PNEUMONIA

STRATEGY OVERVIEW

OUR MISSION

Guided by the belief that all lives have equal value, the Bill & Melinda Gates Foundation works to help all people lead healthy, productive lives. Our Global Health Program supports this mission by harnessing advances in science and technology to save lives in poor countries.

We focus on problems that have a major impact on people in the developing world but get too little attention and funding. Where proven tools exist, we support sustainable ways to improve their delivery. Where they don't, we invest in research and development of new interventions, such as vaccines, drugs, and diagnostics.

Our financial resources, while significant, represent a very small fraction of the overall funding needed to improve global health on a large scale. We therefore advocate for policies and resources to provide people with greater access to health solutions. Strong partnerships are also essential to our success in making a difference and saving lives.

THE OPPORTUNITY

Significantly reducing pneumonia, an acute infection of the lower respiratory tract caused by a number of different viruses and bacteria, is within the global health community's grasp. There are now proven vaccines available against *Streptococcus pneumoniae* (pneumococcus), *Haemophilus influenzae* type B (Hib), and influenza. There are also vaccines against measles, and an improved vaccine against meningococcus A will be available soon. These are all a part of our pneumonia strategy.* Partners such as the **GAVI Alliance** (formerly the Global Alliance for Vaccines and Immunisations), the **Measles Initiative,** and the **Hib Initiative** have already achieved significant reductions in the burden of pneumonia through the adoption and scale-up of these vaccines. For example, between 2000 and 2007, measles deaths in Africa fell by 89 percent as a result of improvements in routine immunization coverage during the first year of life and in mass vaccination campaigns (which provide a second opportunity for vaccination).[1]

However, with more than 2 million infant and child deaths each year,[2] pneumonia is the leading cause of childhood mortality in the developing world. About 156 million childhood pneumonia cases occur each year, with 97 percent in the developing world.[3] Pneumonia remains "the forgotten killer of children" due to a lack of attention and funding.[4]

Reducing the burden of pneumonia involves risk reduction through proper nutrition, early and exclusive breastfeeding, and reducing indoor air pollution, as well as vaccination and accurate diagnosis and treatment. Ideally, vaccines would be the best way to prevent pneumonia. However, current vaccines have a number of drawbacks, as they can only reduce pneumonia caused by certain pathogens. For example, vaccines against pneumococcus are limited in supply and often too costly for health programs in developing countries to afford, so they are not yet reaching all the infants and children who need them. Some are not tailored to the needs and epidemiological situations of various target countries. Knowledge gaps within the etiology and epidemiology of pneumonia delay the creation and implementation of new vaccines.

Children who are sick need adequate care, but access to effective diagnostics and treatments is currently insufficient. The global community's lack of awareness of pneumonia and its impact on families and communities limits funding needed to save lives.

OUR STRATEGY

We aspire to reduce the number of children in the developing world who are sick or dying from pneumonia, meningitis, influenza, and measles. Our approach emphasizes the prevention of pneumonia through the discovery, development, and delivery of vaccines.

* Our pneumonia strategy addresses pneumonia, meningitis, influenza, and measles. These diseases are grouped together because they are caused by respiratory pathogens, including pneumococcus, Hib, respiratory syncytial virus (RSV), the measles and influenza viruses, and *Neisseria meningitidis* (meningococcus).

Reducing the incidence of measles in young children through vaccination is also key to helping reduce deaths due to pneumonia. Details of our efforts to control measles are included in our Delivery strategy.

To ensure the health and survival of the children and infants who develop pneumonia, we are also investing in the creation and delivery of diagnostics and treatment. We aim to close knowledge gaps in order to inform the development of better interventions against pneumonia and advocate for expanded financing to ensure these interventions reach all who need them.

Our strategy relies on deep partnerships with both the public and private sectors to foster the development of products that will be affordable and accessible for use in the developing world.

INTERVENTION AREAS

Develop a better understanding of the origins and causes of pneumonia

There are still major knowledge gaps regarding the amount of pneumonia infection due to pathogens other than pneumococcus, Hib, and measles. More specific information on the etiology and epidemiology of childhood pneumonia is urgently needed to better describe the distribution of pneumonia by its principal causes, and highlight appropriate actions to reduce mortality.

We are supporting the **Johns Hopkins Bloomberg School of Public Health** to lead the Pneumonia Etiology Research for Child Health project, which aims to characterize the etiology of severe pneumonia in developing countries using standardized clinical and epidemiologic methods and state-of-the-art laboratory tests. This project will provide new information to drive development of vaccines and improvements in diagnosis and treatment policies.

Develop and deliver more affordable and effective vaccines

In cases where proven vaccines against pneumonia exist (such as pneumococcus and Hib), we are supporting their rapid scale-up and delivery. In cases where vaccines against pneumonia are ill-suited to the epidemiological profile of developing countries, we support the development of more affordable and effective vaccines. Additional research is needed to develop new or improved low-cost, effective vaccines that offer long-lasting immunity against pneumococcus and other pneumonia-causing pathogens.

To ensure access, our strategy promotes the development of first- or second-generation vaccines by low-cost vaccine manufacturers in developing countries. Details of our investment activities by each disease are outlined below.

Pneumococcus

Pneumococcal disease is the leading cause of child pneumonia deaths, as well as the second-leading cause of childhood meningitis deaths. Annually, up to 1 million children under 5 worldwide die each year from pneumococcal disease.[5]

More than 90 strains of pneumococcus have been identified, but only about a dozen routinely cause invasive pneumococcal disease (IPD). In 2000, PCV7, a seven-valent pneumococcal conjugate vaccine that confers immunity against seven common serotypes in young children, was approved in the United States and made part of routine childhood immunization. The vaccine has seen broad uptake in rich countries and has reduced the incidence of IPD in both children and their contacts. However, the cost of PCV7 has remained so high that developing countries cannot afford to introduce it into their immunization programs. Furthermore, the vaccine does not protect against some key serotypes that cause significant disease and are found more frequently in children in the developing world.

We are working to address this challenge through two initiatives. First, we are helping create and implement the **Advance Market Commitment (AMC) for Pneumococcal Vaccines,** which aims to stimulate the late-stage development and manufacture of suitable and affordable vaccines against pneumococcus for developing countries. Through the AMC, donors commit money to guarantee the price of vaccines once they have been developed, thus creating the potential for a viable future market. These commitments provide vaccine makers with an incentive to invest the considerable sums required to conduct research and development and build manufacturing capacity. The AMC will allow GAVI to purchase pneumococcal vaccines for developing countries for $3.50 (U.S.) per dose, and countries will co-pay a percentage of that price.

In some populations, vaccination with PCV7 has coincided with an increase in the rate of illness caused by non-vaccine pneumococcal strains, a phenomenon termed "serotype replacement."[6] Thus, while PCV7 remains highly effective, serotype replacement may erode its benefits over time. Careful tracking of serotypes and the development of vaccines with broader serotype coverage is critical. This is why we are supporting partnerships led by **PATH** to develop next-generation, protein-based vaccines to prevent pneumococcal infection regardless of serotype.

Hib

Hib is responsible for nearly 400,000 deaths each year in children under 5, and around 3 million cases of serious illness resulting in long-term consequences such as deafness, learning disabilities, paralysis, and mental retardation.[7,8]

Effective vaccines against Hib have been available for more than two decades, and a substantial portion of the population in wealthy nations routinely uses Hib vaccines in childhood immunization programs, resulting in virtual elimination of the disease. Numerous studies have demonstrated the impact on hospitalization rates and outpatient disease upon introduction of the Hib vaccination[9] and the World Health Organization (WHO) has recommended that the vaccine be included in all countries' routine infant immunization programs. However, vaccine coverage remains low in the developing world due to the vaccine's high cost and limited information about this disease in some areas.

Expanding coverage of this effective vaccine is urgently needed. To improve immunization coverage against Hib and other diseases, our primary investment is in the **GAVI Alliance.** More information about our work with GAVI can be found in our Delivery strategy.

Meningococcus

Meningococcus is an important cause of life-threatening infections, including sepsis, pneumonia, and meningitis, in infants, children, and young adults. The major pathogenic meningococcus serogroups are A, B, C, W135, and Y. Serogroup A causes devastating epidemics across what is known as the African meningitis belt, which extends from Ethiopia to Senegal, putting more than 400 million people at risk.

Current polysaccharide vaccines against the main serogroups A and C are used to contain meningitis outbreaks through reactive mass-vaccination campaigns. However, these vaccines have poor efficacy in young children, do not provide long-lasting protection, and do not generate community immunity. As a result, they can limit the impact of epidemics but not stop them from occurring. Polysaccharide-protein conjugate vaccines have proven effective in developed countries, but they are too expensive for use in the meningitis belt.

With our support, the **Meningitis Vaccine Project** is addressing these issues by developing and licensing a new serogroup A conjugate vaccine. Licensure is expected in 2009. The availability of this vaccine is expected to allow countries to develop proactive vaccination strategies in order to eliminate epidemics of meningitis A.

Respiratory syncytial virus

Respiratory syncytial virus (RSV) is perhaps the most important viral cause of lower respiratory tract infection in infants and children worldwide. The global disease burden is estimated at 64 million cases and 160,000 deaths every year.[10]

While monoclonal antibodies are available in the developed world to prevent serious RSV in the most at-risk infants, they are too expensive and difficult to administer in developing countries. We believe the best solution would be a vaccine, but development has been difficult for several reasons. Natural immunity to RSV is transient and incomplete, so reinfection is common. The virus is highly seasonal and causes the greatest number of deaths in those younger than 6 months, which has complicated the design and execution of clinical studies. Finally, host immune responses appear to play a significant role in the pathogenesis of the disease. In the 1960s, an inactivated virus vaccine administered to young children subsequently resulted in exacerbated illness when they were naturally infected, resulting in two deaths. This major setback to RSV vaccine development took decades of research into pathogenesis to untangle. Currently, companies in the United States are pursuing both purified protein and live-attenuated virus vaccine candidates, and one is conducting Phase I/II studies of a live-attenuated vaccine.

To build the evidence base for interventions against RSV in the developing world, we are investing in studies to evaluate the burden of RSV in developing countries. This will help predict the potential impact of new interventions, such as vaccines, and target them for greatest cost-effectiveness.

Influenza

Influenza, a viral infection of the respiratory tract, is a priority investment area for us because of the ongoing toll of seasonal influenza epidemics. Influenza primarily affects infants, pregnant women, and the elderly, and causes 250,000 to 500,000 deaths around the world each year.[11] Many vaccines are available against seasonal influenza, but in developing countries the majority of the population at risk of complications from influenza is not vaccinated. This is in part because the true burden of influenza in developing countries is under-recognized, and also because the seasonal influenza vaccines require annual re-administration. Maternal immunization and the resulting passive immunization of young babies may be an important strategy to reduce infections from influenza, but more research is needed on this promising approach.

The emergence of the new influenza A (H1N1) virus underscores the importance of the ability to rapidly manufacture influenza vaccines in more countries. New, affordable vaccines are urgently needed to protect developing-country populations and strengthen worldwide efforts to contain an outbreak. Based on discussions with partners, we have proposed a set of eight principles to guide global allocation of pandemic vaccine in order to reduce the adverse effects of an influenza pandemic in developing countries.

In light of current shortages of existing vaccines, the growing H1N1 pandemic, and the need to find alternate vaccine strategies, we are making investments to:

- determine the impact of influenza in the developing world
- support the development of new low-cost and cross-protective vaccines to address pandemic and seasonal influenza in the developing world
- evaluate the potential benefits of maternal influenza immunization
- advocate for equitable access to pandemic influenza vaccines

Develop novel diagnostics and improve access to treatments

Chest radiographs are considered the best method for diagnosing pneumonia, but are limited in poor countries. WHO recommends the use of clinical signs, such as fast breathing, for the diagnosis of non-severe pneumonia. However, these signs can have causes other than pneumonia, and many children receive antibiotics unnecessarily.[12] Conversely, in malaria-endemic areas, many children are treated presumptively for malaria when they may in fact have pneumonia. This results in unnecessary use of expensive antimalarial drugs and delays in the appropriate treatment of children with pneumonia.[13] New methods to diagnose infection are urgently needed to inform the care of sick children.

As infants are not fully immunized until 6 months of age, infant vaccines are not fully effective. Specialized approaches are needed to treat serious infections in infants less than 6 months old. While antibiotics and oxygen therapy hold promise to improve clinical outcomes for children who contract pneumonia, there are challenges to these approaches, including the poor availability of pediatric antibiotic formulations and a lack of a reliable source of oxygen in hospitals. To address these challenges and support the diagnosis and care of sick children, we are investing in activities to:

- develop diagnostics to inform treatment
- improve the availability of pediatric medicines, particularly antibiotics for young babies and children, by encouraging safe dosages, low-cost raw inputs, and smart procurement strategies

Advocacy for commitment to and funding for pneumonia

WHO and the United Nations Children's Fund (UNICEF) recently embarked on a collaborative effort to advance the case for the rapid control of childhood pneumonia through their Global Action Plan for the Prevention and Control of Pneumonia.[14] This effort is a positive sign that the global health community is coalescing around a common agenda and sees the critical importance of addressing pneumonia.

However, even though pneumonia contributes to such a large burden of disease, pneumonia's funding still lags behind other diseases. The framework for international

Grand Challenges in Global Health

Through our Grand Challenges in Global Health initiative (www.grandchallenges.org), we are working to stimulate innovation in vaccine research and other health issues facing the developing world. This includes projects to:

- design, build, and validate a high-throughput platform for vaccines to optimize vaccine stability
- develop vaccines that are resistant to freezing and form protective matrices at elevated temperatures
- develop a targeted, mucosal, vaccine-delivery technology
- develop a live recombinant attenuated salmonella anti-pneumococcal vaccine for newborns

We also award small grants of $100,000 (U.S.) each to support early-stage research projects through our Grand Challenges Explorations initiative. Some of the grants in the area of pneumonia include ways to:

- understand the mechanisms of mucosal immunity in the lungs and explore the potential for a vaccine based on these findings
- explore biosynthetic immunotargeting for pneumococcal treatment

cooperation in the event of a flu pandemic also remains fragile. We are currently making investments to catalyze the global agenda in support of pneumonia by supporting activities to:

- foster cooperation between governments, the private sector, and nongovernmental organizations to improve pandemic preparedness in developing countries
- link with maternal and child health advocates to increase resources and highlight strategies to reduce childhood mortality, including the burden of pneumonia

PROGRESS

The following is a snapshot of some of the preliminary successes in reducing childhood death and illness due to pneumonia:

- The **Meningitis Vaccine Project** is completing the development of a new serogroup A conjugate vaccine. In a recent clinical study, the vaccine showed excellent safety and immunogenicity in children ages 12 to 23 months.[15] With licensure expected in 2009, the new vaccine will hopefully shift the control of epidemic meningitis from reactive attempts to limit the size and duration of meningitis outbreaks to routine prevention of epidemics.
- **GAVI** helped the governments of Rwanda and Gambia launch the first national immunization programs against pneumococcal disease in the developing world by facilitating the delivery of the PCV7 vaccine.
- **GAVI** helped launch the pneumococcal AMC, which obligates donors to commit money to guarantee the price of pneumococcal vaccines once they have been developed, thus creating the potential for a viable future market. The currently existing pneumococcal vaccine is sold at more than $70 (U.S.) per dose in industrialized countries. However, thanks to the AMC, the long-term price for developing countries will be $3.50 (U.S.).
- **PATH** and **Intercell AG** supported the launch of a first-in-human clinical trial for a "common protein" pneumococcal vaccine candidate. The Phase I clinical trial, which is taking place in Germany, will test the safety and immunogenicity of IC47, a recombinant subunit vaccine consisting of three conserved surface proteins from pneumococcus. Vaccines containing proteins common to all pneumococcus serotypes are promising because they could provide broad protection to children worldwide.

CHALLENGES

As interventions such as vaccines and antibiotics are delivered more widely, they may promote changes in the pathogen landscape such as serotype replacement and the spread of antibiotic resistance. A timely response to these changes will require ongoing monitoring, which in turn requires efficient detection methods, capable laboratories, and robust reporting systems. A failure to implement these systems and integrate new data into planning and policy will allow the erosion of gains made by these interventions. We are working to improve the ability of laboratories to detect these changes in the pathogen landscape and summarize the results in support of setting appropriate policies.

THE WAY FORWARD

Thanks to the work of our partners, including WHO, UNICEF, GAVI, the Hib Initiative, PneumoADIP, and others, the global health community is beginning to recognize pneumonia as a major health problem and take action to address it. We must capitalize on this momentum and act quickly to accelerate uptake of current interventions and those in the pipeline. Strong partnerships will continue to be the key to success. We look forward to working with all our government, donor, private-sector, research, nongovernmental, and community partners to save children from pneumonia.

TO LEARN MORE

About the Global Health Program:
www.gatesfoundation.org/global-health

About Pneumonia:
www.gatesfoundation.org/pneumonia

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