A Perspective on Vaccines

President’s Address
Institute of Medicine Annual Meeting

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This has been an exceptionally busy and productive year at the Institute of Medicine (IOM), with our annual program budget exceeding $50 million in direct costs. This past year, we undertook a number of critical policy studies related to health reform, ranging from geographic variation in costs and quality to criteria for essential health benefits. Altogether, we released 75 reports and workshop summaries since our last annual meeting, another high water mark. An examination of the impact of this year’s work, along with detailed information about IOM activities and financial matters, can be found in the Supplement to the President’s Report.

Many of my annual addresses present a broad overview of the past year, typically highlighting one or more themes. Instead, this morning’s annual address reviews more than 30-years’ experience at IOM with studies related to vaccines, the theme of today’s meeting. Vaccines have probably saved more lives than any other single class of medical interventions. Perhaps clean water is a strong competitor in the public health domain, but few more powerful examples exist in the realm of medical interventions.

The modern era of immunization dates from Edward Jenner’s experimental vaccination with cowpox to prevent smallpox. Jenner was not the first to observe that milkmaids generally did not get smallpox, nor was he the first to immunize with cowpox, but he was the first to test immunity by deliberately exposing his cowpox-vaccinated subjects to smallpox. This anonymous print from 1796 depicts the first vaccination of James Phipps (see image). Fortunately, he survived the smallpox challenge.

Over the years, immunization has become a cornerstone of public health. A 2005 study published in Archives of Pediatrics & Adolescent Medicine showed that seven childhood vaccines in the United States prevent more than 14 million cases of disease and avert more than 33,000 deaths over the lifetimes of the cohort of immunized individuals born in one year. In addition to saving lives, every $1 spent on these vaccines returns $16.50 in direct and indirect savings (Zhou et al., 2005).

Despite the unquestionable success of vaccines, scientifically unfounded concerns and refusal to be immunized lead to avoidable illness, death, and expense in the United States and other countries. Such objections and concerns are not new, and they continue to have profound effect: in 2003-04, suspicion among some groups in Nigeria that the polio vaccine was a deception used to sterilize the population led to rejection of the vaccine and allowed polio to recrudesce, dealing a severe
setback to the global polio eradication effort (Altman, 2003, 2004; Pincock, 2004). Vaccine refusal also affects public health in the United States—recent outbreaks of measles, mumps, and pertussis have endangered whole communities and led to numerous hospitalizations among groups who refuse immunization (Adashi and Offit, 2011; CDC, 2010).

Despite scientific progress and stunning practical achievement, there remain many unanswered scientific and policy questions about vaccines. The late Maurice Hilleman, legendary vaccine developer at Merck, was responsible for vaccines that protect against measles, mumps, hepatitis A, hepatitis B, chickenpox, meningitis, pneumonia, and \textit{Haemophilus influenzae}, saving millions of lives around the world. A blunt-spoken man, he once observed to me, “We don’t know squat about how vaccines work.” Only Dr. Hilleman did not say “squat.” Among the unanswered questions are ways to make effective or improved and longer-lasting vaccines against such global threats such as malaria, tuberculosis, HIV and influenza.

Vaccines are not only matters of biomedical science and public health. Vaccines and the diseases they are intended to prevent evoke profound social, cultural, and ethical questions about what it means to live in a civilized society and the responsibilities we have toward one another. A special feature of this meeting is a multimedia exhibit on the cultural, artistic, and humanistic aspects of infection and immunization. These social dimensions convey the meaning of vaccines in contemporary society. Priscilla Wald, in her book titled \textit{Contagious: Cultures, Carriers and the Outbreak Narrative}, writes, “The social experience of disease...the image of communicability, the materialization of interdependence that characterizes depictions of epidemics suggest an epidemiology of belonging...” These elements of social purpose, shared risk, and common solution are the essence of the social meaning of vaccines.

\textbf{Vaccine work at the IOM}

The Institute of Medicine’s work on vaccines ranges across science and policy from domestic to global, affecting individuals in every stage of life. Since its founding in 1970, the IOM has published at least 60 reports bearing on vaccines: one report between 1970 and 1979, seven reports between 1980 and 1989, thirteen reports between 1990 and 1999, thirty-seven reports between 2000 and 2009, and two reports in 2010-11 (see Figure 1 and Appendix).

Approximately two thirds of these reports were consensus studies, and all save one of the remainder were workshop summaries. The sole exception is a statement issued by the IOM Council in 2001 calling for the establishment of a National Vaccine Authority “to advance the development, production, and procurement of new and improved vaccines of limited commercial potential but of global public health need.”
Another way to look at these 60 studies is by topic area covered. Nine dealt with policy on specific infectious agents and their respective vaccines, and twice that number—eighteen—focused on vaccine safety. Twelve studies evaluated vaccine programs; thirteen covered vaccine planning, production, financing, and use; and the remaining eight assessed vaccine needs and priorities (see Figure 2 and Appendix). Let me provide a few highlights from each of these areas.
Policy for specific infectious agents and their respective vaccines

The first IOM vaccine study, in 1977, evaluated poliomyelitis vaccines. This was part of a long-running debate about the pros and cons of attenuated, oral (Sabin) vaccine vs. inactivated, injectable (Salk) vaccine. The Sabin vaccine was easier to take, cheaper, and immunologically more effective, and it had become the standard worldwide. However, the live, attenuated virus vaccine also had the rare consequence of causing paralytic polio, sometimes in the immunized person and sometimes in a care-giving family member. The trade-off was whether to protect against additional cases of polio by using the oral polio vaccine or to return to the inactivated virus vaccine to avoid any vaccine-induced paralysis. In this first study, the committee reaffirmed the then current strategy of oral polio vaccination. A second study in 1988 was more tentative, but ultimately came down on the same side. It was only in 1996—two years after polio had been eradicated in the western hemisphere—that a workshop raised a series of alternatives to exclusive reliance on the oral polio vaccine.

In subsequent years, the Advisory Committee on Immunization Practices at the Centers for Disease and Prevention (CDC) adopted an interim strategy using initial doses of inactivated and then later doses of oral vaccines, attempting to get the advantages of both and avoid the higher incidence of paralytic polio that attended the first dose of the oral vaccine. By 2000, the recommendations moved to full reliance on the inactivated vaccine.


Vaccine safety

Studies of vaccine safety, the largest cluster of IOM vaccine studies, culminate in a wide-ranging review published earlier this year (2011). The Committee on the Review of Adverse Effects of Vaccines examined 158 pairs of vaccines and putative adverse effects. While the majority of cases did not have adequate evidence to support or reject a causal link, the conclusion of the committee was that very few health problems are caused by or are clearly associated with vaccines.

This report follows a series of eight reports on vaccine safety that appeared between 2001 and 2004. The eighth report in this series examined the evidence about autism and vaccines, and it found no scientifically based association.
Vaccine program evaluation

The IOM has evaluated vaccine programs against naturally occurring infections and biological weapons. The organisms in question include smallpox (2002, 2003, 2005), anthrax (2002), and influenza (2009, 2010). In the case of the smallpox studies, we were able to produce a series of letter reports virtually in real time to help guide and advise the CDC’s program as it was unfolding.

Vaccine planning, production, financing

A key report in 2000, *Calling the Shots*, examined whether immunization programs were adequately financed and appropriate to protect against infectious disease. The Senate Appropriations Committee requested the study, which garnered support from the CDC. The report was followed by a series of four workshops aimed at promoting a strategic vision for immunization finance and delivery (2002-2003) and an additional report on vaccine financing (2003).

Other studies deal with vaccine planning, production, and financing and cover the prospects for viral disease eradication (2002), vaccine acquisition and availability for the military (2002), and guidance for the U.S. National Vaccine Plan (2008, 2009).

Vaccine needs and priorities

Two key studies in the mid-1980’s dealt with priorities for new vaccine development. The first, in 1985, assessed domestic priorities, and the second, in 1986, considered global needs. A study in 2000 revisited the difficult challenge of ways to set priorities for vaccine development. In 2012, we anticipate a new study on vaccine priorities. One distinctive feature of the forthcoming study is a working decision model that policy makers can update in real time with new data or with different preferences, allowing the study model to contribute over time as technologies and conditions change.

A Personal Perspective

I hope you will permit me a brief reflection on my own engagement with IOM vaccine studies and more generally with vaccines. I had the privilege of serving on the first IOM committees to examine priorities for new vaccine development
in the United States and in developing countries in 1985 and 1986. Then, in 1991, I was invited to chair the first IOM committee that took up the question of vaccine safety, a study of pertussis and rubella vaccines.

Studies of influenza vaccine programs bookend my work. Early in my career, I coauthored a report with Richard Neustadt, *The Swine Flu Affair*, a study of the ill-fated effort in 1976 to protect the American public against the flu that never came. Then-president of the IOM, David Hamburg, was good enough to prepare the foreword for the book. Most recently, this past spring, I concluded service as chair of a World Health Organization (WHO) committee empanelled to review the functions of the International Health Regulations (2005) and the performance of the WHO during the 2009 H1N1 influenza pandemic. This report is available online [http://apps.who.int/gb/ebwha/pdf_files/WHA64/A64_10-en.pdf].

I have also worked collaboratively with others on studies of the effectiveness of different vaccines and their performance. One of these studies, on the effectiveness of BCG (Bacille Calmette-Guérin) in preventing tuberculosis, happily involved collaboration with my wife, Dr. Mary Wilson, and others. The conclusion of our meta-analysis was that BCG appears to be about 50% effective.

The only two clinical trials in which I have been a subject are vaccine trials. The most recent was a study at the Massachusetts General Hospital of Hepatitis A vaccine. The first occurred when I was growing up in Pittsburgh, where I was among the school children who were immunized in the early field trials of the Salk polio vaccine the 1950’s.

**Impressions and lessons from the IOM experience**

Let me suggest six impressions from the IOM experience in the study of vaccines.

First, the IOM has reflected *society’s sustained interest in vaccines* with its remarkable array of studies on many aspects of vaccine needs; research strategy; program planning, design, financing and conduct; safety and communication; and better modes of production, storage, and delivery. The topic has been of sustained importance and consequence for the U.S. and around the world.

Second, it is striking how often IOM *studies have been conducted in clusters*, as illustrated by the immunization safety series, the periodic re-examination of policy toward variola, and the periodic re-visiting of priorities for new vaccine
development. In part, re-examination is prompted by new scientific findings (as arise on questions of safety) that warrant a fresh assessment. Similarly, new epidemiologic, economic, and social conditions, and new scientific capacities can prompt a re-assessment in such areas as priorities for vaccine development. One virtue of such periodic visits to the same or similar vaccine topics is that it enables us to take account of different aspects of a problem and to drive home key lessons.

A third impression is the tenacity of concern about vaccine risk among some segments of the public. This is an unrelenting challenge to science-based evidence and public health. Rarely does a single study, no matter how well grounded in evidence, demolish all doubt. As Gardiner Harris wrote in the New York Times after the release of the IOM’s comprehensive vaccine safety report in 2011:

The Institute of Medicine is the nation’s most esteemed and authoritative adviser on issues of health and medicine, and its reports can transform medical thinking around the world. The government has asked the medicine institute to assess the safety of vaccines a dozen times in the past 25 years, hoping the institute’s reputation would put to rest the concerns of some parents that vaccines cause a host of problems, including autism. It has not worked (Harris, 2011).

Unfounded concerns about vaccine have proved remarkably impervious to scientific evidence.

Fourth, in a number of instances—responding to requests for real-time evaluation of the smallpox immunization program in 2002, or providing guidance on influenza or anthrax vaccines—the IOM has proved capable of responding with alacrity, sometimes in a matter of weeks. The IOM wields more tools than the conventional consensus study; the key is to fit the response to the timing and nature of the questions we are being asked to examine.

Fifth, the value of the IOM as an independent entity—apart from government and beholden to no interest groups—is amply demonstrated by our work on vaccines. The entire series on vaccine safety, if rendered by the same government that promoted the immunizations, would be suspect. The courageous experts and staff who have participated in these studies over the years have received more than their share of unjustified opprobrium from diehard critics. However, these studies reveal the IOM, with its reliance on science and evidence and the high caliber of our exceptional expert volunteers and staff, at its very best.
Finally, vaccine studies at the IOM are emblematic of the **global outlook and reach of the IOM program**. These studies, and the infections and vaccines that are their subject, portray the unity of global health as a simultaneous reality for the United States and for other countries of the world. Our domestic concerns for health are integrally connected to the needs and health problems of those living elsewhere. The studies of vaccine illustrate perfectly the meaning of the last sentence in the IOM mission: *The mission of the Institute of Medicine embraces the health of people everywhere.*
REFERENCES


APPENDIX

IOM Vaccine Publications by Chronology

Adverse Effects of Vaccines: Evidence and Causality (2011)

The 2009 H1N1 Influenza Vaccination Campaign—Summary of a Workshop Series (2010)

The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic: Global Challenges, Global Solutions. Workshop Summary (2009)

Live Variola Virus: Considerations for Continuing Research (2009)

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Immunization Safety Review: Multiple Immunizations and Immune Dysfunction (2002)


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Risk Communication and Vaccination Workshop Summary (1997)


Vaccines Against Malaria: Hope in a Gathering Storm (1996)

The Children's Vaccine Initiative: Continuing Activities (Summary of Two Workshops) (1995)

Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality (1994)

DPT Vaccine and Chronic Nervous System Dysfunction: A New Analysis (1994)

Research Strategies for Assessing Adverse Events Associated with Vaccines (Summary of a Workshop) (1994)


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New Vaccine Development: Establishing Priorities; Volume II, Diseases of Importance in Developing Countries (1986)

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