WEBSITE: chem-tox-ecotox.org/ScientificReviews.. 1 July 2020

SCIENTIFIC REVIEWS

History of Vaccines and Immunization.
Cornerstone of public health for 200 years that saved millions of human lives

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Abstract

The history of vaccines and immunization to combat infectious diseases goes back many centuries. Chinese employed smallpox inoculation as early as the 16th century. But the scientific history of the creation of the world's first vaccine for smallpox started with the doctor Edward Jenner in England in the 1790s. It is very difficult to estimate the global contribution of vaccines in saving lives. Reasonable estimates are in the range of around 5 million lives per year, between 1980 and 2018. In the last 200 years vaccines became a cornerstone of public health and have saved millions of human lives. More than any other public health innovation with the possible exception of improvements in sanitation and clean drinking water. Vaccines proved to be the most cost-effective means of preventing several infectious diseases, chronic diseases and some virus-related human cancers (e.g. liver and cervical cancer). The launch by WHO and its partners of the Global Polio Eradication Initiative in 1988, reduced infections by 99%, and some 5 million people have escaped paralysis. Between 2000 and 2008, measles deaths dropped worldwide by over 78% and maternal and neonatal tetanus has been eliminated in 20 of the 58 high-risk countries. During the past decades 3 major infectious diseases have attracted special attention from the international public health community: HIV (Human Immunodeficiency Virus), Malaria and Tuberculosis (TB). International campaigns and vast investment efforts have been made to develop effective vaccines against each of these infections. Today, the Global Fund Partnership (GFP) has saved 32 million lives (2018), while building resilient and sustainable systems of health. The Global Alliance for Vaccines and Immunisation (GAVI) vaccinates almost half of the world's children, and negotiates vaccines at prices that are affordable for the poorest countries. This review contains some of the most important vaccines for the most deadly and contagious diseases, global statistics on infectious diseases and the millions of lives (mainly children) lost every year. Vaccines are now the cornerstone of global health and history shows that they have saved millions from serious disabilities and premature death.

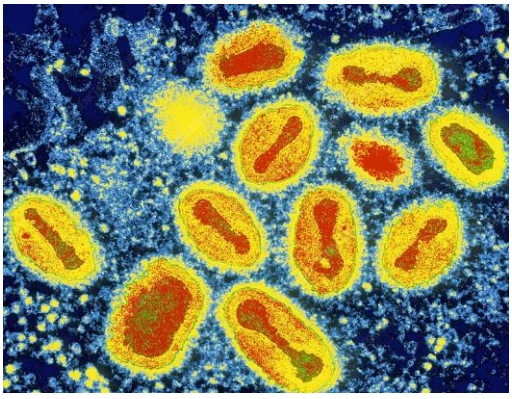
Introduction: History of vaccines and immunization

The history of vaccines and immunization goes back to evidence that Chinese employed smallpox inoculation as early s the 16th century. Also, it was thought vaccinations for smallpox to be practiced long time ago in Africa and Turkey as well before it spread to Europe and the Americas. Thanks revolutionary medical technologies, vaccines made enormous contribution to the health of modern society by preventing not only infectious diseases in all ages, but also noncommunicable diseases such as cancer and neurodegenerative disorders. [1,2]

The origin of infectious disease **smallpox** (ευλογιά) is unknown. Smallpox is thought to date back to the Egyptian Empire around the 3rd century BCE based on a smallpox-like rash found on three mummies. The earliest written description of smallpox appeared in China in the 4th century CE (Common Era). Early written descriptions also appeared in India in the 7th century and in Asia Minor in the 10thcentury. Smallpox was a devastating disease. On average, 3 out of every 10 people who got it died. Those who survived were usually left with scars, which were sometimes severe. [CDC Center of Disease Control and Prevention, USA, History of smallpox , https://www.cdc.gov/smallpox/history/history.html].

Figure 1. Infectious diseases spread among flourishing human civilizations, particularly in urban areas where large numbers of people living in close proximity to each other and with animals, with poor sanitation and low nutritional foods. These conditions provided fertile grounds for the spread of infectious diseases.This is a famous historical painting of doctor Edward Jenner performing the first vaccination against smallpox on the young boy James Phipps around 1796.

One of the first methods for controlling the spread of smallpox was the use of variolation. Named after the virus that causes smallpox (variola virus). Variolation is the process by which material from smallpox sores (pustules) was given to people who had never had smallpox. This was done either by scratching the material into the arm or inhaling it through the nose. With both types of variolation, people usually went on to develop the symptoms associated with smallpox, such as fever and a rash. The practice of variolation, infecting people with low doses of smallpox, dates back to 1000 BC in Asia. [Science Direct https://www.sciencedirect.com/topics/immunology-and-microbiology/variolation].



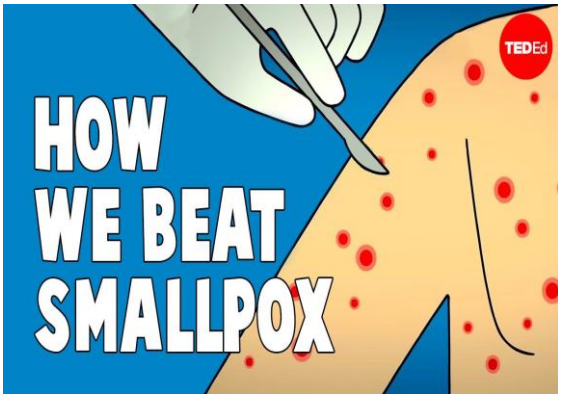


Figure 2. Variola virus is the causative agent of smallpox. Smallpox was declared eradicated in 1980 by the World Health Organization (WHO), with no known cases of naturally occurring smallpox having occurred since 1977. The last outbreak of smallpox in the United States was in 1949.

The scientific basis for vaccination began in 1796 when an English doctor named Edward Jenner observed that milkmaids who had gotten cowpox (a viral disease of cows' udders which, when contracted by humans through contact, resembles mild smallpox, and was the basis of the first smallpox vaccines) did not show any symptoms of smallpox after variolation. The first experiment to test this theory involved milkmaid Sarah Nelmes and James Phipps, the 8 year-old son of Jenner's gardener. Dr. Edward Jenner took material from a cowpox sore on Nelmes' hand and inoculated it into Phipps' arm. Months later, Jenner exposed Phipps a number of times to variola virus, but Phipps never developed smallpox. More experiments followed, and, in 1801, Jenner published his treatise

“On the Origin of the Vaccine Inoculation,” in which he summarized his discoveries and expressed hope that “the annihilation of the smallpox, the most dreadful scourge of the human species, must be the final result of this practice.”

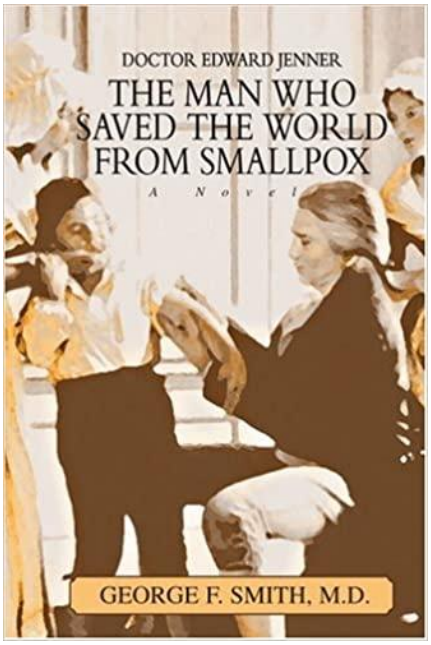


Figure 3. Edward Jenner (1749-1823) was an English physician from Gloucestershire who was a contributor to the development of the smallpox vaccine. The practice of vaccination was popularized by Edward Jenner who administered the world’s first vaccination as a preventive treatment for smallpox, a disease that had killed millions of people over the centuries.

Doctor Edward Jenner was the first to publish evidence that the vaccine was effective and provided scientific advice on its production. Louis Pasteur (1822-1895), renowned for his discoveries of the principles of vaccination, microbial fermentation and pasteurization, furthered the concept of immunization through his work in microbiology. Later, the immunization was called *vaccination* because it was derived from a virus affecting cows (Latin: *vacca* 'cow'). Smallpox was a contagious and deadly disease, causing the deaths of 20–60% of infected adults and over 80% of infected children. When smallpox was finally eradicated in 1979, it had already killed an estimated 300–500 million people in the 20th century.[3]

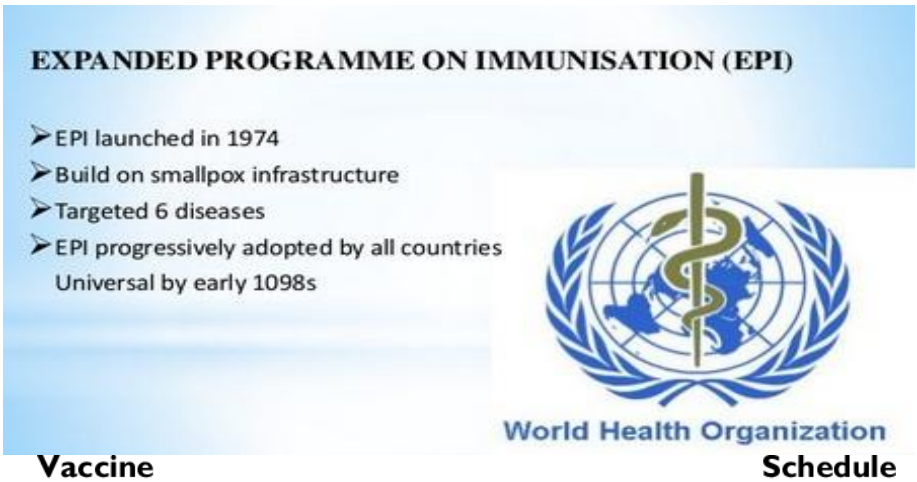
The story of Edward Jenner, a country doctor living in Berkeley (Gloucestershire), England, who in 1796 performed the world's first vaccination is very interesting how vaccination was invented and supported by experiment and scientific knowledge. Jenner took a sample of pus from a cowpox lesion on a milkmaid's hand and inoculated the boy, James Phipps. Six weeks later Jenner variolated two sites on Phipps's arm with smallpox, yet the boy was unaffected by this as well as subsequent exposures. Based on 12 such experiments and 16 additional case histories he had collected since the 1770s, Jenner published at his own expense a volume that swiftly became a classic text in the annals of medicine: *Inquiry into the Causes and Effects of the Variolae Vaccine.* The publication gave the opportunity to other scientists and medical experts to test the validity of the experiment. Jenner in his book made the assertion "that the cow-pox protects the human constitution from the infection of smallpox", that laid the foundation for modern vaccinology. Edward Jenner, a country doctor, in order to formulate the vaccine discovery relied extensively on his knowledge of the local customs of farming communities in England and the awareness that milkmaids infected with cowpox, visible as pustules on the hand or forearm, were immune to subsequent outbreaks of smallpox that periodically swept through the area. The results spread all over the world and doctors all over Europe soon adopted Jenner's discovery and method, leading to a dramatic decline of this terrible infectious disease. In the 19th and 20th centuries scientists followed the model and developed new vaccines to fight infectious diseases, such as polio (πολιομυελίτιδα), whooping cough (κοκκύτης), measles (ιλαρά), tetanus, yellow fever, typhus (τύφος), hepatitis B, HIV, etc.[4-,8]

The importance of vaccines for global health

Looking at the global health history of the last 200 years, vaccinations have probably saved as many human lives as any other public health innovation with the possible exception of improvements in sanitation and clean drinking water. The Expanded Programme on

Immunization (EPI) started by WHO in 1974. Global policies for immunization and establishment of the goal of providing universal immunization for all children by 1990 were established. This goal was considered an essential element of the WHO strategy to achieve health for all by 2000, particularly in developing countries.

[WHO The Expanded Programme of Immunization (EPI), last adapted 2013 [https://www.who.int/immunization/programmes_systems/supply_chain/benefits_of_immunization/en/].



Vaccine	Schedule
Bacillus Calmette-Guerin (BCG)	Birth
Diphtheria, pertussis and tetanus (DPT) I	6 weeks
Oral polio vaccine (OPV) I	6 weeks
Diphtheria, pertussis and tetanus (DPT) II	10 weeks
Oral polio vaccine (OPV) II	10 weeks
Diphtheria, pertussis and tetanus (DPT) III	14 weeks
Oral polio vaccine (OPV) III	14 weeks
Measles	9 months

Figure 4. The Expanded Program on Immunization (EPI) is one of the WHO programmes, which has a goal to make vaccines available to all the children through-out the world. Vaccines saved millions of children from diseases and mortality.

The WHO through EPI remains committed to its goal of universal access to all relevant vaccines for all at risk. The programme aims to more targeted groups including older children, adolescents and adults and work in synergy with other public health programmes in order to control infectious disease and achieve better health for all populations.

Immunization is a proven tool for controlling and even eradicating infectious diseases. An immunization campaign carried out by the World Health Organization (WHO) from 1967 to 1977 resulted in the eradication of smallpox. When the programme began, the disease still threatened 60% of the world's population and killed 25% of infected victims.

Another very ambitious goal of WHO was the eradication of poliomyelitis, a goal which is now within reach. Since the launch by WHO and its partners of the Global Polio Eradication Initiative in 1988, infections have fallen by 99%, and some five million people have escaped paralysis. Between 2000 and 2008, measles deaths dropped worldwide by over 78%, and some regions have set a target of eliminating the disease. Maternal and neonatal tetanus has been eliminated in 20 of the 58 high-risk countries.[9]

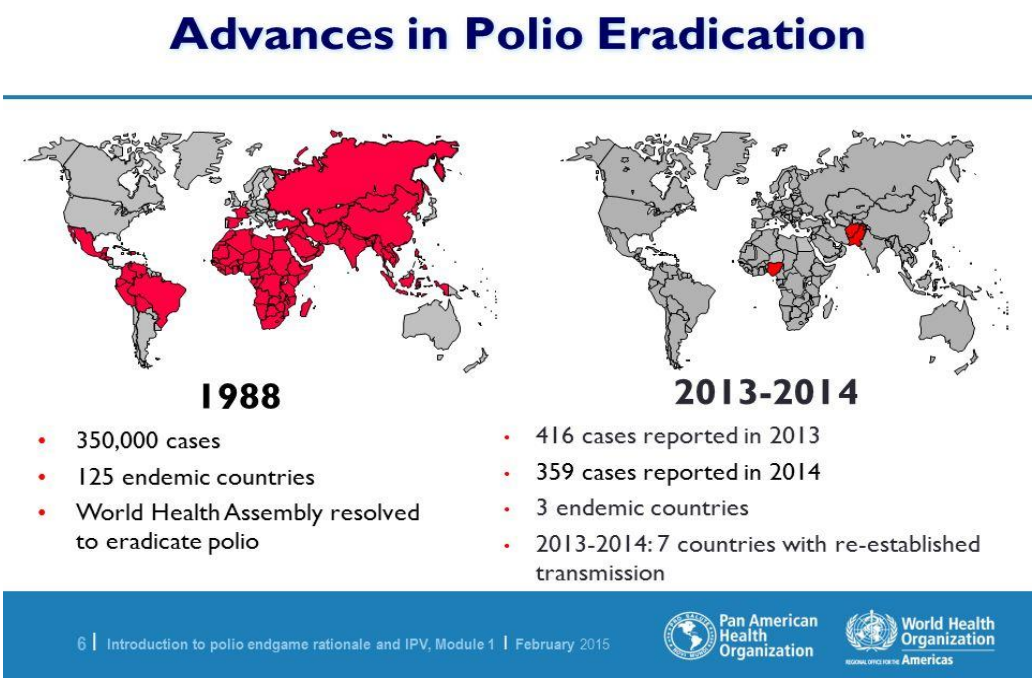


Figure 5. In May 2012 the World Health Assembly of WHO declared poliovirus eradication to be a global public health emergency. Afghanistan, Nigeria and Pakistan are still the only 3 countries with poliomyelitis cases.

According to WHO in 2018 an estimated 6.2 million children and adolescents under the age of 15 years died (globally), mostly from preventable causes. Of these deaths, 5.3 million occurred in the first 5

years. Leading causes of death are preterm birth complications, pneumonia, birth asphyxia, congenital anomalies, diarrhoea and malaria. Nearly half of these deaths are in newborns. 50% of these child deaths are preventable or can be treated with simple, affordable interventions including immunization, adequate nutrition, safe water and food. In the last decades vaccines are available for some of the most deadly childhood diseases, such as measles, polio, diphtheria, tetanus, pertussis, pneumonia due to *Haemophilius influenza* type B and *Streptococcus pneumonia* and diarrhoea due to rotavirus. Vaccines can protect all children from infectious illness and death. [WHO, Children: reducing mortality, 2020, https://www.who.int/news-room/fact-sheets/detail/children-reducing-mortality].

In the last decades the proportion of the world's children who receive their basic vaccines has increased from 15% to nearly 90%, although considerable regional, national and local differences remain. Vaccination has led to eradication of smallpox and the elimination of poliomyelitis and measles from large parts of the world, saving millions of lives. However, despite these successes, vaccination still has the potential to make an even greater contribution to global health. Every year on a global scale, 3 million children in poor countries still die each year from vaccine preventable diseases. Pneumonia, meningitis and diarrhoea account for a 25% of childhood deaths, many of which could be prevented with currently available vaccines. Malaria and improved tuberculosis vaccines are on the horizon and vaccination against human immunodeficiency virus (HIV) may ultimately become possible. The scope of diseases that can be prevented by vaccination is expanding. Hepatitis B virus (HBV) and human papilloma virus (HPV) vaccines are already being used successfully to prevent liver and cervical cancers, and progress is being made on the therapeutic use of vaccines in the treatment of cancer and in the management of non-communicable disease such as hypertension, diabetes and addiction.[9]

Infectious diseases eradicated by effective vaccines

Eradication and elimination of viral and infectious diseases are increasingly a part of the global health agenda of the World Health Organization (WHO) and national medical organizations. At present only two infectious diseases, smallpox and rinderpest (also known as cattle plague, a contagious viral disease affecting cloven- hoofed animals mainly cattle and buffalo), have been eradicated worldwide. Eradication is increasingly part of the international efforts of the global health community. Each infectious disease poses a unique set of challenges and therapeutic issues which make some campaigns of immunization difficult.

Eradication of poliomyelitis, measles and rubella

The eradication of **SMALLPOX** is the only successful global eradication campaign thus far and is testament to the immeasurable public health benefits that can be achieved through successful vaccines. At present there is optimism that several other viral and infectious diseases are candidates for global eradication in the near future given sufficient resources, effort (systematic vaccinations), and international cooperation.

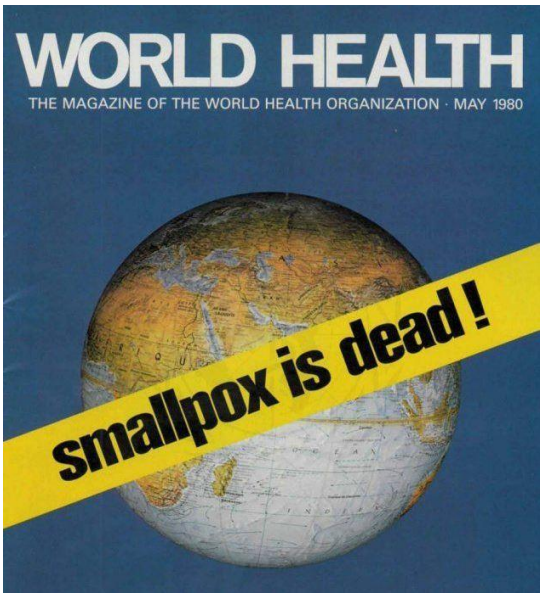


Figure 6. After a global eradication campaign lasting more than 20 years, on May 8, 1980, the World Health Assembly declared smallpox eradicated (eliminated), and no cases of naturally occurring smallpox have happened since. Smallpox killed more than 300 million people in the 20th century.

The most important infectious diseases which are most likely to be eradicated are, poliomyelitis (or polio), measles, and rubella, all of which satisfy the necessary preconditions for eradication. There were many factors that uniquely favoured smallpox eradication, but major challenges remained with eradication of other infectious diseases. [CDC, 2020, https://www.cdc.gov/smallpox/history/history.html].

MEASLES. Despite the availability of highly effective measles vaccines, measles results in approximately 900,000 deaths each year, half of which occur in Africa. The complications of measles (such as bronchopneumonia, diarrhea, and blindness) are most severe in malnourished young children, especially those with vitamin A deficiency. Based on estimates by WHO, each year measles accounts for 30% of all deaths due to vaccine-preventable diseases and 7% of deaths due to all causes among children under five years of age. In 1995, an estimated $1.1 billion was spent worldwide on measles treatment. [National Foundation for Infectious Diseases, Measles, 2020, https://www.nfid.org/infectious-diseases/measles/].

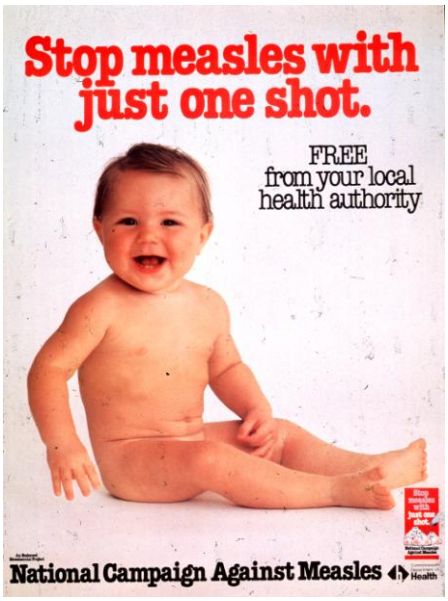


Figure7. Measles is a highly contagious respiratory disease that can result in severe, sometimes permanent, complications including pneumonia, seizures, brain damage, and even death. The measles, mumps, rubella (MMR) vaccine is a safe way to protect all members of a family.

POLIOMYELITIS

Wild poliovirus cases have decreased by over 99% since 1988, from an estimated 350,000 cases per year in more than 125 endemic countries then, to only 33 reported cases in 2018. Poliomyelitis can cause paralysis and even death in children. The polio virus usually affects children under 5 years of age who are not fully vaccinated. It can also affect adolescents and adults. There are two vaccines for polio: the Oral Polio Vaccine (OPV) and the Inactivated Polio Vaccine (IPV). OPV is taken orally as drops and can be easily administered. It does not require a trained health worker. OPV is still the main preventive measure against polio. [WHO,https://www.who.int/immunization/diseases/poliomyelitis/inactivated_polio_vaccine/Key_mess_FAQs.pdf].

The global polio eradication initiative which is driven by both public and private partnerships, is spearheaded by WHO, Rotary International, Centers for Disease Control and Prevention, and the United Nations Children's Fund (UNICEF), relies on age-specific routine childhood immunizations supplemented with mass OPV immunization. National immunization days (NIDs) with OPV are conducted two or more times annually for all children under the age of five years. As nationwide polio cases decline, immunization strategies are increasingly targeted to virus reservoir and high-risk population areas through sub-national immunization days and house-to-house mop-up operations. Aggressive surveillance is key to a successful immunization strategy. Endemic transmission is continuing in border areas of Afghanistan and Pakistan, resulting in 200,000 new cases every year [WHO, https://www.who.int/news-room/fact-sheets/detail/poliomyelitis].

Poliomyelitis was once a disease feared worldwide, striking suddenly and paralysing mainly children for life. WHO is a partner in the Global Polio Eradication Initiative (GPEI), the largest private-public partnership for health, which has reduced polio by 99%. Polio now survives only among the world's poorest and most marginalized communities, where it stalks the most vulnerable children. [WHO, Polio, https://www.who.int/features/factfiles/polio/en/].

Figure 8. After successful campaigns of immunization more than 18 million people (mostly children) are able to walk today, who would otherwise have been paralysed by poliomyelitis. An estimated 1.5 million childhood deaths have been prevented, through the systematic administration of vitamin A during polio immunization activities.

In 1988 paralytic poliomyelitis was endemic in 125 countries on five continents, with an estimated 350,000 cases annually. The last indigenous case of polio in the Americas was in 1991 and the in the European Region in 1998. Wild poliovirus type 2 has not been found anywhere in the world since mid-1999. In 2000, polio still occurred in 20 countries, with less than 3,000 cases identified worldwide. Slightly more than 250 cases were detected in India, the world's major exporter of wild polioviruses, despite major advances in surveillance. Vaccination has eliminated polio in almost all countries in the world, except for 3 countries in the world, Afghanistan, Pakistan and Nigeria (endemic countries)– and it is hoped that the disease will soon be eradicated globally. Provision of clean water, improved hygienic practices and sanitation are important for reducing the risk of transmission of polio in endemic countries. [European Center for Disease Prevention & Control, https://www.ecdc.europa.eu/en/ poliomyelitis/facts].

RUBELLA

Rubella (ερυθρά) is a contagious disease caused by a virus. It is also called German measles, but it is caused by a different virus than measles. Most people who get rubella usually have mild illness, with symptoms that can include a low-grade fever, sore throat, and a rash that starts on the face and spreads to the rest of the body. Rubella can cause a miscarriage or serious birth defects in an unborn baby if a woman is infected while she

is pregnant. Rubella can be prevented with MMR vaccine. This protects against three diseases: measles, mumps, and rubella. Centers of Diseases Control and Prevention (CDC) recommends children get two doses of MMR vaccine, starting with the first dose at 12 through 15 months of age, and the second dose at 4 through 6 years of age. Teens and adults also should also be up to date on their MMR vaccination. MMR vaccine is very safe and effective. One dose of the MMR vaccine is about 97% effective at preventing rubella. [Centers of Disease Control and Prevention, https://www.cdc.gov/vaccines/vpd/rubella/index.html].

Figure 9. Rubella can be prevented with MMR vaccine. Recommended for children to get two doses of MMR vaccine, starting with the first dose at 12 through 15 months of age, and the second dose at 4 through 6 years of age. MMR vaccine is very safe and effective. One dose of the MMR vaccine is about 97% effective at preventing rubella.

MUMPS, disease caused by virus and prevented by vaccine

Mumps (παρωτίτιδα) is an infectious disease that is caused by a virus. Mumps typically starts with fever, headache, muscle aches, tiredness, and loss of appetite. Then, most people will have swelling of their salivary glands and swollen jaw. Mumps can be prevented with the MMR triple vaccine. This vaccine protects against three diseases: measles, mumps, and rubella. Medical pediatricians recommend children to be immunized with two doses of MMR vaccine, starting with the first dose at 12 through 15 months of age, and the second dose at 4 through 6

years of age. The MMR vaccine is very safe and effective. The mumps component of the MMR vaccine is about 88% (range: 31-95%) effective when a person gets two doses; one dose is about 78% (range: 49%−92%) effective. Children may also get MMRV vaccine, which protects against measles, mumps, rubella, and varicella (chickenpox, ανεμοβλογιά). This vaccine is only licensed for use in children who are 12 months through 12 years of age. Before the vaccine, about 186,000 cases of mumps were reported each year in the USA. Mumps cases decreased by 99% in the USA and in other developed countries after systematic vaccinations.
[CDC, Centers for Disease Control and Prevention, Mumps vaccination, https://www.cdc.gov/vaccines/vpd/mumps/index.html].

International campaigns for the major infectious diseases: HIV, Malaria and Tuberculosis

During the past decades 3 major infectious diseases have attracted special attention from the international public health community: HIV (Human Immunodeficiency Virus), Malaria and Tuberculosis (TB).

International campaigns and vast investment efforts have been made to develop effective vaccines against each of these infections. Today, the Global Fund Partnership (GFP) has saved 32 million lives (2018), while building resilient and sustainable systems of health. The Global Fund to Fight AIDS, Tuberculosis and Malaria was created in 2002 to raise, manage and invest the world's money to respond to three of the deadliest infectious diseases the world has ever known. The Global Fund Partnership mobilized and invested more than USS$4 billion a year to support AIDS, Tuberculosis and Malaria vaccination programmes run by local experts in more than 100 countries. The money comes 93% from donor governments and 7% from the private sector and foundations. The mission of the GFP is to invest the world's money to defeat these three diseases. [https://www.theglobalfund.org/en/overview/].

Figure 10. Health programmes supported by GFP have saved 32 million lives (2018). Deaths caused by AIDS, Malaria and TB have been reduced by 40%. There are 18.9 million people on antiretroviral drugs therapy for HIV where GFP invests. The GFP distributed 130 million mosquito nets in 2018 saving millions of children lives from malaria. Also, 5.3 million people were treated with drugs for TB in countries where GFP invests.

Deaths from AIDS have been cut in half since 2005. New drugs for TB have significantly improved treatment outcomes, even for drug-resistant TB. The combination of mosquito nets treated with insecticide, and improved diagnostics and treatment have radically reduced the impact of malaria. The estimated annual number of malaria deaths was around 405,000 in 2018. Tuberculosis (TB) still kills 1.6 million people a year, more than any other infectious disease. AIDS, a disease that only appeared some 30 years ago, that has killed over 35 million people, and for which the world still do not have a vaccine or cure despite major efforts in the last decades.[10,11]

Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency syndrome (AIDS).

Acquired immunodeficiency syndrome (AIDS) is a chronic, potentially life-threatening condition caused by the Human Immunodeficiency Virus (HIV). The infectious virus damages the human immune system, and interferes with the body's ability to fight the organisms that cause disease. HIV is a sexually transmitted infection and can also be spread by contact with infected blood or from mother to child during pregnancy, childbirth, or breast-feeding. Without medication, HIV gradually weakens the immune system to the point that an infected

individual may develop AIDS. Approximately 1.1 million people in the US are living with HIV today. About 15% of them are unaware they are infected. There is currently no cure (vaccine) for HIV/AIDS, but there are medications that can slow the progression of the disease. These drugs have reduced AIDS deaths in many developed nations. [National Foundation for Infectious Diseases, https://www.nfid.org/infectious-diseases/hiv-aids/]. According to the *Global Burden of Disease* study, almost one million (954,000) people died from HIV/AIDS in 2017. To put this into context: this was just over 50% higher than the number of deaths from malaria in 2017.

Figure 10. The number of people living with HIV: 36.7 million, newly infected 1.8 million (2018). AIDS-related deaths: 940,000 people (2018). 20.9 million people living with HIV were accessing antiretroviral therapy. Source: UNAIDS, 2018. The World AIDS Day is 1st of December.

Despite many efforts there is no Effective Vaccine for AIDS. Initial optimism that advances in molecular biology would lead to the rapid development of safe and effective HIV vaccines has been dashed. Although success has been achieved in animal models, only one of many trials conducted in man has given any suggestion of protection. The reason for not having a vaccine of HIV is that it has a long dormant period before it progresses to AIDS. During this period, the virus hides itself in the DNA of the infected person. The body can't find and destroy all of the hidden copies of the virus to cure itself. So, a vaccine to buy more time

won't work with HIV. The HIV mutates quickly, so it's hard to create a vaccine to work against it. [Healthline. HIV Vaccine: How close we are? https://www.healthline.com/health/hiv-aids/vaccine-how-close-are-we#obstacles]. Despite these obstacles, researchers continue to try to find a vaccine for HIV two main types of vaccines: prophylactic and therapeutic. Most vaccines are prophylactic, which means they prevent a person from getting a disease. Therapeutic vaccines, on the other hand, are used to increase the body's immune response to fight the disease. Therapeutic vaccines are also considered sufficient treatments.

Resources mobilized from all sources for HIV programmes in low and middle-income countries increased by an additional US$ 250 million from 2012 to reach US$ 19,100 million in 2013 and then increased again to an estimated US$ 21,007 million in 2015. The rising trend was due mainly to greater domestic investments, which comprised about 57% of the total in 2014. Nevertheless, investments in HIV will need to grow to US$ 31,900 million in 2020 and 29,300 million in 2030 if long-term control of the epidemic is to be achieved. [12]

Despite a massive investment in HIV vaccine research which has resulted in the development of candidate vaccines inducing humoral or cellular immune responses to several viral antigens. A major reason for the failure of these first generation vaccines is the extraordinary ability of the HIV to mutate its key surface proteins involved in binding to host cell receptors. Thus, any highly effective HIV vaccine must be able to induce an immune response that provides protection against each of these mutant strains. The disappointing efficacy of HIV vaccines evaluated so far has led to a return to the laboratory and renewed attempts to define in more detail the antigenic structure and potential variability of key HIV proteins and the immune responses that they induce.

Various conspiracy theories were connected with HIV and confused the issue. When the Human Immunodeficiency Virus (HIV) was discovered in the 1980s, people immediately wondered where it had come from and how it had found its way into humans. One conjecture that arose in the 1990s put the blame for HIV on a public health measure: a polio vaccine.

Conspiracy theories from journalists and rumours concerning the oral polio vaccine having been intentionally contaminated with drugs to cause sterility and “viruses which are known to cause HIV and AIDS” led to local refusals to accept the vaccine in parts of Africa. It’s likely that these rumours are related to the original OPV/HIV accusations. Partially as a result of these refusals, polio flared back up in parts of Africa after vaccination had led to positive steps toward eradication.

[History of Vaccines, Debunked the polio vaccine and HIV link, https://www.historyofvaccines.org/content/articles/debunked-polio-vaccine-and-hiv-link,
Cohen J. Forensic Epidemiology: Vaccine Theory of AIDS Origins Disputed at Royal Society. *Science* 289(5486):1850-1851, 2000.
Jegede A. What Led to the Nigerian Boycott of the Polio Vaccination Campaign? *PLoS Med.* 4(3): e73-, 2007.]

Malaria, the most severe public health problems worldwide

Malaria is an infectious disease caused by parasites that invade red blood cells. The protozoan parasites are among several species of the genus Plasmodium. This malaria parasite is transmitted by mosquitoes (vectors) to humans through mosquito bites that, during the bite, release parasites into the person's blood. Antimalarial drugs taken for prophylaxis by travelers can delay the appearance of malaria symptoms by weeks or months, long after the traveler has left the malaria-endemic area. This can happen particularly with *P. vivax* and *P. ovale*, both of which can produce dormant liver stage parasites; the liver stages may reactivate and cause disease months after the infective mosquito bite.

Since the beginning of the 21st century, millions of people have died from malaria (mostly children). In these 15 years the global death toll has been cut in half: from 839,000 deaths in 2000 to 438,000 in 2015. Africa is the world region that is most affected by malaria: In 2015, the African continent held 9 out of 10 malaria victims. From 2000 to 2015, African deaths from malaria were reduced from 764,000 to 395,000. [Our World in Data, Malaria, 2019, https://ourworldindata.org/malaria].

Several companies have developed long-lasting insecticide-treated nets (LLINs) that maintain effective levels of insecticide for at least 3

years, even after repeated washing. The WHO Pesticide Evaluation Scheme External (WHOPES) has given either full or interim approval to these nets. In 2008-2010, a total of 294 million nets were distributed in sub-Saharan Africa. [Centers for Disease Control and Prevention https://www.cdc.gov/malaria/malaria_worldwide/reduction/itn.html].

The UN Millennium Development Goals promoted a furious spate of donations worth almost $255 billion for malaria. Between 2000 and 2009 the global malaria aid budget grew by 28.3%. In 2015 more than 400,000 malaria global deaths were recorded (compared to more than 2 million few years ago). As the world observes World Malaria Day, World Health Organization (WHO) figures show reasons for optimism: the fight against malaria has been successful in the past, with 33 countries reporting fewer than 1,000 cases of malaria in 2015, and mortality rates cut by 60% globally since 2000. [CNN, https://edition.cnn.com/2016/04/25/health/world-malaria-day-funding/index.html].

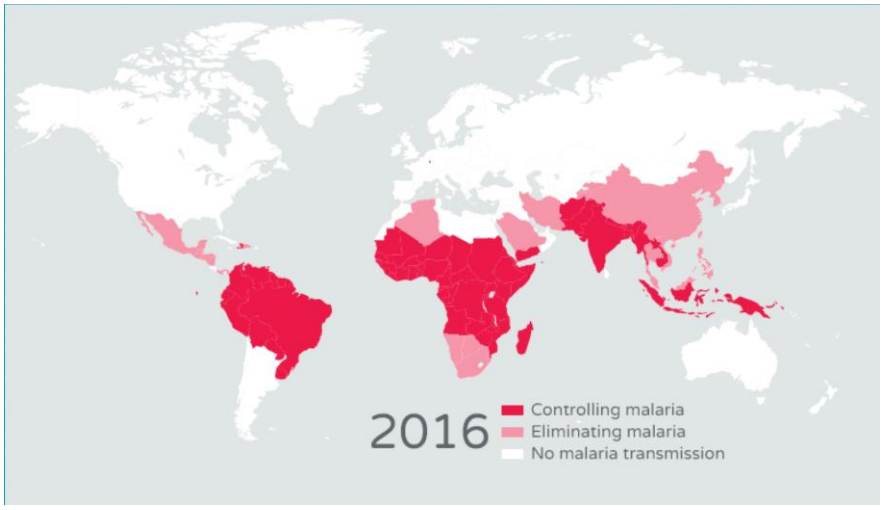


Figure 11. Medical experts believe that **global malaria eradication** is possible within a generation, but only with renewed focus, new tools and sufficient financial support. Since 2000, great progress has been made around the globe, driven largely by the progress made by the eliminating countries. In these malaria-eliminating countries, malaria cases declined 91%, from 1.6 million cases to 150,000, while malaria deaths dropped 81% between 2000 and 2014.

The only approved vaccine for malaria as of 2015 is RTS,S, known by the trade name Mosquirix. It requires four injections, and has a

relatively low efficacy. The complexity of the malaria parasite makes development of a malaria vaccine a very difficult task. Recent progress has been made with the completion of a Phase 3 trial of the RTS,S/AS01 candidate vaccine and review by the European Medicines Agency and WHO. There is currently no commercially available malaria vaccine. Over 20 other vaccine constructs are currently being evaluated in clinical trials or are in advanced preclinical development. The malaria vaccine candidate RTS,S/AS01 is the most advanced vaccine candidate against the most deadly form of human malaria, Plasmodium falciparum. A Phase 3 trial with 15,460 children in seven countries in sub-Saharan Africa (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and the United Republic of Tanzania) began in May 2009 and has now been completed. After review of the study data, the European Medicines Agency (EMA) issued a positive Scientific Opinion about the risk-benefit balance, upon agreement with the manufacturing company about further research plans as part of Phase 4 evaluation. [WHO, Malaria vaccines https://www.who.int/immunization/research/development/malaria/en/].

Tuberculosis (TB): deadly infectious disease with 1.5 million deaths per year

Tuberculosis (TB) is an infectious disease usually caused by *Mycobacterium* tuberculosis (MTB) bacteria. Tuberculosis generally affects the lungs, but can also affect other parts of the body. On a global scale, 1.5 million people died from TB in 2018 (including 251,000 people with HIV). Worldwide, TB is one of the top 10 causes of death and the leading cause from a single infectious agent. In 2018, an estimated 10 million people fell ill with tuberculosis (TB) worldwide. 5.7 million men, 3.2 million women and 1.1 million children. An estimated 58 million lives were saved through TB diagnosis and treatment between 2000 and 2018. Ending the TB epidemic by 2030 is among the health targets of the Sustainable Development Goals of the United Nations. [WHO, Turberculosis, 20.3.2020 https://www.who.int/news-room/fact-sheets/detail/tuberculosis].

The tuberculosis vaccine was discovered 90 years ago. Bacille Calmette-Guérin (BCG) is the vaccine for tuberculosis often given to infants and small children in countries where TB is common. But BCG does not always protect people from getting TB.

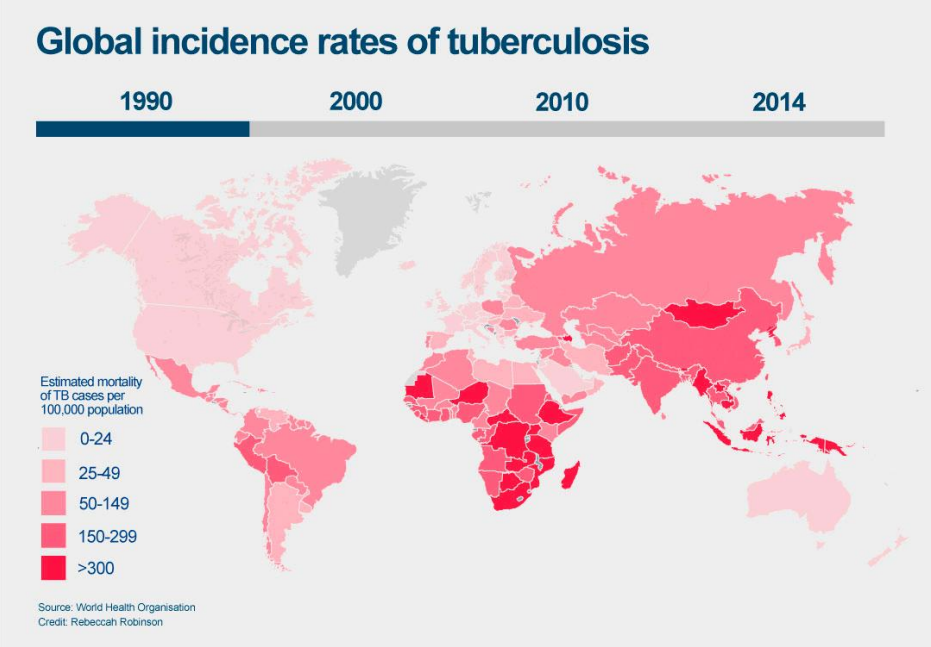


Figure 12. Rates of TB globally have been declining at a meagre rate of 1.5% per year since 2000, making rates 18% lower today than at the start of this century. Certain regions of the world have slowly eliminated the TB disease. Absolute numbers of people infected remain high in India and China. Another region has become an epicentre based on actual rates of infection found there: countries in sub-Saharan Africa, fuelled by HIV.

The BCG vaccine against tuberculosis is an attenuated strain of *Mycobacterium bovis*—bacillus Calmette—Guérin (BCG), which has been available for 90 years, but induces only limited protection.

Although millions of doses of BCG are given to newborn babies across the developing world each year, it is an inadequate tool to control completely tuberculosis (TB). TB is now experiencing a resurgence as a consequence of the HIV epidemic in Africa. Many years ago TB caused nearly two million deaths each year, predominantly in the developing world, which was reduced to 1,5 million recently. Medical experts believe that new and more effective anti-tuberculosis vaccines are needed urgently.

Figure 13. Medical experts agree that ultimate defeat of TB lies in the development of a new and effective vaccine. At present Bacillus Calmette-Guérin (BCG) is the only licensed tuberculosis vaccine. The first human subject trial took place in early 1920. In 1973, the WHO Expert Committee on Tuberculosis recommended that BCG be used as widely as possible; today, 90% of all children are vaccinated with BCG making it the most administered vaccine in the world.

Two main approaches to the development of improved new TB vaccines are being explored. One involves genetic manipulation of the bacterium to increase its expression of a 30 kDa secretory antigen which is thought to play a key role in the induction of the protective immune response induced by BCG. The second approach involves incorporation of a bacteriolysin gene from *Listeria moncytogenes* into BCG. A recent review (2018) provided an overview of the innate and adaptive immune response during *M. tuberculosis* infection, and presents current developments and challenges to novel TB vaccines. A comprehensive understanding of vaccines in preclinical and clinical studies provides extensive insight for the development of safer and more efficient vaccines, and may inspire new ideas for TB prevention and treatment.[13]

GAVI , Global Alliance of Vaccines and Immunisation

By the late 1990s, the progress of international immunisation programmes was stalling. Nearly 30 million children in developing countries were not fully immunised against deadly diseases, and many others went without any immunisation at all. At the heart of the challenge

was an acute market failure; powerful new vaccines were becoming available, but developing countries simply could not afford most vaccines.
In response, the Bill and Melinda Gates Foundation and a group of founding partners brought to life an elegant solution to encourage manufacturers to lower vaccine prices for the poorest countries in return for long-term, high-volume and predictable demand from those countries.
In 2000, that breakthrough idea became the Global Alliance for Vaccines and Immunisation (GAVI) [https://www.gavi.org/our-alliance/about].

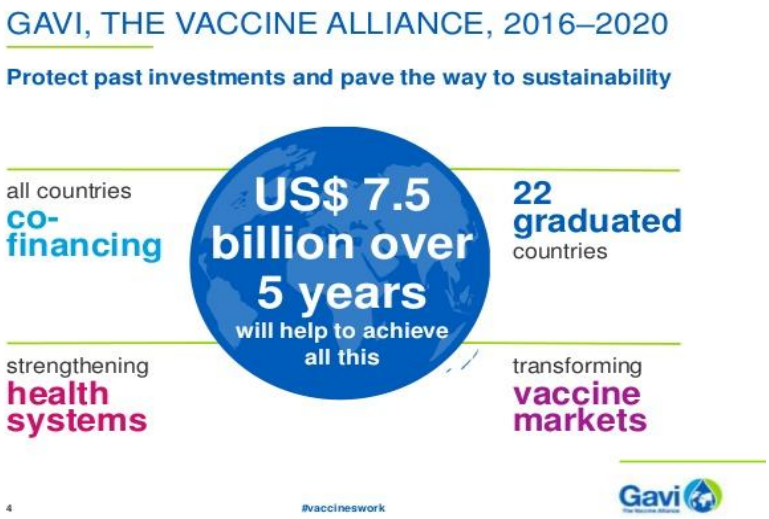


Figure 14. GAVI currently supports vaccine programmes in all 41 countries, which have a combined population of 1.52 billion. The countries were selected based on the availability of data from Demographic and Health Surveys.

The **Global Alliance for Vaccines and Immunisation** (**GAVI**) now vaccinates almost half of the world's children, giving it tremendous power to negotiate vaccines at prices that are affordable for the poorest countries and to remove the commercial risks that previously kept manufacturers from serving them. Because of these market shaping efforts, the cost of fully-immunising a child with all 11 WHO-recommended childhood vaccines now costs US$ 28 in Gavi-supported countries, compared to about US$ 1,100 in the US. At the same time, the pool of manufacturers producing prequalified Gavi -supported vaccines has grown from five in 2001 (with one in Africa) to 17 in 2017 (with 11 in Africa, Asia and Latin America). Gavi shares the cost developing countries pay for vaccines,

which has resulted in more than 460 vaccine campaigns and dramatically boosted immunisation against virulent diseases. For example, in 2000, 3% of low-income countries administered the *Haemophilus influenza* type b vaccine that protects against diseases like pneumonia and meningitis. Today, Gavi has enabled all low-income countries to introduce this vaccine. So far, 15 countries that were formerly supported by Gavi have begun to fully self-finance their national vaccination programmes.

GAVI, the Vaccine Alliance is supported by donor governments (Australia, Brazil, Canada, Denmark, France, Germany, India, Ireland, Italy, Japan, the Kingdom of Saudi Arabia, Luxembourg, the Netherlands, Norway, the People's Republic of China, Republic of Korea, Russia, South Africa, Spain, the State of Qatar, the Sultanate of Oman, Sweden, United Kingdom, and United States), the European Commission, Alwaleed Philanthropies, the OPEC Fund for International Development (OFID), the Bill & Melinda Gates Foundation, and His Highness Sheikh Mohamed bin Zayed Al Nahyan, as well as private and corporate partners (Absolute Return for Kids, Anglo American plc., The Children's Investment Fund Foundation, China Merchants Group, Comic Relief, Deutsche Post DHL, the ELMA Vaccines and Immunization Foundation, Girl Effect, The International Federation of Pharmaceutical Wholesalers (IFPW), the Gulf Youth Alliance, JP Morgan, "la Caixa" Foundation, LDS Charities, Lions Clubs International Foundation, Majid Al Futtaim, Philips, Unilever, UPS and Vodafone). [https://www.gavi.org/news/media-room/study-vaccines-prevent-not-just-disease-also-poverty].

Vaccines do not just save lives, they also have a huge economic impact on families and communities. A healthy child is more likely to go to school and become a more productive member of society in later life, while their families can avoid the often crippling healthcare costs that diseases can bring. The development of effective vaccines has led to a huge decrease in childhood deaths. Vaccines are among the two global public health interventions that have had the greatest impact on the world's health: clean drinking water-sanitation and immunization by vaccines.'

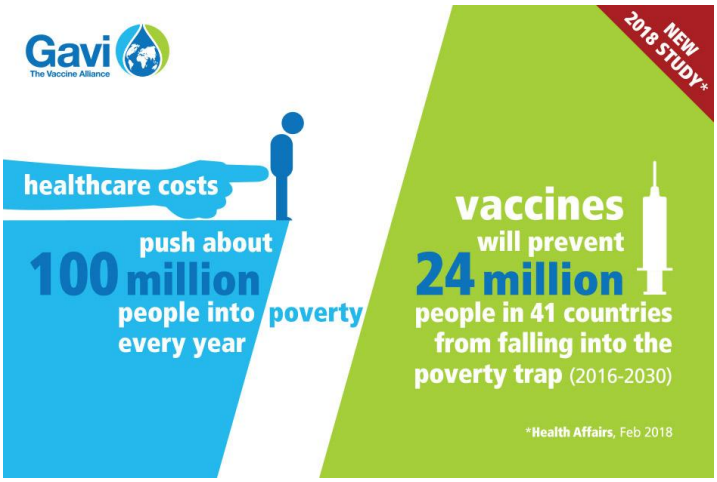


Figure 15. In addition to saving millions of lives, vaccines will help prevent some of the world's poorest countries from slipping into poverty by 2030. Health care costs forces 100 million people into poverty every year. Vaccines and immunisation efforts will prevent 24 million people in 41 countries from failing into the poverty trap (2016-2030).

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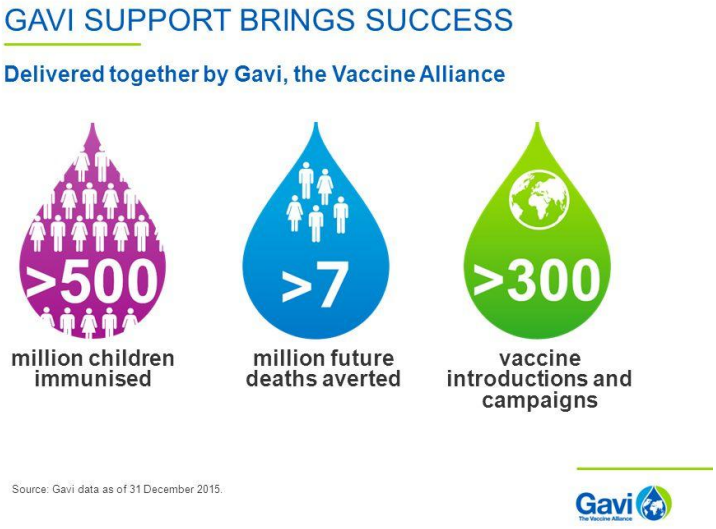

Figure 16, Since 2007 GAVI has been funding new Health System Strengthening (HSS) programs that encourage and enable countries to identify infrastructure and resource weaknesses that are barriers to the achievement of immunisation and other public health goals.

Pneumococcal disease can be life threatening

Pneumococcal disease is a common and often mild infection, but it can sometimes result in serious health problems. These include a middle ear infection, a blood infection, pneumonia, or bacterial meningitis. The bacterium *Streptococcus pneumonia* (*S. pneumoniae*), is also known as pneumococcus, causes pneumococcal disease. Invasive pneumococcal disease is a life-threatening condition that is fatal in 10% of cases. Older people and those with underlying medical conditions have a higher risk than others of serious complications. Regular vaccinations can prevent many types of pneumococcal disease and the potential complications that may arise.

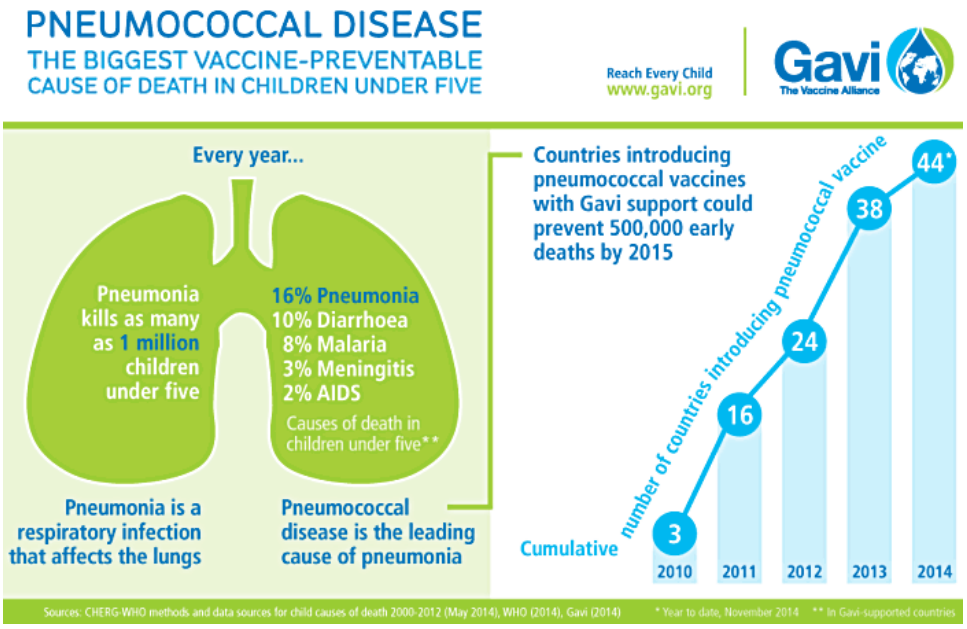

Figure 17. GAVI the Vaccine Alliance. Pneumonia is the most important cause of death in childhood, killing around two million children under the age of 5 each year, mostly in the developing world. GAVI supports countries to introduce vaccines and prevent half a million deaths in 2015.

The development of pneumococcal polysaccharide/protein conjugate vaccines that are effective in young children has been a major step forward in reducing global child mortality. There are 2 kinds of vaccines that help prevent pneumococcal disease: a. Pneumococcal

conjugate vaccine or PCV13, and b. Pneumococcal polysaccharide vaccine or PPSV23. **All Children Should Get Pneumococcal Vaccines.** It is recommended for pneumococcal vaccination for all children younger than 2 years old and all adults 65 years or older. In certain situations, other children and adults should also get pneumococcal vaccines.

Influenza (flu), contagious respiratory illness

Influenza viruses that infect the nose, throat, and lungs cause respiratory diseases. Ihflenza can cause mild to severe illness, and can lead to hospitalization and even death. Every year in most developed countries, millions of people are sickened, hundreds of thousands are hospitalized and thousands or tens of thousands of people die from the flu. Anyone can get the flu (even healthy people) and serious problems related to the flu can happen at any age, but some people are a higher risk of developing serious flu-related complications if they get sick. This includes people 65 years and older, people of any age with certain chronic medical conditions (such as diabetes, asthma, or heart disease), pregnant women, and young children. The best way and most important step to prevent the flu is by getting a flu vaccine each year. It is recommended by all medical authorities that everyone 6 months of age and older get a flu vaccine each year. Flu vaccination can reduce flu illnesses, doctors' visits, and missed work and school due to flu, as well as prevent flu-related hospitalizations.

There are 4 types of seasonal influenza viruses, types A, B, C and D. Influenza A and B viruses circulate and cause seasonal epidemics of disease. [WHO, Seasonal Influenza, https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal)].

Influenza A viruses are further classified into subtypes according to the combinations of the hemagglutinin (HA) and the neuraminidase (NA), the proteins on the surface of the virus. Currently circulating in humans are subtype A(H1N1) and A(H3N2) influenza viruses.

Influenza B viruses are not classified into subtypes, but can be broken down into lineages.

Influenza C virus is detected less frequently and usually causes mild infections, thus does not present public health importance.

Influenza D viruses primarily affect cattle and are not known to infect or cause illness in people.

The current strain of avian flu (H5N1) is not highly transmissible in humans but has the potential to cause a very serious illness with a high mortality rate when it does. The recent variant of swine flu (H1N1) is not especially virulent but causes serious illness in younger subjects more frequently than do the influenza strains that have circulated in industrialized countries in recent years. In temperate climates, influenza occurs as regular seasonal outbreaks interspersed with periodic large epidemics associated with the emergence of a new strain.

The World Health Organization (WHO) estimates that worldwide, annual influenza epidemics result in about 3-5 million cases of severe illness and about 250,000 to 500,000 deaths. The most recent data for the mortality (death rates) from influenza for the United States in 2016 indicates that mortality from influenza varies from year to year. Death rates estimated by the CDC (USA) range from about 12,000 during 2011-2012 to 56,000 during 2012-2013. In the 2017-2018 season, deaths (USA) reached a new high of about 79,000. Experts suggest that a large percentage of people went unvaccinated or refused to vaccinate family members. [Medscape, Influenza, 2020, https://www.medscape.com/answers/219557-3459/what-is-the-global-incidence-of-influenza].

Vaccines against enteric infections

Acute gastrointestinal infections and pneumonia are the most important causes of death in children in the developing world. Cholera is endemic in South East Asia and in parts of Africa and regularly causes major epidemics. *Salmonella typhi* and related bacteria are major causes of severe illness, especially in Asia, and non-typhoidal salmonella infection is an important cause of severe illness in children and HIV-infected adults in Africa. Vaccines against enteric bacterial infections, including typhoid

and cholera, have been available for many years but their use has been restricted largely to tourists and travellers and they have been little used in developing countries where they would be of most value. However, as a result of recent epidemiological studies, there is increasing recognition of the high burden of disease attributable to bacterial enteric infections and of the role that more widespread deployment of these vaccines could play in improving health, especially in Asia.

Diarrheal diseases remain a leading cause of mortality globally. Recent estimates of the Global Burden Disease study showed that nearly 1.65 million diarrheal diseases deaths occurred in 2016 in all ages globally, of which 446,000 deaths occurred among children aged under 5 years. More than 85% of diarrheal diseases deaths occurred in South Asia and sub-Saharan Africa. Rotavirus was the leading cause of diarrheal diseases deaths, being responsible for 228,000 deaths in all age groups, followed by *Shigella* causing 212,000 deaths, *Vibrio cholera* (107,000 deaths), adenovirus (93,000 deaths), non-typhoidal *Salmonella* (NTS) (87,000 deaths), *Campylobacter* (75,000 deaths), *Cryptosporidium* (57,000 deaths), and enterotoxigenic *Escherichia coli* (ETEC) (51,000 deaths).[14]

There are 2 internationally available oral live-attenuated rotavirus vaccines (licensed around 13 years ago): **Rotarix™** (GSK Biologicals, Rixensart), and **RotaTeq ™** (Merck & Co., Whitehouse, Pennsylvania). These vaccines showed high efficacy in preventing severe rotavirus gastroenteritis in clinical trials conducted among infants. as well as acceptable safety profile. These vaccines have been prequalified by the World Health Organization (WHO) in 2009; the WHO recommended the introduction of universal rotavirus immunization globally.[14\]

Cholera remains a major public health problem, with an estimated burden of 2.86 million cases and 95,000 deaths in endemic countries in Asia and Africa.⁻There are three licensed and WHO prequalified cholera vaccines. The first vaccine is Dukoral that contains the cholera toxin B-subunit (CTB), the other two vaccines Shanchol and Euvichol-plus showed good effectiveness and were prequalified by the WHO in 2011 and 2015,

respectively. In the past few years, cholera vaccines have been available for emergencies through a global stockpile funded by GAVI.[15]

Vaccines against non-infectious diseases. Cancer.

Vaccines can be used to control of cancer—prevention of the development of a cancerous malignancy or control of a cancer once it has developed. Chronic infections with the hepatitis B virus (HBV) and high-risk human papillomaviruses (HPVs) are important risk factors for hepatocellular carcinoma (HCC) and cervical cancer (CC), respectively.

On a global scale, approximately 2 million new cancer cases are attributed to infectious agents each year worldwide. There are now successful vaccines for the HBV), and HPV) are considered major successes in clinical chemoprevention of cancer. Widespread deployment of these effective vaccines play now an important role in reducing the increasing burden of these types of cancer in the developing world. There are many strains of HPV but, fortunately, only a few appear to play an important role in the causation of cervical cancer. Currently available HPV vaccines are likely to be highly effective in preventing this cancer.[16,17]

Global efforts to develop vaccines for protection against COVID-19

In June 2020 there were more than 160 potential vaccines for COVID-19 under study, optimistic experts hope that a viable vaccine may be ready by the end of 2020 or beginning of 2021. This large global effort to develop vaccines for protection against COVID-19 have at least 10 vaccine candidates, as of early June 2020, entered clinical trials, including phase II trials (there are 3 clinical trials, I, II and III). The European Medicines Agency (EMA) has been in discussion with developers of 33 potential SARS-CoV-2 vaccines since May 2, 2020. However, the EMA expects that it may take at least one year before a vaccine is approved and available for widespread use in the EU/EEA

[European Centre for Disease Prevention and Control 11.6.2020, https://www.ecdc.europa.eu/en/covid-19/latest-evidence/vaccines-and-treatment].

On June 19, 2020 the weekly journal of the American Chemical Society, *Chemical and Engineering New*s published an interesting article: Crose R. COVID-19 vaccines and antibodies advance even faster than expected. With large vaccine trials planned and monoclonal antibody trials underway, efficacy data could come this fall or winter. *C&E NEWS*, JUNE 19, 2020 , VOLUME 98, (ISSUE 24).

" ……Early in the COVID-19 pandemic, infectious disease experts said that developing a vaccine for the virus would take at least 12–18 months. Now, in their continued blitzkrieg against SARS-CoV-2, the novel coronavirus that causes COVID-19, several drug companies are keeping pace with their ambitious timelines, and some are moving even faster than they initially predicted.

"…Three companies with funding from the US government—**AstraZeneca, Johnson & Johnson, and Moderna—**are on track to distribute the first commercial batches of their experimental vaccines in late 2020 or early 2021. Those firms are top players in Operation Warp Speed, the US plan to have 300 million doses of a safe and effective COVID-19 vaccine by January 2021. Separately, several groups began clinical trials in June of monoclonal antibodies designed to target and neutralize SARS-CoV-2. Although many older drugs are being repurposed as potential COVID-19 therapies, the antibody trials helmed by **Eli Lilly** and Company, **Regeneron Pharmaceuticals**, and **Singapore-based Tychan** are the first to test drugs created specifically for treating COVID-19…"

"…..The pandemic is pushing drug companies to develop and test their wares at unparalleled speeds. "There is no reason you couldn't speed up drug development if you really focused on it, and that's what the pandemic has brought," says Lisa Kennedy, CEO of the life sciences consulting firm Innopiphany.

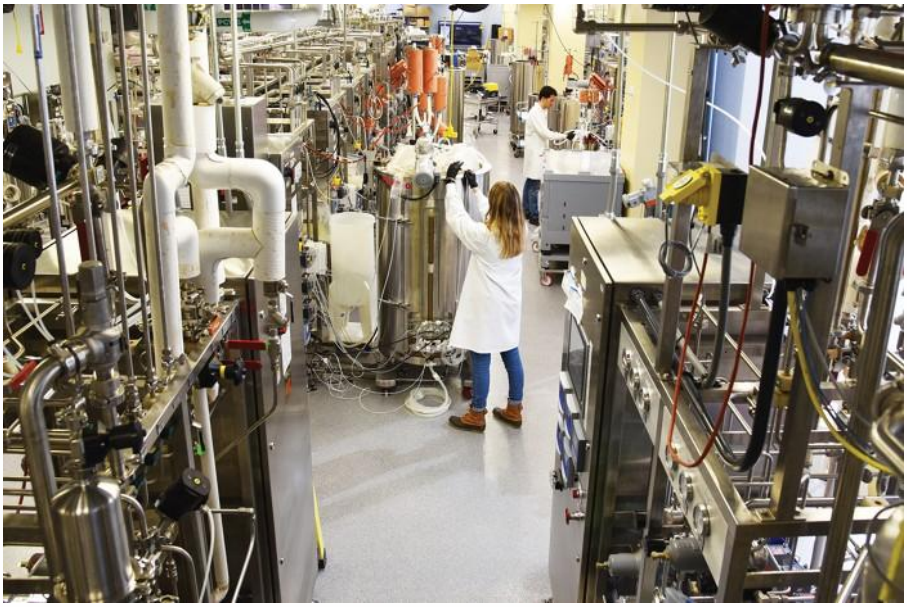

Figure 18. **Regeneron's** preclinical manufacturing laboratory, where selected antibodies for preclinical and toxicology studies will be made in stainless steel bioreactors. (Board of Directors: Schleifer LS, Yancopoulos GD).

"…..Never have so many groups been working on vaccines and treatments for the same disease, says Esther Krofah, executive director of FasterCures, a medical research advocacy division of the Milken Institute. "We have to be cautiously optimistic," Krofah says. "Clinical trials are notorious for not going well."

"…Large trials this summer and fall could provide the first evidence that some of the experimental COVID-19 vaccines are working. AstraZeneca, which is developing an adenoviral vector vaccine designed at the University of Oxford (**Jenner Institute**, https://www.jenner.ac.uk/), is recruiting 10,000 people in the UK, 30,000 people in the US, and potentially 2,000 people in Brazil for its Phase III study to determine if the vaccine is effective. If the trial is successful, **AstraZeneca** says, it could start distributing the vaccine as early as September in the UK and October in the US…"

"…Moderna plans to begin a 30,000-person Phase III study of its messenger RNA (mRNA) vaccine in July. The firm is working with the contract manufacturer Lonza to produce 500 million doses or more per year. **Johnson & Johnson (J&J),** which like AstraZeneca is developing

an adenoviral vector vaccine, says it will begin its first clinical trial in the second half of July—two months earlier than anticipated. The trial will test the vaccine in 1,045 healthy volunteers in the US and Belgium. J&J is also trying to move faster on planning for its larger trials…"

"…The Chinese companies **Sinovac** and China National Pharmaceutical Group—also known as **Sinopharm**—are prepping for Phase III studies of their vaccines outside China. Both firms are developing vaccines made from chemically inactivated SARS-CoV-2. They say people receiving their vaccines in Phase II studies developed neutralizing antibodies to the virus, but the data have not been published. Krofah says monoclonal antibodies could "be a bridge to a vaccine" before vaccines are widely available…"

"…Eli Lilly was the first company to begin clinical trials of monoclonal antibodies, discovered by the Canadian company AbCellera Biologics and the Chinese firm Shanghai Junshi Biosciences. It took only about 90 days from the start of AbCellera's discovery program to the first injection of the antibody in a clinical trial. "Typically, that process could take between 1 1/2 to 2 years minimum, so doing it in 3 months is extraordinary," says Janice Reichert, executive director of The Antibody Society, a trade organization. Others are also moving fast. Regeneron has begun two clinical trials of an experimental therapy that includes two monoclonal antibodies that target SARS-CoV-2. **Tychan** says it has begun clinical trials of its antibody in China.."

"…By Reichert's estimation, there could be upward of 20 SARS-CoV-2 antibody programs in clinical studies by the end of the year, and it should not take long to determine if these drugs are effective. Lilly says it could have data by the end of the summer. "The readout is pretty quick with COVID-19," Reichert says. "You either get better or you don't." If the clinical trials are successful, vaccine and antibody developers alike have suggested that their products could be available to certain groups through the US Food and Drug Administration's **emergency use authorization** (EUA), rather than a formal approval. The FDA announced an EUA for the

antiviral drug **Remdesivir** in May, three weeks before data from clinical trials were published…"

"…Vaccines for COVID-19 are likely to first be available through EUA, Krofah says, and she stresses the need for companies to publish data quickly in such a situation. "It is very important that all of the safety and efficacy data is shared and available publicly so that the public has confidence that this is not being hurried…".

Conclusions

Vaccination has made an enormous contribution to global health. Global coverage of vaccination against many infectious diseases of childhood has been enhanced dramatically since the creation of WHO's Expanded Programme of Immunization (EPI) in 1974 and of the Global Alliance for Vaccination and Immunization (GAVI) in 2000. Polio has almost been eradicated and success in controlling measles makes this infection another potential target for eradication. Despite these successes, approximately **6.6 million children still die each ye**ar and about a half of these deaths are caused by infections, including pneumonia and diarrhoea, which could be prevented by vaccination. Development of vaccines against more complex infections, such as malaria, tuberculosis and HIV, has been challenging and achievements so far have been modest. But in the longer term, widespread campaigns for vaccines are likely to be used to prevent or modulate the course of some non-infectious diseases. Progress has already been made with therapeutic cancer vaccines and future potential targets for new vaccines include addiction, diabetes, hypertension and Alzheimer's disease.

It is indisputable that vaccines and immunization has made the greatest contribution to global health, second only to the introduction of clean water and sanitation. From the end of the 19th century onwards vaccines contributed to the decline in child mortality from infectious diseases and has made an enormous contribution to human health, especially in the developing world.

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