LISA ROSNER

VACCINATION AND ITS CRITICS

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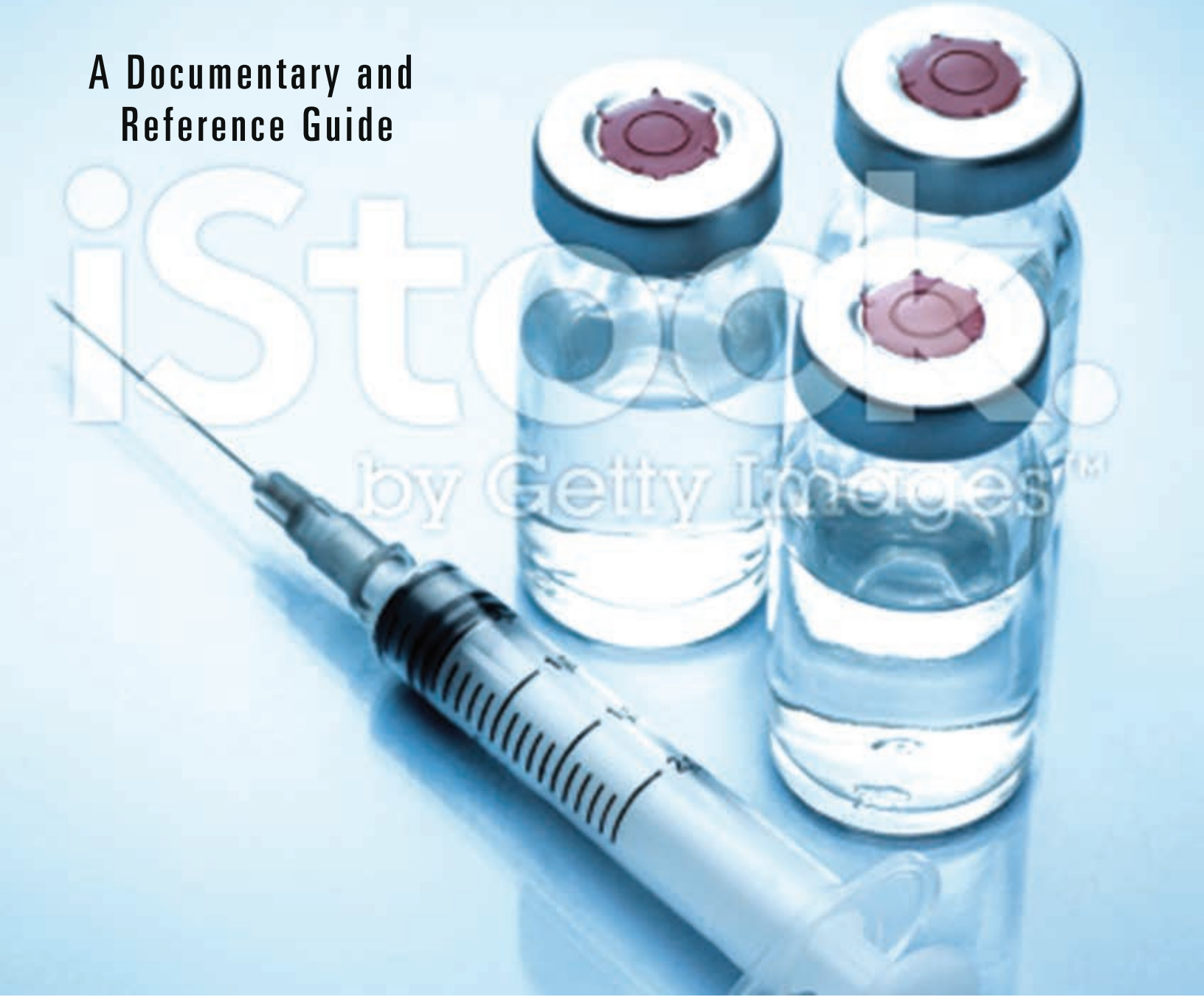
A Documentary and Reference Guide



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INTRODUCTION

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Anne Gibbons's comic is intended as a wry joke about the contested status of vaccination in 21st-century America. However, it also conveys a profound truth about the history of vaccination and its critics for the past 300 years: we are all survivors of an ongoing conversation about the efficacy, safety, cost, policies, practices, values, and beliefs surrounding immunization.

For most of us, the term *survivor* may seem overblown, because we have not, ourselves, undergone any particular trauma beyond a series of injections when we were very young. Perhaps we may remember the pain caused by the syringe or the sore arm and slight fever. But the real trauma took place years before we were born, before the vaccine was available to the 21,000 children and their families in the United States who contracted diphtheria between 1936 and 1945 and the 1,800 who died, to the 530,000 who contracted measles between 1953 and 1962 and the 440 who died, to the 16,000 who contracted polio between 1951 and 1954 and the 1800 who died (Rousch, Murphy, and Vaccine-Preventative Table Working Group, 2007, Table 1). The immunizations we get as children or adults mean that we are not at risk from those diseases. More children live to grow up and to lead healthy lives free from epidemic diseases than at any previous time in the world's history.

We are also survivors of the historical conversation about vaccination if the only adverse effect we encountered was a little pain and fever, instead of something worse. The history of immunization preceded the science of how vaccines work and what risks this new scientific achievement carried. Before government regulation and quality control, the practice of vaccination carried risks to individuals and to public health. Even now, with all our scientific knowledge, medical professionals and prospective patients —or their parents—must weigh the risks of an adverse reaction against the benefits of immunization.

The U.S. National Vaccine Injury Compensation Program (NVICP) statistics from 2006 to 2014 gives some measure of the risks. The NICP process was set up to provide a mechanism for compensating patients or their families for adverse reactions related to vaccination. For diphtheria, 198 million doses of vaccine were administered throughout the country. Only 323 patients came forward claiming adverse reactions—an average of about 35 per year—with a total of 180 cases awarded compensation. For measles, 80 million doses were administered in the same period; 178 cases were brought forward, and 96 were awarded compensation. For polio, 62 million doses were administered. Six cases were brought forward, and four were awarded compensation. Those cases, and indeed the NVICP itself, can be considered survivors of the conversation on vaccination.

There is another kind of trauma associated with the history of vaccination and that is when people over the world die from vaccine-preventable diseases. This is especially heartrending when children die, since their young lives hold so much promise. Historically, the most common reasons for deaths from vaccine-preventable diseases had been poverty and lack of access. Often, of course, the two go together. Even in the modern world, those two conditions hinder the progress of vaccination. Only smallpox, of all the major vaccine-preventable diseases, has been completely eradicated worldwide. Polio is very close, with only 359 cases reported in 2014.

In order to further explore the dynamics of the historical conversation on vaccination, we can take a close look at one of the most important settings in which it has recently taken place, the June 2015 meeting of the Advisory Committee on Immunization Practices (ACIP) at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. The ACIP is, in its quiet way, one of the most influential committees in the United States. Once the Food and Drug Administration (FDA) has approved a specific vaccine for manufacture, the ACIP is charged with formulating official recommendations for its use. If the CDC director approves those recommendations—as generally happens—they become official federal policies.

ACIP recommendations, therefore, carry enormous weight. By statute, they must be incorporated into the recommended vaccination schedule, the schedule that determines doses and timing of all those childhood and young adult injections. ACIP recommendations have the power to compel insurance companies to cover specific kinds of immunizations for all Americans of a specific age or at-risk group. Since 1993, they have had the power to require the federal government to pay for vaccination under the Vaccines for Children (VFC) program. Since 2010, that power has been expanded, since the Affordable Care Act (ACA) requires all vaccinations to be provided free of charge, with no co-payment. If the ACIP decides a particular vaccine belongs on the vaccination schedule, it means, in effect, that every American has the right to receive it.

Many people present at the June meeting, however, would have a much more succinct statement of the power of the ACIP: the power of life and death. One of the key items on the meeting's agenda concerned recommendations for the MenB vaccine, the only protection against the potentially deadly B strain of meningitis (formally known as "serogroup B meningococcal disease") that had unexpectedly attacked college-age men and women in 2013 and 2014. High-profile cases at Princeton University, the University of California at Santa Barbara, Georgetown University, and San Diego State University had led the FDA to facilitate an accelerated process for licensing two potential vaccines, previously approved in other countries, in order to protect at-risk students. Now it was up to the ACIP to decide whether this would remain an emergency measure or whether the MenB vaccine would be added to the vaccination schedule, joining the existing vaccines against other strains of meningitis.

The conversation about vaccination at the ACIP meetings proceeds in a deliberate, formal manner. At this June meeting, the Meningococcal Work Group charged with examining the MenB vaccine had formulated a recommendation. They were tasked with presenting it, not just to the full committee but also to members of the public. There was a public comments section, and anyone could register to present a comment, limited to six minutes. ACIP meetings are also open to any other members of the public who wish to attend, whether or not they wish to speak. Nowadays the meetings are also live-streamed, and the minutes of every meeting since the 1990s are available to anyone who contacts the ACIP, with minutes, presentations, and videos available on the webpage. As Jonathan Temte, the ACIP chair during the June 2015 session, reminded everyone, the ACIP was a federal advisory committee and was therefore obligated to take public comments into account. "During this

meeting's meningococcal session," he noted, "there would be an unprecedented number of public comments." The committee had also received over 40 letters, including one "with approximately 1200 co-signatures and a petition with 601 co-signatures." It is ACIP's duty, he said, "not only to review all the [scientific] evidence, but also to consider other issues such as values and preferences" as expressed in public comments (ACIP, 2015a, 17).

The ensuing interaction between the committee and the public showcased many of the key issues in the history of vaccination and its critics: efficacy, safety, cost-effectiveness, access, and equity. The ACIP had three recommendation options with respect to the new MenB vaccines. It could choose a Category A recommendation, so the new vaccine would become a mandatory part of the vaccination schedule, like vaccines against diphtheria, measles, polio, and other strains of meningitis (strains A, C, W, and Y). All insurance companies as well as the VFC program and ACA would have to pay for it. A majority of primary care physicians and clinics would keep it in stock so that it would be readily available to all prospective patients. A Category A recommendation would also require the ACIP to decide just where in the schedule to fit the new, required vaccine.

A Category B recommendation, sometimes called a "permissive" recommendation, would still require all insurance companies, the VFC program, and the ACA to pay for the new vaccine. The ACIP would still have to decide where the new vaccine fit in the existing schedule. However, it would leave the decision about recommending the vaccine up to the individual physician in consultation with the patient or parent. Although the ACIP does not make any recommendation to individual physicians about whether they should or should not stock any particular vaccine, a Category B recommendation might well mean the MenB vaccine would be less available. Patients or their parents might have to advocate to ensure they could get it.

The third option open to the ACIP was no recommendation for use of the vaccine, but that was not the anticipated outcome for the June 2015 meeting. Both MenB vaccines had evidence to support some sort of recommendation. The question was, which one was best for the American people?

It may seem puzzling and distressing that anyone, let alone a committee made up of physicians, researchers, and public health professionals, would even think twice about providing the widest possible protection for a potentially deadly disease, and that point of view was clearly expressed during the public comments. As Frankie Milley, founder of the national advocacy group Meningitis Angels put it, a Category B recommendation "to me, is like having a ship that's sinking. You have 100 passengers, 100 life vests, and you only give out 50, and the other 50 people on that boat drown as they watch their life vest hanging in the closet" (ACIP, 2015a, 43). But ACIP members are bound, by charter, to consider "disease epidemiology and burden of disease, vaccine efficacy and effectiveness, vaccine safety, economic analyses and implementation issues. The committee may revise or withdraw their recommendation(s) regarding a particular vaccine as new information on disease epidemiology, vaccine effectiveness or safety, economic considerations or other data become available." They must carefully consider all the evidence available for a particular vaccine, what is known about it and what is unknown. They must also be aware that

the science of immunization is fast-moving and constantly evolving, and therefore, as Temte put it, they must pay particular attention to the "known unknowns and unknown unknowns" that might arise in the course of their deliberations (ACIP, 2015a, 37).

In order to assess the complex data concerning "safety, efficacy, and burden of illness" with respect to vaccines, ACIP members use a framework for evidence-based decision making called GRADE, short for Grades of Recommendation Assessment, Development, and Evaluation. Health-care professionals throughout the world use the GRADE framework to make recommendations and decisions. The framework is designed for "transparency; use of evidence of varying strengths; considering of individual and community health" (ACIP, 2010, 93). ACIP working groups tasked with evaluating a particular vaccine use GRADE to assess all the knowns and unknowns in order to decide whether there is enough hard data to make a recommendation, either for or against its use.

Although there are a number of steps to the GRADE process, the overall structure is very simple. First, the working group must look at all the scientific evidence available for a particular vaccine and decide whether the evidence is complete enough, and good enough, to provide solid answers to their questions. Do they have confidence, from the existing data, that the vaccine will work as expected? Do they have confidence, from the existing data, that the vaccine is safe? If the answer is no, then they stop. They do not have enough evidence to make a recommendation. If the answer is yes, then they continue. They can make a firm recommendation, either that the vaccine should become part of federal immunization policy or that it should not. In effect, the evidence-based framework codifies an enormous amount of complex decision making that, in the 18th through late 20th centuries, would have taken place through trial and error, only after new vaccines had been used on patients.

On June 24, 2015, members of the Meningococcal Work Group presented an overview of the committee's work that highlighted the complexities of assessing and recommending new vaccines. Vaccines for other strains of meningitis had been recommended and administered for years; indeed, many colleges and universities in the United States require proof of the meningitis vaccine before allowing a student to live on campus. But the two existing MenB vaccines had only been licensed following the outbreaks on college campuses: by Pfizer, on October 29, 2014, and by Novartis, on January 23, 2015, respectively. They had been licensed under an accelerated pathway with very careful CDC oversight so that they could be made available to patients and reduce the risk that this especially virulent strain would spread. But that also meant the evidence was more limited and so required the most careful assessment. As Rubin put it, "MenB vaccines certainly are challenging for ACIP. Of course, the goal is to prevent the largest proportion of cases of meningococcal disease possible. The recently licensed MenB vaccines are an important step forward. However, data for making policy decisions for vaccine use are not complete in terms of effectiveness, strain coverage in the US, duration of protection, effect on carriage and herd immunity, and expanded safety. In addition, the burden of serogroup B meningococcal disease in adolescents and young adults is currently low" (ACIP, 2015a, 23).

Several members of the working group presented their overall assessment. The process began with a study question, a specific question that can be answered based on available evidence. Choosing the right study question is key to the ensuing analysis: the more precise the question, the more precise the assessment of the available evidence. The MenB study question was, "Should MenB vaccines be routinely administered to all adolescents and young adults (including college students)?" The answers had addressed the evidence for making the decision. The two options were: 1) There was strong evidence for saying yes or no to the question; and 2) There was not strong evidence for saying yes or no, and therefore, no recommendation could be made.

The next step was "to select outcomes that the WG [working group] believed to be important and critical to answer this question." The first had to do with burden of disease. How many cases were there? How likely was the disease to kill patients who contracted it? Did the disease carry with it any long-term effects? The second had to do with how well the existing MenB vaccines worked against the known strains of meningitis B. There was not just one "B strain" of meningitis. Indeed, there were thousands. It was important for the working group to assess whether the existing vaccines would be useful against all the MenB strains out there or only a subset.

These outcomes were essential to the assessment process. The incidences of all cases of meningococcal disease were reported to be at "historic lows" in the United States: there were only 564 cases in 2013. For meningitis B, there were only 55–65 cases each year among young adults, with 10%–15% ending in death. As reported, it was not only a life-threatening but also a rare disease: to put it into perspective, as one ACIP participant pointed out, "There are 20,000 to 30,000 deaths a year in this country from mental health-related diseases in the same age category" (ACIP, 2015a, 40).

It was, therefore, the first task of the working group to decide how confident they were in that data: did they think it was accurate? Did they feel they needed additional research to improve its accuracy? Or did they believe that no additional research was necessary for them to accurately characterize the burden of disease?

After carefully reviewing the data, the working group felt very confident in the evidence on burden of illness. As one of its members noted, "Meningitis is one of the better reported diseases in the US" (ACIP, 2015a, 56). That is, the disease was not overreported or underreported: there was no evidence to suggest that there might be much higher, or much lower, numbers of MenB disease now or in the foreseeable future.

Breadth of coverage was a different matter. The existing vaccines had been introduced to save the lives of at-risk young people, and there simply was not much data available on all possible meningitis B strains. The vaccine manufactures had provided estimates, but they had used different methods. Additional scientific studies were still in progress and had not yet published any results. That meant further research was certainly necessary to fully assess how well either vaccine would work against the many strains of serogroup B. The working group was not confident that they had enough scientific evidence to answer this question.

The working group also identified additional five outcomes for their formal, evidence-based assessment:

1. Efficacy in producing short-term immunity, defined as one month after the patient receives the vaccine. This would ensure that a patient who received the vaccine was protected for the duration of a meningitis B outbreak.
2. Efficacy in producing long-term immunity, defined as 11–24 months for one vaccine or 48 months in the other. This was essential if the vaccine was to become part of a routine vaccination schedule. Patients—and their parents—would have to be informed whether they might need one injection at age 16 or one at age 16 and another at 18. And they would have to be certain that an injection at, say, 18 would provide protection for two or four years of college.
3. Efficacy when administered with other vaccines. Nowadays, no routine immunization is given in isolation. Existing recommendations for other meningitis vaccines stated that one dose was to be given around age 11 and a booster at age 16. As one of the ACIP members pointed out, it was hard enough getting adolescents back to their pediatricians to get the currently recommended meningitis booster shot. If the ACIP recommended the new MenB vaccines for the same age group, it would have to be effective when administered at the same time as the existing meningitis vaccines.
4. Serious adverse effects caused by the vaccine. Vaccines have to be safe as well as effective.
5. Safety when administered with other vaccines. Would the new vaccines add to the existing adverse effects of currently administered vaccines?

Again, the point of the GRADE assessment process was to assess the quality of the evidence. Working group members used published and unpublished data in their assessment. They divided the existing scientific studies into two groups, randomized control trials (RCTs) and observational studies. RCTs were usually taken as the gold standard for clinical research, so they are assigned an initial number of "1" as the highest ranking, while observational studies are ranked lower, at "3." But studies could move up or down on the table, based on a number of factors: risk of bias or other methodological limitations, inconsistency, indirectness, imprecision, publication bias. They could also be moved up in the table, though only if they have not previously been moved down.

The working group examined each vaccine in turn. The first was Bexsero (MenB-4C), produced by Novartis. There were only five studies, one noncontrolled study and four RCTs. None of them dealt with efficacy or safety when administered with other vaccines. The second was Pfizer's Trumenba (MenB-FHbp). Again, the evidence was limited, two noncontrolled studies and five RCTs. For Trumenba, there was some evidence on its impact with other vaccines. This question was especially important for its administration to young adults. Young adults are not an easy population to vaccinate. If young adults did not go to their pediatrician for the current vaccine, which was strongly recommended for their age group, it was unlikely they would go for this new vaccine. The best way to get patients to take it would be to incorporate it into the existing MenB vaccine—but to recommend that, the working group would need more data.

Modern reporting data have changed the nature of vaccine evidence, particularly when it comes to reporting severe adverse effects (SAEs). Of the approximately 70,000 patients who received the vaccines, fewer than 300 reported any SAEs. The deaths that occurred were caused by car accidents and intoxication, unrelated to the vaccine and unfortunately often linked to the age group who had received the vaccines.

The working group found it could not assign a "1" type to any of the evidence. The evidence for benefits seemed strongest in the short term but less certain in the long term. For short-term efficacy of both vaccines, the working group designated the evidence type 2, "further research may change the estimate of effect." For long-term efficacy, the evidence type was designated type 3 and 4, indicating that more research would be necessary for them to have confidence in the results. When it came to safety, the evidence seemed clearer, as the evidence for SAEs for both vaccines was assessed as evidence type 2. But there were significant gaps: the evidence for the MenB-4C vaccine with other vaccines could not be assessed at all.

What this meant was that the working group did not have enough confidence in the existing scientific evidence to make a Category A recommendation, one that would require the routine use of the new MenB vaccines for all children. This decision was bolstered by a cost-effectiveness analysis carried out by the CDC. The ACIP is not charged to consider the cost, in dollars, of their recommendations. As Temte had noted in a previous meeting, "ACIP has always been asked specifically to make recommendations based on safety and efficacy first. Other considerations follow that. ACIP has never been asked to make a recommendation based solely on the cost of a vaccine. In fact, ACIP should be fairly neutral to that based upon its charge" (ACIP, 2010, 40).

But ACIP members are able to include consideration of what is known as Number Needed to Vaccinate (NNV) when making their recommendations. This is the number of patients who would need to be vaccinated in order to prevent a case of or a death from a disease. In the case of meningitis B, the CDC's analysis found that, assuming a population of 4 million adolescents and young adults, between 100,000 and 400,000 would have to be vaccinated to prevent even a single case of the disease. Between 1 million and 3 million adolescents and young adults would have to be vaccinated in order to prevent a single death. The NNVs are thus very high compared to the number of cases and deaths they would prevent. They also have a wide range: there is clearly a very great practical difference between vaccinating 100,000, 400,000, 1 million, or 3 million people. Currently, only 30% of adolescents and young adults routinely get their recommended booster shot for the existing meningitis vaccine—that is, what would be 1.33 million of the hypothetical 4 million people in the CDC analysis. If "1 million" was the correct NNV, then adding the MenB vaccine to the routine schedule would be effective in preventing that one death. But what if "3 million" was the correct number? Clearly—again—more evidence on cost-effectiveness would be necessary before the working group could agree on a Category A recommendation (ACIP, 2015a, 31).

The Meningococcal Work Group concluded their report by acknowledging "that meningococcal disease is a rare but serious illness and each case is life-threatening." There was "a strong desire" within the working group "to ensure access to MenB

vaccines." However, they felt "important data for making policy recommendations for MenB vaccines are not yet available." For that reason, they favored "a Category B rather than a Category A recommendation." The key reasons were "First, the current burden of diseases is low. This means that the [Number Needed to Vaccinate] to prevent a case and death is high, and the number of cases prevented may be comparable to the number of [serious adverse effects] to vaccine. Second, additional data are still needed to consider a routine recommendation. Most importantly, a better understanding is needed of the true proportion of serogroup B cases that could be prevented with MenB vaccine." They were aware that "it is difficult to accept that, in the absence of a vaccination program, there may be cases that are preventable. However, even with a fully implemented vaccination program," the evidence indicated that "the MenB vaccines will not prevent all cases" (ACIP, 2015a, 32).

The Meningococcal Work Group had provided an exemplary analysis, fully living up to the standards of "transparency; use of evidence of varying strengths; considering of individual and community health." It was clear, scientific, and evidence-based: as one ACIP member put it, it was "one of the best presentations of the data she had ever heard" (ACIP, 2015a, 40).

But it is part of the historical conversation on vaccination as well as part of the charge of the ACIP that good science must form the basis for any recommendation but cannot be the only consideration. Values and preferences, from professional colleagues and from the public, must be incorporated into the ACIP's deliberations. In the June 2015 meeting, criticism of the working group's recommendations stemmed from the historical success of the United States' vaccination program and the enormous power of the ACIP to influence that success in the case of individual diseases and individual patients. Routine vaccination saved millions of lives every day and billions of dollars in health-care costs every year. The data showed, time and again, that Category A recommendations worked better than Category B recommendations to make vaccines available to American citizens. By the early 21st century, governments worldwide were working to end vaccine-preventable diseases. When it came to MenB, as the working group itself said, "It is difficult to accept that . . . there may be cases that are preventable." But Frankie Milley was more forceful: "How many tears do we have to cry and how many children and young adults have to be debilitated or die before . . . we do the right thing and just stop this disease?" (ACIP, 2015a, 44).

While the working group's recommendations recapitulated techniques promoted by vaccine advocates over the previous three centuries, the questions and comments from ACIP members and the public distilled many of the concerns of their critics. One medical professor pointed out the problem of translating the recommendation in its current form into actual practice. As "the parent of one college-aged child," she said, "and one child who just finished college, she was completely unclear about what the [ACIP] expected parents to do. If she or her daughter goes to the doctor and indicates that they have heard there is a vaccine that will protect her daughter from a deadly disease, they would have to rely on the doctor to make a value-based judgment about whether she should receive this vaccine. This kicks it back to the 19-year-old who is going to call her mother, who is just as confused." They already knew, from their professional experience, that it can be very hard to get a healthy

young adult to go to a doctor. Another physician pointed out that "unlike huge health maintenance organizations (HMOs), it has been her experience with permissive recommendations in the past that smaller practices may not even carry Category B vaccines in their offices. While practitioners can council patients, the patients may have to go elsewhere to be vaccinated" (ACIP, 2015a, 40).

That, of course, assumed that practitioners were knowledgeable about the dangers of meningitis. ACIP members "emphasized that it is the responsibility of physicians to educate themselves on the risks and benefits of vaccines. Physicians must understand the risk of the disease and make recommendations as appropriate for the child. If there is a vaccine that works, it should be ACIP's job to educate their colleagues and promote its use if a Category B recommendation is made." A representative from the National Association of Nurse Practitioners "acknowledged the importance of the use of the vaccines for outbreak management and that local public health and colleges have to be prepared in advance to use the vaccine. Education of clinicians, adolescents, and parents about the signs and symptoms of meningococcal disease and early recognition, early treatment, and prompt community response may be one of the most important efforts they could make with regard to this disease" (ACIP, 2015a, 41).

If only it were that simple, argued Steven Black, a pediatric infectious disease specialist, during the six minutes he was allocated as part of the public comments. "I've been a Pediatric Infectious Disease Specialist and Vaccinologist for more than 30 years," he said, going on to make "two disclosures. [First,] I'm a consultant for GSK, Protein Sciences, Takeda, and WHO. And secondly, I really hate this disease . . ." The problem with a Category B recommendation, which made the MenB vaccine optional, is that the disease "evolves too rapidly . . . I became a doctor to save lives, and I think that it's difficult to save lives one on one, especially with meningococcal B disease . . . One . . . of the greatest fears of pediatricians and parents is to miss a case of this disease because, once it commences, the risk of sequelae and mortality is so high. So, I think the committee has an opportunity today to prevent these deaths, to prevent the suffering and loss of life potential in dozens of children each year." He, therefore, urged "the committee members to seize that opportunity and to routinely recommend this vaccine for children" (ACIP, 2015a, 42).

Those ideas—the rapid spread of the disease among otherwise healthy young adults who had no reason to go to a doctor, the difficulty of diagnosis on the ground, the devastating effect of even a few hours' delay—were repeated over and over by family members and meningitis survivors during the public comments. Ryan Milley, Frankie Milley's son, developed a fever on the Father's Day after his high school graduation. Like any concerned parents, the Milleys put Ryan to bed and called his doctor Monday morning to make an appointment. Within a few hours it was clear he was very sick, and they rushed him to the emergency room. He died at 10:15 that night. Since that time, Frankie Milley has worked tirelessly to advocate for meningitis vaccines. As she said, "I've been coming to these ACIP meetings for 12 years. I've testified at almost all of them, almost 36 times. For a total of 108 minutes, I've been allowed to speak about my son and the importance of immunizing kids. In those 12 years, the working groups, the ACIP voting committee, and us old warriors that are here every time have come very far. We've left here

celebrating, and we've left here crying. One of the worst was when we had a vaccine to prevent meningococcal B in infants and we didn't get a recommendation for it." We know from past experience, she said, "that permissive recommendations don't allow for education of the disease and the vaccine. We know, in many cases, there's no affordability or accessibility. We know that there's a hesitancy of physicians and healthcare providers to give it because [they feel] it's really not recommended . . . We know that there [are] provider reimbursement problems" with the Category B recommendation (ACIP, 2015a, 42–43).

Scott Parkhurst told a similar story of his son Jacob, a 17-year-old high school junior who died within 36 hours of falling ill. Once again, he felt sick on Sunday and by Monday morning, "he was in the emergency room. The ER doctor pulled Jake's mom and I aside and informed us that Jake may not survive and appeared to have bacterial meningitis. I told Jake to fight for his life and he yelled back to me, "Okay" as he was taken off to intensive care and put into a medically induced coma. That was the last contact I ever had with Jake" (ACIP, 2015a, 44). Alicia Stillman, founder and director of the Emily Stillman Foundation, got a call from her daughter Emily, a college sophomore, reporting, "I have a headache." I said, "Why do you think you have a headache? I bet you're coming down with the flu." She said, "No, mom, I was up all night studying for two big tests. But don't worry. I did good." I said, "Great, so take a couple of MOTRIN® and we'll see how you feel in the morning." "The morning never came. By the time I was called back to the hospital the next day and told to get en route immediately, Emily was in a coma" from which she never awoke (ACIP, 2015a, 45).

Nor was it only parents sharing the heartbreak seeing their healthy child move inexorably from a headache to a life-threatening disease, from a rare "case," in the ACIP's clinical language to a "fatality." ACIP members had talked about the need to educated colleges and universities, but those same colleges and universities begged the ACIP for help. Dozens of colleges, universities, and professional associations wrote letters to the ACIP, pointing out, time and again, that though all adolescents and young adults were at risk for meningitis B, the conditions of college living were particularly conducive to its spread. They pointed out the potentially devastating effects on college and university communities, whatever the outcome of a specific case. And they pointed out the historical evidence of two centuries of vaccine-related public health measures that routine immunization is the most efficacious and most cost-effective way of eliminating vaccine-preventable diseases (ACIP, 2015a, 185–254).

The public comments hammered home the limitations to the most scientific analyses of burden of illness. As Scott Parkhurst said, "I understand this disease only affects a small percentage of the population. But when it's your son, daughter, grandchild, cousin, niece, or friend, it's 100%. I don't think anyone here who has children would want to lose their child to something that is preventable" (ACIP, 2015a, 45). Mike Barnes described how his family "lost our 20-year old son, Jimmy, to serogroup B meningococcal disease this March. He went to the ER on a Monday with a terrible headache, neck pain, and high fever. He was told it was the flu and sent home. He was gone in 28 hours. He was not a college student living in a dorm, and his story was not covered by the media, so I'm here to share it with you today. He was, however, we thought, fully vaccinated, including with the meningitis vaccine . . . In my

family, among my two children, the incidence of men B was 50%. For Jimmy, it was 100%" (ACIP, 2015a, 46).

Andy Marso, meningitis survivor, brought up the question of cost-effectiveness when it came to the shouldering the burden of illness. "I know there's concerns about the cost of these vaccines, but I hope you're accounting for all of the costs of not vaccinating and you're also accounting for the cost burden and who bears the cost burden. Is it society at large, or is it just families like mine?" As he explained, "Unfortunately, most people don't know how afraid of this disease they should be. I know because 11 years ago, I went from a perfectly healthy college student to almost dead within 24 hours. Then I spent four months in the hospital having my skin debrided and parts of my limbs amputated. As I told you all a few months ago, the first year of my medical bills were almost $2 million. That's just for the initial year. $2 million. That would've bought a lot of vaccines, right? And that doesn't even account for the year of work that my parents missed and that I missed as I was recovering, nor for the ongoing medical costs that I've had every year since. I've been fortunate to have health insurance, but I've basically maxed out my out-of-pocket every single year and I probably will for most of my life . . ." (ACIP, 2015a, 49–50).

ACIP members had pointed out that a Category B recommendation could be seen as "fairly neutral" on cost, since it would place the MenB vaccines on the list of vaccines paid for through the VFC program and ACA. But as public presenters responded, there still might be enormous inequities in who actually could afford to get the vaccines. Before the FDA licensed the vaccine, Alicia Stillman had driven "busloads to Canada and I protected whole families in Canada with this vaccine. Now we have it here and I field phone calls and emails all day long from parents all over the country who can't get their hands on this vaccine" (ACIP, 2015a, 45). Jacqueline Ross, sister of a Drexel University student who had died of meningitis B, described how "since December, my parents have worked to get me the serogroup B vaccine. This was no easy task. It took many phone calls and e-mails between them, the vaccine manufacturers, my pediatrician, various pharmacies, and even the Department of Public Health. I was finally able to get vaccinated just last week, but the process took nearly six months and it only occurred because our pediatrician finally thought to recommend that we look into a travel vaccination clinic. My parents also tried to get the vaccine through several pharmacies. Most did not have the access to it, and those that could get it did not have anyone on staff that could administer it, so ordering it would not have mattered. Parents should not have to work this hard to get an FDA-approved vaccine to protect their children" (ACIP, 2015a, 48). If the vaccine was that inaccessible for families of advocacy groups, how accessible would it be for less privileged or informed families?

The public comments also raised the issue of vaccination as a human right and a right of all American citizens, which the ACIP, like other federal agencies, had a responsibility to protect and serve. Neil Raisman, who lost his son Isaac to meningitis, concluded "that informed people with the money to pay for the vaccine have lived and those who can't afford it or don't even know about it have been infected. This is counter to everything the ACIP, the CDC, the FDA, and the NIH stand for. Your endorsement vote for the FDA recommendation would realign this committee with its mission . . . We expect the government to tell us when the health of our

children is in danger, and then help us decide what to do" (ACIP, 2015a, 55). Kamay Lafalaise, from the National Consumers League, pointed out that healthcare advocacy is part of consumer advocacy and that "making safe and effective medications and healthcare widely available to all Americans has been a longstanding priority to NCL . . . 84% of parents cite protecting a child from disease as the top reason to vaccinate . . . and of all childhood diseases, parents are most concerned about meningitis. Not only do these findings highlight that there is an ongoing need for vaccine education, but that Americans see vaccines as a way to protect our children and community from disease, and they take very seriously the threat of meningitis." A Category A recommendation would be much more effective in creating opportunities for consumer education and would make that education available to the largest number of potential patients, "not just those who are aware of the vaccine and specifically request it or those who can pay out-of-pocket costs." Lafalaise concluded, in words that echoed the "values and preferences" expressed by so many others, "You have heard powerful testimony today from several people afflicted by this frightening disease. If we wait, it could be too late. How many lives need to be lost before we take preventative action?" (ACIP, 2015a, 54).

Of all the advocacy groups, the only one that supported a Category B recommendation came from the National Vaccine Information Center (NVIC), described in its own statement as "advocates for the institution of vaccine safety and informed consent protections and public health policy and laws." ACIP members may have been disconcerted to find themselves on the same side as the NVIC, which has promoted anti-vaccination campaigns since the 1990s. As a consumer education group, however, the NVIC has been consistent in "supporting the availability of all preventive healthcare options, including vaccines, and the right of consumers to make educated, voluntary healthcare choices." Like many other anti-vaccination advocates in the past 200 years, they have insisted that vaccination must be voluntary, not required by law. For that reason, while agreeing that "parents have a right to know about the benefits and risks and availability of meningococcal vaccines so they can make an informed decision for their children," they did not recommend what they termed a "universal-use recommendation." Instead, they encouraged "ACIP and the CDC to revisit stakeholder support and need for greater flexibility in the ACIP recommendations" (ACIP, 2015a, 46).

Though there have been times when the NVIC and other anti-vaccination advocacy groups have seemed like the strongest voices, it was not true in the June 2015 meeting. Instead, a representative from the Immunization Action Coalition, a pro-vaccine advocacy group, opposed to the NVIC in this as in so many other arenas and summarized the overwhelming public opinion when she noted, "As public health professionals, we are all dedicated to prevention. I know that you as ACIP members are charged with making recommendations that balance difficult and seemingly competing objectives. But to me, the answer is clear. I choose prevention, and I ask you to choose a routine recommendation to protect all teens with MenB vaccine. You have the power to prevent a deadly and devastating disease that can have an overwhelming impact on young people and all the people who love them, as we have just heard. A routine recommendation is quite simply the right thing to do" (ACIP, 2015a, 53).

At the end of the public session, Temte thanked all of the participants "for sharing what must be very difficult stories, and expressed ACIP's appreciation for their heartfelt and very thoughtful comments" (ACIP, 2015a, 55). ACIP members had additional discussion to address, at least in part, some of the public comments. One committee member "stressed that members considering support of a Category B recommendation were not doing so because they were wildly enthusiastic that it would be exactly the right recommendation long-term for this vaccine. There simply was not adequate information at this point to support a Category A recommendation. In that context, she urged the manufacturers to provide those data as quickly as possible." She as well as others explained that they did not consider burden of disease solely in terms of statistics and that they recognized how important it was "to understand the long-term consequences and the cost of medical expenses to survivors and families out-of-pocket. Survivors are dealing with profound lifelong consequences, which should be factored in."

In order to address concerns about practitioner and patient education, ACIP members on the Childhood Vaccination Schedule working group agreed to put information about the MenB vaccines on the official U.S. Childhood Vaccination Schedule and to make it available on all other information outlets. There was some discussion of the need for revising the color-coding on the family-friendly vaccination schedule charts. In response to the many letters from colleges and universities, a representative from the American College Health Association noted, "They are pleased to have reached a point of making some recommendations, which offers a springboard before the fall semester" (ACIP, 2015a, 57).

The final point of discussion was the recognition that a Category B recommendation, if approved, was not set in stone. As more evidence became available or as new vaccines were approved, the ACIP could move quickly to review and, if appropriate, revise the recommendation to a Category A. One promising possibility for the future was a combined vaccine that could combine protection against meningitis B with the other meningococcal vaccines already available for routine use.

Having completed the discussion, the ACIP prepared to vote on the Meningococcal Work Group's proposed recommendation for use of MenB vaccines in adolescents:

> A serogroup B meningococcal (MenB) vaccine series may be administered to adolescents and young adults 16 through 23 years of age to provide short term protection against most strains of serogroup B meningococcal disease. The preferred age for MenB vaccination is 16 through 18 years of age. (Category B)
>
> In addition, the following language would be provided as guidance for use:
>
> - MenB should be administered as either a 2-dose series of MenB-4C or a 3-dose series of MenB-FHbp
> - The same vaccine product should be used for all doses
> - Based on available data and expert opinion, MenB-4C and MenB-FHbp may be administered concomitantly with other vaccines indicated for this age, but at a different anatomic site, if feasible
> - No product preference to be stated

The ACIP approved the working group's recommendation by a vote of 14-1. It was subsequently approved by the director of the CDC and thereby became federal policy. In October 2015, the ACIP and CDC approved a new system of color-coding to emphasize the importance of MenB vaccines in protecting the health of the nation's adolescents and young adults.

At the conclusion of the June 2015 meeting, ACIP members, public participants, and the entire country had survived yet another of the historical conversations about vaccination. The rest of this book will show how that conversation began and how it has grown, added significant features, and engaged global participants, through to the present day.

FURTHER READING

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