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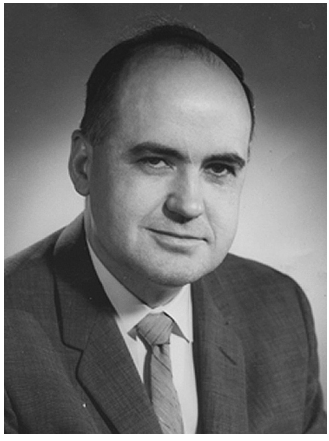
Chapter 19

Maurice Hilleman: Creator of Vaccines That Changed the World

ABSTRACT

Maurice Ralph Hilleman (1919–2005) was one of the greatest microbiologists/vaccinologists of all time. He played a key role in developing vaccines for Asian flu in 1957 and Hong Kong flu in 1968. Over six decades, most of which were spent at Merck & Company, his leadership and innovations blazed new trails in virology, epidemiology, immunology, cancer research, and vaccine development that were unmatched. His work resulted in current vaccines used for the prevention of measles, mumps, hepatitis A and B, chickenpox, meningitis, and pneumonia, which have saved millions of lives across the globe. The need for close cooperation between public and private agencies, including donors, to promote research in vaccinology is reemphasized by recent global health crises such as the Ebola and Zika viruses, as well as the annual influenza virus threats. Eradication of many diseases is feasible, but requires political support for resources, vaccine development and harmonization of vaccination policies, to be achievable. Hilleman worked with many collaborators in academic centers, in industrial management, with which he led his research and development team to produce world-changing achievements.



Maurice Ralph Hilleman (1919-2005). Creator at Merck Company of most vaccines used routinely in child care. *Courtesy: Mrs. Lorraine Hilleman.*

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Vaccinating Hilleman's daughter, Kirsten, with the Jeryl Lynn Mumps strain Vaccine derived from her sister. *Courtesy, Mrs Lorraine Hilleman. Available at: http://www.historyofvaccines.org/content/articles/mumps (accessed 27 August 2016).*

BACKGROUND

Maurice R. Hilleman was born in 1919 in Miles City, Montana, United States, but tragically his mother died 2 days after his birth. Hilleman was raised by his uncle while his father struggled to cope with raising his eight children under harsh circumstances on their family farm. Hilleman graduated from high school in 1937 in the midst of the Great Depression. As a poor farm boy without prospects or means, he took jobs in local stores and worked very hard but had little opportunity to advance his education. Inspired by an older brother studying at a divinity school, Hilleman applied for, and won, a full scholarship to Montana State University where he graduated first in his class at the age of 21 with a joint degree in chemistry and microbiology. He was offered scholarships at ten universities, and chose the University of Chicago for graduate studies in microbiology where, despite scholarships, he lived under squalid conditions. He received his PhD in 1944 with an award-winning dissertation which was on Chlamydia.

After graduating, Hilleman elected to work in the pharmaceutical industry instead of accepting offers to continue in academia. He took a position in E.R. Squibb & Sons and immediately started researching vaccine development. Viruses and other infectious agents which can cause disease can also be used to stimulate the host—i.e., the vaccinated person—to produce antibodies that act to defend against the infecting agent. Producing vaccines requires introducing a weakened live- or dead agent—i.e., virus, bacteria, parasite, or other infective organism, or part of the organism—that can stimulate the production of protective antibodies. He developed a vaccine against Japanese B encephalitis, which was urgently needed to immunize troops at the Pacific front of World War II.

In 1948, Hilleman joined the Walter Reed Army Medical Center as chief of the Department of Respiratory Diseases, where he was assigned to study respiratory illnesses which had military significance, and to devise a science and strategy for dealing with influenza. He demonstrated that influenza A viruses underwent "*gradual and progressive minor antigenic characteristics called 'drift and shift,' which are the basis of modern influenza vaccine strategies*" (Olanski, Lancet 2005).

In 1957, at age 38, Hilleman was recruited by the pharmaceutical company Merck & Company at West Point, Pennsylvania, to lead its virus and vaccination research programs for the next 47 years, continuing to direct the Merck Institute for Vaccinology for another 20 years—after compulsory retirement from Merck Research Labs in 1984 at age 65—until his death at age 85. From the 1950s to the 1990s, Hilleman and his team created more than 40 experimental and licensed human and animal vaccines, including those in use currently offering protection against measles, mumps, chickenpox, rubella, hepatitis A, hepatitis B, pneumococcal pneumonia, meningitis, pandemic influenza, and chlamydia.

Hilleman led the development of the Asian flu vaccine in 1957 which was important in alleviating the world-wide pandemic. Influenza remained a yearly occurrence after the horrendous 1918 Swine Flu pandemic which killed tens of millions of people, primarily young men. But no new, virulent influenza type emerged until early 1957. In February 1957, a life-threatening wave of flu was spreading across China with reports of 20,000 cases in Hong Kong. Then still a microbiologist at Walter Reed Army Medical Center, Hilleman suspected this could become a pandemic threat and coined the term Asian flu. He obtained a sample of the virus from an ill US serviceman and determined that most people lacked antibody protection for this new influenza virus. He initiated vaccine production by sending virus samples to manufacturers and urging them to develop a vaccine within four months, producing 40 million doses of vaccine and so reducing the US epidemic, which caused an estimated 70,000 deaths in the United States. World-wide, from 1957 to 1958, some two million people died from Asian flu. Subsequently new influenza strains have continuously emerged in Asia.

In 1968, Hilleman was active in developing a vaccine for the Hong Kong influenza pandemic. Because of the continuing threat of annual flu epidemics, the World Health Organization (WHO) developed new pandemic guidelines in 2005 to upgrade pandemic-preparedness plans in cooperation with vaccine manufacturers and national public health agencies, especially addressing the need for quicker development and distribution of influenza vaccines (College of Physician of Philadelphia).

He worked with academic scientists, but was also responsible for the field work of collecting samples for vaccine development as well as administrative and scientific leadership, which resulted in field testing and the production of many new—or improved—vaccines. He characterized and isolated antigens, performed the basic- and process research as well as doing clinical studies, all

the way through to the manufacturing process which resulted in fundamental breakthroughs in vaccine development. Table 19.1 shows the timeline of vaccines licensed in the United States.

Leonard Hayflick, born in Philadelphia, Pennsylvania in 1928, graduated with a bachelor's degree in microbiology at the University of Pennsylvania on a GI (US veterans) bill after completing his army service. He continued studying and received his master's degree in 1953, and was awarded full scholarship toward a PhD in medical microbiology and chemistry. Working at the University of Texas in Galveston from 1956 to 1958, Hayflick learned techniques of cell cultures producing large numbers of selected cells with long term survival and replication living in controlled conditions. Fetal cells were considered safer than other cell lines as the latter could be genetically abnormal, contain undetected viruses such as those of animal origin, or carry cancer genes. The famous HeLa cell line was the oldest and most commonly used human cell line derived from cervical cancer cells from Henrietta Lacks, a patient who died of her cancer in 1951. The cell line, extremely readily grown and survivable, was used extensively in scientific research including production of the inactivated Salk vaccine in 1954. Considerable controversy surrounds this even today because the sample was taken without the patient's permission and because of the possibility of its carrying cancer genetic material.

Lung cells from human fetal specimens developed by Hayflick from a legal abortion in Stockholm were considered promising, but controversial, due to ethical questions disputes over the source, ownership, and distribution rights. The Hayflick strain developed at the Wistar Institute in Philadelphia called WI-38 was widely accepted as an alternative to primary monkey kidney and HeLa cells. WI-38 provided a cell line from normal human embryonic tissues with a normal chromosomal constitution with no transfer of tumors in animal models. This cell strain was accepted in Europe where Hayflick's WI-38 cell line was approved for use in vaccines. Since the 1960s, WI-38 became the most widely used and highly characterized normal human cell population in the world. WI-38 was provided by Hayflick to Stanley Plotkin for use for the development of a new rubella virus growth and its resultant vaccine, licensed in 1970. WI-38 was also used in the production of the first oral polio vaccine made on a continuously propagated cell strain. Hayflick is renowned as a professor of gerontological studies at the University of California, San Francisco. His landmark studies are characterized as "Hayflick Limit" in cellular ageing and basic longevity studies. His contribution to vaccinology is the WI-38 cell line along with chick embryo cells which have been used for the manufacture of most human virus vaccines world-wide. Vaccines using WI-38 cells have immunized many hundreds of millions of people, include oral poliomyelitis (Sabin), measles, rubella, varicella, mumps, rabies, adenoviruses, and hepatitis A vaccines. Hilleman and his team using WI-38 cells developed the majority of the

TABLE 19.1 Selected Vaccine Development, Developer and Year of Licensure, 1798–2014

Vaccine	Developer	Year
Smallpox	Jenner	1798
Anthrax (animal)	Pasteur	1881
Rabies	Pasteur	1885
Cholera	Hafkine	1911
Diphtheria	von Behring	1913
Tetanus	Glenny	1924
Pertussis	Bordet and Gengou	1926
Tuberculosis (BCG)	Calmette and Guerin	1927
Diphtheria-pertussis-tetanus (DPT) combined[a]	Eldering, Gordon, Kendrick	1948
Japanese encephalitis	Hilleman	1944
Poliomyelitis, Salk inactivated vaccine[a]	Salk	1955
Hong Kong flu	Hilleman	1957
Poliomyelitis, Sabin attenuated vaccine	Sabin	1960
Measles	Hilleman	1963
Mumps	Hilleman	1967
Hong Kong flu pandemic	Hilleman	1968
Rubella	Hilleman	1969
MMR[a]	Hilleman	1969
Meningococcal polysaccharide	Hilleman	1974
Pneumococcal pneumonia[a]	Hilleman	1977
Hepatitis B subunit	Hilleman	1981
Varicella—Chicken pox[a]	Hilleman	1981
Hepatitis B recombinant[a]	Hilleman	1986
Conjugate Haemophilus influenza b (Hib)[a]	Robbins and Schneerson	1987
Hepatitis A[a]	Hilleman	1995
Diphtheria, tetanus toxoids and acellular pertussis vaccine adsorbed (DTaP)[a]	Commercial firms	2002
Rotavirus[a]	Clark, Plotkin, and Offit	2006
Human papilloma virus[a]	Frazer and Zhou	2006
Meningococcal group B	Pfizer	2014

[a]*Vaccines recommended for routine use in US children. BCG vaccine is not used routinely in the United States, but selectively for persons considered to be at risk for TB. Smallpox routine vaccination ended in 1971. The United States discontinued routine usage of Sabin vaccine in 2000.*

Source: Adapted from Centers for Disease Control and Prevention. Achievements in public health, 1900–1999: impact of vaccines universally recommended for children—United States, 1990–1998. MMWR Morb Mortal Wkly Rep. 1999;48(12):243–248. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/00056803.htm (accessed 2 February 2018); Centers for Disease Control and Prevention. Vaccines and immunization: human papillomavirus. Available at: http://www.cdc.gov/vaccines/pubs/pinkbook/hpv.html#vaccines (accessed 29 April 2017); College of Physicians of Philadelphia. The history of vaccines: vaccine development and licensing of vaccines. Last updated 17 January 2018. Available at: https://www.historyofvaccines.org/content/articles/vaccine-development-licensing-events (accessed 1 February 2018).

14 vaccines currently recommended for childhood routine immunization and led in the development of other vaccines.

In 1968, Hilleman produced a more attenuated measles vaccine derived from the virus isolated by John Enders in 1962, which is still used today. The Hillman rubella vaccine was also more attenuated i.e., less likely to cause the disease but still induce antibodies in the vaccinated person than the 1962 vaccine and remains in use today. In 1963, Hilleman isolated the mumps virus from a throat swab from his five-year old daughter and developed a new vaccine, which was licensed in 1967, and was officially named "Jeryl Lynn" after her. Hilleman's iconic Measles, Mumps, Rubella (MMR) combination vaccine was licensed by the FDA in 1971, and is used worldwide. Hilleman also produced the 1967 Hong Kong A2 pandemic influenza vaccine and the meningococcal polysaccharide vaccine, which was licensed in 1974.

After many decades of searching for a pneumococcal pneumonia vaccine, in 1977 Merck licensed a polysaccharide vaccine i.e., long chains of sugar molecules that make up the cell wall of a bacteria, offering protection against 14 types of pneumococcal bacteria. In 1983, the vaccine was extended to include 23 types of pneumococcal bacteria based on the work of selection by Robert Austrian—University of Pennsylvania School of Medicine—who isolated cell lines from more than 90 types of pneumococcal bacteria as types most appropriate for the vaccine. Austrian provided this information to Hilleman who, with associates at Merck, then developed the vaccine from the polysaccharide outer coatings of the bacteria (College of Physicians of Philadelphia, Vaccine Timeline, 2016).

Hilleman's work was based on cooperation with leading scientists to translate scientific studies into safe and effective vaccines suitable for mass production. The measles vaccine went through a long process of development with many key players, including John Enders and Samuel L. Katz, who isolated measles virus in a blood sample from 13-year-old David Edmonston, subsequently called the "Edmonston strain." Working with other scientists, Enders and Katz turned this strain into a vaccine licensed in the United States in 1963. This was an attenuated i.e., using a live, but weakened, measles strain so that it would not cause the disease, but rather act as a vaccine by promoting the production of sufficient antibodies to protect against subsequent exposure to the natural measles virus. In 1968, Hilleman and colleagues developed and further improved the "Edmonston-Enders" strain, which remains the primary measles vaccine used in the United States. In 1981 Hilleman developed the first viral subunit vaccine based on the work of Baruch Blumberg and Wolf Szmuness on the Australian antigen, a cell membrane surface protein of the hepatitis B virus, rather than the entire virus, producing a vaccine licensed in 1986. Hepatitis B recombinant vaccine is inexpensive to produce and is used worldwide for newborns to prevent later development of chronic liver disease, cirrhosis, and liver cancer.

The recombinant hepatitis B vaccine is based on Hepatitis B surface antigen (HBsAg) gene inserted into yeast or cells free of any concerns associated with human blood products. This was a breakthrough in vaccinology as recombinant vector vaccines methods promised improvements in vaccine research, production, lower costs, temperature stability, and ease of administration. This also provided hope for faster vaccine response to emerging infectious agents. In 1987 Hilleman produced and the first US FDA licensed congugate vaccine based on fat from the bacterial cell wall attached to a protein to produce Hemophilus influenza type b (Hib) vaccine. This vaccine protects against this serious respiratory infection in babies aged 0–18 months with dramatic reductions in cases and deaths within a few years. Hilleman also developed varicella (chicken pox) and hepatitis A vaccines—both licensed in 1995—with important public health benefits.

Hilleman traveled the world as an advisor to the World Health Organization (WHO) and to many other public health and infectious disease groups. His outstanding scientific endeavors led to vaccines that saved millions of lives, extended human life expectancy, and improved the economies of numerous countries. While he received many professional awards for his lifetime achievements, he never received a much-deserved Nobel Prize, nor the level of public or professional recognition given to other great scientists in immunology such as Pasteur (for anthrax and rabies vaccines) and Salk or Sabin (for poliomyelitis vaccines). Hilleman's death in 2005 was reported in many scientific journals and major news media with laudatory obituaries.

CURRENT RELEVANCE

Hilleman's innovations advanced the filed of vaccinology providing a base for further progress in vaccine development to address many old devastating diseases including malaria, tuberculosis, and dengue, as well as meeting the challenges of relatively new diseases being transmitted to wider habitats becoming endemic, including spreading diseases of West Nile virus (WNV), Lassa fever, Rift Valley fever (RVF), Middle East respiratory syndrome coronavirus (MERS-CoV), chikungunya, and long-known diseases such as dengue and yellow fever which were spreading via travelers and vectors bringing these older diseases into new habitats. More recently, alarming epidemics of the Ebola virus in West Africa (2013-2016) killed over 11,000 people. The Zika virus, known since 1947, burst into an epidemic in Brazil in 2016, and spread widely to South American, Caribbean and southern US states. Both Ebola and Zika for which there are no vaccines, were declared global public health emergencies by WHO. With the emergence of these viral diseases, society has returned to the era of infectious diseases, the control of which depends on population support through education, hygiene, vector control and relentless, well-funded searches for safe and effective vaccines are developed (National Academies Press, 2016).

New scientific breakthroughs may also lead to improvements in current vaccines by lowering their cost and ease of administration with increasing global coverage rates, and with enhanced effectiveness and safety. The value and benefits of vaccines for disease control include prevention of infection, clinical or subclinical, (such as in poliomyelitis, hepatitis B), or cancer (e.g., cancer of the liver and cervix), and prevention or mitigation of disease severity, such as in pneumococcal pneumonia, and influenza. We now have proven capacity to eliminate, and even eradicate, a disease and its causative agents in nature, such as smallpox (1980), poliomyelitis and measles in the 2020s. Vaccination reduces mortality, morbidity, and complications by protecting individuals and also the community by reducing the spread of disease.

Vaccines protect the immunized individual, but when a sufficient percentage of a population are vaccinated this provides "herd immunity," in which a critical portion of the community—over 95 percent—is immunized resulting in protection for vulnerable individuals who may not have been immunized due to neglect or refusal, being in an age group that was underimmunized in childhood—e.g., by receiving only one dose of measles vaccine, being underage for immunization—e.g., in early infancy—or with an auto-immune disease—e.g., rheumatoid arthritis, systemic lupus erythematosus, or Crohn's disease— with a weakened immune system—e.g., HIV positive—or being medically immunosuppressed, e.g., under cancer treatment and after an organ transplant.

Immunization for individual and herd immunity is a vital factor in public health. Levels of immunization coverage required for herd immunity can vary for different disease organisms, but in the case of measles it requires over 95 percent immunization coverage over a long period of time by an adequate two-dose policy, with monitoring, funding, and quality assurance for immunization programs. Adequacy means coverage of the population at risk of the disease as groups with inadequate vaccination become unexpectedly vulnerable as, for example, in recent importation and spread of measles and mumps in the Americas where these diseases had previously been considered eliminated. New challenges emerge requiring increasing vaccination coverage including tetanus, diphtheria, pertussis, and influenza for pregnant women, and their family members and care givers to protect newborns who are vulnerable until their immunization can be completed. Herd immunity (i.e., immunity by vaccination among a high percentage of a population sufficient to reduce the risk of transmission by isolated cases which varies for different diseases) must be achieved and maintained to reduce the potential for transmission of a disease to vulnerable people such as people with immune deficiency due to infection with HIV, cancer chemotherapy, or immunodeficiency diseases. In other cases, giving rubella vaccine to boys as well as girls to reduce or eliminate circulation of the virus prevents infections during pregnancy, which can lead to congenital rubella syndrome in

infants, a disease that can result in lifelong disability (see Chapters 3, 12, 16).

As vaccination programs reach a higher percentage of the vulnerable population, elimination of diseases locally can be achieved without global eradication of the causative microorganism. Global eradication of an infectious disease once seemed an impossible dream, but when achieved for smallpox demonstrated that human diseases with no animal host—such as smallpox, poliomyelitis, measles, mumps, and rubella—could also be eradicated. Efforts to eradicate poliomyelitis are coming close to success, while eradication of measles and rubella is targeted by WHO to be achieved by 2020.

Vaccination to prevent cancer is an important advance in public health with success of hepatitis B immunization (see Figure 19.1), which will prevent many cases of liver cirrhosis and liver cancer globally. The impact of Hilleman's hepatitis B virus (HBV) vaccine first issued in 1982 in the United States (Figure 19.1), is used in other high, medium and low-income countries. Incidence of HBV where vaccination with high coverage of newborns has declined dramatically. Chronic HBV infection produces high risk

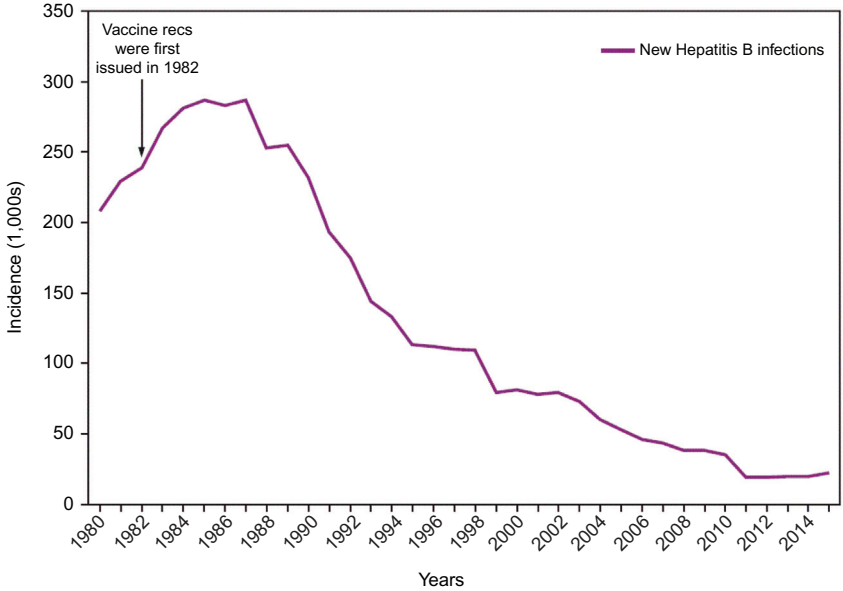

FIGURE 19.1 Incidence of hepatitis B virus infection, United States, 1980–2015. *Source: Schillie S, Vellozzi C, Reingold A, Harris A, Haber P, Ward JW, Nelson NP. Prevention of Hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018;67(No. RR-1):1–31. Available at: https://www.cdc.gov/mmwr/volumes/67/rr/rr6701a1.htm (accessed 21 January 2018)*

for cirrhosis and liver cancer. The recommended practice is for HBV carrier status testing in pregnancy with universal hepatitis B vaccination of all newborns within 24 hours of birth. CDC recommends completion of the vaccination series in infants, vaccination of other children and adolescents who missed infancy coverage, as well as adults at risk for liver disease. Despite progress, HBV remains a major global problem. WHO reports that globally 84% of children born in 2015 received the three recommended doses of hepatitis B vaccine, but HBV mortality remained high in 2015 with 887,000 deaths globally mostly from cirrhosis and liver carcinoma. HBV is also an important occupational hazard for health workers.

More recently, slowly increasing use of Human papilloma virus (HPV) vaccination will prevent cervical cancer being reduced by Pap smear screening but ultimately the HPV vaccine will be the dominant factor in control of HPV infection causing cancer of the cervix. In addition, boys are also immunized to reduce spread of the virus by heterosexual intercourse, as well as reducing the increasing rates of oral and anal cancers from homosexual relations.

The search for vaccines against other cancers will benefit from the significant progress over recent decades in genetic, microbiologic, computer, and molecular sciences. The scientific and manufacturing advances led by Hilleman produced vaccines with economic and health sector benefits for many nations. Their increasing use for preventing pneumococcal pneumonia, meningitis, and measles reduces dependence on antibiotics for the complications of these diseases a factor in reducing antibiotic usage thus slowing the development of antibiotic resistance. Vaccines protect people with chronic medical conditions such as chronic lung-, heart- or kidney diseases as in the success of pneumococcal pneumonia and influenza vaccines reducing serious complications, hospitalizations, and avoidable deaths (see Figure 19.2).

Globally, it is estimated that 14.5 million episodes of serious pneumococcal disease occur annually. These include pneumonia, meningitis, and sepsis mainly in children aged under five years resulting in some 500,000 deaths, mostly in low- and middle-income countries. Pneumococcal conjugate vaccine (PCV), first licensed in 2000, provided protection against seven of the most common pneumococcal serotypes. In 2006, WHO recommended that this vaccine be included in all routine immunization programs, particularly in high incidence countries. In 2010, new PCV formulations protecting against 10 and 13 serotypes became available, providing better coverage for serotypes common in low- and middle-income countries. Pneumococcal polysaccharide vaccine for 23 serotypes of pneumococcal bacteria is now in use and recommended for adults 65 years or older, for children at high risk and increasingly for all older adults. More and more, this vaccine is recommended for all children, and adults, including pregnant women.

Hilleman demonstrated the value of combining vaccines such as in the enormously successful measles, mumps, rubella vaccine (MMR) and later

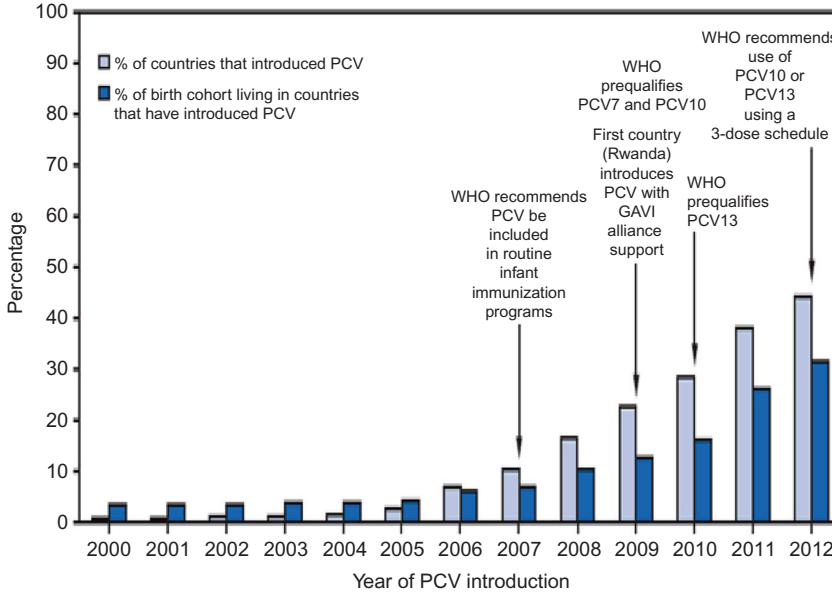

FIGURE 19.2 Progress in introduction of pneumococcal conjugate vaccine (PCV), worldwide, 2000–2012, by World Health Organization (WHO). Abbreviations: *PCV7*, 7-valent PCV; *PCV10*, 10-valent PCV; *PCV13*, 13-valent PCV. *Source: Centers for Disease Control and Prevention. Progress in introduction of pneumococcal conjugate vaccine world-wide 2000–2012. Morb Mort Wkly Rep. 2013;62(16):308–311. Available at: <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6216a4.htm> (accessed 4 September 2016).*

adding inactivated poliomyelitis vaccine (IPV) and varicella (chickenpox) vaccine. Standard vaccine combinations have been expanded with the addition of polio (IPV) along with hemophilus influenza (Hib) in the combination of diphtheria, pertussis, tetanus (DPT). This pentavalent vaccine can be given to infants simultaneously with rotavirus, meningitis B, and pneumococcal pneumonia vaccines without loss of effectiveness. The benefits include better compliance with improved coverage and injection safety, less cost and fewer visits to a medical service. Vaccination also provides protective safety from some potential biological forms of bioterrorism, such as smallpox, anthrax, and potential respiratory infectious agents.

A large-scale epidemic of measles spread across Europe between 2010 and 2017. Travelers spread measles to North and South America. In 2017, measles cases were registered in 14 European countries: Austria, Belgium, Bulgaria, the Czech Republic, Hungary, France, Germany, Iceland, Italy, Portugal, Romania, Spain, Switzerland, and Sweden with an estimated total of over 7,500 cases of measles, with Romania being the most affected country with 4,793 measles patients reported between January 2016 and

April 2017, according to the European Centers for Disease Prevention and Control (ECDC). In total, there have been 25 deaths in Europe, of which 22 occurred in Romania. Portugal, Switzerland, and Bulgaria also had measles fatalities. The ECDC is exploring national Immunization Information Systems to improve the monitoring of immunization coverage at local geographical levels, linking individual immunization histories with health outcome data for vaccine safety, effectiveness, as well as failures, and educational material for vaccine researchers, producers, providers, and recipients.

Imported and secondary measles cases appeared in California in 2015, a state that allowed personal beliefs exemptions to easily override laws requiring full immunization such as two doses of MMR vaccine for all children and young adults attending schools. This led to extremely low MMR vaccination rates at some schools, particularly private schools, with even zero coverage in some kindergartens. The outbreak led to 2016 changes in Californian law requiring parents to consult with the local public health office and requiring a medical certificate stating medical reasons for exemption. This process will make it more difficult for parents to deny this immunization to their children, which puts all unimmunized children at risk due to the highly infectious nature of measles. The new immunization requirement in California has resulted in increased coverage of MMR and other vaccines to over 95 percent.

The science behind vaccine development has increased its capacity markedly in recent years with genetics and immunology entering new spheres of research for vaccines to combat cancers and genetic diseases, which is expected to play a major role in clinical medicine and public health in the coming decades. The cases of measles and hepatitis B are prime examples of vaccines that have been developed in partnership with many contributing laboratories, manufacturers and public health leaders with shared information and scientific advances leading to reduced global mortality rates. Scientists and manufacturers worked together to create the HBV vaccine produced by using one element of the cellular wall of the virus instead of the whole virus, increasing the safety of the vaccine. Hilleman later developed the first immunizations with recombinant vaccines, contributing to the application of advances in genetic sciences for vaccinology in the future to provide low-cost and widely effective new approaches to vaccination.

ETHICAL ISSUES

Public trust in vaccines has become an important global health issue, with negative attitudes due to fears over false but highly publicized side-effects and hesitancy among some doctors. Italy and Germany are making vaccination mandatory after health officials warned that a fall-off in vaccination rates had triggered a measles epidemic. In 10 European countries, cases of measles

doubled in number in the first two months of 2017 compared to 2016, as reported by the ECDC, with more than 2,000 cases in 2017, almost ten times the number in 2015. Notwithstanding the astonishing success of vaccines in saving millions of lives and promoting civil societies, vaccine development, production, and implementation have many ethical issues and controversies. These range from ideological anti-vaccinatonism, to professional jealousies and controversies, along with economic and legal disputes over cell lines for vaccine production, to allegations of vaccines causing diseases in children, slow adoption of life-saving vaccines, inadequate resource allocation in developing countries, lack of harmonization of vaccination policies, and others.

Anti-vaccinationism has been around since the days of Jenner's discovery of vaccination to prevent smallpox in the 18th century and continues to the present time (see Chapter 2). Recently, rates of parental refusals of vaccination have increased. This is due, in part, to increased public skepticism of public health professionals, policymakers, and the pharmaceutical industry. Reduced public health awareness is also due to the successful control and near-elimination of many once dreaded infectious diseases such as smallpox and poliomyelitis. Today, most parents, health care staff and doctors have never seen the diseases prevented by vaccines and do not understand their gravity.

Public anxiety surrounding vaccinations rose in the United Kingdom in the 1980s in response to concerns about the safety of the pertussis vaccine. This resulted in a decline of immunization coverage and the return of this once well controlled disease. In the mid - 1990s UK uptake of MMR vaccination fell from a peak of 92 percent at the age of two to 82 percent in 2003, with uptake falling below 75 percent in parts of London. This has serious implications for mutual protection of the population, i.e., herd immunity. In the US and elsewhere, recent outbreaks of pertussis and diphtheria, and spread of imported measles after decades of control raise the need to ensure immunization of pregnant women and their close family members to protect the fetus and newborns from serious preventable infections before the infants' immunization protection takes hold.

The harm created by publication of fraudulent and unethical research activities has had an adverse impact on professional and public perception of matters such as vaccines. In 1998, an article published in *Lancet* by Andrew Wakefield purported to show that the measles−mumps−rubella (MMR) vaccine caused autism. This created a storm of public concern and parental refusals of the MMR vaccine. Media investigation and professional studies proved the study was fabricated, and many reliable studies have since disproved its claims. Following an ethics investigation by the UK's General Medical Council, Wakefield's medical license was revoked in 2010, and the article partially retracted by *Lancet* in 2004 was fully withdrawn by the journal in 2010. However, despite the media coverage and retraction of the article, the credibility of vaccinations—specifically MMR vaccine—in the eyes of the public was damaged substantially. The allegation, although

proven to have been fabricated, continues to be widely believed and spread via the internet and social media.

Popular resistance to vaccination is both a legal and ethical question as reflected in current controversies in the United States, where opting out of mandatory vaccination has contributed to measles outbreaks, a disease that was considered eradicated many years ago. Compulsory immunization is currently not politically acceptable due to concerns over parental rights of refusal and active lobbying on the internet and in public media against "government medicine." But state mandates requiring certification of complete immunization are well established in the United States. All 50 US states have legislation requiring specified vaccines for students. However, exemptions are allowed for medical reasons, and for reasons of religious beliefs and 18 states allow philosophical exemptions for those who object to immunizations because of personal, moral, or other beliefs (National Conference of State Legislatures, 2017).

Pediatricians in the United States are reporting increased refusal of parents to immunize their children, prompting the American Academy of Pediatrics (AAP), the American Medical Association (AMA) and the American College of Physicians to recommend the elimination of non-medical exemptions in state immunization laws. to call for State legislators to increase limitations on exemption clauses for philosophical reasons. Refusal of vaccination can be seen as posing a threat to other children, as well as a form of child neglect such as having a child in a car without an appropriate child car seat. In part, this action is stimulated by concern over increasing resistance of parents to vaccination along with return of previously controlled diseases. Failure to vaccinate is a form of child neglect.

Both the public and private sectors, including the pharmaceutical industry, have contributed greatly to increasing vaccine coverage rates, and public−private partnerships remain vital to vaccinology. As a senior staff member of Merck, responsible for vaccine development at a major pharmaceutical company, Hilleman conducted industry-funded research and his contribution led directly to manufacture of the majority of vaccines created in the latter half of the 20th century that have been, and remain, vital for public health in the US and globally. The role of the private pharmaceutical industry needs to be recognized as crucial for advances in this field, but is equally dependant on scientists at universities and public research institutions with their contribution to the knowledge base that enabled breakthroughs in vaccine production and distribution. In the period 2014−2016, large epidemics of two deadly "new" viruses, Ebola and Zika, were designated by WHO as a global health crises with justifiable concern that they could spread rapidly to many parts of the world. The Zika virus transmitted to a pregnant woman by Anopheles mosquitoes, or by sexual relations with a Zika infected partner may produce a mild illness. but has tragic effects on fetuses resulting in serious birth defects including small head size, i.e., microcephaly, and brain

damage. The race to develop effective vaccines must involve public−private cooperation to achieve a working vaccine within several years. The media and WHO concern have reminded skeptics of the essential role of vaccine research with cooperation between governments, donors, academics and industrial scientists as promoted by Maurice Hilleman in his life's work.

The long time gap from availability and proof of vaccine success until it is adopted globally is an ethical issue for reducing global health inequities as well as a question of priorities and resource allocation in public health. Adoption and implementation of vaccination is slow to respond to important advances, especially in low-income countries where policy-makers have traditionally given health low priority in governmental financing. Delays in vaccine adoption lead to preventable infections, with high rates of illness, deaths, human misery, and slowing of economic progress.

Lack of harmonization of vaccination policies is a major professional, public policy, ethical issue and a limiting factor in achieving the full potential of proven successful and safe vaccines. Europe, and the European Union, still does not have a common harmonized immunization program, in some cases not even in the same country, which contributed to the massive measles epidemics since 2010.

ECONOMIC ISSUES

The benefits to society of vaccination are enormous, not only in saving lives and reducing morbidity, but also in reduced health care costs. Vaccines are life-saving and cost-effective, and they should be supported by national governments and international donor programs alongside the buildup of public health education and infrastructure development within recipient countries. Vaccines have been crucial in reducing child illness and birth defects —e.g., congenital rubella syndrome. Vaccines help men, women and especially children to have healthy lives without morbidity of many previously common childhood diseases (e.g., poliomyelitis). They also lessen infections among people with chronic medical and disabling conditions such as pneumococcal pneumonia and influenza vaccines. Reducing disease and high mortality rates promotes economic growth as supported by the World Bank and other economic analyses. Successful vaccination also increases equity in society by reducing diseases that were often more common among poorer populations.

Expansion of vaccine coverage during the "Decade of Vaccines" funded by the Bill and Melinda Gates Foundation in 2010 in the world's poorest countries from 2011 to 2020 is estimated to save more than US$5 billion in acute care costs and increased productivity value of at least US$151 billion (Stack et al., 2011). The CDC estimates savings from averted direct health care costs of US $402 billion USD and more than one trillion dollars in societal costs for the cohort of children born in the United States between 1994 and 2013 (Whitney et al., 2014). Since 1993, the World Bank and economic

analysts have accepted that the economic benefit to low- and medium-income countries (LMICs) of reducing child mortality—mostly resulting from reduced morbidity and mortality from infectious diseases—is vital to their economic and social advancement.

Nearly universal use of hepatitis B vaccine for newborns has helped to prevent mother-to-child transmission and subsequent prevention of liver cirrhosis and liver cancer, which is of enormous economic value to health systems. The vaccine to prevent the spread of hepatitis A is available and used in many countries, but a vaccine for the more serious disease of Hepatitis C has regrettably not yet been developed. Although effective, life-saving treatments are available, these are costly and an effective vaccine would bring greater benefits and advances.

Vaccine coverage in low- and middle-income countries (LMICs) such as Brazil, Russian Federation, India, China, and South Africa (BRICS) varies widely. A review of cost effectiveness and economic benefit studies of vaccines in LMICs concluded that vaccination brings important economic benefits and recommends that policy-makers should consider vaccines to be an efficient investment. For example, the health, economic, and social benefits of vaccination with Hemophilus influenza b (Hib), pneumococcal pneumonia, and rotavirus vaccine coverage in BRICS countries have been estimated at more than US$15 billion annually (see Table 19.2).

Immunization averts an estimated two to three million deaths every year from diphtheria, tetanus, pertussis (whooping cough), and measles. However, an additional 1.5 million deaths could be prevented if global vaccination coverage improves from under 85 percent to 90 percent. GAVI, the Global Vaccine Alliance, is a major entity working to increase coverage in low-income countries. GAVI is a public−private global alliance for vaccine implementation supported by WHO, UNICEF, the World Bank, the Gates Foundation, pharmaceutical companies, and others. Since its founding in 2000, GAVI helps finance adoption of vaccines in low-income countries dependent on external support to finance vaccination. The percentage of low-income countries financing vaccines in their national budgets rose from 64 percent in 2000 to 75 percent in 2006, with a modest increase in national government share of routine immunization rising from 35 percent to 39 percent between 2000 and 2008.

A 2017 study reviewed publications from 27 countries which introduced rotavirus vaccine into their national routine immunization programs since 2006. Substantial reductions (30%−60%) were found in rotavirus and all-cause acute gastroenteritis (AGE) hospitalizations and AGE mortality among children under age one and age five years.

Measles is a highly contagious and potentially fatal disease which is a leading cause of death among young children (see Box 19.1). Efforts to control, eliminate, and ultimately eradicate measles are part of international organizations and WHO strategy. An economic analysis by Levin et al. in

TABLE 19.2 Estimated Annual Economic and Social Benefits from Increased Haemophilus Influenza Type b, Pneumoncoccal Conjugate Vaccine, and Rotavirus Vaccine Coverage in Brazil, the Russian Federation, India, China, and South Africa (BRICS)

Country	GDP per Capita 2012 (US$)	Life Expectancy at Birth (Years)	Estimated Annual No. of Averted Deaths				Estimated Annual Economic and Social Benefits (Million USD)
			Hib	SP	RV	Total	
Brazil	11,359	73.8	0	25	10	35	18.2
Russian Federation	14,302	67.9	373	474	31	878	559.7
India	1,501	66.3	52,709	54,429	29,612	136,820	9,084
China	6,071	75.2	9,538	10,079	1,170	20,787	5,796.8
South Africa	2,525	57.1	856	319	85	1,260	398.0

Note: *GDP*, gross domestic product; *Hib*, Haemophilus influenza type b; *RV*, rotavirus; *SP, Streptococcus pneumonia*; *US$*, United States dollars.
Source: Mirelman A, et al. The economic and social benefits of childhood vaccinations in BRICS. Bull World Health Organ. 2014;92:454–456. Available at: http://www.who.int/bulletin/volumes/92/6/13/132597.pdf (accessed 29 April 2017).

BOX 19.1 Global Impact of Measles Vaccine

- Measles is a highly contagious, serious disease caused by a virus.
- In 1980, before widespread vaccination, measles caused an estimated 2.6 million deaths globally each year.
- Measles is still a leading global cause of death among young children even though a safe and cost-effective vaccine is available since the 1960s.
- Global measles deaths decreased by 84 percent world-wide from 550,100 deaths in 2000 to 89,780 in 2016.
- An estimated 20.4 million people were affected by measles in 2016, particularly in Africa and Asia.
- In 2015, about 85 percent of the world's children received one dose of measles vaccine by their first birthday through routine health services—an increase up from 73 percent in 2000.
- During 2000–2015, measles vaccination prevented an estimated 20.3 million deaths making measles vaccine one of the most cost-effective investments in public health.

Source: *World Health Organization. Measles fact sheet, reviewed March 2017. Available at: <http://www.who.int/mediacentre/factsheets/fs286/en/> (accessed 29 April 2017) and World Health Organization. Immunizations, vaccines, biologicals: measles. Last updated November 2017. Available at: http://www.who.int/immunization/diseases/measles/en/ (accessed 20 January 2018).*

2011, indicated that measles eradication by 2020 was the most cost-effective scenario in the six countries studied and globally. WHO's "Global Measles and Rubella Strategic Plan: 2012–2020" considers the economic benefits for promotion of public health and economic growth to be powerful justification for targeting measles and rubella for eradication as a high priority in LMIC. In recent years, many cost-effectiveness studies of vaccines for hepatitis B, rotavirus, human papilloma virus, and influenza have shown that vaccination is an effective economic tool with significant health benefits. Global targeting of rubella for eradication along with measles for achievement by 2020 will require new tactics in Europe, such as harmonization of immunization programs across the region, and certainly in the European Union where there is free border crossing between member states and large-scale refugee entry without evidence of past immunization. The tools exist in outstanding vaccine combinations, especially the MMR vaccine created by Hilleman. Measles and rubella control—and ultimately eradication—are within the capacity of well-led public health policy and resources (see Box 19.2).

The sciences of vaccinology depend on academic research and on the private sector of the limited number of vaccine producers in the world. With a drumbeat of public health emergencies in the 21st century with SARS, H1N1 influenza, Ebola and Zika virus epidemics indicate the problem. Long known diseases such as malaria, HIV, TB, dengue, West Nile fever and

BOX 19.2 Global Impact of Rubella Vaccine

- Rubella is a contagious, generally mild viral infection that occurs most often in children and young adults.
- There is no specific treatment for rubella, but the disease is preventable by vaccination.
- Rubella infection in pregnant women may cause fetal death or congenital defects known as congenital rubella syndrome (CRS).
- A rubella pandemic developed during 1962–1965 in the United States, with more than 20,000 babies born with congenital rubella syndrome.
- Children with CRS can suffer hearing impairments, eye- and heart defects and other lifelong disabilities, including autism, diabetes mellitus, and thyroid disorders.
- Worldwide, an estimated 100,000 babies are born with CRS every year.
- The recommendation of CDC and WHO is two doses of measles- and rubella-containing vaccine, preferably as MMR.
- WHO has set a target for the end of 2020, when the world should achieve measles- and rubella-elimination in at least five WHO regions.
- After the US licensed rubella vaccine in 1969 the number of reported cases of CRS declined dramatically to <one case per year or four cases in total during 2005–2011.
- In 2004, a panel of internationally recognized experts reviewed rubella epidemiology and unanimously agreed that rubella elimination (i.e., the absence of year-round endemic transmission) was achieved in the United States.

Sources: *WHO. Rubella fact sheet, reviewed March 2017. Available at: <http://www.who.int/mediacentre/factsheets/fs367/en/> (accessed 29 April 2017).*
Centers for Disease Control and Prevention. Vaccines and immunization. Chapters 14, 15. Rubella and congenital rubella syndrome, updated 1 April 2014. Available at: <http://www.cdc.gov/vaccines/pubs/surv-manual/chpt14-rubella.html and http://www.cdc.gov/vaccines/pubs/surv-manual/chpt15-crs.html#> (accessed 29 April 2017).

others are also part of the urgent call for new vaccines challenging the research capacity of academia and private manufacturers. The process of discovery is only part of a long and costly process of initial testing of safety and efficacy. New institutional and funding arrangements will be needed to make the most of new technology and genetics in vaccine development for these and new challenges that may be expected to arise. We will also need "future Maurice Hillemans."

CONCLUSION

Vaccine development and distribution have saved millions of lives, and have the potential to save millions more as new vaccines emerge from public and private research centers, through the pioneering achievements of the next generations of Hilleman and colleagues. Science will continue to develop

new tools, such as finding ways to produce vaccines using genetic techniques of adding key genes to simple microorganisms to produce protective antibodies and improving heat stability of vaccines to eliminate the cumbersome and costly "cold chain" (i.e., storing and transportation of vaccines within a specified temperature range). Policy-makers in public health systems will continue to improve vaccine delivery and to implement vaccination programs for reduced morbidity and mortality rates across the globe.

Vaccines are among the most efficient preventive measures available to both clinical medicine and public health. However gains from successful immunization campaigns are being rolled back as rates of vaccine refusal increase. Public support can be won or eroded by pro- and contra-advocacy groups. Public concerns over vaccine safety can become wildly exaggerated and has the effect of reducing vaccine acceptance. The support of medical practitioners and the media is vital to promote adoption and acceptance of newer vaccines by an often skeptical public.

Neither the science, nor the application of its advances, occur automatically. Instead, vaccine discovery, development and implementation coverage requires the skill and dedication of future "Hillemans", a well-trained public health workforce, and a strong organizational base for public health. Hilleman believed and demonstrated that academic and industry-based scientists could work in a complementary fashion in support of global public health goals for disease control and eradication, as vaccine development and distribution have a crucial role in population health. The prospects look favorable for scientific advances leading to new vaccines and to the potential for further disease control and eradication. This process requires long and expensive periods of basic sciences research and vaccine testing, and when proven effective and safe, the implementation of immunization programs. Academic/industry partnerships with government support should be encouraged to improve the efficiency of vaccine development.

In many countries, adoption of new vaccines in routine immunization programs has proven to be slow. A CDC publication, "Framework for Preventing Infectious Diseases, 2011", emphasizes: modernization of infectious disease surveillance; expanding the role of public health and laboratories for disease control and prevention; and advancing workforce development and training to sustain, and strengthen, public health practice, and above all the committed leadership role of national governments. Disease control depends on monitoring case reports including quantity, common factors such as time, location, risk factors, and available intervention that can be applied to control epidemic or endemic diseases. It is essential to reach out to especially vulnerable groups living in urban poverty areas as well as remote villages and those with particular risk factors for diseases. This is the context in which vaccines are of enormous social and economic benefit, as well as being critical to improve health, prevent disease, and

avoidable mortality. A well-trained public workforce is required to meet these challenges.

Ultimately, ensuring the development of these key preventive measures to reduce—and in some cases, eradicate—infectious diseases requires public health and governmental leadership. The public health system is responsible for total population health and must take the lead to finance, organize, monitor, and deliver needed services such as child vaccination. Public health widely suffers from low priority in national government budgets. Harmonization of immunization policies and public support are needed, as are resources. Strong support by national government policy and funding are key to the reduction in incidence, prevalence, and control of diseases which can be ameliorated by known, as well as yet-to-be discovered, vaccines.

The CDC considers vaccines to be "*one of the greatest achievements of biomedical science and public health*" (CDC 1999). The vast majority of vaccines used currently were developed in the 20th century on the basis of Louis Pasteur's work on anthrax and rabies in the 19th century and over 40 vaccines were developed by Maurice Hilleman with academic and industry colleagues at Merck (College of Physicians of Philadelphia, 2016). Hilleman was undoubtedly the leading vaccinologist of the 20th century, and perhaps of all time. In 1988, he was awarded the National Medal of Science, the highest scientific honor in the United States, and although he received many professional honors he never achieved the popular recognition or fame of other pioneers in vaccine development and implementation such as the developers and leaders in poliomyelitis vaccine, Jonas Salk and Albert Sabin.

In 1997 Hilleman was awarded the Albert Sabin Gold Medal Award. Dr. Anthony Fauci, Director of the US National Institute of Allergy and Infectious Diseases at the US National Institutes of Health, called Hilleman "one of the true giants of science, medicine and public health in the 20th century." When Hilleman died in 2005, after a truly magnificent scientific career of 60 years, Dr. Paul Offit, chief of infectious diseases at the Children's Hospital of Philadelphia, told the BMJ: "*His commitment was to make something useful and convert it to clinical use. Maurice's genius was in developing vaccines, reliably reproducing them, and he was in charge of all pharmaceutical facets from research to the marketplace*." The BMJ obituary for Hilleman stated: "*Almost all of Hilleman's career was in the pharmaceutical industry to develop, in cooperation with academic scientists, vaccines that brought science to the direct benefit of mankind saving millions of deaths especially of children*." Dr. Faucci, stated: "*Maurice was perhaps the single most influential public health figure of the twentieth century, if one considers the millions of lives saved and the countless people who were spared suffering because of his work. Over the course of his career, Maurice and his colleagues developed more than forty vaccines. Of the fourteen vaccines currently recommended in the United States, Maurice developed eight*."

Although largely unknown among the general public and even among public health practitioners and teachers, Maurice Hilleman was the outstanding scientist in the field of vaccinology in the 20th century who brought dynamism and creativity to develop vaccines saving countless lives and bringing the means and the hope for eradication of important diseases such as measles, congenital rubella syndrome, and hepatitis B. He introduced new approaches to vaccinology which others following his path can use help to control—or eliminate—important diseases now, and others that in the future may face humanity. Hopefully "new Hillemans" will emerge to advance the sciences of genetics and vaccinology to face existing and new challenges of science and population health.

RECOMMENDATIONS

1. Progress in vaccinology application relies on funding, prioritizing, monitoring, surveillance, routine immunization programs, and outbreak control as cornerstones of public health goals in disease control or its eradication.
2. Public health must improve its leadership responsibility and realize its important role in reaching out to at-risk, vulnerable segments of the population in outlying rural areas and urban dwellers.
3. Harmonization of vaccination policies is urgently needed in Europe and low-income countries to halt resurgence and achieve eradication of still significant diseases including measles, rubella, and other targeted vaccine-preventable disease in the coming years.
4. Public health should increase advocacy efforts in health promotion to extend vaccine development and to assure public support for measles control and eradication, as well as other vaccine-preventable diseases.
5. Resources for science advancement and for service delivery are equally important and must be accepted as a governmental responsibility in LMICs as well as in high-income countries.
6. Training of public health and community health workers is vital to meet old and new vaccine challenges of premature death, disease, and disability in aging populations, with severe climate and social inequality challenges.
7. Governments, academic research centers, vaccine manufacturers, and public health authorities require well-designed plans to respond to pandemic illnesses, especially in recognizing the global importance and urgency of the need for quicker development and distribution of the influenza vaccine, as well as for newly emerging infectious disease such as Ebola and Zika, among others.

STUDENT REVIEW QUESTIONS

1. What are the roles of public and private sector research in vaccine development?
2. Why was Maurice Hilleman so important in vaccinology?
3. Why are vaccines important in public health and modern societal development?
4. Why is it slow and costly to develop new vaccines and to adopt them in public health practice?
5. What mechanisms exist to help adoption of new vaccines by LMICs?
6. Which infectious diseases would you place on a priority list for vaccine development to save the maximum feasible number of people from disease and avoidable death?
7. Should vaccination be made mandatory for well-proven vaccines? Why, or why not?
8. Why has measles rebounded after being considered eliminated in Europe and the Americas?
9. Discuss factors that affect progress toward the eradication of infectious diseases such as measles?
10. What methods of public health are available to control diseases for which there is no vaccine?
11. What new methodologies are expected to become available to produce vaccines in less-costly and more easily-usable ways?
12. Why is vaccinology a crucial field in research and practice for cancer control?

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