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Vital progress in immunization yet an unfinished agenda

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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 20th 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 occuring

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 articles[4,5], 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 2011-2020[6].

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 annually[7]. 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 deaths[8].

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[9]. Over 14 million deaths are estimated to be prevented through measles vaccination alone between 2011 and 2020[6].

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[10]. 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[11-13]. These differences of required critical vaccination coverage rates are due to R_0[14], the basic reproductive ratio of an infection, which can vary greatly among various infectious diseases. R_0 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[15]. 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[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[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[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[20]. This is compared with the cost per DTPcv3 (having received all three doses of DTP containing vaccine) vaccinated child of $27[21]. In the USA, net economic benefits of vaccination in one birth cohort amount to almost $69 million[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[23,24]. There is also evidence that vaccination improves childhood physical development, educational outcomes, and equity in distribution of health gains[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[26-28], and can be reduced by immunization[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[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[32]. Particular immunologic pathways have been identified[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[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[35]. This maternal immunisation strategy may be expanded with promising vaccines against Group B streptococcus and Respiratory Syncytial Virus[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[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[40]. Vaccination of the elderly with existing vaccines could prevent up to 90 000 deaths per year in the United States alone[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[42]. Despite national recommendations[43,44], vaccine coverage among adults in high income countries is uneven[45] (vaccine coverage for herpes zoster among adults aged ≥60 was 24% compared with 65% for influenza among those aged ≥65 in the US), and very low or not even available in most low and middle income countries[46]. Yet, several studies have shown good cost-effectiveness of adult vaccinations against influenza, pneumococcal infection, shingles, human papilloma virus and tetanus-diphtheria-pertussis[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[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[49-51], and international travel has played a role in the resurgence of measles in the USA and elsewhere[52].

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[53] created after the 2014-2015 Ebola epidemic in West Africa to accelerate development of vaccines against epidemic pathogens[2,4,54].

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 rVSV 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[55], 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 [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 clinincal trials and harmonization of regulatory practices[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 assitance[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[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[61]. 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[62].

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 the wide range of antigens with often a complex life cycle exhibiting different antigens relevant for vaccine protection. Thus the RTS,s vaccine, the first ever malaria vaccine deployed in a routine immunization system[63], took nearly 30 years since it's creation by GSK in 1987[64] 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[65]. 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[66], pertussis vaccine[67] and others[68]. A recent example is the finding from a retrospective analysis of long term efficacy trials showing that although there is a clear overall population benfit 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[69]). 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[70].

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[71]. 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 immunogenicitiy and safety in the presence of chronic conditions and changes

related to older age, but large scale applicability is questionable for the time being[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[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 variatons, but also stagnation in coverage over the last 10 years[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 [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[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[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%[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[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[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[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[86], leading to a WHO declaration of a grade 2 health emergency[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[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[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[89]. 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[90].

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[91]). 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 [53], US BARDA (Biomedical Advanced Research and Development Authority)[92] and the European IMI (Innovative Medicines Initiative) [93,94].

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[95]. Nearly 100 polio vaccinators and their security guards have been targeted and killed while attempting to reach children for vaccination[96].

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[97], 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[98]. 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[99], and the Wellcome Global Monitor on Trust in Science and Health as

part of their 144 country study[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[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”[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[102].

While uncertainty is the norm in science, the political and social worlds of the public have become less tolerant of ambiguity and risk[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[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[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[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%[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[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.

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[6]. 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[108] 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[78].

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)[58] 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 countries[2]. 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 incentive, 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[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, combining coverage and regional variations, 1980-2018.
3. Global confidence in vaccine safety by country
4. Changing levels of vaccine confidence in The Philippines between 2015 and 2019.

References

1 WHO. *Vaccines and diseases*, <https://www.who.int/immunization/diseases/en/> (2019).
2 Kaslow, D. C. *et al.* Vaccine candidates for poor nations are going to waste. *Nature* **564**, 337-339, doi:10.1038/d41586-018-07758-3 (2018).
3 CDC. Ten great public health achievements--United States, 1900-1999. *MMWR. Morbidity and mortality weekly report* **48**, 241-243 (1999).

4 Rappuoli, R., Black, S. & Bloom, D. E. Vaccines and global health: In search of a sustainable model for vaccine development and delivery. *Sci Transl Med* **11**, doi:10.1126/scitranslmed.aaw2888 (2019).

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.

5 Rappuoli, R., Mandl, C. W., Black, S. & De Gregorio, E. Vaccines for the twenty-first century society. *Nature Reviews Immunology* **11**, 865, doi:10.1038/nri3085 (2011).

6 WHO. Global Vaccine Action Plan 2011-2020. (World Health Organization, Geneva, 2013).

This is THE global reference for most national immunisation programmes.

7 WHO, UNICEF & World Bank. State of the World's Vaccines and Immunization, 3rd edition. (World Health Organization, Geneva, 2009).

8 Orenstein, W. A. & Ahmed, R. Simply put: Vaccination saves lives. *Proceedings of the National Academy of Sciences of the United States of America* **114**, 4031-4033, doi:10.1073/pnas.1704507114 (2017).

9 Bill & Melinda Gates Foundation. *The Goalkeepers Report*, <https://www.gatesfoundation.org/goalkeepers/report> (2018).

10 Hammitt, L. L. *et al.* Population effect of 10-valent pneumococcal conjugate vaccine on nasopharyngeal carriage of Streptococcus pneumoniae and non-typeable Haemophilus influenzae in Kilifi, Kenya: findings from cross-sectional carriage studies. *The Lancet. Global health* **2**, e397-405, doi:10.1016/s2214-109x(14)70224-4 (2014).

11 WHO. Rubella vaccines: WHO position paper. *Weekly Epidemiological Record* **86**, 301-316 (2011).

12 WHO. Summary of WHO position paper on measles. (World Health Organization, Geneva, 2017).

13 Chan, J. *et al.* Determining the pneumococcal conjugate vaccine coverage required for indirect protection against vaccine-type pneumococcal carriage in low and middle-income countries: a protocol for a prospective observational study. *BMJ open* **8**, e021512, doi:10.1136/bmjopen-2018-021512 (2018).

14 Vynnycky, E. & White, R. *An introduction to infectious disease modelling*. (OUP oxford, 2010).

15 Guerra, F. M. *et al.* The basic reproduction number (R0) of measles: a systematic review. *The Lancet. Infectious diseases* **17**, e420-e428, doi:10.1016/s1473-3099(17)30307-9 (2017).

16 Aaby, P., Kollmann, T. R. & Benn, C. S. Nonspecific effects of neonatal and infant vaccination: public-health, immunological and conceptual challenges. *Nature immunology* **15**, 895-899, doi:10.1038/ni.2961 (2014).

17 Meeting of the Strategic Advisory Group of Experts on immunization, April 2014 -- conclusions and recommendations. *Wkly Epidemiol Rec* **89**, 221-236 (2014).

18 Wilder-Smith, A. *et al.* The public health value of vaccines beyond efficacy: methods, measures and outcomes. *BMC medicine* **15**, 138, doi:10.1186/s12916-017-0911-8 (2017).

19 Bärnighausen, T., Bloom, D. E., Cafiero-Fonseca, E. T. & O'Brien, J. C. Valuing vaccination. *Proceedings of the National Academy of Sciences of the United States of America* **111**, 12313-12319, doi:10.1073/pnas.1400475111 (2014).

20 Ozawa, S. *et al.* Return On Investment From Childhood Immunization In Low- And Middle-Income Countries, 2011-20. *Health affairs (Project Hope)* **35**, 199-207, doi:10.1377/hlthaff.2015.1086 (2016).

The economic analysis in this paper of 10 vaccines administered in 73 low- and middle-income countries between 2011 and 2020 shows that a total of 20 million lives and over 350 billion dollars could be saved, making vaccines a best buy in public health.

21 Brenzel, L. What have we learned on costs and financing of routine immunization from the comprehensive multi-year plans in GAVI eligible countries? *Vaccine* **33 Suppl 1**, A93-98, doi:10.1016/j.vaccine.2014.12.076 (2015).
22 Zhou, F. *et al.* Economic evaluation of the routine childhood immunization program in the United States, 2009. *Pediatrics* **133**, 577-585, doi:10.1542/peds.2013-0698 (2014).
23 Riumallo-Herl, C. *et al.* Poverty reduction and equity benefits of introducing or scaling up measles, rotavirus and pneumococcal vaccines in low-income and middle-income countries: a modelling study. *BMJ global health* **3**, e000613, doi:10.1136/bmjgh-2017-000613 (2018).
24 Chang, A. Y. *et al.* The equity impact vaccines may have on averting deaths and medical impoverishment in developing countries. *Health affairs (Project Hope)* **37**, 316-324, doi:10.1377/hlthaff.2017.0861 (2018).
25 Jit, M. *et al.* The broader economic impact of vaccination: reviewing and appraising the strength of evidence. *BMC medicine* **13**, 209, doi:10.1186/s12916-015-0446-9 (2015).
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.
26 Smith, R. D., Keogh-Brown, M. R., Barnett, T. & Tait, J. The economy-wide impact of pandemic influenza on the UK: a computable general equilibrium modelling experiment. *Bmj* **339**, b4571, doi:10.1136/bmj.b4571 (2009).
27 Putri, W. C. W. S., Muscatello, D. J., Stockwell, M. S. & Newall, A. T. Economic burden of seasonal influenza in the United States. *Vaccine* **36**, 3960-3966, doi:https://doi.org/10.1016/j.vaccine.2018.05.057 (2018).
28 World Bank. From panic and neglect to investing in health security : financing pandemic preparedness at a national level. (World Bank Group, Washington, D.C., 2017).
29 VoICE. *The Value of Immunization Compendium of Evidence*, <https://immunizationevidence.org/about/> (2019).
30 Grassly, N. C., Kang, G. & Kampmann, B. Biological challenges to effective vaccines in the developing world. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences* **370**, doi:10.1098/rstb.2014.0138 (2015).
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.
31 Permar, S., Levy, O., Kollman, T. R., Singh, A. & De Paris, K. Early Life HIV-1 Immunization: Providing a Window for Protection Before Sexual Debut. *AIDS research and human retroviruses* **34**, 823-827, doi:10.1089/aid.2018.0018 (2018).
32 Lee, A. H. *et al.* Dynamic molecular changes during the first week of human life follow a robust developmental trajectory. *Nature communications* **10**, 1092, doi:10.1038/s41467-019-08794-x (2019).
33 Kobayashi, M. *et al.* Group B Streptococcus vaccine development: present status and future considerations, with emphasis on perspectives for low and middle income countries. *F1000Research* **5**, 2355-2355, doi:10.12688/f1000research.9363.1 (2016).
34 Madhi, S. A. & Dangor, Z. Prospects for preventing infant invasive GBS disease through maternal vaccination. *Vaccine* **35**, 4457-4460, doi:10.1016/j.vaccine.2017.02.025 (2017).
35 Yen, L. M. & Thwaites, C. L. Tetanus. *Lancet* **393**, 1657-1668, doi:10.1016/s0140-6736(18)33131-3 (2019).
36 Munoz, F. M. *et al.* The Fourth International Neonatal and Maternal Immunization Symposium (INMIS 2017): Toward Integrating Maternal and Infant Immunization Programs. *mSphere* **3**, doi:10.1128/mSphere.00221-18 (2018).
37 Westphal, D. W. *et al.* A protracted mumps outbreak in Western Australia despite high vaccine coverage: a population-based surveillance study. *The Lancet. Infectious diseases* **19**, 177-184, doi:10.1016/s1473-3099(18)30498-5 (2019).

38 Fields, V. S. *et al.* Mumps in a highly vaccinated Marshallese community in Arkansas, USA: an outbreak report. *The Lancet. Infectious diseases* **19**, 185-192, doi:10.1016/s1473-3099(18)30607-8 (2019).
39 Hotez, P. America and Europe's new normal: the return of vaccine-preventable diseases. *Pediatric Research* **85**, 912-914, doi:10.1038/s41390-019-0354-3 (2019).
40 Alliance for Aging Research. *The Silver Book®: Infectious Diseases and Prevention through Vaccination*, <http://www.silverbook.org/publication/infectious-diseases/> (2013).
41 de Gomensoro, E., Del Giudice, G. & Doherty, T. M. Challenges in adult vaccination. *Annals of medicine* **50**, 181-192, doi:10.1080/07853890.2017.1417632 (2018).
42 International Federation on Ageing. *World Coalition on Adult Vaccination*, <https://www.ifa-fiv.org/project/adult-immunization-advocacy-2/> (2019).
43 Kim, D. K., Riley, L. E., Harriman, K. H., Hunter, P. & Bridges, C. B. Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States, 2017. *Annals of internal medicine* **166**, 209-219, doi:10.7326/m16-2936 (2017).
44 National Health Service. *Vaccinations - Adults*, <https://www.nhs.uk/conditions/vaccinations/?tabname=adults> (2016).
45 Bridges, C. B. *et al.* Meeting the Challenges of Immunizing Adults. *Vaccine* **33 Suppl 4**, D114-120, doi:10.1016/j.vaccine.2015.09.054 (2015).
46 Phillips, D. E., Dieleman, J. L., Lim, S. S. & Shearer, J. Determinants of effective vaccine coverage in low and middle-income countries: a systematic review and interpretive synthesis. *BMC health services research* **17**, 681, doi:10.1186/s12913-017-2626-0 (2017).
47 Leidner, A. J. *et al.* Cost-effectiveness of adult vaccinations: A systematic review. *Vaccine*, doi:10.1016/j.vaccine.2018.11.056 (2018).
This paper provides insights into the biological challenges to advance the concept of a life course of vaccination.
48 Derhovanessian, E. & Pawelec, G. Vaccination in the elderly. *Microbial biotechnology* **5**, 226-232, doi:10.1111/j.1751-7915.2011.00283.x (2012).
49 Public Health England. *Complete routine immunisation schedule*, <https://www.gov.uk/government/publications/the-complete-routine-immunisation-schedule> (2019).
50 Centers for Diseass Control and Prevention. *Vaccines & Immunizations*, <https://www.cdc.gov/vaccines/index.html> (2016).
51 PHE. *Immunisation of healthcare and laboratory staff: the green book, chapter 12*. (Public Health England, 2013).
52 Sarkar, S., Zlojutro, A., Khan, K. & Gardner, L. Measles resurgence in the USA: how international travel compounds vaccine resistance. *The Lancet. Infectious diseases* **19**, 684-686, doi:10.1016/s1473-3099(19)30231-2 (2019).
53 *The Coalition for Epidemic Preparedness Innovations*, <https://cepi.net/> (2019).
54 Butler, D. Translational research: crossing the valley of death. *Nature* **453**, 840-842, doi:10.1038/453840a (2008).
55 Snoy, P. J. Establishing efficacy of human products using animals: the US food and drug administration's "animal rule". *Veterinary pathology* **47**, 774-778, doi:10.1177/0300985810372506 (2010).
56 Henao-Restrepo, A. M. *et al.* Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ca Suffit!). *Lancet* **389**, 505-518, doi:10.1016/s0140-6736(16)32621-6 (2017).
57 Winslow, R. L. *et al.* Immune Responses to Novel Adenovirus Type 26 and Modified Vaccinia Virus Ankara-Vectored Ebola Vaccines at 1 Year. *Jama* **317**, 1075-1077, doi:10.1001/jama.2016.20644 (2017).

58 Akanmori, B., Bellah, A., Ward, M. & Rago, L. The African vaccine regulatory forum (AVAREF): A platform for collaboration in a public health emergency. *WHO Drug Information* **29**, 127-132 (2015).
59 Kallenberg, J. *et al.* Gavi's Transition Policy: Moving From Development Assistance To Domestic Financing Of Immunization Programs. *Health affairs (Project Hope)* **35**, 250-258, doi:10.1377/hlthaff.2015.1079 (2016).
60 WHO. 2018 Assessment report of the Global Vaccine Action Plan. Strategic Advisory Group of Experts on Immunization., (World Health Organization, Geneva, 2018).
This is the annual update on the state of immunisation in the world with a wealth of data.

61 WHO. *Immunization, Vaccines and Biologicals: Data, statistics and graphics*, <https://www.who.int/immunization/monitoring_surveillance/data/en/> (2019).
62 Findlow, J. Vaccines for the prevention of meningococcal capsular group B disease: What have we recently learned? *Human vaccines & immunotherapeutics* **12**, 235-238, doi:10.1080/21645515.2015.1091131 (2016).
63 WHO. *Malaria vaccine pilot launched in Malawi*, <https://www.who.int/news-room/detail/23-04-2019-malaria-vaccine-pilot-launched-in-malawi> (2019).
64 Roland, D. Malaria vaccine: GSK's thirty-year quest to eradicate a global killer. (Telegraph Media Group Limited, UK, 2013).
65 Larson, H. J., Hartigan-Go, K. & de Figueiredo, A. Vaccine confidence plummets in the Philippines following dengue vaccine scare: why it matters to pandemic preparedness. *Human vaccines & immunotherapeutics* **15**, 625-627, doi:10.1080/21645515.2018.1522468 (2019).
66 Clark, A. *et al.* Efficacy of live oral rotavirus vaccines by duration of follow-up: a meta-regression of randomised controlled trials. *The Lancet. Infectious diseases* **19**, 717-727, doi:10.1016/s1473-3099(19)30126-4 (2019).
67 Burdin, N., Handy, L. K. & Plotkin, S. A. What Is Wrong with Pertussis Vaccine Immunity? The Problem of Waning Effectiveness of Pertussis Vaccines. *Cold Spring Harbor perspectives in biology* **9**, doi:10.1101/cshperspect.a029454 (2017).
68 Khan, M. I. *et al.* Barriers to typhoid fever vaccine access in endemic countries. *Research and reports in tropical medicine* **8**, 37-44, doi:10.2147/rrtm.S97309 (2017).
69 Wilder-Smith, A. *et al.* Deliberations of the Strategic Advisory Group of Experts on Immunization on the use of CYD-TDV dengue vaccine. *The Lancet. Infectious diseases* **19**, e31-e38, doi:10.1016/s1473-3099(18)30494-8 (2019).
70 Cabico, G. K. How the Dengvaxia scare helped erode decades of public trust in vaccines. (Philstar Global Corp., The Philippines, 2019).
71 Plotkin, S., Robinson, J. M., Cunningham, G., Iqbal, R. & Larsen, S. The complexity and cost of vaccine manufacturing - An overview. *Vaccine* **35**, 4064-4071, doi:10.1016/j.vaccine.2017.06.003 (2017).
A must read to understand the complexity and cost of vaccine manufacturing.

72 Poland, G. A., Ovsyannikova, I. G. & Jacobson, R. M. Personalized vaccines: the emerging field of vaccinomics. *Expert Opin Biol Ther* **8**, 1659-1667, doi:10.1517/14712598.8.11.1659 (2008).
73 Poland, G. A., Ovsyannikova, I. G., Jacobson, R. M. & Smith, D. I. Heterogeneity in vaccine immune response: the role of immunogenetics and the emerging field of vaccinomics. *Clinical pharmacology and therapeutics* **82**, 653-664, doi:10.1038/sj.clpt.6100415 (2007).
74 Mentzer, A. J., O'Connor, D., Pollard, A. J. & Hill, A. V. Searching for the human genetic factors standing in the way of universally effective vaccines. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences* **370**, doi:10.1098/rstb.2014.0341 (2015).

75 UNICEF & WHO. *Progress and Challenges with Achieving Universal Immunization Coverage*, <https://www.who.int/immunization/monitoring_surveillance/who-immuniz.pdf?ua=1> (2019).
76 UNICEF & WHO. *Summary presentation of routine immunization key indicators*, <https://www.who.int/immunization/monitoring_surveillance/SlidesGlobalImmunization.pptx?ua=1> (2019).
77 WHO. *Immunization coverage*, <https://www.who.int/en/news-room/fact-sheets/detail/immunization-coverage> (2019).
78 Berkley, S. Vaccination lags behind in middle-income countries. *Nature* **569**, 309, doi:10.1038/d41586-019-01494-y (2019).
79 Hill, H. A., Elam-Evans, L. D., Yankey, D., Singleton, J. A. & Kang, Y. Vaccination Coverage Among Children Aged 19-35 Months - United States, 2017. *MMWR. Morbidity and mortality weekly report* **67**, 1123-1128, doi:10.15585/mmwr.mm6740a4 (2018).
80 Zimlich, R. *How many kids are completely unvaccinated?*, <https://www.contemporarypediatrics.com/pediatrics/how-many-kids-are-completely-unvaccinated> (2018).
81 Gong, W. *et al.* Comparison of three rapid household survey sampling methods for vaccination coverage assessment in a peri-urban setting in Pakistan. *International journal of epidemiology*, doi:10.1093/ije/dyy263 (2018).
82 Cutts, F. T., Izurieta, H. S. & Rhoda, D. A. Measuring coverage in MNCH: design, implementation, and interpretation challenges associated with tracking vaccination coverage using household surveys. *PLoS medicine* **10**, e1001404-e1001404, doi:10.1371/journal.pmed.1001404 (2013).
83 Lam, E., McCarthy, A. & Brennan, M. Vaccine-preventable diseases in humanitarian emergencies among refugee and internally-displaced populations. *Human vaccines & immunotherapeutics* **11**, 2627-2636, doi:10.1080/21645515.2015.1096457 (2015).
84 WHO Regional Office for Europe. *Measles in Europe: record number of both sick and immunized* <http://www.euro.who.int/en/media-centre/sections/press-releases/2019/measles-in-europe-record-number-of-both-sick-and-immunized> (2019).
85 European Centre for Disease Prevention and Control. Monthly measles and rubella monitoring report. February 2019. (Stockholm, 2019).
86 The Lancet. Measles, war, and health-care reforms in Ukraine. *Lancet* **392**, 711, doi:10.1016/s0140-6736(18)31984-6 (2018).
87 WHO EURO. *Over 100 000 people sick with measles in 14 months: with measles cases at an alarming level in the European Region, WHO scales up response*, <http://www.euro.who.int/en/media-centre/sections/press-releases/2019/over-100-000-people-sick-with-measles-in-14-months-with-measles-cases-at-an-alarming-level-in-the-european-region,-who-scales-up-response> (2019).
88 Mosser, J. F. *et al.* Mapping diphtheria-pertussis-tetanus vaccine coverage in Africa, 2000-2016: a spatial and temporal modelling study. *Lancet*, doi:10.1016/s0140-6736(19)30226-0 (2019).
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.
89 Murray, J. Vaccines by air as drone medicine service takes off in Ghana. (Guardian News & Media Limited, London, 2019).
90 WHO. *Immunization, Vaccines and Biologicals: Global Routine Immunization Strategies and Practices (GRISP)*, <https://www.who.int/immunization/programmes_systems/policies_strategies/GRISP/en/> (2019).

91 GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* **392**, 1736-1788, doi:10.1016/s0140-6736(18)32203-7 (2018).
92 *Biomedical Advanced Research and Development Authority*, <https://www.phe.gov/about/barda/Pages/default.aspx> (2019).
93 *Innovative Medicines Initiative*, <https://www.imi.europa.eu/> (2019).
94 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).
95 McNeil Jr., D. G. Polio Cases Surge in Pakistan and Afghanistan. (The New York Times Company, New York, 2019).
96 DW News. *Pakistani government suspends polio vaccination drives*, <https://www.dw.com/cda/en/pakistani-government-suspends-polio-vaccination-drives/av-48677882> (2019).
97 WHO. Report of the SAGE Working Group on Vaccine Hesitancy. (World Health Organization, Geneva, 2014).
98 ECDC. *Rapid literature review on motivating hesitant population groups in Europe to vaccinate*. (European Centre for Disease Prevention and Control, 2015).
99 European Union. *State of Vaccine Confidence in the EU 2018* (Publications Office of the European Union, 2018).
100 Gallup. Wellcome Global Monitor 2018 - Chapter 5: Attitudes to vaccines. (Wellcome Trust, London, 2019).
The study is the largest evaluation of people's attitudes, interest, trust, and beliefs about science including immunization.

101 Lane, S., MacDonald, N. E., Marti, M. & Dumolard, L. Vaccine hesitancy around the globe: Analysis of three years of WHO/UNICEF Joint Reporting Form data-2015-2017. *Vaccine* **36**, 3861-3867, doi:10.1016/j.vaccine.2018.03.063 (2018).
102 Cohet, C. *et al.* Safety of AS03-adjuvanted influenza vaccines: A review of the evidence. *Vaccine* **37**, 3006-3021, doi:10.1016/j.vaccine.2019.04.048 (2019).
103 Karafillakis, E. & Larson, H. J. The benefit of the doubt or doubts over benefits? A systematic literature review of perceived risks of vaccines in European populations. *Vaccine* **35**, 4840-4850, doi:10.1016/j.vaccine.2017.07.061 (2017).
This systematic review of articles on vaccination risk perceptions and concerns published between 2004-2014 across Europe shows that the main concern was vaccine safety, followed by perceptions of low risk of contracting the vaccine-preventable diseases and, if contracted, felt that they were not severe.

104 WHO. *Vaccine Safety Net*, <https://www.who.int/vaccine_safety/initiative/communication/network/vaccine_safety_websites/en> (2019).
105 Larson, H. J. & Schulz, W. S. The State of Vaccine Confidence 2015. (London School of Hygiene & Tropical Medicine, London, U.K., 2015).
This was the first benchmark report by the Vaccine Confidence Project, providing an overview on the key issues affecting confidence globally.

106 Sridhar, S. *et al.* Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. *N Engl J Med* **379**, 327-340, doi:10.1056/NEJMoa1800820 (2018).
107 UNICEF & WHO. Situation Report 8 - Measles Outbreak. (World Health Organization, Geneva, 2019).

108 Gavi. *Gavi Board starts framing Alliance's approach to 2021-2025 period*, <https://www.gavi.org/library/news/press-releases/2018/gavi-board-starts-framing-alliance-s-approach-to-2021-2025-period/> (2018).

109 Bloom, D. E., Black, S., Salisbury, D. & Rappuoli, R. Antimicrobial resistance and the role of vaccines. *Proceedings of the National Academy of Sciences of the United States of America* **115**, 12868-12871, doi:10.1073/pnas.1717157115 (2018).

110 Klugman, K. P. & Black, S. Impact of existing vaccines in reducing antibiotic resistance: Primary and secondary effects. *Proceedings of the National Academy of Sciences of the United States of America* **115**, 12896-12901, doi:10.1073/pnas.1721095115 (2018).

111 Sevilla, J. P., Bloom, D. E., Cadarette, D., Jit, M. & Lipsitch, M. Toward economic evaluation of the value of vaccines and other health technologies in addressing AMR. *Proceedings of the National Academy of Sciences of the United States of America* **115**, 12911-12919, doi:10.1073/pnas.1717161115 (2018).

112 Plotkin, S. L. & Plotkin, S. A. in *Plotkin's Vaccines (Seventh Edition)* (eds Stanley A. Plotkin, Walter A. Orenstein, Paul A. Offit, & Kathryn M. Edwards) 1-15.e18 (Elsevier, 2018).

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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

Organization; JN is Director of the African Centres for Disease Control and Prevention of the African Union, and is a Board member of CEPI. SS is the Director General of the Centre for Vaccine Development, MinistrWHO/SAGE Meningitis Working Groupy of Health, Mali, and is an alternate Board Member of Gavi The Vaccine Alliance; BK is the Director of the LSHTM Vaccine Centre, and has grants from Pfizer and GSK.

Table 1. Historic timeline of introduction of vaccines (year of licensure indicated wherever possible)

Notes: Adapted from Plotkin & Plotkin (2018)[112]. a. Capsular polysaccharide conjugated to carrier proteins. b. An investigational vaccine, rVSV-ZEBOV, was used under "expanded access" during the Ebola outbreak in west Africa in 2015 and the 2018 outbreak in DR Congo. c. Positive opinion from EMA under article 58 issued in 2015. Approved for routine use in pilot implementation settings in Ghana, Malawi, Kenya in 2018. d. Reverse vaccinology. WC: whole cell. rBS: recombinant B subunit.

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

1040 Table 2: From discovery to sustainable impact of immunization: overcoming four major hurdles

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

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Figures

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 lifecourse is available at 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 rapid 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 showen at the top of each bar.

Source: WHO/UNICEF coverage estimates 2018 revision, July 2019.
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.
Reprinted from "Progress Towards Global Immunization Goals - 2018: Summary presentation of key indicators", updated July 2019, WHO/UNICEF, "Global and Regional Immunization coverage with three doses of diphtheria, tetanus, and pertussis (DTP3) containing vaccines, 1980-2018, global coverage at 86% in 2018", Copyright (2019).

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 Sceince 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 confidene in vaccine safety in the Phillipines due partly to the impat of social media and local politics

The months and years of the surveys conducted are represented by the verical bars in different colours.

1082 Source: The Vaccine Confidence Project, Data collected by Gallup International (PSRC)

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