

ACCESS TO VACCINES

Vaccines bring long-term societal benefits to all

Vaccines are powerful tools that help control diseases. Unlike many other health interventions, they help people stay healthy, and in doing so they help remove a major obstacle to human development.

Today, more than 27 common infectious diseases are preventable with vaccines.¹ In addition to their impact on mortality, vaccines contribute significantly to the reduction of illness and long-term disability in children and adults and generate savings by reducing visits to the doctor and hospitalization. Immunization brings broad, long-term economic and societal benefits, including increased educational attainment and productivity gains, as vaccination reduces the time parents need to spend taking care of a sick child, and also has the potential to reduce absences from school, for instance during dengue outbreaks.

In 2012, some of the leading experts on health economics ranked childhood immunization as one of the three most cost-effective ways to advance global welfare. They estimated that spending approximately US\$1 billion annually on expanded immunization coverage would prevent one million children's deaths per year.² Put into economic terms, the benefits would be 20 times greater than the costs.

For more information, see: <http://www.sanofipasteur.com/en/>

What vaccines have brought to society³

The impact of vaccines on global public health has been impressive. Smallpox was declared eradicated by the World Health Organization (WHO) in 1979 after a global vaccination effort. In 1988, polio was endemic in 125 countries, paralyzing an estimated 350,000 children every year. In 2016, the poliovirus remains endemic only in parts of three countries—the smallest geographic area in history. Between 1990 and 2008, estimated measles-related mortality among children under five decreased by 86%. Since the launch of the Global Alliance for Vaccines and Immunization (GAVI) in 2000, an increasing number of developing countries have introduced hepatitis B, Hib, pneumococcal and rotavirus vaccines into their routine vaccination programs, in line with WHO recommendations. Together, the original Expanded Program for Immunization (EPI) vaccines plus hepatitis B and Hib vaccines prevent more than 2.5 million deaths each year.⁴ A recent study concluded that vaccines had avoided 100 million cases of severe infectious disease in the last 90 years in the United States.

Remaining challenges

Despite these significant achievements, there is still a long way to go. More than 22 million children worldwide (one child out of five, mostly in low-income countries) currently do not have access to even the most basic package of childhood vaccines.⁵ At the same time, in other parts of the world, including high-income countries, the benefit of vaccination is becoming less obvious to some populations. As a consequence of lower vaccination coverage, we are witnessing the resurgence of diseases that had almost disappeared, such as measles or pertussis.

Our commitment to sustainable access to vaccines

Access to vaccination is hampered by multiple barriers that may be structural (e.g., health systems, conflicts, affordability, etc.) or societal (behaviors, education, beliefs). This multifactorial challenge can only be addressed by committed partnerships between all those who have a stake in the sustained success of vaccination and prevention programs.

True to our vision of a world where no one suffers or dies from a vaccine-preventable disease, Sanofi Pasteur is committed to working on multiple levels to optimize the impact of vaccination:

- Developing a broad portfolio of vaccines and solutions to address worldwide epidemiological challenges
- Playing an active role in key public-private partnerships
- Providing effective and affordable vaccines and protection to all populations, regardless of their level of wealth
- Contributing to local capacity building of healthcare systems to prevent infectious diseases

¹ <http://www.cdc.gov/vaccines/vpd-vac/default.htm>

² GAVI Alliance Library & News, Mid-term review, October 30, 2013. <http://www.gavialliance.org/library/events/mtr/>

³ Investing in immunization through the GAVI Alliance evidence report.

⁴ *The New England Journal of Medicine*, 369, November 22, 2013, from nejm.org.

⁵ GAVI Alliance Library & News, Mid-term review, October 30, 2013. <http://www.gavialliance.org/library/events/mtr/>

This document presents some of our key commitments and initiatives illustrating our longstanding dedication to global access to health through prevention and vaccination. At Sanofi Pasteur, thousands of men and women work every day towards that goal with the knowledge that they are helping to protect lives and to decrease medical and economic burdens, thereby reducing inequities and poverty.

I. DENGUE: SANOFI PASTEUR LAUNCHES FIRST VACCINE AGAINST DENGUE IN THE WORLD, DENGVAXIA®



Bringing the innovative dengue vaccine first to populations at greatest risk: Our commitment to “flip the model” for vaccine introduction becomes reality with first approvals

On December 9, 2015, Mexico approved Dengvaxia® as the first vaccine available to prevent all four types of dengue fever in individuals 9 to 45 years of age living in endemic areas. With this historic event in the history of infectious disease prevention, Dengvaxia® became the first dengue vaccine in the world, the result of 20 years of dedicated scientific, industrial and international collaboration by our company. This approval in Mexico was closely followed by approvals of the vaccine in the Philippines and Brazil. As of December 1, 2016, Dengvaxia® had been approved in 13 Asian and Latin American endemic countries (Bolivia, Brazil, Cambodia, Costa Rica, Guatemala, El Salvador, Indonesia, Mexico, Paraguay, Peru, the Philippines, Singapore, Thailand) where dengue continues to represent a growing public health threat. Public programs are underway in Brazil (for children, adolescents and adults in Parana State) and the Philippines (a school-based program). The vaccine is available in nine countries (Brazil, Costa Rica, El Salvador, Guatemala, Indonesia, Mexico, Paraguay, Peru, the Philippines). In July 2016, the WHO issued its recommendation that countries with high dengue burden consider vaccine introduction to improve control of the disease.⁶

“Flipping the model” — what does it mean?

Typically, it can take up to 10 years before novel vaccines like Dengvaxia® are first introduced in the tropical and subtropical countries where dengue is a major public health priority. We set out 20 years ago to flip this model and ensure priority introduction of the vaccine in these endemic countries first. This new model, which could serve as an impetus for future industry investment in the health of these nations, required taking risks with a series of commitments by our company, including launching a large-scale clinical development program in 15 countries around the world involving 40,000 participants; a bold industrial commitment of €1.5 million to build a dedicated dengue vaccine production site outside of Lyon and a ground-breaking regulatory strategy to build on the in-country disease expertise and technical competency of endemic country regulatory authorities. The approach also required that we introduce a novel pricing approach for the vaccine, based on rigorous cost-effectiveness evaluations carried out at the country level, to ensure a price that would be fair, equitable and sustainable both for our company and for the low- and middle-income countries where we plan to launch first.



A heavy economic and social burden in 100 tropical and sub-tropical countries

Dengue fever is a viral disease transmitted by mosquitoes with no treatment available today. The WHO estimates that 3.9 billion people live in endemic areas⁷ encompassing 128 countries. The WHO estimates that there are up to 400 million infections per year and 500,000 people affected with dengue hemorrhagic fever, the severe form of the disease. The majority of dengue cases worldwide are reported among patients over nine years of age, who represent a highly mobile and active segment of the populations at risk. They contribute to spreading the disease, and finally being able to vaccinate these individuals holds great promise for reducing the dengue burden globally. Dengue puts tremendous pressure on strained health systems, leading to an estimated global cost of US\$9 billion every year in direct and indirect healthcare costs.

⁶ WHO, Weekly Epidemiological Record, No 30, July 2016, 91, pp. 349 – 364: <http://www.who.int/wer/2016/wer9130.pdf?ua=1>

⁷ WHO, Dengue and severe dengue factsheet: <http://www.who.int/mediacentre/factsheets/fs117/en/index.html#>

A global clinical development and manufacturing plan to address the needs of endemic countries first

Sanofi Pasteur successfully completed large-scale Phase III clinical studies involving 40,000 participants across 15 endemic countries in Asia, Latin America and the Caribbean region⁸ and reported positive results from its Phase III study program in 2014. Our large-scale manufacturing facility in Neuville, France, has planned for full capacity of 100 million doses per year, which will allow us to immunize millions of people upon introduction of the vaccine. This will cut years off the typical delay in access to new vaccines in less developed countries. Disease impact modeling studies published by our company document that vaccinating 20% of the populations in the 10 countries that participated in the Phase III studies has the potential to reduce disease burden by 50% in these countries in five years. Given that the WHO has set 2020 objectives to reduce dengue mortality in endemic countries by 50% and morbidity (hospitalization, illness) by 25%, the first dengue vaccine is expected to be an important addition to integrated dengue-prevention efforts in these countries.

Local communities benefiting from clinical development efforts

Through our network of dengue clinical centers, such as San Pablo City Center in the Philippines and Tegucigalpa Center in Honduras, Sanofi Pasteur has contributed to the development of local communities with new jobs, scientific training, healthcare facilities, education and prevention. In addition, the clinical trial execution experience and infrastructure developed during this extensive clinical program should facilitate future research efforts for other new medical interventions targeting the public health needs of these low- and middle-income countries.

For more information, see: <http://www.dengue.info/>

II. POLIO: PARTNER IN THE END-GAME ERADICATION STRATEGY

Polio eradication is in sight

Poliomyelitis is a contagious disease mainly attacking children under five. One in 200 infections leads to irreversible paralysis, usually in the legs. Among those paralyzed, 5% to 10% die when their breathing muscles become immobilized. Over the last 30 years, under the Global Polio Eradication Initiative (GPEI), 2.5 billion children have been immunized against polio resulting in a 99% reduction in the number of cases worldwide. At the end of 2016, polio was endemic in only three countries (Afghanistan, Nigeria and Pakistan).

A long-term partner in the Global Polio Eradication Initiative

Since 1988, Sanofi Pasteur has supplied more than six billion doses of oral polio vaccine (OPV) to Unicef, protecting millions of children. In September 2011, Sanofi Pasteur donated the type 3 poliovirus strain to the WHO. The WHO is in full control of the vaccine strain and can distribute it to vaccine manufacturers when needed.

Sanofi Pasteur: Committed to making Injectable-Inactivated Polio Vaccine (IPV) accessible to every child in the world

In April 2013, the WHO's committee on policy on immunization (SAGE) recommended that all countries introduce at least one dose of IPV into their routine immunization programs to mitigate the risk of circulating vaccine-derived poliovirus. The introduction of IPV is a key component of the Polio End Game Strategy. Sanofi Pasteur had anticipated this global health strategy with the expansion of its IPV production capacities in France and is in a position to supply the majority of doses for this unprecedented global rollout, including the ShanIPV vaccine, now produced by Shantha in India.

III. YELLOW FEVER: A LONGSTANDING COMMITMENT TO HELP PREVENT AND CONTAIN EPIDEMICS IN TROPICAL REGIONS



A lasting threat to the poorest communities

Yellow fever is a viral hemorrhagic fever transmitted by infected mosquitoes, with no specific treatment. The WHO estimates **that there are 200,000 cases of yellow fever each year, resulting in 30,000 deaths.**⁹ The disease remains a major public health concern in both Africa and South America.

⁸ Sanofi Pasteur Press Release, July 25, 2012/Sabchareon A. *et al.*, "Protective Efficacy of the Recombinant, Live-Attenuated, CYD Tetravalent Dengue Vaccine in Thai Schoolchildren: A Randomized, Controlled Phase 2b Trial", (2012), *The Lancet*, 380 (9853), pp.1559-1567.

⁹ WHO, factsheet No.100, March 2014, accessed on January 26, 2016, <http://www.who.int/mediacentre/factsheets/fs100/en/>

Guaranteeing access to vaccines for large populations in response to outbreak situations

In 2011, in response to demand from GAVI, Sanofi Pasteur launched a significant investment to double its annual production capacity of yellow fever vaccine. Regulatory clearance was obtained in early 2016 so that doses from the new facility could be shipped to Africa to respond to the major yellow fever outbreak on the continent.

IV. HIV: A LONG-TERM COMMITMENT TO THE DISCOVERY OF A VACCINE SOLUTION



Despite progress in access to treatment, HIV remains a worldwide public health burden

Human immunodeficiency virus (HIV) is a blood-borne virus typically transmitted via sexual intercourse and shared intravenous needles. Since the beginning of the epidemic, almost 70 million people have been infected with the HIV virus and about 35 million people have died of AIDS.¹⁰ Sub-Saharan Africa remains the most severely affected area, with nearly one out of 20 adults living with HIV and accounting for 69% of the people living with HIV worldwide.

The first results of a vaccine efficacy study performed in Thailand in 2009

Results from a Phase III vaccine efficacy study called RV-144, which was conducted in Thailand, were published in the fall of 2009. Although efficacy results were modest, this study provided the first evidence that a safe and preventive HIV vaccine was possible for humans. Post-hoc analyses of this study provided a correlation of risk that could be used to substantiate and expand upon such results.

Sanofi Pasteur collaborates in a Phase III clinical trial in South Africa for a vaccine against HIV within the context of the P5 Partnership

An HIV vaccine clinical trial (called HVTN-100) in South Africa was announced on February 18, 2015 by the U.S. National Institutes of Allergy & Infectious Diseases (NIAID) division of the National Institutes of Health (NIH). This clinical trial includes Sanofi Pasteur's ALVAC-HIV investigational vaccine along with the adjuvanted protein vaccine supplied by GSK. This is a preventive vaccine regimen similar to the one used in the RV-144 study in Thailand, which was the first HIV vaccine trial to show any efficacy. Our prime vaccine has been adapted to the clade (strain) circulating in South Africa. The HVTN 100 study is currently enrolling participants in multiple sites in South Africa and the results of this HVTN 100 trial are expected in approximately two years.

Partnering toward a common goal

In 2011, Sanofi Pasteur entered into the P5 Pox-Protein Public-Private Partnership with GSK, the Bill & Melinda Gates Foundation, the U.S. NIH, the HIV Vaccine Trials Network, and the U.S. Military HIV Research Program.¹¹ This collaboration is expected to accelerate progress towards an effective and lasting HIV vaccine solution by bringing together key stakeholders including industrial partners, funders, research organizations, governments and experts in the field of HIV vaccine development.

Investigating alternative paths

Sanofi Pasteur is currently exploring alternative viral vector technologies (i.e., a replication-competent NYVAC-HIV vaccine and a flavivirus-based viral vector, Replivax[®]) through its participation in an international consortium under the Collaboration for AIDS Vaccine Discovery (CAVD) initiative of the Bill and Melinda Gates Foundation.

V. CHOLERA: BRINGING THE MOST SUITABLE VACCINE TO THE POOREST POPULATIONS



¹⁰ WHO, Global Health Observatory (GHO), <http://www.who.int/gho/hiv/en/>

¹¹ P5 flash news, RV144 follow up studies.

A global threat in the poorest countries

Cholera is a severe dehydrating diarrheal disease caused by the ingestion of food or water contaminated by the bacterium *Vibrio cholera*, leading to death if treatment is not given promptly. Every year, there are an estimated 1.4 to 4.3 million cholera cases and 28,000 to 142,000 deaths due to cholera.¹²

At the forefront of the fight against cholera

Since 2009, a bivalent oral vaccine against cholera used in large-scale vaccination campaigns to control epidemics has been made available by Sanofi Pasteur through Shantha, its Indian affiliate. This vaccine, Shanchol®, was developed through a partnership with the International Vaccine Institute (IVI) and was pre-qualified by the WHO in 2011. It is being registered in countries in the most severely affected and at-risk endemic regions, and constitutes the Gavi-funded stockpile managed by the International Coordinating Group (ICG) on Vaccine Provision. Shantha is also investing in additional capacity to scale-up vaccine production in line with greater vaccination policy acceptance from at-risk countries, which could result in increased vaccine demand.

Improving the use of vaccines in the field and reducing the overall cost of immunization

Shantha has worked on the “last miles” flexible cold chain management approach for Shanchol®. The objective is to reduce logistics constraints and costs during the final steps of immunization campaigns in areas where cold chain infrastructures may be a challenge, while guaranteeing that the vaccines that are administered will be fully efficacious. Stability results have demonstrated that Shanchol® can be stored/transported at ambient temperatures up to 40°C (instead of 2-8°) for a given period of time. A change to the packaging text is currently under review by WHO.

Shantha collaborated with IVI and icddr,b to investigate the efficacy of one dose of Shanchol in outbreak conditions (in Bangladesh); the outcomes of the study were published in 2016 and showed an acceptable level of efficacy in this cholera-endemic region among children over age five.

VI. INFLUENZA: REDUCING THE DISEASE'S ECONOMIC BURDEN AND PREPARING FOR A PANDEMIC



A considerable economic burden

Influenza is a highly contagious, acute viral respiratory infection. The intensity of epidemics varies from one year to the next due to the genetic mutation of the virus strains. Each year, three to five million cases of severe forms and 250,000 to 500,000 deaths are recorded by the WHO worldwide, with considerable economic repercussions: hospitalizations, healthcare costs, and loss of productivity.¹³ Vaccination against influenza remains the best way to prevent the disease today.

Building local influenza vaccine production facilities to provide high quality vaccines continuously

Today, Sanofi Pasteur is the world's largest producer and supplier of seasonal influenza vaccines, with more than 220 million doses produced each year. To respond to the growing local demand for seasonal influenza vaccines, Sanofi Pasteur built two new influenza vaccine facilities in China and in Mexico and transferred the technology to Brazil. These facilities are designed to easily switch from seasonal influenza vaccine production to pandemic vaccine production in the event of a pandemic.

Partnering globally to strengthen disease understanding and public health action

Sanofi Pasteur participates in the Global Influenza Hospital Surveillance Network (GIHSN), a public-private partnership with an academic coordinating center — Centro Superior de Investigación en Salud Pública (CSISP) in Valencia (Spain) — and several country sites affiliated with national health authorities. This surveillance platform is intended to generate strong epidemiological and medical evidence on the burden of severe influenza and the public health impact of influenza vaccines. Currently, the network includes sites in France, Czech Republic, India, Mexico, Spain, the Russian Federation, Turkey, China and Brazil. Since 2012, Sanofi Pasteur is involved in the Global Influenza Initiative (GII), which counts 25 key actors from 17 countries that collaborate on influenza prevention through the

¹² WHO factsheet No.107, July 2015, accessed on January 26, 2016: <http://www.who.int/mediacentre/factsheets/fs107/en/>

¹³ WHO, influenza factsheet No.211, March 2014, accessed on January 26, 2016, <http://www.who.int/mediacentre/factsheets/fs211/en/>

sharing of virologic, epidemiological, public health and health economics data.

Sanofi Pasteur cooperates with the WHO within the Pandemic Influenza Preparedness (PIP) framework for the sharing of influenza viruses and access to vaccines. This framework is designed to increase pandemic preparedness (i.e., surveillance and epidemiology) and improve response activities (i.e., real-time access to antivirals, diagnostics and vaccines).

VII. BEYOND VACCINES: UNDERSTANDING AND ACTING TOGETHER TO REMOVE BARRIERS TO VACCINATION ACCESS



Tremendous progress has been made with the introduction of innovative vaccines and the development of large immunization programs in emerging countries, thanks to multi-stakeholder collaborations such as the GAVI. Still, significant inequities remain in the access to vaccination due to multiple barriers that may be structural (e.g., health systems, conflicts, affordability, etc.) and societal (behaviors, education, beliefs).

Strengthening health systems

It is widely recognized that achieving immunization coverage is dependent upon strong service systems. Service delivery in many low-income countries suffers from a lack of, or inability to retain trained health workers, gaps in the cold chain or weaknesses in health system management. The WHO identifies the core components of a strong health system as:

- Health service delivery consisting of a network of health facilities to provide access to primary and secondary care
- Health workers in the right place at the right time with training, experience and incentives
- Health information systems to generate quality data and to measure what is being done and achieved
- Logistics and supply systems so that drugs, equipment and fuel are available
- Health financing to raise sufficient funds for health and improve financial risk protection
- Leadership and governance to ensure that strategic policy frameworks exist and that there is proper accountability and oversight

The EPIVAC Program is a Sanofi Pasteur contribution to the GAVI. The EPIVAC program is implemented by the Preventive Medicine Agency (AMP) and aims at strengthening the performance of the national immunization programs in Francophone Sub-Saharan Africa. The program was developed in conjunction with the national governments of eleven GAVI eligible countries (Benin, Burkina Faso, Cameroon, Central African Republic, Côte d'Ivoire, Guinea, Mali, Mauritania, Niger, Senegal, and Togo) and participating universities (Cocody-Abidjan in Côte d'Ivoire and Paris-Dauphine in France), in collaboration with the WHO and Unicef. Since 2002, more than 525 district medical officers involved in immunization programs have been trained through a one-year on-the-job training degree course in applied vaccinology and management of immunization programs.¹⁴ In 2015, Sanofi Pasteur has announced the expansion of the EPIVAC training programme in Nigeria.

Giving the key to public health players to understand and remove barriers to vaccination access

Sanofi Pasteur has developed a “5 A’s” approach to help public health actors analyze, understand and act on barriers/drivers of vaccination:

- Access: ability of individuals to be reached by or reach recommended vaccines
- Affordability: ability of individuals, states or other providers to finance the purchase and fund the planning and delivery of vaccination programs
- Awareness: knowledge of individuals, families, communities and populations about vaccines and diseases
- Acceptance: the degree to which individuals, families, societies and populations accept or refuse vaccination. This may be driven by the level and nature of education, by ideology and belief systems, by world view and by other media, cultural, or norm group influences and influencers
- Activation: overcoming the final step to vaccination in the absence of apparent access, affordability, awareness or acceptance barriers

Sanofi Pasteur partners across many sectors in a country to:

- Perform detailed analysis of vaccination coverage using 5 A’s tools and methods
- design local interventions based on best-practice and innovative approaches, particularly in driving behavioral change
- Put in place metrics that allow the impact of the corrective actions to be continuously measured and adapted
- Build broad partnerships across the public and private sectors
- Prioritize and protect resources to drive implementation

This framework is being tested in five countries including Gabon, and will be made available to all countries willing to improve their national vaccination programs to better protect populations and optimize health spending.

¹⁴ AMP: <http://www.amp-vaccinology.org/activity/epivacplus>