doctor who they look up to and trust. We also have to remember that most parents are not familiar with the specific vaccines that their children receive and the infections that they prevent. Therefore, it is always useful to describe the infections that are being prevented by the vaccines. Many of our hesitant parents agree to vaccinate their children when they are told that *Hemophilus influenza* and streptococcus pneumonia are two leading causes of meningitis, or that a rotavirus infection is likely to get their child admitted to the hospital for IV fluid. Describing the possible scenario of their children getting IV access, the uncomfortable stay at the hospital, the medical bills, and the possible loss of income from leave of absence usually give the parents a clear picture and a better assessment of their decision.

Among the non-hesitant parents that come to our clinic, some convincingly refuse some or all vaccines. Others,

perennially undecided, postpone the decision to vaccinate for months, years or indefinitely, despite our best effort to provide information and education on the matter. They often have someone in their family or community with autism. They are likely to quote some doctor, Ph.D or scientist who believes that vaccines are futile or dangerous. In our experience, parents belonging to these groups rarely change their mind in the very short term. Our intervention is similar to the approach described above on hesitant parents, with one difference. It is counterproductive to discuss about immunizations and educate non-hesitant parents at each and every visit. They don't feel comfortable with the vaccines, and being too persistent may ultimately make them feel uncomfortable with the provider and the whole clinic. It is more effective to resume the discussion every two or three visits; by allowing these parents to have visits where vaccination is not discussed, we reinforce the idea that we accept their philosophical difference. This should boost the level of trust between the parents and the provider and improve the vaccine debate when it is resumed at a later visit.

Parents who delay or refuse vaccination need to sign an extensive exemption form, like the form provided at www.immunize.org/eatg.d/p4059.pdf. These exemptions help guide more informed decision making because parents have to read the benefits of vaccines and the risks of the decision not to vaccinate. This timely and directly engaging approach is effective because the opinion of health care professionals matters to the parents. Kennedy et al. found that when it comes to making decisions about infant vaccinations, the most frequently cited source was trusted health care providers in 85 percent of cases.[4]

In our practice, we do not generally encounter families with religious reasons to oppose vaccination. True medical exemptions, also, are very rare. We have yet to encounter cases of seizure, encephalopathy or cardiovascular collapse described in the literature as severe side effects of vaccines. We have had very few patients with congenital heart disease (e.g., hypoplastic left heart syndrome) who were exempted from vaccinations after surgery because the irritability that would ensue after vaccination could decrease the venous return to the heart and cause sudden death.

In summary, to become a vaccination champion is to strive for a 100 percent vaccination rate in that population of patients that are not excluded by true medical exemptions. To attain such a goal requires dedicated staff who reliably apply best evidence and use standardized processes to identify and track all patients who need vaccination. In addition, championship vaccine delivery requires system processes that make every patient contact an opportunity to vaccinate and to educate and address questions brought forward in real time. Lastly, to be vaccine champion is to address the challenging situations driven by both socioeconomic and philosophical considerations, addressing these with thoughtful planning. In short, vaccine champions offer patients and their families every chance possible to avoid vaccine-preventable diseases.

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CHAPTER 11

Vaccinating Through a Lifetime: Adult Priorities

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Abstract:

Vaccination strategies for adults have recently been updated to include newer vaccine products and to reflect the changing epidemiology of vaccine-preventable diseases in adults. New products include vaccines against shingles and the human papillomavirus, and a combination vaccine which contains an acellular pertussis component (Tdap). In some cases, existing vaccines have been re-formulated to provide alternate routes of delivery, as is the case with the influenza vaccine, or more effective formulations, as is the case with the meningococcal vaccine. Vaccine strategies for adults are designed to respond to existing, emerging, or re-emerging infectious diseases in populations at risk. This includes the resurgence of pertussis and recent evidence showing that diabetics are at increased risk for hepatitis B.

Unfortunately, large portions of the adult population do not receive recommended vaccinations. As a result, more adults die from vaccine-preventable diseases than die from motor vehicle accidents. Strategies to improve vaccine coverage include public education campaigns and making some vaccines available in nontraditional settings such as retail stores or workplaces. Within health care settings, successful strategies have included the use of standing orders, automatic reminders for physicians using the electronic health record and recall/reminder letters for patients. Appropriate use of adult vaccines plays a key role in prevention of disease and the provision of high-quality care.

Overview

Although vaccines are most recognized for their incredible success in preventing childhood disease, vaccination of adults has also been highly effective in reducing morbidity and mortality from infectious diseases. There are many reasons to vaccinate adults. In some cases, immunity from childhood vaccinations wanes over the years and booster doses must be given to maintain immunity, as is the case for the combined tetanus, diphtheria and pertussis (Tdap) vaccine. In other cases, vaccine-preventable diseases affect adults but are less common in children or affect children in different ways, such as herpes zoster (shingles).

The goal of adult vaccination is to reduce the risk of disease or, in some cases, to reduce the severity of disease if it is acquired. A secondary goal might be to improve herd immunity, leading to fewer hosts which are able to spread disease to vulnerable populations.

Although this chapter focuses on adult vaccines, it is also necessary to discuss selected adult vaccination for those who were not immunized as children. For example, vaccination of adults against hepatitis is discussed because the newer recommendations for universal childhood vaccination has not yet been in place long enough to create a fully immunized adult cohort.

The goal of adult vaccination is to provide optimal protection in populations at risk. Sadly, the U.S. often falls short of this goal. Approximately 40 percent of adults received the influenza vaccine in the 2009-2010 season although South Dakota led the nation with 56 percent coverage.[1] Other vaccines do not fare any better.[2] Only 14 percent of persons 60 years of age and older have received a dose of zoster vaccine. Only 60 percent of adults aged 65 years and older and 18.5 percent of high-risk adults under age 65 have received the pneumococcal vaccine. Approximately 42 percent of high-risk adults aged 19 to 49 have received hepatitis B vaccine, and only 8 percent of adults aged 19 to 64 have received a dose of Tdap. Through

Healthy People 2020, the Centers for Disease Control and Prevention (CDC) has set a national goal of increasing vaccination rates in adults. More information can be found by visiting www.healthypeople.gov/2020.

The consequences of failing to vaccinate adults can be significant. According to the CDC:[3]

- There are an estimated half million cases of pertussis (whooping cough) in adults each year. Although not as severe as childhood pertussis, adult disease still results in hospitalizations, rib fractures (from coughing) and pneumonia. Moreover, sick adults can pass the disease to infants and children.
- Invasive disease from *Streptococcus pneumonia* (pneumococcus) accounts for more than one-third of community-acquired pneumonia and one-half of hospital-acquired pneumonia in adults. Bacteremia occurs in 25 to 30 percent of patients with pneumococcal pneumonia, with associated case-fatality rates of 20 to 60 percent. Pneumococcus remains the most common cause of bacterial meningitis in adults.
- Fulminant hepatitis B kills approximately 200 to 300 Americans each year, and chronic infection with the virus can lead to cirrhosis and death.
- Overall, approximately 42,000 adults die annually from vaccine-preventable diseases, exceeding those killed in automobile accidents.

This article provides an overview of vaccinations for adults and is not meant to be comprehensive. More detailed information is available from the CDC website by visiting www.cdc.gov. Providers should always review the package insert for information on dosage, side effects and contraindications.

Vaccination Schedule for Adults

The Advisory Committee on Immunization Practices (ACIP) publishes recommendations for vaccinations by age group and risk status. Updates to the comprehensive immunization schedule are published annually,[4] although updates for individual vaccinations may be published throughout the year. Some vaccines are recommended for all adults within an age group, regardless of risk for the disease (Table 1).

Table 1. Vaccines Given in All Adults*

	Age in Years				
	18-21	22-26	27-59	60-64	65+
Influenza	All	All	All	All	All
Td/Tdap	Tdap once then Td booster every 10 years				
HPV (f)+	All	All			
HPV (m) ++	All	May**			
Zoster				All	All
Pneumococcal					All

*See package insert for dosage and contraindications.
**Recommended for all males who are immunocompromised (including HIV infection) and men who have sex with men, others may be vaccinated at the discretion or the provider or request of the patient.
+if not given in adolescence.
++if not given in adolescence, use only HPV4 vaccine in males.
HPV4: quadrivalent HPV vaccine.

Table 2. Vaccines Given to Adults with Selected Risk Factors*

Pneumococcal	Chronic liver/kidney/cardiopulmonary disease, cochlear implants asplenia, immunosuppression, HIV infection, diabetes, alcoholism, cancer, asthma, current smoker, residence in a long-term care facility, cerebrospinal fluid leaks, hemoglobinopathies, age 65 years or older
Hepatitis B	Chronic liver disease, end stage renal disease, human immunodeficiency virus (HIV) infection, healthcare worker and others exposed to blood, presenting for evaluation/treatment of sexually transmitted disease (STD), intravenous drug use, multiple sexual partners in last six months, men having sex with men, travelers to countries with high/intermediate endemicity, diabetes, conditions requiring clotting factor concentrates, prisoners, residence or employment in an institution for developmental disability, sexual and household contacts of persons with hepatitis B
Hepatitis A	Chronic liver disease, close contacts of high risk/infected persons, MSM, intravenous drug use, travel to developing countries, conditions requiring clotting factor concentrates, laboratory personnel working with hepatitis A virus; household contacts of an adoptee from a high/intermediate prevalence country
Meningococcal	College students in dormitories up to age 21, asplenia, complement deficiency, military recruits, occupational exposure (microbiology) travel to endemic/epidemic areas
Rubella (MMR)	Health care workers without evidence of immunity Nonpregnant women of childbearing age without evidence of immunity
Varicella	Health care workers without evidence of immunity

*see package insert for full prescribing information.

Other vaccines are recommended only for adults with certain risk factors (Table 2). These include hepatitis A, hepatitis B, and meningococcal vaccines among others. Recommendations may vary according to the age of the patient. For example, pneumococcal vaccination is recommended for all adults over age 65 and for younger adults at high risk for infection.

Use of Vaccines in Adults: Recent changes

Tetanus, Diphtheria and Pertussis Vaccines The standard approach to adult vaccination for tetanus has been to give a booster dose of tetanus/reduced-diphtheria vaccine (Td) at 10-year intervals or in the setting of a contaminated wound. This strategy has been highly effective in reducing the risk of tetanus in the U.S. Cases of tetanus are now rare and often occur in patients who are incompletely vaccinated. Diphtheria has largely been eliminated from the U.S.

More recently, it has been recognized that the existing vaccination strategy was not as effective against pertussis as it was against diphtheria and tetanus. In 2008, there were 27,550 reported cases of pertussis, compared to 26 cases of tetanus and no cases of diphtheria.[5] Reported cases of pertussis are the tip of the ice berg, and true rates are expected to be 100 times this number. Approximately 20 percent of these cases of pertussis occurred in adults. In 2012, a pertussis epidemic in the state of Washington resulted in over 2,500 reported cases of disease.[6]

As a result, a new adult vaccine has been developed that contains an acellular form of pertussis. This vaccine, combined with the usual tetanus and diphtheria components, is referred to as Tdap. The ACIP recommends that a single dose of Tdap be given to all adults who have not yet received a dose, *regardless of the interval since their last tetanus vaccine*[7]. After the single dose of Tdap, people should continue to receive Td at 10-year intervals. If a patient presents with a contaminated wound that would normally require Td, it is appropriate to substitute Tdap if he or she has not yet received it. Although only one Tdap vaccine has been FDA-approved in adults over age 65 (Boostrix®), the CDC believes that any Tdap vaccine may be used if the approved product is not available in the clinic[7]. In December 2012, the Advisory Committee on Immunization Practices provisionally recommended that Tdap be given to all pregnant women with every pregnancy regardless of previous Tdap history, with the optimal timing being between 27 and 36 weeks gestation. If Tdap is not administered during the pregnancy, it is provisionally recommended to give it immediately postpartum.

Side effects of the Tdap vaccine are similar to the Td vaccine. Soreness at the site of injection is common. Persons who had unexplained encephalopathy within seven days of a previous pertussis vaccine should be given Td instead of Tdap.

Human Papillomavirus (HPV) Vaccines HPV infection is very common in the U.S., with an estimate 6.2 million new cases of HPV infection per year and 11,000 new cases of cervical cancer. Genital warts caused by HPV are not tracked as a reportable infection, but are clearly common in sexually active adults. The HPV vaccines are composed of virus-like particles and are not live vaccines. Currently, two types of vaccines are available: a bivalent vaccine (HPV2) of the oncogenic strains of HPV (strains 16 and 18) and a quadrivalent vaccine (HPV4) against both the oncogenic strains and strains associated with genital warts (strains 6 and 11). The vaccine will not cure an infection that already exists. For this reason, vaccination strategies are directed at adolescents. However, since this is a relatively new vaccine, it is common for young adults to have missed the vaccine in adolescence and require "catch-up" vaccination.

Vaccination against HPV is more than 90 percent effective in reducing the incidence of early cervical cancers in women, leading to the recommendation that all women should be vaccinated prior to HPV exposure.[8] Specifically, vaccination is recommended in girls and adolescents, but if this is not done it is appropriate to vaccinate women up to age 26. In 2011, the ACIP recommended routine use of the quadrivalent vaccine (HPV4) in males ages 11 through 21 years, preferably in ages 11 or 12.[9] In immunocompromised men (including those with HIV) and men who have sex with men, vaccination should be given up to the age of 26 years if not previously done. Only the quadrivalent vaccine (HPV4) should be used in males.

Pneumococcal Vaccine There are more than 500,000 infections and 40,000 deaths annually in the U.S. caused by *Streptococcus pneumonia*, commonly known as pneumococcus. Pneumococcus is the most common cause of bacterial meningitis in adults.

The pneumococcal vaccine is comprised of capsular polysaccharides from the 23 most prevalent or invasive strains of the bacteria. The vaccine is 60 percent to 70 percent effective in preventing invasive disease, although it is less effective in older and debilitated persons.[3] Note that the vaccine strategy is directed at reducing mortality and invasive disease. Although commonly referred to as the 'pneumonia' vaccine, the pneumococcal vaccine is not as

effective in preventing pneumonia.

Pneumococcal vaccination is recommended for all persons aged 65 or older. It is also recommended for persons with chronic conditions that put them at risk (Table 2), and in the setting of immunosuppression (including cancer, HIV and those on high-dose or long-term steroids). Ideally, persons undergoing splenectomy, cochlear implantation, or initiation of chemotherapy should be vaccinated at least two weeks prior to these interventions.

A newer recommendation is to vaccinate all current smokers and all patients with asthma. Native Americans are no longer considered a high-risk group and this population should be vaccinated in accordance with the general recommendations.

It is not clear whether immunity wanes predictably over time. Currently, revaccination is recommended at age 65 if the recipient got vaccinated earlier. A single booster dose is recommended five years after the first dose for persons with chronic renal failure, nephrotic syndrome, asplenia or immunosuppression.

Zoster (Shingles) Vaccine Shingles occurs in one in four people over their lifetimes. In addition to the morbidity caused by the acute infection, post-herpetic neuralgia can cause long-term pain and disability, especially in the elderly. The shingles vaccine is made from live, attenuated viruses and is approximately 50 percent effective in reducing the risk of shingles. If a vaccinated person gets shingles, there is a 66 percent reduced risk of post-herpetic neuralgia.[10]

Shingles vaccine is recommended for all persons aged 60 and older, *regardless of whether or not they have had a previous episode of shingles*. Persons with chronic medical conditions should be vaccinated, except in selected cases such as immunosuppression. Although the serological response to the disease is lower in the elderly, the vaccine remains effective enough to be recommended. Ideally, the vaccine should be given at or around age 60. Of note, the FDA has approved the vaccine for persons aged 50 and older, but the recommendations for dosing at age 60 were based on the lower risk of zoster in younger patients and uncertainty about the supply of the vaccine.

It is always important to read package directions on proper storage of vaccines, but this is especially important for the shingles vaccine which must be kept frozen until just prior to use. More information can be found by visiting www.cdc.gov/vaccines/recs/storage/guide. The chickenpox (varicella) vaccine is not the same as the shingles vaccine and should not be used to prevent shingles. Patients who have received varicella zoster immune globulin should wait five months before receiving the shingles vaccine because the globulin contains antibodies that could potentially render the vaccine ineffective.

Influenza Vaccine In recent years, there have been several new influenza vaccine products for adults. The traditional vaccine is an injectable product made from inactivated virus, which is approved for all persons over 6 months of age. A live attenuated vaccine is also available that is given as an intranasal spray and is approved in non-pregnant persons aged 2 to 49 years who do not have asthma, chronic disease or immunosuppression.

More recently, a high-dose inactivated vaccine has been approved which provides a stronger immune response in elderly patients, although it is not known yet if this will translate into lower rates of infection. The high-dose, inactivated vaccine is approved in persons aged 65 and older.

Another newer vaccine contains lower levels of antigen than the other injectable vaccines and is given intradermally rather than intramuscularly. The intradermal vaccine produces the same serologic response as other injectable vaccines in younger adults and is approved in aged 18 to 64 years.

None of the newer vaccines have been proven to be more effective than the traditional, inactivated influenza vaccine. However, trials are ongoing to help us understand if there is a special niche for these new products.

All influenza vaccine package inserts contain warnings about immunizing people who are allergic to eggs. The CDC has recently provided specific guidance on how to evaluate whether a history of egg allergy is a contraindication to vaccination against influenza, which can be found at www.cdc.gov/vaccines/ed/imzupdate/downloads/egg-allergy-algorithm.pdf.

The CDC recommends that all persons aged 6 months and older receive an influenza vaccination annually. This includes pregnant women. The efficacy of influenza vaccination has been the subject of much controversy, especially in the elderly. In an analysis of 12.6 million person-seasons of influenza in community-dwelling elderly, Wong and colleagues[11] found that vaccination reduced the combined risk of pneumonia/influenza, hospitalization and all-cause mortality by 14 percent. Considering the severity of these outcomes, including all-cause mortality, vaccination is clearly important in this group.

Hepatitis A Vaccine The hepatitis A vaccine is a highly effective, inactivated vaccine which has contributed to a steep decline in infection, with only approximately 2,000 cases reported in 2009. Almost 100 percent of vaccine recipients respond to the vaccine, resulting in a 94 percent reduction in risk of infection.[3]

Vaccine recommendations have been expanded in recent years to include universal vaccination of children. Adults with risk factors should also be vaccinated (Table 2). Persons who are planning to adopt a child from a country where hepatitis A is common should be vaccinated prior to getting the child. Household contacts of adoptees should also be vaccinated prior to exposure.

Prescreening for antibodies is not required. However, it is considered in persons who used to live in a developing country and those who abuse intravenous drugs. Native Americans and Alaskan Natives are not considered high risk groups.

Hepatitis B Vaccine It is estimated that there are 1 million Americans who are chronically infected with hepatitis B. The highest incidence of acute infection is in adults aged 25 to 45 years, with almost 80 percent of these occurring from high-risk sexual activity or abuse of intravenous drugs. The ACIP currently recommends universal vaccination in childhood, but this recommendation is only two decades old and many adults are not immune.

Hepatitis B vaccine is made from purified antigens and is not a live vaccine. After a vaccine series, approximately 90 percent of recipients make antibodies. The vaccine is 80 to 100 percent effective in preventing disease. Given the falling rates of disease in the U.S., it is not necessary to routinely screen for previous infection prior to vaccination. However, prescreening should be considered in persons born in developing countries or countries with high endemicity, persons who are close contacts of infected persons, men who have sex with men, and injection drug users. Post-screening for antibodies to test for vaccine response is only recommended in selected settings including health care workers, dialysis patients, immunocompromised patients (including HIV), sexual partners of infected people and infants born to infected mothers. Non-responders should undergo a second 3-dose vaccine series, since up to half will become responders. Persistent nonresponse occurs in fewer than 5 percent of recipients. These persons should be carefully tested to make certain they do not already have chronic infection with hepatitis B.

It is currently recommended that adults be vaccinated when they have conditions that are associated with an increased risk of acquiring disease (Table 2). These include people exposed to blood or blood products, and those with behaviors that put them at risk for parenteral or sexual transmission of hepatitis B.

A new recommendation is that diabetics under the age of 60 be vaccinated and that the vaccine be considered in persons over the age of 60.[12] This recommendation recognizes the fact that persons with type 1 or type 2 diabetes have higher rates of infection with hepatitis B than the general population. The reason for this is not clear, but may be associated with reuse of finger stick devices or other infection control issues. Vaccination should take place as soon as possible after the diagnosis of diabetes.

Meningococcal Vaccine The meningococcal vaccine is a conjugated product (Menactra®) that targets four of the five serovars of *Neisseria meningitidis*, a primary cause of meningitis. The older vaccine product (Menimmune®) is not recommended unless the conjugated vaccine is unavailable.

Universal vaccination against meningococcus is recommended in children ages 11 to 12, but many young adults have not been vaccinated. Meningococcal vaccine is recommended in adults up to age 21 if they are living in college dormitories. Vaccination is also recommended for other adults in high risk settings, including residing in military barracks or travel to endemic/epidemic areas (Table 2). If exposure persists, a booster dose is recommended after five years. Vaccination is recommended in patients with functional or anatomical asplenia, or complement deficiency because these conditions significantly impair the body's ability to respond to infection with meningococcus.

Rubella Vaccine Universal vaccination against mumps, measles and rubella (MMR) is recommended in childhood. Because proof of immunity is required in selected cases (health care workers, women of childbearing age), non-immune adults may occasionally require MMR. MMR is a live vaccine and should not be given to pregnant women.

Rabies Vaccine There are one to two deaths each year in the U.S. due to rabies. Pre-exposure vaccination is recommended for high-risk individuals (veterinarians and staff, animal handlers, researchers working with the rabies virus). Long-term travelers to areas where rabies is common should receive pre-exposure prophylaxis if they are likely to come into contact with rabid animals and not have access to appropriate medical care.

Regardless of whether or not previous vaccination has occurred, individuals who are exposed to a rabid animal should wash any wounds immediately and seek immediate medical attention. The local health department is a valuable resource for physicians trying to determine if post-exposure vaccination is required.

For previously unvaccinated people with a potential rabies exposure, a 4-dose series of rabies vaccine is given. Previously, a 5-dose series had been recommended. The change in part is due to a better understanding of the pathogenesis of rabies. Immunosuppressed individuals should still receive 5 doses. Rabies immune globulin should be given at the time of the first dose, preferably infiltrated into and around the wound.

Giving Multiple Vaccines Simultaneously Giving vaccines simultaneously means that two or more vaccine products are given on the same day or at the same office visit. This requires a separate injection site for each product; it is not recommended that different vaccine products be combined into one syringe/vial by the provider. Commercially available combination products that contain multiple vaccines in a single injection undergo rigorous and lengthy trials to ensure that the components are compatible.

When multiple different vaccinations are required for a patient, such as both the influenza and pneumococcal vaccines, the CDC recommends giving the products at the same visit whenever possible, though each at a different injection site.[13] If for some reason all vaccines cannot be given simultaneously, it is important to determine the appropriate interval between products. In general, inactivated vaccines do not significantly blunt the immune response to other inactivated vaccines or live vaccines (Table 3).

According to the CDC, inactivated vaccines can be given simultaneously with other inactivated vaccines or live vaccines. Inactivated vaccines contain particles of virus or bacteria that have been treated, rendering them unable to replicate and cause infection. Examples include Tdap, HPV, pneumococcal vaccine, injectable influenza vaccines, vaccines for hepatitis A and hepatitis B, meningococcal vaccine and rabies vaccine. Moreover, an inactivated vaccine can usually be given any time after a live vaccine is first given. If multiple live vaccines are required, they should be given simultaneously if possible. If this is not possible, they should be spaced at a minimal interval time period of four weeks.

It is recommended by the FDA that each package insert specifically state whether the vaccine has been evaluated for compatibility with any other vaccine(s). If the vaccine has not been evaluated against any other vaccination product, then that is to also be clearly stated.[14] Providers should review the package inserts for specific information on each product. If no studies have been done, then utilizing CDC general recommendations, live vaccines should be given at least four weeks apart from each other, while inactivated vaccines can likely be given safely at any time, unless otherwise indicated.

Studies of simultaneous vaccine administration have focused largely on serological response, rather than on the efficacy of the products in preventing disease. Controversy may exist over whether a blunted serological response is an indication to avoid simultaneous administration of vaccine products. For example, Zostavax© was initially shown to have decreased immune response when given with Pneumovax 23, but this was improved if the vaccines were given at least four weeks apart.[15] A subsequent study showed that simultaneous use of these two vaccines did not result in an increased risk of shingles.[16] Thus, the CDC-ACIP recommendations do not suggest avoiding simultaneous vaccination, whereas the FDA mandated package insert (last updated in 2009) recommends considering that these two products be spaced four weeks apart. Furthermore, the CDC-ACIP would recommend giving multiple vaccines simultaneously to improve the probability of being fully vaccinated at what is deemed an appropriate age.[13]

Table 3. CDC Recommendations on Giving Multiple Vaccine Products

Antigen combination	Recommended minimum interval between doses
Two or more inactivated*	Simultaneously, or any interval between doses
Inactivated and live	Simultaneously, or any interval between doses
Two or more live injectables**	Simultaneously, or at 28 days minimum interval

* Some experts suggest a 28-day interval between tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine and tetravalent meningococcal conjugate vaccine if they are not administered simultaneously.

**Live oral vaccines can be given simultaneously or at any interval before or after inactivated or live injectable vaccines

Strategies to Improve Adult Vaccination Rates Several approaches have been used to improve vaccination rates in adults. Vaccines recommended for large populations, such as the influenza vaccine, are now available in many pharmacies or workplaces without a prescription. Public education campaigns have been helpful. In health care environments, some employers have made selected vaccinations, including

influenza vaccination, a condition of employment.

Although the above efforts have been helpful, adult patients still rely heavily on their primary care physicians to provide appropriate vaccinations. Successful strategies for clinics have included using standing orders for vaccinations, using the electronic health record to notify physicians when patients are in need of vaccination, or sending reminders to patients that vaccines are due or recommended.[17] Some practices have had success with updating vaccines at an annual visit for a physical examination, whereas others have found that patients are not scheduling annual visits and are thus missing out on vaccines. Regardless of the approach, it is recommended that practices assess their compliance with vaccines on a regular basis.

Summary

Vaccines are a critical part of the care of the adult patient. They provide protection from fatal or debilitating diseases at a fraction of the cost of treating these preventable diseases. In recognition of this, Healthy People 2020 has made improved adult vaccine coverage a national goal. New vaccines and the changing epidemiology of infectious diseases in adults have led to revisions in the vaccination schedule. This has added a layer of complexity to medical practice, which can be addressed through systematic efforts to improve vaccine coverage. Clearly, appropriate adult vaccination should be a high priority for health care providers.

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CHAPTER 12

Pregnancy and Vaccines

By Adrianne Racek, MSIV and Peter Van Eerden, MD

Abstract:
Vaccination during pregnancy is important for both women and their offspring; however, vaccination rates can be improved, and health care providers are in a unique position to be able to do so. This article summarizes current information on vaccinations and strategies for addressing patients' concerns related to immunization during pregnancy. Particular attention is given to influenza and tetanus, diphtheria and pertussis vaccinations.

Introduction

Pregnancy is a unique time for women. Their provider appointments involve more than just their own health care needs, but also those of their future children. Vaccination can serve as protection for more than one person, as preventive medicine is important for both maternal and fetal health. The infant's immune system continues to develop after birth; thus, passive immunity from the mother is imperative in the first six months of life in order for newborns to adapt safely to their environment. This article summarizes current information on vaccinations and strategies for addressing patients' concerns related to immunization during pregnancy. Particular attention is given to influenza and the tetanus, diphtheria and pertussis vaccinations.

Clinical Scenario

A 24-year-old primigravida obstetric patient is meeting you in your office for the first time. She states she normally receives an annual influenza vaccination, but was thinking that she may not receive the immunization this year. She is concerned about what effects the vaccine might have on the fetus. She states she has no medical problems and takes no medications, so she isn't worried about getting sick. How would you address the patient's concerns? What is the current evidence regarding this topic?

Influenza Immunization in Pregnancy

Pregnant women are a vulnerable population with regard to influenza. Influenza vaccination is therefore an essential component of prenatal care since pregnant women are at increased risk of serious illness from influenza. Pregnant women have experienced excess mortality during the influenza pandemics of 1918, 1957 and most recently during the 2009 pandemic.[1]

In response to the risk posed by influenza, seasonality is important. If your patient will be pregnant at any time between October and May in the U.S., she should receive the inactivated influenza vaccine according to both the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) and the American College of Obstetricians and Gynecologists' (ACOG) guidelines.[1,2] Seasonal influenza vaccination rates in pregnancy in recent years, however, have been as low as 15 to 25 percent. The H1N1 vaccination rate was only 38 percent in 2009. As providers, we have the potential to be influential in increasing these rates, and there is room for significant improvement. One of the major barriers to vaccine acceptance is overall lack of knowledge about vaccine benefit. Something as simple as a chart prompt for providers increases the frequency of discussion regarding influenza guidelines.[1]

ACOG recommends that every pregnant and non-pregnant woman receive annual inactivated influenza vaccination. Multiple studies show that the most effective way to increase influenza immunization rates among pregnant women is for the physician to directly recommend the flu shot. The following is a script for consideration:

> "I strongly recommend you get the flu shot today. I offer the influenza vaccine to all of my pregnant patients and to women who are considering getting pregnant. The

vaccine is safe and effective for pregnant women. The risks of getting sick with the flu are far greater for a pregnant woman and her baby than the possibility of having a complication from the vaccine. The flu shot will protect you as well as your baby in the first 6 months of life from getting the flu. Your family members who have contact with your newborn also should be vaccinated."[3]

Another effective way to increase influenza immunization rates is to implement standing orders within your practice. Sample orders can be viewed at www.immunize.org/standing-orders. If your patient does not accept your recommendation, continue to offer her the flu shot on subsequent office visits.

There are a few additional key points which are prompted by the clinical scenario presented above. First and foremost, live vaccines are contraindicated in pregnancy, so ideally, they should be administered before pregnancy due to the theoretical risk of fetal infection from the live virus.[4] That being said, inadvertent vaccination of a pregnant woman with live, attenuated influenza vaccine (LAIV) has not been shown to be harmful and is not an indication for pregnancy termination.[5] In general, make sure to administer any necessary live vaccines in the immediate postpartum period. Women who receive live attenuated influenza vaccine before pregnancy should defer pregnancy for at least 28 days. The nasal spray vaccine is made with the live flu virus and should not be given to pregnant women. This vaccine (FluMist®) is safe for women after they have given birth, even if they are breastfeeding, and there is no risk of spreading vaccine virus to family members. Most vaccines, including live vaccines, are able to be administered to household contacts of pregnant women so family members who are not pregnant should be able to take the nasal spray or FluMist® in most situations.[6]

As noted, pregnant women should only receive the inactivated influenza vaccine. Patients can be reassured that no study to date has shown any type of adverse consequence of the inactivated influenza vaccine in pregnant women or their fetuses. Thimerosal, a type of mercury which is used in trace amounts as a preservative in some vaccines, has not been associated with autism in any evidence-based study. For this reason, the ACIP does not indicate a preference for thimerosal-containing or thimerosal-free vaccines for any specific patient population, including pregnant women.[1] Women who are concerned about exposure to these preservatives can be given the single dose influenza vaccine that contains a mercury-free preservative.

There is increased maternal morbidity and mortality for pregnant women during the influenza season. In some reports, women were more likely to have increased medical visits or longer hospital stays for respiratory illnesses during pregnancy than when not pregnant. These discrepancies were most apparent in the third trimester. Additionally, hospital admission was more pronounced for pregnant women with comorbidities.[1] The benefits of preventing life-threatening illnesses in a mother and child far outweigh any potential risks of the vaccine.

It should be kept in mind that maternal immunity is the only mode of influenza protection for newborn babies, as the influenza vaccine is not approved for use in infants less than 6 months of age. In this regard, some protection from vaccination during pregnancy is transferred to the baby, helping to protect the child from illness during the first months of life.[1] In a prospective, randomized trial, infants whose mothers received influenza vaccinations had fewer cases of laboratory-confirmed influenza as well as fewer cases of respiratory illness with fever.[7]

Tdap Immunization in Pregnancy

Another common concern among providers with particular implications for pregnancy is the rising rate of pertussis. Pertussis, or "whooping cough", continues to be endemic in the U.S. with 27,550 cases of pertussis reported in 2010.[5] Due to the increased incidence of pertussis in the U.S., ACIP updated guidelines on tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) and approved its use during pregnancy in the U.S. in 2011.[4,8,9] The updated guidelines were designed to reduce the burden of pertussis overall in the population and reduce the risk of transmission to infants. ACOG, after a careful review of data including safety factors, encourages women's health care providers to implement a Tdap vaccination program for pregnant women who have not received Tdap. ACOG specifically recommends administration during the third trimester or after 20 weeks of gestation. The CDC and ACOG are not explicit in stating it can or cannot be started in the first trimester (if they have never received Tdap), but it seems that it is the pertussis component in the Tdap they are suggesting for greater than 20 weeks. Women who have gone greater than 10 years without a tetanus booster should be given Tdap, and physicians may consider Tdap if five years have elapsed since a tetanus booster for wound management. More recently, in December 2012 the ACIP voted to recommend Tdap for pregnant women with every pregnancy irrespective of previous Tdap history. This should be incorporated into the Tdap immunization program for all pregnant women. To maximize the maternal antibody response and passive antibody transfer to the infant, optimal timing for Tdap administration is between 27 and 36 weeks gestation. For women not previously

vaccinated with Tdap, if Tdap is not administered during pregnancy, Tdap should be administered immediately postpartum. ACOG and ACIP also stress the importance of immunizing individuals who will spend time with the infant and they ideally should be vaccinated two weeks before exposure.[4,9]

Travel Immunization in Pregnancy

There are specific travel considerations. First, immunizations prior to pregnancy are recommended, since several are live vaccines. However, since around 50 percent of pregnancies are unplanned, it is common to encounter patients who did not have the opportunity to receive immunizations before conception, much less prior to travel. If risk of disease exposure is high, the benefits of vaccination during pregnancy usually outweigh the risks. Second, there are a number of travel-related infectious diseases that are not vaccine-preventable and need to considered as a part of good pre-travel consultation. Hepatitis E is such a potential threat and is of particular concern in pregnant women. As hepatitis E is transmissible through food and water, pregnant patients should be especially cognizant of what they are consuming to reduce their risk for hepatitis E exposure. Food and water risk significantly varies by country; therefore, location-specific assessment should occur prior to travel. Third, pregnant travelers should refrain from traveling to malaria-endemic areas. Malaria chemoprophylaxis is

Table 1. Immunization & Pregnancy (Adapted from the CDC)

Vaccine	Before Pregnancy	During Pregnancy	After Pregnancy	Type of Vaccine	Route
Hepatitis A	Yes, if at risk	Yes, if at risk	Yes, if at risk	Inactivated	IM
Hepatitis B	Yes, if at risk	Yes, if at risk	Yes, if at risk	Inactivated	IM
Human Papillomavirus (HPV)	Yes, if 9 through 26 years of age	No, under study	Yes, if 9 through 26 years of age	Inactivated	IM
Influenza TIV	Yes	Yes	Yes	Inactivated	IM, ID (18-64 years)
Influenza LAIV	Yes, if less than 50 years of age and healthy; avoid conception for 4 weeks	No	Yes, if less than 50 years of age and healthy; avoid conception for 4 weeks	Live	Nasal spray
MMR	Yes, avoid conception for 4 weeks	No	Yes, give immediately postpartum if susceptible to rubella	Live	SC
Meningococcal: -polysaccharide -conjugate	If indicated	If indicated	If indicated	Inactivated	SC, IM
Pneumococcal Polysaccharide	If indicated	If indicated	If indicated	Inactivated	SC, IM
Tetanus/Diphtheria Td	Yes, Tdap preferred	Yes, Tdap preferred if 20 weeks gestational age or more	Yes, Tdap preferred	Toxoid	IM
Tdap, 1 dose only	Yes, preferred	Yes, preferred	Yes, preferred	Toxoid/ inactivated	IM
Varicella	Yes, avoid conception for 4 weeks	No	Yes, give immediately postpartum if susceptible	Live	SC

necessary in these regions and there is not a vaccine that is designed for malaria protection. Many of the anti-malarial medications are safe to use in pregnancy. However, avoidance of these areas while pregnant is strongly encouraged.[5]

Immunization and Lactation Considerations

Most immunizations are considered safe while breastfeeding. There are no lactation precautions when administering Tdap, inactivated or live virus influenza, measles, mumps, rubella (MMR), hepatitis B, inactivated polio and varicella vaccines to postpartum women who wish to breastfeed. There are a few vaccines where there is limited data to support recommendations such as hepatitis A, Japanese encephalitis, pneumococcal, rabies, typhoid and tuberculosis vaccines. However, the CDC advises administering any of these vaccines while breastfeeding if the risk of disease exposure is high. Yellow fever and smallpox vaccines should be avoided while women are nursing.[10]

Comprehensive List of Immunizations

A comprehensive chart adapted from the CDC outlines immunizations before, during and after pregnancy and can be found in Table 1. It is also available online at www.cdc.gov/ vaccines/pubs/downloads/f_preg_chart.pdf. It is a helpful resource for health care teams and patients. Providers may want to consider displaying these in their examination rooms to facilitate conversation.[11,12] All vaccines should be fully documented in the patient's medical record.[1,2] Remember that federal law requires that each patient receive a vaccine information statement (VIS) before receiving a vaccine. To find VIS in more than 35 languages, visit www.immunize.org/vis.

Conclusion

The clinical scenario presented at the beginning is a common encounter for health care providers, and we encourage open dialogue to be initiated at these office visits. The young woman in our example should be offered the influenza vaccination because there is increased morbidity and mortality associated with influenza for pregnant women as well as their offspring. The greatest barrier to vaccinations is lack of education, and health care providers are in a unique position to help inform their patients. It is important to continue the educational process and to continue to offer immunizations even when patients have declined in the past.

All pregnant women should receive appropriate vaccinations during their pregnancy. Appropriate vaccination prior to pregnancy is the ideal time for physicians to ensure that women are up-to-date on all of their immunizations. However, vaccinations should not be withheld if they are indicated simply because a woman is pregnant. Pregnancy is a time when vaccination can help to protect both a pregnant woman and her growing baby. The benefits of vaccinating pregnant women usually outweigh potential risks when the likelihood of disease exposure is high, when infection would pose a risk to the mother and fetus and when the vaccine is not likely to cause harm.[13]

ACOG's immunization web page, Immunization for Women, found at www.immunizationforwomen.org, is an excellent resource for health care providers and patients to find up-to-date information about immunizations and vaccine-preventable diseases. The site provides information on updated immunization recommendations for adult and adolescent females, specific information for pregnant and breastfeeding women and information on how to set up and expand an office-based immunization program.

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CHAPTER 13

Vaccine-Preventable Diseases and Vaccination Rates in South Dakota

By Lon Kightlinger, PhD

Abstract:
Vaccine-preventable diseases have historically caused much illness and death in South Dakota. Sixty-seven diphtheria deaths were reported in 1892 and 1,017 polio cases were reported at the peak of the polio epidemic in 1952. As vaccines have been developed, licensed and put into wide use, the rates of diphtheria, polio, measles, smallpox and other diseases have successfully decreased leading to control, statewide elimination or eradication. Other diseases, such as pertussis, have been more difficult to control by vaccination alone. Although current vaccination coverage rates for South Dakota's kindergarten children surpass the Healthy People 2020 targets of 95 percent, the coverage rates for 2-year-old children and teenagers are below the target rates. Until vaccine-preventable diseases are eradicated globally, we must vigilantly maintain high vaccination coverage rates and aggressively apply control measures to limit transmission when diseases do occur in South Dakota.

History of Vaccine-Preventable Diseases in South Dakota

Vaccines are among the most important means of preventing disease and protecting the public's health.[1] In 1892, during the early years of South Dakota statehood, the State Board of Health stated, "in South Dakota the most dangerous contagious diseases named in the order of importance as causes of deaths are diphtheria, scarlet fever, smallpox, typhoid fever, whooping cough and measles."[2] In the same report, D. Fowler, superintendent of the Board of Health, affirmed that "diphtheria has been generally malignant" with 67 deaths in the state. To prevent diphtheria in this pre-vaccination era, the Board of Health could only recommend patient isolation and airing of the sick room. One-hundred years ago the 1912-1914 Board of Health's morbidity report includes one smallpox, 13 polio, 14 tetanus, 37 diphtheria, 45 measles and 47 whooping cough deaths in South Dakota.[3] During the past century, as vaccines were developed and became broadly used, these disease rates have dramatically decreased, undeniably alleviating much suffering and death in the state.

Since 1950 several vaccine-preventable diseases have been largely controlled or eliminated in South Dakota, namely smallpox, polio, diphtheria, tetanus, rubella, measles, mumps and *Haemophilus influenzae* type b (Hib). Table 1

Box 1 and 2

Routine Vaccines by Age Group

0-6 Years of Age	7-18 Years of Age
• Diphtheria	• Diphtheria
• Hepatitis A	• Hepatitis A
• Hepatitis B	• Hepatitis B
• Hib	• Human papillomavirus
• Influenza	• Influenza
• Measles	• Measles
• Mumps	• Meningococcal
• Pertussis (whooping cough)	• Mumps
• Pneumococcal	• Pertussis
• Polio	• Polio
• Rotavirus	
• Rubella	
• Tetanus	
• Varicella (chickenpox)	

School Entry Vaccinations in South Dakota

Immunizations for school or early childhood programs: **polio, diphtheria, pertussis, measles, rubella, mumps, tetanus and varicella.**[15]

Immunizations for public or private postsecondary education institutions: **2 doses of measles, rubella and mumps (MMR).**[16]

Table 1. Vaccine-Preventable Disease Cases, South Dakota, 1950-2011.[20]

Highlights indicate year vaccine was licensed in the U.S. (diphtheria, pertussis, smallpox and tetanus licensed before 1950).

YEAR	Diphtheria	Hib*	Hepatitis A	Hepatitis B	Measles	Meningo coccal	Mumps	Pertussis	Polio	Rubella	Smallpox	Tetanus
1950	17	nr	nr	nr	1316	nr	nr	189	298	nr	6	nr
1951	9	nr	nr	nr	731	5	nr	103	127	nr	1	0
1952	5	nr	nr	nr	1016	6	nr	61	1017	nr	2	0
1953	2	nr	nr	nr	532	27	nr	44	225	nr	0	1
1954	13	nr	313	nr	765	15	nr	119	114	nr	0	2
1955	45	nr	387	nr	424	18	nr	55	76	nr	0	nr
1956	15	nr	177	nr	650	6	nr	30	29	nr	0	nr
1957	10	nr	36	nr	628	18	nr	26	42	nr	0	nr
1958	21	nr	na	nr	na	na	nr	na	15	nr	0	nr
1959	4	nr	na	nr	na	na	nr	na	11	nr	0	nr
1960	10	nr	na	nr	79	9	nr	14	7	nr	0	nr
1961	5	nr	193	nr	153	7	5	15	4	nr	0	3
1962	22	nr	111	nr	462	8	136	14	2	nr	0	0
1963	14	nr	150	nr	111	4	24	9	1	nr	0	2
1964	3	nr	135	nr	160	5	31	3	0	0	0	2
1965	8	nr	24	nr	116	4	46	3	0	0	0	0
1966	4	nr	14	0	41	6	26	1	0	2	0	0
1967	1	nr	14	0	59	7	na	2	0	3	0	1
1968	0	nr	82	0	4	5	1	9	0	0	0	1
1969	4	nr	88	0	51	1	0	1	0	0	0	0
1970	7	nr	24	0	109	1	57	1	0	4	0	1
1971	26	nr	191	2	223	6	313	8	0	98	0	0
1972	17	nr	149	2	12	3	123	3	0	13	0	0
1973	7	nr	233	1	3	6	21	7	0	24	0	0
1974	0	nr	164	4	31	2	3	3	0	27	0	0
1975	0	nr	39	8	353	0	6	1	0	17	0	0
1976	3	nr	89	5	5	3	11	4	0	21	0	1
1977	0	nr	34	12	75	6	59	1	0	89	0	0
1978	0	nr	242	14	0	4	11	11	0	112	0	1
1979	0	22	207	19	2	4	11	0	0	5	0	0
1980	0	27	72	8	0	6	3	3	0	2	0	0
1981	0	40	38	8	0	10	1	2	0	0	0	0
1982	0	50	14	17	0	11	1	6	0	1	0	0
1983	0	31	187	17	0	4	0	8	0	0	0	0
1984	0	35	206	26	0	6	0	9	0	0	0	1
1985	0	44	313	30	0	5	0	11	0	0	0	0
1986	0	31	171	19	0	8	1	14	0	0	0	1
1987	0	48	15	11	0	4	89	4	0	0	0	0
1988	0	32	30	9	0	6	1	5	0	0	0	0
1989	0	54	27	10	0	9	0	4	0	0	0	0
1990	0	54	493	8	23	3	0	2	0	0	0	0
1991	0	7	837	9	0	3	2	1	0	0	0	0
1992	0	4	215	5	0	1	0	17	0	0	0	0
1993	0	2	18	0	0	7	0	8	0	0	0	0
1994	0	2	39	4	0	9	0	26	0	0	0	0
1995	0	1	99	2	0	11	0	12	0	0	0	0
1996	0	1	43	5	0	10	0	4	0	0	0	0
1997	1	3	27	1	8	6	0	5	0	0	0	0
1998	0	1	40	4	0	9	0	8	0	0	0	1
1999	0	4	10	1	0	11	0	8	0	0	0	0
2000	0	1	3	2	0	6	0	11	0	0	0	0
2001	0	0	3	1	0	5	0	5	0	0	0	0
2002	0	1	3	3	0	2	0	8	0	0	0	0
2003	0	1	0	4	0	1	0	7	0	0	0	0
2004	0	0	4	1	0	4	0	169	0	0	0	0
2005	0	0	1	8	0	4	0	183	0	0	0	0
2006	0	0	9	5	0	4	296	26	0	0	0	0
2007	0	0	6	7	0	3	6	60	0	0	0	0
2008	0	0	4	0	0	3	1	67	0	0	0	0
2009	0	0	4	2	0	4	1	45	0	0	0	0
2010	0	0	1	2	0	0	2	29	0	0	0	0
2011	0	1	2	2	0	3	0	37	0	0	0	0
Total	273	497	6030	298	8142	364	1,288	1,541	1,968	418	9	18

*Hib: *Haemophilus influenzae* type b na: not available nr: not reported

Figure 1. Smallpox cases, South Dakota 1913-2011

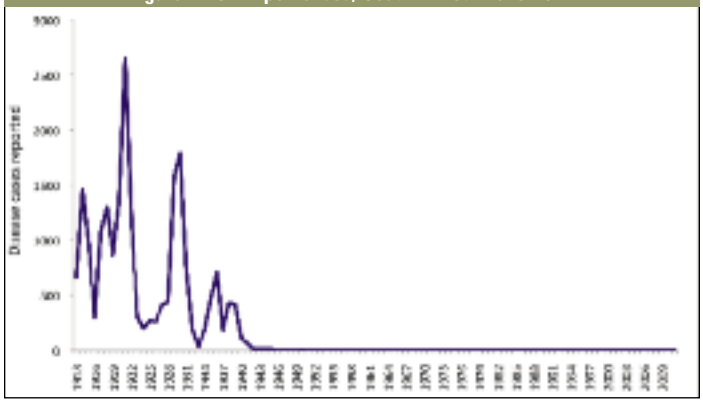


Figure 2. Polio cases, South Dakota 1913-2011

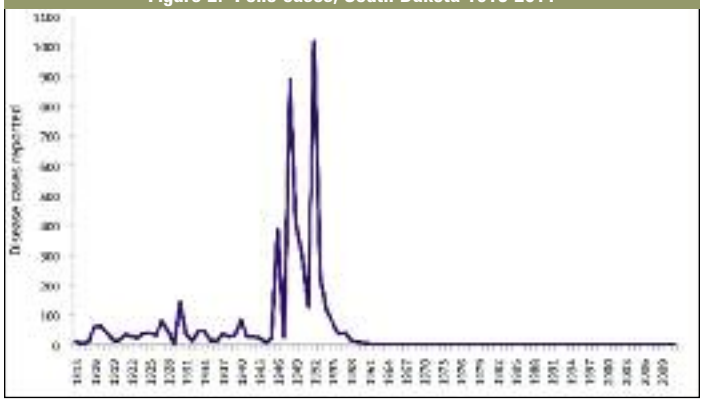
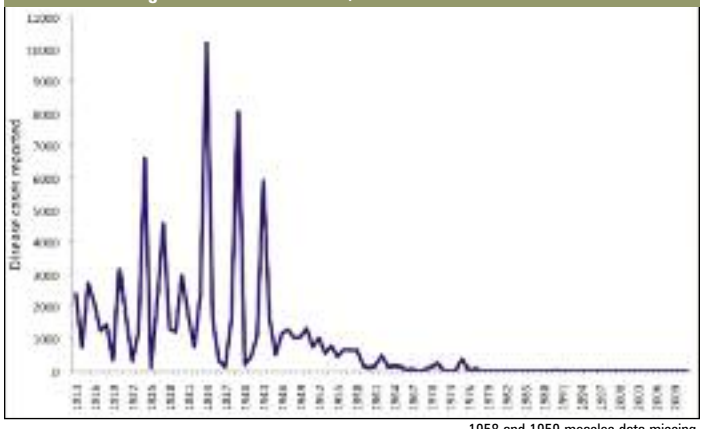


Figure 3. Diphtheria cases, South Dakota 1913-2011

Figure 4. Measles cases, South Dakota 1913-2011



1958 and 1959 measles data missing

shows disease cases reported since 1950 and the year the vaccines were licensed in the U.S. or first used: hepatitis A (1995), *Haemophilus influenzae* type b (1985), hepatitis B (1981), meningococcal invasive disease (1974), rubella (1969), mumps (1967), measles (1963), polio (1955), pertussis, also called whooping cough (1940s), diphtheria (1920s), tetanus (1920s) and smallpox (1796).

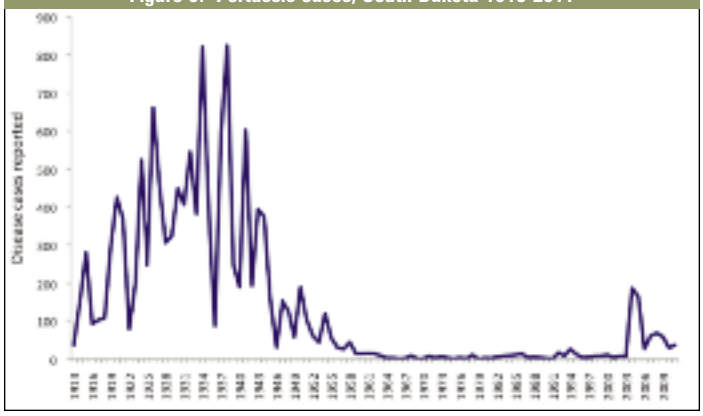
Smallpox peaked in South Dakota in 1921 with 2,653 reported cases (Figure 1). After periodic outbreaks during the 1920s and 1930s, smallpox vaccine came into wide use and cases decreased. South Dakota's last two recorded cases of smallpox occurred in 1952 in residents of Day and Fall River counties.[4] Twenty-five years later, in 1977, the last naturally acquired smallpox case occurred in Somalia and in 1980 the World Health Organization declared global smallpox eradication.[5] In 1952, three years prior to the availability of the polio vaccine, 1,017 cases of polio were reported in South Dakota (Figure 2). Following licensure of the polio vaccine in 1955, cases decreased markedly, with South Dakota's last polio case reported in 1963 in a Minnehaha County resident. Polio is now targeted for global eradication.[6] Although diphtheria toxoid vaccine was developed in the 1920s, it did not come into wide use until the 1940s. During the 1950s, 141 cases of diphtheria were reported in the state (Figure 3). South Dakota's last case of membranous pharyngitis diphtheria was reported in 1997.[7] Prior to the 1960s, thousands of measles cases were reported in periodic wave outbreaks (Figure 4). Although we have not seen measles and rubella in over a decade in South Dakota, the potential for reintroduction and local transmission exists among groups of people who are not vaccinated and not immune. Measles is theoretically eradicable using current vaccine technology, notwithstanding international political obstacles.[8]

Although some vaccine-preventable diseases, such as pertussis, hepatitis A and B and mumps have been drastically reduced, they have been more difficult to control and eliminate. South Dakota was mumps-free for a 14-year period, 1992 through 2005, but an outbreak in 2006 revealed our population's susceptibility to this person-to-person transmissible viral disease, even in a highly vaccinated population. Pertussis persists as an ongoing threat,

despite relatively high vaccination rates. Over the past century South Dakota has only experienced one pertussis free year, 1980 (Figure 5). In fact, in 2005 we reported our highest number of cases since 1950. In 2012 a national resurgence of pertussis is an urgent call to action.[9] Varicella, or chicken pox, is in the early phase of control by immunization, with 67 South Dakota cases reported in 2011.

The dramatic success of vaccination in South Dakota is shown by comparing state disease case reports in the pre- and post-vaccination eras. Table 2 compares South Dakota case counts during the 10 years before vaccine licensure with the 10 years after licensure for polio, measles and hepatitis A. For example, hepatitis A was licensed in 1995 and during the 10 years prior, 1985 through 1994, there were 2,158 cases reported in South Dakota. During the immediate post-vaccination decade, 1996 through 2005, there were 134 hepatitis A cases reported, which is a 94 percent decrease from the pre-vaccine decade. Hepatitis A continued to drop with only 26 total cases reported during the seven years since 2005. Likewise, polio dropped 97 percent in the decade after the vaccine was licensed and measles decreased 86 percent.

Figure 5. Pertussis cases, South Dakota 1913-2011



1958 and 1959 pertussis data missing

Figure 6. Estimated Vaccination Coverage Rates (percentage) for 4:3:1 Series* Among Children 19 to 35 Months of Age, South Dakota and United States, National Immunization Survey 1994-2011[13]

*≥ 4 doses of DTaP, ≥ 3 doses of poliovirus vaccine and ≥ 1 doses of MMR vaccine.

Table 2. Comparison of Selected South Dakota Vaccine-Preventable Disease Cases in Pre- and Post-Vaccination Eras: Polio, Measles and Hepatitis A

Disease	Year vaccine licensed	Cases reported during 10 years prior to vaccine licensure	Cases reported during 10 years after vaccine licensure	Percent Change
Polio	1955	3,509	111	-97% decrease
Measles	1963	5,440	778	-86% decrease
Hepatitis A	1995	2,158	134	-94% decrease

Current Vaccination Coverage

There are currently 17 infant, childhood and adult diseases that are prevented by vaccination and for which vaccines are routinely available in South Dakota (Box 1 and 2).[10] Other vaccines licensed in the U.S. for special circumstances of travel, exposure or occupation include adenovirus, anthrax, Japanese encephalitis, rabies, smallpox, tuberculosis, typhoid and yellow fever.

The most widely-used tool to measure vaccination coverage is the National Immunization Survey (NIS), which samples by random-digit dial telephone household survey and vaccine-provider verification to monitor vaccination coverage in all states.[11, 12] One of the long-standing measures of vaccination coverage is the percent of children 19 to 35 months of age who are fully immunized with the 4:3:1 series of seven vaccine antigens, which includes 4 or more doses of diphtheria, tetanus, pertussis (DTaP), 3 or more doses of polio vaccine, and 1 or more doses of measles, mumps and rubella (MMR) vaccine. Figure 6 shows the 4:3:1 coverage rates for South Dakota and the U.S. since 1994.[13] South Dakota 4:3:1 coverage rates are typically better than the national rates, but were below the national rate in five of the past 18 survey years.

Current vaccination coverage rates, national rankings and Healthy People 2020[14] targets for children, teenagers and adults are shown in Table 3. The 2011 NIS coverage rates for South Dakota children 19 to 35 months of age surpassed the Healthy People 2020 targets of 90 percent for polio, Hib and hepatitis B vaccines,

Table 3. Vaccination Coverage Rates, State Ranking and Healthy People 2020 Targets for Children, Teenagers and Adults, South Dakota and United States, 2011

Vaccine and age group	United States	South Dakota	South Dakota's rank	2020 target[14]
Children 19-35 months[11]				
Diphtheria-Tetanus-Pertussis (DTaP) ≥ 3 doses	95.5%	92.9%	42nd	--
Diphtheria-Tetanus-Pertussis (DTaP) ≥ 4 doses	84.6%	75.8%	48th	90%
Polio ≥ 3 doses	93.9%	92.9%	37th	90%
Measles-Mumps-Rubella (MMR) ≥ 1 dose	91.6%	89.2%	11th	90%
Haemophilus influenzae b ≥ 3 doses	94.0%	91.1%	42nd	90%
Pneumococcal (PCV) ≥ 3 doses	93.6%	88.3%	48th	--
Hepatitis B birth dose	68.6%	70.9%	26th	85%
Hepatitis B ≥ 3 doses	91.1%	92.1%	17th	90%
Hepatitis A ≥ 2 doses	52.2%	29.3%	50th	60%
Varicella ≥ 1 doses	90.8%	84.8%	49th	90%
4:3:1 series*	82.6%	74.9%	47th	--
Kindergarten children[17]				
Diphtheria-Tetanus-Pertussis (DTaP) ≥ 4 doses	95.2%	97.5%	10th	95%
Polio ≥ 3 doses	95.9%	97.2%	14th	95%
Measles-Mumps-Rubella (MMR) ≥ 2 doses	94.8%	97.4%	7th	95%
Hepatitis B ≥ 3 doses	96.6%	95.4%	29th	95%
Varicella 2 doses	93.2%	95.5%	9th	95%
Teenagers 13-17 years[12]				
Td or Tdap ≥ 1 doses since age 10	78.2%	54.4%	48th	80%
Meningococcal ≥ 1 dose	70.4%	37.4%	48th	80%
Human papillomavirus ≥ 3 doses, female	34.8%	50.1%	3rd	80%
Varicella ≥ 2 doses	68.3%	37.1%	49th	90%
Adults aged 65 years and over[18]				
Influenza in past year	61.3%	68.3%	4th	90%
Ever had a pneumonia vaccination	70.0%	67.1%	42nd	90%

*≥ 4 doses of DTaP, ≥ 3 doses of poliovirus vaccine, and ≥ 1 doses of MMR vaccine

and ranked in the top half of state rankings for MMR and hepatitis B vaccinations. However, rates and rankings for South Dakota children in this age group are lagging for DTaP, pneumococcal (PCV), hepatitis A and varicella vaccinations.

School vaccination requirements are important in preventing infectious diseases in children and disease transmission in the community (box).[15,16] Annual vaccination coverage assessments of children entering kindergarten are done by all states. For South Dakota children enrolled in kindergarten for the 2011-12 school year, vaccination rates exceeded the 95 percent coverage Healthy People 2020 targets for all assessed vaccinations and South Dakota ranked in the top third for every vaccine, except hepatitis B.[17] For this same cohort of kindergarteners 30 students had medical exemptions from vaccinations and 120 students had religious exemptions.

The 2011 NIS assessment shows vaccine coverage rates for South Dakota teenagers, 13 to 17 years old, falling short of the Healthy People 2020 targets and ranking in the bottom half nationally.[12] The exception is female human papillomavirus vaccine, for which South Dakota ranked third in the nation for coverage.

Childhood vaccination coverage rates within South Dakota vary by clinic. A snapshot survey at mid-year 2012 of the 85 largest immunization clinics in South Dakota (with 20 or more clients per clinic), which serve 88 percent of the state's children in the 19 to 35 month age group, revealed wide variation of clinic coverage rates for the 4:3:1 series.[19] Of these 85 clinics, only 38 clinics (45 percent) achieved an 80 percent coverage rate for the 4:3:1 series, whereas 20 clinics (24 percent) accomplished less than 70 percent coverage rate. South Dakota clinic coverage rates for the 4:3:1 series ranged from a high of 97.3 percent to a low of

42.1 percent. There is much room for improvement at the front-line clinic level.

The prevention and control of vaccine-preventable diseases depend not only on vaccinating individuals and maintaining high rates of population vaccination coverage, but also vitally important are alert and knowledgeable health care workers, proficient laboratory diagnosis, a robust disease surveillance system to detect cases and outbreaks of disease, and appropriate and aggressive control measures to halt disease transmission. These control measures include patient isolation, exclusion from school or work, antibiotic prophylaxis, vaccination of contacts, and quarantining susceptible persons away from infectious individuals.

Disease prevention, control, elimination and eradication require committed vigilance and altruistic collaboration among parents, children, community members, public health, medical health care and the civic infrastructure. A societal memory of not-too-distant past suffering and death due to vaccine-preventable diseases is essential in maintaining a knowledgeable and vigilant public health and medical infrastructure. We must not only remember past challenges and successes in disease control, but also push forward with research, development and application of new vaccines that will prevent, control, eliminate and eradicate more diseases. This is public health's societal obligation.

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CHAPTER 14

The Impact of Vaccination Among American Indians – Progress and Challenges

By Amy V. Groom, MPH

Background

The burden of infectious diseases is well known to the American Indian and Alaska Native (AI/AN) people. The immigration of European settlers to the Americas led to the exacerbation of existing diseases in the Americas, such as tuberculosis, and the introduction of new diseases, such as smallpox, measles, pertussis and new influenzas, which had a devastating impact on AI/AN people who had little or no immunity to these foreign organisms.[1] The disproportionate impact of infectious diseases on AI/AN people has continued since that time, with AI/AN populations even today suffering a much higher burden of infectious diseases than other race groups.[2,3]

The Northern Plains, encompassing the states of North Dakota, South Dakota, Nebraska, Montana and Wyoming, are home to over 30 tribal groups[4] and the impact of infectious diseases on these tribal populations has been well documented. Historical documents from the Hudson's Bay company, which established fur trading posts in the Northern Plains of the U.S. and Canada starting in 1774,[5] documented a series of infectious disease epidemics, some of which were so severe they contributed to the extinction of certain tribal groups.[1,6] In current times, AI/AN people in the Northern Plains and elsewhere continue to experience higher numbers of deaths and hospitalizations from infectious diseases and have an overall lower health status and higher prevalence of chronic health conditions than the general U.S. population,[2,3, 7-16] likely due in part to the ongoing challenges they face in accessing health care.[7,17,18]

Vaccine-preventable Disease

The dramatic declines in vaccine-preventable diseases in the U.S. and worldwide are a major public health achievement,[19] and the contributions of the AI/AN population to these declines have been significant; many tribes participated in the development of several pediatric and adult vaccines which are now routinely used around the world.[20] Yet some of the gains in the control of vaccine-preventable diseases have been offset by difficulties in access to vaccines for financially vulnerable populations, attributable in part to the increased number of recommended vaccines and a shift over the last 20 years from a largely public to a more privatized vaccine delivery system.[21] While the Vaccines for Children (VFC) program provides funding to cover the cost for vaccines for eligible children and has contributed to the elimination of some health disparities,[22-26] no such vaccine funding program exists for adults.

Thanks to the implementation of robust federal, state, local and tribal vaccination programs, the incidence of diseases that disproportionately affected AI/AN communities in the pre-vaccine era, such as hepatitis A, hepatitis B, *Haemophilius influenza* type b (Hib) and invasive pneumococcal disease, has declined. Some previously identified disease disparities have been eliminated or greatly reduced in the AI/AN population,[2] including demonstrable gains in the Northern Plains. For example, prior to the introduction of the vaccine, hepatitis A was endemic among AI/AN communities in South Dakota with rates of infection four to five times higher than the rest of the U.S. population and epidemics occurring every seven to 10 years.[26] A serosurvey conducted in 1985 in two reservation communities in South Dakota found that by age 40, 90 percent of the population had hepatitis A virus (HAV) antibodies, and high rates of HAV antibody among young children indicated ongoing transmission even between epidemics.[28] The introduction of hepatitis A vaccine in these and other AI/AN communities in 1995 resulted in dramatic declines in hepatitis A infection.[27-29] Today, hepatitis A infection rates among the AI/AN population both in South Dakota and nationwide are actually lower than rates in the general U.S. population.[2,27,30-32]

While the gains have been noteworthy, disparities for some vaccine-preventable diseases remain. Nationally, rates of invasive pneumococcal, Hib and pertussis disease, while reduced, continue to be higher among AI/AN children compared to the general U.S. population.[2,33,34] During the H1N1 pandemic AI/AN people had higher hospitalization rates related to H1N1 influenza than other racial and ethnic groups,[35] and were four times more likely to die from influenza-related complications than the rest of the U.S. population.[36] While data specific to vaccine-preventable diseases in AI/AN populations in the Northern Plains are more limited, data from South Dakota for 2000 through 2011 show that rates for pertussis, varicella, Hib and mumps, while low, were higher among the AI/AN population than the rates for other groups (Table 1). In 1997, after 20 years without a single case of diphtheria, 11 cases were found in an AI community in South Dakota.[37,38] Finally, AI/AN women in the Northern Plains have been found to have a higher rate of cervical cancer, a higher burden of human papillomavirus (HPV) disease, and a higher prevalence of risk factors for HPV infection compared to white women in the region.[39-42]

Table 1. Vaccine-preventable Disease Rates, South Dakota 2000-2011: American Indian/Alaska Natives vs. All Others[30]

Diseases rates per 100,000 per Year	AI/AN	All Others	Total
Haemophilus influenzae b (Hib)	0.22	0.02	0.04
Mumps	3.21	2.81	3.42
Pertussis	17.17	6.16	7.39
Varicella	11.96	6.31	7.49
Hepatitis A	0.11	0.46	0.44

Reasons for continued vaccine-preventable disease disparities are multi-factorial and likely include socio-economic and health care access issues,[7,8,18] a higher prevalence of underlying health problems,[8,12,13] and housing factors such as crowding, use of wood burning stoves, and lack of running water.[2,11,43,44] The presence of these disparities and the potential for ongoing transmission of vaccine-preventable diseases are an important reminder that we must remain vigilant in our vaccination efforts.

Disease Surveillance

Disease surveillance systems are critical for monitoring the impact of vaccination programs on the incidence of vaccine-preventable diseases. Based on national surveillance data, cases of most vaccine-preventable diseases have declined more than 99 percent in the last 50 years.[45] Incomplete race designation in national surveillance systems, however, limit the ability to monitor for vaccine-preventable diseases in some subpopulations and identify disparities. During the 2009 H1N1 pandemic, for example, data from some states early in the pandemic suggested that AI/AN populations were experiencing high rates of morbidity and mortality, but incomplete race designation in national influenza and influenza-like illness surveillance systems did not allow for comprehensive analysis.[36] In order to assess if there was a

disproportionate burden in the AI/AN population, 12 states with large AI/AN populations compiled their surveillance data and found that AI/AN people had an H1N1 influenza mortality rate four times higher than the general population.[36] This critical information contributed to the prioritization of AI/AN people for H1N1 vaccine[46] and changes in H1N1 vaccine distribution policy in several states and ultimately led to the inclusion of AI/AN people as a high-risk group in both H1N1 and subsequent seasonal influenza vaccine recommendations.[47] This example highlights the importance of improving collection of race data in both national and local level surveillance systems in order to identify disparities and inform policies to address them.

Vaccination Coverage Data

Ongoing monitoring of vaccine coverage levels is essential to ensure that the reductions of vaccine-preventable diseases are preserved.[21] There are currently three main data sources for monitoring vaccine coverage among the AI/AN population. These include national surveys funded primarily by the Centers for Disease Control and Prevention (CDC); data from the Indian Health Service (IHS) which provide national and regional level estimates for AI/AN people served by IHS; and state immunization information systems (IIS), population-based computerized systems that consolidate vaccination data for a given client into one record within a certain geographical area.

Monitoring national level vaccination trends for the AI/AN population is challenging. Because they make up less than 2 percent of the U.S. population, AI/AN sample sizes even in nationally representative surveys are small, making it difficult to ascertain whether fluctuations and differences in coverage are true differences or artifacts of the small sample size.[12,26,48] The main national data sources on vaccination coverage include the National Immunization Survey (NIS), which monitors vaccination coverage among children 19 to 35 months; NIS – Teen, which monitors vaccination coverage among adolescents 13 to 17 years of age; the National Health Interview Survey (NHIS), which monitors influenza coverage among children and coverage with adult vaccines; and the Behavioral Risk Factors Surveillance Survey (BRFSS), which monitors vaccination coverage among adults. All of these surveys collect race designation and are the main source for monitoring national level racial disparities in vaccination coverage.

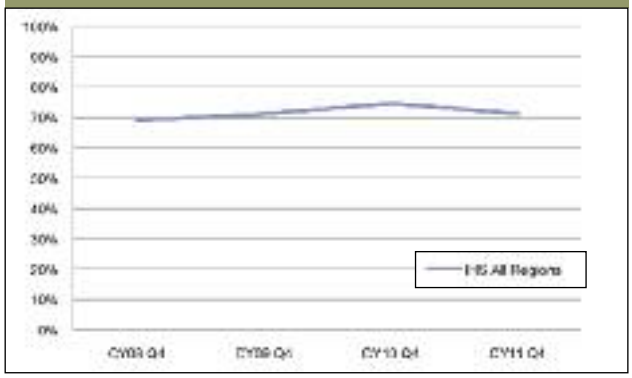
IHS data constitutes a separate national resource on AI/AN vaccination coverage. The IHS is the federal agency responsible for delivering health care to eligible AI/AN people and provides care to approximately 38 percent of the total AI/AN population through a network of IHS, Tribal and Urban Indian Health facilities (I/T/U) located primarily in rural areas. The IHS is divided into 12 administrative regions, which are often further collapsed into six geographic regions for the purposes of analysis.[2,26,39,48] The IHS collects quarterly vaccination coverage data on their patient population, including coverage on children 19 to 35 months, coverage among adolescents 13 to 17 years, coverage with influenza vaccine among all patients 6 months and older, and coverage on adults 19 years and older. While these data provide insight into vaccination coverage at a regional level, they are limited to AI/AN people who receive care from an IHS-funded facility and are not generalizable to the general AI/AN population. In addition, because the data source is limited to the individual facility databases, vaccinations administered outside the facility may not be captured, resulting in an underestimate of coverage. Because of this, state IIS, which consolidate vaccination data from multiple providers into one record, are an increasingly important tool for monitoring vaccination coverage and can be particularly useful for monitoring disparities at the local level. Collection of race designation is a requirement for state IIS, though the completeness and comparability of these data vary from state to state.

Based on the national level data available for children, adolescents and adults, there appear to be few disparities in immunization coverage between the AI/AN population and the non-Hispanic white population.[25,26,49-53] Rates of some vaccine-preventable diseases in certain AI/AN communities, however, remain elevated compared to the general U.S. population. Significant geographic variation in the patterns of disease among AI/AN populations is well-documented[9,10,13] and is to be expected given the heterogeneity of the AI/AN population. Certain regions experience higher burdens of infectious and chronic disease, and lower utilization of certain preventive services[3,9,12,13,39] compared to the general U.S. population. In light of this, it is important that disease surveillance and vaccination coverage monitoring systems allow for more granular levels of analysis in order to effectively identify potential disparities. While helpful for examining overall national trends, current national data may mask important differences at the regional, state or local level. In addition, these surveys are not designed to provide state-level estimates for all subpopulations, limiting their utility for monitoring racial disparities at anything other than the national level.[8]

The IHS data, while not directly comparable to the national level vaccination data, are helpful for examining geographic differences. Figure 1 provides an overview of IHS data on the 4:3:1:3:3:1:4 vaccine series (defined as 4 or more doses diphtheria and tetanus toxoids and pertussis vaccine, diphtheria and tetanus toxoids, or diphtheria and tetanus

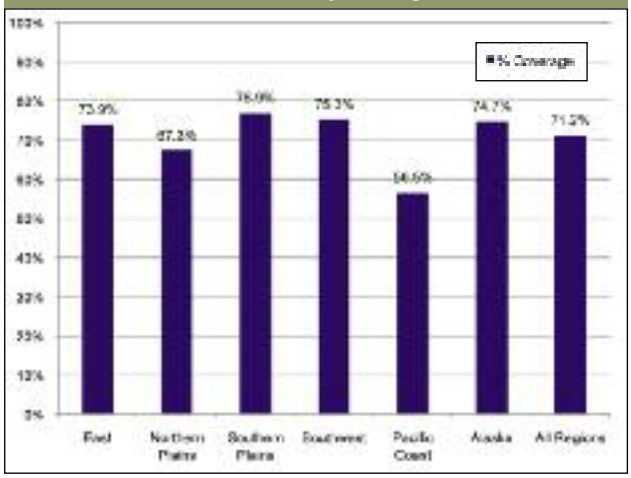
toxoids and any pertussis vaccine, 3 or more doses of oral or inactivated polio vaccine, 1 or more doses of measles, mumps, and rubella vaccine, 3 or more doses of *Haemophilus influenzae* type b vaccine, 3 or more doses of hepatitis B vaccine, 1 or more doses of varicella vaccine, and 4 or more doses of pneumococcal conjugate vaccine) among 19 to 35-month-olds from 2008 through 2011. Overall coverage among AI/AN people seen at IHS-funded facilities ranged from 69 to 71.2 percent during that time period. There is, however, considerable geographic variation, with 4:3:1:3:3:1:4 coverage rates in the different regions for 2011 ranging from 56.5 to 76.9 percent (Figure 2). While differences in state immunization policies, facility vaccination strategies, AI/AN population size, relative proximity to an I/T/U facility, and missing data in the IHS data system likely

Figure 1. IHS Data: Coverage with the 4:3:1:3:3:1:4* Series for Children 19-35 Months: 2008-2011[53]



*Defined as ≥ 4 doses diphtheria and tetanus toxoids and pertussis vaccine, diphtheria and tetanus toxoids, or diphtheria and tetanus toxoids and any pertussis vaccine, ≥ 3 doses of oral or inactivated polio vaccine, ≥ 1 dose of measles, mumps, and rubella vaccine, ≥ 3 doses of *Haemophilus influenzae* type b vaccine, ≥ 3 doses of hepatitis B vaccine , ≥ 1 dose of varicella vaccine, and ≥ 4 doses of pneumococcal conjugate vaccine.

Figure 2. IHS Data: Coverage with the 4:3:1:3:3:1:4* Series by IHS Region, 2011[53]



*Defined as ≥ 4 doses diphtheria and tetanus toxoids and pertussis vaccine, diphtheria and tetanus toxoids, or diphtheria and tetanus toxoids and any pertussis vaccine, ≥ 3 doses of oral or inactivated polio vaccine, ≥ 1 dose of measles, mumps, and rubella vaccine, ≥ 3 doses of *Haemophilus influenzae* type b vaccine, ≥ 3 doses of hepatitis B vaccine , ≥ 1 dose of varicella vaccine, and ≥ 4 doses of pneumococcal conjugate vaccine.

contribute to the variation in coverage levels, the low coverage levels reported for some regions are a concern and highlight the need for additional data to better understand these differences.[54]

Given the challenges of monitoring vaccination coverage for the AI/AN population using the existing national and IHS data – small sample sizes in current national surveys, limited ability to monitor trends at the national and state level, significant geographic variation in health status and health care access, and incomplete data in sources used by IHS – supplementing existing national and regional data with local data is increasingly important to detect disparities. IIS can provide this level of granularity and are particularly useful in identifying pockets of need. An example of this is captured in a study conducted by the state of North Dakota. The North Dakota Immunization Information System (NDIIS) contains data from all providers in the state, including providers in IHS and tribal facilities, who enter data into both NDIIS and the IHS electronic health record. They examined childhood vaccine coverage with the 4:3:1:3:3:1:4 vaccine series for 2010 and found that AI/AN children had significantly lower vaccination coverage compared to white children, and that there was a delay in the initiation of the vaccine series among AI/AN children. They also found varying levels of coverage between the different reservations, ranging from 48.8 to 71.6 percent.[55] These findings highlight the need to provide data at a local level for better monitoring of disparities in populations like the AI/AN population, which allows for targeted public health action by the state, IHS and the tribes. IIS in other states can be used to replicate these analyses, though the completeness of data, including information on race, varies.

Discussion

The significant investment made not just in the development of vaccines themselves but in the associated underlying health care infrastructure has resulted in remarkable declines in vaccine-preventable diseases. Areas of low coverage and high disease are, however, still present, highlighting the need for continued support to strengthen the health infrastructure and local data collection systems to identify and address these disparities.

Among the AI/AN population, overall childhood immunization coverage levels have increased, and some vaccine preventable disease disparities have been eliminated.[25,26] Nationally, vaccination coverage among AI/AN adolescents and influenza vaccine coverage for the AI/AN population 6 months and older are similar to or higher than coverage for non-Hispanic whites.[49-53] In spite of these successes, risks for vaccine-preventable diseases remain for some AI/AN populations. While the IHS data support that overall coverage

among AI/AN people served by IHS is comparable to that for the general U.S. population, the marked differences in coverage between the IHS regions suggests that there may be regions where coverage is, in fact, considerably lower. In addition, as the data from the NDIIS shows, there are disparities at the local level that would remain undetected if we relied solely on the national data. With the overall broad success of vaccination programs in reducing disease, we now have the opportunity and the obligation to focus our attention on specific geographic areas and populations where increased rates of disease persist, and where vaccine coverage remains low.

In order to identify pockets of need and better characterize the geographic variation seen in vaccine coverage data, continuing to develop and improve current data collection systems is essential. While oversampling certain populations and/or geographic areas can help identify disparities that may go undetected using the current national surveys' sampling frames, the costs can be significant, and the data collection are limited to that population or geographic area. Instead, supporting and improving the systematic collection of race data in existing disease surveillance and vaccine monitoring systems, particularly at the state and local level, is essential to ensure we can effectively detect and address health disparities. This is particularly important for regions such as the Northern Plains, where the AI/AN population is more likely than non-Hispanic whites to live in poverty, have underlying health conditions, experience a higher prevalence of health risk behaviors, and where AI/AN people have experienced elevated rates of some vaccine-preventable diseases.[12,31,36,40,41] Improving the collection of race designation in disease surveillance reporting systems and state IIS, and facilitating complete provider participation in these systems is essential for vaccination policy and program planning. In addition, with the increased opportunities for adult vaccination and the potential to further impact the incidence of vaccine-preventable diseases, expanding existing IIS to capture data on adult vaccination to allow for local vaccination coverage assessments among adults is increasingly important.

Finally, establishing interoperability between provider electronic health records and state IIS is an important strategy for both improving participation and implementing expanded data collection efforts, and must continue to be supported. Currently bi-directional data exchange between the IHS electronic health record system and state IIS is operational in 10 states, including Wyoming in the Northern Plains. Technical and funding challenges have slowed the development of bi-directional data exchange efforts in other states in the Northern Plains. Efforts to overcome and address these challenges are needed so that IIS can be utilized for the more granular level of analysis needed to effect change.

Conclusion

The expansion of vaccine programs to include new vaccines and new target populations will allow us to further reduce the burden of vaccine-preventable diseases. With these additional opportunities, however, come new challenges. The successful delivery of vaccinations is contingent on more than just the presence of the vaccine. The underlying infrastructure needed to ensure people are vaccinated includes funding to cover the cost of the vaccine and the vaccine delivery system, and data collection systems to monitor vaccine coverage and assess the impact on disease, all of which require partnerships at the federal, state, tribal and local levels.[21,56] While nationally vaccine coverage among AI/AN has improved, disparities in vaccine coverage and vaccine-preventable diseases persist. Sustaining and expanding current programs can be challenging given often limited resources and the complexity of establishing and maintaining partnerships, but in order to make further progress in eliminating the disparities still present in the AI/AN population, it is imperative to overcome these challenges. Without a dedicated effort to support, sustain and expand our vaccine infrastructure, the gains that have been made over the last decades can be lost.

The opinions expressed in this paper are those of the author and do not necessarily reflect the views of the Indian Health Service, the Centers for Disease Control and Prevention, or the Department of Health and Human Services.

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CHAPTER 15

Immunization and Travel

By Srividya Srinivasan, MD

Introduction

Travel medicine is an interdisciplinary specialty devoted to the health of international travelers. It is concerned with the prevention of infectious diseases, personal safety and avoidance of environmental risk in travelers. Travel medicine is an evolving field which is increasingly based on evidence and less on expert opinion, which makes this emerging discipline more available to the primary care community. It is represented by the International Society of Travel Medicine (ISTM) and by an active clinical group within the American Society of Tropical Medicine and Hygiene (ASTMH).

Travel medicine care should be offered by providers who have knowledge in epidemiology, transmission and prevention of travel-associated infectious diseases and who adhere to guidelines regarding vaccine indications and storage. In addition, the prevention and management of noninfectious travel-associated health risks, as well as recognition of major syndromes in returning travelers such as fever, diarrhea and rash, is optimal.

This brief overview highlights important information on immunization and travel and refers the reader to many publically accessible resources for more detailed information. These include the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), the U.S. Advisory Committee on Immunization Practices (ACIP) and the Infectious Disease Society of America (IDSA).[1] The IDSA travel guideline is an important general resource for approaches to travel medicine. While detailed, comprehensive country-specific and daily updated information may be obtained via subscription through products like Travax,[2] providers can become very proficient in preparing travelers through the publically accessible sites mentioned above.

Broad categories to be covered in this review include general vaccine recommendations, specific vaccine recommendations, selective vaccines, vaccine side effects, special populations and important additional information.

Immunization and Travel – General

All travel clinic visits should focus on pre-travel risk assessment with emphasis on preventive advice, appropriate immunization and maintenance of a permanent travel clinic record. Travelers should also be provided with a written record of all vaccines administered (patient-retained record), preferably using the international vaccination certificate (which is required in the case of yellow fever vaccination).[3]

Appropriate vaccines prior to travel can be decided based on the following factors:

- Risk of exposure to the disease;
- Age, health status, vaccination history;
- Reactions to previous vaccine doses, allergies;
- Risk of infecting others; and
- Cost

Immunization and Travel – Specific

Vaccination recommendations are based on the following three categories:

1. For all travelers – all routine vaccines recommended by the published schedules of the American Council on Immunization Practices (ACIP);
2. Selective vaccines for travelers to destinations with particular risk; and
3. Required vaccination by certain countries to prevent introduction of these illnesses into their country by international travelers.

All Travelers – Routine Vaccination in Children and Adults: ACIP Recommendation[4]

Toxoids

- Diphtheria, tetanus and pertussis.

Inactivated Bacterial Vaccines

- *Haemophilus influenzae* type b;
- Pneumococcal vaccine; and
- Meningococcal vaccine.

Live Virus Vaccines

- Influenza (FluMist);
- Measles, mumps and rubella (MMR);
- Rotavirus;
- Varicella; and
- Zoster.

Inactivated Virus Vaccines

- Hepatitis A;
- Hepatitis B ;
- Poliomyelitis;
- Influenza; and
- Human papillomavirus (HPV).

Selective Use for Travelers to Destinations with Particular Risks[3,5,6]

- Cholera (vaccine not available in the U.S.);
- Tick-borne encephalitis (vaccine not licensed in the U.S.);
- Japanese encephalitis;
- Typhoid fever;
- Rabies;
- Yellow fever;
- Hepatitis A (routine vaccine in the U.S.); and
- Meningococcal disease (routine vaccine in the U.S.).

Required Vaccination[3,5,6]

- Yellow fever (to protect individuals traveling to areas with yellow fever risk and to prevent importation of yellow fever virus from endemic areas into countries with no yellow fever risk);
- Meningococcal disease (against serogroups A, C, Y and W135) required by Saudi Arabia for pilgrims; and
- Polio (required by Saudi Arabia for pilgrims).

Immunization and Travel – Selective Vaccines

Rabies Vaccination Rabies vaccine is recommended for travelers to areas in which rabies is endemic who will have occupational or recreational exposure (e.g., veterinarians, spelunkers and others with animal contact). A complete course of rabies vaccine prior to travel eliminates the need for rabies immunoglobulin following an exposure. Rabies immunoglobulin of either human or equine origin may be very difficult to obtain in resource-poor regions of the world. In addition, pre-exposure to rabies vaccine has the added benefit of protecting against unrecognized or unreported exposures, which may occur in children. The epidemiology of rabies can be determined by reviewing rabies information from the CDC and WHO.[3,6]

Japanese Encephalitis Japanese encephalitis is a mosquito borne, viral disease that is prevalent in most countries of Asia and, with limited risk, in some islands of the Western Pacific and in the Torres Strait Islands of Australia. The risk to travelers is low. Travelers with prolonged residence in an endemic country and those with frequent short visits or shorter visits with intense exposure to mosquitoes during transmission seasons in rural areas will be candidates for the vaccine.

Poliomyelitis All travelers should have completed a primary course of polio vaccine. One additional lifetime dose of the inactivated polio vaccine should be given to adults 18 years and above who are traveling to regions of the world that remain a risk for polio transmission (primarily countries in Africa and Asia).

Typhoid Fever Typhoid immunization is indicated for travelers to areas of endemicity in Central and South America, Asia and Africa. In the U.S., there are two vaccines available for protection against S. Typhi: a live-attenuated oral vaccine (Vivotif Berna) and an injectable Vi capsular polysaccharide vaccine (Typhim Vi). They are 50 to 70 percent effective. Since typhoid vaccines provide incomplete protection and do not protect against S. enterica serovar Paratyphi, travelers need to be counseled on continued food and beverage precautions despite vaccination.

Hepatitis A Hepatitis A vaccine is routinely recommended by ACIP for all children at 1 year of age. Hepatitis A vaccine is indicated for unimmunized travelers to areas of the world where sanitation and hygiene may be poor. Although travelers should try to receive the full 2-dose series of inactivated vaccine, a single dose of monovalent hepatitis A vaccine provides high-level protection in 14 to 28 days. All monovalent, inactivated hepatitis A vaccines are interchangeable. Hepatitis A immunoglobulin can be used in certain groups of travelers allergic to certain components of hepatitis A vaccine, less than 12 months of age, travelers who refuse hepatitis A vaccine, or for the last minute travelers visiting areas endemic for hepatitis A.

Hepatitis B Hepatitis B vaccine is routinely recommended by ACIP for all infants at 0, 1 to 2, and 4 to 6 months of age. Immunization should be considered for all unimmunized adults whether or not they travel. Any traveler at risk for potential contact with blood or body fluids through sex, medical work or other activities should be immunized. An accelerated schedule over two months has been approved in the U.S. with one of the hepatitis B vaccines (Engerix-B)

to achieve protection in travelers who are departing prior to completion of the six-month normal schedule. An additional dose should be given at 12 months to confer long-term protection.

Combination Hepatitis A and B Vaccine A combined hepatitis A and B vaccine (Twinrix) may be used in travelers aged 18 years and above when protection against both antigens is desired. Two doses of vaccine must be given one month apart to achieve protection against hepatitis A, because of lower dose of antigen is used in this preparation, compared with single-antigen hepatitis A vaccines. A third dose should be given six months from the first dose.

Cholera Cholera vaccine is no longer produced in the U.S. and has not been required by the WHO for international travel since the early 1980s.

Tick-borne Encephalitis This viral encephalitis is prevalent in rural forested areas of eastern and central Europe, Scandinavia and Siberia in the spring and summer months. It is most commonly transmitted by Ixodes ticks, but it may also be contracted by ingesting unpasteurized dairy products in areas of endemicity. There are two inactivated vaccines (FSME- Immun and Encepur), but neither of these is licensed in the U.S. or Canada. Expatriates can consider obtaining the vaccine during their overseas residence.

Meningococcal Disease Meningococcal vaccine is required by Saudi Arabia and recommended by the ACIP for religious pilgrims traveling to Mecca for the purpose of the Hajj or Umrah. Meningococcal vaccine is also recommended for travelers to the "meningitis belt" in sub-Saharan Africa (generally extending from Senegal to Ethiopia), particularly if they're traveling during the dry season of December through June or will have extensive contact with the local population.[1,3] Meningococcal conjugated quadrivalent vaccine (MCV4) is routinely recommended by ACIP at 11 to 12 years of age and at 15 years of age if not previously vaccinated. Routine vaccine is also recommended for first-year college students who live in dormitories. Microbiologists with frequent exposure to Neiserria meningitidis, military recruits, those with terminal complement component deficiencies, and individuals with functional or surgical asplenia should also receive the meningococcal vaccine. Meningococcal polysaccharide vaccines (MPSV) are poorly immunogenic in children under the age of 2 years but may be used in older individuals when MCV4 is avoided.

Yellow Fever Yellow fever vaccine is recommended for travelers to equatorial South America and in some regions on either side of the equator in Africa. Information on yellow fever vaccine requirements and vaccination centers in the U.S. can be found in Health Information for International Travel and on the CDC website.[3,6] The yellow fever 17D strain vaccine is live-attenuated and highly effective. International health regulations require that it be administered at least 10 days before travel to allow development of protective antibodies.[7] Boosters are required at 10-year intervals for international travel, although vaccination may confer immunity for decades.

Immunization and Travel – Vaccine Side Effects

Vaccines are generally very safe and serious adverse reactions are uncommon. Mild side effects such as injection site reactions and fever might be associated with some vaccines.

Yellow fever vaccine is associated with severe adverse events such as viscerotropic disease and neurologic disease. These events are rare, in the order of one case for every 200,000 doses administered in the U.S. This should not discourage administration of the vaccine to travelers who are at risk and who are not excluded by contraindication. Yellow fever vaccine is not recommended for use in infants less than 9 months of age, persons with a history of thymus disorder or thymectomy, during pregnancy, those immunocompromised due to AIDS, leukemia, lymphoma, cancer chemotherapy, and receipt of corticosteroids or other immunocompromising processes. Travelers should be advised to follow strict measures to prevent mosquito bites, particularly at dusk and dawn, which are the maximum biting times of the principal human vector, the Aedes mosquito.[8]

Immunization and Travel – Vaccine Indications and Contraindications in Special Populations

Pregnancy BCG, oral typhoid vaccine (Typhoid, Ty21a), HPV and all live virus vaccines are contraindicated in pregnancy. Hepatitis A vaccine, meningococcal polysaccaharide vaccine (MPSV), inactivated polio vaccine (IPV), pneumococcal vaccine, rabies vaccine and injectable typhoid vaccine (Typhoid, Vi) should be used in pregnancy if indicated. No data exist on the safety of meningococcal conjugated vaccine (MCV4) in pregnancy and should be used only if clearly needed. MPSV may be administered in these cases. The safety and efficacy of Japanese encephilitis vaccine has not been established in pregnant or nursing women and should be used only if clearly needed. Yellow fever vaccine should be considered in pregnancy if travel to risk area is unavoidable and the risk of contracting yellow fever is high.

Severe Immunosuppression in the General Population BCG, oral typhoid vaccine (Typhoid, Ty21a) and all live virus vaccines are contraindicated in severely immunocompromised travelers. Hepatitis A vaccine, JE vaccine (Ixiaro), meningococcal vaccine, polio vaccine (IPV), rabies vaccine and typhoid vaccine (Typhoid Vi) should be used if indicated. Varicella vaccine should not be administered to persons with cellular immunodeficiencies, but persons with impaired humoral immunity may be vaccinated.

HIV Infection BCG, oral typhoid vaccine (Typhoid, Ty21a) and all live virus vaccine except MMR and varicella vaccine are contraindicated in individuals with HIV infection. MMR is recommended for all asymptomatic HIV-infected travelers who do not have evidence of severe immunosuppression. Varicella vaccine may be considered for non-immune, asymptomatic or mildly symptomatic children with HIV infection with age-specific CD4+ T-lymphocyte percentage more than or equal to 15 percent and to HIV-infected adults with CD4+ T-lymphocyte counts more than or equal to 200. Yellow fever vaccination can be given to an asymptomatic HIV-infected person with no evidence of immunosuppression based on CD4 counts. Symptomatic HIV infection with moderate immunosuppression is a precaution for yellow fever vaccination. Yellow fever vaccine can be considered for these persons if there is actual risk of yellow fever at the destination. Yellow fever vaccination is contraindicated in persons with AIDS or other clinical manifestations of HIV infection with severe immunosuppression.

Immunization and Travel – Important Additional Information

Malaria Prophylaxis Travelers should be counseled on mosquito avoidance measures, such as using mosquito repellents, mosquito screen, bed-nets, wearing long sleeved clothing, compliance with malaria chemoprophylaxis, and should seek prompt medical attention for any febrile illness during or after return from travel. Malaria chemosuppressive regimens should be administered according to geographic area per published CDC and WHO guidelines.

Traveler's Diarrhea Travelers should be counseled on food and liquid precautions, hand hygiene, avoiding certain high-risk food, as well as to recognize and promptly self treat traveler's diarrhea. Self treatment includes hydration, treatment with loperamide for control of symptoms, if necessary (when there is no temperature greater than 38.5°C or blood in the stool) and a short course of antibiotic therapy. Commonly used antibiotics include a fluoroquinolone, azithromycin in areas with fluoroquinolone resistant enteric pathogens and rifaximin. Antibiotic prophylaxis is not recommended for most travelers. Chemoprophylaxis can be considered in some travelers.

Safety, Behavior, Injury Prevention and Endemic Illness Travelers should be counseled on prevalence of blood borne pathogens such as HIV, hepatitis B, hepatitis C and other sexually transmitted infections such as syphilis, chlamydia and gonorrhea at their destination. Travelers should be advised to avoid high-risk behavior such as injection drug use. Health care and refugee workers should be advised to use adequate precautions if handling bloody secretions, needles and other sharp objects. Travelers should also be counseled on current outbreak of illnesses in the destination countries.

Travelers should be provided information regarding other common illnesses in the destination countries such as tuberculosis, dengue, and other viral infections, as well as vector borne illness such as leishmaniasis. Travelers should be advised about avoiding animal bites including dog, bat and monkey bites, to wash the affected area with soap and water for 10 to 15 minutes in case of animal bites and to seek medical attention even if they have received pre-exposure rabies vaccine.

Travelers should also be informed about marine hazards, road traffic accidents, security warnings, aviation issues and high altitude illness, use of sunscreen and adequate insect precautions. Availability of medical care in the destination countries and importance of evacuation insurance should also be discussed.

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CHAPTER 16

Vaccination and the Health Care Worker

By James M. Keegan, MD; R. Vivian Derby, MA, BSHC, RN; Tamara Rhames, RN, CIC and Beth Boersma, LPN, CIC

Abstract:
Historically, health care worker vaccination has been a strategy to protect the health care worker from infectious work related risk. This article will discuss the transition to health care worker vaccination as a key patient safety initiative for hospitals and health care systems. As the case is evolving toward mandatory influenza vaccination of health care workers, we have outlined key success factors for a voluntary program in a rural frontier referral hospital. Additionally, pertussis vaccination for health care workers is discussed as to the patient safety aspects of a progressive approach further making the case for value creation on behalf of our patients we have the privilege of providing care.

Introduction

The motivation for preventative vaccinations for health care workers is predominantly two-fold – health care worker safety and patient safety. In this article, we will present and discuss national recommendations for immunization of health care workers, discuss our local experience particularly with influenza vaccination in a rural/frontier referral hospital, and finally, expand on influenza vaccination as a discussion point for ongoing best practice opportunities.

History

Reduction of infectious diseases to an all-time low is perhaps the greatest success story in public health for saving lives, preventing debilitating illness and reducing costs in the 20th century.[1-3] It also represents the single greatest promise of biomedicine – disease prevention.[4] Listed as one of the 10 great public health achievements in the U.S.[5,6] from 1900 to 1999 and again from 2001 to 2010, vaccination against preventable diseases has resulted in a substantial decline in cases, hospitalizations, deaths and health care costs associated with these diseases.[6]

Yet opposition to vaccinations has existed as long as vaccinations themselves.[4,7,8] With the prevalence of once-terrifying diseases diminishing, the fear of these diseases subsides as well.[2] Sustaining high vaccine coverage rates may become more of a challenge as people question the limitations of vaccines and new parents no longer see or hear about the devastating diseases from which vaccines protect them.[1] Families no longer live with a frail, under-developed 5-year-old, crippled with polio, learning to walk with forearm crutches and leather clad metal braces, called KAFOs, or knee-ankle-foot orthotics that are hot and sweaty in the warm months but bone-chilling in winter. For that reason, it is taken for granted that a child born in the developed world will grow up without fear from the paralysis, brain damage, blindness and death that plagued previous generations.[2]

Underutilized, vaccines are powerful medical interventions that induce powerful biological, social and cultural reactions.[3,4] In the 1830s, after an initial generation had been vaccinated and the incidence of smallpox declined markedly in the U.S. and Europe, a strident anti-vaccination movement emerged.[4] As well, with the decline of preventable diseases, people have become less attentive to the consequences of illnesses like diphtheria and tetanus.[9]

Opposition to vaccinations is not new. The Vaccination Act of 1853 sparked riots in several British communities[7] and anti-vaccination activity has continued well into the 21st century. And like smallpox, despite prolific clinician education, symptom awareness and a matter of patient safety, influenza vaccination rates for health care workers have remained unacceptably low for more than three decades.[10]

According to the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Advisory Committee (HICPAC), "employers and health care providers have a shared responsibility to prevent occupationally acquired infections and avoid causing harm to patients by taking reasonable precautions to prevent transmission of vaccine-preventable disease."[11,12]

The Centers for Disease Control and Prevention (CDC) guidelines have called for health care workers to receive influenza vaccination since 1981, but vaccination rates among health care workers in the U.S. were as low as 40 percent in 2007 and[13,14] reached a mere 44 percent by 2010, despite a variety of efforts to increase the rate.[15,16] According to the CDC, it is unknown exactly how many people die from seasonal influenza each year:[17]

> "There are several reasons for this. First, states are not required to report individual seasonal influenza cases or deaths of people older than 18 years of age to CDC. Second, seasonal influenza is infrequently listed on death certificates of people who die from influenza-related complications. Third, many seasonal influenza-related deaths occur one or two weeks after a person's initial infection, either because the person may develop a secondary bacterial co-infection (such as bacterial pneumonia) or because seasonal influenza can aggravate an existing chronic illness (such as congestive heart failure or chronic obstructive pulmonary disease). Also, most people who die from seasonal influenza-related complications are not tested for influenza, or they seek medical care later in their illness when seasonal influenza can no longer be detected from respiratory samples. Sensitive influenza tests are only likely to detect influenza if performed within a week after onset of illness. In addition, some commonly used tests to diagnose influenza in clinical settings are not highly sensitive and can provide false negative results (i.e., the misdiagnose influenza illness as not being influenza.) For these reasons, many influenza-related deaths may not be recorded on death certificates. Therefore, CDC and other public health agencies in the U.S. and other countries use statistical models to estimate the annual number of seasonal influenza-related deaths. (Influenza deaths in children were made a nationally notifiable condition in 2004, and since then, states have been required to report influenza-related child deaths in the U.S. through the Influenza Associated Pediatric Mortality Surveillance System)."[17]

Employers and health care workers/personnel share responsibility to prevent the spread of vaccine-preventable disease to patients; consequently any facility or organization that provides direct patient care is encouraged by HICPAC to formulate a comprehensive vaccination policy.[12] Maintaining public support for immunizations is critical for preventing outbreaks of vaccine-preventable diseases; therefore vaccine safety research, monitoring, vaccine injury compensation programs, vaccine risk communication and closure of current gaps and limitations in knowledge is necessary.[1] In addition, during community influenza outbreaks, admitting patients infected with influenza to hospitals has led to nosocomial transmission of the disease, including transmission from staff to patients.[18] Transmission of influenza among medical staff causes absenteeism and considerable disruption of health care.[18]

National Recommendations

Included are the national recommendations for health care worker immunization, as well as a summary of changes (see Table 1 and Table 2).

Table 1. Recommendations for Immunization Practices and Use of Immunobiologics Applicable to Disease Prevention Among Health Care Personnel* – Advisory Committee on Immunization Practices (ACIP), 12 June 9, 1989-August 26, 2011

Subject
General recommendations on immunization
Diphtheria, tetanus and pertussis
Hepatitis B
Influenza¥
Measles, mumps and rubella (MMR)
Meningococcal disease and outbreaks
Mumps (see also MMR and measles)
Pertussis, acellular (see also diphtheria, tetanus and pertussis)
Poliomyelitis
Rubella (see also MMR, measles, and mumps)
Typhoid
Varicella

*Persons who provide health care to patients or work in institutions that provide patient care (e.g., physicians, nurses, emergency medical personnel, dental professionals and students, medical and nursing students, laboratory technicians, hospital volunteers, and administrative and support staff in health care institutions). **Source**: U.S. Department of Health and Human Services. Definition of health care personnel (HCP) available at www.hhs.gov/ask/initiatives/vacctoolkit/definition.html.

¥Each year influenza vaccine recommendations are reviewed and amended to reflect updated information concerning influenza activity in the U.S. for the preceding influenza season and to provide information on the vaccine available for the upcoming influenza season. These recommendations are published periodically in *MMWR*. The most current published recommendations should be consulted available at www.cdc.gov/vaccines/pubs/acip-list.htm.

Table 2. Summary of Main Changes* from 1997 Advisory Committee on Immunization Practices/Hospital (now Health Care) Infection Control Practices Advisory Committee Recommendations for Immunization of Health Care Personnel[12]

Hepatitis B

- HCP and trainees in certain populations at high risk for chronic hepatitis B (e.g., those born in countries with high and intermediate endemicity) should be tested for HBsAg and anti-HBs to determine infection status.

Influenza

- Emphasis that all HCP, not just those with direct patient care duties, should receive an annual influenza vaccination.
- Comprehensive programs to increase vaccine coverage among HCP are needed; influenza vaccination rates among HCP within facilities should be measured and reported regularly.

Measles, mumps and rubella (MMR)

- History of disease is no longer considered adequate presumptive evidence of measles or mumps immunity for HCP; laboratory confirmation of disease was added as acceptable presumptive evidence of immunity. History of disease has never been considered adequate evidence of immunity for rubella.
- The footnotes have been changed regarding the recommendations for personnel born before 1957 in routine and outbreak contexts. Specifically, guidance is provided for 2 doses of MMR for measles and mumps protection and 1 dose of MMR for rubella protection.

Pertussis

- HCP, regardless of age, should receive a single dose of Tdap as soon as feasible if they have not previously received Tdap.
- The minimal interval was removed, and Tdap can now be administered regardless of interval since the last tetanus or diphtheria-containing vaccine.
- Hospitals and ambulatory-care facilities should provide Tdap and use approaches that maximize vaccination rates.

Varicella

Criteria for evidence of immunity to varicella were established. For HCP they include:

- Written documentation with 2 doses of vaccine;
- Laboratory evidence of immunity or laboratory confirmation of disease; and
- Diagnosis of history of varicella disease by health-care provider, or diagnosis of history of herpes zoster by health-care provider.

Meningococcal

- HCP with anatomic or functional asplenia or persistent complement component deficiencies should now receive a 2-dose series of meningococcal conjugate vaccine. HCP with HIV infection who are vaccinated should also receive a 2-dose series.
- Those HCP who remain in groups at high risk are recommended to be revaccinated every 5 years.

Centers for Disease Control and Prevention. *Immunization of Health Care Personnel Recommendations of the Advisory Committee on Immunization Practices*. MMWR 2011;60(7):4.
Abbreviations:
HBsAg = hepatitis B surface antigen
anti-HBc = hepatitis B core antibody
anti-HBs = hepatitis B surface antibody
HCP= health care personnel
Tdap = tetanus toxoid, reduced diptheria toxoid and acellular pertussis vaccine
HIV = human immunodeficiency virus.
* Updated recommendations made since publication of the 1997 summary of recommendations (CDC Immunization of health care workers: Recommendations of the Advisory Committee on Immunization Practices [ACIP] and the Hospital Infection Control Practices Advisory Committee [HICPAC]. *MMWR* 1997;46[No. RR-18]).

Poland, Tosh, and Jacobson, part of the Mayo Vaccine Research Group, suggest that much like the highly successful hepatitis B immunization requirement, an annual influenza vaccine be required for every health care worker with direct patient care activities unless a medical contraindication to the immunization exists, a religious objection exists or an informed declination is signed by the health care worker.[19] As well, through scientific study of the efficacy of the influenza vaccine, "the CDC supports the assertion that immunizing health care workers safely and effectively prevents a significant number of influenza infections, hospitalizations and deaths among the patients they care for, as well as preventing workplace disruption and medical errors by workers absent from work due to illness, or present at work, but ill."[19] With the undeniable truth that influenza vaccination of health care workers does result in improved employee safety, and decreased health care expenditures,[19,20] Poland, Tosh and Jacobson contest that "with voluntary health care worker vaccination programs failing to achieve acceptable immunization rates, the data lead us to conclude that requiring influenza immunization of health care workers is a moral imperative."[21] Influenza kills roughly 36,000 Americans per year and is the sixth leading cause of death among adults; influenza kills more adults than than breast cancer and three times as many as HIV/AIDS.[22]

The following are measures important in a program to optimize health care worker compliance with influenza immunization:[23]

- CEO, vice president, and directors email employees promoting vaccination;
- Rolling carts to deliver vaccine;
- Vaccinated employees entered into a drawing;
- Declination forms signed for those who decline;
- Expanded hours offered along with off-site, weekend, night shift and off-hour sessions;
- Provide candy and stickers to all vaccinated;
- Program has been ongoing for many years;
- Organization covers costs;
- Drop-in clinics near cafeteria and in infection control office;
- Distribute weekly roster of employee compliance by department October through November;
- Visit to departments with low compliance;
- Provide clinic days for family members;
- Services timed during employee work hours, including night shift;
- Provide vaccination on all units, during staff meetings, and in administrative and support staff offices;
- Vaccine nurse floats daily with rolling cart to units for a month;
- Information on influenza disease and vaccine provided by infection control/occupational health staff; and
- Infection control staff available at clinics to provide factual information and counter myths.

All of these measures are a culmination of a voluntary, ineffective immunization program, despite recommendations from the CDC, the Joint Commission, and the Association for Professionals in Infection Control and Epidemiology for influenza vaccination of all health care workers. Realistically, components of influenza vaccination campaigns to improve uptake of vaccination by health care workers is education to raise awareness and increase knowledge, easier access, tracking and role models.[24] However, according to a study by Po-Po Lam et al., in hospital settings, education or promotion resulted in only small improvements in coverage as did improved access. Conversely, campaigns involving legislative or regulatory components such as mandatory declination forms and mandatory masks for unvaccinated personnel achieved higher rates than other interventions.[25,26] In a study by Hofmann, Ferracin, Marsh and Dumas, the most common barriers to influenza vaccination were a) fear of adverse effects, b) misconception that vaccination can cause influenza, c) misconception that individual is not at risk, d) times/locations of vaccination unsuitable, e) doubt that influenza is a serious disease, f) inefficacy of the vaccine, and fear of injections.[27] Poland et al. assert, "the current policy of voluntary vaccination of health care workers is not effective in achieving acceptable immunization rates and thereby endangers the vulnerable patients we care for and are entrusted with."[19]

The Rapid City Regional Hospital Experience

According to King et al., "active campaigns using occupational health programs or a vaccination team to provide education, distribute reminder notices and schedule vaccination times could help increase vaccination rates."[28] Rapid City Regional Hospital has had a dynamic Occupational Health and Infection Control team for nearly 20 years to manage the vaccination activities at this 471 bed hospital. "Essential components of the program included administrative and managerial support, publication of articles to increase awareness and the establishment of a walk-in clinic during the immunization season. Along with the following actions, infection control staff took mobile vaccination carts to inpatient wards and clinic areas to facilitate vaccination of nurses, physicians, and other hospital personnel."[29]

Leadership Support

- Leadership has active participation in news media coverage, being the first to get vaccinated, promoting a culture of expectation to be vaccinated; and
- Reporting of data to directors and administration.

Duty of Care

- Annual budget allocation for the program;
- Staffing of two departments that take the lead and assume accountability for a successful flu campaign;
- Additional clerical and nursing assistance from Quality Division for Halloween kickoff; and
- Information systems support of an electronic monitoring system for ease of tracking.

Free

- There is no charge for the vaccine;
- Funds are budgeted for incentive prizes for those getting vaccinated early (before December 15); and
- Volunteer nurses used when necessary and for the kickoff vaccine clinic.

Education

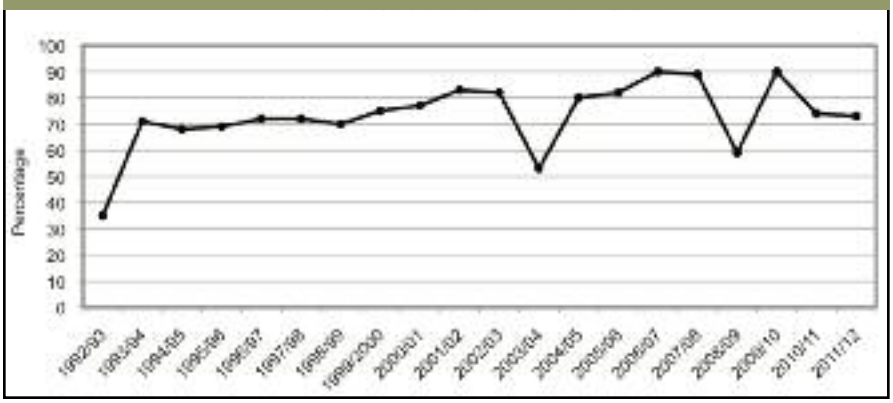
- Messages announce flu shot clinic dates and include where the next convenient place will be and when the traveling cart will be out and about;

- Information disseminated internally by email, posters and fliers;
- Community television coverage of kickoff event featuring CEO and chief medical officer receiving vaccinations; and
- One-on-one counseling by infectious disease physician for those with fear or concern about the effects of the vaccine.

Declination Form

- Information used for improvement – when to offer flu clinics, enhance accessibility and opportunities;
- Track those not vaccinated; and
- Offer flu mist for those declining due to fear of needles and by request if they meet certain criteria.

Rapid City Regional Hospital Health Care Personnel Influenza Vaccination Rate 1993-2012



The 2003-2004 influenza season experienced a shortage of vaccine. 2008-2009 influenza season was the H1N1 outbreak.

In 1994 Rapid City Regional Hospital took action to heighten vaccination awareness. The dates and times that staff, volunteers, students and physicians could receive immunizations were posted in the hospital elevators, on the electronic bulletin board in the cafeteria, and on the hospital office automation system. An added incentive included a chance to win a $50 gift certificate. Candy was also given to persons being immunized. Letters were sent to hospital volunteers to provide them with scheduled times for the annual influenza vaccine. Staff participation increased significantly when vaccinations were offered at the October and November staff meetings."[29] The majority of these measures are continued each year.

One-on-one counseling is an effective measure used by Rapid City Regional Hospital and is supported by Poland et al. to help set aside unfounded fears, preconceptions and misconceptions about influenza and the influenza vaccine.[20] This approach is sustained by the Hofmann et al. study finding that to protect one's patients was a key motivation to immunization of the study group, second only to protection of oneself.[27] Education needs to be geared toward reduction of fears of adverse reactions and efficacy of the vaccine so health care workers recognize their role in spreading influenza to their patients or the possible consequences.[27] At Rapid City Regional Hospital, in addition to Infection Control and Occupational Health, other departments such as Clinical Effectiveness, Quality Improvement, Clinical Integration, Risk Management, Clinical Documentation and Patient Safety have joined the efforts to encourage, counsel and educate the staff and the public.

The current organizational culture is also perfectly designed, because of its established (unconscious) values and resulting belief system, to tolerate the behaviors it is exhibiting.[30] Therefore, the stance of the organization's leaders and visible support is essential. Sullivan, Jacobson and Poland assert, "health organizations must take responsibility for curbing yearly epidemics that profoundly influence the health of our patients, our health care workers, our communities and our global health."[20] Furthermore, with the recognition that voluntary health care worker immunization programs achieve only dismal vaccination rates[52] and certainly do not sustain efforts[19,20] among health care workers, Sullivan, Jacobson and Poland contend, "the medical community should take decisive action to set aside unfounded fears, preconceptions, and misconceptions about influenza, the influenza vaccine and the response of health care workers to such a mandate."[20]

Rapid City Regional Hospital has a long-held tradition kicking off the influenza vaccination season with a 12-hour Halloween Extravaganza. With support of and participation by senior leadership, employees participate in a Halloween costume contest with prizes and treats. Occupational Health, Infection Control and the Clinical Quality Division team up to vaccinate nearly 1,000 employees (one-third of the staff). Vaccination clinics are continued at various times and locations through November and December making access easily available at the employee entrance, in the cafeteria and at hallway intersections. A rolling cart is used to deliver vaccine at staff meetings, employee forums and inservices. In addition, Occupational

Health and Infection Control provide immunization coverage at facilities off the main campus.

Another study of health care worker vaccination is the prevention of pertussis and utilizing tetanus, diphtheria and acellular pertussis (Tdap) vaccine. In this instance those at most risk – the very young – have not had the opportunity to be vaccinated. Therefore, this emphasizes the prevention strategy of exposure avoidance. If all those exposed to the at-risk are immunized, this allows for an interval of protection until vaccination can be achieved for the individual. Rapid City Regional Hospital has taken an aggressive approach to help assure protection by initially vaccinating all those health care workers with Tdap who work around our very young at-risk patients (before these were official recommendations). To further broaden the immunity, workers due for a tetanus booster are then vaccinated. This was done at organizational expense.

Currently we are recommending any family visitors to our Neonatal Intensive Care unit receive both Tdap and influenza vaccination (when seasonally indicated). To help expedite that approach, we are exploring grant options to help provide these vaccinations for those affected individuals.

On review of our surveillance data for the last 10 years, with this approach we have not detected any cases of hospital-acquired pertussis. This approach is especially important this year since there is concern that U.S. rates of pertussis may reach record levels (highest since 1959).[31]

What Other Programs are Doing

In order to reach the Healthy People 2020 goal to increase the health care worker vaccination rate from 45 percent to 90 percent, organizations must think beyond the voluntary approach.[19,32,33]

According to Sullivan, Jacobson and Poland, "the current level of health care workers vaccine uptake has failed to significantly increase over the last decade, despite tremendous visibility and both programmatic and educational efforts."[20,34] For example, during the 2010-2011 influenza season, coverage for influenza vaccination among health care workers was estimated at 63.5 percent by the CDC, compared to 98.1 percent among health care workers who had an employer requirement for vaccination.[35,36]

As the sixth leading cause of death, the annual morbidity and mortality caused by influenza is a serious public health issue,[12] an issue many health care associations and organizations are recognizing as an urgent disease-prevention need. "The extent of the problem becomes evident when aggressive surveillance mechanisms are used, revealing that hospital-acquired influenza can account for up to one-third of all influenza cases when health care worker vaccination rates are low.[37-39] As mentioned previously, Poland et al. conclude that "with voluntary health care worker vaccination programs failing to achieve acceptable immunization rates,[19] the data lead us to conclude that requiring influenza immunization of health care workers is a moral imperative."[12] Furthermore, "continued calls for 'more education' as the answer are shown by 30 years of history, doomed to fail and are indifferent to the available data."[40]

The Society for Healthcare Epidemiology of America (SHEA) views influenza vaccination of health care workers as a core patient and health care worker safety practice with which noncompliance should not be tolerated.[41]

> "It is the professional and ethical responsibility of health care personnel (HCP) and the institutions with in which they work to prevent the spread of infectious pathogens to their patients through evidence-based infection prevention practices, including influenza vaccination. Therefore, for the safety of both patients and HCP, SHEA endorses a policy in which annual influenza vaccination is a condition of both initial and continued HCP employment and/or professional privileges. The implementation of this policy should be part of a multifaceted, comprehensive influenza infection control program; it must have full, visible leadership support with the expectation for influenza vaccination fully and clearly communicated to all existing and applicant HCP; and it must have ample resources and support to implement and to sustain the HCP vaccination program. This recommendation applies to all HCP working in all health care settings, regardless of whether the HCP have direct patient contact or whether the HCP are directly employed by the facility. It also applies to all students, volunteers, and contract workers. SHEA recommends that only exemptions due to recognized medical contraindications to influenza vaccination be considered."[41]

The CDC recommends that all health care workers receive an annual influenza vaccination,[35] and has worked in concert with and provided financial support to the Immunization Action Coalition for the purpose of educating health professionals about U.S. vaccine recommendations.[40]

The Immunization Action Coalition's Honor Roll recognizes stellar examples of mandatory influenza vaccination policies for health care workers. To be included in the honor roll the

Table 3. Immunization Action Coalition: Honor Roll for Patient Safety

Champions	Support Mandatory Vaccination
American Academy of Family Physicians (AAFP)	Yes
American Academy of Pediatrics (AAP)	Yes
American College of Physicians (AAP)	Yes*
American Hospital Association (AHA)	Yes*
American Medical Directors Association (AMDA)	Yes**
American Pharmacist Association	Yes**
American Public health Association (APHA)	Yes*
Association for Professionals in Infection Control (APIC)	Yes*
Infectious Disease Society of America (no exemptions)	Yes
National Business Group	Yes
National Foundation for Infectious Disease (NFID)	Yes
National Patient Safety Foundation (NPSF)	Yes
Society for Health care Epidemiology of America (SHEA)	Yes

*Medical contraindication statement
**Medical contraindication or religious objection exists

mandate you are reporting must require influenza vaccination for employees and must include serious measures to prevent transmission of influenza from unvaccinated workers to patients. Such measures might include a mask requirement, reassignment to non-patient care duties or dismissal of the employee.[4]

In September 2004, Virginia Mason Hospital, an acute care hospital in Seattle became the first facility to implement a mandatory seasonal influenza vaccination program.[15,42-44] Today, approximately 300 facilities across the U.S. have implemented similar vaccination policies.[40,45] The mandatory programs have realized record levels of seasonal influenza vaccination among health care workers. Coverage rates have reached 99.3 percent in several health systems.[15,46-49]

As of June 2011, 20 states (Alabama, Arkansas, California, District of Columbia, Illinois, Kentucky, Maine, Maryland, Massachusetts, New Hampshire, New York, North Carolina, Oklahoma, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Utah and Virginia) had enacted laws that require health facilities to develop influenza vaccination requirements for the workforce. None of the laws have been challenged in any state or federal court, even though some health care workers have argued that the requirements are unconstitutional.[45] However, at Virginia Mason Medical Center, in 2004 the only unionized employees were the inpatient nurses.[10,40] When the fitness-for-duty policy was adopted, the Washington State Nurses Association filed a grievance on behalf of the unionized nurses, claiming that any new requirement for those nurses had to be negotiated as part of their collective bargaining agreement.[15]

Many of the opponents claim the laws violate their Fourteenth Amendment due process rights, the right to the "free exercise" of religion under the First Amendment, the right to "freedom of contract" between employer and employee under the Fifth and Fourteenth Amendments, and the right to privacy and bodily autonomy as a matter of substantive due process under the Fourteenth Amendment.[42,46,50]

Maine is the only state that outlines required sanctions against unvaccinated workers:

- A health care worker may be excluded from work when a public health official determines that the worker poses a "clear danger to the health of others;"
- The employer is not required to continue to pay an excluded worker, unless otherwise provided for by law, contract, or collective bargaining agreement; and
- When a public health official determines the existence of a public health threat, unvaccinated employees must be excluded from work for one incubation period.[45]

Influenza vaccination campaigns will only be effective in the long run if health care workers understand their role in influenza transmission and prevention[51] and if vaccination is free and convenient.[24] Concerted efforts are required to attain these goals and fulfill recommendations.[27,52] However, mandatory vaccination may be a suitable intervention[34,53] or as "an occupational requirement"[54] to cause no harm.[55] Nonetheless, "health care must take responsibility for curbing yearly epidemics that profoundly influence the health of our patients, our health care workers, our communities and our global health."[19,56]

Using influenza and pertussis vaccinations for health care workers as specific topics of discussion allows for an exploration of both the advantages as well as the challenges of these initiatives. There is certainly opportunity for novel and innovative approaches in these areas of patient safety assurance as evidenced by national discussions of mandatory health care worker influenza requirements. Reliability

science would suggest consideration of a condition of employment requirement as an opportunity to minimize patient safety risk. Our internal experience, noticing no recognized hospital-acquired pertussis cases with an aggressive health care worker vaccination program, would support this approach. Also, 20 years ago, putting efforts in place to improve health care worker's influenza vaccination to levels of greater than 70 percent – occasionally reaching 91 percent – have shown a much-improved patient safety risk environment compared to our base year with a rate of 33 percent of health care workers vaccinated. It is our moral imperative to keep our patients safe while under our care; therefore, we should do everything possible to achieve that end.

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CHAPTER 17

Influenza Vaccination: A 21st Century Dilemma

By Marie R. Griffin, MD, MPH

Abstract:

Each year, an average of 5 to 10 percent of the U.S. population has symptomatic influenza illness, 226,000 persons are hospitalized and 24,000 die due to influenza-associated illness. Hospitalization rates are highest at the extremes of age, about one per 1,000 or higher in infants, persons age 65 and older and persons with chronic medical conditions. Ninety percent of deaths are in persons age 65 and older, but deaths also occur rarely in healthy children and young adults. Current influenza vaccines are moderately effective, with current evidence suggesting that they can prevent about half of influenza-associated symptomatic illness, outpatient visits, hospitalizations and deaths, with the evidence weaker for the most serious complications. Current licensed vaccines have mild immediate adverse effects and serious adverse effects are rare. Annual estimates of influenza vaccine effectiveness against the spectrum of clinical illness and in all age groups are needed to evaluate and support current vaccine policies and to help guide more effective vaccine development. Increased use of the current imperfect vaccines could prevent substantial morbidity and mortality in the U.S.

In South Dakota, with a population of 824,000, in an average year, influenza causes an estimated 61,800 acute respiratory illnesses, 18,540 medical care visits, 588 hospitalizations and 62 deaths. Universal influenza vaccination could greatly reduce these numbers most years.

Introduction

There is little doubt about the substantial burden of illness caused by influenza viruses each year. However, because influenza cannot be easily distinguished from other causes of respiratory illness, it is frequently under-recognized by both patients and providers.[1,2] In addition, many patients who receive influenza vaccines will experience acute respiratory illnesses in the months following vaccination. Even if these illnesses are not due to influenza, they create doubts about the effectiveness of current vaccines.

Influenza causes symptomatic illness in about 5 to 10 percent of Americans each year, resulting in an annual average of 226,000 hospitalizations and 24,000 deaths in the U.S.[3,4] Since South Dakota represents about 0.26 percent of the U.S. population, one can estimate the average annual burden of influenza in South Dakota to be about 61,800 symptomatic illnesses, 18,540 health care visits, 588 hospitalizations and 62 deaths (Table 1). In the U.S., influenza vaccine has been recommended for older adults and other groups with conditions that place them at high risk for serious influenza-associated illness for decades. More recently, recommendations for influenza vaccination have been expanded to focus on prevention of illness and medical care visits in all age groups as well as influenza-associated deaths, a threat that increases with age and comorbidity but that can also occur rarely in healthy children and adults.

Yet, some clinicians and public health practitioners find it hard to promote influenza vaccine. This reflects in part the widespread uncertainty about vaccine effectiveness, the reluctance to vaccinate healthy people whose individual risk is relatively low, the lack of evidence that vaccination of healthy persons will protect their vulnerable contacts and concerns about vaccine safety.

Recommendations to vaccinate older adults and persons at high risk which began in 1960 following the 1957

Table 1. Estimated Average Annual Influenza Associated Illnesses in South Dakota

Influenza Spectrum of Illness	Calculation	Estimated Annual Number of Influenza Illnesses in South Dakota
Symptomatic influenza	% of South Dakota population with symptomatic influenza 7.5% x 824,000	61,800
Influenza health care visits	% of South Dakota population with influenza illness seeking medical care 30% x 61,800	18,540
Influenza hospitalizations	% of US influenza hospitalizations in South Dakota 0.26% x 226,000	588
Influenza deaths	% of US influenza deaths in South Dakota 0.26% x 24,000	62

pandemic, were based primarily on evidence of vaccine efficacy in preventing influenza in healthy young adults coupled with evidence of substantial illness burden in older adults.[5] Randomized clinical trials of influenza vaccines in frail older adults, those for whom protection is most vital, have not been performed. Comprehensive evaluations of the impact of U.S. influenza vaccine policies and programs on serious illness and death are challenging and until recently, evaluation has been limited primarily to assessment of vaccine uptake. The lack of evidence of progress in preventing and/or controlling influenza, despite increasing vaccination rates, has created further doubts about the usefulness of vaccination. [6,7]

Observational studies can help fill evidence gaps when randomized clinical trial data are lacking. There have been recent efforts in many countries to perform annual estimates of vaccine effectiveness through standardized observational study methodologies, as exemplified by the Influenza-Monitoring Vaccine Effectiveness (I-MOVE) network in Europe.[8] The expansion of vaccine recommendations will likely encourage more robust evaluations of vaccine effectiveness, as well as development of more effective influenza vaccines. Recent placebo-controlled randomized-controlled trials in healthy adults continue to show that influenza vaccines prevent disease in healthy adults.[9-11] Because of the universal vaccination recommendations, future trials in the U.S. will likely focus on comparative efficacy of differing influenza vaccines. This elevates the importance of robust and efficient observational study designs to estimate both the annual burden of influenza illness and annual influenza vaccine effectiveness.

Decisions to recommend vaccination need to consider the burden of influenza-associated illness, as well as vaccine effectiveness and safety. When the burden of illness is high, even vaccines that have only moderate effectiveness will still have substantial benefit, given a good safety record. This review will summarize evidence on the burden of influenza, vaccine effectiveness and vaccine safety.

Methods

This is an overview of influenza disease and vaccines applicable to the U.S. population, and not a systematic review. Many systematic reviews of some included topics exist and are cited when applicable. The section on burden of influenza relied primarily on systematic reviews of published studies that included influenza attack rates and on U.S. national estimates for medical care visits and deaths, when available. For information on influenza vaccines licensed in the U.S. and vaccine recommendations, data is used from the Centers for Disease Control and Prevention (CDC), available at www.cdc.gov/flu/professionals/vaccination. Information on vaccine effectiveness relied primarily on summaries of data compiled by the Cochrane Collaboration for the section on vaccine effectiveness;[12-14] however, for some sections, more recent information is available.[15] An extensive recent overview of influenza vaccines available at www.cidrap.umn.edu was also reviewed. Interpretation of data summarized in the Cochrane reviews sometimes differed from that of the authors of those reports. I have tried to make clear when the interpretation is mine rather than the authors'. Information on vaccine safety was also obtained from the Cochrane reviews and a recent expert review on vaccine safety,[16] supplemented by more extensive consideration of safety in pregnancy.[17]

The Burden of Influenza

Overview There are multiple sources of information on influenza-associated infection and illness burden. Early household studies in which testing of respiratory samples were complemented by serologic studies gave good information on infection and illness rates, especially within families. More recent studies of working adults and studies of health care workers have added to this body of knowledge. There are real differences based on which influenza viruses are circulating at the time of the study, population

studied and region; other differences in results are due to methods of measurement of influenza. Early studies relied primarily on viral culture and serology. More recent studies have used polymerase chain reaction (PCR) testing methods, which are more sensitive than culture and have a better ability to link to specific illness than serology performed at the start and finish of each season.

For more serious influenza-associated illness, larger populations need to be studied. The CDC has estimated the number of annual deaths due to influenza for decades using modeling studies that take advantage of the availability of death certificates and the strong seasonality of influenza viruses. Increasing availability of computerized health records has enabled similar modeling to be performed to estimate hospitalizations and outpatient visit rates. The direct measurement of influenza-associated health care visits has helped confirm rates estimated from modeling studies.

Influenza Illness In the U.S., influenza viruses cause annual epidemics of illness, with 95 percent of the epidemic illness occurring over about 12 weeks in any given region. Early family studies reported annual respiratory illness associated with influenza virus isolation of 2 to 9 percent in children and 1 to 2 percent of adults but much higher rates of seroconversion – closer to 30 percent in children and 5 to 10 percent in adults.[18] In 14 clinical trials of healthy children, influenza attack rates in children randomized to placebo ranged from 3 to 56 percent, median 32 percent.[12] A meta-analysis of the incidence of influenza in healthy working adults reported a symptomatic infection rate of 5.12 percent (95 percent CI 3.08 to 8.52) among unvaccinated healthy workers. [19]

Influenza Outpatient Visits Outpatient visit rates for influenza have been estimated to be six to 15 per 100 children each year based on modeling studies,[20-22] and associated antibiotic courses have been estimated as three to nine per 100 children annually.[21] These estimates were consistent with a study that directly measured influenza in young children and found rates of six and 12 per 100 children in two influenza seasons.[1] These rates are also consistent with survey data that indicated that 56 percent (55 to 58 percent) of children seek medical care when they develop influenza-like illness.[23] There are few estimates of outpatient visit rates for adults, but survey data indicate that 26 percent (23 to 29 percent) seek medical care when they develop influenza-like illness.[23] Given that symptomatic illness occurs in about 5 percent of adults, we can estimate that one to two per 100 adults seek care for influenza-associated illness each year.

Influenza-associated Hospitalization Rates Several studies have estimated influenza-associated hospitalizations using a combination of administrative data on hospital discharges and surveillance data on circulation of influenza and other viruses. Several models have been used, but all model the excess in hospitalizations that occur when influenza is circulating. The most recent estimates for national rates summarized data from 1993 through 2008 and used data on both influenza and respiratory syncytial virus circulation.[24] Hospitalization rates from this study were similar to prior estimates, with rates of excess respiratory and circulatory hospitalizations highest at the extremes of age, and when influenza A (H3N2) was the predominant virus circulating. Over the 15 study years, hospitalization rates were estimated to be on average 1.5 (range 0.5 to 3.2) per 1,000 children less than 1 year of age and 3.1 (range 1.4 to 5.1) for adults 65 years and older. Hospitalizations were lowest in persons 5 to 49 years of age at 0.2 (range 0.1 to 0.3) per 1,000 (Figure 1). Direct measurement of influenza in young children hospitalized with respiratory illness from three geographic regions over four years yielded similar

Figure 1. Estimated Influenza Hospitalization Rates per 100,000 – U.S. 1993-2008

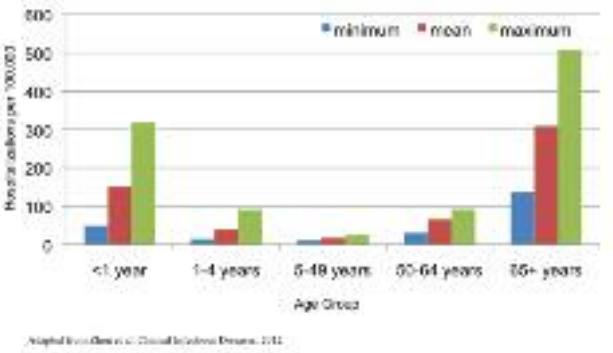
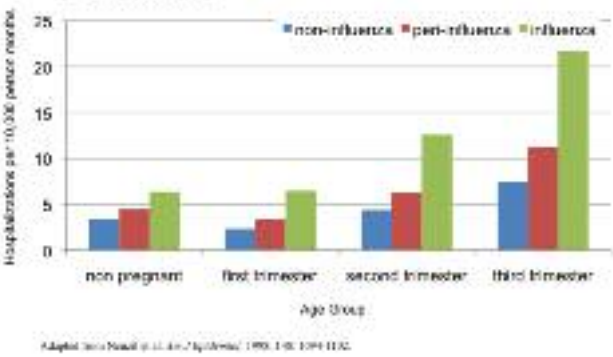


Figure 2. Estimated Influenza Hospitalization Rates – U.S. Women Aged 15-44 years, 1974-1993



results, with an average rate of close to one per 1,000 children less than 5 years of age.[1]

Similar modeling studies have found that persons younger than 65 years of age, but with specific high-risk conditions also have hospitalization rates of one per 1,000 or higher.[25-28] In addition to persons with chronic cardiac or respiratory conditions, those who are immune-suppressed and women in their second and third trimester of pregnancy are at relatively high risk of influenza-associated hospitalizations.[29] Figure 2 illustrates the pattern of health care visits for respiratory illness that has been demonstrated in multiple populations. Acute respiratory hospitalization rates are lowest in the summer and in warmer months (May through October), but increase in colder months (November through April). In these colder months, rates are almost always higher during the time when influenza viruses circulate (influenza) than in other times (peri-influenza).

Influenza-associated Deaths Annual influenza deaths have been estimated with similar methods described above for hospitalizations by using national death certificates and viral surveillance data. Over 31 influenza seasons from 1976-1977 to 2006-2007, the average annual number of influenza-associated respiratory and circulatory deaths has been 23,607 (range 3,349 to 48,614).[4] Investigators further estimated that influenza accounts for 8.5 percent of all pneumonia and influenza deaths and 2.1 percent of all respiratory and circulatory deaths annually. About 90 percent of influenza associated deaths occur in adults age 65 and older. There was an estimated annual average of 124 deaths in children (range 41 to 234). Since influenza-associated pediatric deaths became a nationally notifiable condition in 2004, the number of deaths reported to the CDC has ranged from 46 during the 2005-2006 influenza season to 282 during the 2009-2010 pandemic season. For the 2010-2011 season, 115 influenza-associated pediatric deaths were reported to the CDC. Fifty-six (49 percent) deaths occurred in children without known high-risk medical conditions. The close correlation between the number of annual reported influenza deaths in children and estimates of annual deaths from modeling studies again helps to confirm the validity of these methods.

Influenza Vaccines

Human influenza viruses undergo frequent antigenic changes. Influenza vaccines are unique in that they are reformulated annually to try to achieve the optimal antigenic match between the vaccine and predicted circulating virus strains. The current seasonal influenza vaccines are trivalent vaccines, which include strains of the A subtypes H3N2 and H1N1 and one strain of B virus. The World Health Organization (WHO) issues recommendations each February for which strains should be included in the seasonal vaccine for the northern hemisphere. Once these recommendations have been made, vaccine producers have about six months to manufacture and distribute the seasonal vaccine. During the 2009 pandemic, the influenza A (H1N1) pdm09 strain was identified in April 2009, but the first pandemic vaccines started to become available in the U.S. only in September 2009. Antigenic changes in circulating viruses may occur before the start of the vaccination campaigns or unanticipated strains can circulate and can result in a poor match between vaccine (seasonal and pandemic) and circulating strains.

In 2010, the Advisory Committee on Immunization Practices (ACIP) first recommended annual influenza vaccination for all persons in the U.S. aged 6 months and older.[31] This followed almost a decade of expanding vaccine recommendations to encompass more groups than just those aged 65 years and older and persons at high risk of influenza complications. The age to start vaccination was lowered to 50 years, since a high proportion of persons aged 50 to 64 had chronic conditions putting them at high risk for influenza complications and were not being vaccinated. Recommendations were expanded first to the youngest children aged 6 to 23 months who had a relatively high risk of hospitalization, and then to all children due to the high incidence of influenza illness and rare deaths even in healthy children.[1,20,21,32] Other groups for whom vaccination was recommended such as health care workers and contacts of persons at high risk for influenza created a patchwork of recommendations that included most of the population. Although the ACIP always recommended vaccination for all persons who wanted to avoid influenza illness, many viewed the lack of a specific recommendation as a reason not to vaccinate or be vaccinated. The 2010 recommendation simplified recommendations for patients and providers.

Although the U.S. had influenza vaccination recommendations for older adults and those at high risk for decades, use of vaccine in most other countries has been low. In May 2003, the World Health Assembly recommended annual influenza vaccination for the elderly and persons with underlying diseases. WHO member states committed to attain vaccination coverage in the elderly population of at least 50 percent by 2006 and 75 percent by 2010. [33] These recommendations have helped fuel more rigorous annual evaluations of vaccine effectiveness (see below).

Choices of vaccine products have expanded in the last

decade.[31] For the 2012-2013 season, nine different products by six different vaccine manufacturers were available in the U.S., all of which are designed to protect against three specific influenza viruses (trivalent: two influenza A and one influenza B). The FDA has approved a quadrivalent vaccine by one manufacturer (two influenza A, two influenza B), because there have been frequent mismatches between the B component chosen for the seasonal vaccine, and the B virus that circulates. It is likely that other manufacturers will eventually include antigens for two B viruses as well as two A viruses. Most inactivated influenza vaccines contain similar amounts of viral antigen and are administered intramuscularly, but an antigen sparing vaccine is designed for intradermal use, and a higher antigen vaccine that results in a higher antibody response is licensed for persons aged 65 years and older. Some vaccines, including the only vaccine licensed for children aged 6 to 23 months, now exclude mercury, which, as thimerosol, is used as a preservative. A live attenuated vaccine, delivered by nasal spray, is available for healthy persons aged 2 to 49 years.

Influenza Vaccine Efficacy/Effectiveness

Overview Efficacy is a term used to express how well a vaccine or other intervention works in clinical trials, whereas effectiveness relates to how well a treatment works in practice, in which both patients and handling of vaccines may differ from clinical trial situations. Efficacy studies generally are performed to assure that the vaccine does work under ideal circumstances. Effectiveness studies may be performed to determine if the vaccine works similarly for populations not included in clinical trials or to examine other endpoints such as hospitalizations or deaths rather than influenza illness.

Influenza is one of many viruses that cause acute respiratory illness and the complications that often accompany such illness such as acute otitis media, bronchiolitis in children and pneumonia. In addition, influenza can cause non-respiratory manifestations including high fever alone, febrile convulsions, and rarely Reye's syndrome, myocarditis and Guillain-Barre syndrome. Influenza often presents as fever and cough (influenza-like illness), but this presentation is neither sensitive nor specific for influenza, and the predictive value of this type of definition depends on prevalence of influenza, which varies markedly with timing (predictive value is highest during peak influenza season and can become negligible when influenza circulation is low) and with the activity of other respiratory viruses. This definition also is insensitive in frail, older persons.[34]

The Cochrane reviews include both influenza and influenza-like illness as outcomes. Because of the above considerations, this review focuses only on estimates against diseases for which the vaccine was designed to protect – those due to influenza A and B viruses. As noted in the Cochrane reviews and by others, these viruses account for only 7 to 15 percent of influenza like illness, and a similar proportion of respiratory and circulatory hospitalizations and deaths during winter. One problem with the studies included in the Cochrane review is that the influenza outcomes were measured in different ways: viral culture, serology and polymerase chain reaction (PCR) tests. Viral culture is not as sensitive as PCR, and serology is sensitive in unvaccinated individuals but may be insensitive in those who received inactivated vaccines, biasing estimates in favor of vaccines.[35] A recent review by Osterholm et al. summarized both clinical trials and observational studies that used laboratory-confirmed influenza as an endpoint and excluded serology endpoints for inactivated vaccine studies.[15] Results of this review will also be considered below.

It is hard to measure the impact of influenza vaccine on medical care visits, hospitalizations and deaths in clinical trials for multiple reasons. The trial itself may influence access to medical care; large trials are usually limited to healthy participants who have a lower rate of medical care visits. Such trials would need to be very large, and there is reluctance to do placebo-controlled trials in groups for whom vaccine is recommended, even when there is a dearth of evidence to support the recommendations. Thus, all reviews report a lack of evidence about these endpoints from clinical trials.

Observational studies have attempted to fill knowledge gaps left by the absence of or deficiencies of existing clinical trials. Many cohort studies of influenza vaccine effectiveness have used endpoints other than laboratory confirmed influenza. Since influenza vaccines do not prevent respiratory illness caused by other viruses, these studies will generally underestimate influenza vaccine effectiveness and will vary based not only on the true vaccine efficacy, but also on the prevalence of influenza in relation to other causes of respiratory illness. Some large cohort studies using administrative data have failed to control adequately for differences between vaccinated and unvaccinated persons, and have thus overestimated vaccine effectiveness against outcomes such as respiratory hospitalizations or all-cause deaths.[7,36,37] In general, persons with identified high-risk conditions may have a higher likelihood of vaccination than healthier persons. Some individuals at a very high risk of death, including those with limited life expectancy, may be less likely to be vaccinated. It is difficult to distinguish such

levels of frailty and co-morbidity using administrative data.

More recently, test-positive, control-negative case-control studies have been promoted as an efficient means to obtain vaccine effectiveness estimates.[8,38] In these studies, vaccine history is compared in patients seeking care for respiratory illness who test positive for influenza (cases) versus those who test negative (controls). Thus, controls are more likely to resemble cases in their likelihood of seeking or requiring medical care if they develop a respiratory illness. Indeed, when comparing persons hospitalized for respiratory illness, differences in clinical presentation between those with influenza and those with other respiratory viruses or no viruses identified have been minor.[1,39,40] Most such studies have been performed in outpatient settings, but there are some that have been limited to or include hospitalizations. This methodology has been used in many countries which are now attempting to estimate annual influenza vaccine effectiveness.[8,41]

Influenza Vaccine in Healthy Children The Cochrane review, published online in August 2012, included 75 studies with about 300,000 observations: 17 randomized clinical trials, 19 cohort studies and 11 case-control studies in the analysis of vaccine efficacy and effectiveness.[12] Data for vaccine efficacy for children aged 2 years and older appears to be robust, and the trials reflect what we know about influenza epidemiology. Overall 18 percent of children randomized to placebo-developed influenza compared to 3 percent of children randomized to live-attenuated vaccine. Trials of inactivated vaccine included children aged 6 to 23 months and reported attack rates of 26 percent for those randomized to placebo and 8 percent for those randomized to vaccine. The efficacy of live attenuated vaccine in healthy children was 80 percent and for inactivated vaccine was lower at 59 percent, but direct comparisons between the two vaccines were not reported. Live attenuated vaccine was not licensed for children less than 2 years of age in the U.S. because of an increase in wheezing associated with vaccine in young children. More information can be found by visiting www.cdc.gov/MMWR/preview/MMWRhtml/mm5646a4.htm. There was scant evidence from clinical trials on efficacy of inactivated vaccine in this age group (two trials with a combined relative risk of 0.55 (0.18 to 1.69).

The Cochrane review also summarized the results of the test-positive control-negative case-control studies, but the authors did not take these studies into account in their summaries. Many of these studies were performed in health care settings, so they attempted to estimate protection against medically-attended illness. In addition, unlike clinical trials, they were not restricted to healthy children. Summary estimates of influenza vaccine effectiveness were 40 percent for children aged 6 to 23 months, 60 percent for children aged 24 to 59 months, and an overall vaccine effectiveness of 55 percent for children under 5 years of age. This estimate is very close to the 59 percent overall estimate for inactivated vaccines from clinical trials in healthy children.

The review found influenza vaccines 86 percent effective in preventing school absenteeism based on two small studies. There was little evidence on effectiveness of preventing complications of influenza, and most of the scant evidence relied on non-specific outcomes (e.g., otitis media, pneumonia, etc.)

Thus, current vaccines have considerable ability to prevent influenza illness and health care visits for influenza in children. The live attenuated influenza vaccine appears to be more effective than inactivated vaccine in young children. There is some evidence that vaccines prevent days lost from school, and it would be reasonable to assume that the reported effectiveness against influenza illness results in fewer sick days, less school absenteeism and less missed work for parents.

Influenza Vaccine in Healthy Adults The Cochrane review for healthy adults was last updated in 2010.[13] Inactivated vaccines were 73 percent effective (54 to 84 percent) in preventing influenza illness when there was a good match of vaccine to circulating strains and 44 percent (23 percent to 59 percent) effective when there was not a good match. The proportions of healthy adults with identified symptomatic influenza ranged from 2 to 5 percent in those randomized to placebo compared with 1 percent of those randomized to vaccine. Thus, depending on the year and the match, 1 to 3 percent of persons vaccinated benefit from vaccination by avoiding an influenza illness. An analysis of five trials indicated an average savings of 0.13 work days. Although this seems like a small benefit, it would only accrue to the 1 to 3 percent of vaccinated persons who avoid influenza illness, who would save an estimated two to 13 days each. The pooled efficacy from the recent review of Osterholm et al.[15] for inactivated vaccine in adults 18 to 65 years of age was similar, 59 percent (51 to 67 percent), with efficacy demonstrated in eight of the 12 seasons studied.

Inactivated and live vaccines were compared in three years in which healthy adults aged 18 to 49 years were randomized to inactivated influenza vaccine, live attenuated vaccine, or placebo.[9-11] In the two years with significant influenza activity,

one in which there was a good vaccine match and one in which there was a drifted influenza A strain, inactivated vaccine effectiveness was similar to the 73 percent reported in other trials cited above and was greater than live attenuated vaccine in both of these years. In the third year, there was little influenza activity and only the inactivated vaccine showed modest efficacy.

Thus, inactivated vaccines have an overall average effectiveness of 50 to 60 percent in preventing symptomatic influenza illness in healthy adults less than 50 years of age. The inactivated vaccines appear more effective than live attenuated vaccine in this population. Vaccine also prevents days lost from work. Evidence on more serious complications, rare in the healthy population, is scant.

Influenza Vaccine in Elderly The Cochrane review was last updated in 2010;[14] few randomized trials were available for inclusion and none reported efficacy against influenza complications. Based on three trials in which average influenza attack rates were 6 percent in unvaccinated compared to 2 percent in vaccinated, the efficacy of inactivated vaccine against influenza illness was 58 percent (34 to 73 percent). A large number of other studies were reviewed but were felt to be of poor quality and for the most part used definitions not sensitive or specific for influenza. Both the Cochrane review and that of Osterholm et al. found little evidence available to estimate protection for adults 65 years of age and older.[15] A recent study used the case-positive control-negative method to estimate inactivated vaccine effectiveness in adults 50 years of age and older hospitalized with respiratory illness over the seasons. The estimates of effectiveness in the three years ranged from 56 to 73 percent, but only the pooled estimate was statistically significant at 61 percent (18 to 82 percent), again consistent with moderate protection against complicated influenza.

A number of recent studies have tried to evaluate the effect of influenza vaccination on all-cause mortality, most of which occurs in persons 65 years of age and older. In a number of innovative study designs that controlled for adverse selection associated with non-vaccination[42] and used an instrumental variable approach,[43] vaccination was estimated to prevent 5 to 6 percent of deaths during influenza seasons. Since about 7 to 15 percent of deaths may be due to influenza, these estimates appear to fit with a vaccine that is moderately effective.

Ongoing Surveillance for Vaccine Effectiveness

Many countries are now adopting standardized methods to evaluate vaccine effectiveness each year, including the U.S., Europe, Australia and Canada.[8,41,44-46] The most common method now used is the case-positive control-negative case-control study, and in many countries this provides both sentinel information on circulating strains and annual estimates of vaccine effectiveness. In Europe, annual estimates are available since 2008 when five countries participated through 2012 with eight countries contributing data. Annual estimates of vaccine effectiveness against symptomatic medically-attended laboratory-confirmed influenza illness was 72 percent in the pandemic year, and 59 percent and 52 percent in the other two years, without much variation in these estimates by age.[8] A report of five years of such surveillance in Australia found combined vaccine effectiveness of 41 percent (19 to 57 percent).[47] A study in the U.S. showed moderate effectiveness of influenza vaccines against medically-attended laboratory-confirmed illness in the pandemic year[46] (56 percent, 23 to 75 percent) and moderate effectiveness again in the post-pandemic year (60 percent, 54 to 66 percent).[44] In Spain, the high effectiveness (90 percent) of adjuvanted pandemic vaccine compared to no effectiveness of two seasonal vaccines against the pandemic influenza virus using the same methods lends further credibility to this study methodology.[48] In Canada, a recent mid-season analysis detected surprisingly low effectiveness against influenza A H3N2 that was found to be due to a new genetic variant of the virus.[41]

Influenza Vaccine Safety

Local and Systemic Effects Immediately Following Vaccination The Cochrane review of vaccine safety in healthy children reported that variability in study design and presentation of data was such that a meta-analysis of safety outcome data was not feasible.[12] They also reported that extensive evidence of reporting bias of safety outcomes from trials of live attenuated influenza vaccines impeded meaningful analysis. A recent expert review of vaccine safety found local reactions to inactivated vaccine to be common in children, and systemic reactions to be less common, and associated primarily with first-ever vaccination. An increase in wheezing in young children was associated with live vaccine and is the reason for the lack of indication for children less than 2 years of age.[16]

The Cochrane review of vaccine safety in healthy adults reported mild local effects of inactivated vaccine (local tenderness and erythema) and a modest increase in myalgia, but no other systemic symptoms were statistically different from placebo. Live vaccine was associated with upper respiratory symptoms including sore throat and coryza (RR 1.66, 1.22 to 2.27) but no significant increase in

systemic symptoms.[13]

The Cochrane review of vaccine safety in the elderly found no statistically significant differences in systemic adverse events (malaise, fever, nausea, headache) between vaccine and placebo recipients, although they tended to be numerically higher in the former. Local arm tenderness and pain were significantly higher in vaccine recipients but was generally mild.[14]

There is now extensive experience with inactivated non-adjuvanted influenza vaccines in pregnant women, with no evidence for specific maternal or fetal complications.[17] Breastfeeding does not affect the immune response adversely and is not considered a contraindication for vaccination.

Rare Adverse Events Guillain Barre Syndrome was definitively linked with the 1976 swine influenza vaccine (estimated about five to 10 episodes per 1 million doses in the six weeks following vaccination), but the association with subsequent vaccines is not certain, and if causal, much lower than with the swine influenza vaccine, estimated to be about one per 1 million doses. Monitoring following the 2009 pandemic influenza vaccination campaign showed no increase.[49]

One specific brand of adjuvanted monovalent pandemic vaccine not licensed in the U.S. was associated with cataplexy and narcolepsy in children, but the causal nature of this relationship is uncertain.[50] An intranasal inactivated vaccine not licensed in the U.S. was associated with Bell's palsy.[51] An inactivated vaccine in Australia was linked to severe febrile events in children.[52]

All U.S. licensed vaccines have been evaluated by the FDA for short term safety. Changes to annual vaccines involve change in the antigens included, but the vaccines themselves are otherwise similar. Many of the influenza vaccines used in Europe have been adjuvanted to improve immunogenicity and effectiveness. These adjuvanted influenza vaccines have not been licensed in the U.S., and would require further safety and efficacy testing prior to licensure.

Other Considerations

The 1957 pandemic provided an impetus to change vaccine recommendations because of the devastating effects of influenza associated with that and other influenza pandemics. The 2009 pandemic showed that pandemic vaccines could be produced in a relatively timely way, but there was considerable uncertainty about vaccine supply and the ability to deliver vaccine to the population. These pandemics have spurred interest in both new vaccines and vaccine delivery (see also www.cidrap.umn.edu). A robust influenza vaccine program including annual effectiveness and burden estimates should help with future pandemic preparedness.

It makes sense that if vaccines can prevent influenza, they will reduce spread of the virus and help protect those who are unvaccinated. There is some evidence for this type of "herd protection" in communities.[53-55]

Conclusions

Current influenza vaccines licensed in the U.S. are moderately effective against symptomatic influenza illness. Live vaccine appears to be more effective in children, and inactivated vaccines appear to be more effective in adults. Although the evidence base for prevention of outpatient visits, hospitalizations and death is not as strong as for influenza illness, the existing data are consistent with moderate effectiveness against influenza-associated medical care visits. Although more effective vaccines are needed, currently available vaccines can have a substantial impact now because of the high burden of influenza each year.

In South Dakota, with a population of 824,000, in an average year, influenza causes an estimated 61,800 acute respiratory illnesses, 18,540 medical care visits, 588 hospitalizations and 62 deaths. Universal influenza vaccination could greatly reduce these numbers in most years (Table).

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CHAPTER 18

Safe Handling of Vaccines: The Rewards of Rigorous Routines

By Kelly Hefti, MSN, RN, CNP, COHN-S and Gerard David, MD

Abstract:

A recent report published by the Office of Inspector General (OIG) entitled *Vaccines for Children Program: Vulnerabilities in Vaccine Management* has brought to public awareness the need for increased attention to safe handling of vaccines. The maximum benefit of receiving vaccines for vaccine-preventable diseases can only be attained when we ensure that safe storage and handling occurs through strict adherence to the vaccine cold chain. This compliance can best be accomplished by identifying a vaccine coordinator that is intimately familiar with the components of the vaccine cold chain and provides the necessary oversight to ensure that all links in the chain are maintained. Utilization of helpful resources, including the Centers for Disease Control and Prevention (CDC) resources related to safe handling of vaccines, is central to a well defined process for vaccine handling. This adherence provides reassurance, both to patients receiving vaccine and providers administering it, that the safest and most effective vaccine is being delivered.

In the 1983 famous commercial for Dunkin' Donuts, the late Michael Vale as "Fred the Baker" wearily awakes to his alarm clock and recites over and over, "It's time to make the donuts." The seemingly routine task of making the donuts, however, has great reward for his customers as they savor the delectable taste of donuts made fresh daily. This seemingly routine and possibly even mundane task of "making the donuts" could be applied to a far more critical issue – what we as health care providers must do on a daily basis to ensure the integrity of the vaccines that we administer to our patients. Relentlessly (twice daily for vaccines), we must keep at top of mind, "It's time to check the refrigerator temps." The reward in the end for health care providers is that we are doing everything we can to deliver "fresh" and effective vaccine to our patients.

A recent report published by the Office of Inspector General (OIG) entitled *Vaccines for Children Program: Vulnerabilities in Vaccine Management*[1] looked specifically at a sample of 45 Vaccine for Children (VFC) providers. The Centers for Disease Control and Prevention (CDC) manages the VFC program, and there are a total of 61 recipients of VFC vaccine throughout the country. These 61 recipients, known as grantees, include departments of health from all 50 states, as well as six metropolitan areas and five U.S. territories and protectorates. The OIG report focused on providers from five grantees that had the highest volume of vaccines ordered in 2010. The results were sobering. Seventy-six percent of the 45 providers had vaccines that were stored outside of recommended temperature ranges for at least five cumulative hours during the two-week period of study. Additional concerns over storage of expired vaccines and required documentation led the OIG to recommend that CDC work with grantees and providers to ensure the four following recommendations:

- VFC vaccines are stored according to requirements;
- Expired vaccines are identified and separated from non-expired vaccines;
- Grantees manage providers' vaccine inventories; and
- Grantees meet oversight requirements.

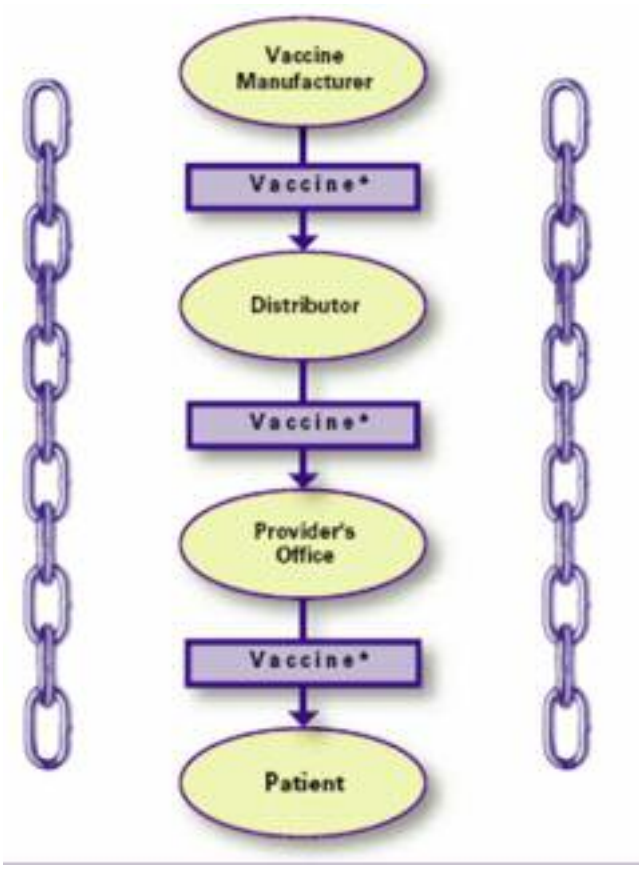
The executive summary from the OIG report further states that "CDC concurred with all four recommendations and noted that vaccination is one of the most successful public health tools in preventing and controlling disease."

For purposes of this discussion, we would like to focus on the OIG's first and second recommendations specific to storage requirements, including expired vaccines. Imagine for a moment that you are a new provider or manager in a clinic setting and during one of your first rounds to really get to know staff and understand their workflow, you ask for the temperature log that is used to monitor and document temperature readings and ranges in the refrigerator that stores vaccines. At first glance, you notice that, for the most part, the temperatures are recorded with a few days missed, "here and there." A small red flag goes up and you get a small pit in your stomach, but you forge ahead and ask to review logs from the last 12 months. The small red flag and now the symptoms of your own growing nausea are quickly moving to an "S.O.S" alert. The gnawing gut ache becomes dominate as you see a three-month period of time when the temperatures recorded on the logs are below the vaccine manufacturer's specifications. There are no documented actions to show how vaccines were handled during these out-of-range periods of time. You then ask for an inventory log to determine what vaccines may have been in the refrigerator during this period of time. Another blank stare makes you realize that keeping an inventory log is not part of the common work flow. As you continue to work through the implications of what you are finding, and in consultation with your state department of health and the vaccine manufacturers, you realize that there are potentially hundreds of patients that may have received vaccine that were exposed to temperatures below manufacturer recommendations, thus potentially yielding them ineffective. This is a scenario that none of us want to become a reality.

Proper storage of vaccines is critical to vaccine integrity. A comprehensive approach to recording and documenting temperatures in refrigerating units used to store vaccines is central to any effective vaccination program. The CDC illustrates this approach via the vaccine "cold chain."[2]

The cold chain contains documentation of the vaccine from the time of manufacturing through distribution to the provider and ultimately to the patient.

At the core of any effective vaccine program is the need to identify and designate a vaccine coordinator who both understands how crucial the vaccine cold chain process is to delivering safe and effective vaccine to patients, and who has accountability for this process.[3] The expectations of the vaccine coordinator need to be clearly articulated. Any delegated duties to other staff members (i.e., documenting of temperature readings and ranges) must also be clearly defined. The vaccine coordinator is responsible for documenting appropriate vaccine cold chain compliance from the time the vaccine arrives at the health care facility until the vaccine is administered to the patient. At the time of delivery, an inventory of all vaccine received, including



type of vaccine, lot number, number of doses, expiration date and date received must be documented. In turn, it must be established when the vaccine is eventually administered or removed from the storage unit. This process allows for full awareness of exactly which vaccines are in a particular storage unit at any given point in time, something that is essential if it is ever necessary to determine what vaccine may have been affected if an out of range temperature is identified. As inventory is documented, coordinators should be cognizant of keeping enough inventory to meet patient needs but to avoid overstocking. Overstocking vaccine increases the potential financial loss if an event occurs where vaccine must be discarded because of a breach in the cold chain. Overstock also increases the potential of having vaccine expire, which could inadvertently be administered to patients and is again a financial loss of the vaccine itself.

Refrigerator temperatures must be maintained at 35° to 46° F (2° to 8° C). Freezer temperatures must be maintained at -58° to 5° F (-50° to -15° C).[4,5] The goal is to maintain temperatures within accepted ranges without extreme highs or lows. As noted above, most vaccine programs recommend recording temperatures twice daily, at the beginning and end of each work day. Ideally a 24-hour monitoring system should be in place to document that temperatures ranges have been maintained within range in any given 24-hour period of time. The thermometer should have a Certificate of Traceability and Calibration.[6] This means that after the thermometer is manufactured, it is calibrated to measurements traceable to one of the following: a testing laboratory accredited by the International Organization of Standardization, the standards of the National Institute of Standards and Technology or to another internationally recognized standards agency. The thermometer must be recalibrated to these measurements at regular intervals according to manufacturer's guidelines. Storage requirements also specify that vaccines should be kept in bins, baskets or some other type of uncovered containers, with slotted sides or openings in the center of the refrigerator, away from the walls and vents. Vaccine should never be stored in the doors or the crispers. All of these storage specifications are necessary to help vaccines maintain the required temperature. In addition, frozen packs are recommended to be placed in the door of the freezer, and water bottles are to be placed in the door of the refrigerator to help stabilize temperatures.

Vaccines and diluents should be rotated to ensure that vaccine with the shortest expiration date is used first. Ensuring that shortest expiration date vaccine is used first avoids expensive loss of vaccine that becomes unusable if expired. All expired vaccine and diluents should be removed to avoid inadvertent administration to a patient.

All facilities need to maintain an emergency plan for outages and a plan for transportation of vaccine if the cold chain cannot be maintained within the current storage space.[7] Transportation of vaccine again requires strict adherence to the vaccine cold chain and involves proper storage containers, packaging materials, packaging protocol and recording of temperature throughout the transport to ensure that vaccine temperatures are maintained. If there is ever a question that the vaccine cold chain has been breached, all vaccine must be quarantined and labeled, "do not use" until a full investigation has been completed.

For anyone trying to establish a vaccine program or if simply trying to validate the processes currently in place, the CDC provides excellent step by step resources for ensuring compliance with the vaccine cold chain. A sampling of these invaluable resources are referenced below:

Selected Vaccine Storage and Handling Resources
(Materials from CDC, the Immunization Action Coalition and the California Department of Public Health's EZ-IZ website.)

Vaccine Storage & Handling Guide
Best practices, storage and handling recommendations for all U.S. vaccines, www.cdc.gov/vaccines/recs/storage/guide/vaccine-storage-handling.pdf

Emergency Response Worksheet
What to do in case of a power failure or another event that results in vaccine storage outside of the recommended temperature range, www.immunize.org/catg.d/p3051.pdf

Refrigerator Buying Guide
VFC requirements, tips and a worksheet for buying a refrigerator for vaccine storage,
http://eziz.org/assets/docs/IMM-940.pdf

Setting Up Your Refrigerator and Freezer for Vaccine Storage
Refrigerator – http:// eziz.org/assets/docs/IMM-963.pdf
Freezer – http:// eziz.org/assets/docs/IMM-965.pdf

Storing Vaccines in Your Refrigerator and Freezer
Refrigerator – http:// eziz.org/assets/docs/IMM-963.pdf
Freezer – http:// eziz.org/assets/docs/IMM-966.pdf

Temperature Logs for Vaccines
Fahrenheit – www.immunize.org/catg.d/p3039f.pdf
Celsius – www.immunize.org/news.d/3039c.pdf

Transporting Refrigerated Vaccines
Guidelines for vaccine transport and short-term storage,
http:// eziz.org/assets/docs/IMM-983.pdf

We all know that even with every safeguard in place, situations may arise beyond our control that require investigation into whether the vaccine cold chain has been maintained and if vaccine can be administered to patients. Imagine for a moment that you are a new provider or manager in a clinic setting, and there was a summer storm in your area over the weekend. When you get to the clinic in the morning, you contact your vaccine coordinator, who is already aware that the refrigerator exceeded maximum acceptable temperatures for a period of time during the power outage. She has taken steps according to the emergency plan and quarantined all vaccines and medications that were in the refrigerator and is in the process of contacting manufacturers and the distributing pharmacy for guidance. She informs you that no patients received any vaccines prior to the quarantine. This scenario is completely different than the first scenario because someone owned the process, had policies and procedures in place and ultimately took accountability for safe and reliable processes to ensure delivery of effective vaccines. Like "Fred the Baker" knows, the highest quality comes from rigorous "routines" that never compromise….so it is with safe vaccine handling.

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CHAPTER 19

The New Vaccine Frontier

By Julie Louise Gerberding, MD, MPH

Scientific advances are creating a new frontier in vaccine research and disruptive innovations in vaccinology are on the horizon. Emerging vaccines for communicable as well as non-communicable diseases promise to add major strengths to our health protection arsenal. Realizing equitable benefit from these advances depends on stakeholder partnerships, regulatory reform, and sustained investment.

Life-threatening infections are a part of the past for many people, thanks to vaccines. Smallpox has been eradicated, and polio eradication is now actively being pursued. In high-and middle-income countries, vaccine-preventable diseases no longer threaten the survival of most children. But even as science has progressed to address some of our greatest infectious threats, new challenges have emerged. Health inequities impede access to vaccines in lower-income countries. Antimicrobial resistant pathogens and other difficult to treat emerging pathogens are on the increase. Misplaced concerns about vaccine safety threaten effective use and population immunity in some communities in higher- income countries. Today's most difficult-to-treat infections – HIV/AIDS, tuberculosis and malaria – are not yet controlled by vaccines and continue to have a major impact on global morbidity and mortality. Neglected tropical infectious diseases also pose formidable challenges. As our population demographics evolve, non-communicable chronic diseases, including cancer, debilitating neurodegenerative conditions and autoimmune states, pose threats to people everywhere.

Fortunately, we are experiencing a golden age of scientific discovery in vaccine research. Our improved understanding of basic biology, host immunity and the genetic mechanisms that influence host-pathogen interactions is being translated into novel methods and techniques to develop better vaccines and delivery mechanisms. We are also on the threshold of understanding how the immune system can play a more prominent role in the prevention and treatment of cancer and other chronic diseases. As a result, diverse stakeholders, including academia, industry, governments, nonprofit organizations and concerned patients have reenergized their commitments to vaccine research and development. This resurgence in vaccine science – the New Vaccine Frontier – has the potential to bring about discoveries that will dramatically change the way diseases are prevented and treated.

New Antigens

New advances in the studies of genetics and structural biology have fundamentally changed the way we think about vaccines. In the past, most vaccines evolved directly from pathogens, their subunits or their toxins, but this approach is most successful for pathogens for which antigens that elicit a protective immune response are easy to identify and remain stable over time. Creating a successful vaccine for diseases caused by pathogens with high mutation rates, hidden protective antigens or with multiple sub-types is more challenging.

Identifying Protective Antigens Faster The advent of rapid and affordable genomic sequencing now allows screening of a pathogen's entire genome to identify potentially useful antigens. Genomic sequence data can be translated into imputed protein structure, and these structures can then be compared to homologous peptides with known antigenic activity to find likely candidates for vaccines. One characteristic that is particularly desirable is an antigen's ability to trigger protection against numerous pathogen variants or strains. Application of such so-called reverse genetic techniques has been exploited in the development of a single vaccine for broad coverage against various *Neisseria meningitides* serogroup B strains that cause meningococcal meningitis.[1] Genomic techniques are also being assessed in the development of vaccines for HIV, tuberculosis, malaria and other infections.

Defining Antigen and Receptor Structure Advances in three-dimensional structural imaging are helping to

elucidate the structural biology of protein antigens as well as host cell surface binding receptors. This structural information can be exploited to develop and test synthetic vaccines – vaccines that are not sourced from biologic material, but are created *de novo* through synthetic chemistry and other novel protein expression synthesis. Synthetic vaccines cannot revert to virulent pathogens, and may also be easier and faster to manufacture. However, synthetic antigens are usually only weakly immunogenic and specialized carriers or adjuvants will likely be needed.[2] If successful, this approach could simplify and speed up vaccine manufacturing processes and augment efforts to reduce the costs and complexity associated with bioproduction.

***In vivo* Antigen Synthesis** Another promising concept in vaccine development is the development of nucleic acid vaccines.[3] Rather than directly exposing the host to the protein antigen, these vaccines use the DNA or RNA sequences that code for that antigen. Injected nucleic acid is taken up by target cells and the host cell's protein synthesis apparatus to produce the target antigen. This approach has been successfully used to license an effective vaccine against West Nile Virus infection in horses[4] and promising research is underway to see if the strategy can be successful for human infections. Nucleic acid vaccines could have several potential advantages over traditional vaccines including improved immune responses, better stability and simpler manufacturing.

Predicting Antigen Response The rapid evolution of human genomics offers new opportunities to understand the molecular basis for immune responses. The ability to search the entire human genome for genetic variants could help detect those individual genetic variations that contribute to acquired or innate immunity, the degree and durability of response to specific antigens and even the prediction of vaccine-related adverse events.

Improving Vaccine Efficacy

Coupled with the potential of these powerful new methods to create novel vaccines are scientific advances that can improve the efficacy, tolerability and delivery of these products.

Boosting Effectiveness Adjuvants have been used to "boost" the body's response to many vaccines and are not a novel concept in vaccine development.[5] Adjuvants on the market in the U.S. include aluminum-based gels and salts, components which have been used in vaccines for many decades. Efforts to develop even more effective adjuvants have been hampered by the fear that potent adjuvant compounds could over stimulate the immune response, but in other countries, experience with vaccines using newer adjuvants appears to be reassuring. In addition to enhancing protective efficacy, adjuvants offer numerous other benefits including the potential to induce faster immunity, elicit longer lasting immunity, and to stimulate immunity in older persons or others with less responsive immune systems. The use of adjuvants usually reduces the amount of antigen required, thereby lessening production time, which is important for diseases such as pandemic influenza when manufacturing response speed is critical. Hence, in theory adjuvants could expand supply and decrease the waiting time for protection during outbreaks or pandemics.

Using Viral DNA to Deliver the Message A major barrier to the development of nucleic acid-based vaccines is difficulty in achieving efficient uptake and expression of DNA or RNA material into host cells once injected. Viral vectors, typically live attenuated viruses, can be used to infect target cells and carry "passenger" DNA or RNA directly into the cells. Such viral vectors may also enhance efficacy by independently activating the immune response, acting as adjuvants themselves. Choice of the vector is important, since prior exposure could result in immune inactivation before successful introduction of the nucleic acid is accomplished.[6]

Eliminating the Need for Eggs The use of modern antigen production techniques will help end our dependence on eggs for production of influenza vaccines. Egg-based vaccine manufacturing processes are tried and true, but introduce limitations on scale, speed and reliability of vaccine production. Egg-based vaccines also pose challenges for those individuals who are allergic to eggs and cell-based or other recombinant technologies offer the promise of improved protection to these people, especially if new-generation influenza antigens with strong and more durable protection are found.[7]

Non-needle Delivery The future of vaccines also holds the potential for continued advancements in their delivery. Pain-free injections, fewer injections, enhanced efficacy, reduced antigen requirement, better tolerability and improved protection are some of the potential advantages of these approaches. Oral vaccines for polio, rotavirus infection and other diseases transmitted by the enteric route are already in use. Intranasal influenza vaccines are on the market and are especially effective in young children.[7] Similar products for other infections are in various stages of development as are creative methods of transcutaneous

antigen delivery that do not require needles.

Protecting Infants Sooner Most vaccines for infants are not given until 2 months or more of age, so there is a critical period of vulnerability if transplacental antibody transfer does not result in protective antibody titers in the newborn. Immunization of expectant mothers is one strategy to eliminate this risk. Prenatal vaccines could be especially useful for infections that are problematic in newborns, including respiratory syncytial virus (RSV) and group B streptococcal.

Protecting the Developing World

There is an urgent need to find effective vaccines for infections that pose the largest global burden of morbidity and mortality. Developing an effective HIV/AIDS vaccine is a global priority, but success remains elusive.[6] Numerous targets have been pursued; very modest efficacy of one HIV vaccine regiment has provided proof of concept and follow-up clinical trials to confirm and extend these results are underway. Nevertheless, a highly efficacious vaccine is not on the horizon. Likewise, prevention of tuberculosis is a global priority especially in India, China and lower-income countries. Developing an improved vaccine for TB is challenging because the bacteria "hides" intracellularly and escapes immune detection. The emergence of multi-drug resistant tuberculosis has enhanced the urgency of this quest. Bacille Calmette-Guerin (BCG) vaccine is modestly protective for children but is not effective for the prevention of tuberculosis in adults. The third in this triad of large-scale global threats is malaria. Numerous approaches to creating an effective malaria vaccine are completed or underway. One potential candidate, known as RTS,S, appears to be effective, albeit modestly so, in young African children. RTS,S works by preventing the malaria parasite from invading and proliferating in the liver before red blood cells are infected.[8]

Confronting Non-Communicable Diseases

In both the developed and developing worlds, non-communicable diseases are the most important sources of morbidity and mortality. Not surprisingly, these conditions are emerging targets for vaccine research and development. Both preventative and therapeutic anticancer vaccines are areas of intense investigation.[9] Hepatitis B virus vaccine and human papillomavirus vaccine have already had a major impact on the incidence of cancers associated with chronic infection. Other chronic infections with oncogenic potential that are prime candidates for vaccination include hepatitis C virus (liver cancers) and Epstein-Barr virus (lymphoma, nasopharyngeal cancer), *Helicobacter pylori* (stomach cancer) and the parasite *Schistosoma hematobium* (bladder cancer). Finding immunologic solutions to Alzheimer's disease is also a focus of intense research. Beta amyloid protein, the protein present in the neurofibrillary tangles characterized by Alzheimer's disease, is one potential target for a therapeutic vaccine that is currently undergoing investigation. Chronic autoimmune conditions could also be ameliorated with vaccines, some of which are already in early development.

Challenges to Future Vaccine Development

From a scientific perspective, the future of vaccines is bright. We are on the brink of creating products that have the potential to eliminate major categories of human disease and suffering. However, to realize this promise requires sustained commitments from manufacturers as well as governments, academic institutions, multi-lateral organizations and other stakeholders if we are to overcome significant impediments to success.

Vaccine research and development are expensive and time consuming, in some cases taking decades typically at a price exceeding $1 billion. Investments are also made in pre-clinical and clinical vaccine candidates that are not approved, and these costs also have to be covered. From the private sector perspective, investment of this magnitude weighs heavily in decisions about how to allocate scarce research dollars. Without confidence that commercialization is feasible and that a clear regulatory pathway to approval can be found, it is difficult to prioritize the long and expensive runway to a new vaccine. Furthermore, vaccine clinical trials must have a very high bar for safety, and this adds to the size, length and expense of studies required for approval. This will be especially relevant for studies of vaccines in pregnant women and newborns. Vaccines target for the developing world do not have a developed world market to help absorb costs. Innovative partnerships, government participation, philanthropy and corporate social responsibility are required to successfully fund development and deployment of these products.

Regulatory science must evolve to take advantage of innovations in bioprocessing, assay development and other aspects of modern manufacturing. Unlike tablet formulation, creation of vaccines and other biologics is highly influenced by the nuances of the manufacturing process. Today's regulatory framework simply does not allow for much adjustment or flexibility in bioprocess improvements. As a result, quality improvement innovations to lower

costs, speed production time or accelerate localized production in new markets are difficult to execute without additional expensive clinical trials. Regulatory innovations will be necessary to speed access to the innovative vaccines on the horizon as well.

Summary

Vaccines are one of the greatest public health achievements and have had a tremendous impact on people's health and survival around the world. Nevertheless, highly prevalent infectious disease threats unresponsive to traditional immunization strategies, emerging and re-emerging threats, and non-communicable diseases amenable to immunization remain critical global health challenges. Scientific advances will reveal solutions, but it will take political, social and economic commitment from all stakeholders for these solutions to achieve their health protection benefit among the people who need them most.

Conflict of Interest Statement: Julie Louise Gerberding, MD, MPH, is a full-time employee of Merck Vaccines.

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AFTERWORD

Vaccines in the 21st Century: A Cautionary Tale

By Nicholas S. Kelley, PhD and Michael T. Osterholm, PhD, MPH

This special edition of *South Dakota Medicine* highlights one of public health's greatest successes of the 20th century: vaccines and their impact on vaccine-preventable disease morbidity and mortality. Today, U.S. public health officials recommend childhood or adult vaccination of civilians for 17 different infectious diseases; additional vaccines are recommended for those in the military, selected occupations or for international travelers.[1] These successes are nicely highlighted by Schuchat and Kightlinger.[2,3]

While these successes provide optimism about the future of vaccination, especially in light of the current "decade of vaccines," this optimism is tempered by perceptions that a growing number of the general public have about vaccination. With so few people aware of the diseases that vaccines have made rare, we have seen a rise in resistance or hesitancy to vaccinate, as noted by Marshall, Robertson, and Cunningham and Boom.[4-6] In essence, our success in vaccination is making people question the need for it. As noted by Poland, Hoffman, Marshall, and others in this edition,[4,7,1,8] a mounting anti-science/anti-vaccine movement perceives vaccines to be detrimental to health. These groups selectively cite evidence to make their unscientific perspectives appear on equal footing to public health, evidence-based guidance.

Public health has faced resistance to vaccination for as long as it has been used to protect the public's health, but today the scope of the challenge facing public health to address these challenges has grown, including the increasing dependence of consumers on obtaining health information online.[9] For decades, public health has accomplished its mission using its most valuable currency – trust and credibility. The public's trust in public health and our credibility in using the best scientific and outcome-based evidence to drive our policies have enabled the dramatic successes in vaccination. Maintaining that trust and credibility is key to the success of future public health activities.[10-15] If, to counter resistance to vaccines, public health overstates vaccine efficacy and effectiveness, the risk of being infected, and experiencing serious illness as the result of a vaccine-preventable disease, or the safety of vaccines, we will ultimately lose public trust and credibility. Our ability to promote vaccines will then be seriously challenged.

We recently completed an exhaustive three-year cradle-to-grave review of the influenza vaccine enterprise, in which our team examined every aspect of influenza vaccines, including a review of more than 12,000 articles, documents, transcripts and notes dating back to 1936.[1] An analysis of the best evidence currently available to evaluate influenza vaccines found that they are not as effective as commonly noted by public health authorities.[1,16] We concluded, "During some influenza seasons vaccination offers substantially more protection for most of the population than being unvaccinated; however, influenza vaccine protection is markedly lower than for most routinely recommended vaccines and is suboptimal."[1] For those adults 65 years of age and older, where 90 percent of the seasonal influenza mortality occurs, we found a paucity of evidence for protection with currently licensed vaccines.[1] We strongly encourage the continued use of influenza vaccine, with responsible promotion, as it is the best intervention we have until new and more effective vaccines are available. Current influenza vaccine policies and promotional activity are largely based on the 2010 Advisory Committee on Immunization Practices (ACIP) statement. In that statement we found 30 instances of influenza vaccine efficacy and effectiveness being overstated.[1] We also found that the 2006 Healthcare Infection Control Practices Advisory Committee (HICPAC) statement on influenza vaccination of health care personnel overstates the evidence for vaccination of health care personnel and its impact on patient outcomes.[1] These statements have reinforced the perception that our current influenza vaccines are good enough, which has stifled investment needed to research and develop more effective, novel-antigen, game-changing influenza vaccines.

During our review of influenza vaccines, we were constantly

reminded about how many times the influenza literature perpetuated statements that are no longer valid based on re-evaluations of the best evidence. As our understanding of the evidence changes based on scientific advances or new analysis, our public health promotion should change to reflect this new information. Public health policy and promotion for all vaccines should always be based on the best evidence available; however, there are circumstances in which expert opinions must be used. In either case, it should be clear to the public what evidence or opinion was used to create that policy or promotion.

We must not become pro-science activists who use the same approaches as the anti-science activists to sell our programs. If we do, we will lose the public's trust and our credibility. But we do need to embark on an aggressive program of research to understand how to best promote public health action without becoming what we deplore in the anti-science movement. *The Story of Immunization: A Special Edition of South Dakota Medicine* brings together a variety of perspectives to start the conversation on how we can ensure this does not happen on our watch.

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Quality Focus:

Seasonal Flu Vaccines Advancing the Delivery of Colorectal Cancer Screening

By Michael Potter, MD

Flu shot clinics aren't just about flu shots anymore.

Annually, more than 56.2 percent of South Dakotans receive a flu shot, so while your staff has their attention, why stop at the flu? When patients register for the flu shot, they may be reminded about other preventive services that are due. From a patient's perspective, it's convenient to receive multiple services at one drop in visit – your flu shot and screening or referral for colorectal, cervical, and breast cancer. While colorectal cancer is the second leading cause of cancer deaths in the U.S., mortality from colorectal cancer can be reduced by screening adults between the ages of 50 and 75. Not everyone can get or wants a colonoscopy, and for those people, yearly testing with fecal immunochemical tests (FIT) provide an inexpensive, non-invasive, and effective alternative. We need more ways to get FIT into the hands of more people every year.

The FLU-FIT Program is a clinic-based colorectal cancer screening (CRCS) intervention that can help. The FLU-FIT Program takes advantage of annual flu shots as a time to offer FIT to eligible patients. What makes this program worthwhile? For some people, flu shot season is the only time they come to clinic, and this is our time to catch them. And for everyone else, flu shots are a great time to remind them that colorectal cancer screening is another important form of prevention. The program spreads the positive and important message to clinic teams, patients, families, and the larger community that "just like flu shots, annual FIT can be easy, non-invasive, and lifesaving."

FLU-FIT Programs are being put into practice in a variety of practice settings, from safety net settings such as community health centers, and in large HMO's like Kaiser Permanente. With proper planning (i.e., having well trained staff that is prepared to reach out to every eligible patient between the ages of 50 and 75 as they pass through the clinic each fall), attention to follow-up of test completion (with phone calls or postcards), and referral for colonoscopy for those who test positive, the program can reach many people who are due for screening.

The FLU-FIT Program does not replace other forms of outreach – and in fact no program can reach everyone. However, this program can reach many patients who would otherwise not get screened and increase clinic awareness about an important preventive service. In some cases, FLU-FIT Programs are even being transformed into "prevention clinics," where flu shots are provided along with FIT plus referrals for mammograms or other overdue tests.

FLU-FIT Programs are a perfect opportunity to improve CRCS rates in your clinic.

- Flu shot season is an opportunity to reach many patients who are due for screening;
- FIT is an yearly home test that is effective, inexpensive, and takes just a minute or two to provide to patients;
- FIT is simple enough to be provided by medical assistants with just a little training; and
- The program reminds patients that CRCS saves lives and that, just like flu shots, they need to get FIT every year.

Information about how to plan a successful FLU-FIT Program, including videos of the program in action, can be found at www.flufit.org. To learn more contact Nancy Beaumont at nbeaumont@sdqio.sdps.org

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For more information about the SDFMC, visit their website at www.sdfmc.org.

Child, Adolescent & "Catch-up" Immunization Schedules

FIGURE 1: Recommended immunization schedule for persons aged 0 through 6 years—United States, 2012 (for those who fall behind or start late, see the catch-up schedule [Figure 3])

Vaccine ▼ Age ►	Birth	1 month	2 months	4 months	6 months	9 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
Hepatitis B[1]	Hep B	HepB			HepB							
Rotavirus[2]			RV	RV	RV[2]							
Diphtheria, tetanus, pertussis[3]			DTaP	DTaP	DTaP		see footnote[3]	DTaP				DTaP
Haemophilus influenzae type b[4]			Hib	Hib	Hib[4]		Hib					
Pneumococcal[5]			PCV	PCV	PCV		PCV				PPSV	
Inactivated poliovirus[6]			IPV	IPV	IPV							IPV
Influenza[7]					Influenza (Yearly)							
Measles, mumps, rubella[8]							MMR		see footnote[8]			MMR
Varicella[9]							Varicella		see footnote[9]			Varicella
Hepatitis A[10]							Dose 1[10]				HepA Series	
Meningococcal[11]						MCV4 — see footnote[11]						

Range of recommended ages for all children

Range of recommended ages for catch-up immunization

Range of recommended ages for children at high risk

This schedule includes recommendations in effect as of December 23, 2011. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/pubs/acip-list.htm. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800 822 7967).

1. **Hepatitis B (HepB) vaccine.** (Minimum age: birth)
   At birth:
   - Administer monovalent HepB vaccine to all newborns before hospital discharge.
   - For infants born to hepatitis B surface antigen (HBsAg)–positive mothers, administer HepB vaccine and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) 1 to 2 months after completion of at least 3 doses of the HepB series, at age 9 through 18 months (generally at the next well-child visit).
   - If mother's HBsAg status is unknown, within 12 hours of birth administer HepB vaccine for infants weighing ≥2,000 grams, and HepB vaccine plus HBIG for infants weighing <2,000 grams. Determine mother's HBsAg status as soon as possible and, if she is HBsAg-positive, administer HBIG for infants weighing ≥2,000 grams (no later than age 1 week).

   Doses after the birth dose:
   - The second dose should be administered at age 1 to 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks.
   - Administration of a total of 4 doses of HepB vaccine is permissible when a combination vaccine containing HepB is administered after the birth dose.
   - Infants who did not receive a birth dose should receive 3 doses of a HepB-containing vaccine starting as soon as feasible (Figure 3).
   - The minimum interval between dose 1 and dose 2 is 4 weeks, and between dose 2 and 3 is 8 weeks. The final (third or fourth) dose in the HepB vaccine series should be administered no earlier than age 24 weeks and at least 16 weeks after the first dose.
2. **Rotavirus (RV) vaccines.** (Minimum age: 6 weeks for both RV-1 [Rotarix] and RV-5 [Rota Teq])
   - The maximum age for the first dose in the series is 14 weeks, 6 days; and 8 months, 0 days for the final dose in the series. Vaccination should not be initiated for infants aged 15 weeks, 0 days or older.
   - If RV-1 (Rotarix) is administered at ages 2 and 4 months, a dose at 6 months is not indicated.
3. **Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine.** (Minimum age: 6 weeks)
   - The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.
4. ***Haemophilus influenzae* type b (Hib) conjugate vaccine.** (Minimum age: 6 weeks)
   - If PRP-OMP (PedvaxHIB or Comvax [HepB-Hib]) is administered at ages 2 and 4 months, a dose at age 6 months is not indicated.
   - Hiberix should only be used for the booster (final) dose in children aged 12 months through 4 years.
5. **Pneumococcal vaccines.** (Minimum age: 6 weeks for pneumococcal conjugate vaccine [PCV]; 2 years for pneumococcal polysaccharide vaccine [PPSV])
   - Administer 1 dose of PCV to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
   - For children who have received an age-appropriate series of 7-valent PCV (PCV7), a single supplemental dose of 13-valent PCV (PCV13) is recommended for:
     — All children aged 14 through 59 months
     — Children aged 60 through 71 months with underlying medical conditions
   - Administer PPSV at least 8 weeks after last dose of PCV to children aged 2 years or older with certain underlying medical conditions, including a cochlear implant. See *MMWR* 2010;59(No. RR-11), available at http://www.cdc.gov/mmwr/pdf/rr/rr5911.pdf.
6. **Inactivated poliovirus vaccine (IPV).** (Minimum age: 6 weeks)
   - If 4 or more doses are administered before age 4 years, an additional dose should be administered at age 4 through 6 years.
   - The final dose in the series should be administered on or after the fourth birthday and at least 6 months after the previous dose.
7. **Influenza vaccines.** (Minimum age: 6 months for trivalent inactivated influenza vaccine [TIV]; 2 years for live, attenuated influenza vaccine [LAIV])
   - For most healthy children aged 2 years and older, either LAIV or TIV may be used. However, LAIV should not be administered to some children, including 1) children with asthma, 2) children 2 through 4 years who had wheezing in the past 12 months, or 3) children who have any other underlying medical conditions that predispose them to influenza complications. For all other contraindications to use of LAIV, see *MMWR* 2010;59(No. RR-8), available at http://www.cdc.gov/mmwr/pdf/rr/rr5908.pdf.
   - For children aged 6 months through 8 years:
     — For the 2011–12 season, administer 2 doses (separated by at least 4 weeks) to those who did not receive at least 1 dose of the 2010–11 vaccine. Those who received at least 1 dose of the 2010–11 vaccine require 1 dose for the 2011–12 season.
     — For the 2012–13 season, follow dosing guidelines in the 2012 ACIP influenza vaccine recommendations.
8. **Measles, mumps, and rubella (MMR) vaccine.** (Minimum age: 12 months)
   - The second dose may be administered before age 4 years, provided at least 4 weeks have elapsed since the first dose.
   - Administer MMR vaccine to infants aged 6 through 11 months who are traveling internationally. These children should be revaccinated with 2 doses of MMR vaccine, the first at ages 12 through 15 months and at least 4 weeks after the previous dose, and the second at ages 4 through 6 years.
9. **Varicella (VAR) vaccine.** (Minimum age: 12 months)
   - The second dose may be administered before age 4 years, provided at least 3 months have elapsed since the first dose.
   - For children aged 12 months through 12 years, the recommended minimum interval between doses is 3 months. However, if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.
10. **Hepatitis A (HepA) vaccine.** (Minimum age: 12 months)
    - Administer the second (final) dose 6 to 18 months after the first.
    - Unvaccinated children 24 months and older at high risk should be vaccinated. See *MMWR* 2006;55(No. RR-7), available at http://www.cdc.gov/mmwr/pdf/rr/rr5507.pdf.
    - A 2 dose HepA vaccine series is recommended for anyone aged 24 months and older, previously unvaccinated, for whom immunity against hepatitis A virus infection is desired.
11. **Meningococcal conjugate vaccines, quadrivalent (MCV4).** (Minimum age: 9 months for Menactra [MCV4-D], 2 years for Menveo [MCV4-CRM])
    - For children aged 9 through 23 months 1) with persistent complement component deficiency; 2) who are residents of or travelers to countries with hyperendemic or epidemic disease; or 3) who are present during outbreaks caused by a vaccine serogroup, administer 2 primary doses of MCV4-D, ideally at ages 9 months and 12 months or at least 8 weeks apart.
    - For children aged 24 months and older with 1) persistent complement component deficiency who have not been previously vaccinated; or 2) anatomic/functional asplenia, administer 2 primary doses of either MCV4 at least 8 weeks apart.
    - For children with anatomic/functional asplenia, if MCV4-D (Menactra) is used, administer at a minimum age of 2 years and at least 4 weeks after completion of all PCV doses.
    - See *MMWR* 2011;60:72–6, available at http://www.cdc.gov/mmwr/pdf/wk/mm6003.pdf, and Vaccines for Children Program resolution No. 6/11-1, available at http://www.cdc.gov/vaccines/programs/vfc/downloads/resolutions/06-11mening-mcv.pdf, and *MMWR* 2011;60:1391–2, available at http://www.cdc.gov/mmwr/pdf/wk/mm6040.pdf, for further guidance, including revaccination guidelines.

This schedule is approved by the Advisory Committee on Immunization Practices (http://www.cdc.gov/vaccines/acip/), the American Academy of Pediatrics (http://www.aap.org), and the American Academy of Family Physicians (http://www.aafp.org).
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Visit www.cdc.gov/vaccines for 2013 immunization schedule updates.

Child, Adolescent & "Catch-up" Immunization Schedules

FIGURE 2: Recommended immunization schedule for persons aged 7 through 18 years—United States, 2012 (for those who fall behind or start late, see the schedule below and the catch-up schedule [Figure 3])

Vaccine ▼ Age ▶	7–10 years	11–12 years	13–18 years
Tetanus, diphtheria, pertussis[1]	1 dose (if indicated)	1 dose	1 dose (if indicated)
Human papillomavirus[2]	see footnote[2]	3 doses	Complete 3-dose series
Meningococcal[3]	See footnote[3]	Dose 1	Booster at 16 years old
Influenza[4]	Influenza (yearly)		
Pneumococcal[5]	See footnote[5]		
Hepatitis A[6]	Complete 2-dose series		
Hepatitis B[7]	Complete 3-dose series		
Inactivated poliovirus[8]	Complete 3-dose series		
Measles, mumps, rubella[9]	Complete 2-dose series		
Varicella[10]	Complete 2-dose series		

Range of recommended ages for all children

Range of recommended ages for catch-up immunization

Range of recommended ages for certain high-risk groups

This schedule includes recommendations in effect as of December 23, 2011. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/pubs/acip-list.htm. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967).

1. **Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine.** (Minimum age: 10 years for Boostrix and 11 years for Adacel)
   - Persons aged 11 through 18 years who have not received Tdap vaccine should receive a dose followed by tetanus and diphtheria toxoids (Td) booster doses every 10 years thereafter.
   - Tdap vaccine should be substituted for a single dose of Td in the catch-up series for children aged 7 through 10 years. Refer to the catch-up schedule if additional doses of tetanus and diphtheria toxoid–containing vaccine are needed.
   - Tdap vaccine can be administered regardless of the interval since the last tetanus and diphtheria toxoid–containing vaccine.
2. **Human papillomavirus (HPV) vaccines (HPV4 [Gardasil] and HPV2 [Cervarix]).** (Minimum age: 9 years)
   - Either HPV4 or HPV2 is recommended in a 3-dose series for females aged 11 or 12 years. HPV4 is recommended in a 3-dose series for males aged 11 or 12 years.
   - The vaccine series can be started beginning at age 9 years.
   - Administer the second dose 1 to 2 months after the first dose and the third dose 6 months after the first dose (at least 24 weeks after the first dose).
   - See *MMWR* 2010;59:626–32, available at http://www.cdc.gov/mmwr/pdf/wk/mm5920.pdf.
3. **Meningococcal conjugate vaccines, quadrivalent (MCV4).**
   - Administer MCV4 at age 11 through 12 years with a booster dose at age 16 years.
   - Administer MCV4 at age 13 through 18 years if patient is not previously vaccinated.
   - If the first dose is administered at age 13 through 15 years, a booster dose should be administered at age 16 through 18 years with a minimum interval of at least 8 weeks after the preceding dose.
   - If the first dose is administered at age 16 years or older, a booster dose is not needed.
   - Administer 2 primary doses at least 8 weeks apart to previously unvaccinated persons with persistent complement component deficiency or anatomic/functional asplenia, and 1 dose every 5 years thereafter.
   - Adolescents aged 11 through 18 years with human immunodeficiency virus (HIV) infection should receive a 2-dose primary series of MCV4, at least 8 weeks apart.
   - See *MMWR* 2011;60:72–76, available at http://www.cdc.gov/mmwr/pdf/wk/mm6003.pdf, and Vaccines for Children Program resolution No. 9/11-1, available at http://www.cdc.gov/vaccines/programs/vfc/downloads/resolutions/09-11mening-mcv.pdf, for further guidelines.
4. **Influenza vaccines (trivalent inactivated influenza vaccine [TIV] and live, attenuated influenza vaccine [LAIV]).**
   - For most healthy, nonpregnant persons, either LAIV or TIV may be used, except LAIV should not be used for some persons, including those with asthma or any other underlying medical conditions that predispose them to influenza complications. For all other contraindications to use of LAIV, see *MMWR* 2010;59(No.RR-8), available at http://www.cdc.gov/mmwr/pdf/rr/rr5908.pdf.
   - Administer 1 dose to persons aged 9 years and older.
   - For children aged 6 months through 8 years:
     - For the 2011–12 season, administer 2 doses (separated by at least 4 weeks) to those who did not receive at least 1 dose of the 2010–11 vaccine. Those who received at least 1 dose of the 2010–11 vaccine require 1 dose for the 2011–12 season.
     - For the 2012–13 season, follow dosing guidelines in the 2012 ACIP influenza vaccine recommendations.
5. **Pneumococcal vaccines (pneumococcal conjugate vaccine [PCV] and pneumococcal polysaccharide vaccine [PPSV]).**
   - A single dose of PCV may be administered to children aged 6 through 18 years who have anatomic/functional asplenia, HIV infection or other immunocompromising condition, cochlear implant, or cerebral spinal fluid leak. See *MMWR* 2010;59(No. RR-11), available at http://www.cdc.gov/mmwr/pdf/rr/rr5911.pdf.
   - Administer PPSV at least 8 weeks after the last dose of PCV to children aged 2 years or older with certain underlying medical conditions, including a cochlear implant. A single revaccination should be administered after 5 years to children with anatomic/functional asplenia or an immunocompromising condition.
6. **Hepatitis A (HepA) vaccine.**
   - HepA vaccine is recommended for children older than 23 months who live in areas where vaccination programs target older children, who are at increased risk for infection, or for whom immunity against hepatitis A virus infection is desired. See *MMWR* 2006;55(No. RR-7), available at http://www.cdc.gov/mmwr/pdf/rr/rr5607.pdf.
   - Administer 2 doses at least 6 months apart to unvaccinated persons.
7. **Hepatitis B (HepB) vaccine.**
   - Administer the 3-dose series to those not previously vaccinated.
   - For those with incomplete vaccination, follow the catch-up recommendations (Figure 3).
   - A 2-dose series (doses separated by at least 4 months) of adult formulation Recombivax HB is licensed for use in children aged 11 through 15 years.
8. **Inactivated poliovirus vaccine (IPV).**
   - The final dose in the series should be administered at least 6 months after the previous dose.
   - If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age.
   - IPV is not routinely recommended for U.S. residents aged 18 years or older.
9. **Measles, mumps, and rubella (MMR) vaccine.**
   - The minimum interval between the 2 doses of MMR vaccine is 4 weeks.
10. **Varicella (VAR) vaccine.**
    - For persons without evidence of immunity (see *MMWR* 2007;56(No. RR-4), available at http://www.cdc.gov/mmwr/pdf/rr/rr5604.pdf), administer 2 doses if not previously vaccinated or the second dose if only 1 dose has been administered.
    - For persons aged 7 through 12 years, the recommended minimum interval between doses is 3 months. However, if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.
    - For persons aged 13 years and older, the minimum interval between doses is 4 weeks.

This schedule is approved by the Advisory Committee on Immunization Practices (http://www.cdc.gov/vaccines/recs/acip), the American Academy of Pediatrics (http://www.aap.org), and the American Academy of Family Physicians (http://www.aafp.org).
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Child, Adolescent & "Catch-up" Immunization Schedules

FIGURE 3. Catch-up immunization schedule for persons aged 4 months through 18 years who start late or who are more than 1 month behind—United States • 2012

The figure below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age. **Always use this table in conjunction with the accompanying childhood and adolescent immunization schedules (Figures 1 and 2) and their respective footnotes.**

Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to dose 2	Dose 2 to dose 3	Dose 3 to dose 4	Dose 4 to dose 5
Persons aged 4 months through 6 years					
Hepatitis B	Birth	4 weeks	8 weeks and at least 16 weeks after first dose; minimum age for the final dose is 24 weeks		
Rotavirus[1]	6 weeks	4 weeks	4 weeks[1]		
Diphtheria, tetanus, pertussis[2]	6 weeks	4 weeks	4 weeks	6 months	6 months[2]
Haemophilus influenzae type b[3]	6 weeks	4 weeks if first dose administered at younger than age 12 months 8 weeks (as final dose) if first dose administered at age 12–14 months No booster dose needed if first dose administered at age 15 months or older	4 weeks[3] if current age is younger than 12 months 8 weeks (as final dose)[3] if current age is 12 months or older and two doses administered at younger than age 12 months and second dose administered at younger than 15 months No booster dose needed if previous dose administered at age 15 months or older	8 weeks (as final dose) This dose only necessary for children ages 12 months through 59 months who received 3 doses before age 12 months	
Pneumococcal[4]	6 weeks	4 weeks if first dose administered at younger than age 12 months 8 weeks (as final dose for healthy children) if first dose administered at age 12 months or older or at least age 24 months 24 months No booster dose needed for healthy children if first dose administered at age 24 months or older	4 weeks if current age is younger than 12 months 8 weeks (as final dose for healthy children) if current age is 12 months or older No booster dose needed for healthy children if previous dose administered at age 24 months or older	8 weeks (as final dose) This dose only necessary for children ages 12 months through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age	
Inactivated poliovirus[5]	6 weeks	4 weeks	4 weeks	6 months[5] minimum age 4 years for final dose	
Meningococcal[6]	6 months	8 weeks[6]			
Measles, mumps, rubella[7]	12 months	4 weeks			
Varicella[8]	12 months	3 months			
Hepatitis A	12 months	6 months			
Persons aged 7 through 18 years					
Tetanus, diphtheria, pertussis, diphtheria, pertussis[9]	7 years[9]	4 weeks	4 weeks if first dose administered at younger than age 12 months 6 months if first dose administered at 12 months or older	6 months if first dose administered at younger than age 12 months	
Human papillomavirus[10]	9 years	Routine dosing intervals are recommended[10]			
Hepatitis A	12 months	6 months			
Hepatitis B	Birth	4 weeks	8 weeks and at least 16 weeks after first dose)		
Inactivated poliovirus[5]	6 weeks	4 weeks	4 weeks[5]	6 months[5]	
Meningococcal[6]	6 months	8 weeks[6]			
Measles, mumps, rubella[7]	12 months	4 weeks			
Varicella[8]	12 months	3 months if person is younger than age 13 years 4 weeks if person is aged 13 years or older			

1. **Rotavirus (RV) vaccines (RV-1 [Rotarix] and RV-5 [Rota Teq]).**
   - The maximum age for the first dose in the series is 14 weeks, 6 days, and 6 months, 0 days for the final dose in the series. Vaccination should not be initiated for infants aged 15 weeks, 0 days or older.
   - If RV-1 was administered for the first and second doses, a third dose is not indicated.
2. **Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine.**
   - The fifth dose is not necessary if the fourth dose was administered at age 4 years or older.
3. ***Haemophilus influenzae* type b (Hib) conjugate vaccine.**
   - Hib vaccine should be considered for unvaccinated persons aged 5 years or older who have sickle cell disease, leukemia, human immunodeficiency virus (HIV) infection, or anatomic/functional asplenia.
   - If the first 2 doses were PRP-OMP (PedvaxHIB or Comvax) and were administered at age 11 months or younger, the third (and final) dose should be administered at age 12 through 15 months and at least 8 weeks after the second dose.
   - If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a final dose at age 12 through 15 months.
4. **Pneumococcal vaccines. (Minimum age: 6 weeks for pneumococcal conjugate vaccine [PCV]; 2 years for pneumococcal polysaccharide vaccine [PPSV]).**
   - For children aged 24 through 71 months with underlying medical conditions, administer 1 dose of PCV if 3 doses of PCV were received previously; or administer 2 doses of PCV at least 8 weeks apart if fewer than 3 doses of PCV were received previously.
   - A single dose of PCV may be administered to certain children aged 6 through 18 years with underlying medical conditions. See age specific schedules for details.
   - Administer PPSV to children aged 2 years or older with certain underlying medical conditions. See *MMWR* 2010;59(No. RR-11), available at http://www.cdc.gov/mmwr/pdf/rr/rr5911.pdf.
5. **Inactivated poliovirus vaccine (IPV).**
   - A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.
   - In the first 6 months of life, minimum age and minimum intervals are only recommended if the person is at risk for imminent exposure to circulating poliovirus (i.e., travel to a polio-endemic region or during an outbreak).
   - IPV is not routinely recommended for U.S. residents aged 18 years or older.
6. **Meningococcal conjugate vaccines, quadrivalent (MCV4). (Minimum age: 9 months for Menactra [MCV4-D]; 2 years for Menveo [MCV4-CRM]).**
   - See Figure 1 ("Recommended immunization schedule for persons aged 0 through 6 years") and Figure 2 ("Recommended immunization schedule for persons aged 7 through 18 years") for further guidance.
7. **Measles, mumps, and rubella (MMR) vaccine.**
   - Administer the second dose routinely at age 4 through 6 years.
8. **Varicella (VAR) vaccine.**
   - Administer the second dose routinely at age 4 through 6 years. If the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.
9. **Tetanus and diphtheria toxoids (Td) and tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccines.**
   - For children aged 7 through 10 years who are not fully immunized with the childhood DTaP vaccine series, Tdap vaccine should be substituted for a single dose of Td vaccine in the catch-up series; if additional doses are needed, use Td vaccine. For these children, an adolescent Tdap vaccine dose should not be given.
   - An inadvertent dose of DTaP vaccine administered to children aged 7 through 10 years can count as part of the catch-up series. This dose can count as the adolescent Tdap dose, or the child can later receive a Tdap booster dose at age 11–12 years.
10. **Human papillomavirus (HPV) vaccines (HPV4 [Gardasil] and HPV2 [Cervarix]).**
    - Administer the vaccine series to females (either HPV2 or HPV4) and males (HPV4) at age 13 through 18 years if patient is not previously vaccinated.
    - Use recommended routine dosing intervals for vaccine series catch-up; see Figure 2 ("Recommended immunization schedule for persons aged 7 through 18 years").

Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967). Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for vaccination, is available from CDC online (http://www.cdc.gov/vaccines) or by telephone (800-CDC-INFO [800-232-4636]).

Visit www.cdc.gov/vaccines for 2013 immunization schedule updates.

Adult Immunization Schedule

FIGURE 1. Recommended adult immunization schedule, by vaccine and age group[1] — United States, 2012

VACCINE ▼ / AGE GROUP ▶	19–21 years	22–26 years	27–49 years	50–59 years	60–64 years	≥65 years
Influenza[2,3]	1 dose annually					
Tetanus, diphtheria, pertussis (Td/Tdap)[3,4]	Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 years					Td/Tdap[4]
Varicella[5,6]	2 doses					
Human papillomavirus (HPV)[5,*] Female	3 doses					
Human papillomavirus (HPV)[5,*] Male	3 doses					
Zoster[6]					1 dose	
Measles, mumps, rubella (MMR)[7,8]	1 or 2 doses			1 dose		
Pneumococcal (polysaccharide)[8,9]	1 or 2 doses					1 dose
Meningococcal[10,*]	1 or more doses					
Hepatitis A[11,*]	2 doses					
Hepatitis B[12,*]	3 doses					

* Covered by the Vaccine Injury Compensation Program

- For all persons in this category who meet the age requirements and who lack documentation of vaccination or have no evidence of previous infection
- Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications)
- Tdap recommended for ≥65 if contact with <12 month old child. Either Td or Tdap can be used if no infant contact
- No recommendation

FIGURE 2. Vaccines that might be indicated for adults, based on medical and other indications[1] — United States, 2012

INDICATION ▶ / VACCINE ▼	Pregnancy	Immunocompromising conditions (excluding human immunodeficiency virus [HIV])[1,4,7,13]	HIV infection[4,13,14] CD4+ T lymphocyte count <200 cells/µL	HIV infection[4,13,14] CD4+ T lymphocyte count ≥200 cells/µL	Men who have sex with men (MSM)	Heart disease, chronic lung disease, chronic alcoholism	Asplenia[14] (including elective splenectomy and persistent complement component deficiencies)	Chronic liver disease	Diabetes, kidney failure, end stage renal disease, receipt of hemodialysis	Health-care personnel
Influenza[2,*]	1 dose TIV annually				1 dose TIV or LAIV annually	1 dose TIV annually				1 dose TIV or LAIV annually
Tetanus, diphtheria, pertussis (Td/Tdap)[3,*]	Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 years									
Varicella[5,*]	Contraindicated		2 doses							
Human papillomavirus (HPV)[5,*] Female		3 doses through age 26 years				3 doses through age 26 years				
Human papillomavirus (HPV)[5,*] Male		3 doses through age 26 years				3 doses through age 21 years				
Zoster[6]	Contraindicated				1 dose					
Measles, mumps, rubella[7,*]	Contraindicated		1 or 2 doses							
Pneumococcal (polysaccharide)[8,*]		1 or 2 doses								
Meningococcal[10,*]	1 or more doses									
Hepatitis A[11,*]	2 doses									
Hepatitis B[12,*]	3 doses									

* Covered by the Vaccine Injury Compensation Program

- For all persons in this category who meet the age requirements and who lack documentation of vaccination or have no evidence of previous infection
- Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications)
- Contraindicated
- No recommendation

Visit www.cdc.gov/vaccines for 2013 immunization schedule updates.

Adult Immunization Schedule

1. **Additional information**
   - Advisory Committee on Immunization Practices (ACIP) vaccine recommendations and additional information are available at http://www.cdc.gov/vaccines/pubs/acip-list.htm.
   - Information on travel vaccine requirements and recommendations (e.g., for hepatitis A and B, meningococcal, and other vaccines) available at http://www.cdc.gov/travel/page/vaccination.htm.
2. **Influenza vaccination**
   - Annual vaccination against influenza is recommended for all persons 6 months of age and older.
   - Persons 6 months of age and older, including pregnant women, can receive the trivalent inactivated vaccine (TIV).
   - Healthy, nonpregnant adults younger than age 50 years without high-risk medical conditions can receive either intranasally administered live, attenuated influenza vaccine (LAIV) (FluMist), or TIV. Health-care personnel who care for severely immunocompromised persons (i.e., those who require care in a protected environment) should receive TIV rather than LAIV. Other persons should receive TIV.
   - The intramuscular or intradermal administered TIV are options for adults aged 18–64 years.
   - Adults aged 65 years and older can receive the standard dose TIV or the high-dose TIV (Fluzone High Dose).
3. **Tetanus, diphtheria, and acellular pertussis (Td/Tdap) vaccination**
   - Administer a one-time dose of Tdap to adults younger than age 65 years who have not received Tdap previously or for whom vaccine status is unknown to replace one of the 10 year Td boosters.
   - Tdap is specifically recommended for the following persons:
     - pregnant women more than 20 weeks' gestation;
     - adults, regardless of age, who are close contacts of infants younger than age 12 months (e.g., parents, grandparents, or child care providers); and
     - health-care personnel.
   - Tdap can be administered regardless of interval since the most recent tetanus or diphtheria-containing vaccine.
   - Pregnant women not vaccinated during pregnancy should receive Tdap immediately postpartum.
   - Adults 65 years and older may receive Tdap.
   - Adults with unknown or incomplete history of completing a 3-dose primary vaccination series with Td-containing vaccines should begin or complete a primary vaccination series. Tdap should be substituted for a single dose of Td in the vaccination series with Tdap preferred as the first dose.
   - For unvaccinated adults, administer the first 2 doses at least 4 weeks apart and the third dose 6–12 months after the second.
   - If incompletely vaccinated (i.e., less than 3 doses), administer remaining doses.

   Refer to the ACIP statement for recommendations for administering Td/Tdap as prophylaxis in wound management (See footnote 1).
4. **Varicella vaccination**
   - All adults without evidence of immunity to varicella (as defined below) should receive 2 doses of single-antigen varicella vaccine or a second dose if they have received only 1 dose.
   - Special consideration for vaccination should be given to those who
     - have close contact with persons at high risk for severe disease (e.g., health-care personnel and family contacts of persons with immunocompromising conditions) or
     - are at high risk for exposure or transmitting (e.g., teachers; child care employees; residents and staff members of institutional settings, including correctional institutions; college students; military personnel; adolescents and adults living in households with children; nonpregnant women of childbearing age; and international travelers).
   - Pregnant women should be assessed for evidence of varicella immunity. Women who do not have evidence of immunity should receive the first dose of varicella vaccine upon completion or termination of pregnancy and before discharge from the health-care facility. The second dose should be administered 4–8 weeks after the first dose.
   - Evidence of immunity to varicella in adults includes any of the following:
     - documentation of 2 doses of varicella vaccine at least 4 weeks apart;
     - U.S.-born before 1980 (although for health-care personnel and pregnant women, birth before 1980 should not be considered evidence of immunity);
     - history of varicella based on diagnosis or verification of varicella by a health-care provider (for a patient reporting a history of or having an atypical case, a mild case, or both, health-care providers should seek either an epidemiologic link to a typical varicella case or to a laboratory-confirmed case or evidence of laboratory confirmation, if it was performed at the time of acute disease);
     - history of herpes zoster based on diagnosis or verification of herpes zoster by a health-care provider; or
     - laboratory evidence of immunity or laboratory confirmation of disease.
5. **Human papillomavirus (HPV) vaccination**
   - Two vaccines are licensed for use in females: bivalent HPV vaccine (HPV2) and quadrivalent HPV vaccine (HPV4), and one HPV vaccine for use in males (HPV4).
   - For females, either HPV4 or HPV2 is recommended in a 3-dose series for routine vaccination at 11 or 12 years of age, and for those 13 through 26 years of age, if not previously vaccinated.
   - For males, HPV4 is recommended in a 3-dose series for routine vaccination at 11 or 12 years of age, and for those 13 through 21 years of age, if not previously vaccinated. Males 22 through 26 years of age may be vaccinated.
   - HPV vaccines are not live vaccines and can be administered to persons who are immunocompromised as a result of infection (including HIV infection), disease, or medications. Vaccine is recommended for immunocompromised persons through age 26 years who did not get any or all doses when they were younger. The immune response and vaccine efficacy might be less than that in immunocompetent persons.
   - Men who have sex with men (MSM) might especially benefit from vaccination to prevent condyloma and anal cancer. HPV4 is recommended for MSM through age 26 years who did not get any or all doses when they were younger.
   - Ideally, vaccine should be administered before potential exposure to HPV through sexual activity; however, persons who are sexually active should still be vaccinated consistent with age-based recommendations. HPV vaccine can be administered to persons with a history of genital warts, abnormal Papanicolaou test, or positive HPV DNA test.
   - A complete series for either HPV4 or HPV2 consists of 3 doses. The second dose should be administered 1–2 months after the first dose; the third dose should be administered 6 months after the first dose (at least 24 weeks after the first dose).
   - Although HPV vaccination is not specifically recommended for health-care personnel (HCP), based on their occupation, HCP should receive the HPV vaccine if they are in the recommended age group.
6. **Zoster vaccination**
   - A single dose of zoster vaccine is recommended for adults 60 years of age and older regardless of whether they report a prior episode of herpes zoster. Although the vaccine is licensed by the Food and Drug Administration (FDA) for use among and can be administered to persons 50 years and older, ACIP recommends that vaccination begins at 60 years of age.
   - Persons with chronic medical conditions may be vaccinated unless their condition constitutes a contraindication, such as pregnancy or severe immunodeficiency.
   - Although zoster vaccination is not specifically recommended for health-care personnel (HCP), HCP should receive the vaccine if they are in the recommended age group.
7. **Measles, mumps, rubella (MMR) vaccination**
   - Adults born before 1957 generally are considered immune to measles and mumps. All adults born in 1957 or later should have documentation of 1 or more doses of MMR vaccine unless they have a medical contraindication to the vaccine, laboratory evidence of immunity to each of the three diseases, or documentation of provider-diagnosed measles or mumps disease. For rubella, documentation of provider-diagnosed disease is not considered acceptable evidence of immunity.

   Measles component:
   - A routine second dose of MMR vaccine, administered a minimum of 28 days after the first dose, is recommended for adults who
     - are students in postsecondary educational institutions;
     - work in a health-care facility; or
     - plan to travel internationally.
   - Persons who received inactivated (killed) measles vaccine or measles vaccine of unknown type from 1963 to 1967 should be revaccinated with 2 doses of MMR vaccine.

   Mumps component:
   - A routine second dose of MMR vaccine, administered a minimum of 28 days after the first dose, is recommended for adults who
     - are students in postsecondary educational institutions;
     - work in a health-care facility; or
     - plan to travel internationally.
   - Persons vaccinated before 1979 with either killed mumps vaccine or mumps vaccine of unknown type who are at high risk for mumps infection (e.g., persons who are working in a health-care facility) should be considered for revaccination with 2 doses of MMR vaccine.

   Rubella component:
   - For women of childbearing age, regardless of birth year, rubella immunity should be determined. If there is no evidence of immunity, women who are not pregnant should be vaccinated. Pregnant women who do not have evidence of immunity should receive MMR vaccine upon completion or termination of pregnancy and before discharge from the health-care facility.

   Health-care personnel born before 1957:
   - For unvaccinated health-care personnel born before 1957 who lack laboratory evidence of measles, mumps, and/or rubella immunity or laboratory confirmation of disease, health-care facilities should consider routinely vaccinating personnel with 2 doses of MMR vaccine at the appropriate interval for measles and mumps or 1 dose of MMR vaccine for rubella.
8. **Pneumococcal polysaccharide (PPSV) vaccination**
   - Vaccinate all persons with the following indications:
     - age 65 years and older without a history of PPSV vaccination;
     - adults younger than 65 years with chronic lung disease (including chronic obstructive pulmonary disease, emphysema, and asthma); chronic cardiovascular diseases; diabetes mellitus; chronic liver disease (including cirrhosis); alcoholism; cochlear implants; cerebrospinal fluid leaks; immunocompromising conditions; and functional or anatomic asplenia (e.g., sickle cell disease and other hemoglobinopathies, congenital or acquired asplenia, splenic dysfunction, or splenectomy [if elective splenectomy is planned, vaccinate at least 2 weeks before surgery]);
     - residents of nursing homes or long-term care facilities; and
     - adults who smoke cigarettes.
   - Persons with asymptomatic or symptomatic HIV infection should be vaccinated as soon as possible after their diagnosis.

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Adult Immunization Schedule

- When cancer chemotherapy or other immunosuppressive therapy is being considered, the interval between vaccination and initiation of immunosuppressive therapy should be at least 2 weeks. Vaccination during chemotherapy or radiation therapy should be avoided.
- Routine use of PPSV is not recommended for American Indians/Alaska Natives or other persons younger than 65 years of age unless they have underlying medical conditions that are PPSV indications. However public health authorities may consider recommending PPSV for American Indians/Alaska Natives who are living in areas where the risk for invasive pneumococcal disease is increased.

9. Revaccination with PPSV

- One-time revaccination 5 years after the first dose is recommended for persons 19 through 64 years of age with chronic renal failure or nephrotic syndrome; functional or anatomic asplenia (e.g., sickle cell disease or splenectomy), and for persons with immunocompromising conditions.
- Persons who received PPSV before age 65 years for any indication should receive another dose of the vaccine at age 65 years or later if at least 5 years have passed since their previous dose.
- No further doses are needed for persons vaccinated with PPSV at or after age 65 years.

10. Meningococcal vaccination

- Administer 2 doses of meningococcal conjugate vaccine (quadrivalent (MCV4) at least 2 months apart to adults with functional asplenia or persistent complement component deficiencies.
- HIV-infected persons who are vaccinated should also receive 2 doses.
- Administer a single dose of meningococcal vaccine to microbiologists routinely exposed to isolates of *Neisseria meningitidis*, military recruits, and persons who travel to or live in countries in which meningococcal disease is hyperendemic or epidemic.
- First-year college students up through age 21 years who are living in residence halls should be vaccinated if they have not received a dose on or after their 16th birthday.
- MCV4 is preferred for adults with any of the preceding indications who are 55 years old and younger; meningococcal polysaccharide vaccine (MPSV4) is preferred for adults 56 years and older.
- Revaccination with MCV4 every 5 years is recommended for adults previously vaccinated with MCV4 or MPSV4 who remain at increased risk for infection (e.g., adults with anatomic or functional asplenia or persistent complement component deficiencies).

11. Hepatitis A vaccination

- Vaccinate any person seeking protection from hepatitis A virus (HAV) infection and persons with any of the following indications:
  - men who have sex with men and persons who use injection drugs;
  - persons working with HAV-infected primates or with HAV in a research laboratory setting;
  - persons with chronic liver disease and persons who receive clotting factor concentrates;
  - persons traveling to or working in countries that have high or intermediate endemicity of hepatitis A; and
  - unvaccinated persons who anticipate close personal contact (e.g., household or regular babysitting) with an international adoptee during the first 60 days after arrival in the United States from a country with high or intermediate endemicity. (See footnote 1 for more information on travel recommendations). The first dose of the 2-dose hepatitis A vaccine series should be administered as soon as adoption is planned, ideally 2 or more weeks before the arrival of the adoptee.
- Single-antigen vaccine formulations should be administered in a 2-dose schedule at either 0 and 6–12 months (Havrix), or 0 and 6–18 months (Vaqta). If the combined hepatitis A and hepatitis B vaccine (Twinrix) is used, administer 3 doses at 0, 1, and 6 months; alternatively, a 4-dose schedule may be used, administered on days 0, 7, and 21–30 followed by a booster dose at month 12.

12. Hepatitis B vaccination

- Vaccinate persons with any of the following indications and any person seeking protection from hepatitis B virus (HBV) infection:
  - sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., persons with more than one sex partner during the previous 6 months); persons seeking evaluation or treatment for a sexually transmitted disease (STD); current or recent injection-drug users; and men who have sex with men;
  - health-care personnel and public-safety workers who are exposed to blood or other potentially infectious body fluids;
  - persons with diabetes younger than 60 years as soon as feasible after diagnosis; persons with diabetes who are 60 years or older at the discretion of the treating clinician based on increased need for assisted blood glucose monitoring in long-term care facilities, likelihood of acquiring hepatitis B infection, its complications or chronic sequelae, and likelihood of immune response to vaccination;
  - persons with end-stage renal disease, including patients receiving hemodialysis; persons with HIV infection; and persons with chronic liver disease;
  - household contacts and sex partners of persons with chronic HBV infection; clients and staff members of institutions for persons with developmental disabilities; and international travelers to countries with high or intermediate prevalence of chronic HBV infection; and
  - all adults in the following settings: STD treatment facilities, HIV testing and treatment facilities, facilities providing drug-abuse treatment and prevention services; health-care settings targeting services to injection-drug users or men who have sex with men; correctional facilities; end-stage renal disease programs and facilities for chronic hemodialysis patients; and institutional and noninstitutional daycare facilities for persons with developmental disabilities.
- Administer missing doses to complete a 3-dose series of hepatitis B vaccine to those persons not vaccinated or not completely vaccinated. The second dose should be administered 1 month after the first dose; the third dose should be given at least 2 months after the second dose (and at least 4 months after the first dose). If the combined hepatitis A and hepatitis B vaccine (Twinrix) is used, give 3 doses at 0, 1, and 6 months; alternatively, a 4-dose Twinrix schedule, administered on days 0, 7, and 21–30 followed by a booster dose at month 12 may be used.
- Adult patients receiving hemodialysis or with other immunocompromising conditions should receive 1 dose of 40 µg/mL (Recombivax HB) administered on a 3-dose schedule or 2 doses of 20 µg/mL (Engerix-B) administered simultaneously on a 4-dose schedule at 0, 1, 2, and 6 months.

13. Selected conditions for which Haemophilus influenzae type b (Hib) vaccine may be used

- 1 dose of Hib vaccine should be considered for persons who have sickle cell disease, leukemia, or HIV infection, or who have anatomic or functional asplenia if they have not previously received Hib vaccine.

14. Immunocompromising conditions

- Inactivated vaccines generally are acceptable (e.g., pneumococcal, meningococcal, and influenza [inactivated influenza vaccine]), and live vaccines generally are avoided in persons with immune deficiencies or immunocompromising conditions. Information on specific conditions is available at http://www.cdc.gov/vaccines/pubs/acip-list.htm.

These schedules indicate the recommended age groups and medical indications for which administration of currently licensed vaccines is commonly indicated for adults ages 19 years and older, as of January 1, 2012. For all vaccines being recommended on the adult immunization schedule, a vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Licensed combination vaccines may be used whenever any components of the combination are indicated and when the vaccines' other components are not contraindicated. For detailed recommendations on all vaccines, including those used primarily for travelers or that are issued during the year, consult the manufacturers' package inserts and the complete statements from the Advisory Committee on Immunization Practices (http://www.cdc.gov/vaccines/pubs/acip-list.htm).

Report all clinically significant postvaccination reactions to the Vaccine Adverse Event Reporting System (VAERS). Reporting forms and instructions on filing a VAERS report are available at http://www.vaers.hhs.gov or by telephone, 800-822-7967.

Information on how to file a Vaccine Injury Compensation Program claim is available at http://www.hrsa.gov/vaccinecompensation or by telephone, 800-338-2382. Information about filing a claim for vaccine injury is available through the U.S. Court of Federal Claims, 717 Madison Place, N.W., Washington, D.C. 20005; telephone, 202-357-6400.

Additional information about the vaccines in this schedule, extent of available data, and contraindications for vaccination also is available at http://www.cdc.gov/vaccines or from the CDC-INFO Contact Center at 800-CDC-INFO (800-232-4636) in English and Spanish, 8:00 a.m. to 8:00 p.m., Monday through Friday, excluding holidays.

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