Preface

Vaccination against infectious diseases has changed the future of the human species, saving millions of lives every year, both children and adults, and providing major benefits to society as a whole. However, national and sub-national coverage of vaccination varies greatly and major unmet needs persist. Whereas scientific progress opens exciting perspectives in terms of new vaccines, the road from discovery to sustainable implementation can be long and rocky, from financing, development and licensing to programme implementation and public acceptance. Immunisation is one of the best investments in health and should remain a priority for research, industry, public health and society.

On 14 May 1796, 73 years before *Nature’s* first issue, and inspired by Lady Montagu’s “variolation” concept, Edward Jenner inoculated 8-year old James Phipps with cowpox pus to prove that the less virulent cowpox would protect against smallpox. This experiment was a game changer in medicine and health. For the first time it was possible to medically prevent infection in a healthy person. Whereas vaccines were widely introduced in high income countries since the late 1950s, it took 180 years since Jenner before the Expanded Programme on Immunisation was launched in 1974, promoting access to 6 essential vaccines in all countries worldwide. Today, vaccines against 26 infectious diseases are internationally available according to WHO\(^1\), although more have been licensed worldwide, changing the future of the human species. Others are in experimental public health use, such as Ebola vaccines, or pilot implementation such as the RTS,s malaria vaccine, and about 240 vaccine candidates are in development\(^2\). The US Centers for Disease Control and Prevention declared vaccination the number one success story for public health in the 20\(^{th}\) century\(^3\).

However, progress in vaccine coverage remains highly uneven, between and within countries, threatening hard-won progress and raising uncertainty about how to make further advances. Vaccine-preventable diseases such as measles are on the rise, and episodes of vaccine reluctance and refusal are occurring
globally, questioning one of the most transformative interventions for survival and health.

This review focuses on *preventive immunisation in humans* and its impact (rather than on *vaccines* themselves), including in low, middle and high income countries. We discuss the current status of vaccine coverage, as well as unmet needs, four hurdles to overcome to ensure sustainable immunisation programmes starting with discovery of a new vaccine, the growing issue of vaccine confidence, and conclude with a number of opportunities and needed actions in order to ensure the full potential of immunisation for human health and society. Vaccine product development challenges for low and middle income countries, which were recently discussed in separate articles⁴,⁵, and therapeutic vaccines are not discussed.

Vaccines are biological products that induce protective immunity against infection and disease; they consist of sub-components, killed, or inactivated organisms which train the immune system for a future response to a natural infection. They are probably the only medical intervention recommended for every single individual on the planet. Unlike therapeutics, vaccines are used in healthy people, demanding a very high standard of safety, and requiring continuous monitoring for potential side effects. Besides considerations of safety, effectiveness, impact, and cost, this raises complex governance, regulatory, and public trust issues. All countries have a national immunisation plan, often with goals inspired by the Global Vaccine Action Plan (GVAP) global immunization goals for 2011-2020⁶.

*How immunisation has critically contributed to health and society*

It is hard to imagine a world without vaccines. A decade ago, WHO, UNICEF and the World Bank estimated that routine childhood immunization programmes were preventing over 2.5 million deaths annually⁷. With the increase in vaccine coverage, the growth of populations, and the introduction of new life-saving vaccines, immunization is ever more important for survival. Apart from preventing deaths, vaccines prevent disease and disability, including in adults and the elderly. In a high income country such as the USA, for a single birth cohort, vaccines prevent nearly 20 million cases of disease, and over 40,000 deaths⁸.

A vaccine has for the first time in history eradicated a human disease, smallpox. Efforts to eradicate polio are in the final stages with only two
countries, Afghanistan and Pakistan still experiencing wild polio virus transmission. All countries except 13, have eliminated neonatal and maternal tetanus. Without vaccination, there would be far more infections requiring antibiotic therapy, exacerbating the major problem of drug resistant infections.

Between 1990 and 2017, immunisation contributed to a 55% global decline in under-5 mortality with a drop from 87 to 39 deaths per 1000 live births. Over 14 million deaths are estimated to be prevented through measles vaccination alone between 2011 and 2020.

Vaccination benefits not only those who are vaccinated, but others in their family and community. This population wide benefit, called “herd immunity”, reduces the exposure of unvaccinated individuals to pathogens through a reduction or interruption of the chains of transmission. A recent study in Kenya not only showed that the introduction of a pneumococcal vaccine resulted in a major reduction in invasive pneumococcal disease, but also a nearly 100% decline in incidence among infants too young to be vaccinated, and over 74% reduction among unvaccinated children. Community- or herd immunity is an important consideration when estimating the full public health value of immunisation. The threshold to achieve such community protection can be as high as 95% for measles, but as low as 80% for rubella, and 60% in high income settings for the effect to begin for pneumococcal vaccination, meaning the programme strength required to derive additional impact varies substantially by vaccine. These differences of required critical vaccination coverage rates are due to R₀, the basic reproductive ratio of an infection, which can vary greatly among various infectious diseases. R₀ of a specific infection indicates the average number of cases one case generates in a population- in the case of measles it is 12 to 18, which is among the highest. It is an indicator of how contagious an infection is, and determines the minimum level of vaccination coverage needed to generate herd immunity.

Potential long-term effects beyond direct protection against a specific pathogen or disease have been attributed to a number of vaccines, in particular the BCG vaccine against tuberculosis and measles vaccine, where observational studies suggested a survival advantage compared to children who had remained unvaccinated. These non-specific effects (also called heterologous) would add to the disease-specific, proven benefits of vaccines, and have been attributed to epigenetic changes in innate immune cells as opposed to the adaptive immunity induced by the antigen-specific responses.
to the vaccine\textsuperscript{16,17}. However, the importance of heterologous effects remains controversial and plausible immunological findings still need to be validated in large-scale clinical trials.

The benefits of vaccines in general go beyond health, and include economic, educational, health security and other benefits\textsuperscript{18}. Their full economic value is not sufficiently quantified in assessments of cost-benefit, nor in investment terms, and is an increasing area of inquiry and empiric measurement\textsuperscript{19}.

Vaccination is a sound investment. Thus, the return on investment from childhood immunization in Low and Middle Income Countries (LMIC) is high. For every $1 invested in immunization against 10 diseases, $16 to $18 are saved in health care costs, and the net return is as high as $44 per dollar spent when the broad economic benefits are considered, though return on the investment varies by individual vaccine\textsuperscript{20}. This is compared with the cost per DTPcv3 (having received all three doses of DTP containing vaccine) vaccinated child of $27\textsuperscript{21}. In the USA, net economic benefits of vaccination in one birth cohort amount to almost $69 million\textsuperscript{22}.

Modelling and observational data suggest that in LMIC vaccination contributes to poverty alleviation and protection. Financial risk protection benefits of vaccination are accrued by the poorest households through reduction of catastrophic and impoverishing health expenditures\textsuperscript{23,24}. There is also evidence that vaccination improves childhood physical development, educational outcomes, and equity in distribution of health gains\textsuperscript{25}. Finally, without vaccines, absenteeism from school and work would be much higher, and periodic epidemics would disrupt society. The economic impact of periodic influenza epidemics for example is enormous\textsuperscript{26-28}, and can be reduced by immunization\textsuperscript{29}.

**Vaccination is a life time investment (Figure 1)**

In addition to being the backbone of maternal and child health, vaccines provide important health benefits for all stages in life. Given adaptations of the immune system throughout life, not all vaccines work equally well at all stages of life or in all geographical regions\textsuperscript{30,31}.

Starting in infancy, the presence of maternal antibodies in the newborn can impede vaccine response, as the neonatal immune system undergoes its own journey of ontogeny, which allows its adaptation from the “sterile” in utero environment to the confrontation with colonising and potentially pathogenic microorganisms\textsuperscript{32}. Particular immunologic pathways have been identified\textsuperscript{33}.

Despite significant progress in reducing under-5 mortality, important gaps remain in addressing neonatal morbidity and mortality. Neonates are particularly vulnerable to infection with gram-negative bacteria and Group B streptococcus, for which no neonatal vaccines currently exist\textsuperscript{33,34}. The gap in early protection can potentially be bridged by administering vaccines to women in pregnancy, relying on passively transferred antibody to protect infants in the first few months of life, until vaccinations administered in infancy or later can provide protection. Based on this principle, tetanus, influenza and pertussis vaccination are recommended for pregnant women to prevent neonatal infections, such as neonatal tetanus\textsuperscript{35}. This maternal immunisation strategy may be expanded with promising vaccines against Group B streptococcus and Respiratory Syncytial Virus\textsuperscript{36}.

For adolescents, lifesaving vaccines against human papilloma virus (the cause of cervical, anal, penile and head and neck cancers) are being increasingly introduced and must be administered prior to the likely acquisition of HPV via sexual contacts. Vaccines against meningococcal meningitis, a potentially lethal infection with a second peak in adolescence, have also been introduced into this age group in some countries. New platforms such as schools had to be engaged to administer these vaccines.

Outbreaks of mumps have very occasionally been seen in teenagers, despite a solid vaccination record. This highlights the need for surveillance of all age groups for outbreaks and could be due to waning of protection induced by vaccines otherwise regarded as highly efficacious\textsuperscript{37-39}.

Booster vaccines against diphtheria, tetanus and polio are required to guarantee long-lasting protection and are required throughout adulthood to maintain protective immunity levels – though recommendations may vary by country.

A life course approach to vaccination has become ever more pressing with pneumonia, influenza and shingles differentially affecting older adults, and death rates from pneumonia and influenza are 130 times higher for adults over 85, as compared to younger adults\textsuperscript{40}. Vaccination of the elderly with existing vaccines could prevent up to 90 000 deaths per year in the United States alone\textsuperscript{41}.

Adult immunization does not have a clear prioritization in low- and middle income countries, and is a complex programme across high income countries.
It is different from pediatric immunization which has a global programme and focused, substantial funding. As the demographics are shifting across the world to an older distribution a focus on adult immunization will become increasingly relevant, as advocated by the World Coalition on Adult Immunization\textsuperscript{42}.

Despite national recommendations\textsuperscript{43,44}, vaccine coverage among adults in high income countries is uneven\textsuperscript{45} (vaccine coverage for herpes zoster among adults aged \(\geq 60\) was 24\% compared with 65\% for influenza among those aged \(\geq 65\) in the US), and very low or not even available in most low and middle income countries\textsuperscript{46}. Yet, several studies have shown good cost-effectiveness of adult vaccinations against influenza, pneumococcal infection, shingles, human papilloma virus and tetanus-diphtheria-pertussis\textsuperscript{47}.

Important gaps also exist in our understanding of fundamental biology of adult immunisation. Due to “immunosenescence,” vaccination of older adults is in general not as effective as in younger people, but the reasons for poorer responsiveness are not well defined, requiring a new effort in terms of strategies and products for immunization of adults. However, it is likely that several compartments of the immune system are affected\textsuperscript{48}.

There are three areas where alterations to increase vaccine efficacy in the elderly could be considered: (i) increase vaccine potency; (ii) use adjuvants to enhance immunity; and (iii) apply immune modulators or other interventions to alter host immunity generally.

As populations age across the world, it will be increasingly important to identify how to integrate immunisation programmes in health and care services to reach all age groups.

In addition, travel, certain professions or health conditions require specific vaccinations\textsuperscript{49-51}, and international travel has played a role in the resurgence of measles in the USA and elsewhere\textsuperscript{52}.

\textit{From discovery to impact: overcoming four major hurdles}

There are still major infectious diseases whose control and ultimate elimination would require an effective vaccine, such as HIV infection and tuberculosis. Therefore continuing development of new vaccines is a public health imperative. Unfortunately, the majority of early vaccine candidates in discovery phase never make it as a safe and effective product. Development and deployment of vaccines is a long and complex process. We describe here
briefly four hurdles that have to be overcome from the discovery phase of a
new vaccine to sustainable population impact. (Table 2).

The first hurdle is a so-called “valley of death” from discovery to early clinical
development, when a potential antigen, adjuvant or new vaccine formulation
developed in the laboratory is further tested for clinical proof of concept and
safety in humans, in addition to optimizing production elements. Real progress
has been made in recent years thanks to a number of public and private
initiatives, which are helping partly to overcome this first major challenge,
such as CEPI, the Coalition for Epidemic Preparedness Innovation\(^5\) created
after the 2014-2015 Ebola epidemic in West Africa to accelerate development
of vaccines against epidemic pathogens\(^2,4,5\).

The second hurdle in vaccine development, also referred to as “second valley
of death”, relates to the shift from early clinical development to the large and
very expensive efficacy trials most often needed\(^4\), unless a previous similar
vaccine is already developed and a new product can be licensed using an
established correlate of protection. This is also the most expensive phase of
vaccine development, absorbing over two thirds of the total costs of
development of a new vaccine, including building special manufacturing
facilities and conducting Phase 3 trials in several countries, ideally with
independent research partners. Often, this major financial effort is beyond the
means of smaller biotech companies, and in general only big pharmaceutical
companies and large foundations or public institutions have the financial
bandwidth to support such trials which can cost as much as hundreds of
millions of dollars. For vaccine candidates without a prospect of a high income
market, ensuring return on investment, when the potential market for the new
vaccine is limited to low and middle income countries, there is a quasi
unsurmountable valley of death unless philanthropic and public funding
intervene\(^2\).

The needs and unique challenges of vaccines against epidemic pathogens
demand innovation in product development pathways. The Merck \(r\)VSV Ebola
vaccine has been deployed on a large scale during the outbreak in eastern DR
Congo prior to product licensure, even for indications for which no efficacy
data are available such as primary prevention in health care workers. Well
informed country leadership and transparent governance of such use are
critical, as is genuine community involvement. The “animal efficacy rule” when
human efficacy trials are not feasible or ethical\(^5\), should also be considered for
vaccines against epidemic pathogens. The development of Ebola vaccines has
shown how this type of ‘learning by doing’ model, can offer early access in
humanitarian situations \textsuperscript{56,57}, though it should be stressed that nearly five years
after the first Ebola vaccine clinical trials in West Africa, no Ebola vaccine is
licensed despite well documented immunogenicity, safety, and human and/or
non-human primate efficacy data. When a crisis such as Ebola is no longer
head line news, the sense of urgency is lost, and regulators and normative
committees go back to often extraordinarily long processes.

Following a successful phase 3 trial, there is a complex road to licensure of any
new vaccine, requiring reproducibility and safety tests of multiple batches of
vaccines, while manufacturing facilities are finalized. Several countries still
request clinical trial data conducted locally, delaying country licensure and
implementation significantly, while further raising costs of development. In
Europe there is advanced harmonization in regulatory approval of vaccines
through the European Medicines Agency, and in sub-Saharan Africa the Africa
Vaccine Regulatory Forum (AVAREF) is aiming to strengthen regulatory
capacity for clinical trials and harmonization of regulatory practices \textsuperscript{58}.

Following all of these activities which can take as long as ten years or more, a
new vaccine is now ready for deployment, but a third hurdle can occur
between licensure of a vaccine and broad scale implementation, which is
dependent on both a policy recommendation and the ability to implement.
Many years can go by before important new vaccines reach communities in
need, the cost of which is measured in human lives that could have been saved
as well as money for their development.

There are many contributors to this third hurdle: first is cost, especially
relevant for countries that are neither wealthy enough to procure vaccines at
high cost, nor poor enough to receive funding assistance from Gavi the
Vaccine Alliance. However, when a Gavi eligible country transitions out of the
program on the basis of an increase of it’s GNI per capita, it must increasingly
mobilise domestic resources or other development assistance \textsuperscript{59}. Even when
the broader value proposition of a new vaccine is substantial, there remains
the question of affordability. Second, is the question of country capacity to
take on new vaccines: the past decade has been an extraordinary era for
vaccine introduction with 113 countries having introduced at least one new
vaccine – a real success story \textsuperscript{60}. Country capacity to introduce and sustain ever
growing programmes involves human and financial resources, and time to
build political support and community demand. Both pneumococcal conjugate vaccine and rotavirus vaccine now have coverage in low income Gavi countries that meets or exceeds the global average, however this reflects that not all countries in any income strata have yet introduced these vaccines in spite of their availability. Even high income countries can experience delays. Thus, in the UK, a meningococcal B vaccine was licensed in January 2013, recommended for introduction in March 2014 and finally announced for introduction in May 2015. It then took over 12 months to resolve procurement discussions to enable implementation.

For products that address priority diseases for low income countries the uncertainty of the market may risk products collapsing unless a full end-to-end product solution is articulated, with non-commercial support. Inclusion of the new vaccine in WHO’s Pre-qualification list is a requirement for procurement through Unicef and Gavi and other funders. Some of these are vaccines against parasitic diseases, which are much more complex than bacterial or viral vaccines due to the wide range of antigens with often a complex life cycle exhibiting different antigens relevant for vaccine protection. Thus the RTS, vaccine, the first ever malaria vaccine deployed in a routine immunization system, took nearly 30 years since it’s creation by GSK in 1987 before EMA issued a positive scientific opinion in 2015, and in 2016 WHO recommended large scale pilot programmes. These took another three years to start in several African countries, and illustrate the sometimes extraordinary long development, licensure, and introduction times. It is also an example of a vaccine whose clinical trial performance of partial protection led to a policy decision to advance in a step-wise manner rather than full programmatic deployment. This may become a more common pathway for future products, in part because these vaccines have performance and implementation characteristics that are more complex than those of current vaccines.

We are entering an era where the path from vaccine licensure to routine implementation requires more than safety and efficacy data. Policy recommendations for new vaccines may only be realized following implementation research to determine how to most effectively ensure use and impact. Cost effectiveness deliberations, full value of vaccine assessments, and country priorities in the face of constrained resources remain drivers for delays associated with the third hurdle. National immunisation technical advisory groups (NITAGS) will be increasingly important to guide evidence based decision making.
Even after the lengthy and costly trajectory to introduce a new vaccine, ensuring sustainable impact faces a fourth set of hurdles that must be overcome. These include supply and demand sustainability, and resilience and acceptance of immunisation. Logistical issues such as in-country cold chain, procurement management, and the organisation of vaccination clinics in remote areas, vaccine hesitancy, equity of access can all present challenges. In addition, the misuse of vaccination campaigns as political tools has seriously damaged vaccine confidence in areas such as the Philippines, Nigeria, Afghanistan, Italy and Pakistan. Some side effects or limitations of duration of protection may only become obvious after larger scale use, such as for live oral rotavirus vaccination in high-mortality settings, pertussis vaccine and others. A recent example is the finding from a retrospective analysis of long term efficacy trials showing that although there is a clear overall population benefit of the Dengvaxia vaccine against dengue, the vaccine also caused an excessive risk of severe dengue in seronegative vaccinees (i.e. those not exposed to dengue virus). In the Philippines this new risk was reported after over 800,000 school children were vaccinated, prompting a dramatic reaction by the public in 2018.

Stock outs and vaccine manufacturing capacity have been problematic for certain vaccines, even in high income countries. Manufacturers emphasize the time needed to build and commission a factory. Whereas middle income country manufacturers are now supplying most low cost vaccines globally, they face low profit margins, ferocious tenders, and often unpredictable procurement schemes. More efficient and modular production technologies may allow decentralised production with lower capital costs.

Each of the four hurdles can be overcome, though the fourth one should be a continuing concern for every national immunisation programme. Depending on the phase, they may require different sets of actors, and sometimes are a matter of policy, management and leadership, rather than money.

Throughout development and use of vaccines, vaccine safety is an overriding concern, and requires a continuous and careful scientific and societal assessment. Safety monitoring during manufacturing typically occupies a major part of the process and costs of a vaccine, and is a key element of any vaccine programme. In specific high income populations, such as in the elderly, personalized medicine approaches have been proposed to maximize both immunogenicity and safety in the presence of chronic conditions and changes
related to older age, but large scale applicability is questionable for the time being\textsuperscript{72-74}.

**Persistent unmet needs for vaccination**

The extraordinary achievement of vaccines is reflected in countries having vaccinated over 116 million infants in 2018 alone\textsuperscript{75}, a similar success story to that of 2017 when a similar number of infants were estimated to have been vaccinated --- the greatest number, ever. Figure 2 shows global and regional; coverage of DPT3 vaccination between 1980 and 2018, showing overall high coverage, with regional variations, but also stagnation in coverage over the last 10 years\textsuperscript{76}. Nonetheless, there still remained 19.4 million un- or under-vaccinated children, leaving them vulnerable to diseases they could and should be protected from. In some countries substantial improvements in coverage have been achieved, while in others coverage is backsliding, often because of social disruption, conflict, or political upheaval, pointing out the highly dynamic nature of vaccine programme performance.

Around 60\% of all children who did not receive basic immunisation in 2018 live in 10 countries: Angola, Brazil, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Nigeria, Pakistan, The Philippines, and Vietnam\textsuperscript{77}. To achieve rapid change in this situation requires the full commitment of governments, supported by international organisations. Gavi provides funding for vaccination programmes in low- and low-middle income countries and has had substantial impact. The technical support provided by the Gavi Alliance partners will be key to addressing persistent gaps. Consistently delivering vaccines with high coverage, reaching at least the minimum coverage required to achieve herd immunity in line with the basic reproductive ratio of an infection as mentioned above, remains a struggle in many other countries including in middle- and high- income settings, with poor children not being reached\textsuperscript{78,79}. For example, in the USA in 2017 100,000 children under 2 years (1.3\% of the population of that age) were not immunised against DTP/MMR, a fourfold increase since 2001\textsuperscript{79,80}.

Of particular concern are countries whose vaccination coverage has declined. There are 19 countries who had over 80\% first dose measles coverage at some point between 2011-2017 and whose 2018 coverage is at least 10\% lower than their peak coverage. The measles vaccine coverage of those 19 backsliding countries now ranges from 38\% - 88\%, with 10 well below 80\%\textsuperscript{61}. Some of the backsliding on coverage may represent improvements in data rather than
actual slippage in coverage. The data systems to accurately monitor both the
number of children born and the number of children vaccinated are highly
variable in quality\textsuperscript{81,82}. In some settings management and reward systems likely
incentivize inaccurate reporting of coverage data to meet targets, rather than
incentivizing accurate reporting.

Measles, diphtheria, and yellow fever outbreaks are the result of what
happens when the world is complacent and immunisation coverage declines.
Diphtheria outbreaks surged in Russia in the early 1990s, and among Rohingya
refugees from Myanmar in 2017, outbreaks of meningitis occurred in refugee
camps, and transmission of polio persists in parts of Afghanistan and
Pakistan\textsuperscript{83}. Measles outbreaks are occurring in all regions of the world. The
recent 80-fold increase in reported measles cases in the WHO Europe Region
over 4 years to over 82,000 cases in 2018 with 72 deaths\textsuperscript{84,85} are a result of a
mix of vaccine refusals, cultural beliefs, and access issues including
interruptions in vaccine supply, such as in Ukraine\textsuperscript{86}, leading to a WHO
declaration of a grade 2 health emergency\textsuperscript{87}. In the Americas, thousands of
cases have been reported in Venezuela due to the political and economic crisis,
with cases also appearing in Brazil, Colombia and Ecuador, resulting in the loss
of regional elimination status granted in 2016.

These outbreaks reflect failures to achieve and maintain high vaccination
coverage, community by community. Low vaccination coverage and high
heterogeneity in coverage are most deeply seen among African countries
where routine immunisation rates in many countries are well below the GVAP
targets\textsuperscript{88}.

Since 2010, routine immunization levels have either stagnated or decreased in
54 of 85 middle income countries, who do not qualify for Gavi support\textsuperscript{78}.
Vaccine expenditures per child are often lower in middle income countries
than in low income Gavi countries. The issue may not be so much lack of
funding capability, but lack of prioritization of immunization, not participating
in pooled procurement mechanisms such as via Unicef, low volumes,
insufficient efforts to reach vulnerable populations, vaccine choices, and
duplicative local regulatory requirements delaying introduction of new
vaccines.

Another unmet need concerns new vaccine introduction. Rapid progress has
been made to scale up the introduction of vaccines through Gavi investments
in low income countries, but not all vaccines have progressed at the same
rapid pace. The adolescent HPV vaccine has been particularly slow to be 
introduced outside of high income settings because of programmatic 
challenges, public access issues, supply constraints and pricing.

Addressing these unmet needs will require both dogged implementation of 
strategies that have been shown to be effective, like detailed microplanning of 
local efforts to assure all children are identified and immunized, special 
campaigns, to implementation of novel approaches like drone delivery of 
vaccines in hard to reach areas. Systematic evaluation and implementation 
research should be part of these efforts in order to develop a firm evidence 
base for overcoming such programmatic challenges. The World Health 
Organization has elaborated guidance on implementing high impact 
immunization programmes (Global Routine Immunization Strategies and 
Practices, GRISP) to address these unmet needs. Middle income countries not 
benefiting from Gavi funding need procurement mechanisms that can secure 
more predictable tiered pricing. No set of strategies, however, will succeed 
without substantially enhanced domestic investment and local political 
commitment, which continue to limit progress in many parts of the world. As 
demand for services from communities increases, responsiveness to that 
demand from governments, the funder of such services in most countries is 
more likely.

In addition to the unmet needs related to existing vaccines, nearly half of all 
Deaths from infectious diseases are from infections for which no vaccine is 
available (e.g. more than 0.5 million deaths under 5 years from enteric 
infections for which there is no vaccine). These should be priorities for 
vaccine R&D, while improvements are needed for vaccines such as against 
rotavirus, pertussis, polio, and yellow fever. Innovations in delivery devices are 
also important (e.g. micro patches, temperature stable vaccines, improved cold 
chain equipment).

**The Equity Imperative**

Equity has been a primary goal of immunization programmes. Reaching those 
in greatest need means addressing issues of vaccine availability, affordability, 
accessibility, acceptability, and financing. An effective immunization system 
that delivers vaccine with high equity across social and ethnic strata, maternal 
and community education, and geographies, is a purpose built programme to 
deliver impact, and has been shown to be the critical programmatic target.
Country level coverage values mask subnational inequity, risking disease outbreaks and backsliding on achievements of vaccination. Immunization improvement should focus at the subnational level, as well as on other determinants of inequity, not all of which would be addressed through focused supplemental vaccine campaigns.

There is a special case for vaccine development for pathogens that cause epidemics. These diseases have little to no market incentive to drive product development hence the need for innovative arrangements such as CEPI, US BARDA (Biomedical Advanced Research and Development Authority) and the European IMI (Innovative Medicines Initiative).

*Humanitarian crises* are another increasing impediment to immunisation. The number, size and duration of conflicts, migration of refugees, and natural disasters, have caused major disruptions to immunisation programmes and resulted in serious disease outbreaks. The persisting hurdles to polio eradication reveal how political, social and conflict situations can disrupt access to populations and risk violence targeting vaccinators such as in Pakistan and Afghanistan. Nearly 100 polio vaccinators and their security guards have been targeted and killed while attempting to reach children for vaccination.

*The growing challenge of vaccine confidence*

Despite the success and wide-acceptance of the importance of immunization, there are growing groups of people delaying or refusing vaccines. In 2013 WHO/SAGE established a working group to investigate the scope and scale of vaccine hesitancy, the US National Vaccine Advisory Committee (NVAC) convened a Vaccine Confidence Working Group to investigate the situation in the US (National Vaccine Advisory Committee, 2015), and the European Centre for Disease Prevention and Control (ECDC) published a review of the state of vaccine hesitancy in Europe. In January 2019, the World Health Organization named vaccine hesitancy as one of the top ten global health threats.

Since 2015, the Vaccine Confidence Index™ has surveyed over 300,000 respondents globally to pick up early signals of waning public confidence in vaccine importance, safety, and effectiveness in order to prompt early intervention where needed (See Figure 3 for world map of confidence in vaccine safety in 2018). The European Commission adopted the Index as part of a new effort to strengthen cooperation against vaccine-preventable diseases, and the Wellcome Global Monitor on Trust in Science and Health as
part of their 144 country study\textsuperscript{100}. Safety was not only identified as a key issue in the 2018 European study, but also in a larger 144-country global study using the VCI™. In the Wellcome Global Monitor, public confidence in vaccine safety was consistently lower than confidence in vaccine effectiveness and importance\textsuperscript{100}.

Whereas lack of familiarity by both physicians and parents with many childhood diseases because of years of successful vaccination programmes may play a role in a lack of interest in vaccines, the reasons for a decline in vaccine confidence are far more complex. Newer challenges to vaccine confidence include social media campaigns which have disrupted measles-rubella vaccination efforts in southern India, collapsed HPV vaccination efforts in Japan, provoked false scares of vaccine poisoning in Pakistan, and undermined vaccination programmes in Indonesia.

Vaccine confidence issues are highly varied by setting and vaccine. In a three-year review (2015-2017) of the WHO/UNICEF Joint Reporting Form (JRF) completed annually by national immunization programmes, over 90% of the 194 countries reported that they experienced vaccine hesitancy. The top three reasons for hesitancy were “risk-benefit (scientific evidence)” i.e. safety concerns, “lack of knowledge on benefits of immunization,” and “religion, culture and socio-economic issues”\textsuperscript{101}.

Challenges around building confidence in vaccine safety are well beyond communication, although more accessible public communication around the complex issues of safety and risk benefit analysis are important. What needs to be addressed is not only better communication around the known, albeit sometimes misinterpreted, risks and benefits of vaccination, but investing in more research in the areas where the public is asking questions and the science is incomplete. Findings that Pandemrix, an AS03-adjuvanted influenza vaccine, was linked to increased cases of narcolepsy in Europe prompted further research, but a systematic review concluded that more research is needed\textsuperscript{102}.

While uncertainty is the norm in science, the political and social worlds of the public have become less tolerant of ambiguity and risk\textsuperscript{103}. New modes of listening to the public, with rapidly evolving technologies to monitor social media, can harvest emerging safety questions as well as pick up signals of possible issues that need investigation. Working towards better aligned public questions and accessible, evidence-based answers, should be a goal. The
Vaccine Safety Net initiative at WHO is an important resource and can be further built on to address new questions as they emerge, as well as make new research accessible\textsuperscript{104}. Social and political contexts and the reliability of health services are important levers of trust, and a low trust setting will have less tolerance for risk than one with high trust. A 2015 study showed that high trust in immunization services clearly correlated with lower rates of vaccine hesitancy\textsuperscript{105}. The public’s experience with health services and health workers is highly influential in vaccine decision, but both are needed. The Wellcome Monitor showed that, in Japan for example, despite low trust in vaccines and low trust in government, confidence in health providers remained high.

Introducing new vaccines into populations requires adequate time to train and prepare front line health workers and vaccinators to be ready to manage public questions, and ongoing dialogue between scientists and the public will be important to build confidence from the start, as well as anticipate and manage adverse events.

In the Philippines reported risks of a recently introduced dengue vaccine\textsuperscript{106} amplified into public outrage mediated through Facebook pages, made more complex because the events occurred during political elections. The result was a dramatic drop in public confidence in vaccines more generally from 99.5\% in 2015 to 76.2\% in 2018, while confidence in vaccine safety plummeted from 99.5\% to 65.2\%\textsuperscript{65}. (Figure 4) The overall drop in public trust affected willingness to accept even the measles vaccine, prompting measles outbreaks with over 25,000 measles cases and 355 deaths by March 2019\textsuperscript{107} requiring considerable efforts to rebuild public confidence and increase vaccine uptake.

Conflict situations also affect confidence in vaccines and vaccinators due to an environment of distrust and uncertainty, such as in Pakistan and Afghanistan, and in the Democratic Republic of Congo where local violence and conflict in the Ebola affected areas has been an obstacle to vaccination efforts.

\textit{The future of immunisation: sustainability and new opportunities}

The contribution of immunisation to human health, security and prosperity, has been matched by few other activities in health and development, and has
been crucial for progress in child survival. As immunisation coverage among adults is generally low, it is another area where greater advances can be made.

Addressing the following issues will be crucial to ensure optimizing the impact of vaccination:

1. **Leadership and funding**: Achieving immunisation for all those in need should be a top priority for every country. This will require stronger political leadership and a continuing increase in investments in immunisation, both domestically and internationally. The power of immunisation to achieve wider health and societal benefits should be further documented. Prioritization of vaccines is particularly critical for middle income countries no longer benefiting from Gavi support and for countries that are transitioning out of Gavi support.

   A successful replenishment of Gavi resources in 2020 for the proposed Gavi 5.0 strategy is vital for the next decade of progress in child survival, and will be a test of the international community’s commitment to immunisation and global health.

2. **Universal vaccine coverage and equity**: Overcoming the stagnation in reaching all people in need with even the basic vaccines is an overriding priority in all countries, especially in those with the lowest coverage and the greatest number of unvaccinated children. As we look toward the next decade ensuring that vulnerable people all countries are not left behind should be a top concern, particularly in middle income countries since there will be more poor people living there than in poorer countries.

   Ensuring a sustainable and affordable supply of quality vaccines, with differential pricing according to the wealth of a country, is fundamental to achieving sustainability and equity of immunisation. Only a few multinational companies are producing vaccines, and a growing number of middle income manufacturers are major suppliers. There is a risk that continuous lowering of prices may lead to new monopolies, and possibly higher prices. Healthy vaccine markets with sustainable supply is an important objective for vaccine programmes. Harmonisation and strengthening of regulatory capabilities of LMIC are key. Initiatives such as the Africa Vaccine Regulatory Forum (AVAREF) deserve support. The fact that some countries require local clinical trials despite WHO prequalification, can be a source of major delays in the introduction of vaccines.

3. **People-centred programmes** Immunisation programmes can become more effective with a systems-driven and “precision public health” approach, taking
into account local variation in immunisation levels, specific needs, cultural specifics, and circumstances of vulnerable populations. Quality data at administrative levels closer to communities should be collected to inform “micro-planning” and adaptive programme delivery. Thoughtful integration of immunisation into health services, education systems, and elderly care, among other innovative efforts are needed.

As most vaccines have incomplete efficacy, tailored approaches to optimize their impact will be needed particularly for vaccines against malaria, influenza, dengue, and probably HIV when it becomes available.

4. Vaccine confidence: Vaccine confidence must be addressed up front and be an integral part of immunisation programmes. Many approaches to increasing vaccine uptake do not take into account the social, historical and political realities of the public for whom information alone is not the antidote to vaccine reluctance. Instead of older demand-creation models, a new model and language of engaging with the public is needed, starting with better listening and prompt responding to concerns as well as building on local capacities. Inclusion of non-traditional partners, new modes of digital communication, social scientists, and religious and traditional leaders have been invaluable in addressing hesitancy around polio vaccination, and the engagement of teenage girls in co-designing social media outreach to address HPV vaccination concerns had positive impacts on vaccine uptake in Denmark. With safety anxieties being reported as one of the top reasons for vaccine hesitancy, aligning vaccine safety research with dominant safety concerns will also be important for confidence building.

5. Invest in research and innovation: Many issues mentioned in the other recommendations require further research in a wide range of disciplines. Product innovation as a result of the formidable progress in immunology and infection pathogenesis has been a strong driver of immunization programmes. There is reluctance of industry to develop vaccines, when market incentives are limited, and licensure is uncertain. While companies such as Merck and Johnson & Johnson invested considerably in the development of Ebola vaccine candidates, partly supported by public funds in North America and Europe, but without a prospect of a return on investment, it would be unrealistic to expect that industry will follow this example for each new emerging pathogen. There is a major role for the public sector and philanthropy to support mechanisms such as CEPI to develop vaccines for low income countries². As discussed under the “2nd hurdle” on the challenge to fund and conduct late clinical
development to market introduction for vaccines for which there is no market
centive, there is an urgent need to address this gap through possibly a
specific global initiative or at least a concerted action of several funders.
There is also a need for innovation in trial design (for faster trials with smaller
sample size and including collection of valuable biosamples to inform
correlates of protection) and in trial analysis, as well as in vaccine delivery.
Escalating antimicrobial resistance (AMR) is a powerful incentive to develop
vaccines against bacterial infections, malaria, TB and HIV infection.\textsuperscript{109-111}
Innovation in delivery of vaccination programmes is as important as product
innovation.

The world cannot afford to turn the clock back on immunisation, and ever
more innovative vaccines will offer additional opportunities to reduce
mortality and improve quality of life for every person on the planet. This will
require the best of science, entrepreneurship, programme implementation on
the ground, and politics.

Tables

1. Historic timeline of introduction of vaccines.
2. From discovery to sustainable impact: Overcoming four major hurdles

Figures

1. Vaccines across the human life cycle.
2. Coverage of DTP3 (containing products) immunisation over time globally,
3. Global confidence in vaccine safety by country
4. Changing levels of vaccine confidence in The Philippines between 2015 and
   2019.

References

2 Kaslow, D. C. et al. Vaccine candidates for poor nations are going to waste. Nature \textbf{564}, 337-
3 CDC. Ten great public health achievements--United States, 1900-1999. \textit{MMWR. Morbidity
The authors demonstrate how promising and much needed vaccines for global health fail to reach full development because of inadequate financial incentives, and propose mechanisms to overcome this problem.

This is THE global reference for most national immunisation programmes.
This paper considers the broader economic benefits around childhood development, household behaviour, and macro-economic indicators in addition to the usual microeconomic evaluations of immunisation.

This article introduces a series of papers presented at a scientific meeting held at the Royal Society in London in 2015 addressing the wide range of biological reasons for the variability in vaccine efficacy, such as age, sex, environment, genetics and co-infections.


This paper provides insights into the biological challenges to advance the concept of a life course of vaccination.


*This is the annual update on the state of immunisation in the world with a wealth of data.*


*A must read to understand the complexity and cost of vaccine manufacturing.*


This paper shows that vaccine coverage monitoring over time, at local rather than national levels is critical for programme management, improvement and for implementing operational approaches that enhance vaccine coverage equity.

Murray, J. Vaccines by air as drone medicine service takes off in Ghana. (Guardian News & Media Limited, London, 2019).


*Biomedical Advanced Research and Development Authority,* [https://www.phe.gov/about/barda/Pages/default.aspx](https://www.phe.gov/about/barda/Pages/default.aspx) (2019).


Panteli, D. & Edwards, S. in *Ensuring access to medicines: How to stimulate innovation to meet patients’ needs?* (eds E. Richardson, W. Palm, & E. Mossialos) (World Health Organization Regional Office for Europe, 2018).


ECDC. *Rapid literature review on motivating hesitant population groups in Europe to vaccinate.* (European Centre for Disease Prevention and Control, 2015).


*The study is the largest evaluation of people’s attitudes, interest, trust, and beliefs about science including immunization.*


*This was the first benchmark report by the Vaccine Confidence Project, providing an overview on the key issues affecting confidence globally.*


Gavi. Gavi Board starts framing Alliance's approach to 2021-2025 period,


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*Disclaimer: This review does not necessarily reflect the position of the World Health Organisation

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**Author contributions**

All authors contributed to the development and writing of the manuscript.

**Competing Interests Statement**

PP is a board member of the Coalition for Epidemic Preparedness Innovation (CEPI), and the Global Health Innovative Technology Fund; HL has a grant from GSK, and is on an Advisory Board of Takeda; KLO is the director of the Department of Immunization, Vaccines, and Biologicals at the World Health
Table 1. Historic timeline of introduction of vaccines (year of licensure indicated wherever possible)

<table>
<thead>
<tr>
<th>Year</th>
<th>Disease</th>
<th>Year</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1798</td>
<td>Smallpox</td>
<td>1999</td>
<td>Rotavirus (reassortant)</td>
</tr>
<tr>
<td>1885</td>
<td>Rabies</td>
<td>2000</td>
<td>Pneumococcal conjugate (heptavalent) a</td>
</tr>
<tr>
<td>1896</td>
<td>Cholera</td>
<td>2003</td>
<td>Influenza (intranasal, cold-adapted)</td>
</tr>
<tr>
<td>1896</td>
<td>Typhoid</td>
<td>2005</td>
<td>Meningococcal conjugates (quadriivalent) a</td>
</tr>
<tr>
<td>1897</td>
<td>Plague</td>
<td>2006</td>
<td>Human papillomavirus recombinant (4-valent)</td>
</tr>
<tr>
<td>1923</td>
<td>Diphtheria toxoid</td>
<td>2006</td>
<td>Rotavirus (attenuated and new reassortants)</td>
</tr>
<tr>
<td>1926</td>
<td>Pertussis (WC)</td>
<td>2006</td>
<td>Varicella Zoster</td>
</tr>
<tr>
<td>1926</td>
<td>Tetanus toxoid</td>
<td>2008</td>
<td>Rotavirus (monovalent)</td>
</tr>
<tr>
<td>1927</td>
<td>Tuberculosis (bacille Calmette-Guérin)</td>
<td>2009</td>
<td>Japanese encephalitis (Vero cell)</td>
</tr>
<tr>
<td>1935</td>
<td>Yellow fever</td>
<td>2009</td>
<td>Cholera (WC only)</td>
</tr>
<tr>
<td>1936</td>
<td>Influenza</td>
<td>2009</td>
<td>Human papillomavirus recombinant (2-valent)</td>
</tr>
<tr>
<td>1937</td>
<td>Tickborne encephalitis</td>
<td>2010</td>
<td>Meningococcal type A conjugate (monovalent)</td>
</tr>
<tr>
<td>1938</td>
<td>Typhus</td>
<td>2010</td>
<td>Pneumococcal conjugate (13-valent)</td>
</tr>
<tr>
<td>1955</td>
<td>Polio (inactivated)</td>
<td>2014</td>
<td>Human papillomavirus (9-valent)</td>
</tr>
<tr>
<td>1963</td>
<td>Measles</td>
<td>2014</td>
<td>Meningococcal type B (FH factor)</td>
</tr>
<tr>
<td>1963</td>
<td>Polio (oral)</td>
<td>2015</td>
<td>Ebola (unlicensed) b</td>
</tr>
<tr>
<td>1967</td>
<td>Mumps</td>
<td>2015</td>
<td>Malaria c</td>
</tr>
<tr>
<td>1969</td>
<td>Rubella</td>
<td>2015</td>
<td>Dengue</td>
</tr>
<tr>
<td>1970</td>
<td>Anthrax secreted proteins</td>
<td>2015</td>
<td>Meningococcal type B d</td>
</tr>
<tr>
<td>1974</td>
<td>Meningococcus polysaccharide</td>
<td>2016</td>
<td>Cholera (oral)</td>
</tr>
<tr>
<td>1977</td>
<td>Pneumococcus polysaccharide (14-valent)</td>
<td>2018</td>
<td>Typhoid conjugate e</td>
</tr>
<tr>
<td>1980</td>
<td>Adenovirus</td>
<td>2006</td>
<td>Human papillomavirus recombinant (4-valent)</td>
</tr>
<tr>
<td>1980</td>
<td>Rabies (cell culture)</td>
<td>2006</td>
<td>Rotavirus (attenuated and new reassortants)</td>
</tr>
<tr>
<td>1981</td>
<td>Tickborne encephalitis</td>
<td>2006</td>
<td>Varicella Zoster</td>
</tr>
<tr>
<td>1981</td>
<td>Hepatitis B (plasma derived)</td>
<td>2008</td>
<td>Rotavirus (monovalent)</td>
</tr>
<tr>
<td>1983</td>
<td>Pneumococcus polysaccharide (23-valent)</td>
<td>2009</td>
<td>Japanese encephalitis (Vero cell)</td>
</tr>
<tr>
<td>1985</td>
<td><em>Haemophilus influenzae</em> type b polysaccharide</td>
<td>2009</td>
<td>Cholera (WC only)</td>
</tr>
<tr>
<td>1986</td>
<td>Hepatitis B surface antigen recombinant</td>
<td>2009</td>
<td>Human papillomavirus recombinant (2-valent)</td>
</tr>
<tr>
<td>1987</td>
<td><em>H. influenzae</em> type b conjugate a</td>
<td>2010</td>
<td>Meningococcal type A conjugate (monovalent)</td>
</tr>
<tr>
<td>1989</td>
<td>Typhoid (<em>Salmonella</em> Ty21a)</td>
<td>2010</td>
<td>Pneumococcal conjugate (13-valent)</td>
</tr>
<tr>
<td>1991</td>
<td>Cholera (WC-rBS)</td>
<td>2014</td>
<td>Human papillomavirus (9-valent)</td>
</tr>
<tr>
<td>1992</td>
<td>Japanese encephalitis (mouse brain)</td>
<td>2014</td>
<td>Meningococcal type B (FH factor)</td>
</tr>
<tr>
<td>1993</td>
<td>Cholera (recombinant toxin B)</td>
<td>2015</td>
<td>Ebola (unlicensed) b</td>
</tr>
<tr>
<td>1994</td>
<td>Typhoid (Vi) polysaccharide</td>
<td>2015</td>
<td>Malaria c</td>
</tr>
<tr>
<td>1994</td>
<td>Cholera (attenuated)</td>
<td>2015</td>
<td>Dengue</td>
</tr>
<tr>
<td>1995</td>
<td>Varicella</td>
<td>2015</td>
<td>Meningococcal type B d</td>
</tr>
<tr>
<td>1996</td>
<td>Hepatitis A</td>
<td>2016</td>
<td>Cholera (oral)</td>
</tr>
<tr>
<td>1996</td>
<td>Pertussis (Acellular)</td>
<td>2018</td>
<td>Typhoid conjugate e</td>
</tr>
<tr>
<td>1998</td>
<td>Lyme OspA</td>
<td>2006</td>
<td>Human papillomavirus recombinant (4-valent)</td>
</tr>
<tr>
<td>1999</td>
<td>Meningococcal conjugate (group C) a</td>
<td>2006</td>
<td>Rotavirus (attenuated and new reassortants)</td>
</tr>
</tbody>
</table>
Table 2: From discovery to sustainable impact of immunization: overcoming four major hurdles

<table>
<thead>
<tr>
<th>Issues</th>
<th>Selected actions needed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First hurdle</strong>: from discovery to early clinical development</td>
<td></td>
</tr>
<tr>
<td>Few discoveries make it to actual products</td>
<td>Incentives for industry for vaccines with no high income countries market</td>
</tr>
<tr>
<td>High risk for companies</td>
<td>Public-private partnerships and philanthropy</td>
</tr>
<tr>
<td>Safety key issue</td>
<td></td>
</tr>
<tr>
<td><strong>Second hurdle</strong>: from early clinical development to large efficacy trials</td>
<td></td>
</tr>
<tr>
<td>Very expensive—two thirds of total costs of new vaccine development</td>
<td>End-to-end product planning Need for major boost from private and public funding</td>
</tr>
<tr>
<td>Particularly challenging for vaccine candidates without high income market potential</td>
<td>Clinical trial capacity and rationalizing trial methodology</td>
</tr>
<tr>
<td>Safety major issue, besides immunogenicity and efficacy</td>
<td>Regulatory harmonization and speed</td>
</tr>
<tr>
<td>Complex road to licensure</td>
<td>Manufacturing availability for GMP-products to be used in trials</td>
</tr>
<tr>
<td>Can take 3 to 10 years or longer</td>
<td></td>
</tr>
<tr>
<td><strong>Third hurdle</strong>: from vaccine licensure to broad scale implementation</td>
<td></td>
</tr>
<tr>
<td>Dependent on policy recommendations, cost effectiveness deliberations, and political priority</td>
<td>End-to-end product solution</td>
</tr>
<tr>
<td>Country capacity to take on new vaccines i.e. – human and financial resources and the time to build political support and community demand</td>
<td>National and international funding, Gavi transition management, tendering processes</td>
</tr>
<tr>
<td>Logistical issues, e.g. cold chain, procurement management, organisation of vaccination to ensure equity of access</td>
<td>National regulatory harmonisation</td>
</tr>
<tr>
<td>Supply not always sufficient</td>
<td>Policy clarification and political leadership</td>
</tr>
<tr>
<td>Highly variable time-line by country</td>
<td>Manufacturing capacity</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fourth hurdle</strong>: achieving consistent, long term supply and demand sustainability</td>
<td></td>
</tr>
<tr>
<td>Continuing concern for every national immunisation programme</td>
<td>Policy and political commitment</td>
</tr>
<tr>
<td>Issues may arise even after years of implementation</td>
<td>Sustainable funding</td>
</tr>
<tr>
<td>Complex interplay of service delivery, supply and demand, societal trust, political and humanitarian conflicts</td>
<td>Management and logistics</td>
</tr>
<tr>
<td>Never ending</td>
<td>Tender processes</td>
</tr>
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</table>


Figure 1. Vaccines across the human life cycle

Legend: Not only do vaccines provide important health benefits for all stages in life. They also do so for travellers, health care workers as well as those who are in special health conditions.

Note: The list of vaccines by different phases of life-course are illustrative, rather than exhaustive, and do not imply these are universally recommended for each life phase in all countries. Vaccines recommended by WHO by phase of life-course is available at [https://www.who.int/immunization/policy/immunization_tables/en/](https://www.who.int/immunization/policy/immunization_tables/en/) (last accessed: 3 September 2019).

Figure 2. Coverage of DTP3 (containing products) immunisation over time globally, combining coverage and regional variations, 1980-2018

Legend: The coverage of DTP3 immunisation improved rapidly in the 80s with large regional variations. Stagnation over the last 10 years meant 19.4 millions children remained un- or under-vaccinated.

Solid lines represent regional coverages. Vertical bars represent global coverages with percentages shown at the top of each bar.


Note: DTP3: Diphtheria, tetanus, and pertussis; AFR, AMR, EMR, EUR, SEAR, and WPR are World Health Organization subregions of Africa, Americas, Eastern Mediterranean, Europe, South-East Asia, and Western Pacific, respectively.


Figure 3. Global Confidence in Vaccine Safety, 2018

Legend: Levels of confidence in vaccine safety varied considerably across countries and regions with a number of countries showing very low levels of confidence.

The colour chart at the bottom shows increasing levels of confidence from red and dark green.

Source: Vaccine Confidence Index™ data from Wellcome 2018 Global Monitor 144 country survey on Trust in Science and Health.

Note: The question asked in the survey is “vaccines are safe?”.

Map Credit: Alexandre De Figueiredo, The Vaccine Confidence Project

Figure 4. Changing levels of vaccine confidence in the Philippines between 2015 and 2019 (in percentages)

Legend: Dramatic fall in public confidence in vaccine safety in the Philippines due partly to the impact of social media and local politics.

The months and years of the surveys conducted are represented by the vertical bars in different colours.
Source: The Vaccine Confidence Project, Data collected by Gallup International (PSRC)