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The HHS National Vaccine Program and Global Immunization

NVAC Report and Recommendations Approved by the National Vaccine Advisory Committee on September 12, 2013

COMMENTARY

NVAC REPORT

ASSOCIATION OF SCHOOLS & PROGRAMS OF PUBLIC HEALTH

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On the cover: ©Juan Andres Rodriguez. A child is given a polio vaccine at the Behsood Clinic in Jalalabad, Afghanistan, during National Immunization Day, March 13, 2011.

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Jennifer L. Gordon, PhD, Department of Health and Human Services, Office of the Assistant Secretary for Health, National Vaccine Program Office, Washington, D.C., Guest Editor

COMMENTARY

NVAC REPORT

The views represented in this report are those of the National Vaccine Advisory Committee. The positions expressed and recommendations made in this report do not necessarily represent those of the U.S. Department of Health and Human Services, the U.S. government, or the individual working group members who served as authors of, or otherwise contributed to, this report.

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HHS—Supporting Global Immunization through Policies, Programs, and Partnerships

Nils Daulaire, MD, MPH[a]

The primary mission of the U.S. Department of Health and Human Services (HHS) is to protect and promote the health of Americans. Now, more than any other time in our history, improving the well-being of those within our country must be done within a global context, taking into account both the threats and the opportunities that we find beyond the borders of the United States.

The infectious disease community has long been sensitive to this reality, with examples ranging from smallpox and polio to the rapid spread of H1N1. In our increasingly globalized and interconnected world, health threats can travel more quickly than ever. Fortunately for us, so too can the vaccines that can often be relied upon to prevent them. Vaccine-preventable diseases (VPDs) have been an area of major success for the global health community, but also one in which we must continue to search for new solutions as new and reemerging diseases become serious health threats. As former HHS Secretary Kathleen Sebelius has said, "We can no longer separate global health from America's health."[1]

The U.S., and particularly the scientific community, has a special leadership role to play in addressing VPDs. Global immunization and the prevention of infectious diseases is an arena in which U.S. leadership is not only welcomed but also in high demand. HHS's scientific, policy, and programmatic expertise in the immunization field is vast. The National Institutes of Health (NIH) conducts research to develop new vaccines; the Food and Drug Administration (FDA) licenses and regulates vaccines; the Centers for Disease Control and Prevention (CDC) provides guidance on immunization practices and guidelines, while providing technical assistance to establish and strengthen programs; and multiple HHS agencies deliver immunizations to at-risk populations. The National Vaccine Advisory Committee and the National Vaccine Program play vital roles advising on the key policy, operational, and programmatic issues that are integral to conducting safe and effective immunization programs. Together, HHS agencies working with other U.S. government agencies, public and private partners, and international organizations are reducing the worldwide burden of VPDs and improving the health of people in every country, including our own.[2,3]

The work on VPDs being conducted in the U.S.—from our collaborations to develop new vaccines, to our technical assistance to improve surveillance systems, to our rapid outbreak responses—is a key example of health diplomacy in action.

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We reflect on the significant historical precedent that the U.S. and the Soviet Union set in the 1970s, setting aside our Cold War conflicts to work together for the global eradication of smallpox.[4] Today, our ongoing efforts to help low- and middle-income countries develop their own influenza vaccine manufacturing capabilities has been a major factor in bringing countries to the table to rapidly share the natural influenza viruses that arise in their animal and human populations—critical steps to better understand and respond to new influenza threats.[5,6] These partnerships expand and diversify our capacity to respond to outbreaks, making all of us safer and more secure.

Vaccines are at the very top of public health's greatest success stories, averting millions of deaths annually.[7] It is precisely because of the enormous impact of immunizations that we must do more to increase the use of existing vaccines and accelerate the discovery and development of new ones. No mother anywhere should have to experience her child dying from a VPD; yet, every year, 2.5 million children worldwide who have not been adequately immunized die as a consequence before reaching their fifth birthday.[8] However, we must remember that vaccines no longer just save the lives of children. With the continued development of new vaccines against viruses proven to cause cancer, such as the human papillomavirus (HPV) and hepatitis B vaccines, we now have the capability to prevent nearly 900,000 adult deaths each year.[9,10] The growing global focus on chronic conditions provides increased opportunities to focus needed attention on vaccine-preventable cancers and expand access to these new or underused vaccines. In addition to reducing preventable cancer deaths, strengthening HPV vaccine delivery systems presents new opportunities to serve populations often not effectively reached by health systems (e.g., adolescents) and ensure that routine vaccines such as tetanus are up-to-date and that adolescents have had their hepatitis B shots. And while no successful vaccine against human immunodeficiency virus (HIV) has yet been developed, the global collaboration on vaccine discovery efforts has yielded important knowledge about other promising methods to prevent and control the spread of HIV/acquired immunodeficiency syndrome.[11]

Although HHS has enormous scientific capacity, the development and dissemination of vaccines cannot be accomplished by one agency, country, or sector alone. As the MenAfriVac™ story demonstrates, successes come from collaborations with other U.S. departments and agencies, nongovernmental organizations, industry, international organizations, and the governments of other countries. In 2000, the Meningitis Vaccine Project (MVP) was established as a public-private partnership to develop a better, more effective, low-cost vaccine that would prevent meningitis outbreaks due to the type A strain of the meningococcal bacteria endemic throughout sub-Saharan Africa.[12] Through collaborations with MVP partners including HHS agencies (e.g., FDA and NIH), the MVP succeeded in developing, licensing, and achieving WHO prequalification status for MenAfriVac by 2010.[13] In addition, MenAfriVac is the first vaccine licensed for storage and handling outside of the typical cold chain conditions (2°C–8°C), allowing for broader distribution in remote areas.[14] By December 2012, more than 100 million people had received the vaccine within three years of the vaccine being licensed for use.[15]

Public-private partnerships are an important way to expand vaccine access, as demonstrated by the collaboration among Walgreens, CDC, and the World Health Organization to distribute seasonal flu vaccine to developing countries. Walgreens, the largest retail provider of flu shots in the U.S., donated $10 million of seasonal flu vaccine vouchers during the 2013–2014 flu season to HHS to help increase immunization rates among underserved U.S. populations. The company donated its unused flu vaccines to the country of Laos in 2012, and expanded the program to Nicaragua in 2013. This collaborative effort not only enabled populations identified as high risk for flu complications, including pregnant women, to benefit from this important vaccine, but will also help the countries develop or strengthen their own vaccination programs. Because of this partnership, thousands of people at risk for severe influenza are protected for the first time.[16,17]

The prevention of preventable diseases such as influenza requires not only access to and the availability of these important vaccines, but also putting an end to unfounded and disproven claims about the safety and purpose of vaccinations. Although scientifically debunked, the mistaken but oft-echoed belief that certain childhood vaccinations lead to autism has resulted in children worldwide being denied lifesaving immunizations—even in wealthy communities.[18–21] Outbreaks of measles and pertussis in the U.S. and Europe, carried by people who have chosen not to vaccinate their families, have claimed the lives of other children who are too young to receive the vaccines and sickened thousands more.[22–24] We have also seen unfounded rumors derail global immunization efforts and lead to unnecessary illness and death. In Nigeria, a mass boycott followed false stories that polio vaccine was a Western ploy to spread HIV and sterilize Muslim girls, resulting in a rash of new polio infections in the country and the further spread of the polio virus to 20 countries across Africa, the Middle East, and Southeast

Asia.[25–27] Outbreaks in unstable areas of the Middle East and East Africa are further jeopardizing global polio eradication.[28]

The medical truth is proven and straightforward: vaccines are safe and effective and save thousands of lives every day. Yet, while we celebrate the successes of vaccines, we must also acknowledge the work still to be done. The world still suffers from many potentially preventable diseases for which no widely effective vaccines yet exist, including HIV, tuberculosis, malaria, and hepatitis C. Continued research is crucial to developing new vaccines for these and other diseases that cut lives short and leave survivors with life-long disabilities. In the meantime, we need to work toward universal access for existing vaccines so that every person in the world receives the full benefit of the greatest contribution that science has made to public health.

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Global Immunization through the Lens of Development

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Supporting global immunization programs is a profound way to control disease and improve the lives of many, particularly in the developing world. In 1974, the World Health Organization (WHO) created the Expanded Programme on Immunization (EPI), a worldwide effort mobilized to help countries increase immunization coverage of basic childhood vaccines—diphtheria, measles, pertussis, polio, tetanus, and tuberculosis—using the third dose of diphtheria, tetanus, and pertussis (DTP3) as a measure of progress. Building on the historical success of smallpox eradication, the WHO sought to increase global vaccination coverage (which was <5% in 1974) among children younger than one year of age. However, one-fifth of the world's children, especially those who live in low-income countries, are not fully vaccinated with these traditional vaccines during their first year of life.[1]

The Global Vaccine Action Plan (GVAP) for 2011–2020 has established immunization coverage targets of at least 90% DTP3 coverage nationally and at least 80% DTP3 coverage in every district.[2] Countries can take a variety of actions to attain these targets, depending on their needs and the current status of their health system and immunization program.

This year, on the 40th anniversary of EPI, through the collective work of many partners, we are witnessing a time of unprecedented support and commitment to ending preventable child and maternal deaths within a generation, a top priority of the U.S. Agency for International Development (USAID). In this Decade of Vaccines,[2] we join global efforts to extend the full benefits of immunization to all people, regardless of where they are born, who they are, or where they live. And USAID continues its long-standing partnership with the U.S. Department of Health and Human Services (HHS) and other actors on the global stage. Our work as a development agency contributes to global efforts outlined in this report by the National Vaccine Advisory Committee (NVAC) Global Immunizations Working Group, "Enhancing the Work of the Department of Health and Human Services National Vaccine Program in Global Immunization: Recommendations of the National Vaccine Advisory Committee."[3] The challenges and recommendations in the report highlight holistic approaches

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to technical and financial investments in health as well as increased coordination among the partnership of actors. We support these efforts, particularly through a developmental lens, emphasizing support to national governments toward investing in health, immunization programs, and human and institutional resources.

A DEVELOPMENT APPROACH

USAID's long-standing strategy provides technical assistance to countries and the global technical community by focusing on improving the efficiency and equity of EPI worldwide. Central to USAID's work is supporting countries through a development lens—an approach largely centered on long-term investments in addressing weaknesses within the health sector. Health programs also intersect other domains of development, layering on top of social, economic, and environmental objectives toward fulfilling country needs. USAID and other donor investments across the development spectrum (e.g., democracy, governance, and education) affect the sustainability and infrastructure of immunization programs. Reaching into these other domains is important for influencing the proximate determinants of health and poor outcomes.

We know vaccines are cost-effective interventions and that immunization programs save lives, improve the health of children and communities, and lead to healthier, more productive people. We also know that for programs to be sustained, they must operate successfully within country-specific cultural, social, and economic circumstances. The development context underpins USAID's approach to building capacity and capability to work in sustainable ways, particularly given the country resources available. The provision of accessible, country-financed, quality primary health care, with immunizations as a cornerstone of such a system, is central to prospects for genuine human development. Although primary and vertical health programs coexist, USAID uses a systems approach to strengthen immunization as an integral part of the broader health system. Moreover, the functionality of immunization as part of an overall primary health-care system requires the recognition and need to enhance the integration of sound technical interventions with socioeconomic development programs, including training of human resources for health to achieve sustained success.[4]

A BRIEF LOOK AT USAID

As part of a worldwide effort undertaken by the WHO in 1966 to eradicate smallpox, USAID entered into the global immunization arena supporting a large regional project in Africa to control measles and eradicate smallpox. Investments in the development of a jet gun injector accelerated smallpox eradication by advancing the use of new technology for mass immunization campaigns. USAID support for smallpox and measles elimination marked an initial foray into what would be a long history in supporting global immunization. In 1985, USAID launched the Technology and Resources for Child Health (REACH) project, its first major global project in support of childhood immunization services. Since then, USAID has continuously supported immunization programs at the national and sub-national levels and worked to scale up evidence-based, equitable, locally adapted solutions with country partners.[5] Our technical assistance in immunization continues to be deliberately designed to respond to local needs and circumstances. Grounded in close collaboration with national Ministries of Health and district health teams, USAID invests in a process of joint identification of problems and priorities and negotiates strategies to address these challenges, balancing the need for results with the directive to build local capacity in line with USAID's developmental mandate. Other field contributions include groundbreaking clinical field research on the efficacy of pneumococcal vaccine and improved methods for addressing behavioral and social determinants of vaccine utilization.

We have made essential and globally important contributions to polio eradication beginning early on in the global polio eradication efforts. USAID-provided support beginning in 1988 was geared toward efforts by the Pan American Health Organization (PAHO) to strengthen routine immunization systems, control and eventually eliminate measles, and rid the region of polio. In 1996, we expanded our polio investments globally to extend to the other WHO regions of the world—Africa, Southeast Asia, Eastern Mediterranean, Europe, and the Western Pacific—providing technical assistance to improve all aspects of implementing and monitoring polio campaigns and supporting surveillance and communication activities as part of the global eradication effort. Since 2000, USAID has also been a central and strategic partner in the GAVI Alliance (GAVI). To date, USAID has provided more than $1 billion in financial support to GAVI, primarily to purchase vaccines in low-income countries. Our U.S. government contribution to GAVI expands access to life-saving vaccines by shortening the time from when a vaccine becomes licensed for use to when it is introduced into immunization programs in GAVI-eligible countries, closing the inequity gap between the industrialized and developing world.

Past USAID investments in technologies have led

to products that now reach millions of people, including safe injection technologies such as the SoloShot™ syringe, which is automatically disabled after one use and cannot be refilled or reused, thereby preventing the transmission of bloodborne diseases from needle reuse. USAID also supported UniJect™—a combined needle and syringe prefilled with vaccine that can also only be used once—which has been used for childhood vaccination. These prefilled syringes can have practical field advantages for use in hard-to-reach geographic communities. Perhaps most widely used is the small label that is affixed to vaccine containers, changing color to indicate that the vial has been exposed to heat outside the recommended temperature range indicated for storage. These vaccine vial monitors, which were developed by USAID in response to field needs, have transformed the way we deliver vaccines and have helped to increase the effectiveness and coverage of national immunization programs worldwide.[6]

USAID: PART OF THE U.S. GOVERNMENT FABRIC

As with other U.S. government agencies, including the Department of Agriculture and Department of Defense, USAID's role and mission clearly differs from that of HHS. As the foreign assistance arm of the federal government, USAID functions as a development partner with technical capability in a broad range of domains, including health. For more than three decades, USAID has contributed to the canvas of public and private collaboration that comprises the vaccine and immunization enterprise.

We stand at a point where we must invest diligently and thoughtfully in host country capacity and in routine immunization systems. Immunization programs are cornerstones of health systems—a public good that virtually all governments rely upon to safeguard the health of their populations. Achieving and sustaining high and equitable coverage is needed to end deaths from vaccine-preventable diseases. To reach this goal, we must work together to invest in creative approaches to recognize families and communities as partners with the health system; support the managerial capability needed at the national, district, and facility levels to strengthen routine immunization; and support the needs of countries to address their challenges and weaknesses.

Our collective U.S. government contribution to global health is significant, and our investments capitalize on technological advances that enable the development and delivery of vaccines for diseases once considered beyond the reach of biomedicine. As we enter the 40th anniversary of EPI, the global community celebrates the success of a system for immunization service delivery, management, and program monitoring that is able to reach even the most peripheral parts and marginalized communities in countries around the world. We look strategically forward to the future as USAID, together with partners, works to end preventable child death by 2035.

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The Contribution of Immunization: Saving Millions of Lives, and More

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The Expanded Programme on Immunization was established in 1974 as the world moved ever closer to smallpox eradication.[1] Confidence was high that, with international commitment and cooperation, other vaccine-preventable diseases (VPDs) could be conquered. The 1979 certification of smallpox eradication—humanity's greatest triumph—was taken as proof of the power of vaccines to permanently improve the world.[2] At that time, no one could have foreseen that the 1980s would bring an oil crisis, a worldwide economic recession, and a dramatic shrinking of funds for international health development. At the end of what became known as the "lost decade for development," the World Health Organization (WHO) singled out childhood immunization as the one true success story where momentum continued to build, with outstanding results.[3]

Today, as then, immunization has compelling political and public appeal as a cost-effective intervention with an immediate and measurable impact on childhood morbidity and mortality. A single statistic summarizes its remarkable success. In 1974, fewer than 5% of the world's children were protected by vaccines against six killer diseases. Today, that figure is 83%, with some developing countries reaching 99% immunization coverage.[4]

Immunization programs have another advantage: their great moral authority. The establishment in 2000 of the Global Alliance for Vaccines and Immunization, or GAVI Alliance, operationalized the principle that every child, regardless of place of birth or income status of the parents, deserves the very best that medicine and science can offer, including access to newer and more expensive vaccines.[5] Immunization, which makes universal coverage imperative, is also a potent social equalizer. Even in very wealthy countries such as the United States, it offers equal protection to rich and poor, privileged and marginalized, promoting equally good health outcomes for all.

In a sense, the purpose of expanded immunization is straightforward: to deliver multiple vaccines to more children through a simple schedule of child health visits. Yet, as experience has shown, beneath this apparent simplicity lie multiple layers of complex problems—scientific as well as operational—that need to be solved in the interest of further progress. The success of smallpox eradication illustrated the critical importance of constant research and innovation, and of flexible operational approaches that can respond quickly to advances

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in knowledge and technology. Since its inception four decades ago, expanded immunization has been a story of progressive building on success in a never-ending quest to do more things better. As new problems arose, the determination to solve them brought out the best in human ingenuity and creativity.

Global immunization efforts have been vastly enriched by the commitment of the U.S. government, including substantial financial support and the leadership of the U.S. Department of Health and Human Services (HHS). Thanks to the work of agencies such as the U.S. Centers for Disease Control and Prevention (CDC), the U.S. Food and Drug Administration, and the National Institutes of Health, the pages of this report are a catalogue of wide-ranging innovations, game-changing solutions, and progressive successes. They are also a tribute to the decisive impact of U.S. engagement.[6]

The legacy of the global drive to expand immunization is vast. Immunization programs were the proving ground for what are now core principles of public health: the importance of country ownership, community engagement, appropriate technology, and sustainable results. Immunization also demonstrated the value of setting ambitious but realistic goals and making fair access to services an explicit policy objective. Successes have been seen at the cutting edge of science and among the harsh realities of vaccine delivery in very poor places, in the creation of novel survey designs for tracking and measuring progress, and in constant simplifications and improvements in the cold chain.

As a spearheading partner in the Global Polio Eradication Initiative,[7] CDC has done much to push the world toward the finish line. The same is true for plans, now approved in all six WHO regions, to eliminate measles and rubella. In my visits to countries, I see the results: the increasingly rare sight of a child crippled by polio, the emptied measles wards in hospitals.

Another characteristic of immunization success is its spillover benefits for overall health system capacities. CDC's renowned laboratory expertise has supported networks of WHO-certified laboratories for polio, measles, and other diseases. This work has given developing countries the infrastructural asset of high-quality national laboratories to build surveillance capacity for multiple infectious diseases, including yellow fever and epidemic meningitis. Other innovations have simplified and streamlined essential work. For example, CDC introduced new laboratory procedures that reduced the time to detect and confirm polio infections by 50%.[8] As yet another contribution to operational support, CDC has trained thousands of health-care workers, field epidemiologists, laboratory staff, and program managers.

As this report is issued,[6] global immunization efforts continue to expand, this time guided by a Global Vaccine Action Plan that supports the Decade of Vaccines.[9] Immunization is making a value-added contribution to child survival, as vaccines are distributed together with insecticide-treated bednets, deworming tablets, vitamin A supplements, and tools for growth monitoring. Most recently, scientific evaluations supported by CDC, WHO, and UNICEF have shown how well-functioning immunization services can provide the foundation for integrated delivery of multiple health services.[10,11] In other words, efforts to reach every child with a growing number of vaccines have doubled as a capacity-building strategy that benefits the entire health system—and the people it serves.

Perhaps the best news, as noted in this report, is the widespread conviction that the potential of immunization to save lives and build capacity has not yet been fully realized. The stunning results to date can be surpassed. The U.S. government should be lauded for its commitment, HHS for its ingenious and innovative contributions, and the American people for their generosity. Expanded immunization has served as a platform by which the U.S. has shared its world-class capabilities with less fortunate countries for the benefit of all.

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Global Health and U.S. Health—Inextricably Linked

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There have been many triumphs in public health during the last half-century; however, none have been more significant than the advancements in vaccines that have contributed to a dramatic decline in child mortality and infectious disease in the United States and many other parts of the world. As recently as 1967, an estimated 2 million people were dying each year from smallpox. With the development of an effective vaccine and worldwide immunization campaign, the disease was eradicated by 1980. A quarter-century ago, polio was endemic in 125 countries and paralyzing an estimated 350,000 children every year. In 2013, there were just three polio-endemic countries (i.e., countries that have never terminated indigenous poliovirus transmission) remaining—Nigeria, Pakistan, and Afghanistan—and 400 reported cases.[1]

In the U.S., vaccine-preventable diseases (VPDs) are at or near record lows,[2] thanks to new or improved vaccines and immunization systems that protect children against 16 diseases.[3,4] In the U.S., our commitment to immunizations is also an investment in our children. A recent study estimated that vaccination of each U.S. birth cohort with the recommended childhood immunizations prevents 42,000 deaths and 20 million cases of disease over the lifetime of the cohort, with a net savings of about $13.5 billion in direct costs and nearly $69 billion in direct and indirect societal costs.[5]

It is hard to argue with such numbers. Yet, worldwide, VPDs still account for one of every five deaths among children younger than 5 years of age.[6] That burden falls most heavily on poor countries, but the potential spread of infectious diseases poses a significant public health threat to people in all 50 states and the District of Columbia. For example, although the number of polio cases worldwide remains near the record low, reported wild poliovirus cases in countries that had previously eliminated polio increased from six cases in 2012 to 256 cases in 2013. The increase is largely attributable to the difficulty of reaching children in areas of conflict and civil war.[7] In the U.S. in 2013, there was a significant spike in measles cases, due almost entirely to people who brought the infection home after traveling overseas.[8] Both examples are reminders that

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infectious diseases can strike people anywhere, and that U.S. health is inextricably linked to global health.

U.S. GOVERNMENT LEADERSHIP

In the last century, the average lifespan of Americans increased by more than 30 years and mortality from most VPDs decreased by 99%, and public health initiatives such as vaccination were a big contributor.[9] In fact, many of the most important breakthroughs in vaccines would not have occurred without the leadership, innovation, and sustained investment of U.S. government agencies. For example:

- The National Institutes of Health (NIH) has played a vital role in understanding infectious diseases and funding the research and development of vaccines that have saved millions of lives in the U.S. and worldwide.
- The U.S. Centers for Disease Control and Prevention (CDC) is the global leader in disease detection, prevention, and control strategies, and has been a central player in eradicating smallpox, eliminating polio from most countries, and advancing other key immunization initiatives.
- The U.S. Food and Drug Administration (FDA) has unparalleled expertise working with other national regulatory authorities and with the World Health Organization (WHO) to shape global regulatory standards for the development and manufacture of safe and effective vaccines.
- The U.S. Agency for International Development (USAID) has been deeply involved in global immunization efforts, and has been a leader in innovations such as the first technology to enable mass immunization campaigns, as well as research to better understand the behavioral and social determinants of vaccine utilization.

Although vaccines have been enormously effective in reducing the prevalence of infectious diseases in the U.S., sustaining U.S. support for global immunization efforts is as important now as it has ever been.

Despite significant progress, more than one million children younger than 5 years of age still die each year from VPDs.[10] Additionally, more than 3.5 million individuals die annually from human immunodeficiency virus (HIV), tuberculosis, and malaria, diseases for which U.S. government-funded researchers are still searching for effective vaccines.[11]

The continued efforts of NIH are essential to discovering and developing new vaccines and other therapies to prevent the most deadly infectious diseases. The FDA plays a vital role in reviewing the safety and efficacy of these new immunizations. CDC monitors safety and coverage. And USAID helps ensure that immunizations get to everyone who needs them. These agencies also play essential roles in reducing the threat of infectious diseases within the U.S., such as the importation of pandemic influenza, polio, and measles.

We welcome the report of the National Vaccine Advisory Committee (NVAC).[12] This important analysis underscores the vital role the U.S. government plays in reducing childhood mortality and the burden of infectious disease. The report's greatest contribution, however, is its identification of opportunities for federal agencies to drive toward a more integrated way of working that sustains and strengthens global immunizations and helps realize the vision of the Global Vaccine Action Plan endorsed by the World Health Assembly in 2013.

The recent development of a vaccine to combat the deadly meningitis A epidemics that frequently swept through sub-Saharan Africa is an example of the impact U.S. government agencies can have when working together. After an outbreak in the 1990s that killed more than 100,000 people, African leaders asked for help to create an affordable vaccine to protect children and young adults against the meningitis A strain that was prevalent in Africa.[13]

In a testament to integrated, coordinated government effort, USAID provided funding to improve surveillance and address regulatory issues concerning the vaccine's approval. The FDA developed a key manufacturing method used to produce the vaccine. NIH facilitated the transfer of technology to an Indian vaccine manufacturer. And CDC developed and conducted clinical tests to evaluate the immune response of people to the new vaccine, and supported surveillance by the government of Burkina Faso that documented the vaccine's effectiveness in the field. In just a few years, more than 150 million people in Africa have received the MenAfriVac™ vaccine. In 2013, the WHO reported that the number of meningitis cases had dropped to the lowest level in a decade—a decrease associated with the introduction and rollout of the new vaccine.[13]

The Bill & Melinda Gates Foundation was a partner in the MenAfriVac effort—supporting an innovative partnership led by the WHO and PATH—and for more than a decade has worked collaboratively with U.S. government agencies to advance other vaccine research and development and delivery efforts. For instance, The Bill & Melinda Gates Foundation works closely with CDC on the Polio Oversight Board of the Global Polio Eradication Initiative and with USAID on other efforts related to polio eradication. We partner

with USAID on the International AIDS Vaccine Initiative, which is helping scientists create a safe, effective, preventive HIV vaccine. We collaborate with the FDA on the Critical Path to Tuberculosis Drug Regimens, an initiative to speed the development of better drug regimens for tuberculosis. We are working with NIH to establish a consortium of contract manufacturers and laboratories to conduct analytical work to support academic researchers. And we've joined the U.S. government and many others in supporting the GAVI Alliance as one of the best values for money in all of global health.

CONCLUSION

The NVAC Global Immunization Working Group report underscores the critical role the U.S. government plays in advancing vaccine research, streamlining and accelerating government reviews and approvals, and ensuring vaccines are affordable and accessible.[12] The reality that infectious diseases can and do cross national borders is a reminder that we are all in this together, and that we can be most effective and achieve the greatest impact by aligning our efforts. Global collaborative efforts such as the GAVI Alliance, the Global Polio Eradication Initiative, and the Global Fund are evidence that tackling global health challenges together works. By leveraging the whole of the U.S. government and continuing to work closely with its partners, this report illustrates a path for federal agencies to continue providing a unique leadership role in vaccines and immunization—for the U.S. and the world.

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Enhancing the Work of the Department of Health and Human Services National Vaccine Program in Global Immunization: Recommendations of the National Vaccine Advisory Committee

Approved by the National Vaccine Advisory Committee on September 12, 2013

EXECUTIVE SUMMARY

The global commitment to immunization programs has led to unparalleled successes in public health. In 2011, 83% of the world's children received all three doses of the diphtheria-pertussis-tetanus vaccine primary series,[1] and routine immunizations now save the lives of approximately 2.5 million children per year.[2] Polio is on track for eradication.[3] During the past decade, annual measles-related mortality has been reduced by 71%[4] and neonatal deaths from tetanus were reduced by >90%.[5] The world has committed to the common vision of a Decade of Vaccines,[6] where global efforts are focused on extending the full benefits of immunization to all people, regardless of where they are born, who they are, or where they live. There is much to celebrate, but there is also still much to do.

Vaccine-preventable diseases (VPDs) still account for one-quarter of deaths in children younger than 5 years of age.[7] Vaccines against common causes of pneumonia and diarrheal diseases, the leading causes of death in children, are still not widely accessed by developing countries.[7–9] Children in the lowest wealth quintiles are still the least likely to receive immunizations.[10] Systems for routine immunizations in a number of low- and middle-income countries (LMICs) remain limited in their ability to accommodate new vaccines because of financial and logistical barriers.[11–13] Countries continue to lack the capacity to collect quality data on the impact of immunization programs,[10,14,15] report and evaluate adverse events following immunizations,[16] or detect outbreaks of public health importance.[17,18] Moreover, vaccines are still unavailable for a number of preventable diseases such as human immunodeficiency virus (HIV) and malaria. Despite these challenges, the global community is finding new and innovative ways to solve these issues through international collaborations, public-private partnerships, and sustainable, evidence-based, country-led initiatives.[19]

A recent survey by the Kaiser Family Foundation showed that U.S. global immunization efforts in developing countries are broadly supported by most people in the United States.[20] But support of global immunizations is not limited to humanitarian aid. Recent threats from infectious diseases such as pandemic influenza or importations of VPDs such as measles highlight the fact that U.S. health is intricately linked to global health,[21,22] and efforts to strengthen global immunization systems and reduce the global and economic burden of VPDs have a clear and added benefit for both the U.S. and the global community.[23–25] The U.S. Department of Health and Human Services (HHS) has responded to this changing environment by supporting strategies and policies that weave together its mission to protect the health and well-being of the U.S. population with other U.S. government (USG) efforts to bring about a safer and healthier world.[26–30]

In February 2012, the U.S. Assistant Secretary for Health (ASH) charged the National Vaccine Advisory Committee (NVAC) with reviewing the role of HHS in global immunizations, the effect of global immunizations on global populations, the effect of global immunizations on U.S. populations, and recommending how HHS can best continue to contribute, consistent with its newly established Global Health Strategy[28] and

Goal 5 of the 2010 National Vaccine Plan.[27] The NVAC was also asked to make recommendations on how to best communicate this information to decision makers and the general public to ensure continued sufficient resources for global vaccination efforts. The NVAC formed a Global Immunizations Working Group, consisting of experts in issues relevant to all aspects of the global immunization efforts, to address this charge.

The NVAC's analysis includes a review of several global initiatives and efforts to reduce the morbidity and mortality caused by VPDs through safe and effective immunizations. However, this review was not intended to represent an exhaustive catalog of all global immunization activities. Thus, this report does not represent the full range of USG efforts that support global immunization. Rather, the NVAC recommendations focus on six areas where HHS efforts should be further leveraged to achieve the greatest contributions to reducing health burdens through global immunization efforts:

1. Tackling time-limited opportunities to complete polio eradication and to advance measles mortality reduction and regional measles/rubella elimination goals
2. Strengthening global immunization systems
3. Enhancing global capacity for vaccine safety monitoring and post-marketing surveillance
4. Building global immunization research and development capacity
5. Strengthening capacity for vaccine decision making
6. Unifying HHS global immunization efforts: leadership and coordination

NVAC RECOMMENDATIONS

A brief summary of the NVAC's findings within the six key focus areas and the resulting NVAC recommendations are provided hereafter. A more extensive discussion of the background and rationale for each recommendation is provided in the full report.[31]

1. Tackling time-limited opportunities to complete polio eradication and to advance measles mortality reduction and regional measles/rubella elimination goals

Global goals, including achieving certification of global polio eradication and measles/rubella elimination in at least five World Health Organization (WHO) regions by 2020, will be important measures of success for the Decade of Vaccines.[6,19] However, progress toward these goals has been threatened by global economic uncertainty, misperceptions regarding the benefits of vaccines and vaccination programs, weak health systems, and violence toward campaign vaccinators.[3,21,32–35] A resurgence of these diseases will have economic and public health consequences that will affect both global and U.S. populations.[35–37] Although significant technical and financial support has been provided by HHS thus far, better communication of the achievements made, the challenges to completing these goals, and the consequences for failure is needed to garner the continued financial and political support to take these landmark efforts to the finish line.

1.1. The ASH should lead efforts to coordinate briefings, public events, and educational outreach to policy makers, legislators, and the general public, in coordination with other U.S. agencies, multilateral partners, and nongovernmental organizations (NGOs), to communicate the urgency of completing global goals for polio eradication and advancing global measles mortality reduction goals and regional goals for measles/rubella elimination.

1.1.1. The ASH should emphasize that polio eradication efforts and measles mortality reduction and regional elimination efforts should complement and strengthen routine immunization systems.

1.1.2. The ASH should emphasize that failure to complete polio eradication goals or to advance goals for measles mortality reduction and regional goals for measles/rubella elimination may threaten the health of U.S. populations due to importations of these diseases from endemic areas.

1.1.3. The ASH should emphasize that political and public support is fundamental to achieving polio eradication and advancing global goals for measles mortality reduction and regional goals for measles/rubella elimination. Achieving these goals would equal a monumental public health and humanitarian accomplishment for the entire global community and, if done appropriately, will potentially strengthen support for routine immunization goals.

1.2. The ASH should strongly encourage the HHS Secretary to seek additional funding to facilitate the achievement of unique, time-limited opportunities to complete global goals for polio eradication and to support measles mortality reduction and regional goals for measles/rubella elimination. The ASH should advocate to the HHS Secretary that completion of these goals will yield significant economic and public health returns on investments and shed new light on the value of vaccines and immunization and the potential for future cost savings.

1.3. The ASH should encourage the U.S. Centers for Disease Control and Prevention (CDC) to continue to enhance the public health impact of its Stop Transmission of Polio (STOP) Program by increasing the number and length of training opportunities. STOP Team assignments should focus on building broad subject-matter expertise that can be applied to polio and measles efforts, as well as strengthening routine immunization systems and disease surveillance.

1.4. The ASH should work with CDC to create opportunities to bring together stakeholders and leadership from the Global Polio Eradication Initiative and the Measles Rubella Initiative to (*1*) discuss lessons learned and best practices and (*2*) consider opportunities for joint programming that can lead to program efficiencies and improve the delivery of vaccines using routine systems. As a leading partner in both initiatives, CDC should work to capture and review these findings to inform current programming, the introduction of new vaccines, and other global public health efforts.

2. Strengthening global immunization systems

Weak immunization systems jeopardize the substantial investments that have gone into reducing the global burden of VPDs. Prioritizing efforts to strengthen global immunization systems will build long-term capacity for routine immunization systems, ensure equitable access to currently recommended routine immunizations, and accelerate the uptake of new or underutilized vaccines.[17,18] HHS can provide the greatest contributions toward strengthening global immunization programs by improving data collection systems to maximize the impact of national immunization programs; building comprehensive and integrated VPD surveillance systems; and supporting better management, integration, and implementation of immunization delivery services, including vaccine supply chain and logistics.

2.1. The ASH should advocate for HHS efforts that support the U.S. Agency for International Development (USAID), the GAVI Alliance (GAVI), and multilateral organizations such as the WHO and the United Nations Children's Fund (UNICEF) in the development of best practices and technologies to support countries in their efforts to more accurately track immunization coverage at the national and sub-national levels and improve data quality and use. Where problems have been identified, data should be used to guide corrective actions when necessary.

2.2. The ASH should work with other HHS offices to develop sustainable support for quality global VPD surveillance systems, including the existing global and regional VPD laboratory surveillance networks. This support ideally should include technical and financial resources needed to support early warning/outbreak surveillance; laboratory diagnostics; emergency communication systems to detect and respond to outbreaks of VPDs; surveillance requirements for the eradication of targeted VPDs, including case-based polio, measles, and rubella surveillance; and laboratory networks to support the introduction and monitor the impact of new and underutilized vaccines.

2.3. The ASH should work with CDC and USAID to increase core support to CDC's Field Epidemiology and Laboratory Training Program (FE[L]TP) as a key tool to transfer epidemiologic and laboratory capacities to strengthen programs. This support should specifically be used to incorporate immunization topics into FE(L)TP training.

2.4. The ASH should support the work of HHS and its partners within the international community to define standards for measuring the impact of routine delivery strategies such as the Reaching Every District/Community strategy. These metrics can be used to evaluate how well these strategies perform in fully vaccinating children with routine immunizations.

2.5. The ASH should endorse and facilitate HHS coordination with other USG agencies to support efforts that provide routine overseas administration and documentation of vaccinations for all U.S.-bound refugees with vaccines that have been identified for pre-departure administration.

2.6. The ASH should support the work of other USG agencies and partners to strengthen global efforts pertaining to immunization program logistics management, including building and sustaining the necessary capacity for vaccine supply chain, logistics, and forecasting.

2.7. The ASH should work with the Office of Global Affairs and CDC to assist national governments, development agencies (including USAID), multilateral organizations (including WHO and UNICEF), and civil society in encouraging the use of immunization contacts (through routine systems and campaign activities) as a platform for delivering additional health and aid services and vice versa. Evaluations of these efforts should include the types of interventions, the cost benefits of combining new interventions with global immunization efforts, and the effect these strategies have on building community demand for health services overall.

3. Enhancing global capacity for vaccine safety monitoring and post-marketing surveillance

As coverage of existing vaccines increases and new and underused vaccines are introduced to larger populations, countries will need support to monitor, identify, and respond to vaccine safety concerns and adverse events following immunizations.[16] Global approaches to vaccine safety benefit all countries, and ongoing efforts are working to overcome the barriers to vaccine safety monitoring that continue to challenge resource-poor countries.[38] HHS agencies can contribute expertise, training, and the development of standardized tools, guidelines, and processes to enhance global vaccine safety monitoring capacity and help build public trust and demand for vaccines.

3.1. The ASH should identify mechanisms to encourage ongoing collaborations and technical support between HHS agencies involved in post-licensure vaccine safety and related global agencies and partners to (*1*) enhance capacities to build vaccine safety surveillance systems to monitor the safety of vaccines as they are broadly administered, (*2*) assess and respond to vaccine safety concerns or signals, (*3*) effectively communicate vaccine risks, and (*4*) support the political will to respond to vaccine safety concerns with evidence-based decisions.

4. Building global immunization research and development capacity

Continuing HHS commitments to global efforts in scientific discovery and vaccine research and development (R&D) are necessary to address remaining unmet public health needs such as the prevention of HIV, tuberculosis, malaria, neglected diseases, and other emerging infectious diseases of global health importance. However, the development of future vaccines, particularly for the prevention of diseases predominately affecting LMICs, will require innovative product development partnerships, greater global regulatory capacity, and the growing involvement of emerging vaccine manufacturers in developing countries. HHS's support of these efforts will not only increase access to new or improved vaccines and immunization technologies, but will also contribute to augmenting global vaccine manufacturing capacity. As a benefit, these efforts will help to achieve national and global influenza pandemic preparedness objectives.

4.1. The ASH should support efforts that increase global health research capacity through partnerships among health research institutions in the U.S. and abroad. These partnerships create opportunities to train the next generation of U.S. and foreign scientists to better address current and future global health needs, including the development and evaluation of new vaccines, new vaccine delivery systems, country-specific immunization schedules, and new technologies that facilitate global immunization efforts.

4.2. The ASH should encourage HHS agencies to work closely with USAID, WHO, UNICEF, GAVI, end users (including national immunization program managers, Ministries of Health, national immunization technical advisory groups [NITAGs]), nonprofit product development partners, and vaccine manufacturers to support WHO in its efforts to define vaccine target product profiles.

4.3. The ASH should support the ongoing efforts of the National Institutes of Health and the U.S. Food and Drug Administration (FDA) to communicate strategies for minimizing barriers to the development of vaccine products. These efforts enhance the identification, testing, and evaluation of promising vaccine candidates to ensure that candidate vaccines advance more quickly through the development pipeline. HHS should work with other USG agencies, such as USAID and the U.S. Department of Defense (DoD), to coordinate, where appropriate, R&D prioritization to assure that efforts are optimized to meet global health needs.

4.4. The ASH should support efforts to strengthen national regulatory authorities in other countries through collaborations with the FDA. The ASH should support ongoing FDA efforts with other national regulatory authorities and the WHO to continue seeking opportunities to inform, shape, and communicate global regulatory standards and requirements for the development and manufacture of safe and effective vaccines. In doing so, HHS will continue to strengthen international programs, including building and strengthening global regulatory capacity and quality systems.

4.5. The ASH should support HHS agencies in their ongoing efforts to develop training modules and workshops for vaccine manufacturers in developing countries on best practices and approaches for vaccine manufacturing and guidelines for good manufacturing practices.

5. Strengthening capacity for vaccine decision making

The introduction of new and/or underused vaccines into national vaccine programs, combined with currently recommended vaccines, has the potential to save 23 million lives by 2020.[8] However, countries are faced with a number of competing public health priorities,

and decision makers must have the capability to evaluate the available data to support the introduction of new vaccines into national immunization programs. HHS technical expertise can assist countries in the use of standardized decision analysis tools, technical evaluations, and the engagement of external immunization technical advisory groups to support the adoption of new vaccines into routine programs, argue for government or donor funding, and build credibility and acceptance of vaccine policies among the public.

5.1. The ASH should continue to support the development of quality baseline data and ongoing collection of key data to support informed country-level decisions regarding the development, introduction, and monitoring of new vaccines based on the evaluation of disease incidence and prevalence, financial sustainability, vaccine safety and efficacy, cost benefits, and programmatic considerations.

5.2. The ASH should work with HHS offices and non-HHS partners to increase investments in national evidence-based decision making by NITAGs (similar to the U.S. Advisory Committee on Immunization Practices). Support should include technical assistance and provisions to develop and train these NITAG bodies.

6. Unifying HHS global immunization efforts: leadership and coordination

Finally, the full and continued participation of HHS agencies and their staff in global immunization efforts helps to build international cooperation toward the common goal of reducing the global burden of VPDs. Supporting the long-term assignment of HHS personnel to multilateral organizations, bilateral assignments to support country Ministries of Health, and assignments to public-private global health partnerships ensures that U.S. policies and proposed solutions to global immunization challenges are adequately voiced in the global health arena. Likewise, improving collaborations within HHS agencies in global immunization efforts will ensure efficiencies and a unified focus for HHS contributions toward global immunization programs.

6.1. The ASH should support ongoing policy revisions to facilitate long-term assignment of HHS professional staff to advance USG immunization priorities, and particularly to international multilateral organizations, bilateral assignments to support country Ministries of Health, public-private global health partnerships, and other U.S. federal agencies and departments.

6.2. As the director of the National Vaccine Program, the ASH should work with the HHS Secretary, the HHS Office of Global Affairs, and HHS Operating Divisions to define a process to strengthen coordination of HHS-led global immunization efforts. Enhanced coordination would ensure alignment of priorities, minimize duplication of global immunization efforts, help track progress in a consistent and transparent manner, and facilitate discussing and addressing challenges and barriers on an ongoing basis.

6.2.1. As part of these efforts, HHS should consider convening an HHS cross-departmental working group to create an HHS Global Immunizations Implementation Plan that includes measurable outcomes defined by HHS agencies, how the agencies will track progress toward these outcomes, and potential barriers to achieving the NVAC recommendations and other objectives described in Goal 5 of the National Vaccine Plan.

6.2.2. This HHS cross-departmental working group should also determine a mechanism to enhance HHS coordination with USG agencies (e.g., USAID and DoD) and other critical non-USG partners (e.g., GAVI, UNICEF, WHO, the Bill & Melinda Gates Foundation, NGOs, and product development partners) for improved information sharing and decision making on USG global immunization activities.

6.2.3. The HHS cross-developmental working group should develop an annual report to Congress on HHS investments and impacts on global immunization efforts. This report could be presented as an expanded section of an existing report to Congress or as a standalone product.

6.2.4. When communicating the value of vaccines to the public and decision makers, the ASH should emphasize all of the comprehensive efforts required to optimize disease prevention through vaccination. The ASH should communicate to decision makers that investments in USG efforts in all areas of immunization are required to ensure optimal disease and death prevention. The ASH should also communicate that global vaccination efforts not only save lives in other countries, but they also enhance our own domestic health security because the potential for importation of vaccine-preventable infectious organisms into this country is reduced.

6.2.5. This HHS cross-departmental working group should also collaborate with USG agencies to understand how the whole of USG global immunization efforts are supporting implementation of the Decade of Vaccines Global Vaccine Action Plan, and identify areas where enhanced collaboration can increase the impact of U.S. efforts.

CONCLUSION

While recognizing that the HHS activities described throughout this report[31] are only one pillar of the USG efforts to strengthen global immunization programs and reduce the global burden of VPDs, the NVAC believes HHS has a vital role to play in the global efforts to make the Decade of Vaccines vision a reality. The recommendations and supporting rationale are intended to raise awareness of ongoing HHS efforts in the context of broader global initiatives, to build political and public support around these activities, and to ensure that these efforts will enhance USG efforts to continue to move the global immunization agenda forward. In turn, the recommendations and efforts outlined in the NVAC report will help better communicate HHS's accomplishments and resource gaps to decision makers and the public. The recommendations should serve as a potential roadmap for better coordination and tracking of HHS global immunization efforts. The continued participation of HHS in the six priority areas identified by NVAC will make certain that global immunization remains at the forefront of HHS global health priorities.

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INTRODUCTION

Global immunization programs strive to achieve high levels of disease prevention and equitable access to healthy communities. Immunizations are estimated to have saved 20 million lives during the past two decades. Yet, vaccine-preventable diseases (VPDs) continue to cause 1.9 million childhood deaths every year, which translates to a child dying of a VPD every 20 seconds.[1]

During the Child Survival Call to Action summit hosted in June 2012, world leaders stated that unless global efforts were increased, the world would fail to reach the 2015 Millennium Development Goal of reducing childhood mortality by two-thirds of the levels recorded in 1990 (Millennium Development Goal #4).[2,3] It was noted that accelerated strategies would need to include "cost-effective, evidenced-based interventions and delivery strategies that have the largest potential for sustained impact."[3] A global commitment to strengthening immunization programs is paramount to reaching these goals.

The United States has been a leader in supporting global immunization efforts. U.S. investments in global vaccines and immunization infrastructure have been leveraged to improve the health and well-being of individuals through better access to health-care systems, protect against international and national public health threats, and foster global health diplomacy. Protecting these assets and determining how to optimize the contributions of the U.S. toward achieving global health goals should remain a priority for the U.S. government (USG).

Charge to the National Vaccine Advisory Committee

In February 2012, the Department of Health and Human Services (HHS) Assistant Secretary for Health (ASH) charged the National Vaccine Advisory Committee (NVAC) with:

- Reviewing the role of HHS in global immunization
- Reviewing the effects of global immunization on global populations
- Reviewing the effects of global immunization on U.S. populations
- Recommending how HHS can best continue to contribute to global immunization, consistent with its newly established Global Health Strategy[4] and Goal 5 of the National Vaccine Plan (NVP)[5]
- Recommending how to best communicate this information to decision makers and the general public to ensure sufficient resources for the global vaccination effort

The NVAC formed a Global Immunization Working Group consisting of experts in issues relevant to all aspects of the global immunization efforts to address these charges.

The NVAC's findings outline a number of global initiatives and global efforts toward improving the prevention and control of important infectious diseases through immunizations that require participation by the full range of global immunization stakeholders. This report is not intended to represent an exhaustive catalog of global immunization activities; rather, it highlights those activities that could be further strengthened through enhanced HHS efforts. It should also be noted that the U.S. global immunization efforts include a number of significant contributions made by other U.S. agencies that are not detailed in this report. These contributions include efforts by the U.S. Agency for International Development (USAID), the U.S. Department of Defense (DoD), and the State Department. Although these efforts are not described in detail, the ongoing contributions by these U.S. agencies, especially USAID, in collaboration with HHS are vital to achieving objectives for global health. Finally, while the NVAC's focus was specifically on providing input to strengthen HHS-led activities, these recommendations are also intended to inform, guide, and create new opportunities for the coordination of global immunization efforts across federal agencies and the full spectrum of immunization stakeholders.

Global immunization: high impact, high returns

Global immunization is one of the best investments in public health. Immunization programs save the lives of approximately 2.5 million children every year.[6] In 2011, 83% of children worldwide were fully vaccinated with three doses of the diphtheria-tetanus-pertussis (DTP) vaccine, and 84% were vaccinated with at least one dose of measles-containing vaccine.[7] Liu et al. estimate that from 2000 to 2010, global campaigns against measles contributed to an 18% reduction in overall childhood mortality (for those <5 years of age).[1] This amazing accomplishment is predicted to have averted a cumulative 12.7 million deaths.[8,9] The recent Global Burden of Disease Study indicated that accelerated measles control efforts led to an 80% reduction in measles-related mortality from 1990 (630,000 deaths) to 2010 (125,000 deaths).[10] Others have presented more conservative estimates of a 71% reduction in measles-related deaths from 2000 (542,000 deaths) to 2011 (158,000 deaths).[11] These achievements in global measles control have resulted in a lower risk of measles importations into the U.S., where measles has not been endemic for more than a decade.

Although routine immunization programs already have had an enormous impact on reducing child mortality, their potential is much greater.[6] As of 2010, one-quarter of the 7.6 million annual deaths in children <5 years of age were still due to VPDs.[1] Progress toward the Global Immunization Vision and Strategy (GIVS) (2006–2015) goal of 90% coverage for the third dose of DTP-containing vaccines and single dose of measles-containing vaccines is suboptimal, particularly among priority countries.[12] For example, it is estimated that 22.4 million children annually are still not being fully immunized with three doses of DTP (also called the DTP vaccine primary series [DTP3]) according to recommendations.[7]

In addition to strengthening access to routine immunizations through systems-strengthening efforts, creating increased access to new and underutilized vaccines has the potential to greatly affect further reduction in childhood mortality. For example, vaccines targeting *Haemophilus influenzae* type b (Hib), pneumococcal disease, and rotavirus as part of coordinated efforts that also target water, sanitation, and nutrition are expected to significantly reduce the global incidence of pneumonia and diarrhea, two of the leading causes of under-five mortality (i.e., mortality in those <5 years of age) in children.[1,13,14] Modeling estimates predict that 23 million future deaths could be averted during the next decade (2011–2020) if high global coverage can be achieved for both routine and new/underutilized vaccines, underscoring the remarkable impact that improved, equitable access to immunizations could have on reducing mortality (Table 1).[13]

In addition to disease prevention, immunization programs provide broad economic and societal benefits.[15] Immunizations with seven routine vaccines[1] in one U.S. birth cohort were estimated to result in a savings of $10 billion in direct costs and $43 billion in societal costs (1995–2001).[16] From another perspective, every dollar spent during this time period on childhood immunizations in the U.S. resulted in savings of $5 in direct costs and $11 in societal costs.[16] On a global scale, the economic impact of investments to reduce the mortality caused by VPDs is also significant. Bloom et al. estimated that by 2020, the benefits of investments

Table 1. Number of deaths averted by antigen and vaccination strategy vs. no vaccination in people forecasted to be vaccinated from 2011 to 2020 in 73 GAVI-eligible countries[a]

Antigen	*Strategy*	*Number of people vaccinated*	*Number of future deaths averted*
Hepatitis B	Routine[b]	585,467,590	4,851,930
Haemophilus influenzae type B	Routine	544,375,979	1,395,024
Human papillomavirus	Routine	34,734,805	525,869
Japanese encephalitis	Campaign	86,709,020	7,778
Japanese encephalitis	Routine[c]	137,837,848	57,178
Measles	Routine first dose	623,754,317	10,296,017
Measles	Routine second dose	154,153,515	288,394
Measles	SIA[c,d]	808,840,938	2,860,093
MenA	Campaign	238,708,529	248,257
MenA	Routine	59,280,269	4,742
Rotavirus	Routine[c]	262,065,510	805,561
Rubella	Campaign[e]	587,376,493	404,959
S. pneumoniae	Routine	358,561,865	1,544,762
Yellow fever	Routine	174,242,766	34,849
Total		4,656,109,444	23,325,413

[a]This table has been adapted from: Lee LA, Franzel L, Atwell J, Datta SD, Friberg IK, Goldie SJ, et al. The estimated mortality impact of vaccinations forecast to be administered during 2011–2020 in 73 countries supported by the GAVI Alliance. Vaccine 2013;31 Suppl 2:B61-72.

[b]Assumes no birth dose

[c]The impact of routine vaccination with Japanese encephalitis and MenA was calculated as the incremental impact above one-time mass-vaccination campaigns. The impact of routine second-dose measles vaccination was calculated as the incremental impact above routine first-dose measles vaccination; the impact of measles supplementary immunization activities was calculated as the incremental impact above routine first- and second-dose measles vaccination.

[d]Measles SIAs include catch-up (aged 9 months to 14 years) and follow-up (aged 9 months to 10 years) campaigns.

[e]Because of the computationally intensive nature of the rubella model and time constraints, the number of congenital rubella syndrome deaths averted were calculated for only the 50 countries projected to introduce rubella vaccine with GAVI Alliance support; another 18 GAVI Alliance-eligible countries—primarily in Europe and the Americas—that have already introduced rubella vaccine with other funding were not included.

MenA = *Neisseria meningitidis* serogroup A

SIA = supplementary immunization activity

made by the GAVI Alliance (GAVI) could yield an internal rate of return up to 18%.[17] This rate of return does not include other benefits such as medical costs averted and reduced suffering.

Diseases such as paralytic poliomyelitis, congenital rubella syndrome, or Japanese encephalitis can result in permanent disabilities that have lasting effects on a child's quality of life and ability to contribute to and benefit from a global economy.[17] For example, in the U.S., the lifetime costs of caring for a severely disabled survivor of the 1964 U.S. rubella epidemic are estimated at $159,530 per year (Personal communication, Steve Cochi, Centers for Disease Control and Prevention [CDC], July 2013). In contrast, the cost to fully vaccinate a child in a developing country with two doses of the measles-rubella combination vaccine (MR) is approximately $1.00 (2012 projected weighted average reported by the United Nations Children's Fund [UNICEF] for MR 10-dose vial was $0.51 per dose, excluding delivery costs).[18]

Part of the challenge of measuring the impact of vaccines is that when they work, healthy people remain healthy. Although more difficult to quantify, childhood vaccinations also contribute to societal benefits such as improved cognitive function, greater health equity, productivity gained, and overall population health through herd immunity.[17,19,20]

Investments in immunization programs also benefit other global programs, as immunizations are often combined with the delivery of other health services.[8,21–23] Immunizations are only one component of a comprehensive prevention package, and programs should be implemented in such a way that creates synergy with other health intervention activities. During the early implementation of the Expanded Programme on Immunizations (EPI) in 1976, the Director General of the World Health Assembly (WHA) wrote that the "EPI should preferably be part of UNICEF's 'social package' of primary health care activities but only exceptionally develop as a programme per se."[24] Immunization activities (both routine and supplemental) create contact opportunities to provide other critical preventive health services, such as the administration of deworming medications, vitamin A supplements, insecticide-treated bed nets, additional vaccines, and other health services targeting women and the impoverished.[8,21,22,25–28]

The ultimate expression of vaccination is the complete eradication of a VPD. Eradication or elimination is not always technically feasible or cost-effective for

The cost of measles outbreak response in the U.S.

Outbreak response to imported vaccine-preventable diseases (VPDs) is labor and resource intensive, requiring both state and federal resources. Recent U.S. measles outbreaks have incurred significant costs despite their relatively small size.[a]

- In Iowa, a student infected with measles while traveling internationally subsequently led to two additional measles cases upon return to the United States. Public health officials had to track >1,000 contacts including airplane passengers and local residents. The response involved >2,500 hours of personnel time, and the costs to the public sector exceeded $140,000. These costs did not include resources used outside of the state public health infrastructure, including collaborations with the airlines, the U.S. Centers for Disease Control and Prevention, and other containment efforts.[b]
- A health-care-associated measles outbreak related to an imported case occurred in an Arizona hospital with 14 confirmed cases of measles. The outbreak required follow-up on the vaccination status of 14,844 health-care workers in seven hospitals and the emergency vaccination of 4,500 health-care workers with unknown immunity status. The cost of this response in two hospitals with seven cases was estimated to be $800,000.[c]
- An imported measles case in a refugee child was identified shortly after the child's family was resettled in Louisville, Kentucky. Although only the single index case occurred, the outbreak investigation and public health response activities were estimated to cost the state $19,000–$30,000. This cost did not include any of the costs incurred at the federal level.[d]

Response efforts detract time and resources from other vital activities in which public health departments engage to guard national health. Reducing the global burden of VPDs does more than provide humanitarian aid for developing countries. It is also necessary to protect public health systems in the U.S.

[a]Measles—United States, 2011. MMWR Morb Mortal Wkly Rep 2012;61(15):253-7.

[b]Dayan GH, Ortega-Sánchez IR, LeBaron CW, Quinlisk MP. The cost of containing one case of measles: the economic impact on the public health infrastructure—Iowa, 2004. Pediatrics 2005;116:e1-4.

[c]Chen SY, Anderson S, Kutty PK, Lugo F, McDonald M, Rota PA, et al. Health care-associated measles outbreak in the United States after an importation: challenges and economic impact. J Infect Dis 2011;203:1517-25.

[d]Coleman MS, Garbat-Welch L, Burke H, Weinberg M, Humbaugh K, Tindall A, et al. Direct costs of a single case of refugee-imported measles in Kentucky. Vaccine 2012;30:317-21.

all VPDs. However, when achievable, eradication has proven to have significant cost benefits. It is estimated that the total U.S. investments in the smallpox eradication campaign are returned every 26 days.[29] Others estimate that the incremental global net benefits of the Global Polio Eradication Initiative (1988–2035) are approximately $40–$50 billion, with most savings occurring in developing nations.[30] Again, this estimate does not include projected estimates of medical costs averted. In a retrospective analysis of the total cost benefits of polio vaccination efforts in the U.S. from 1955 to 2015, Thompson and Tebbens calculated that the U.S. alone will benefit with cost savings of about $180 billion (in 2002 U.S. dollars) based on the number of deaths averted, number of paralytic polio cases averted, and total savings from treatment costs averted.[31] Moreover, savings from these efforts can provide the potential opportunity to use funds that had been dedicated to disease control efforts for broader purposes, such as strengthening health systems.

VPDs: a priority for the U.S.

Global immunization efforts are mutually beneficial for the U.S. population as well as the global community. When global immunization programs in other countries begin to weaken, disease incidence increases, creating vulnerabilities for the U.S. population from disease importations, especially for those who are too young to be vaccinated or who are immunocompromised. Moreover, the public health resources and taxpayer dollars required to respond to and contain VPD outbreaks are substantial. The U.S. celebrated the elimination of indigenous measles transmission in 2000. However, in 2011, the U.S. experienced 220 measles cases resulting from 17 outbreaks across 31 states because of importations of measles viruses from other countries.[32] This outbreak was the highest number of measles cases reported in the U.S. in 15 years. It was determined that 18 cases occurred in children who were too young to be vaccinated. Seventy-two cases were importations from other countries (52 of these cases occurred in U.S. residents returning from abroad and 20 occurred in individuals visiting the U.S.). The remaining cases were due to presumed importations.

U.S. investments in global immunizations ensure safer, healthier environments for U.S. citizens abroad, while preventing the consequences of outbreaks due to VPDs at home. In 2012, Orenstein wrote, "[r]egarding vaccine-preventable diseases, the best defense for the United States is a good offense in reducing, eliminating, or eradicating these diseases in other countries, which are reservoirs for the infectious agents."[33]

Immunization efforts: a shared responsibility

Disease transmission rarely respects political boundaries, and because of the availability of modern forms of travel, it often supersedes geographical barriers. Disease control must therefore be a shared responsibility.[34] The global immunization enterprise comprises a wide range of stakeholders, including developing and donor countries, multilateral organizations, development agencies, philanthropic organizations, academia, vaccine manufacturers, civil societies, health-care workers, advocacy groups, and the private sector. Routine immunization programs may be wholly or partially funded by the countries themselves, and the majority of World Health Organization (WHO) member states now include specific line items in their national budgets for the purchase of vaccines.[35]

Global collaborations and public-private partnerships focused on either specific pathogen-driven initiatives or broader immunization-related issues are also critical to garnering the political support, community involvement, and scientific, technical, and economic resources needed to achieve targeted disease control efforts. Coordinated efforts such as the Global Polio Eradication Initiative (GPEI),[36] the Measles/Rubella Initiative (MRI),[27] the Meningitis Vaccine Project,[37] the Maternal and Neonatal Tetanus Elimination Initiative,[38] and the GAVI Alliance[39] are examples of the global community's joint commitment to overcoming VPDs.

In 2005, the WHO and UNICEF presented the 2006–2015 GIVS to the 58th WHA as a 10-year strategic guidance document for further improving immunization access. The GIVS emphasizes making immunization programs a national priority, not only because equitable and sustainable access to immunizations saves lives, but also because immunization programs can be used as a platform for building better health delivery systems.[40]

The shared momentum for global immunization efforts continues to build, fueled in large part by the Decade of Vaccines collaboration launched in 2010. Following its endorsement by all member states at the 64th WHA, the Decade of Vaccines represents a pledge from all immunization stakeholders to commit to realizing "a world in which all individuals and communities enjoy lives free from vaccine-preventable diseases."[41]

A Global Vaccine Action Plan (GVAP) was developed by the Decade of Vaccines leadership[2] (WHO, UNICEF, the Bill & Melinda Gates Foundation, GAVI, the U.S. National Institute of Allergy and Infectious Diseases, and the African Leaders Malaria Alliance) in consultation with more than 1,100 stakeholders from more than 140 countries and 290 organizations. Approved by the 194 countries of the 65th WHA in May 2012, the GVAP

The roots of the Expanded Programme on Immunization[a]

The triumph of smallpox eradication in 1980 is often viewed as a transcendent achievement in public health. In his introduction to the book *Smallpox: The Death of a Disease*, Preston wrote, "It was one of the noblest and best things that we have ever done as a species."[b] The smallpox eradication campaign demonstrated that universal access to a vaccine was attainable and that a vaccine-preventable disease could be vanquished when global resources and political will were galvanized toward common public health goals.

Countries saw an opportunity to leverage the momentum gained by the smallpox campaign's unprecedented success to create a broader platform for delivering other life-saving vaccines and health interventions.[a] In 1974, the World Health Assembly (WHA) voted to create the Expanded Programme on Immunization (EPI).[c] The EPI resolution called on all member states "to establish and maintain immunization and surveillance programs against vaccine-preventable diseases with the goal of reducing overall morbidity and mortality."[a]

The WHA noted that success would depend on the full participation of member states in designing immunization programs that were suitable to the needs and capabilities of their countries.[c] In turn, the World Health Organization committed to collaborating with countries to provide the technical and operational support to implement programs; provide high-quality, safe vaccines; create a reliable supply system; and promote research and development activities.

Finally, UNICEF was granted responsibility for the procurement of EPI-recommended vaccines to ensure the equitable distribution of vaccines for all regions and to incorporate vaccinations into other health-care packages.[c] Later, the Pan-American Health Organization would establish the Revolving Fund to finance the purchase of vaccines and vaccine supplies for the Region of the Americas.

[a]Okwo-Bele JM, Cherian T. The Expanded Programme on Immunization: a lasting legacy of smallpox eradication. Vaccine 2011;29 Suppl 4:D74-9.

[b]Henderson DA, Preston R. Smallpox: the death of a disease. Amherst (NY): Prometheus Books; 2009.

[c]World Health Organization. The third ten years of the World Health Organization: 1968–1977. Geneva: WHO; 2008.

builds on the GIVS by evaluating the lessons learned from the first few years of GIVS implementation.[42]

The GVAP provides a roadmap for bringing the full benefits of immunizations to all people by 2020. It stresses six key principles for success: country ownership, shared responsibility and partnership, equitable access to immunizations, integration of immunizations into health systems, financial sustainability, and innovation.[43]

Overcoming key challenges to global immunization programs

Numerous challenges can weaken routine immunization systems. Difficult-to-reach populations may face barriers to providing equitable access to immunization services, leading to a range in coverage rates between and within countries. Mass vaccination campaigns following outbreaks can greatly stress limited resources, such as the number of available trained health-care workers needed to carry out routine programs. Moreover, poor program management can create difficulties in monitoring and evaluating programs, thereby further complicating planning efforts.[44,45]

Countries with weak routine systems can face further challenges when trying to incorporate new or underutilized vaccines into their programs. Insufficient surveillance capabilities may underestimate the disease burden within a region, leading decision makers to question the need for or cost effectiveness of a new vaccine, resulting in unnecessarily prolonged delays in introduction.[46] Some countries may need additional technical and financial support to accommodate additional vaccines into their immunization programs to overcome barriers such as cost or a lack of logistical capacity to safely deliver vaccines, including a reliable cold chain, a vaccine safety monitoring system, and a trained workforce.[47]

GAVI was formed in 2000 as a mechanism to address resource constraints for vaccine financing and systems strengthening in the poorest countries. GAVI represents a global partnership between a diverse representation of public and private entities whose combined resources provide financial support to eligible low-income countries. GAVI's mission is to save children's lives and improve people's health by increasing access to immunization in poor countries. GAVI has four strategic goals: (*1*) accelerating the uptake and use of new and underutilized vaccines, (*2*) contributing to strengthening the capacity of integrated health systems to deliver immunization, (*3*) increasing the predictability of global and national financing, and (*4*) shaping vaccine markets.[39]

Eligible countries are required to have a per-capita gross national income (GNI) of ≤$1,550 and must demonstrate that they are able to achieve at least 70% coverage for three doses of the DTP vaccine prior to

Innovations in immunization financing: vaccine bonds and advance market commitments

Support from the GAVI Alliance (GAVI) comes from a number of funding mechanisms, including direct donor support, monies from the sale of vaccine bonds through the International Finance Facility for Immunization (IFFIm), and advanced market commitments from donors. The IFFIm functions by issuing bonds from legally binding, long-term donor pledges, which are sold on the international capital markets. Proceeds from the sale of these bonds become a cash resource available immediately to fund GAVI activities.[a]

Advanced market commitments establish a guaranteed market for vaccines tailored to meet the specific public health needs of developing countries.[b] Donor pledges establish a fixed price for a vaccine once it has been developed and manufactured. Once donor commitments are spent, companies are obligated to offer accessible vaccine pricing, helping introduce new vaccines in resource-poor countries.

[a]GAVI Alliance. GAVI Alliance progress report 2011. Geneva: GAVI Alliance; 2011.

[b]World Health Organization, UNICEF, World Bank. State of the world's vaccines and immunization. 3rd ed. Geneva: WHO; 2009.

the introduction of new vaccines.[39] Financial support is based on a sliding scale, and countries are expected to bear increasing shares of the vaccine costs as their GNI per capita increases, allowing for a sustainable and fair funding mechanism. Co-financing reinforces a country's ownership of immunization programs and upholds a country's commitment to prioritize immunizations as an essential component of its broader health delivery services. In addition, countries must submit a costed, comprehensive, multiyear plan for immunization to ensure that their programs are sustainable.[35]

Currently, more than 26 donors (including government, nonprofit, and private contributions) have jointly pledged more than $7 billion to GAVI from 2011 to 2015 (Figure 1) to help low-income countries better provide immunization services to all people. Activities funded by GAVI are estimated to have expanded immunization access to more than 325 million children.[48] However, middle-income countries and those that do not qualify for GAVI support still face financial barriers to introducing new vaccines as they become available.[20]

The U.S. commitment to global immunization efforts

Even in the current economic climate, most people in the U.S. support maintaining or increasing U.S. funding for global immunization programs and global health. In 2012, the Kaiser Family Foundation reported on a survey that assessed the public opinion of the U.S.'s role in improving the health of people in developing countries. A striking 58% of participants stated that improving children's health, including through vaccinations, should be a top priority for U.S. assistance in developing countries. An additional 28% stated that it should be considered important but not a top priority.[49]

The U.S. support for global immunization programs is reflected in the USG's financial commitments during the last decade. In the 10-year period spanning 2001–2011, the U.S. financial contributions to GAVI totaled $736 million, made through USAID, exclusively for vaccine procurement. In recent years, the USG has shown a strong commitment to global health initiatives, including disease-specific goals such as worldwide polio eradication. During fiscal years 2009 through 2012, the U.S. contributed a total of $541.3 million toward polio eradication (Table 2) and funded $192.0 million for work to control other VPDs, including measles.[50–55] Additionally, these numbers do not reflect the resources dedicated to providing technical assistance, vaccine research and development (R&D) efforts, and other activities that benefit global populations by creating and enhancing access to vaccines.

Global health and the role of HHS

The USG is committed to creating a safer and healthier world by reducing the global burden of VPDs, improving equitable access to health-care services for all people, and achieving health security and health diplomacy through international collaborations. A number of U.S. agencies including HHS, USAID, DoD, and the State Department provide specific support for these objectives through pro-vaccination policies, programmatic activities, collaborations, and financial assistance. Although the specific global health mandates of each agency may differ, their collective actions bolster the capabilities of the entire global immunization enterprise.

Global health prevention and disease control, particularly through safe and effective vaccination, are stated priority goals of HHS, as evidenced in both the HHS Global Health Strategy and the 2010 NVP.[4,5,56] The HHS Global Health Strategy underscores the role of HHS as a leader in global health and highlights HHS's commitment to a more systematic approach

Figure 1. GAVI Alliance donors' contributed or pledged funding, 2011–2015

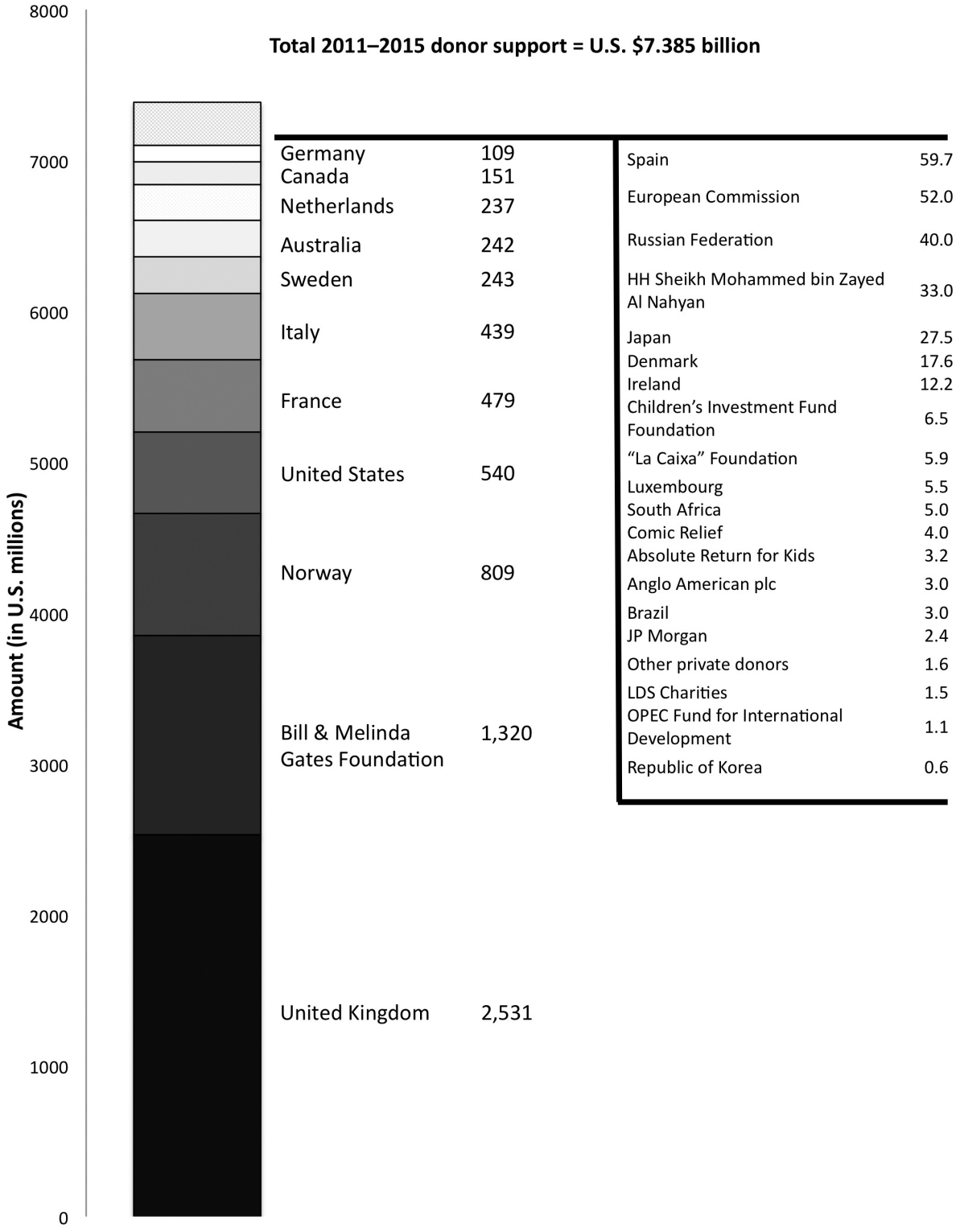


Table 2. U.S. government contributions to global polio eradication efforts, 2009–2012

Year	*U.S. Agency for International Development*	*Economic support fund account (State Department)*	*U.S. Centers for Disease Control and Prevention, Department of Health and Human Services*	*Total*
2009	$20.7 million	NA	$101.5 million	$133.5 million
2010	$29.0 million	$3.0 million	$101.8 million	$136.1 million
2011	$32.9 million	NA	$101.6 million	$133.9 million
2012	$35.0 million	$4.5 million	$111.3 million	$150.9 million
Total	$131.6 million	$6.5 million	$416.2 million	$554.4 million

NA = not available

to global health issues. The Strategy's 10 objectives describe a spectrum of health capacity-building efforts that directly impact global immunization efforts. The 2010 NVP, put forth by the HHS National Vaccine Program Office (NVPO), outlines a 10-year strategic vision for coordinating national immunization efforts both within and outside of the federal government. The NVP specifically highlights "supporting the global introduction and availability of new and underutilized vaccines to prevent diseases of public health importance" as a priority for implementation to create an "umbrella of protection" for public health within the U.S.[5]

HHS consists of 11 agencies and 18 staff offices that serve to protect the well-being of people within the U.S. and abroad by supporting advances in science, medicine, public health, and the delivery of social services. This support includes global initiatives as well as the establishment of national objectives to raise the standards for global public health. In particular, agencies and offices under HHS, including CDC, the National Institutes of Health (NIH), the U.S. Food and Drug Administration (FDA), the NVPO, and the Office of Global Affairs (OGA), demonstrate core competencies that will be necessary to realize the full benefits of the Decade of Vaccines. These activities include, but are not limited to, expanding scientific research capacity, forwarding innovations in vaccine development, manufacturing and licensure, optimizing disease control efforts, building public demand for vaccines, and establishing a strong evidence base to support the decision-making process regarding the introduction of new vaccines.

NVAC ANALYSIS AND RECOMMENDATIONS

The NVAC recognizes that the HHS activities described throughout this report are critical to achieving national and global goals for strengthening immunization programs and reducing morbidity and mortality due to VPDs. Building political and public support around these activities will be necessary to ensure that these efforts will continue to move the global immunization agenda forward. This effort includes continued financial investments in a range of activities associated with global immunizations. As the ASH's charge to the NVAC was to focus on HHS activities, this analysis concentrates on those activities and is not intended to represent a comprehensive description of all USG efforts.

NVAC RECOMMENDATION 1: TACKLING TIME-LIMITED OPPORTUNITIES TO COMPLETE POLIO ERADICATION AND TO ADVANCE MEASLES MORTALITY REDUCTION AND REGIONAL MEASLES/RUBELLA ELIMINATION GOALS

NVAC recommendation 1.1: completing global goals for polio eradication and advancing global measles mortality reduction goals

The ASH should lead efforts to coordinate briefings, public events, and educational outreach to policy makers, legislators, and the general public, in coordination with other U.S. agencies, multilateral partners, and nongovernmental organizations (NGOs), to communicate the urgency of completing global goals for polio eradication and advancing global measles mortality reduction goals and regional goals for measles/rubella elimination.

1.1.1. The ASH should emphasize that polio eradication efforts and measles mortality reduction and regional elimination efforts should complement and strengthen routine immunization systems.

1.1.2. The ASH should emphasize that failure to complete polio eradication goals or to advance goals for measles mortality reduction and regional goals for measles/rubella elimination may threaten the health of U.S. populations due to importations of these diseases from endemic areas.

1.1.3. The ASH should emphasize that political and public support is fundamental to achieving polio eradication and advancing global goals for measles mortality reduction and regional goals for measles/rubella elimination. Achieving these goals would equal a monumental public health and humanitarian accomplishment for the entire global community and, if done appropriately, will

potentially strengthen support for routine immunization goals.

As the arm of HHS dedicated to operationalizing disease prevention and control strategies, CDC has provided unparalleled scientific and technical leadership in combating VPDs within the U.S. and worldwide. CDC has been, and continues to be, a pivotal player in a number of disease elimination and eradication efforts, including the Smallpox Eradication Campaign, the GPEI, the MRI, and the Maternal and Neonatal Tetanus Elimination Initiative.

In 2010, global immunization initiatives, including polio eradication, were declared one of CDC's 10 "winnable battles" as a way to spotlight the issues and draw up greater support from partner organizations and public leaders. Winnable battles represent public health priorities that have a large-scale impact on health with known, effective strategies for addressing them.[57] As part of the battle plan for achieving global immunization goals, CDC's 2011–2015 Global Immunization Strategic Framework describes six overarching goals that harmonize CDC activities with international immunization priorities. The framework ensures progress toward these goals by setting metrics on specific objectives to be tracked over time.[56] Included in these objectives are 2015 targets to certify polio eradication and to reduce estimated global measles mortality by 95% or more compared with 2000 levels. The Decade of Vaccines GVAP states that measures of success for the Decade of Vaccines initiative will include achieving certification of global polio eradication and measles/rubella elimination in at least five WHO regions by 2020.[43]

These goals are achievable. In fact, the world is closer than ever before to realizing these goals. However, despite the impressive progress that has been made on both of these fronts, the headway gained during the past three decades toward polio eradication and measles mortality reduction are fragile. As long as these diseases persist, all countries will remain vulnerable to resurgence, and disrupting the transmission of the disease will require ongoing global action. Every new birth cohort introduces susceptible individuals into the population, and weakening of efforts to sustain high vaccine coverage levels throughout a population will result in outbreaks, threatening regions that have already made significant progress against these diseases.[35,58] For example, measles transmission can be maintained even when >90% of the population is protected.[59]

The GPEI. In the 1980s, an estimated 350,000 cases of paralytic polio occurred annually in 125 endemic countries around the world.[60] More than 200,000 of these cases occurred in India, translating to approximately one case every three minutes.[61,62] In 1988, the WHA unveiled a vision for polio eradication with a target date of 2000, prompting the creation of the GPEI, a public-private partnership launched by the WHO, Rotary International, UNICEF, and CDC and led by national governments.[60] By 2002, the efforts of the GPEI had reduced the global incidence of polio worldwide by 99%, and only seven countries remained endemic.[63,64] Polio had been eliminated in the Americas (1994), the Western Pacific (2000), and Europe (2002).[62] However, momentum was difficult to sustain over time, and the prolonged eradication efforts began to exhaust the public health community.

From 2001 to 2011, the reduction in polio cases plateaued.[65,66] Barriers in the remaining endemic countries—including weak immunization programs, poor management and accountability, suboptimal quality of implementation strategies, misconceptions about vaccine safety (resulting in a widespread loss of public demand for vaccination), political turmoil, and armed conflict—caused significant gaps in vaccine coverage and, in some cases, complete disruption of polio campaign activities.[67–74] This disruption led to exportation of polio cases from endemic countries

Public support of global immunizations programs: access to vaccines saves lives

The global vaccination effort ultimately depends on millions of families around the world demanding access to immunizations to protect their children from disease. In China, an outbreak of polio in 2011 prompted the swift vaccination of 4.5 million children and young adults in the span of only five weeks.[a] When parents in clinics were asked why they went through so much effort and walked so far to get to the clinics, a mother responded:

> "You are a mother. How could you look your child in the eyes if you are not giving them the best chance to be healthy and avoid being sick with a virus that causes our children to be disfigured and limp? We cannot do that to our families."[a]

[a]Venczel L. Snapshot: vaccinating children in China. 2012 [cited 2012 Aug 6]. Available from: URL: http://www.impatientoptimists.org/Posts/2012/05/Snapshot-Vaccinating-Children-in-China?p=1

into polio-free countries, causing 59 polio outbreaks in 39 countries that were previously deemed polio-free during the past decade.[65]

In 2002, countries in the European region began to experience complacency in maintaining high vaccination coverage rates. The national polio vaccination coverage rates in the country of Tajikistan fell from 86% in 2000 to 76% in 2006.[75] As a consequence, in 2010, an imported case of wild polio virus (WPV) from India led to 458 cases of laboratory-confirmed polio in Tajikistan. Factors leading to the rapid spread of the virus included poor vaccine coverage, inadequate surveillance, and a resource-limited health system. Subsequent importations from Tajikistan spread the virus to three other polio-free countries including Russia, Turkmenistan, and Kazakhstan. In total, the outbreak resulted in 476 confirmed cases and 26 deaths.[76] Supplemental immunization activities (SIAs) were conducted in all affected countries and the outbreak in the region was contained within six months.

In four countries in the African region (Angola, Chad, Dominican Republic of Congo, and Sudan), imported polio outbreaks led to reestablished transmission, defined as previously polio-free countries in which reintroduction of poliovirus led to sustained transmission lasting >12 months. The consequences were significant: more than 1,500 children were left paralyzed, and outbreak response efforts cost the global community more than U.S. $500 million.[64]

The spread of polioviruses and the reestablishment of polio transmission in countries that had been deemed polio-free serve as a cautionary tale for what can happen when polio is not eradicated from all countries. The risk of exportation of polioviruses from endemic countries has elicited calls for substantially enhancing current efforts and strategies from some, including the GPEI Independent Monitoring Board, which recommends that WHO member states require those traveling from a polio-endemic country to other countries to present certified documentation of vaccination to reduce the spread to polio-free countries. Their report states that "no country should allow a citizen from any endemic polio state to cross their border without a valid vaccination certificate," underscoring the significance of this threat to eradication goals.[77] In alignment with this statement, the WHO's 2012 edition of International Travel and Health recommends the full polio vaccination of travelers and indicates that some polio-free countries already require travelers from countries or areas reporting WPVs to show certification that they have been immunized against polio to obtain an entry visa.[78]

Although earlier goals to interrupt WPV transmission by 2012[79] were not met, there has been substantial progress in the past few years. Polio cases have dropped from 1,352 cases in 2010 to 223 cases in 2012.[36] Circulation of naturally occurring WPV type 2 has not been documented since 1999, and, as of July 2013, no cases of WPV type 3 had been recorded for 2013. The GPEI estimates that it has administered more than 10 billion doses of oral polio vaccine (OPV) to 2.5 billion children worldwide, preventing more than 10 million cases of paralytic polio.[80]

As the number of polio cases dwindles, countries will need to maintain high-quality surveillance efforts for the rapid detection and investigation of all acute onset flaccid paralysis cases. Moreover, environmental sampling and virologic characterization of stool samples will be important for detecting ongoing silent (i.e., asymptomatic or non-paralytic) transmission of polioviruses in communities. Laboratory networks will also need to be able to recognize and diagnose polio cases caused by circulating vaccine-derived polioviruses (cVDPV, vaccine viruses that, through transmission and mutation, have acquired the neurovirulence characteristics of WPVs) from continued use of live-attenuated OPV. Importations of cVDPVs can also threaten polio-free communities where lower vaccination coverage is no longer at levels high enough to ensure herd immunity.[81–83] To this end, experts now support the administration of at least one dose of the inactivated poliovirus vaccine (IPV) and the transition from the use of trivalent OPV (containing poliovirus types 1, 2, and 3) to bivalent OPV (containing poliovirus types 1 and 3) to mitigate the risk of continued cVDPV type 2 circulation.[84]

To guide accelerated efforts to achieve polio eradication, CDC activated its Emergency Operations Center (EOC) on December 2, 2011, to respond to polio eradication as a global public health emergency. This activation has allowed CDC to scale up partnership efforts, including expanding technical assistance for vaccination and surveillance activities, improving program management and accountability, and strengthening immunization infrastructure to support the polio response. Since its activation, more than 400 CDC personnel, both within the EOC and in the field, have contributed to the analysis, validation, and exchange of critical information to increase the program's situational awareness and enhance program support.[85] Similarly, the WHO's executive board declared polio eradication efforts a global programmatic emergency in January 2012, followed by the release of the 2012–2013 Global Polio Emergency Action Plan, which outlined specific efforts focused on overcoming the significant challenges posed by

the last three endemic countries: Nigeria, Pakistan, and Afghanistan.[86]

In April 2013, the GPEI introduced the 2013–2018 Polio Eradication and Endgame Strategy (hereafter, Endgame Strategy) at the 2013 Global Vaccine Summit in Abu Dhabi, Dubai. Building off the momentum gained from the country-specific activities implemented in the 2012–2013 Emergency Action Plan, the Endgame Strategy was developed by the GPEI through extensive consultation with a number of stakeholders, including the national health authorities in countries most affected by poliomyelitis.

As it states, the Endgame Strategy "…accounts for the parallel pursuit of wild poliovirus eradication and cVDPV elimination, while planning for the backbone of the polio efforts to be used for delivering other health services to the world's most vulnerable children."[80] It advocates that strong, reliable routine immunization systems will be central to the GPEI's success and that sustaining routine systems will continue to benefit from GPEI investments long after polio eradication has been achieved. Furthermore, the Endgame Strategy includes a comprehensive cost analysis for completing the objectives within the strategy, the responsible parties for ensuring oversight of goals and activities, a description of possible risks to completing goals and milestones, steps that will be taken to mitigate those risks, and a set of contingency options to minimize potential roadblocks.[80,87]

The Endgame Strategy includes a comprehensive description of the GPEI's four objectives for achieving polio eradication within the six-year 2013–2018 time frame and provides a new strategic focus based on the evaluation of previous program weaknesses and lessons learned.[80] Major milestones outlined in the Endgame Strategy include (*1*) stopping all WPV transmission by the end of 2014 and stopping new outbreaks of cVDPV outbreaks within 120 days of an index case, (*2*) achieving at least a 10% year-on-year increase in DTP3 coverage in the worst performing districts in focus countries from 2014 to demonstrate routine immunization system-strengthening activities, (*3*) introducing at least one dose of IPV in all OPV-using countries in 2015 and withdrawing OPV-2 globally in 2016, (*4*) establishing a comprehensive legacy plan by the end of 2015, and (*5*) certifying eradication and containing all facility-based WPVs by the end of 2018[80] (Figure 2).

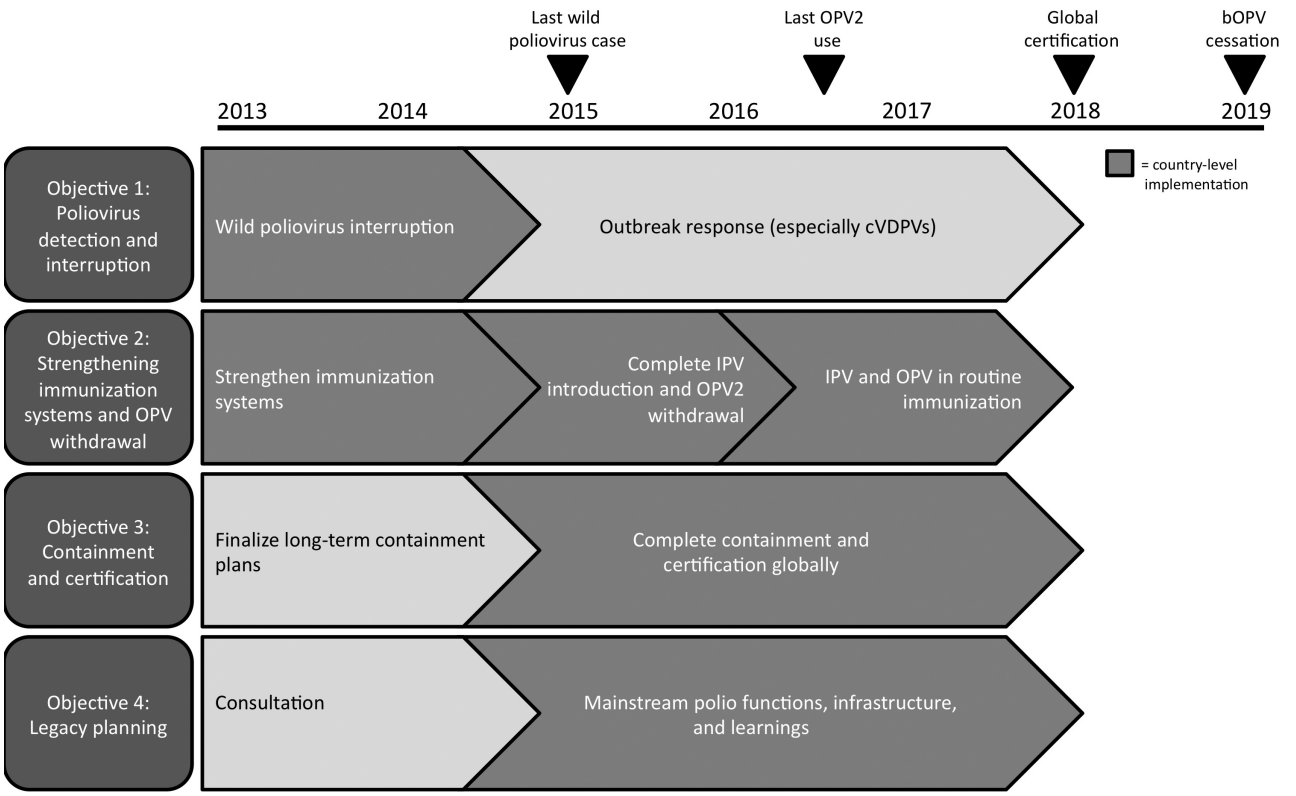
The Endgame Strategy outlines a parallel approach to eradicate WPV while simultaneously pursuing strategies to eliminate all cases of cVDPV by asking countries to include administration of at least one dose of IPV into their routine immunization programs by 2015 in preparation for the withdrawal of trivalent OPV and the switch to bivalent OPV.[84] However, the use of IPV-containing vaccines is considered cost-prohibitive for many countries, and efforts to increase the affordability and availability of IPV and IPV-containing combination vaccines are ongoing.[88] These efforts include, but are not limited to, developing intradermally administered IPV, adjuvant-containing IPV, and other antigen-sparing strategies to support the routine use of IPV that requires fewer overall doses of vaccine.[89] Investments in R&D efforts will continue to be essential for developing new tools to help the global community complete polio eradication and ensure ongoing protection against accidental or intentional reintroduction of the virus post-eradication.

Delivery of IPV will also require a continuing global commitment to bolstering immunization systems more holistically. Polio-endemic countries and other countries at increased risk of polio reintroduction correlate with regions that persistently report high numbers of un- and under-vaccinated children.[7] Weak immunization systems pose an ongoing barrier to completing polio eradication goals. To address these challenges, the Endgame Strategy indicates that activities to strengthen the overall immunization systems will be given the same importance and urgency as campaign activities. In support of this effort, the GPEI will devote at least 50% of polio-funded personnel's time to activities that have a measurable impact on strengthening immunization systems and health services. Moreover, legacy planning (objective 4) will include the development of a framework to ensure that the capabilities and infrastructure created by the GPEI will serve as a platform to continue to build and strengthen global immunization systems as a whole (including trained public health workers, surveillance and laboratory capacity, response and containment functions, and tools for immunization program planning and monitoring).[80]

Finally, expert scientific and technical assistance is required to ensure that the polio Endgame Strategy fulfills the promise of stamping out polio forever. In April 2013, more than 450 scientific and technical experts from more than 80 countries signed a scientific declaration on polio eradication voicing their "conviction that the eradication of polio is an urgent and achievable global health priority."[90] The scientific declaration endorses the Endgame Strategy and urges all stakeholders to commit the financial and programmatic efforts required to complete the goals outlined in the Endgame Strategy.[91]

Risks to completing polio eradication. One of the greatest obstacles against completion of the polio eradication goals is insufficient funding to conduct immunization

Figure 2. Parallel global objectives, as described in the Polio Eradication and Endgame Strategic Plan 2013–2018,[a] with target dates for the completion of stated objectives



[a]Global Polio Eradication Initiative. Polio eradication and endgame strategic plan 2013–2018. Geneva: World Health Organization; 2013.

OPV2 = wild polio virus Type2-containing oral polio vaccine

bOPV = bivalent oral polio vaccine

cVDPV = circulating vaccine-derived polio virus

IPV = inactivated polio vaccine

OPV = oral polio vaccine

campaigns and program activities. The GPEI estimates that the 2013–2018 Endgame Strategy will require a total budget of $5.5 billion, with costs peaking at $1 billion in 2013 and declining annually to U.S. $760 million in 2018 (Figure 3[87]). Currently, the GPEI faces a 2013–2018 budget shortfall of $2 billion necessary for continuing critical SIAs and efforts to strengthen existing vaccination programs. This shortfall assumes that donors are able to maintain their current levels of $3.1 billion.[87,92,93]

The majority of the projected GPEI budget is dedicated to immunization activities, both OPV campaigns, and incorporating IPV into routine immunization systems. The breakdown of these costs is detailed in the Endgame Strategy companion document "Key Elements of the Financial Resource Requirements 2013–2018."[87]

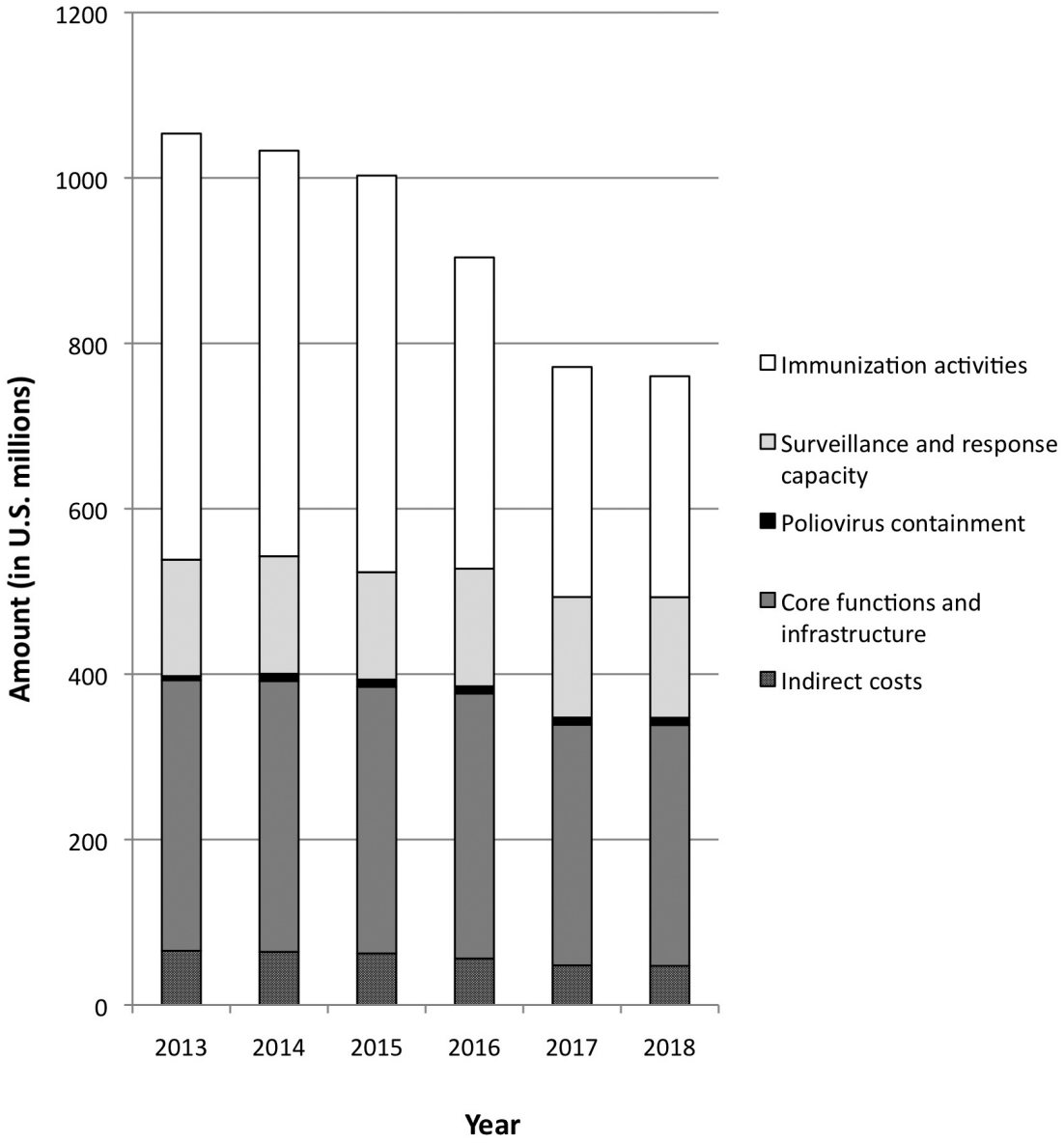
Budget shortfalls in 2012 led to the cancellation and scaling back of polio campaign activities in 24 high-risk polio-free countries.[86] Analysis conducted by Thompson and Tebbens indicated that if GPEI efforts are abandoned and countries with high risk factors resort to low polio control efforts due to perceived cost savings, the number of polio cases could undergo a resurgence, resulting in 3 million polio cases during a 20-year time frame (or 200,000 cases per year). The polio immunizations, as defined in the report by Thompson and Tebbens, are those immunizations given solely as part of routine systems with no additional funding for SIAs, outbreak response, or active surveillance for acute flaccid paralysis.[94]

On May 27, 2013, the WHA endorsed the new 2013–2018 Polio Eradication and Endgame Strategic Plan[80] and urged for its full implementation and financing.

Delegates acknowledged the progress achieved in the past year to reduce polio incidence to historical lows, thanks to the actions of member states that prioritized program activities by placing polio eradication on an emergency footing.

The Measles/Rubella Initiative (MRI). In 2000, the number of reported measles cases worldwide was estimated to be greater than 850,000, and an estimated 542,000 deaths were reported for that year,[11] ranking measles the 19th leading cause of death worldwide. The Measles Initiative was founded in 2001 as a partnership among the WHO, UNICEF, CDC, the American Red Cross, and the United Nations Foundation (UNF) to work with national governments, global and regional leaders, and donor organizations to financially and technically support accelerated measles control activities.[95] That same year, the Measles Initiative partnered with 19 African countries to implement measles control strategies. Within two years, the Measles Initiative had successfully

Figure 3. The budget needed to achieve the objectives of the GPEI Eradication and Endgame Strategy (2013–2018),[a] by funding category



[a]Global Polio Eradication Initiative. Financial resource requirements 2013–2018. Geneva: World Health Organization; 2013.

GPEI = Global Polio Eradication Initiative

vaccinated more than 82.1 million children and had reduced the number of measles-related deaths in the African region by 20%.[96] By 2010, the Measles Initiative had invested $875 million in donor funds for measles control activities that have supported the vaccination of more than one billion children in more than 80 countries.[95] Moreover, accelerated measles control efforts have led to a decrease in measles-related deaths by 71% from 2000 to 2011.[11]

Congenital rubella syndrome (CRS) is one of the leading causes of preventable congenital birth defects worldwide. Similar to measles, rubella is also transmitted via the respiratory route, and infection results in fever and an erythematous rash.[97] As measles cases began to decline, measles surveillance systems revealed that the incidence of rubella and CRS was significant in many populations and that testing for both diseases was necessary for accurate surveillance. In 2003, WHO established the Measles and Rubella Laboratory Network to strengthen capabilities for rubella and CRS case identification and confirmation.[98] The incorporation of rubella/CRS into measles surveillance systems and expanded use of rubella-containing measles vaccines in a number of countries[99] provided an opportunity for the Measles Initiative to broaden its mission and include regional rubella elimination goals as part of its measles control and elimination efforts. Now called the Measles/Rubella Initiative (MRI), the initiative's strategy incorporates goals for achieving and maintaining the elimination of both measles and rubella.[27]

As of September 13, 2013, all six WHO regions had committed to regional measles elimination goals by 2020. In 2010, the WHA endorsed interim goals proposed by the WHO that, by 2015, all member states should achieve 90% coverage with at least one dose of measles vaccine at the national level (80% coverage in all districts) and a 95% reduction in mortality rates from 2000 levels.[100] The Decade of Vaccines GVAP also endorses global goals that measles and rubella regional elimination goals will be achieved in at least five WHO regions by 2020.[43] Moreover, the MRI released an eight-year (2012–2020) Global Measles and Rubella Strategic

The use of supplemental immunization activities to help achieve measles elimination in the Americas

In countries with high disease incidence and low vaccination rates, supplementary immunization activities (SIAs) may be necessary. SIAs include implementing mass vaccination campaigns that effectively target a wide age range of children, irrelevant of vaccination status, to rapidly achieve immunity in a population.[a] SIAs have been successful in reducing vaccine-preventable diseases in a number of countries and World Health Organization (WHO) regions and have been useful in strengthening the capacity of immunization programs.[b–e]

In 1994, the Pan American Health Organization (PAHO) adopted a strategy toward measles elimination that included a three-phase approach: a "catch-up phase," a "keep-up phase," and a "follow-up phase." The catch-up phase involved vaccinating all children aged 9 months to 14 years regardless of vaccination status to rapidly achieve high immunization coverage in the population. This phase was then followed by a keep-up phase to reach susceptible infants through routine immunization services, with the goal of achieving >90% vaccine coverage for each new birth cohort. Strategically implemented follow-up campaigns were used to vaccinate all 1- to 4-year-old children regardless of vaccination status to close any gaps in immunization.[f] By 1996, measles incidence in the Americas had been reduced by 99% vs. 1990 levels,[g] and the WHO adopted the strategy implemented by PAHO leadership into its recommendations.[h] In 2003, the Americas succeeded in eliminating endemic measles transmission throughout the region.[g]

[a]Hall R, Jolley D. International measles incidence and immunization coverage. J Infect Dis 2011;204 Suppl 1:S158-63.

[b]Otten M, Kezaala R, Fall A, Masresha B, Martin R, Cairns L, et al. Public-health impact of accelerated measles control in the WHO African Region 2000–03. Lancet 2005;366:832-9.

[c]Khetsuriani N, Deshevoi S, Goel A, Spika J, Martin R, Emiroglu N. Supplementary immunization activities to achieve measles elimination: experience of the European Region. J Infect Dis 2011;204 Suppl 1:S343-52.

[d]Koehlmoos TP, Uddin J, Sarma H. Impact of measles eradication activities on routine immunization services and health systems in Bangladesh. J Infect Dis 2011;204 Suppl 1:S90-7.

[e]Ma C, An Z, Hao L, Cairns KL, Zhang Y, Ma J, et al. Progress toward measles elimination in the People's Republic of China, 2000–2009. J Infect Dis 2011;204 Suppl 1:S447-54.

[f]De Quadros CA, Olivé JM, Hersh BS, Strassburg MA, Henderson DA, Brandling-Bennett D, et al. Measles elimination in the Americas. Evolving strategies. JAMA 1996;275:224-9.

[g]De Quadros CA, Andrus JK, Danovaro-Holliday MC, Castillo-Solórzano C. Feasibility of global measles eradication after interruption of transmission in the Americas. Expert Rev Vaccines 2008;7:355-62.

[h]Measles eradication: recommendations from a meeting cosponsored by the World Health Organization, the Pan American Health Organization, and CDC. MMWR Recomm Rep 1997;46(RR-11):1-20.

Plan that focuses support on 67 priority countries based on the level of their routine vaccination coverage for measles and status of introduction of rubella vaccine.[27] GAVI has enhanced the impact of this support by creating a funding window for eligible countries to introduce rubella-containing measles vaccines into their national programs.

Although worldwide measles vaccine coverage has increased from 16% in 1980 to 84% in 2011, regions in Africa and Southeast Asia continue to report <79% coverage.[7,101] Countries with a high burden of disease that are in most need of accelerated measles control efforts are deemed priority countries. In 2008, these countries accounted for 98% of measles-related deaths.[102]

Since 2007, donor investments in the MRI have decreased by 55% and a U.S. $10 million funding gap has led to the postponement of vaccine campaigns and campaign activities.[103] Decreasing support for global immunization programs could jeopardize the momentum gained from the accomplishments of the measles efforts. Furthermore, priority countries have not been able to raise the funds needed to support SIAs.[104] As a consequence, in 2009, Africa reported a drastic resurgence of >200,000 measles cases and >1,400 deaths in 28 sub-Saharan countries.[103]

Goals to reduce the global burden of measles cases are further complicated by public skepticism regarding the safety of measles vaccine, resulting in persistent suboptimal vaccination coverage in many European countries. In 2011, more than 30,000 measles cases and seven deaths were reported from 29 countries in Europe.[105] Almost all of the cases occurred in unvaccinated individuals or in those whose vaccination status was unknown, despite the region's full adoption of the WHO recommendations.[106,107]

However, decrease in public demand is not restricted to developed countries, and attitudes about vaccination have created challenges worldwide.[108–110] Concerted global efforts will need to enhance communication strategies regarding misconceptions about vaccines, concerns regarding vaccine safety, a lack of understanding of the seriousness of VPDs, skepticism regarding the benefits of vaccination, and religious/philosophical objections to vaccination.[106,108,109] These efforts will not only ensure continued success with measles/rubella elimination efforts, but will also increase demand for greater global immunizations as a whole.

NVAC recommendation 1.2: sustaining efforts for polio eradication and measles mortality reduction

The ASH should strongly encourage the HHS Secretary to seek additional funding to facilitate the achievement of unique, time-limited opportunities to complete global goals for polio eradication and to support measles mortality reduction and regional goals for measles/rubella elimination. The ASH should advocate to the HHS Secretary that completion of these goals will yield significant economic and public health returns on investments and shed new light on the value of vaccines and immunization and the potential for future cost savings.

The continued march toward success for both the GPEI and the MRI are made possible through the contributions and tireless efforts of their partners in the public and private sectors. Partnerships provide opportunities to combine resources and create new synergies between programs and organizations. CDC helped spearhead both initiatives and remains a global leader, working with multilateral organizations, Ministries of Health, and others such as Rotary International, the International Federation of Red Cross and Red Crescent Societies, the Bill & Melinda Gates Foundation, and the UNF. These partnerships are critical to achieve both the objectives of polio eradication and measles mortality reduction, as well as broader international objectives for reducing morbidity and mortality due to VPDs.

The NVAC specifically highlighted polio eradication and measles mortality reduction efforts because they represent time-limited opportunities that require focused political and public support if the goals are to be accomplished by the 2015–2020 target dates. Moreover, HHS continues to play a pivotal role in driving these efforts toward completion through the epidemiologic, laboratory, and programmatic support that CDC provides to its partners and fellow USG agencies.

HHS funding for polio eradication and measles mortality reduction activities. CDC includes global immunization activities as a line item in its annual appropriations request to Congress (Table 3).[52–55] The majority of this

Table 3. Centers for Disease Control and Prevention appropriations for global polio, global measles, and other VPDs, 2009–2012

Year	Polio	Global measles and other VPDs
2009	$101.5 million	$41.8 million
2010	$101.8 million	$51.9 million
2011	$101.6 million	$49.3 million
2012	$111.3 million	$49.0 million
Total	$416.2 million	$192.0 million

VPD = vaccine-preventable disease

funding is allocated toward activities that support polio eradication and the control of measles and other VPDs within the global context. As a measure of efficiency, the program targets 90% of the annual global immunizations budget to directly support mission-critical activities in the field through cooperative agreements with WHO, UNICEF, the Pan-American Health Organization (PAHO), UNF, and other USG agencies such as USAID and the State Department.

Working through UNICEF, CDC contributed to the procurement of about 289 million doses of OPV in 2009. However, in 2010, CDC funding for OPV was not sufficient to meet all country needs, and the purchase of additional doses of OPV resulted in the reduction of available funds for other non-vaccine-related support (e.g., operational costs) of SIAs. Cooperative agreements with UNICEF are also in place for the procurement of MR vaccines.

Both polio eradication and global measles elimination efforts will fail if funding needs are not addressed. The spread of WPV into previously polio-free countries is speculated to be related to acute funding gaps that occurred in 2002, leading to canceled campaigns and scaled-back activities in Western and Central Africa.[64] The 2012–2013 shortfall in GPEI funding led to reduced or canceled polio campaign activities in 24 high-risk countries in 2012. Similarly, African countries saw an increase in 2009 in measles outbreaks when countries were unable to fund needed SIAs.[104]

Although the funding gap cited for both the GPEI and the MRI are not solely a U.S. responsibility, increased funding for U.S. efforts does directly affect the quality and reach of these initiatives. In 2010, due to the necessary purchase of additional OPV, CDC was required to reduce operational support of supplemental polio vaccination campaign activities. While CDC maintained support to vaccinate 29.5 million children, this number was well below its target to vaccinate 45 million children.

NVAC recommendations 1.3 and 1.4: enhancing CDC technical assistance for reaching polio eradication and measles mortality reduction goals

1.3. The ASH should encourage CDC to continue to enhance the public health impact of its Stop Transmission of Polio (STOP) Program by increasing the number and length of training opportunities. STOP Team assignments should focus on building broad subject-matter expertise that can be applied to polio and measles efforts, as well as strengthen routine immunization systems and disease surveillance.

1.4. The ASH should work with CDC to create opportunities to bring together stakeholders and leadership from the GPEI and the MRI to (*1*) discuss lessons learned and best practices and (*2*) consider opportunities for joint programming that lead to program efficiencies and improve the delivery of vaccines using routine systems. As a leading partner in both of these initiatives, CDC should work to capture and review these findings to inform current programming, the introduction of new vaccines, and other global public health efforts.

In addition to financial support, CDC also provides staffing support and human resources to the WHO, UNICEF, USAID, and other HHS partners. CDC technical experts conduct evaluations and risk assessments for improved GPEI and MRI activities within countries. CDC field staff conduct research studies in epidemiology, vaccine efficacy, and disease prevention and control feasibility that have contributed to operational changes to improve the impact and reach of immunization programs.

CDC also serves as a WHO global specialized reference laboratory for polio (and other picornaviruses) and for measles and rubella. Both CDC and WHO provide renowned expertise in virologic surveillance, virus characterization, quality assurance/quality control, and serological and specimen testing. They provide technical support and guidance for all global laboratory networks for rapid outbreak identification and response. In 2009, CDC's Polio and Picornavirus Laboratory supported the introduction of new laboratory procedures that reduced the time to detect and confirm polio infections by 50%. The CDC Measles/Rubella Laboratory facilitates measles and rubella outbreak control efforts at the national, regional, and global levels to investigate and contain the spread of measles and rubella infections both within the U.S. and abroad. These laboratory capabilities are significant, as many countries continue to lack access to certification quality surveillance for polio eradication or measles/rubella elimination.

In addition to surveillance and data collection, CDC-trained staff assist countries in planning, monitoring, and managing polio eradication and measles mortality reduction efforts within the scope of their national immunization plans. CDC assistance has included targeted operational support for disease control and eradication in high-risk countries. For example, CDC is currently contributing to efforts to support Nigeria's Polio Eradication Emergency Response Plan by improving program leadership and management. However, increasing travel and administrative costs has reduced the overall number of technical assistance days CDC staff are able to provide. Currently, 31 CDC immunization field staff members are detailed overseas. This

number is not sufficient to meet the programmatic demands of the polio eradication efforts. Additional field staff details are required.

The STOP Program. To help meet the increasing demands for in-country support, CDC has trained and deployed more than 1,550 public health volunteers on more than 2,200 assignments in 69 countries as part of its STOP Program.[111] CDC's STOP Program, established in 1999, includes CDC staff and members of the international community who assist with field operations, surveillance activities, communications, and data management during three-month assignments. In partnership with WHO and UNICEF, the STOP Team members have provided the equivalent of 262 person-years of support to countries at the national and subnational level. Moreover, CDC has lengthened STOP Team member assignments from three months to five months to meet the increasing demands for trained technical assistance by the GPEI.[112] To enhance the impact of these efforts, specialized National STOP Programs have been implemented in polio-endemic countries such as Nigeria and Pakistan to build country-level capacity and country ownership to support programmatic activities. These teams facilitate the work of the GPEI, especially in areas deemed hard to reach due to security concerns.[111]

The program's success has created opportunities to expand the work of the STOP Teams to include support for measles mortality reduction efforts as well as other global immunization efforts, including strengthening routine immunization systems and supporting more integrated disease surveillance. In 2013, it was reported that volunteers spent an average of 49% of their time

Recent violence in polio-endemic countries and the toll on polio eradication efforts

During December 2012 and January 2013, the World Health Organization (WHO) and UNICEF were forced to temporarily suspend planned polio campaigns following a series of attacks targeting polio vaccine workers that resulted in 17 deaths.[a] The three-day campaign, which aimed to vaccinate 30 million children, involved 250,000 vaccinators[a] who were mainly Pakistani female nationals considered to be the backbone of the polio campaign. Then, on February 8, 2013, attacks on clinics in Northern Nigeria resulted in the deaths of nine polio vaccine workers just after the end of a four-day polio vaccination campaign.[b]

Violence from militant groups on vaccination workers has been fueled by a number of factors, including misperceptions about the motives behind immunization campaigns.[a,c] These misperceptions were aggravated in Pakistan and around the world following the U.S. Central Intelligence Agency's use of a vaccination drive to collect information as part of the search for Osama Bin Laden in 2011.[d] Polio vaccination in Nigeria was suspended for almost a year in 2003 due to misperceptions and unfounded suspicions of the polio vaccine and polio immunization campaigns, including beliefs that campaigns aimed to cause sterilization or acquired immunodeficiency syndrome.[b] Ten years later, some of these misperceptions were again stated and supported by three radio journalists only days before the February 2013 attacks, which some say ignited the violence against the polio workers.[e]

Global health organizations and the Pakistani and Nigerian governments condemned the attacks as a tragic setback at a critical moment in the fight to eradicate polio.[f] However, leaders stressed the importance of continuing polio eradication work while taking precautions to protect workers and prevent opportunities for violence. Elias Durry, the head of the WHO's polio eradication team in Pakistan, stated that surgical, discrete campaigns would continue to be carried out in areas that experience polio outbreaks and heavy polio circulation.[g] Durry insisted that Pakistan was ready to keep moving forward, stating that, "The bottom line is that the country is determined to finish the job."[h]

[a]Walsh D, McNeil DG Jr. Female vaccination workers, essential in Pakistan, become prey. The New York Times 2012 Dec 20 [cited 2014 May 10]. Available from: URL: http://www.nytimes.com/2012/12/21/world/asia/un-halts-vaccine-work-in-pakistan-after-more-killings.html?pagewanted=all&_r=2&

[b]McNeil DG Jr. Gunmen kill Nigerian polio vaccine workers in echo of Pakistan attacks. The New York Times 2013 Feb 8 [cited 2014 May 10]. Available from: URL: http://www.nytimes.com/2013/02/09/world/africa/in-nigeria-polio-vaccine-workers-are-killed-by-gunmen.html?_r=0

[c]Gulland A. More polio workers are killed in Pakistan. BMJ 2013;346:f15.

[d]Roos R. WHO says polio drive must push on despite Pakistan setbacks. Center for Infectious Disease Research and Policy 2013 Jan 3 [cited 2013 Feb 25]. Available from: URL: http://www.cidrap.umn.edu/cidrap/content/other/news/jan0313polio.html

[e]Madu C, Brock J, Williams A. Nigeria arrests journalists over polio worker killings. Reuters 2013 Feb 11 [cited 2013 Feb 25]. Available from: URL: http://www.reuters.com/article/2013/02/11/nigeria-polio-violence-idUSL5N0BBGDF20130211

[f]UNICEF. UNICEF, WHO condemn attacks on polio "heroes" in Pakistan. UNICEF Press Centre [press release] 2012 Dec 19 [cited 2013 Feb 25]. Available from: URL: http://www.unicef.org/media/media_66901.html

[g]Roberts L. Killings force rethinking of Pakistan's anti-polio drive. Science 2013;339:259-60.

[h]Callaway E. Polio campaign at turning point, after Pakistan killings. Nature 2012 Dec 21 [cited 2013 Feb 25]. Available from: URL: http://www.nature.com/news/polio-campaign-at-turning-point-after-pakistan-killings-1.12127

on capacity-building activities, including training health-care workers, routine childhood immunization-strengthening activities, and supporting other health initiatives.[111] As polio eradication goals are completed, these programs and expertise will have continued value for other high-priority immunization goals.

NVAC RECOMMENDATION 2: STRENGTHENING GLOBAL IMMUNIZATION SYSTEMS

Accelerated disease-control efforts and mass vaccination campaigns remain important for putting countries back on track to achieve global immunization objectives. Nevertheless, each country's national routine immunization program remains the backbone of global immunization efforts. For instance, two-thirds of the total measles deaths averted are a result of measles immunizations administered through routine programs.[8,9] Weak routine immunization systems can create barriers to reaching all children. For example, one in every five children continues to go unvaccinated against measles.[75] Furthermore, many countries currently do not have the capability to monitor the impact of traditional EPI vaccines or introduce new and underutilized vaccines because of significant gaps in epidemiologic surveillance and data collection.

The NVAC notes that strengthening global immunization and vaccine delivery systems is fundamental to increasing immunization access and coverage for children. Strategies such as better data collection and enhanced surveillance activities will improve the quality of existing programs and will translate to more children receiving the full benefits of immunization. They will also fortify the framework for incorporating future vaccines, such as those for human immunodeficiency virus (HIV), malaria, dengue, and others. Importantly, strong routine systems can serve as a platform for delivering other health interventions (e.g., insecticide-treated bed nets, vitamin A supplementation, and maternal health interventions), and building a country's immunization capacity has the potential to yield benefits across global health.

Immunization coverage monitoring and disease surveillance

Global health experts have argued that "…the most important single contribution that public health makes to strengthening health systems is [the] provision of relevant and scientifically valid epidemiologic data upon which to base decisions and policies affecting all aspects of the larger health system."[29] The outcome measure for a successful vaccination program is the reduction in overall disease burden related to the number of people vaccinated against that disease. The performance of a national immunization program is evaluated both by monitoring the accuracy and reach of vaccine coverage and by measuring the impact the program has had on reducing the disease burden within a population. Outbreaks of VPDs can point to program weakness, such as regions where vaccination coverage is suboptimal or where a change in the epidemiology of a disease is occurring. Surveillance can also help determine whether the major contributor to disease is failure to vaccinate or vaccine failure. If failure to vaccinate is a contributor to disease, then improving vaccine uptake would be the focus of interventions. If vaccine failure is a contributor to disease, then changes in the immunization schedule (e.g., adding doses or changing ages for vaccine administration) or assuring vaccines are stored at recommended temperatures can be implemented as possible interventions. In addition, VPD surveillance can alert the global community to outbreaks of global public health importance.

NVAC recommendation 2.1: strengthening vaccine data monitoring—estimating vaccination coverage

The ASH should advocate for HHS efforts that support USAID, GAVI, and multilateral organizations such as WHO and UNICEF in the development of best practices and technologies to support countries in their efforts to more accurately track immunization coverage at the national and subnational levels and improve data quality and use. Where problems have been identified, data should be used to guide corrective actions when necessary.

Each year, national rates of immunization coverage of routine childhood vaccinations, cases of VPDs, and indicators of immunization system performance are reported to the WHO and UNICEF through the WHO/UNICEF Joint Reporting Process.[113,114] Immunization coverage estimates are based on data measuring coverage of the third dose of DTP3 among children up to 12 months of age.[7,113] DTP3 coverage serves as a surrogate indicator for access to immunization services and program performance, as it requires repeated contact with a health worker over a period of time.[115]

Immunization coverage data are generally used to monitor immunization program performance, and data quality is important in evaluating program weaknesses and identifying areas for improvement. Official coverage estimates are often based on administrative data of doses administered in clinics divided by estimates of the target population to be vaccinated. Data regarding the number of vaccine doses administered are collected by national governments via local public health authorities in the course of routine and cam-

paign immunization program work.[113,116] Other ways to estimate coverage that may be more accurate include household survey data in which parents are queried about a child's immunization status and usually asked to present immunization cards to verify immunization histories. These data are reported to the WHO,[116] UNICEF,[117] and others. However, methodologies for collecting both administrative and survey data are often problematic,[113] and recent analyses have unveiled persistent discrepancies between coverage estimates based on officially reported administrative data and data collected through household surveys by international organizations. These differences cast doubt on the accuracy of reported DTP3 coverage levels.[118–121] In addition, coverage estimates often mask wide disparities in coverage between and within countries.[122] Better systems for monitoring and evaluating immunization coverage data are needed to (*1*) manage immunization program performance and (*2*) allocate resources to identify ongoing inefficiencies that impede access to immunizations and prevent programs from achieving the greatest health impact.[44]

Administrative data. Administrative immunization coverage data that are collected and analyzed by national public health authorities and governments are used as the basis of officially reported immunization coverage levels sent to the WHO and UNICEF by the 194 WHO member states.[7,113] These data are reported to national public health authorities and governments by health service providers such as health center staff, vaccination teams, and private physicians.[113] Estimates of immunization coverage taken from administrative data are calculated by dividing the number of vaccine doses administered to children in the target age group by the estimated number of children in the target age group within the population.[7]

Administrative data may be subject to inaccuracies due to a number of factors such as staffing restraints, challenges with immunization recordkeeping, quality of supervision of data collection, and logistical barriers to communicating coverage data from local health clinics to higher levels of administration (e.g., Ministries of Health). Administrative data also contain possible biases in both the numerator (e.g., inaccurate and/or incomplete records of doses administered) and denominator (e.g., issues with population level estimates, inaccurate census data, inaccurate correction for population growth, and/or population migration).[113,118,119,123,124] The key barriers to achieving accurate immunization coverage data are (*1*) poor recording and reporting of immunization data, which has the potential to deteriorate further as new vaccines are added to the immunization schedule; (*2*) a lack of an accurate population size estimate, which is complicated because immunization services extend past infancy and childhood; and (*3*) discrepancies in data from different surveys, which casts doubt about reported numbers. Another criticism of administrative data is the potential for donor funding to influence officially reported immunization coverage (e.g., there may be incentives to report high coverage to show donors that progress is being made).[120,125–128]

Experts and scholars have suggested that improvements to data collection systems to increase the accuracy of administrative data could include creating free-of-charge birth registrars to improve estimates of the target population size or establishing vaccine registries housed in health facilities.[123,129] Ideally, these information systems would be standardized and interoperable, allowing for easy data sharing. Data collection at the district level could also be improved through the increased use and improvement of district-level monitoring tools such as the WHO's District Vaccine Data Management Tool. However, establishing immunization registries at the national or district level does not necessarily require the creation or uptake of new and expensive technologies to strengthen data gathering efforts. For example, the country of Oman successfully sustained immunization coverage of 98% for 10 years using a paper-based registry.[123,130]

It is also shown that data quality can be improved by training health workers with basic skills to track and monitor immunization coverage, and helping them understand how data collection can inform and improve their work.[127,131,132]

Governments and NGOs have launched a series of programs to improve vaccine coverage data and data usage, and several tools are available to improve administrative data collection and quality. The WHO's Health Metrics Network toolbox, Data Quality Self-Assessment, Revised Immunisation Data Quality Assessment, and denominator guidance tool are available for countries to assess and improve their immunization data quality.[116,120,133,134] USAID's Data Quality Audit Tool and Routine Data Quality Assessment Tool verify the quality of reported administrative data.[135] Other organizations such as the Clinton Health Access Initiative, the Bill & Melinda Gates Foundation, and UNICEF also work to support countries to improve routine coverage data.

Household survey data. Alternative data collection mechanisms such as household survey data collection conducted and supported by WHO, UNICEF, and USAID are often considered to be more accurate and reliable than administrative data collection.[123] Examples of reliable household surveys include the WHO EPI Cluster Surveys, the UNICEF Multiple Indicator Cluster

Summary of outcomes from the January 2013 GAVI Alliance Data Summit

Priority strategic area	*Actions*
Strengthen country systems and capacities	• Develop and harmonize common frameworks for investing at the country level to improve data quality, disease surveillance, and analytical capacity. • Implement a routine, systematic approach to monitoring routine data quality within all countries. • Improve denominator estimates through improved vital registration as one critical piece to better population data and provide more accurate coverage estimates. • Reward accurate reporting on the number and proportion of children immunized.
Improve survey design, frequency, methods, and content	• Increase the frequency of household surveys. Countries with less stability or more rapid change are likely to need surveys more frequently. • Invest in improving quality and retention of home-based records. • Increase survey availability and utility at subnational levels, and further explore innovative analytical techniques that improve estimates at subnational levels. • Track full immunization status by each individual child so that full immunization can be assessed.
Advance innovation in use of biomarkers, technology, and triangulation	• Consider use of available biomarkers to assess coverage data discrepancies and impact, while accelerating investment of future biomarker technologies. • Develop a systematized approach to address discrepancies between coverage estimates from different sources. • Explore the potential of mobile and digital technologies to be transformative in data quality. • Develop global and country-level guidance on synthesis of data sources to improve coverage estimates and strengthen country capacities to conduct such analyses.

Survey (MICS), and the Demographic and Health Surveys supported by USAID. These household surveys collect immunization coverage data at the household level by gathering information on children's immunization status through immunization cards kept and updated by each family or parent. This information is sometimes supplemented by parental recall[136] (or replaced by parental recall if no immunization card is available).[123]

The WHO EPI Cluster Survey uses a strategy of random sampling of neighborhoods and villages, followed by sampling of a cluster of houses whose selection is based on survey worker judgment, to collect information on immunization coverage.[137] The UNICEF MICS is a more extensive survey with a variety of health indicators[117] that relies heavily on random sampling to ensure representative sampling of the population.[113] Similarly, USAID's Demographic and Health Surveys program supports the collection of information on a variety of health and development topics[138] and relies on the selection of a representative sample of households taken from census records.[139]

Despite household survey data being held as the gold standard when estimating immunization coverage,[140] household survey data are also subject to a variety of biases and misreporting issues. At the household level, research has shown that the methodology used to collect information from families can be problematic.[123] Inaccuracies in survey data may arise due to the lack of availability of a vaccination card or an inaccurate record on a child's vaccination card.[141] Parents may not always receive vaccination cards, and the cards may be incomplete or inaccurate if parents neglect to bring vaccination cards to all visits to clinics where immunizations are provided, or if health-care providers fail to take note of vaccinations given on the vaccination card.[123] When immunization cards are not available, immunization histories must rely on parental recall. However, parental recall can also be inaccurate due to parents' inability to recall vaccine types and doses,[136,141,142] their desire to provide socially desirable responses, a lack of knowledge regarding whether another family member took a child to a vaccination appointment, or if they received incorrect information regarding their child's vaccination schedule from their provider.[123]

Nevertheless, household survey data collection is considered essential to assure a more accurate estimation of immunization coverage and should be

expanded and conducted more frequently.[121,140] Suggestions to improve and increase household survey data collection include integrating coverage surveys into other monitoring processes at the district level and into the strategic design of immunization campaigns.[124,129] Other opportunities include increasing the frequency of regular multi-topic health surveys to improve the ability to monitor both immunization coverage and other health indicators (e.g., child mortality).[120] The applicability of these suggestions may vary depending on the scope and purpose of the household survey in question.

Household survey data quality might be improved by increasing the publicity, promotion, and availability of immunization cards and improving communication between parents and health-care providers about what immunizations are being given and how many doses are needed.[123] It has also been suggested that data collectors should request that parents recall their children's immunizations before being asked to produce the child's immunization card, thereby allowing for more accurate analysis of parental self-report among children with immunization cards.[120] Comparison of parental recall and immunization cards with medical records and/or immunization registries might also help to improve data if that information is available.[123,136] Experts note that it should be ensured that survey data collectors are trained and supervised adequately, and that the data quality is monitored regularly and corrective action is taken when necessary.[123]

Household survey data accuracy might also be improved through the measurement of antibody titres such as tetanus toxoid. The cost of this approach could be minimized by using dried blood spots, saliva, or a random subsample in conjunction with immunization cards and parental recall. The comparison of the antibody titers with immunization cards and parental recall would also provide valuable information.[120]

Finally, coverage levels from household surveys should be routinely compared with administrative data in collaboration with local staff and community members in an effort to progressively improve immunization data quality.[123]

Innovations to improve immunization program data collection. Mobile and digital technologies are also being explored as a user-friendly way to improve field data collection. For example, the International Federation of Red Cross and Red Crescent Societies launched the Rapid Mobile Phone-based (RAMP) survey, allowing field workers to enter answers to health survey questions directly into a mobile device for rapid collection and transmission of health data.[143] Developed in collaboration with the WHO and CDC, the RAMP survey method allows for more accurate collection of a range of information, including local population size and composition, household survey data, and real-time data on children living in areas that are difficult to reach. While pilot-testing has focused on monitoring and evaluating malaria programs in Kenya, Namibia, and Nigeria, RAMP surveys can be readily adapted to meet the needs of immunization programs.[144]

HHS efforts in estimating global immunization coverage. CDC's Strengthening Quality and Use of Immunization Data (SQUID) Team of the Global Immunization Division (GID) works with WHO regional and country partners to improve data quality and enhance the ability of countries to conduct data analysis, interpret data, and use data for program management. At a country's request, CDC/SQUID staff will assist national immunization programs in evaluating the quality of their data and data collection systems to enhance country capacity to collect and use immunization and VPD surveillance data. CDC/SQUID conducts detailed gap analyses to help countries identify program strengths, weaknesses, areas of opportunity, and potential program threats/risks. They then work with government and public health officials to formulate action plans to address those gaps.[145] CDC also works with USAID to train immunization program managers to better perform data assessments and to implement standard procedures of data collection and verification to improve data quality.

NVAC recommendation 2.2: strengthening global VPD surveillance capacity

The ASH should work with other HHS offices to develop sustainable support for quality global VPD surveillance systems, including the existing global and regional VPD laboratory surveillance networks. This support ideally should include technical and financial resources needed to support early warning/outbreak surveillance; laboratory diagnostics; emergency communication systems to detect and respond to outbreaks of VPDs; surveillance requirements for the eradication of targeted VPDs, including case-based polio, measles, and rubella surveillance; and laboratory networks to support the introduction and monitor the impact of new and underutilized vaccines.

The important role VPD surveillance plays in strengthening the capacity for global immunization systems is highlighted in the GIVS, the GVAP, the NVP, and the CDC Global Immunization Strategic Framework.[5,40,43,56] Disease surveillance is needed to establish and monitor the burden and epidemiology of VPDs within countries to mobilize resources; evaluate the performance (and impact) of each country's immunization program,

including the impact of newly introduced vaccines; direct response activities; inform decisions regarding the introduction of new and underutilized vaccines; and detect outbreaks of diseases with epidemic/pandemic potential. Robust VPD surveillance and access to high-quality laboratory networks are also fundamental to tracking progress toward eradication and elimination goals. For example, global polio eradication goals and regional goals for measles/rubella elimination require certification-standard surveillance to verify when endemic transmission has been successfully interrupted.[146] Disease surveillance data provide feedback to guide programmatic activities and improve the quality of immunization program service delivery.

Historically, VPD surveillance has been tied to disease-specific initiatives and disease-specific donor funding. On the one hand, initiatives such as the GPEI and MRI have created access to surveillance systems and laboratory networks in the most resource-limited countries. On the other hand, disease-specific initiatives have also led to fragmented, duplicative efforts that result in missed opportunities to coordinate information sharing and maximize limited resources (e.g., trained personnel, transport, technologies, and operational/administrative space).[147–149] Targeted disease initiatives may not represent the greatest public health concern in a country, causing conflicting priorities and unmet pressing public health needs.[148,149] Moreover, national and subnational surveillance networks supported by donor-driven priorities may not be sustainable once disease-specific goals are met and funding dissipates. Finally, global goals to accelerate access to new and underutilized vaccines in low- and middle-income countries (LMICs) will require additional resources to create and expand surveillance and laboratory capabilities.[40]

The global framework for immunization monitoring and surveillance. To meet these challenges, WHO, CDC, and other collaborating partners developed the Global Framework for Immunization Monitoring and Surveillance (hereafter, the Framework) as guidance for strengthening surveillance and laboratory capacity for all VPDs through an approach to streamline, when possible, common processes such as data collection and management, training, reporting, and evaluation.[150] The Framework seeks to expand access to high-quality national laboratories and WHO-accredited regional reference laboratories that can accurately diagnose viral and bacterial VPDs and to formalize VPD laboratory networks for establishing the baselines of disease burden and measuring the potential impact for newly introduced vaccines.

Resources required for adequate surveillance and program monitoring are minimal compared with program costs of implementing immunization programs. These small investments make the public health system more effective and efficient, resulting in cost savings. For example, the timely detection of outbreaks allows early control measures, reducing costs and preventing a larger number of cases and deaths. Monitoring can identify problem areas and reduce vaccine wastage.[151]

The Framework also promotes linking different VPD surveillance and monitoring efforts, as well as VPD surveillance, with other priority disease efforts (e.g., malaria and HIV) to achieve greater program efficiencies and create sustainable, country-owned programs.

Obtaining certification-quality surveillance for polio eradication

Eradication certification criteria state that endemic transmission of the wildtype virus must not be detected through high-quality surveillance systems (both laboratory and environmentally confirmed) for three years.[a] Acute flaccid paralysis (AFP) occurs in one out of every 200 cases of polio.[b] Therefore, to obtain certification-quality surveillance data, every case of AFP is investigated and confirmed through laboratory diagnostics. At a minimum, laboratories within the network must be able to detect at least one case of non-polio AFP per a population of 100,000 people aged <15 years.[c] In addition, more than 80% of AFP cases should have two stool samples collected more than 24 hours apart and within 14 days of onset of paralysis and examined by an accredited network laboratory.[d]

[a]Smith J, Leke R, Adams A, Tangermann RH. Certification of polio eradication: process and lessons learned. Bull World Health Organ 2004;82:24-30.

[b]Acute flaccid paralysis surveillance: a global platform for detecting and responding to priority infectious diseases. Wkly Epidemiol Rec 2004;79:425-32.

[c]World Health Organization. Acute flaccid paralysis (AFP) surveillance: the surveillance strategy for poliomyelitis eradication. Wkly Epidemiol Rec 1998;73:113-7.

[d]Evaluating surveillance indicators supporting the Global Polio Eradication Initiative, 2011–2012. MMWR Morb Mortal Wkly Rep 2013;62(14):270-4.

As the world moves closer to achieving polio eradication and regional measles/rubella elimination goals, there is a growing opportunity to use the successful platform of the polio and measles/rubella surveillance systems to expand surveillance to include other priority infectious diseases (both VPDs and non-VPDs).[150,152]

The poliomyelitis surveillance network currently provides a structure for rapidly detecting and responding to diseases of national and international importance, particularly in resource-poor countries.[151] However, recent experience trying to build surveillance for diseases preventable by the newer vaccines on the polio network suggests that polio infrastructure does not work well for all VPD surveillance, particularly for bacterial VPDs, which require immediate processing of specimens. Some elements of the surveillance system, however, can be integrated, such as logistics for specimen transfer, supplies shipping, and overall effective laboratory management and quality control.

WHO Global Polio Laboratory Network. The WHO Global Polio Laboratory Network was established as a key strategy in achieving polio eradication through case-based surveillance of acute flaccid paralysis (AFP).[146,153] Eradication certification criteria require that every case of AFP is investigated and confirmed through laboratory diagnostics.[146] Standardized case definitions and established guidelines for specimen collection, transport, and processing ensure the quality and sensitivity of the surveillance system.[152]

The network comprises 146 laboratories organized in a three-tiered system that operates in all six WHO regions with laboratory-confirmed surveillance at the national, regional, and global levels.[154] Laboratories at all levels are accredited through a WHO-sponsored process that is dependent on meeting set performance standards for timeliness, workload, operational procedures, and proficiencies in isolating and serotyping virus from specimens.[155]

WHO Global Measles and Rubella Laboratory Network. As measles control efforts increased, measles incidence subsequently declined, and the global MRI began implementing case-based surveillance. A key component of case-based surveillance is laboratory confirmation of suspected cases of measles and rubella. Laboratory confirmation is essential because the positive predictive value of case classification based solely on clinical presentation is very low in low-incidence settings.[156]

Case-based surveillance for measles with the associated laboratory confirmation further highlighted a high incidence of rubella among populations, leading to the incorporation of rubella testing into the standard testing strategy of the laboratory network.[94] Incorporating rubella testing strengthened laboratory capabilities to more accurately track progress toward regional measles and rubella control goals (i.e., measles/rubella elimination or measles mortality reduction, depending on the region).[25,98,99,157]

In many instances, the measles/rubella laboratory network was expanded by leveraging the existing laboratory and administrative infrastructure initially used by the WHO Global Polio Laboratory Networks.[152,156] The WHO Global Measles and Rubella Laboratory Network now includes 690 laboratories with a large number of laboratories at the subnational, national, regional, and global levels.[157] The network laboratories employ a systematic testing approach using well-validated assays, common quality-control indicators, and standardized reagents and procedures for laboratory testing and reporting.[156] The WHO provides evaluation and accreditation of laboratories to monitor performance and identify areas for further systems strengthening.[157]

Integrating disease surveillance systems. Both the Global Polio and Global Measles and Rubella Laboratory Networks have successfully established high-quality national laboratories in resource-limited countries, war-torn countries, and countries with little to no public health infrastructure.[152,155] These laboratories, in turn, are now being used by countries to build surveillance capacity for other priority infectious diseases, including Japanese encephalitis, yellow fever, neonatal tetanus, dengue, and rotavirus.[152,157,158] Surveillance medical officers trained in these networks have responded to outbreaks of cholera, dengue, hemorrhagic fevers, malaria, severe acute respiratory syndrome (SARS), and reports of avian influenza.[157,159,160]

The WHO-African Region (WHO/AFRO) member countries have used the infrastructure created from polio surveillance systems as a platform to implement an Integrated Diseases Surveillance and Response (IDSR) strategy.[161] Adopted in 1998 by the WHO/AFRO member countries, the IDSR strategy integrates district-level surveillance activities for a number of VPDs and other high-priority diseases to streamline resources and strengthen public health response by linking surveillance and laboratory data.[149,162] Surveillance activities include monitoring for epidemic-prone diseases, diseases targeted for eradication and elimination, and other diseases of public health importance such as pandemic influenza.[149] Developed in collaboration with CDC, the WHO, and the WHO/AFRO member countries, the IDSR strategy uses an action threshold approach for each specified disease that triggers coordinated activities for each tier of the surveillance system for early detection and rapid outbreak response.[163,164]

At the subnational and national levels, VPD surveillance linked to formal laboratory networks can strengthen routine immunization systems and significantly broaden a country's ability to detect and respond to emerging global public health threats, such as pandemic influenza. However, many countries do not include VPD surveillance and laboratory support in their national immunization budget planning. Adopting strategies that integrate surveillance activities across multiple VPDs and, when possible, linking these efforts to laboratory network capabilities, will create opportunities for sustainable, country-owned programs.[150]

Building capacity for new and underutilized vaccines—expanded disease surveillance needs for the successful introduction of new and underutilized vaccines. Extending surveillance and laboratory capabilities to support the introduction of new and underutilized vaccines creates additional challenges for country-level programs. Recently available new and underutilized vaccines that have highlighted the need for more local data include hepatitis B, rubella, rotavirus, influenza, conjugate Hib, conjugate pneumococcal and meningococcal, and human papillomavirus (HPV) vaccines.

Decision makers need to accurately estimate the disease burden of VPDs and describe their local epidemiology to determine the costs, appropriateness, and potential impact of vaccine interventions. Surveillance capacity may need to be created or augmented to establish a baseline of VPD morbidity and mortality before introducing new interventions.

Surveillance for new vaccines may have different objectives than for polio and measles surveillance, which currently require nationwide, often intensive elimination/eradication-level efforts. Certain new vaccines, such as the regional conjugate meningococcal vaccine, aim to eliminate epidemic diseases and would benefit from nationwide surveillance as well.[165] The objectives of new vaccine surveillance depend on the type of evidence countries would need to help introduce new vaccines. If local disease burden data are needed rather than relying on global estimates, countries may choose to conduct their own population-based surveillance, which can be resource intensive.[166,167]

Currently, most countries have established hospital-based sentinel surveillance sites that can provide a description of the distribution of disease due to various pathogens; sentinel surveillance for bacterial meningitis can identify the proportion of disease due to Hib, *Neisseria meningitides*, *Streptococcus pneumoniae,* or influenza. Similarly, surveillance for diarrhea can provide the proportion due to rotavirus.[150] In addition, such surveillance can provide data on the distribution of the strains responsible for disease within a country to determine whether they match available vaccine strains and provide baseline data to subsequently assess the impact of immunization programs on strain epidemiology.[47,158,168,169] Such data have proven particularly helpful for diseases caused by multiple strains that are not all contained in the new vaccines, such as for meningococcal, pneumococcal, influenza, and rotavirus vaccines. For those diseases where sentinel surveillance is usually the only surveillance system available (e.g., invasive bacterial disease [IBD] and rotavirus surveillance), measuring the impact on a nationwide basis is not possible or must be estimated.

In addition, in well-performing sites, case-control and other studies can be conducted to evaluate vaccine effectiveness. Immunization program managers need to be able to measure the impact the vaccine has on reducing disease burden once interventions are widely introduced. Moreover, surveillance data must be collected during a sufficient time frame to accurately capture the epidemiology of disease in a given region. WHO, in partnership with CDC and others, has recently published guidelines to help countries evaluate the impact of new vaccines such as rotavirus, Hib, and pneumococcal conjugate vaccine (PCV).[170,171] New vaccine sentinel surveillance has been more readily achievable for rotavirus, for which it was easier to use some of the existing polio surveillance infrastructure, but has been much more challenging for IBD surveillance, where developing adequate capacity for bacteriology requires more intensive support and rapid processing of specimens such as cerebrospinal fluid.

Finally, subnational and national laboratories must be able to absorb this greater workload without unnecessarily taxing the existing VPD surveillance systems. Unlike polio and measles/rubella surveillance networks, funding for these expanded activities is not broadly supported by global initiatives, and lower- and middle-income countries may struggle to meet the core capacities required to inform public health investments in these newer vaccines.[150]

Establishing global surveillance and laboratory networks for new and underutilized vaccines. Surveillance for VPDs can vary greatly by district and geographic region, thereby complicating decision makers' ability to compare data and establish baselines of VPD burden. To facilitate meaningful, evidence-based decision making, several initiatives have begun to formalize and systematize epidemiologic and laboratory surveillance for diseases targeted by new and underutilized vaccines. The initial framework for the Global Invasive Bacterial Disease Surveillance Network was laid by participating sites that incorporated standardized case definitions and common data reporting methods to monitor the burden

of meningitis, pneumonia, and sepsis caused by Hib, *Streptococcus pneumoniae,* and *Neisseria meningitidis.*[47,168,169] Similar efforts have led to the establishment and expansion of the WHO Global Rotavirus Surveillance Network.[158]

Integrating surveillance for these diseases into existing programs and routine systems at the subnational level has also facilitated data collection for the introduction of new and underutilized vaccines. CDC led preliminary efforts to use the existing polio and measles/rubella networks in Bangladesh, China, and India to monitor for viral and bacterial VPDs causing acute meningitis/encephalitis syndrome and acute encephalitis syndrome.[172] Similarly, other countries have demonstrated the feasibility of honing surveillance for meningitis/encephalitis syndromes by integrating both viral and bacterial laboratory testing for case confirmation.[173]

For underutilized vaccines such as seasonal influenza, robust surveillance systems are already established and can be expanded to further provide the evidence base supporting greater uptake of seasonal influenza vaccines in developing countries. Global influenza virological surveillance has been conducted through the WHO's Global Influenza Surveillance and Response System (GISRS) for more than half a century. Formerly known as the Global Influenza Surveillance Network, the new name came into effect following the adoption of the Pandemic Influenza Preparedness Framework in May 2011. WHO GISRS monitors the evolution of influenza viruses and provides recommendations in areas including laboratory diagnostics, vaccines, antiviral susceptibility, and risk assessment. WHO GISRS also serves as a global alert mechanism for the emergence of influenza viruses with pandemic potential. National Influenza Centres (NICs) collect virus specimens in their country and perform preliminary analysis. They ship representative clinical specimens and isolated viruses to WHO Collaborating Centres for advanced antigenic and genetic analysis. The results form the basis for WHO recommendations on the composition of influenza vaccine each year, as well as relevant WHO risk assessment activities. NICs are national institutions, designated by national Ministries of Health and recognized by the WHO, that form the backbone of the GISRS. There are currently 140 NICs in 117 countries.

The role of HHS in global VPD surveillance. All VPD laboratory networks are tiered, with the number of levels dependent on the surveillance questions addressed at each level, the technical capabilities achievable at each level, and the resources available for the network. Most networks have at least three levels, originally designated as National Laboratories, Regional Reference Laboratories, and Global Specialized Reference Laboratories. As the VPD laboratory networks have matured, capabilities continually develop in the more local laboratories, facilitating their ability to perform laboratory procedures initially defined for the Regional and Global Specialized Reference Laboratories. Formal accreditation procedures have been developed for each level in the VPD laboratory networks. Consequently, the network structure becomes flexible, and an important role of the Reference Laboratories is to support the introduction of the most powerful and appropriate technologies into the entire network.

CDC serves as a Global Specialized Reference Laboratory to a number of WHO-coordinated laboratory networks including the Global Polio Laboratory Network, the Global Measles/Rubella Laboratory Network, the Global Rotavirus Surveillance Network, the Global Influenza Surveillance and Response System, and the Global Invasive Bacterial Disease Surveillance Network, as well as regional surveillance and laboratory networks for yellow fever, Japanese encephalitis, pediatric bacterial meningitis, and hepatitis B. The responsibilities of Global Reference Laboratories vary with the disease agent but include distribution of reagents, cell lines, primary virus and bacterial isolation and confirmation, quality control/quality assurance of the networks through development and distribution of proficiency panels, parallel testing of specimens, serotyping or serogrouping, genetic sequencing, serological diagnosis, polymerase chain reaction and other technology transfer, training of Regional Reference Laboratories and selected national laboratories on advanced diagnostic techniques, troubleshooting, consultation, accreditation reviews, development of new diagnostic methods and reagents, participation in regional and global laboratory network meetings, and research relevant to surveillance needs.

In addition, CDC has recently participated and copartnered with the WHO, NGOs, and academic institutions on many vaccine introduction initiatives supported by the GAVI Alliance, such as the Pneumococcal conjugate Accelerated Development and Introduction Plan, the Rotavirus Vaccine Program, the Hib Initiative, and the Accelerated Vaccine Initiative Technical Assistance Consortium. Through these initiatives, funding was provided to support multiple surveillance activities to measure disease burden and monitor the impact of newly introduced vaccines.[47,174]

CDC's Influenza Division has supported more than 50 countries since 2003 to develop laboratory and epidemiologic capacity to conduct surveillance for influenza disease, both hospital- and clinic-based,

using WHO standard case definitions for severe acute respiratory syndrome (SARS). These systems allow for the assessment of virologic characteristics of circulating influenza viruses, clinical characteristics of strains, and data to assess the burden and impact of intervention such as vaccination. These platforms can be used for other respiratory pathogens. Regional networks such as the Africa Network for Influenza Surveillance and Epidemiology also allow for standardization of epidemiologic surveillance. In addition, the Influenza Division also directly supports more than 100 domestic, state, local, and military laboratories by providing diagnostic testing kits, ancillary reagents, and staff through the Influenza Reagent Resource and Epidemiology and Laboratory Capacity for Infectious Disease programs.

Although not focused primarily on VPD surveillance, CDC's Global Disease Detection and Emergency Response (GDDER) program contributes to strengthening VPD surveillance and laboratory capacity at the global, regional, and local levels by improving public health preparedness and response during humanitarian emergencies and outbreaks of global health importance.[175] The program serves to build the country-level surveillance capacity needed to implement the International Health Regulations.[176] As a liaison to the WHO Global Outbreak Alert and Response Network, the GDDER has assisted in response efforts for a number of VPD outbreaks including measles, meningitis, polio, and cholera outbreaks.[175] Moreover, the program has supported the expansion of existing polio and measles/rubella laboratory networks for broader VPD detection and response.[172]

NVAC recommendation 2.3: building country-level surveillance capacity through CDC's FE(L)TPs

The ASH should work with CDC to increase core support to CDC's FE(L)TP as a key tool for transferring epidemiologic and laboratory capacities to strengthen programs. This support should specifically be used to incorporate immunization topics into FE(L)TP training.

One important barrier to incorporating sustainable VPD surveillance and laboratory networks into routine immunization programs is an insufficient number of competent, trained public health personnel.[150] Developing a trained public health workforce is a key building block of systems strengthening, and strengthening immunization systems at the national and subnational levels includes creating training opportunities as part of a country's public health infrastructure. The CDC-supported FE(L)TPs are a proven strategy to develop locally trained personnel in applied field epidemiology and laboratory practice for VPD surveillance and response.[177,178]

The Field Epidemiology Training Program (FETP) is modeled on CDC's Epidemic Intelligence Service and consists of a two-year, full-time program that incorporates classroom training and field assignments. The FE(L)TP includes an additional competency-based training component to support laboratory surveillance and outbreak response.[179] Eligible participants are typically junior- to mid-level employees in service to a country's Ministry of Health.[178] Training modules consist of courses in epidemiology, communications, economics, monitoring and evaluation of surveillance systems, achieving performance measures for disease control and prevention, and program management.[179] Graduates of the program are capable of operating national public health surveillance and response programs and are expected to go on to train additional personnel. Since 1980, CDC has worked in collaboration with USAID to develop 41 FETPs that serve 57 countries. The program has graduated more than 2,300 trainees and has greatly contributed to augmenting the global public health workforce.[29,180,181] FE(L)TPs also provide short courses and training workshops for surveillance officers and frontline public health workers at the subnational levels.

FE(L)TPs are initiated in countries through partnerships with CDC, the WHO, Ministries of Health, and donors or development agencies such as USAID.[178] CDC provides an in-country resident technical advisor to aid in program development and training for four to six years, and countries are expected to take on increasing financial and technical responsibility of the program over time to ensure long-term country-driven sustainability.

CDC also collaborates to coordinate FE(L)TPs at the global level through the Training Programs in Epidemiology and Public Health Interventions Network (TEPHINET). TEPHINET is a professional alliance of more than 55 FE(L)TPs around the world.[182] With more than 80 participating countries, TEPHINET joins the national and regional FE(L)TPs to support information sharing and best practices through scientific conferences, meetings, and training workshops. The TEPHINET Secretariat, in collaboration with program directors, has also created criteria and processes for program accreditation and quality improvement.[183] In addition to TEPHINET, regional networks have grown up that have been critical in supporting the expansion and growth of national programs. One such regional network, the African Field Epidemiology Network (AFENET), has been essential in promoting the growth of epidemiology training throughout sub-Saharan

Africa.[184] These coordinated network FE(L)TPs are now playing a major role in developing a sustainable global public health workforce.

NVAC recommendation 2.4: improving the delivery of immunization services—reaching every district/community

The ASH should support the work of HHS and its partners within the international community to define standards for measuring the impact of routine delivery strategies such as the Reaching Every District/Community (RED/C) strategy. These metrics can be used to evaluate how well these strategies perform in fully vaccinating children with routine immunizations.

Although global immunization coverage with DTP3 rose to 83% in 2011 from only 23% in 1981,[7,113] large inequalities between and within countries persist. Closer examination of global immunization coverage reveals that despite overall gains, low-income countries continue to have lower immunization coverage than high-income countries, and significant disparities persist between wealth quintiles, where the poorest children are the least likely to receive immunizations.[115,122] For example, in India, which is home to about one-third of the world's unimmunized children, the overall national coverage rate of DTP3 in 2010 was 72%. However, in Indian states such as Mizoram, coverage rates between the richest and the poorest children differed by 71 percentage points. In the state of Arunachal Pradesh, only 8% of children in the poorest quintile were fully vaccinated with DTP3.[122]

In addition, the average DTP3 coverage rate for low-income countries in 2010 was shown to equal the average DTP3 coverage rate for high-income countries in 1986, meaning that low-income countries are more than 20 years behind.[122] In a survey of the literature, it was found that factors such as lack of access to immunization services, poor quality of health services, missed opportunities, hidden financial and opportunity costs to families, and lack of vaccine availability were the most cited reasons for why children were not immunized.[122,185]

The provision of immunization services to children in remote and hard-to-reach rural areas is often restricted due to factors such as physical distance from health clinics, geographical barriers, and the difficulty of travel for health workers.[122,186–192] Similarly, children living in urban slums often face barriers to immunizations such as a lack of access to health information and/or a limited interchange of information regarding immunization services.[193–195] Mobile and nomadic populations also have low immunization coverage, as they are often overlooked during immunization campaigns, and delivering subsequent doses of vaccine becomes difficult once population groups have moved to another location.[187,196,197] Finally, during times of political unrest or violence, immunization activities are sometimes temporarily halted, leaving children unimmunized,[198–202] such as following the recent violence against polio workers in Pakistan.[203]

In response to the challenges of immunizing these hard-to-reach children, the WHO, UNICEF, and other partners in the GAVI Alliance developed the RED/C approach in the Africa region.[190,204] The RED/C approach uses five tactics in an effort to overcome common obstacles to increasing immunization coverage among hard-to-reach populations, with a special focus on planning and monitoring.[190] The five elements of the RED/C strategy are:

1. Reestablishing outreach services to all communities;
2. Supportive supervision of health workers, including on-site training, regular visits, and assistance with problem solving;
3. Linking services with communities to increase community participation and ownership;
4. Monitoring and using data for action to make adjustments and improvements in vaccine delivery; and
5. Planning and managing resources, including microplanning for each district based on a local situation analysis.[190]

The RED/C approach also encourages the use of coverage data to prioritize districts that need the most help in improving access and utilization of immunizations, along with the use of microplanning to address local problems with solutions that are appropriate to the community.[190] Since 2002, most countries in the WHO regions of Africa, Eastern Mediterranean, Europe, Southeast Asia, and the Western Pacific have used the RED/C approach in their efforts to extend routine immunization to all populations.[205]

Evaluations of RED/C implementation in the Africa region and Assam, India, have shown overall good results. Although the authors indicate that it is difficult to attribute improved vaccine coverage directly to implementation of the RED/C strategy, the overall quality of immunization programs improved in intervention districts.[206–208] For example, implementation of the RED/C approach reportedly increased the frequency of supportive supervisory visits to local immunization providers, with increased constructive feedback on how to improve immunization services.[206]

Researchers who conducted these evaluations noted that further research is needed to examine the

sustainability of the impact of the RED/C approach on immunization coverage, and that variability in the interpretation of the RED/C guidelines leads to diverse implementation strategies across countries.[207,208] Additionally, although many countries in several WHO regions have implemented RED/C, only 11 have undergone in-depth country-level evaluations of their program implementation, and all have been in the African region.[206,207] Researchers also noted that several of these countries were selected for evaluation on a volunteer basis, indicating that the sample of countries being evaluated was not necessarily representative, and within each country a limited number of districts were visited.[206]

HHS evaluation of immunization strategies—reaching every child. CDC has been an important contributor to developing and evaluating strategies to reach every child with vaccines, but more work is needed. In 2008, WHO's Scientific Advisory Group of Experts on Immunization requested more information on the epidemiology of the unimmunized child. In response to this request, the WHO coordinated a three-part review of the current literature and available data to explore the reasons and factors linked to low vaccine uptake in LMICs.[209] The GID at CDC conducted the peer-reviewed literature review.

A total of 901 reasons and factors associated with the under-vaccinated child were identified from these 209 articles. Of these reasons and factors, 393 (44%) were related to immunization systems, 255 (28%) were related to parental attitudes and knowledge, 199 (22%) were linked to family characteristics, and 58 (6%) were associated with communication and information. Thirty-three reasons and factors were abstracted from 12 articles describing the completely unvaccinated child. Of these reasons and factors, 18 (55%) were related to parental beliefs and knowledge, nine (27%) were linked to family characteristics, four (12%) were related to immunization systems, and two (6%) were related to communication and information. The distribution of reasons and factors associated with these four major themes were relatively constant during the review period.[209]

Several common themes were identified in this review to describe the epidemiology of the under-vaccinated child in LMICs. Access due to geographic barriers (e.g., living in remote/rural areas or clinic too far away) and missed opportunities to vaccinate (e.g., not having a vaccination card at time of visit) were linked to low vaccine uptake in most countries from which articles were identified. Other reasons and factors, especially those linked to parental attitudes and knowledge (e.g., role of gender), were regionally focused and more difficult to interpret. Many of the identified parental attitudes regarding vaccinations may be proxies for more complex health-seeking behaviors and perceived barriers.[209]

NVAC recommendation 2.5: ensuring immunization coverage among U.S.-bound refugees

The ASH should endorse HHS coordination with other USG agencies to support efforts that provide routine overseas administration and documentation of vaccinations for all U.S.-bound refugees with vaccines that have been identified for pre-departure administration.

Complex emergencies can create situations that promote the spread of VPDs among vulnerable refugee populations. In many of these countries, immunization levels are typically lower than in most developed countries, and routine health services may break down for extended periods of time due to instability prior to, during, and after a complex emergency.[119,210–216] Additionally, refugees often temporarily relocate to refugee camps and urban slum settings where they experience crowding, high population density, inadequate sanitation, malnutrition, and a scarcity of clean water, which create ideal conditions for the spread of VPDs such as measles, mumps, cholera, meningitis, and yellow fever.[119,210,212,213,217–223] Measles is particularly dangerous in crowded refugee camps and urban environments, as high population density creates ideal conditions for measles to spread, creating heightened risks for children in complex emergencies.[210,212,213,219–221]

Targeted and rapid vaccination campaigns are critical to controlling disease outbreaks, particularly measles outbreaks, during complex emergencies.[119,210,219,220,224,225] It has been shown specifically that measles vaccination with SIAs during complex emergencies is a very cost-effective prevention strategy.[219] Proper vaccination of refugees in transit camps and surrounding areas also prevents delays in relocation to the receiving country.[226]

Complex emergencies such as political conflicts and other humanitarian crises account for 50,000–75,000 refugees who enter and resettle in the U.S. each year.[227,228] The U.S. has the largest refugee settlement program worldwide.[227,229] In fact, more than 650,000 refugees have resettled in the U.S. since 2000.[229,230] Refugees are not required to be vaccinated or provide proof of vaccination before entering the U.S.; thus, immunizations are provided after their arrival.[214,227,228,231,232] Currently, many refugees arrive from countries with low vaccination rates, possessing poor or no vaccination documentation,[233] resulting in concentrated populations susceptible to VPDs.[215,233–239]

Immunization of refugees prior to their arrival in the U.S. can prevent costly outbreak control efforts and added morbidity caused by disease importations.[227,231,232,238,240] After resettlement, refugee children are vaccinated through the Vaccines for Children Program, and coverage for vaccination of adult refugees depends on the laws and policies of the receiving state.[232] Certain adult vaccinations are covered for refugees by Refugee Medical Assistance, a program of the HHS Office of Refugee Resettlement, which provides funds to states for post-arrival medical screenings for refugees.[233,241,242] Although immunization does not usually occur until after resettlement in the U.S., there is a four- to six-month period between their required overseas health assessment and their arrival when immunizations could be administered.[243]

Immunization catch-up after arrival and resettlement may be inadequate. One study demonstrated that in 2006, only 50% of refugee children aged 0–35 months were completely up-to-date on immunizations 15 months after resettlement.[239] In another study, 23% of refugees never completed their initial health assessment, which is necessary to determine which vaccines were needed after arrival to the U.S., due to loss to follow-up when they moved to another state, refusal to receive the health assessment, missed appointments, or provider failure to follow protocol.[235]

It has been shown that in addition to the cost savings through the prevention of disease importations, the estimated cost of immunizing refugees overseas prior to arrival in the U.S. is substantially lower due to the lowered cost of vaccines provided internationally by UNICEF. In 2005, immunization in the U.S. of 50,787 U.S.-bound refugees with data available in the CDC Information on Migrant Populations database was estimated to cost $25,990,579 in the U.S. (including vaccine purchase and administration), compared with only $7,706,026 to vaccinate these refugees overseas.[244]

HHS efforts to promote pre-departure immunization of U.S.-bound refugees. Currently, the CDC Division of Global Migration and Quarantine (DGMQ) and the HHS Office of Refugee Resettlement are collaborating with the State Department and others to analyze the economic benefits of overseas vaccination. In addition, CDC/DGMQ and the State Department are collaborating with partners to conduct a vaccination pilot program for U.S.-bound refugees in five countries. These efforts are intended to support a policy shift in the near future to provide selected routine vaccinations and possibly other preventive medical interventions overseas to U.S.-bound refugees.

NVAC recommendation 2.6: strategies to improve immunization supply and logistics management

The ASH should support the work of other USG agencies and partners to strengthen global efforts pertaining to immunization program logistics management, including building and sustaining the necessary capacity for vaccine supply chain, logistics, and forecasting.

Insufficient vaccine supply chains can further exacerbate challenges to providing immunization services for hard-to-reach populations. Poorly managed or underresourced logistics systems can weaken already fragile immunization programs, and weak systems can lead to significant vaccine wastage and vaccine stock-outs, adding to program costs, resource constraints, and interruption of immunization service delivery. Furthermore, inadequate vaccine supply chain capacity may cause unnecessary delays in the introduction of new vaccines, as national immunization programs struggle to incorporate transport and storage requirements for increasing volumes of vaccine products.[245]

Zaffran et al. note that "[w]ith few exceptions, vaccine supply and logistics systems around the world are unable to keep pace with growing immunization programs."[245] As a result, a number of global initiatives to innovate and fortify these systems have been launched. USG efforts toward improving global vaccine supply chain and logistics systems are predominantly supported by USAID and other partners, with HHS agency staff mainly serving as representatives on advisory panels. However, the NVAC has highlighted a few examples of global initiatives here as they represent important contributions to the goal of achieving strong, well-functioning immunization delivery systems.

UNICEF Cold Chain and Logistics Taskforce. The UNICEF-led Cold Chain and Logistics (CCL) Taskforce first met in 2007 as an initiative to strengthen and expand vaccine supply chain and logistics capacity within national immunization programs.[246] The Taskforce is divided into five subgroups focusing on guidance, monitoring, advocacy, integration, and systems of the future.[247]

Early efforts of the CCL Taskforce involved a collaboration with Project Optimize (described hereafter) and numerous other CCL partners and stakeholders to conduct a comprehensive landscape analysis to survey ongoing efforts to improve the management of vaccine supply and logistics, to define a common vision for the future of vaccine supply chains, and to identify the critical barriers to realizing that vision.[248] The landscape analysis was then used to create an action plan for aligning CCL capacity-building efforts at all levels (global to program level) under a common vision

that "by 2020, the capacity of National Immunization Programmes is strengthened so that every individual can benefit from vaccines of assured quality delivered in the right amount at the right time through efficient logistics, proper vaccine management, and a well-functioning cold chain system."[247] The resulting action plan is organized under five priority areas (or tenets):[249]

1. Introduce innovative vaccine products and packaging that are tailored to meet the needs and constraints of developing countries.
2. Facilitate efficient and effective vaccine delivery and leverage proven methods from other sectors.
3. Assess and minimize the environmental impact of energy, materials, and processes used.
4. Design information systems to help plan and manage immunization activities and resources while ensuring that adequate quantities of vaccines are always available to meet demand.
5. Include human resources policies that provide adequate numbers of trained, motivated, and empowered personnel at all levels of the system.

Under each of the five tenets, the action plan describes the envisioned end goals for closing the identified gaps, the actions needed to achieve the desired outcomes, and the potential partners that are best suited to tackle these issues.[249]

As the CCL Taskforce moves forward with implementing the activities described in the action plan, discussions have included efforts to define performance indicators, evaluate tools for assessing vaccine supply chains within countries, and discuss ways to improve management of supply chains (e.g., minimizing waste, better forecasting needs, and creating training modules for program managers and logisticians).[250] The UNICEF CCL Taskforce has collaborated with TechNet-21.org to provide a Web page offering resources such as recommended guidelines and best practices for better management of national vaccine supply chain and logistic systems.[251] TechNet-21.org is an online community resource center that has contributed discussion forums, document libraries, and numerous other tools and resources for strengthening immunization services since 2005.

UNICEF is now partnering with the WHO and TechNet to create an Immunization Supply Chain and Logistics Hub (iSCL Hub) to serve as a global resource center for vaccine supply chain and logistics knowledge and expertise. The iSCL Hub will provide partners with resources, guidelines, policies, and technical assistance for capacity building and coordination of ongoing CCL initiatives to create synergy between parallel efforts. Work to establish the iSCL Hub was initiated in January 2013.[252]

Project Optimize (2007–2012). Project Optimize (2007–2012), led by the WHO and PATH with funding from the Bill & Melinda Gates Foundation, was initiated to innovate, demonstrate, and facilitate advances in the vaccine supply chain through the use of new and emerging technologies.[253] In 2008, Project Optimize conducted a number of landscape analyses and stakeholder workshops to provide a comprehensive picture of the existing vaccine supply chain to develop a strategy to focus efforts on key areas that would benefit most from technological and scientific advances.[254] Moreover, these initiatives would benefit not only immunization systems, but also supply chains for other pharmaceutical products used by global health initiatives (e.g., maternal health interventions). Project Optimize considered better coordination with the private sector[255] as well as new cool chain technologies. For example, innovation projects resulted in the use of passively cooled produce carts to transport greater volumes of vaccines at more consistent temperatures than could be attained with traditional vaccine cold boxes. Advances in battery-free, solar-powered refrigerators were explored to aid communities that lack reliable access to electricity.[256]

In addition to innovations in equipment, Project Optimize has also supported the development of information systems, training toolkits, technologies, and operational models that were tested and evaluated in the field. The results of these projects and other information are shared at conferences, workshops, in a quarterly newsletter (*Op.ti.mize*),[253] and on the PATH, WHO, and TechNet-21 websites. To make sure that the progress made by Project Optimize continues as the initiative itself comes to an end, Project Optimize has developed a traveling exhibit entitled "Supply Systems for Today and Tomorrow" to reach audiences and share information on how different countries can use the knowledge of potential solutions and remaining gaps to improve their own vaccine supply chains and logistics systems.[257] Building off the accomplishments and areas of opportunity highlighted by Project Optimize, GAVI has also initiated larger efforts to prepare an end-to-end vaccine supply chain strategy.[258]

One of Project Optimize's most notable collaborations has been to demonstrate the feasibility of delivering vaccines using a controlled temperature chain (CTC) vs. the traditional cold chain (where vaccines are maintained at 2°–8°C). CTC is defined as "storing and transporting vaccines in a controlled temperature chain within a temperature range appropriate to the particular vaccine's heat stability profile."[259]

The vaccine MenAfriVac™ was developed specifically

for protection against type A meningococcal disease in sub-Saharan Africa.[260] However, many countries that comprise the meningitis belt have limited cold chain capacity and pose difficult challenges to vaccine delivery. Promising data from the manufacturer indicated that MenAfriVac was stable for a limited time at temperatures up to 40°C, making it a suitable candidate for the CTC approach.

Working with the Drug Controller General of India, Health Canada, and the manufacturer, WHO and PATH were able to obtain a license variation for MenAfriVac, and immunization campaigns using CTC to deliver the vaccine began in November 2012 in northern Benin. The system included temperature indicator cards to designate whether the vaccines exceeded the maximum temperature threshold as well as individual vaccine vial monitors to monitor each vial's cumulative exposure to heat.[261] The CTC approach was considered easy to implement and preferable by vaccinators and supervisors. Moreover, the CTC approach showed numerous benefits including reduced wastage and greater flexibility, as health workers could travel several days to reach target populations without having to return each night to the health post.[261,262]

The use of existing vaccines outside the traditional cold chain has the potential to reduce costs, increase program flexibility, and improve the number of people reached by vaccination efforts (particularly underserved and hard-to-reach populations). However, data must support that temperature variations do not affect the safety and efficacy of a vaccine.[263] Delivery of vaccines using the CTC approach will require additional regulatory guidance and oversight. The FDA's Center for Biologics Evaluation Research (CBER) is working with the WHO to develop scientifically appropriate guidelines for vaccine use that can be used to support handling at the temperature extremes encountered during vaccine transport and delivery during immunization campaigns. Addressing these key issues will be necessary to further facilitate the distribution of other vaccines such as hepatitis B and OPV.

Vaccine Presentation and Packaging Advisory Group. The Vaccine Presentation and Packaging Advisory Group (VPPAG) is a forum in which the public sector can engage vaccine manufacturers on issues related to vaccine packaging and presentation to better support the development of products suitable for the capacities and operational capabilities of developing countries to facilitate vaccine introduction and uptake. Originally established by GAVI in 2007, the forum is now a subcommittee under the WHO's Immunization Practices Advisory Committee. The VPPAG includes members from the International Federation of Pharmaceutical Manufacturers and Associations, the Developing Country Vaccine Manufacturers Network, WHO, PATH, UNICEF, CDC, USAID, GAVI Alliance, the Bill & Melinda Gates Foundation, and others. They have provided guidance to industry on issues such as (*1*) reducing vaccine packaging volumes to accommodate limited cold-chain storage capacity in developing countries, (*2*) the use of vaccine preservatives in multi-dose vials, and (*3*) recommendations for identifying the desired target attributes (i.e., target product profiles) of future vaccines in the development pipeline.[264]

Vaccine stock management and vaccine forecasting. Another fundamental component of immunization logistics management within countries is having the technical capacity to nimbly manage vaccine stock inventories and to accurately forecast future needs for program planning and budgeting purposes at both the national and subnational levels.

At the global level, the PAHO Revolving Fund and the UNICEF Supply Division collect demand forecasts from participating countries to communicate an aggregated demand forecast to suppliers. Demand forecasts are dependent on each country's programmatic requirements including current coverage rates, target populations, estimated wastage, information about current stocks, and stock-outs experienced by the country in previous planning years.[265]

Accurate forecasting of vaccine demand is needed to limit the discrepancies between the estimated number of vaccines communicated to manufacturers and the actual number of vaccines purchased. On the one hand, if the forecasted demand is too low, countries may face critical vaccine shortages or added costs that negatively impact public health. On the other hand, if the anticipated amount of vaccines needed is much higher than the actual number procured, vaccine manufacturers may be adversely affected as a result of excess production, potentially impacting future vaccine pricing and availability.[266]

Importantly, overcoming challenges to accurate vaccine forecasting and logistics management at the country level will include solutions at the local levels to better track vaccine usage and overall demand. A number of initiatives are now under discussion to determine how mobile and digital technologies can be used to manage vaccine inventories at the service delivery level to record the actual number of vaccines administered and to better ensure supplies are available where and when they are needed. For example, the GAVI Alliance has recently partnered with the telecommunications company Vodafone and the U.K. Department of International Development to use mobile technologies to help immunization programs

in remote locations in sub-Saharan Africa manage their vaccine stocks. The program is based on Vodafone's success in providing mobile stock management services to track malaria treatments in more than 5,000 clinics across Tanzania. Pilot tests will be conducted in 100 clinics in Mozambique to test the feasibility, effectiveness, and costs associated with these types of technology solutions.[266]

Recently, the VPPAG has explored the use of two-dimensional barcodes on vaccine labels and packaging in developing country vaccine supply chains to improve the tracking and tracing of vaccines and strengthen stock control.[267,268] In support of these efforts, the GAVI Alliance is working with its partners to develop standards for manufacturers, including guidance regarding the type, format, and information that should be included in vaccine packaging barcodes. Feasibility testing of this technology to track vaccine stock movements from the national to regional to district level is currently being conducted in Tanzania.[268]

NVAC recommendation 2.7: integrating health services with immunization programs to optimize health delivery systems

The ASH should work with the OGA and CDC to assist national governments, development agencies (including USAID), multilateral organizations (including WHO and UNICEF), and civil society in encouraging the use of immunization contacts (through routine systems as well as campaign activities) as a platform for delivering additional health and aid services, and vice versa. Evaluation of these efforts should include the types of interventions, the cost benefits of combining new interventions with global immunization efforts, and the effect these strategies have on building community demand for health services overall.

Vaccines address a limited but important range of specific diseases, but many vaccine programs do not comprehensively address other major public health problems (e.g., vector-borne disease prevention, HIV testing, and availability of contraception). When health services are delivered independently, incentives to use essential public health services may decrease,[22] negatively affecting overall participation in health prevention programs. Conversely, evidence indicates that vaccine coverage rates tend to be higher at health centers that offer a range of services.[269] For example, a study in Zambia that linked immunization to multiple child health interventions in a routine setting (e.g., growth monitoring, vitamin A supplementation, family planning, and health education) was associated with a significantly improved proportion of children who were fully immunized.[270]

The current state of the global economy creates circumstances whereby global health programs are competing against multiple health and non-health priorities for scarce donor and in-country resources. Using patient-centered approaches to combine strategies among immunization and non-immunization programs, especially where programs are synergistic, can potentially decrease competition for resources and reduce intervention-specific costs, especially where transport and distribution mechanisms are shared.[22,40,269] In addition, efforts to link immunization with other essential health interventions can lead to improved efficiency in public health services and broaden the partnership base. For example, the Global Action Plan for the Prevention of Pneumonia and Diarrhea (GAPPD) is a program that has set goals and strategies to scale interventions such as immunizations with strategies such as breastfeeding promotion and antibiotic treatment.[271] Similar integration models have been developed by the WHO.[269,272]

A recent study of NGO-facilitated projects using community-based intervention packages found improved coverage for multiple high-impact interventions simultaneously at the scale of one or several districts. All projects analyzed in a community-based intervention were effective in rural settings in Africa, Asia, and the Caribbean with moderate-to-high child mortality, and all were in countries prioritized on the Countdown to 2015 list, which tracks coverage levels for health interventions proven to reduce maternal, newborn, and child mortality. Coverage levels for all interventions substantially increased despite weak settings.[273] In a health survey in sub-Saharan Africa, researchers found that if non-vaccine interventions were integrated with routine vaccination, coverage for all interventions examined could be substantially higher than current levels. Dramatic increases in coverage of several critical interventions, as high as 5–15 times the current levels, could theoretically be achieved in sub-Saharan African families through such linked delivery.[274]

The ability to efficiently deliver multiple non-vaccine interventions along with routine vaccinations would depend on many factors, including acceptability of the selected services to the public and to health providers, ability to augment facilities to provide adequate storage for commodities (e.g., bed nets) and privacy for delivery of sensitive services (e.g., HIV testing and contraception), sufficient staffing and training of health providers to ensure that the added services do not place undue burden on vaccination programs, financing and logistical support, and improved monitoring and evaluation tools.[274]

Integrating other health interventions with immu-

nization at outreach sessions requires a series of carefully planned and implemented steps. These steps include: (*1*) selecting interventions that can be feasibly integrated at the outreach level; (*2*) instituting inter-sector coordination at all program levels; (*3*) exploring service funding sources; (*4*) conducting joint training and supervision of health workers and program managers; (*5*) ensuring the participation of community-based organizations, leaders, and volunteers; and (*6*) establishing a robust monitoring and review mechanism that provides timely information to communities, health workers, program managers, and policy makers.[275]

Integrated programs have the potential to deliver a multitude of services; however, they can be compromised due to lack of political and financial commitment, shortages of human resources, inadequate monitoring and information systems, and lack of management skills, among others.[40] The unique situation and priorities of each country, along with available resources and any potential impact on existing vaccination programs, must be considered when determining whether and which services to integrate with routine vaccinations.

Examining the theoretical impact of integration is the first step in quantifying and capitalizing on the true potential of integrating delivery of other health services with routine vaccinations.[274] By incorporating scientific evaluation into integration efforts, programs can mitigate the risks that are intrinsic to the bundling of services or systems. Scientific assessments of integrated programs can reveal surprising results and can highlight the key areas that require focus for the successful scale-up of integration efforts. When the integration of diverse interventions is under review, five factors should be examined: coverage, quality, acceptability, complexity, and unintended consequences. It cannot be taken for granted that coverage, quality, and acceptability of immunization will immediately translate to an effective integrated program.[276]

HHS support of efforts to integrate preventive health services with immunization programs. CDC has been at the forefront of evaluating the role of immunization systems as a platform on which to build a robust public health system through the appropriate integration of other health services, and has recently sponsored, and contributed to, a special journal supplement devoted to this issue.[211] CDC works with other global immunization partners to incorporate strong evaluation and operations research into the integration of services and systems to ensure successful integration and the absence of unintended consequences, such as the erosion of acceptance, program performance, or the quality of individual services.

Vaccine advocacy: increasing global demand for vaccines. Ensuring adequate rates of coverage cannot be achieved without a high level of community acceptance and demand for vaccines, regardless of the strength of immunization programs. The second strategic objective of the Decade of Vaccines GVAP is that "individuals and communities understand the value of vaccines and demand immunization as both their right and responsibility."[43] When disease incidence is high, the benefits of vaccination are clear and more accepted by the public. However, as traditional and new vaccines continue to drive down the burden of disease, populations are beginning to face a change in risk perception, where the risks associated with vaccination are disproportionately weighed against the benefits of preventing disease. The public's perception of risk may be further affected by the propagation of misinformation about vaccine safety or adverse events falsely attributed to vaccination.[277] Increases in disease incidence due to public misperceptions about vaccines have been most clearly demonstrated recently in Pakistan and Nigeria, where inadequate acceptance of polio vaccines has contributed to the continued spread of polio during the past decade.[278,279]

While the roots and patterns of these concerns are not completely understood, public health researchers are actively studying ways to analyze factors that contribute to community demand for vaccines. Current studies are investigating global patterns of vaccine safety concerns being voiced in the news and social media to better understand and address concerns and misperceptions of vaccine safety. These findings will help public health officials develop tools and communication strategies to rapidly address public concerns about vaccine safety as they emerge.[280,281]

Research has also shown that a community that is engaged and invested in its immunization program has higher rates of coverage. Interventions using strategies that develop community awareness of the importance of vaccines and integrate community members into immunization programs have increased immunization coverage.[282–287] For example, the GPEI found that in areas where community volunteers participate in polio eradication activities, campaign awareness is higher, fewer parents refuse to give OPV to their children, and there are less missed opportunities to vaccinate. Additionally, they found that when local influential people such as religious, educational, and business leaders in the community endorse polio vaccination and encourage resistant parents to accept OPV for their children, confidence in the safety and efficacy of the vaccine increases. The GPEI also included social mobilization and community engagement in its 2013–2018 Endgame

Strategic Plan, stating that "poliovirus circulation stands little chance of surviving in fully mobilized communities, even in the most difficult contexts."[80]

In addition to developing demand for vaccines among community members, advocacy and outreach efforts should also target health-care workers, as they are integral to vaccine delivery and have a large impact on both the supply of and demand for vaccines in communities.[288–291] Training programs for local health-care workers can provide added skills and knowledge to help promote immunization to patients and increase coverage rates.[292] Many programs have demonstrated how effectively health-care workers can encourage reluctant parents to vaccinate their children.[293–295]

Public confidence in vaccines and immunization programs is critical to continuing the momentum of current vaccination programs and providing the benefits of vaccination to the greatest number of people. The NVAC is currently conducting a comprehensive analysis on vaccine confidence and its impact on vaccination programs. The findings will be detailed in a future NVAC report.

NVAC RECOMMENDATION 3: ENHANCING GLOBAL CAPACITY FOR VACCINE SAFETY MONITORING AND POST-MARKETING SURVEILLANCE

NVAC recommendation 3.1: building global capacity for vaccine safety surveillance

The ASH should identify mechanisms to encourage ongoing collaborations and technical support among HHS agencies involved in post-licensure vaccine safety, the WHO, and related global agencies and partners to (*1*) enhance capacities to build vaccine safety surveillance systems to monitor the safety of vaccines as they are broadly administered, (*2*) assess and respond to vaccine safety concerns or signals to effectively communicate vaccine risks, and (*3*) support the political will to respond to vaccine safety concerns with evidence-based decisions.

Vaccine pharmacovigilance is defined as "the science and activities relating to the detection, assessment, understanding, prevention, and communication of adverse events following immunization, or of any other vaccine- or immunization-related issues."[296] The U.S. has a number of vaccine safety monitoring and surveillance systems that serve as models for data collection and epidemiologic investigation of the causal links between immunizations and adverse events. For example, the Vaccine Adverse Events Reporting System (VAERS), jointly managed by the FDA/CBER and CDC's Immunization Safety Office (CDC/ISO), is a post-licensure, spontaneous (passive) reporting system that detects patterns of severe adverse events following immunization (AEFIs) in the U.S.[297] The CDC/ISO also oversees the Vaccine Safety Datalink, an active surveillance system that collects and links health outcome data and vaccination registry data from participating managed health-care databases to assess vaccine safety signals and conduct epidemiologic studies to verify the role of vaccination in reported adverse outcomes.[298] These and other vaccine safety activities that are ongoing in the U.S. have been comprehensively reviewed in previous NVAC reports.[299]

Maintaining high public demand for vaccination, and consequently high coverage in communities, is dependent on public confidence in immunization programs and the ability to rapidly detect and respond appropriately to vaccine safety signals. Conversely, a lack of a coordinated vaccine safety system, poor risk communication strategies, or a weak capacity to rapidly conduct scientific investigation in response to real or alleged safety concerns can negatively impact vaccination campaigns and feed misperceptions and fears of vaccines.[300–302] The experience and expertise accrued by HHS agencies through the use of these systems can and should be used by the global community in efforts to optimize intelligence on vaccine safety and to build a global platform for vaccine safety monitoring and communication efforts.

Vaccine safety: a global priority. While infrequent, all vaccines are associated with a risk of adverse reactions. Vaccines undergo stringent safety testing during clinical trials prior to their licensure, but often the size and composition of clinical trials may not be large enough to capture rare AEFIs or AEFIs that may occur in subpopulations not enrolled in the clinical trials. As vaccines are broadly introduced into the general population, rare AEFIs may become detected. Moreover, vaccine coverage has increased substantially during the past 30 years,[75] especially in LMICs that may not have the systems in place to monitor for vaccine safety signals. Therefore, it is imperative to implement global post-marketing surveillance systems that can identify rare but serious AEFI signals across countries, estimate the rate of incidence of these signals in local populations, and take action to minimize the potential effects of real or perceived AEFIs on the public and on the immunization system.[303]

The growing global demand for vaccines has generated new opportunities for developing countries to actively participate in the development and manufacture of vaccines, and vaccine manufacturers in developing countries now produce an increasing majority of the world's vaccine products.[304] However, manufacturers

in different countries may have different regulatory standards and capacities than the countries in which the vaccines will be used.

To overcome this challenge, the WHO has created the prequalification process for all United Nations-procured vaccines. Countries that manufacture vaccines for PAHO and UNICEF procurement must meet WHO prequalification standards for vaccine formulation, manufacturing, and quality control set by the WHO's Expert Committee on Biological Standardization.[305] Manufacturing countries must also have a functional national regulatory authority (NRA) in place that meets key performance indicators determined through a WHO assessment process, including the ability to monitor for AEFIs.[306] The benefits of the WHO prequalification process are twofold in that it ensures that procuring countries with poorly developed regulatory capacities have access to reliable, high-quality vaccines, while also providing a mechanism to strengthen the regulatory capacity in manufacturing countries.[307]

Once vaccines have been deployed, there remains a continued need to monitor for rare or unexpected vaccine safety signals that only become apparent when vaccines are used among larger populations and groups with more diverse demographics. The need to monitor for rare or unexpected AEFIs is especially true in LMICs, where use in immunocompromised populations or populations with other known or yet to be recognized medical conditions may reveal important contraindications.[308] Furthermore, many vaccines that are currently under development, such as those targeting dengue, malaria, and tuberculosis, are intended primarily for use in LMICs. Enhanced efforts to implement active surveillance for these and other newly introduced vaccines are needed to determine baselines for AEFIs and refine vaccine recommendations based on safety evidence derived from use in these populations.

The Global Advisory Committee on Vaccine Safety. The WHO Global Advisory Committee on Vaccine Safety (GACVS) was established in 1999 as a group of experts who provide the WHO with an independent evaluation of vaccine safety signals and vaccine safety assessments, enabling the WHO to identify and address global vaccine safety concerns with prompt scientific rigor.[309] The GACVS comprises vaccine safety experts from different academic disciplines, sectors, and countries, and has included representatives from CDC and the FDA.

Their professional judgment is consulted in the development of vaccine policy decisions that affect global vaccination programs and strategies. They provide validation of vaccine safety profiles for all WHO prequalified vaccines, assessments of causality for severe adverse events linked in time to vaccines, and judgment in defining high-risk populations and contraindications for vaccines recommended by the WHO.[303,309] Similarly, national AEFI review committees may consult with the GACVS for their knowledge and evaluation of vaccine safety signals detected within a specific country or region.[309] In addition, the GACVS improves the accessibility of reliable vaccine safety information for the general public.[310]

The GACVS serves as a global forum to discuss new and evolving information on vaccine safety and vaccine safety-related efforts. Although not directly involved in implementing international vaccine safety activities, the GACVS provides the WHO with an independent evaluation of efforts to strengthen global pharmacovigilance and institute standardized approaches to post-marketing vaccine safety surveillance, particularly in LMICs.[309] The work of the GACVS includes supporting, through expert input and evaluation, the drafting and implementation of a WHO-led global vaccine safety strategy that provides a detailed blueprint for achieving effective vaccine pharmacovigilance systems in all countries. The Global Vaccine Safety Blueprint is discussed in detail hereafter.[311]

International vaccine safety activities—a landscape analysis. Before a strategy for achieving global vaccine safety could be conceived, a landscape analysis of existing vaccine pharmacovigilance activities, post-marketing vaccine monitoring capacities, and available resources in LMICs was commissioned by the WHO to provide greater situational awareness of the key barriers to creating an effective global vaccine safety system. The landscape analysis includes a number of studies surveying stakeholder perceptions of the existing processes and procedures, an evaluation of existing systems, and a financial assessment intended to guide global investment priorities.[312]

The analysis showed that 65% of WHO member states, including the majority of LMICs, do not have post-marketing vaccine safety monitoring systems in place.[312,313] In many cases, LMICs that primarily procured vaccines assumed that the producing/exporting countries were monitoring for AEFIs and other vaccine safety issues in the procuring countries as well. In reality, this assumption proved untrue in most cases and highlighted a significant gap in AEFI reporting.[312]

These gaps were further exacerbated in many LMICs by the lack of an adequate and empowered NRA that could respond to potential serious vaccine safety signals.[313,314] Current unmet needs for many countries include a lack of clear mandates to carry out post-marketing surveillance for AEFIs, the legal authority to take action when vaccine safety signals are detected, and regulations and guidelines that establish the roles

and responsibilities for vaccine safety among the regulatory authorities, the national vaccine program, and vaccine manufacturers. Regulators in LMICs called for regulatory mentors and indicators for post-marketing AEFI surveillance activities included in WHO NRA assessments as mechanisms to strengthen regulatory capacity for vaccine pharmacovigilance.[312]

Data collection and information sharing were also significant challenges identified in the landscape analysis. There was general agreement that a global vaccine safety information database would create opportunities to actively collect, aggregate, analyze, and report vaccine safety data, which could enhance causality assessments and investigations.[312] Yet, an understanding of the types of serious AEFIs and case definitions were found to vary at all levels of the reporting system. Health-care workers in LMICs sometimes expressed fear or a lack of knowledge to report AEFIs, which could lead to insufficient and incomplete data due to underreporting of AEFIs.[312,315] Furthermore, a lack of technology infrastructure, such as limited computer access and insufficient Internet capabilities, restricted a country's ability to contribute comprehensive reports.[315]

In 2007, the WHO, under the guidance of the GACVS, initiated a pilot project called the Post-Marketing Surveillance Network (PMS Network) to test the ability to create an international platform for strengthening vaccine safety monitoring and stimulating the reporting and sharing of vaccine safety data for countries that had recently introduced newly prequalified vaccines. By 2011, the PMS Network included 12 eligible LMICs, half of which reported AEFIs to a centralized database run by the Uppsala Monitoring Centre (UMC), the WHO collaborating center for international drug monitoring.[315] Although participation in the PMS Network enhanced country-level capacity to monitor and report vaccine safety data in general, the results of the pilot project underscored many of the important challenges described previously.[312]

Finally, the landscape analysis highlighted that very few countries or international initiatives sufficiently addressed vaccine safety risk communications. Access to reliable vaccine safety information, educational materials on the risks and benefits of vaccinations, an understanding of circulating public perceptions, and a well-developed vaccine safety crisis communications plan are necessary to maintain public trust and participation in vaccination programs.[312]

Standardizing tools to build vaccine pharmacovigilance capacity in LMICs. Surveys of vaccine safety stakeholders and studies on vaccine pharmacovigilance efforts all cited a lack of harmonized tools, such as standard AEFI reporting forms, common databases and compatible information-sharing platforms, wider adoption of standard case definitions, and commonly agreed-upon guidelines, protocols, and codes of conduct, to be major barriers to achieving a truly global vaccine safety support structure.[312,313] A lack of standardized tools within and between countries causes data collected from different countries to be incomparable, thereby limiting their functionality in the aggregation of data for rare vaccine safety signal detection.[312] The use of uniform case definitions and mutually compatible datasets facilitates the ability to (*1*) conduct international epidemiologic investigations by linking multi-country datasets and (*2*) communicate consistent scientific information on vaccine safety to decision makers and the public when serious AEFIs of global concern are suspected.[316–318]

The Brighton Collaboration was formed in 2000 as an independent partnership of volunteers to generate, evaluate, and communicate high-quality information about vaccine safety through the development of standardized AEFI case definitions and vaccine safety monitoring and assessment tools that could be used universally across settings with diverse expertise and resource availability.[319] AEFI case definitions are comprised of the definitions themselves as well as guidelines for the collection, analysis, and presentation of vaccine safety data developed by AEFI-specific working groups.[320] They are then vetted through a separate reference group of experts before being endorsed and disseminated for public use. Currently, the Brighton Collaboration has developed more than 20 standardized case definitions for use in pre-licensure, post-licensure, and post-marketing vaccine safety studies, and definitions have been used for both passive and active AEFI surveillance activities.[321]

Brighton Collaboration AEFI-specific working groups have also developed bridging tools, such as AEFI-specific reporting forms, checklists, and term glossaries, to facilitate uptake and implementation of the case definitions.[322] The Automatic Brighton Classification (ABC) tool is a specialized software tool that helps standardize AEFI classification based on user-entered information on patient symptoms.[323] Wide-scale adoption and use of these standardized tools by LMICs has the potential to greatly enhance the global impact of vaccine safety monitoring activities.

The Council for International Organizations of Medical Sciences (CIOMS) is also instrumental in creating common vaccine pharmacovigilance terminologies and guidelines.[296,311] Members contribute to, endorse, and disseminate the Brighton Collaboration definitions. CIOMS is a nonprofit international organization

formed in partnership between the WHO and the United Nations Educational, Scientific, and Cultural Organization (UNESCO). The CIOMS/WHO Working Group on Vaccine Pharmacovigilance (2005–2011) included international representatives from all sectors to deliberate on consensus definitions and evaluation tools for vaccine pharmacovigilance efforts for use by regulators, national programs, and industry.[296,324]

The ability to coordinate linked datasets of spontaneously reported AEFIs and relevant vaccine safety data also provides a powerful tool for detecting and verifying rare or unexpected vaccine safety signals. The WHO also collects spontaneous surveillance information on AEFIs from member countries through the VigiBase database managed by the UMC.[325] Participating countries have the option to use common software to enter vaccine safety information that has been collected through national pharmacovigilance centers, NRAs, and/or national immunization programs. This information is continuously updated, and vaccine safety signals are detected through an automated data-mining signal detection process using a statistical approach to compare the frequency of potential signals with background levels.[326] When a signal is identified, the WHO conducts case evaluations and, if warranted, causality assessments, and communicates study findings on individual case safety reports through a periodic newsletter. The UMC also provides guidance for countries wishing to establish a national pharmacovigilance center and assists the GACVS in managing the PMS Network.[327]

As the Brighton Collaboration has expanded its mission, it now also includes a number of activities that leverage the growing network of partner vaccine safety experts through the use of data safety monitoring boards and large data linkage projects, such as the European Vaccine Safety Data Link.[328] The Brighton Collaboration has already established a multinational partnership of databases with information on more than 50 million individuals for vaccine outcome studies.

Building off the Brighton Collaboration, the VaccineGRID is an international health information technology platform for linking and sharing health-care information online from diverse health-care databases.[329] This partnership allows public health agencies, health-care organizations, and academics to collaborate on large-scale, hypothesis-driven vaccine safety studies to quantify vaccine effects across populations. Information can be accessed for studies on vaccines and vaccine safety such as meta-analyses, determining incidence rates of AEFIs, comparative effectiveness studies, AEFI signal detection, and quantitative benefit-risk assessments.

Finally, harmonized tools and definitions are effective only if they are understood and used properly by personnel trained in vaccine pharmacovigilance activities. The WHO provides training modules and learning opportunities for national public health officials, immunization program managers, vaccination staff, and members of AEFI review committees through its Global Vaccine Safety Resource Centre.[330] The Resource Centre includes Web-based courses on vaccine safety, training workshops, and vaccine safety training toolkits that are intended to build vaccine safety capacity within countries. For example, a vaccine safety basics course is available online at www.vaccine-safety-training.org. The resources provided by the Global Vaccine Safety Resource Centre are shown in Figure 4.

The Global Vaccine Safety Initiative—blueprint and implementation. As stated in the Decade of Vaccines GVAP, creating greater access to traditional vaccines and introducing new vaccines into LMICs will require an international commitment to coordinating and managing vaccine safety activities.[43,311] The Global Vaccine

Figure 4. World Health Organization Vaccine Safety Resource Centre safety training packages[a]

Area of vaccine safety training	*Available resources*
Basic training needs (remote areas)	• Learning course—Vaccine Safety Basics • Vaccine Safety Basics Training
Basic training needs (requiring direct interaction)	• E-learning course—Vaccine Safety Basics • Vaccine Safety Basics Training • Vaccine Safety Advanced Training
Advanced training needs (e.g., AEFI review committee members)	• Vaccine Safety Basics Training • Vaccine Safety Advanced Training
National trainers (e.g., advanced training participants)	• Trainer resources

[a]World Health Organization. Technical support and trainings: GVS training material [cited 2014 May 14]. Available from: URL: http://www.who.int/vaccine_safety/initiative/tech_support/en/

AEFI = adverse event following immunization

Safety Blueprint (hereafter, the Blueprint) was created to meet this challenge by focusing on overcoming the barriers and gaps in LMICs that were identified in the global vaccine safety landscape analysis and the PMS Network pilot project.

The Blueprint centers on defining three main goals: (*1*) establishing minimal vaccine pharmacovigilance capacity at the country level, (*2*) providing enhanced capacity for vaccine safety assessments in countries introducing newly developed vaccines and countries

-

cines, and (*3*) supporting international coordination and strategic planning to create a collaborative global vaccine safety system. These improved systems will allow for active surveillance of vaccine safety signals, more rapid verification of potential safety signals, scientific investigation of the causal link between vaccines and AEFIs, and better communication of vaccine safety information to decision makers and the public.

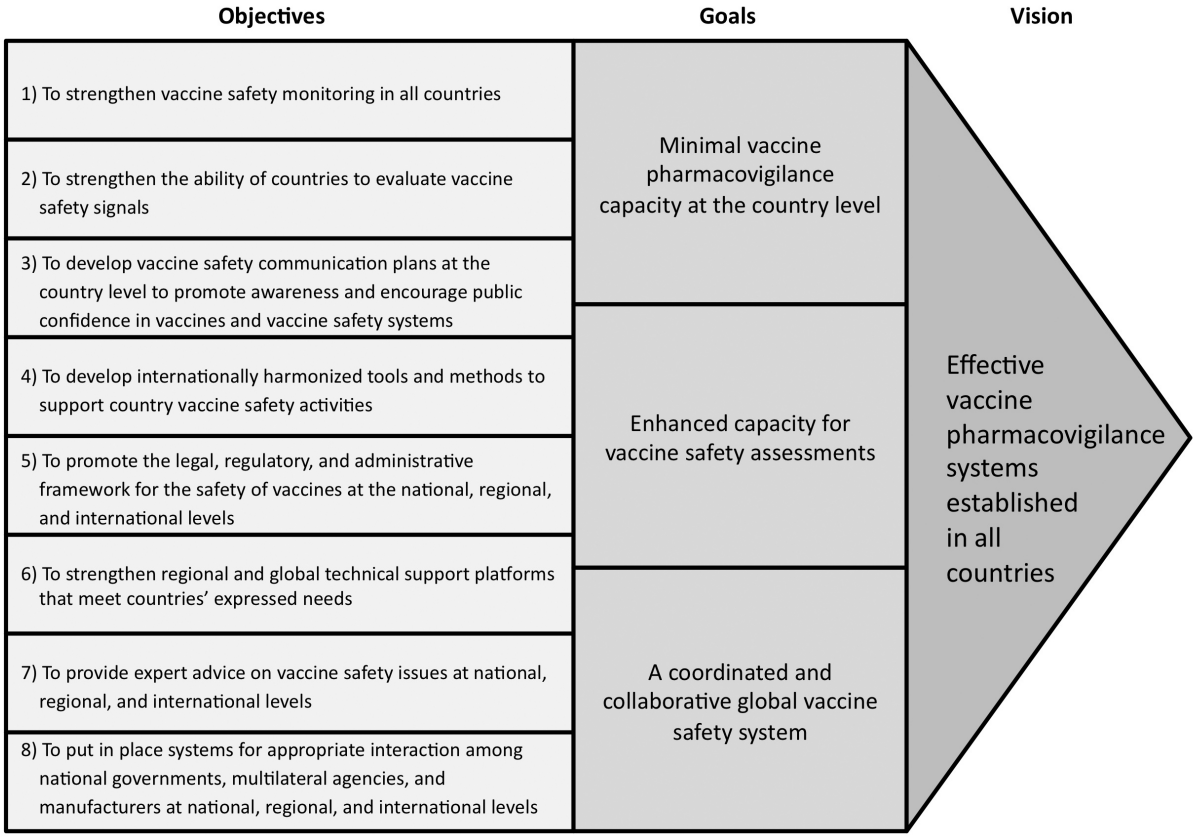
The Blueprint is organized into eight objectives that will achieve each of the Blueprint's three overarching goals. The objectives described in the Blueprint are shown in Figure 5. Under each objective, a rationale is provided in the Blueprint that justifies why the objective is included, as well as target indicators for achieving the objective and the expected outputs that will result when the target indicators have been achieved.[311]

The Blueprint recognizes that country-level programs will require varying levels of international assistance (both financial and technical) to implement the strategies described, especially as new vaccines are introduced into national immunization programs. To guide its implementation, the WHO has created the Global Vaccine Safety Initiative to coordinate international vaccine safety activities and allow a forum for discussion and input from the GACVS and other immunization experts.[315]

The Global Vaccine Safety Initiative is charged

that manufacture and/or use WHO prequalified vac

Figure 5. Overview of the vision, goals, and objectives outlined in the 2011 WHO Global Vaccine Safety Blueprint[a]



[a]World Health Organization. Global vaccine safety blueprint. Geneva: WHO; 2011.

WHO = World Health Organization

with creating a global vaccine safety support structure and includes a detailed work plan for implementing and achieving the vision outlined in the Blueprint.[331] The work product portfolio currently includes more than 80 proposed or ongoing vaccine safety capacity-building activities that are periodically evaluated and prioritized based on their potential impact, the degree of change they will implement, future uses, and if they are standalone or enabling activities.[332] Based on these criteria, projects are given a priority for current and future funding. Detailed descriptions of the different international vaccine safety activities improve visibility of ongoing efforts, thereby preventing duplication or overlap and facilitating resource allocation. The product portfolio will be used as a management tool to track progress and mark milestones of activities under the eight objectives outlined in the Blueprint.[332,333]

HHS activities to promote global vaccine safety monitoring. As mentioned previously, vaccines are used worldwide, and the ability to detect and communicate rare and serious vaccine safety signals is a priority for all nations. HHS participation in these initiatives will help to achieve stronger vaccine safety surveillance both within the U.S. and abroad. CDC participates through its ISO, and FDA/CBER has established the Global Regulatory Utilization of Vaccine Safety Surveillance Initiative[334] to coordinate their respective roles in vaccine safety capacity-building activities.

Experts from both CDC/ISO and FDA/CBER have been called upon to serve as representatives on a number of WHO advisory committees, including the GACVS, the Strategic Advisory Group of Experts (for vaccines and immunizations), and the Expert Committee on Biological Standardization. FDA/CBER and CDC/ISO also participate as members of CIOMS and have contributed to reports issued by the CIOMS/WHO Working Group on Vaccine Pharmacovigilance described previously. CDC/ISO and FDA/CBER also provided input and feedback on the Blueprint and will continue to actively participate in the Global Vaccine Safety Initiative through pilot projects, evaluations, and assistance in prioritizing portfolio activities.

CDC/ISO and FDA/CBER are actively involved in global efforts to standardize vaccine safety case definitions and create harmonized tools for better AEFI detection and response. Both entities support the Brighton Collaboration by reviewing manuscripts and case definitions as part of the AEFI working groups and downstream reference groups. CDC hosts international scientists from LMICs to train with experts in the CDC/ISO to develop AEFI surveillance systems. CDC/ISO also assists WHO in hosting causality workshops and developing causality toolkits to help countries better assess vaccine safety signals that have been detected through passive and active vaccine safety surveillance systems.

As part of the Global Research in Pediatrics Network of Excellence (GRiP Network),[335] CDC/ISO and FDA/CBER have collaborated with the UMC in comparing pediatric AEFIs reported to VAERS and reports sent to Vigibase. Results from these studies are being used to optimize data integration and hone global AEFI signal detection. This pilot project will serve as a foundation for subsequent collaborations with UMC. Similarly, CDC/ISO and FDA/CBER participated in an international study to assess the risk of Guillan-Barré Syndrome following influenza A (H1N1) 2009 pandemic vaccines.[336]

Moreover, CDC/ISO and FDA/CBER support global vaccine safety capacity building through participation in the development of a Pan American Vaccine Safety Network. Efforts include forming a regional committee on vaccine safety, implementing pilot projects to strengthen vaccine safety monitoring, and developing activities focused on crisis prevention and management.[337] FDA/CBER also functions as a PAHO/WHO Collaborating Center for Biological Standardization.

As part of its mission, FDA/CBER works with the global community to increase regulatory capacity through training, sharing of best practices, and serving as a WHO reference NRA for eight prequalified vaccines. Many LMICs are limited in their abilities to successfully implement vaccine pharmacovigilance activities because of insufficient regulatory capacity. In 2012, FDA/CBER awarded a cooperative agreement grant to the WHO to support innovative approaches to vaccine clinical trial design, use of pharmacovigilance tools, and scientific collaboration in pharmacovigilance to advance global access to safe and effective vaccines. An example of these activities includes evaluating the use of social media and mobile communication devices for gathering public health information from LMICs.[338] FDA/CBER also collaborates with the WHO to host seminars and workshops for sharing methods used by FDA/CBER scientists to assess post-marketing safety data and inform subsequent regulatory actions taken for vaccines and other biologics. For example, FDA/CBER collaborated with USAID and others to provide a comprehensive evaluation of regulatory capacity in sub-Saharan Africa[339] and hosted workshops in these countries to provide guidance on how to design strategies that apply a systems perspective to strengthening vaccine pharmacovigilance.

NVAC RECOMMENDATION 4: BUILDING GLOBAL IMMUNIZATION R&D CAPACITY

Vaccine R&D is a global enterprise. Scientific discovery and innovations in immunization technologies, vaccine production, and regulatory science benefit all populations by offering greater access to disease prevention tools and new avenues for product development. Advances in vaccinology are allowing the global community to overcome challenges to vaccine development and extend the benefits of immunization to new target populations. Also, innovative collaborations between the public and private sectors are leading to more efficient approaches to vaccine R&D and manufacturing. These scientific and technological advances are expanding the global capacity to develop, produce, and deliver vaccines for known infectious diseases and those that may emerge.

Yet, the potential impact that vaccines could have on public health has yet to be fully realized. Effective vaccines are still not available for numerous infectious diseases of global concern, such as HIV and malaria. Advances in these areas will require the ongoing support of scientific research to identify new antigenic targets, better understand the immune response, and move novel vaccine platform technologies forward. Research into the implementation of immunization programs can also elucidate factors that affect access to and public demand for vaccines and immunization services, as well as highlight the scientific, technical, and market barriers that may impede continued progress in vaccine development, manufacture, and delivery.

The NVAC recognizes HHS's leadership in vaccine and immunization R&D and the interdependence between domestic and global efforts in these areas. The collective expertise provided by HHS agencies should be used to strengthen and expand vaccine and immunization R&D capacity in many countries. These efforts will increase the likelihood that vaccine candidates and evolving technologies will be identified, tested and evaluated, accessed, and used by the global community. As a result, a robust global capacity for vaccine development and manufacturing will create a world that is better prepared to respond to and protect against new or evolving infectious disease threats more quickly and efficiently.

NVAC recommendation 4.1: basic research: the building blocks for vaccine discovery, development, and delivery

The ASH should support efforts that increase global health research capacity through partnerships between health research institutions in the U.S. and abroad. These partnerships create opportunities to train the next generation of U.S. and foreign scientists to better address current and future global health needs, including the development and evaluation of new vaccines, new vaccine delivery systems, country-specific immunization schedules, and new technologies that facilitate global immunization efforts.

In the past 30 years, basic scientific discovery has been instrumental in creating opportunities for new vaccine development. Breakthroughs in the fields of genomics, bioinformatics, molecular biology, proteomics, and biophysics now make it possible to take a directed approach to identifying and verifying vaccine targets.[340] Infectious disease research has led to a better understanding of the molecular characteristics of pathogens and how specific antigens lead to disease pathologies. Systems biology approaches have helped to elucidate the complex interactions between vaccine antigens and the host immune response.[341]

Furthermore, the expanding repertoire of molecular tools presents a growing number of technologies that serve as development platforms for new and future vaccines. Recombinant protein expression systems[342,343] and conjugation technologies[344] have made it possible to develop safer, more effective vaccines against a number of once intractable infectious diseases. These technologies are undergoing further refinement to optimize their efficiency and use for developing vaccines against new targets, such as bacterial pathogens and other emerging infectious disease threats.[342,343] Promising platform technologies such as deoxyribonucleic acid (DNA) vaccines are still under development. Although none are currently licensed for use in humans, DNA vaccine technologies have the potential to open entirely new avenues in vaccine development.[345] A number of DNA vaccines have entered clinical trials, including dengue vaccine candidates. Finally, there is considerable interest in using adjuvants as a tool to improve the effectiveness and equitable distribution of vaccines to the global market.[346,347] Adjuvants can increase the benefits of vaccines to broader patient populations by stimulating seroconversion in typically hypo-responsive individuals such as the elderly, immunocompromised patients, and nonresponders.[347,348] Importantly, studies indicate that adjuvants boost the effectiveness of antigens, allowing less antigen to be used per dose, thus maximizing vaccine supplies when needed to meet sudden global demands, such as during an influenza pandemic.[349]

Vaccine delivery technologies that have directly benefited LMICs. Advances in vaccine technologies have not only led to the discovery and development of new vaccines, they have also made vaccine delivery safer and more efficient. Innovations are overcoming many of

the logistical barriers immunization programs face in developing countries due to limited human resources, weak supply chains, and fragile health systems. Continued efforts toward developing new vaccine delivery technologies will optimize and strengthen routine immunization activities and SIAs. Examples of vaccine delivery technologies that have already expanded access to safe and effective immunization programs are described hereafter.

Needle-free vaccine delivery systems. In 1999, a systematic review of injection safety in developing countries found that a significant number of injections were deemed unsafe in such countries mainly due to the improper reuse of disposable syringes.[350] Importantly, poor adherence to safety protocols caused increased transmission of bloodborne pathogens in these countries,[350] prompting UNICEF to implement procurement policies that require auto-disabled syringes (a.k.a., auto-disposable syringes or reuse-prevention syringes) for vaccines delivered via routine and mass immunization programs.[351] Now, new strategies to minimize the risks associated with unsafe injection practices involve the development of needle-free delivery systems, including aerosolized vaccines, jet injectors, and microscopic arrays called microneedles.[352–356] Because they do not use needles and syringes, needle-free technologies reduce biohazardous waste, minimize the risks of accidental needle-sticks, and prevent the reuse of disposable materials that can lead to the transmission of bloodborne pathogens between patients. They may also require less training of personnel for delivery, indicating that a greater number of vaccines could be deployed during vaccine campaigns.[353,355] Lastly, needle-free systems can also alleviate fears related to injections, creating the potential for higher acceptance and better completion within populations.[357]

Innovations in the vaccine cold chain. Cold-chain systems have been established to ensure that vaccines are kept at optimal temperatures at each stage of the supply chain until they reach their target populations. However, in many developing countries, poorly functioning equipment, frequent power outages, variations in cold chain needs by product, and the need for better training in cold-chain requirements can often expose vaccines to improper temperatures. Vaccine storage and transport are growing concerns, as the incorporation of new vaccines into national immunization programs can stress already fragile vaccine supply chains.[358] Vaccine vial monitors (VVMs) were developed in 1996 as a technology to identify and discard vaccines that had been damaged by excessive heat exposure.[359] Developed through a partnership among PATH, WHO, USAID, and the Temptime Corporation, VVMs use a HEATmarker™ (Temptime Corporation, Morris Plains, New Jersey) present on the vaccine labels, which irreversibly changes color to indicate a vaccine's cumulative exposure to heat over time, that allows vaccinators to quickly identify damaged vaccine stocks. This technology has aided in expanding vaccine access during campaigns in hard-to-reach areas, and PATH estimates that within a 10-year time span, VVMs will facilitate the delivery of more than 1.4 billion doses of vaccines to people in remote settings.[359] VVMs are also available to indicate if vaccines have been frozen (e.g., FREEZEmarker™ [Temptime Corporation]).

Additional solutions to overcoming vaccine cold-chain challenges have included research on the stability and potency of existing vaccines outside of the standard cold-chain temperature range (see "NVAC Recommendation 2.6: Strategies to Improve Immunization Supply and Logistics Management" section, pages 49-52), developing lyophilized (dry) vaccine formulations and advanced processing technologies to improve vaccine stability and novel vaccine stabilizers that can withstand unfavorable temperature conditions.[360] Recent promising innovations in vaccine thermostabilizing agents have included the use of silk matrices to stabilize vaccine antigens at temperatures up to 60°C (140°F) for up to six months.[361]

Future research needs. Scientific discovery is delivering promising new vaccine candidates, tools, and technologies to take on seemingly intractable infectious diseases such as HIV, malaria, tuberculosis, and dengue. Progress is also being made in gaining a greater understanding of emerging infectious diseases and neglected diseases and their impact on global populations. Despite these encouraging steps forward, important knowledge gaps remain. In some cases, these gaps include a basic understanding of pathogenesis, host-pathogen interactions, the role of specific antigens in eliciting a protective response, or a better understanding of how findings in animal models correlate with human disease.

The immune response to VPDs is not always well characterized. Better understanding of the host immune response; correlates of protection; and impacts of the environment, genetics, age, and other factors on vaccine efficacy and safety are all needed to guide vaccine development efforts, advance candidates through the development pipeline, and direct post-marketing safety surveillance efforts.[362]

Global immunization programs would also benefit from advances in operations and implementation research to identify and overcome programmatic and logistical barriers to routine immunizations and

the introduction of new or underutilized vaccines. Currently, the WHO is conducting a comprehensive assessment of the recommended childhood vaccine schedules at the global and country levels to identify epidemiologic, social, and economic considerations for optimizing national vaccine programs based on local circumstances and data.[363] Likewise, studies to assess immunization program effectiveness and best practices will facilitate the development of tools and strategies to best meet the health needs of developing countries.[364] There is also a continuing need for technological innovations in vaccine supply chain and logistics management to optimize the transport, storage, and delivery of vaccines; to accurately forecast vaccine supply needs; and to create mechanisms to better integrate immunization programs with the delivery of other health services without adversely impacting the required resources of immunization programs.[249]

Finally, interdisciplinary approaches will be necessary to create novel strategies for tackling VPDs. For example, the One Health Initiative facilitates interdisciplinary collaborations to better understand and address the interconnectedness of human and animal health and the health technologies that can benefit both.[365] These efforts are advancing the discovery and development of vaccines for existing and emerging zoonotic diseases. Following the 1999 emergence of West Nile virus (WNV) in the U.S., simultaneous efforts were launched to develop vaccine candidates for both humans and horses using a live chimera vaccine technology originally developed for Japanese Encephalitis Virus vaccine candidates (ChimeriVax™, Sanofi-Pasteur, Swiftwater, Pennsylvania). With funding from the NIH, vaccine developers used a functional backbone of the attenuated yellow fever virus, YFV 17-D, to express structural antigens from WNV.[366] In 2006, the WNV live flavivirus chimera vaccine was licensed by the U.S. Department of Agriculture for use in horses under the trade name PreveNile™ (Merck, Summit, New Jersey). While a WNV vaccine candidate was not further pursued in humans, this technology has been applied to the development of other human vaccines, including vaccine candidates for dengue virus.[367,368]

Building capacity in developing countries through scientific collaboration. In 2011, NIH funded approximately $1.7 billion in vaccine-related research (total of all research activities).[369] Although primarily supported through the National Institute of Allergy and Infectious Diseases (NIAID), multiple NIH institutes support research projects on all aspects of vaccines, immunizations, and global health. In general, NIH-funded research benefits the global community by creating knowledge that can be universally applied to global health problems. For instance, NIH was identified as the single largest funder of neglected disease research, accounting for one-third of the total global support in 2009.[370] More directly, NIH supports researchers in LMICs by helping them obtain the tools, resources, and networks to tackle their own priority health issues.

The NIH's Fogarty International Center (FIC) focuses exclusively on supporting global health research conducted by both U.S. and international scientific investigators and promotes advancing global health by "taking science to where the problems are."[371] FIC, in collaboration with other NIH institutes, has

U.S. collaborations to support vaccine development: the Indo-U.S. Vaccine Action Program

Since 1987, the U.S. has partnered with the government of India to form the Indo-U.S. Vaccine Action Program (Indo-U.S. VAP). This bilateral collaboration includes broad support for vaccine-related research and innovations including laboratory-based research, epidemiologic studies, field trials, vaccine quality control, and vaccine delivery.[a]

The Indo-U.S. VAP has awarded more than $10 million, matched in Indian rupees, to more than 60 collaborative projects involving U.S. and Indian researchers from both academia and government. This fruitful collaboration has produced an estimated 300 publications in peer-reviewed journals. In addition, the program has sponsored more than 30 workshops and expert consultations on vaccines and infectious diseases.[b]

Early Indo-U.S. VAP projects have included the development of a rabies vaccine, a typhoid vaccine, and, most recently, a rotavirus vaccine. The rotavirus vaccine, marketed under the trade name RotaVac™, is a notable achievement. When licensed, it will be the first vaccine developed completely in India.[c]

[a]National Institutes of Health (US), National Institute of Allergy and Infectious Diseases. Indo-U.S. Vaccine Action Program (VAP) [cited 2013 Jun 28]. Available from: URL: http://www.niaid.nih.gov/about/organization/dmid/indo/Pages/default.aspx

[b]McSweegan E. A quarter-century of Indo-U.S. vaccine research collaboration. Microbe 2012;7:1-5.

[c]National Institutes of Health (US), National Institute of Allergy and Infectious Diseases. Results of the RotoVac rotavirus vaccine study in India: statement of Anthony S. Fauci. 2013 [cited 2013 Jul 8]. Available from: URL: http://www.nih.gov/news/health/may2013/niaid-14.htm

supported more than 5,000 scientists in LMICs in investigator-led research and research training programs,[372] and each year more than 2,500 scientists from outside of the U.S. work within intramural NIH laboratories on a number of global health issues. Moreover, the Fogarty International Research Collaboration Award has provided more than 450 grants to support international research partnerships, and approximately 20% of Fogarty awards are granted directly to research institutions in LMICs.[371] These types of collaborations ensure that all populations continue to benefit from cutting-edge science and innovations to solve problems related to health and disease.

NVAC recommendations 4.2 and 4.3: vaccine R&D capacity—strategies to bring forth the next generation of vaccines

Recommendation 4.2
The ASH should encourage HHS agencies to work closely with USAID, WHO, UNICEF, GAVI, end users (including national immunization program managers, Ministries of Health, and national immunization technical advisory groups [NITAGs]), nonprofit product development partners, and vaccine manufacturers to support the WHO in its efforts to define vaccine target product profiles.

Recommendation 4.3
The ASH should support ongoing efforts by NIH and FDA to communicate strategies for minimizing barriers to the development of vaccine products. These efforts enhance the identification, testing, and evaluation of promising vaccine candidates to ensure that candidate vaccines advance more quickly through the development pipeline. HHS should work with other USG agencies, such as USAID and DoD, to coordinate, where appropriate, R&D prioritization to assure efforts are optimized to meet global health needs.

Despite many important scientific advances, the vaccine development pipeline continues to be challenged by high risk and rising costs. The majority of vaccine candidates do not progress successfully through the product development pipeline, and studies suggest that technologically complex targets and increasingly stringent regulatory requirements contribute to high rates of attrition.[373,374] To counter R&D costs, developers have previously focused on vaccines that primarily meet the demands of high-priced markets, which were more likely to generate a sufficient return on investment.[375] For example, in 1993, vaccine sales in high-income countries comprised only 12% of the global volume yet generated 82% of the total revenue.[376] Now, new strategies are being used to stimulate R&D efforts for less lucrative vaccines that are specifically intended to address the needs of developing countries. These strategies include establishing clear vaccine priorities, providing resources to support product development partnerships, and offering technical assistance to facilitate the progression of products through the development pipeline.

Setting and communicating vaccine R&D priorities. Vaccine developers need to know that their products will be met with sufficient demand and a supportive policy environment to rationalize their investments. Yet, epidemiologic considerations, economic considerations, public health awareness, and demand for vaccines can vary significantly across countries. Decision makers can guide R&D efforts by specifying vaccine priorities based on comprehensive evaluations of the local need and the capacity to incorporate new vaccines into the existing national health system. For developing countries with limited resources and health infrastructure, setting vaccine priorities may also help to advocate for greater resource allocation by donor organizations, NGOs, policy makers, and industry partners.

The Decade of Vaccines GVAP does not outline a list of global vaccine R&D priorities in recognition that these priorities may be country-specific. However, the WHO Initiative for Vaccine Research Strategic Plan (2010–2020) was developed to establish a global research agenda to guide the WHO and others in developing research priorities, standards, and guidelines and incorporating research results into policies and practice. The priority areas discussed in the plan emphasize the WHO's role in convening global stakeholders and facilitating the involvement of developing countries in these efforts.[364]

The HHS NVPO, in collaboration with the Institute of Medicine, is supporting the development of a software tool that can help prioritize vaccine development efforts. The Strategic Multi-Attribute Ranking Tool for Vaccines (SMART Vaccines) software prioritizes vaccine products based on attributes chosen and weighted by the user.[377,378] Attributes span broad categories such as disease burden, business opportunities, economic considerations, demographic considerations, scientific/technical considerations, public concerns, programmatic considerations, and policy considerations.[377] The resulting ranked list of vaccines can then be evaluated by stakeholders using a common and transparent platform for discussion.

Stakeholders can also communicate vaccine priorities to the R&D community through the formulation of target product profiles (TPPs), which serve as technical strategies for achieving the characteristics that a vaccine should possess to maximize its adoption by end users. These attributes are usually defined through preliminary assessments at the national level of the need, demand, cost-effectiveness, and feasibility of delivering

the desired vaccine. A TPP may specify characteristics such as target pricing, efficacy, or age range of the population intended for the intervention. TPPs can also be used to formulate clinical research questions that may generate data to answer future policy questions related to the vaccine and its use.[379] For example, a TPP was established as part of the Advanced Market Commitment strategy employed in the development of PCV for use in Africa and Asia (November 2007 SAGE meeting, Session: Pneumococcal Conjugate Target Product Profile).[380]

Product development partnerships. Product development partnerships (PDPs) have played a major role in stimulating R&D activities for vaccines by uniting resources and efforts across academia, NGOs, and the public and private sectors toward achieving a common technological goal. PDPs may also stimulate the market by drawing attention to the prevalence or importance of a public health problem. One study noted that government funding of PDPs through agencies such as USAID and the U.K. Department of International Development increased from 7% of their total support in 2000 to 34% in 2007.[260] Consequently, these investments encourage the participation of new players in the R&D process.[381]

PDPs divide the development process into segments, which can be addressed through the expertise of the individual partners. For example, NIH assists both individual investigators and development partners in evaluating potential vaccine candidates early in the development process by assisting in feasibility studies and providing preclinical and clinical services.[382] In addition, both NIH and FDA assist development partners in identifying and planning for moving a candidate product through different phases of the development pipeline.

The coordination of resources and technical expertise allows the PDPs to pursue a portfolio of more innovative, high-risk projects, including vaccines and technologies that the private sector might not otherwise pursue.[383] In addition, the PDP portfolio approach can reduce the time needed to bring a vaccine to market by pursuing a number of promising candidates in parallel.

To date, one of the most successful vaccine PDPs has been the Meningitis Vaccine Project. Global efforts to control group A meningococcus were ignited following a massive outbreak in sub-Saharan Africa's meningitis belt region. The limited market and pricing requirements (≤$0.50 per dose) for a potential vaccine were among the factors prompting the formation of the Meningitis Vaccine Project as a partnership among the WHO, PATH, and the Bill & Melinda Gates Foundation to accelerate vaccine development.[260] The technology to produce the vaccine was developed by the FDA/CBER and transferred to the Serum Institute of India, Ltd., for manufacturing.[384] Working through the NRA of India, the vaccine was licensed in 2009 under the name MenAfriVac and earned prequalification status by the WHO in 2010.[260] By December 2012, through significant support from the GAVI Alliance, 100 million doses of MenAfriVac were administered in 10 countries,[385] and preliminary evidence suggests MenAfriVac has already had a significant impact on bacterial transmission in vaccinated communities.[386]

In 2000, a study analyzing the global burden of pneumococcal disease estimated that 826,000 deaths occurred in children younger than 5 years of age,

NIH's vaccine and treatment evaluation units and the HIV Vaccine Trials Network

The National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID) supports the development and testing of vaccines both within the U.S. and globally through its network of vaccine and treatment evaluation units (VTEUs).[a] Established in 1962, these sites carry out clinical studies and trials spanning a wide spectrum of infectious diseases. The scope of the VTEUs' work is being expanded to encompass studies in international populations, including in resource-poor settings and in populations with diseases endemic to the specific location.

Internationally, the NIH/NIAID also supports the HIV Vaccine Trials Network (HVTN), a consortium of leading researchers across 27 cities in four continents all focused on developing a safe and globally effective vaccine to prevent human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome. The HVTN works together to optimize clinical trial designs to test and evaluate HIV vaccine candidates on safety, immunogenicity, and efficacy.[b]

[a]National Institutes of Health (US), National Institute of Allergy and Infectious Diseases. Vaccine and treatment evaluation units (VTEUs) resources for researchers [cited 2013 Jun 29]. Available from: URL: http://www.niaid.nih.gov/LabsAndResources/resources/dmid/resources/Pages/default.asp

[b]HIV Vaccines Trials Network. HIV Vaccines Trials Network home page [cited 2013 Jun 28]. Available from: URL: http://www.hvtn.org

NIH = National Institutes of Health

HIV = human immunodeficiency virus

GAVI Alliance pneumococcal advanced market commitments

In contrast with product development partnerships, which focus on supporting the research and development (R&D) process, the advanced market commitment (AMC) approach has been proposed as an alternative strategy to provide incentives for vaccine manufacturers by creating markets through long-term advanced purchase commitments of vaccines at set prices and quantities once the vaccines have been developed.

United Nations agencies, working closely with the GAVI Alliance (GAVI) and the governments of developing countries, procure vaccines developed by the manufacturers at a pre-agreed-upon set price.[a] Donor funds are then used to supplement manufacturers to offset the fixed costs incurred in the R&D process.[b] Once donor funds are depleted, vaccine manufacturers are committed to continue providing a set volume of vaccines at a set price for the duration of the commitment (e.g., 10 years). During this time, GAVI progressively transfers the costs of vaccines to developing countries to ensure that the governments of developing countries create sustainable budget plans for vaccines once the AMC is fulfilled and market forces are in play.[a]

As a proof of concept, the pneumococcal AMC was implemented in 2009 for the development and delivery of pneumococcal vaccines for developing countries. The AMC was supported by donor funds from the Bill & Melinda Gates Foundation and the governments of the United Kingdom, Italy, Canada, Russia, and Norway. Working with vaccine manufacturers, GAVI began introducing pneumococcal vaccines into eligible countries in 2010. Since 2010, GAVI has facilitated the introduction of pneumococcal vaccines to 18 eligible countries and plans to immunize 90 million children with pneumococcal vaccines in more than 50 GAVI-supported countries by 2015.[a]

[a]GAVI Alliance. Pneumococcal AMC [cited 2013 Apr 7]. Available from: URL: http://www.gavialliance.org/funding/pneumococcal-amc

[b]Hargreaves JR, Greenwood B, Clift C, Goel A, Roemer-Mahler A, Smith R, et al. Making new vaccines affordable: a comparison of financing processes used to develop and deploy new meningococcal and pneumococcal conjugate vaccines. Lancet 2011;378:1885-93.

with 95% of these deaths occurring in Africa and Asia.[166] Following the 2000 study, a broad coalition of international partners, including the Gambian government and the British Medical Research Council, NIH/NIAID, the London School of Hygiene and Tropical Medicine, WHO, USAID, CDC, Wyeth-Lederle Vaccines, and PATH, partnered to conduct pneumococcal vaccine trials using a conjugate vaccine containing nine of the pneumococcal serotypes most common in Gambia. Findings from this study indicated that vaccinating infants with pneumococcal vaccines could substantially reduce death and illness from pneumococcal infections.[387] In 2010, the FDA partnered with PATH to advance the development of a low-cost pneumococcal vaccine using conjugation technologies developed by the FDA, as was used for the meningococcal vaccines.[388] Following successful adaptation of the technology in May 2012, FDA scientists trained staff from the China National Biotec Group's Chengdu Institute of Biological Products for five weeks in FDA laboratories to perform the procedure and transfer the technology at no cost.

Other examples of PDPs with vaccines currently under development include:

- The PATH Malaria Vaccine Initiative (http://www.malariavaccine.org)
- Dengue Vaccine Initiative (http://www.denguevaccines.org)
- Aeras (http://www.aeras.org)
- The International AIDS Vaccine Initiative (http://www.iavi.org)

Future product development partnerships may also be used to develop vaccines with improved delivery mechanisms, greater effectiveness, lower costs, or as part of combination vaccines.

NVAC recommendation 4.4: harmonizing regulatory standards to support global vaccine development

The ASH should support efforts to strengthen NRAs in other countries through collaborations with the FDA. The ASH should support ongoing FDA efforts with other NRAs and the WHO to continue seeking opportunities to inform, shape, and communicate global regulatory standards and requirements for the development and manufacture of safe and effective vaccines. In doing so, HHS will continue to strengthen international programs, including building and strengthening global regulatory capacity and quality systems.

Ongoing international collaborations to standardize clinical trial guidelines and strengthen regulatory capacity in developing countries can help minimize the financial and logistical burden on both manufacturers and regulatory authorities. The use of standardized tools and procedures can also strengthen the capabilities of existing regulatory authorities, provide guidance to those just starting to establish regulatory capacity,

and promote transparency of the regulatory process between manufacturers and regulators.[389]

Global harmonization of regulatory standards. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was formed in 1990 as a collaboration between regulatory authorities and industry leaders in the U.S., Europe, and Japan. The ICH works to align technical requirements for reporting and evaluating data on quality, safety, and efficacy of new medicinal products.[390] These efforts include establishing common data requirements and implementing compatible data submission formats for investigational new drug (IND) applications to minimize the redundancies and inefficiencies experienced by vaccine manufacturers when submitting applications to regulatory authorities in multiple regions.[384] For example, the ICH developed a common technical document to harmonize the documentation needed for a new drug application among the three ICH regions. This platform saves both time and resources by providing a common electronic format for documenting and submitting technical data requirements and allowing vaccine manufacturers to simultaneously submit IND applications to multiple ICH regions.[389,391] The common technical document also benefits regulatory agencies by facilitating the exchange of information during the review process.[389]

As interest in harmonizing regulatory practices has grown, ICH has linked its efforts to the broader global community by establishing a Global Cooperation Group (ICH GCG). Members work closely with the WHO and other international organizations to share information about ongoing regional harmonization efforts and to facilitate the adoption and implementation of ICH guidelines regionally and globally. The ICH GCG includes representatives from five regional harmonization initiatives (Asia-Pacific Economic Cooperation, the Association of Southeast Asian Nations, the Gulf Cooperation Council, the Pan American Network for Drug Regulatory Harmonization, and the Southern African Development Community) and focuses on providing tools and resources for participating members.[389]

Although not limited to vaccine development, the ICH has developed standardized guidelines for a number of regulatory issues relevant to the evaluation of vaccine quality, safety, and efficacy. As such, representatives from FDA/CBER participate as members on the ICH's Steering Committee, and FDA works closely with the ICH to promote regulatory harmonization as part of its strategic objectives for improving global public health through international collaboration, including research and information sharing (FDA/CBER Strategic Plan 2012–2016, Goal 2).[392]

Building regulatory capacity in developing countries. Ensuring that national immunization programs can consistently deliver vaccines that have passed high quality and safety standards is paramount to protecting global health. In 1987, the WHO implemented the prequalification program, requiring that all UNICEF- and PAHO-procured vaccines meet the standards for vaccine formulation, manufacturing, and quality control set by the WHO's Expert Committee on Biological Standardization.[305] To date, 27 manufacturers in 21 countries have achieved prequalification status.[393] Prequalification also requires countries that manufacture prequalified vaccines to have a functional NRA in place that meets key performance indicators determined by a WHO assessment process. However, an analysis by the WHO (1997–2007) found that only 58 out of 193 member countries had functional NRAs.[394] Importantly, several countries where clinical trials were planned were found to have inadequate regulatory capabilities or technical expertise to competently evaluate vaccine clinical trial protocols.[395]

The WHO's Developing Country Vaccine Regulators Network (DCVRN) was established in 2004 to strengthen the NRAs of countries with emerging vaccine manufacturing capabilities. These countries include Brazil, China, Cuba, India, Indonesia, the Republic of Korea, Russia, South Africa, and Thailand. Convened annually, the DCVRN offers NRA representatives of member countries the opportunity to build consensus on standards, voice gaps in regulatory competencies, discuss best practices for evaluating clinical trials, and identify areas for increased coordination with more established NRAs (e.g., the FDA).[396]

The original emphasis for DCVRN efforts focused on developing competencies to authorize, monitor, and evaluate vaccine clinical trials. However, discussions now also include information on new vaccines, vaccines in development, and post-marketing issues following vaccine introduction. Their accomplishments include the development of common methodologies and procedures, such as a checklist for Good Clinical Practice inspections and the implementation of an investigational new drug application-like system for NRAs in developing countries (piloted in Brazil and Indonesia).[397] Their efforts have also highlighted the need for NRAs to establish formal mechanisms to interact with NITAGs for better communication regarding the scientific evidence of disease burden, vaccine safety and effectiveness, and potential off-label uses.[398]

The WHO also identified important regulatory gaps in African countries that did not produce vaccines but had been designated to host large, multicenter vaccine clinical trials. In response, the African Vaccine

Regulatory Forum (AVAREF) was established in 2006 as part of regional efforts to provide regulatory expertise and training to these countries. The AVAREF convenes biannually and includes representatives from the NRAs, ethics committees, and scientific advisory committees of 19 African countries. Similar to the DCVRN, the forum's efforts are focused on promoting communication and collaboration among member countries and cooperating partners such as the FDA, the European Medicines Evaluation Agency, PATH, and the European and Developing Countries Clinical Trials Partnership.[395]

AVAREF representatives have collaborated with the WHO, vaccine manufacturers, and clinical trial sponsors to conduct joint reviews of clinical trial applications and clinical trial site inspections. Joint reviews and inspections include all countries currently selected for clinical trials, as well as those targeted for future clinical trial sites. These efforts streamline the approval of clinical trial applications while strengthening the regulatory capabilities in the participating countries. Moreover, joint evaluations give regulators and ethics committee members the opportunity for a more complete understanding of ethical and scientific considerations required when reviewing clinical trial applications and implementing Good Clinical Practice. It has also created better understanding of, and in some cases formalized, the roles and responsibilities of both the NRA and national ethics committees in the clinical trials evaluation process.[399]

FDA/CBER works closely with these types of organizations to provide technical assistance and strengthen global regulatory capacity. FDA/CBER supports the DCVRN through a recurring Foreign Regulators Seminar that provides opportunities for sharing FDA practices and procedures via face-to-face and Web-based interactions. For example, the WHO and FDA hosted a training workshop for the Thai NRA that was intended to strengthen its regulatory capabilities to perform independent evaluation of marketing authorization applications for Japanese encephalitis vaccines. These workshops improve information sharing and work to create a greater network of regulatory expertise for LMICs to consult when planning regulatory capacity-building activities. Similarly, FDA/CBER supports the AVAREF by providing technical support for implementing institutional review boards, attending annual meetings as expert advisors, interacting with ethics committees, conducting joint reviews and clinical trial site inspections, training in adverse event monitoring, and providing advice on how to conduct vaccine clinical trials using global Good Clinical Practice standards.

NVAC recommendation 4.5: supporting the emergence of developing country vaccine manufacturers

The ASH should support HHS agencies in their efforts to develop training modules and workshops for vaccine manufacturers in developing countries on best practices and approaches for vaccine manufacturing and good manufacturing practice GMP guidelines.

Traditionally, multinational pharmaceutical companies have dominated the market, with 70% of revenues generated from the sale of vaccines in high-income countries.[400] However, vaccine manufacturers in developing countries are now emerging as competitive players in the global vaccine market. In-country or regional manufacturing of vaccines provides the advantage of manufacturers working closely with national immunization programs to focus production on vaccines that meet the endemic public health needs, as well as the regulatory standards, of that country.[401,402] Importantly, the increased number of developing country vaccine manufacturers involved in vaccine production contributes to the overall supply of quality vaccines, thereby driving down costs and opening markets to a greater range of developing countries.[402] In addition, broader distribution of manufacturing sites improves the global capacity to provide vaccines, decreases the possibility of vaccine shortages, and creates better surge response capabilities that could be leveraged during an influenza pandemic.[349]

Developing Country Vaccine Manufacturers (DCVM) Network. The DCVM Network was formed in 2000 as an alliance "to provide a consistent and sustainable supply of quality vaccines at an affordable price to the entire globe." Organizations such as the WHO, HHS, and USAID provide technical support to aid in these efforts, which may ultimately lead to achieving WHO prequalification status.[401] The DCVM Network now consists of 38 members, eight members of which are WHO prequalified, enabling the DCVM Network to supply the majority of vaccines purchased by UNICEF and PAHO.[401,403] It is estimated that two-thirds of the world's children now receive at least one vaccine that was produced by a manufacturer in a developing country.[403]

The success of these emerging markets has led to collaborations that use the collective strengths of the DCVM Network. Significant contributions from the DCVM Network expanded the production of prequalified pentavalent vaccines (i.e., DTP, hepatitis B, and Hib), lowering the price per dose and creating a mechanism for the GAVI Alliance to better incorporate these vaccines into its programs.[402] Now, the global

community is leveraging the DCVM Network to augment domestic and regional vaccine manufacturing to maximize vaccine production capacity in the event of an emerging infectious disease of global public health importance, such as pandemic influenza.

Global vaccine production capacity as a key strategy in influenza pandemic preparedness efforts. In 2006, the WHO convened a meeting of subject-matter experts to address concerns regarding the impact of insufficient vaccine supplies on influenza pandemic preparedness efforts. An analysis by the WHO revealed that global production capacity for seasonal influenza vaccines fell several billion doses below the number needed to protect the world in the event of a severe influenza pandemic. Notably, 90% of the world's population does not reside in countries with influenza vaccine manufacturing capacity and would most likely suffer from restricted access to the vaccine in the event of a pandemic. The WHO concluded that protecting these populations would require strategies to expand seasonal and pandemic influenza vaccine production capacity in vulnerable countries.[404] The Global Action Plan for Influenza Vaccines (GAP) was developed to address these concerns.

As part of the action plan, the WHO, in collaboration with the HHS Biomedical Advanced Research and Development Authority (BARDA), implemented the Influenza Vaccine Technology Transfer Initiative, which included assistance to 11 DCVM chosen through a competitive grant process.[404] This initiative facilitated the transfer of technology for influenza vaccine production to the DCVM Network through an innovative technology platform, or technology hub, where multiple DCVM members could access a centralized training facility to learn the basics of producing pilot-scale vaccine lots. Participants could then use this technical knowledge to scale up production in their own facilities.[405] As a result of this initiative, a number of developing countries have incorporated seasonal influenza vaccinations into their national immunization programs. Moreover, the technology hub model was also seen as a cost-effective mechanism for incorporating new vaccines into DCVM portfolios to increase immunization access.[404]

HHS leadership in ensuring global influenza manufacturing capacity for pandemic influenza preparedness. Augmenting global influenza vaccine manufacturing capacity to enhance pandemic preparedness protects both U.S. and global populations from the potential consequences of a severe influenza pandemic. These efforts have been a priority for HHS, and a number of HHS offices and agencies coordinate with the WHO and many other global stakeholders to contribute to the GAP. These efforts also help advance U.S. strategies for national pandemic preparedness.

Since January 2010, the HHS OGA has regularly partnered with the WHO to conduct a series of workshops for governments, international donor organizations, academic institutions, vaccine manufacturers, and other key stakeholders on several topics including technology transfer, regulatory capacity building, global workforce development, health and economic impact of influenza, business modeling for sustainability, and communications on influenza vaccines as a mechanism to foster international collaboration and improve global influenza vaccine manufacturing capacity (Figure 6).[406]

These workshops have been attended by more than 100 participants from more than 30 countries and provide opportunities to build and strengthen partnerships that are necessary for creating local, sustainable influenza vaccine manufacturing capacity. When viewed separately, individual workshops have addressed a main pillar necessary to build and maintain successful influenza vaccine manufacturing capacity. When viewed together, the workshop series has cultivated broad contextual and societal support necessary to sustain vaccine manufacturing. The workshops have added value in that they have led to collaborations extending beyond pandemic preparedness. For example, the African Vaccine Manufacturers Initiative, consisting of 12 African vaccine manufacturers, was launched at the September 2010 workshop in Hyderabad, India, as a direct outcome of the workshop series. The goal of this group is "... to develop and establish capacity in Africa for [the] manufacture of vaccines and biologicals of assured quality and at affordable cost."[407]

BARDA, part of the HHS Assistant Secretary for Preparedness and Response, has also assisted the WHO in expanding influenza vaccine manufacturing in 10 countries, including Brazil, Egypt, India, Indonesia, Mexico, Romania, Russia, Serbia, Thailand, and Vietnam, through U.S.-based and on-site training workshops that provide technical assistance in the science, practice, and implementation of current good manufacturing practices (cGMP) for influenza vaccine manufacturing.[408] For example, in 2011, BARDA collaborated with the WHO, Utah State University, and North Carolina State University to initiate a series of three-week industry-focused training courses for DCVM to build core competencies in influenza vaccine production using cGMP.[408,409] Workshop participants are expected to use the information gained to implement influenza vaccine manufacturing and training of personnel within their own countries.[409] Efforts are also

Figure 6. Influenza vaccine manufacturing workshops co-hosted by the U.S. Department of Health and Human Services/Office of Global Affairs and the World Health Organization, 2010–2013

Date	*Workshop title*	*Location*
January 11–13, 2010	Sustainable Influenza Vaccine Production Capacity Stakeholder's Workshop (http://www.globalhealth.gov/global-health-topics/communicable-diseases/influenza/vaccine-workshops/january2010/index.html)	Washington, D.C.
September 17–18, 2010	International Vaccine Technology Workshop (http://www.globalhealth.gov/global-health-topics/communicable-diseases/influenza/vaccine-workshops/september2010/index.html)	Hyderabad, India
June 8–10, 2011	Workshop on International Regulatory Capacity Enhancement for Influenza Vaccines (http://www.globalhealth.gov/global-health-topics/communicable-diseases/influenza/vaccine-workshops/june2011/index.html)	Sao Paulo, Brazil
November 30–December 2, 2011	Workshop on Enhancing the Global Workforce for Vaccine Manufacturing (http://www.globalhealth.gov/global-health-topics/communicable-diseases/influenza/vaccine-workshops/november2011/wegwvm.html)	Cape Town, South Africa
June 5–7, 2012	Workshop on Health and Economic Impact of Influenza (http://www.globalhealth.gov/global-health-topics/communicable-diseases/influenza/vaccine-workshops/june2012/disease-economic-analysis-workshop.html)	Bali, Indonesia
January 14–16, 2013	Workshop on Business Modeling for Sustainable Influenza Vaccine Manufacturing (http://www.globalhealth.gov/global-health-topics/communicable-diseases/influenza/vaccine-workshops/(Jan%202013)%20Workshop%20on%20Business%20Modeling%20/workshop.html)	Washington, D.C.
June 11–13, 2013	Workshop on Enhancing Communication Around Influenza Vaccination (http://www.globalhealth.gov/global-health-topics/communicable-diseases/influenza/vaccine-workshops/Communication%20around%20Influenza%20Vacciniaition%20(June%202013)/commwrkshp.html)	Atlanta, Georgia

ongoing to work with WHO grantees to support the development and testing of royalty-free adjuvants for use in pandemic vaccines.[408]

HHS agencies continue to contribute to global influenza pandemic preparedness in a number of ways. The FDA/CBER helps support influenza vaccine introduction in LMICs through its function as a WHO Collaborating Centre for Biological Standardization and its work to build and strengthen the regulatory capabilities of NRAs in LMICs. To this end, FDA/CBER awarded a cooperative agreement to the WHO in 2011 as a mechanism to enhance technical cooperation among FDA, the WHO, and member states by providing NRA assessments, training programs for regulators, development of a WHO guideline for nonclinical evaluation of adjuvanted vaccines, and other regulatory capacity-building activities intended to enhance global access to safe and effective vaccines.[410]

Developing new and improved influenza vaccines that would enhance global preparedness is a high priority for NIH/NIAID. The NIAID influenza vaccine research program supports activities in a number of areas, including innovative technologies to improve production flexibility; more broadly protective vaccines; vaccines effective against newly emerging influenza viruses; adjuvant development, from early discovery to clinical evaluation; and safety and efficacy in special populations. NIAID is also working closely with academia and industry to explore the development of universal influenza vaccines based on highly conserved regions of the influenza virus. Such vaccines could obviate the need for annual reformulation and could be readily manufactured in the event of a pandemic.

NIAID's comprehensive influenza research program enabled a rapid response when the H1N1 influenza pandemic began in 2009. NIAID was able to swiftly evaluate the safety and immunogenicity of candidate H1N1 vaccines, conducting nine clinical trials that enrolled almost 3,900 volunteers. NIAID's prior evaluation of H5N1 vaccines established a framework for a coordinated, rapid response to H1N1. As a result, NIAID was instrumental in determining the doses needed to elicit protective responses to H1N1 in healthy adults as well as in special populations.[411]

Incorporating the lessons learned from the 2009 H1N1 pandemic, the Global Action Plan for Influenza Vaccines II (GAP II) will continue to support developing country manufacturers in the development of new influenza vaccines. The revised GAP II will include demand creation activities to complement the push mechanisms of direct assistance to manufacturers. CDC serves as the implementing partner for this part of the GAP-II plan. In this capacity, CDC leverages its international surveillance collaborations and research portfolio to transform disease burden data into communications and cost-effectiveness data that will allow Ministries of Health and international partners to make decisions about the introduction and expansion of

influenza vaccines. A key strategy is the International Vaccine Donation Program, which is a public-private partnership among CDC, Walgreens, vaccine manufacturers, and several low-income countries. This program allows low-income countries to receive vaccine and supplies, with support from CDC, to evaluate the vaccine's safety and effectiveness. The country commits to developing a sustainable influenza vaccine program using the data and value created during the multiyear donation period. Fostering greater use of influenza vaccine in middle-income and developing countries will serve both the USG's disease-reduction goals and its pandemic preparedness priorities.

NVAC RECOMMENDATION 5: STRENGTHENING THE CAPACITY FOR VACCINE DECISION MAKING

Introducing new and underutilized vaccines into national vaccine programs, combined with traditional vaccines, has the potential to save 23 million lives by 2020.[13] Yet, previous experience with the global introduction of the Hib vaccine demonstrates that unnecessarily prolonged delays in introduction can occur when decision makers are unaware of the potential impact that a vaccine can have in improving the health of their populations.[46]

Incorporating new and underutilized vaccines can positively affect national immunization programs, but the overall net benefits are often dependent on a country's ability to adequately plan for and finance new vaccines and new technologies prior to their implementation.[412,413] Therefore, efforts to accelerate vaccine introduction into national immunization programs have focused on creating a systematic approach to vaccine decision making by linking decision-making processes directly to an evidence base founded on vaccine need, cost-effectiveness, potential impacts on the overall health systems, and the vaccine's role in achieving national health priorities.[414] Once policies are implemented, the evidence generated by evaluating their introduction can be used to support those policies, further strengthen communications about the vaccines, and advocate for their uptake and sustained use by the community.[415,416]

NVAC recommendation 5.1: developing an evidence framework for decision making

The ASH should continue to support the development of quality, baseline data and ongoing collection of key data to support informed country-level decisions regarding the development, introduction, and monitoring of new vaccines based on evaluation of disease incidence and prevalence, financial sustainability, vaccine safety and efficacy, cost benefits, and programmatic considerations.

Country-level decisions to support the introduction of new and underutilized vaccines can now be based on the greater abundance of the data expected to emerge from the improved systems that have been described throughout this report, including strengthening VPD surveillance systems and vaccine pharmacovigilance activities. As previously noted, improved data collection and information sharing at the country level will help better establish evidence baselines for disease burden, calculate the predicted impact of vaccine introduction, and emphasize important safety signals and efficacy data expected in a given population. These data can then be used at all levels (i.e., global, regional, and national) to prioritize public health efforts, justify financial commitments in vaccine R&D, and help build public demand for immunization.

In addition to disease burden and expected vaccine efficacy, countries may now consider vaccine introductions on a wider, more complex set of criteria that include economic, logistical, and social factors. These data will ideally represent each country's situation to best plan for vaccine acceptance and sustainability in the national immunization program for the long term.[414,417,418] The WHO has summarized the full scope of considerations within the 2005 guidance document "Vaccine Introduction Guidelines—Adding a Vaccine to a National Immunization Programme: Decision and Implementation."[414]

Economic data and cost-effectiveness analyses are priority areas for most countries when considering investments in new vaccines or immunization technologies, but lack of access to this type of data is also cited as the biggest area of weakness in country-level decision making.[418–421] Following a series of training workshops conducted in 2004 and 2006 by PAHO, the WHO, CDC, and the Bill & Melinda Gates Foundation, Ministers of Health in PAHO's Directing Council Meeting requested that PAHO formalize a mechanism to assist PAHO member countries in better incorporating cost-effectiveness data into vaccine decision making. The ProVac Initiative was formed in 2006 as a region-wide effort to provide technical assistance and resources to countries in Latin America and the Caribbean to better evaluate decisions to introduce new vaccines, such as those against rotavirus, pneumococcus, HPV, and seasonal influenza.[417,419] The ProVac Initiative has supported 24 analyses in 14 Latin American and Caribbean countries to implement the ProVac model in planning/forecasting their vaccine needs.[422] The ProVac Initiative's success has sparked an interest in

other WHO member countries to expand this type of technical support to other LMICs through the formation of ProVac International Working Groups, which facilitate information sharing and dissemination of analytical tools to countries outside of the PAHO region.[423]

In collaboration with the Bill & Melinda Gates Foundation, the PAHO ProVac Initiative has focused on providing participating countries with models and tools to conduct economic evaluations, financial sustainability assessments, and cost-effectiveness analyses.[420,422–424] For example, the On-Line International Vaccine Economics and Statistics repository provides country-specific data on disease burden, population demographics, healthcare use, health-care costs, gross domestic product per capita, and information related to vaccine coverage and immunization services.[425]

In addition to the technical and economic information that informs vaccine decision making, countries should also consider the logistical factors and operational criteria that could be impacted by new vaccine introductions, such as possible effects on the vaccine supply chain or the availability of trained personnel.[358,426,427] Tools to examine and predict the potential impact of incremental changes to a country's national immunization program can help identify unanticipated costs, possible weaknesses, or potential bottlenecks in the vaccine supply chain that would impede their ability to successfully implement a new vaccine into their program. For example, CostVac, developed through the ProVac Initiative, helps to standardize the mechanisms for estimating the total cost of vaccine delivery within a country's routine immunization program. The CostVac tool accounts for all costs due to vaccines and supplies, personnel, and cold-chain requirements and assists countries in establishing a baseline of expenditures for national immunization programs. These data are then used to more accurately forecast the financial impact that programmatic changes (e.g., adding a new vaccine) could have at each administrative level of the immunization program (e.g., central vs. health facility level).[424]

The Cold Chain Equipment Manager (CCEM) tool, developed by PATH in collaboration with UNICEF, WHO, and USAID, assists immunization programs in calculating storage capacity and managing vaccine-related equipment inventories. Similar to tools that track vaccine supplies, the CCEM tool can be used to determine equipment needs (e.g., refrigerators) and help countries budget over time by calculating the financial and programmatic costs of procuring and maintaining program equipment requirements.[428]

Although local data and country-led efforts are important to building sustainable immunization programs, developing countries will still greatly benefit from ongoing scientific and technical support provided by WHO partner organizations.

In 2008, the WHO released guidance to countries for conducting economic evaluations of their immunization programs in preparation for introducing new and underutilized vaccines. This document is intended to standardize the approach to economic analyses so that data shared between countries is transparent, complete, and comparable. It emphasizes the need to present cost-effectiveness data in formats that are easily

GAVI Alliance's Accelerated Vaccine Introduction initiative

At the end of 2008, based on lessons learned from investments in the accelerated development and introduction plans (ADIPs) for *Haemophilus influenzae* type B, pneumococcal conjugate, and rotavirus vaccines, the GAVI Alliance (GAVI) established the Accelerated Vaccine Introduction (AVI) initiative. Working through GAVI partners, the AVI is intended to facilitate a comprehensive approach to preparatory and introduction activities of GAVI-supported vaccines, with an initial focus on rotavirus and pneumococcal vaccines and informing decision making at the country level.[a]

In 2012, the project shifted its focus to vaccine implementation, reflecting the need for GAVI to focus on the post-introduction phase and expand coverage following introduction. These efforts are led by the GAVI Secretariat in partnership with the World Health Organization, UNICEF, and the Vaccine Implementation Technical Assistance Consortium, which consists of representatives from PATH, the U.S. Centers for Disease Control and Prevention, and the Johns Hopkins University Bloomberg School of Public Health. These partners contribute to country-level decision making through numerous activities including, but not limited to, conducting pre-vaccine introduction assessments and post-introduction evaluations, developing communication strategies, providing logistical and management support, formulating policy guidelines and recommendations, establishing National Immunization Technical Advisory Groups, and reviewing applications for GAVI support. The AVI also provides staff support at the country and regional levels to assist in preparing for and implementing GAVI-funded programs.[b]

[a]GAVI Alliance. Accelerated Vaccine Introduction initiative [cited 2013 Jun 29]. Available from: URL: http://www.gavialliance.org/about/gavis-business-model/avi

[b]GAVI Alliance. GAVI Alliance strategy and business plan 2011–2015. 2011 [cited 2014 May 11]. Available from: URL: http://www.gavialliance.org/library/gavi-documents/strategy/gavi-alliance-strategy-and-business-plan-2011-2015

digestible by a range of immunization stakeholders and decision-making bodies. It also includes a summary of attributes of good practice and questions for critical appraisals to aid in improving the quality and usability of the analyses by creating a comprehensive checklist for data collection and evaluation.[429] The checklist can also point to knowledge gaps or areas where further research is needed.

In 2010, the WHO issued the Global Plan of Action for New and Underutilized Vaccines Implementation as a dynamic framework for WHO partner organizations to prioritize and implement programmatic and technical support activities to assist countries in gathering the data needed to inform country-level decisions regarding new vaccines (e.g., generating guidance documents on optimal vaccine formulations/presentations to meet specific country needs). The specified focus areas included norms and standards; country decision making; planning, financing, and procurement; vaccine delivery; integrated approaches to disease control; and monitoring and surveillance. In addition, the Action Plan outlined issues for partner agency assistance particular to each of the designated high-priority vaccines, including vaccines against Hib, pneumococcus, rotavirus, HPV, meningococcus type A, Japanese encephalitis, yellow fever, cholera, and typhoid. Considerations for coordination and support are also posed for dengue and malaria in preparation for future vaccines. This Global Plan of Action for New and Underutilized Vaccines Implementation is presented as a living document with the intention that it will be updated annually with input and lessons learned from partner organizations based on their shared experiences and changing country needs.[430]

NVAC recommendation 5.2: building vaccine decision-making capacity through expert technical advisory groups

The ASH should work with HHS offices and non-HHS partners to increase investments in national evidence-based decision making by NITAGs (similar to the U.S. Advisory Committee on Immunization Practices [ACIP]). Support should include technical assistance and provisions to develop and train these national immunization technical advisory bodies.

Apart from gathering the data that are needed to inform and support decisions about vaccine use and the introduction of new or underutilized vaccines, technical assistance and expert judgment is also needed to interpret, use, and translate this information into effective policies and strategies. To aid the WHO in setting global standards and developing immunization-related policy recommendations and guidance for its member states, the WHO established the Strategic Advisory Group of Experts (SAGE). SAGE is an independent advisory committee consisting of a multidisciplinary group of technical experts that is mandated to provide evidence-driven recommendations, technical evaluations, and position statements on all aspects of VPDs, vaccine research and development needs, vaccine administration, immunization strategies and policies, and linking immunizations to other health interventions.[431]

SAGE work products are often developed in close consultation with other WHO technical advisory committees such as the GACVS, the Expert Committee on Biological Standardization, the Immunization Practices Advisory Committee, and the Quantitative Immunization and Vaccine-Related Research Advisory Committee. The resulting guidance is therefore comprehensive and represents a consensus opinion of the broader scientific and public health communities. Strong supporting evidence leads to strong WHO recommendations, which has been shown to greatly influence a country's willingness to implement new vaccines into their national programs.[46]

Once approved, WHO recommendations may be used to inform country-level decisions and guide assistance programs, donor funding, and vaccine procurement priorities from organizations such as GAVI and UNICEF.[431] Further input advising on the incorporation of new vaccines and immunization technologies may also occur at the regional level through WHO regional Immunization Technical Advisory Groups. However, decisions to introduce and implement new or underutilized vaccines into national immunization programs should ultimately occur at the country level, and WHO recommends that each country establish a NITAG to assist in country-led vaccine decision making.[43]

Although all countries are capable of making national-level decisions about vaccines and vaccine introduction, the capacity to develop evidence-based vaccine and immunization decision making varies among countries. In one study surveying WHO member countries in 2008, NITAGs were reported in 89 of 147 countries (147 of 193 responded), with LMICs being the least likely to report the presence of a NITAG.[432] Similarly, another 2008 survey looking at the Americas found that 12 out of 35 PAHO countries lacked NITAGs. Importantly, this study also found that many NITAGs lacked the necessary financial support from their governments. Moreover, several did not include a sufficient diversity of scientific disciplines among their members (e.g., clinicians, microbiologists, and cold-chain logisticians), and none of the NITAGs in the

Latin American and Caribbean countries included economic expertise.[433] Other analyses have also indicated that the processes and procedures used by individual NITAGs for developing recommendations and policies often differ between countries.[432,434]

Several efforts are now underway to overcome these challenges by providing guidance for establishing NITAGs in countries that lack expert advisors and by providing tools to strengthen evidence-based decision making in countries with existing NITAGs. As mentioned previously, the PAHO ProVac Initiative works to assist PAHO member countries in conducting evaluations of their national immunization programs based on defined technical, operational, social, and economic criteria. Technical support includes networking to academic ProVac Centers of Excellence (focused on decision science and policy research), regional training workshops, Web-based resources, direct technical support when requested, and coordination with more established NITAGs.[419,420,423] For example, as part of ProVac coordination efforts, CDC hosts delegations that include senior Ministers of Health and representatives from national immunization programs in PAHO countries to attend quarterly meetings of CDC's ACIP.[435] The participation of country delegations in the ACIP meetings is facilitated by staff from the PAHO Washington, D.C., office and supported by the Sabin Vaccine Institute. Attendance includes an orientation to the ACIP, an introduction to the framework ACIP uses to establish its evidence-based recommendations,[436] and working sessions devoted to strengthening countries' NITAGs.

Related efforts are being conducted by the Supporting Independent Immunization and Vaccine Advisory Committees (SIVAC) Initiative, which supports the establishment and strengthening of NITAGs in GAVI Alliance-eligible and middle-income countries throughout Africa, Asia, the Middle East, and parts of Europe.[437] The SIVAC Initiative[438] was formed in 2008 as a seven-year partnership among the French Agence de Médecine Préventive, the Bill & Melinda Gates Foundation, the WHO, and the South Korean International Vaccine Institute. SIVAC supports the establishment of NITAGs through a consultative process working directly with national health authorities, WHO, UNICEF, and others to make certain the necessary expertise is available to achieve evidence-based, country-driven decisions.[437] SIVAC provides support and technical assistance to countries to strengthen and improve NITAG efforts either through scientific/technical assistance to committee members or direct support to the secretariat with increasing responsibility shifted to the country to ensure long-term sustainability.[438] In addition, SIVAC has an online resource center, hosts technical workshops, and conducts operational research to enhance the reach and impact of NITAGs.

Recently, SIVAC collaborated with the WHO and CDC to develop a set of performance indicators for assessing NITAGs. These indicators are intended to help evaluate the impact of expert advisory committees on national immunization programs, to better understand their effectiveness, and to aid in activities to further strengthen national vaccine decision-making capacity. Over time, these indicators may also be used to highlight best practices and guide the establishment of NITAGs in an even wider range of countries.[439]

NVAC RECOMMENDATION 6: UNIFYING HHS GLOBAL IMMUNIZATION EFFORTS: LEADERSHIP AND COORDINATION

The culture of HHS is shifting toward a more institutionalized coordination of global health work, as it has become widely accepted that the health of the U.S. is inextricably linked to the health of global populations. Global goals are now integrated into domestic goals, and strategies such as the HHS Global Health Strategy, the NVP, and CDC's Global Immunization Strategic Framework are closely aligned with overarching global health initiatives such as the Decade of Vaccines GVAP. HHS shares its extensive technical expertise, exchanges best practices, and collaborates on health-related issues that contribute to a healthier, safer world in partnership with other USG agencies engaged in global health.

NVAC recommendation 6.1: cultivating HHS leaders in global immunization

The ASH should support ongoing policy revisions to facilitate long-term assignment of HHS professional staff to advance USG immunization priorities, and particularly to international multilateral organizations, on bilateral assignments to support country Ministries of Health, public-private global health partnerships, and other U.S. federal agencies/departments.

The leadership of HHS in global health and global immunizations is apparent in its priorities, defined strategies, and participation in forums dedicated to identifying the best solutions to global health problems. HHS representatives serve as technical resources and delegates to a number of multilateral organizations and international initiatives. The HHS Secretary leads the U.S. delegation to the WHA, representing U.S. interests in global health issues including health security, international guidelines and standards, emergency response, and public health capacity building. HHS

experts contribute to multiple aspects of the Decade of Vaccines, including a representative from NIH/NIAID on the leadership council and HHS members of the Decade of Vaccines Steering Committee and working groups. Representative members from all HHS agencies also serve on expert committees, advisory committees, and technical panels for the WHO, including a number that have been described throughout this report.

Currently, HHS has more than 300 staff stationed in 75 countries in support of advancing global health.[440] HHS has often seconded staff to multilateral organizations, Ministries of Health, other USG departments, and global health organizations to accomplish critical global health work, including in the area of immunizations. These staff assignments have ranged from short-term details to long-term assignments, all within the bounds of HHS-wide policies regarding staffing, which are oriented primarily toward HHS's domestic health work; thus, they sometimes overlook the unique circumstances of global health undertakings.

Efforts have been underway to revise the human resource policies to ensure that they support HHS' global health strategy and its overall priorities, which include strengthening and expanding HHS health diplomacy capabilities. The ability to provide key technical and policy expertise to HHS partners, including in the area of vaccines and immunizations, is critical for international health cooperation efforts. Such assignments are also part of a long-term HHS effort to establish a more formalized global health career track, elements of which could be instrumental in HHS's ability to attract, deploy, and retain key expert staff for global health activities.

NVAC recommendation 6.2: improving HHS coordination across global immunization

As the director of the NVP, the ASH should work with the HHS Secretary, the HHS OGA, and HHS Operating Divisions to define a process to strengthen coordination of HHS-led global immunization efforts. Enhanced coordination would ensure alignment of priorities, minimize duplication of global immunization efforts, support the tracking of progress in a consistent and transparent manner, and facilitate discussing and addressing challenges and barriers on an ongoing basis.

6.2.1. As part of these efforts, HHS should consider convening an HHS cross-departmental working group to create an HHS Global Immunizations Implementation Plan that includes measurable outcomes defined by the HHS agencies, how the agencies will track progress toward these outcomes, and potential barriers to achieving the NVAC recommendations and other objectives described in Goal 5 of the NVP.

6.2.2. An HHS cross-departmental working group should also determine a mechanism to enhance HHS coordination with other USG agencies (e.g., USAID and DoD) and other critical non-USG partners (e.g., GAVI Alliance, UNICEF, WHO, the Bill & Melinda Gates Foundation, NGOs, and product development partners) for improved information sharing and decision making on USG global immunization activities.

6.2.3. The HHS cross-developmental working group should develop an annual report to Congress on HHS investments and HHS impacts on global immunization efforts. This report could be presented as an expanded section of an existing report to Congress or as a standalone product.

6.2.4. When communicating the value of vaccines to the public and decision makers, the ASH should emphasize all of the comprehensive efforts required to optimize disease prevention through vaccination. The ASH should communicate to decision makers that investments in USG efforts in all areas of immunization are required to ensure optimal disease and death prevention and that global vaccination efforts not only save lives in other countries, but also enhance our own domestic health security because the potential for importation of vaccine-preventable infectious organisms into this country is reduced.

6.2.5. This HHS cross-departmental working group should also collaborate with USG agencies to understand how the whole of USG global immunization efforts are supporting implementation of the Decade of Vaccines GVAP, and identify areas where enhanced collaboration can increase the impact of U.S. efforts.

HHS efforts toward global immunizations are many, and global health activities are now tightly woven into the day-to-day operations of many individual HHS agencies. However, it has been difficult to readily identify areas for enhanced collaboration among HHS agencies due to the lack of a unified process for tracking HHS programs, projects, and progress. Better coordination of global immunization efforts within HHS would potentially multiply their impact by allowing agencies and staff offices to build off each other's progress, thereby enhancing HHS's global immunization efforts beyond the sum of its individual parts. Additionally, establishing a more institutionalized platform for coordination of activities can assist HHS in communicating its successes and global health service to leadership and the public. Finally, better coordination within HHS will also facilitate communicating about critical public health issues and departmental priorities, capabilities, and resources for global immunizations with other USG agencies (e.g., USAID) and other critical non-USG partners (e.g., GAVI Alliance, UNICEF, WHO, and the Bill & Melinda Gates Foundation).

CONCLUSIONS

Vaccines save millions of lives every year and are deemed one of the most cost-effective strategies in public health. As new vaccines become available and routine immunization systems are strengthened to more effectively reach greater populations, the global health community has the potential to substantially reduce childhood mortality and alleviate the economic and societal burdens VPDs impose on nations around the world. Deemed the Decade of Vaccines, there is now a unique opportunity to build on the momentum of these and other global health efforts to ensure that all individuals and communities enjoy lives free from VPDs.

The global immunization efforts described in this report demonstrate the power and reach these programs can achieve in improving global health for all people. In accordance with its charge, the NVAC has provided an analysis of HHS's role in global immunization efforts to identify key areas where HHS can best continue to contribute, consistent with the HHS Global Health Strategy and Goal 5 of the NVP.

These efforts showcase how the expertise housed within HHS is being applied to numerous important, yet unresolved, challenges in global immunizations. The NVAC believes HHS has a vital role to play in the global efforts to realize the Decade of Vaccines vision. The NVAC calls on the ASH to continue to make certain that global immunizations remain at the forefront of HHS global health priorities. HHS activities should take into consideration the available resources and how they can be applied to areas with the greatest opportunity to enhance global immunization programs. New HHS activities and collaborations should not adversely affect the funding or impede the progress of existing activities. As such, the NVAC submits these recommendations to the ASH for his consideration.

The views represented in this report are those of the National Vaccine Advisory Committee. The positions expressed and recommendations made in this report do not necessarily represent those of the U.S. Department of Health and Human Services, the U.S. government, or the individual working group members who served as authors of, or otherwise contributed to, this report.

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