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Vaccine impact: Benefits for human health

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ABSTRACT

Unlike most drugs, whose benefit is restricted to the individual who takes the drug, prophylactic vaccines have the potential for far-reaching effects that encompass health service utilisation, general health and wellbeing, cognitive development and, ultimately, economic productivity. The impact of immunisation is measured by evaluating effects directly on the vaccinated individual, indirectly on the unvaccinated community (herd protection), the epidemiology of the pathogen (such as changing circulating serotypes or prevention of epidemic cycles), and the additional benefits arising from improved health. Aside from protection of the individual, the broader success of immunisation is dependent on achieving a level of coverage sufficient to interrupt transmission of the pathogen. When evaluating the cost-effectiveness of vaccines, all of these potential benefits need to be accounted for. In many countries where immunisation programmes have been highly successful, the control of disease has meant that the benefits of immunisation have become less obvious. Once a well-known and much-feared disease appears to have disappeared, individuals, including healthcare professionals, no longer view ongoing prevention with the same sense of urgency. Reduced coverage is inevitably associated with resurgence in disease, with outbreaks potentially leading to significant morbidity and loss of life. Ensuring the continued success of immunisation programmes is the responsibility of all: individuals, healthcare professionals, government and industry.

1. Introduction and historical perspective

Prophylactic vaccination is one of the cheapest and most effective forms of medical intervention. From Jenner's work in 1796, to new vaccines based on our better understanding of molecular biology, immunisation has reduced the consequences of catastrophic infections. In the 18th century we had the vaccinia virus vaccine, in the 19th, Louis Pasteur and Émile Roux demonstrated that inactivated or attenuated organisms could provide protection and, in the 20th century, we experienced an accelerated development of new vaccines involving many new technologies.

"*Millions of human lives, as I shall show, have been preserved by the fruits of Jenner's genius; yet today, thousands upon thousands of men, some intelligent though designing, some intelligent though deluded, the great mass of them fanatical and ignorant, decry vaccination as not only being of no service to humanity, but positively a nuisance injurious to health and life, while millions of our fellow men are utterly ignorant of, or indifferent to the matter.*" These words written by Eugene Foster and published in 1896 [1] were relevant introductory remarks for his publication on the statistical evidence of the value of immunisation, and are still relevant today. It is astonishing how in some ways, things have not changed, despite the measurable impact of vaccines.

This paper reviews how to measure impact both from the clinical and from the health economics standpoint. A wider range of assessments of the value of immunisation, including the importance at a population level and adherence to immunisation programmes, are explored. There is a clear need for appropriate surveillance to evaluate immunisation strategies, and the means to ensure future success is discussed.

Abbreviations: GAVI, the Global Vaccine Alliance; GDP, gross domestic product; HBV, hepatitis B virus; Hib, *Haemophilus influenzae* type b; HPV, human papillomavirus; IQ, intelligence quotient; OPV, oral polio vaccine; QALY, quality adjusted life year; UMV, universal mass vaccination; US, United States; USD, US dollars; WHO, World Health Organization.

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2. How is the impact of vaccines measured?

Immunisation has been controversial since its introduction, with opponents claiming it was unnatural or contaminating [2]. Despite this, immunisation has become one of the most widespread and successful of all health interventions after the provision of safe drinking water. The reason for this is simple: the first immunisation campaigns were directed at diseases that had very high mortality and morbidity in their communities. The dramatic impact of immunisation on diseases which had previously been considered an unavoidable part of everyday life was so great, and so readily visible, that public support for immunisation was overwhelming.

Subsequent programmes to finally eradicate smallpox and today, to eradicate poliomyelitis, were built on the same kind of public consensus. The benefits of eradicating a well-known and much-feared disease are so obvious, that once it becomes technically feasible, the public and political support needed to carry out the programme is assured. This can still be seen today; the 2014 Ebola epidemic in West Africa inevitably generated political pressure to develop vaccines for the disease. But beyond the obvious health benefits, it is estimated that the eradication of smallpox; which cost roughly 100 million US dollars (USD) in total, generates annual savings of 1.35 billion USD [3]. The polio eradication campaign, once completed, is likewise expected to save about 1.5 billion USD per year, and millions of lives [4]. But the polio eradication campaign also highlights one of the factors which make measuring impact so important, and so difficult; which is, that as formerly-feared diseases disappear, the benefits of immunisation become less clear-cut, while the costs remain visible (see Box 1).

Box 1 The paradox of vaccination.

The oral polio vaccine (OPV) is a live attenuated vaccine. Although cheap to use and highly effective, it has the very rare side effect of actually causing paralytic poliomyelitis in roughly 1 in a million recipients [63]. While this risk is negligible when compared to the 1 in 200 risk from natural infection, it starts to become significant once the disease has been eradicated in a region. For that reason, once natural polio infections are controlled, it makes sense to switch to the inactivated vaccine despite a resulting higher cost for the vaccine programme. But determining exactly at what point this switchover should be made requires balancing the extra resources required against the risk of disease. For this kind of decision, one can no longer rely solely on public consensus, because the risks are so small that they become invisible to the general public; including many medical practitioners, who will never see a case of paralytic polio in their entire career. By contrast, the increased costs are readily visible. Paradoxically, this effect can also apply to diseases which remain common. For example, varicella infection is a highly infectious disease that affects virtually all individuals in unvaccinated communities [64]. Although death and disability from chickenpox are rare, the extremely high number of varicella infections means that cases of encephalitis and post-varicella stroke still constitute a significant burden of disease in children [65]. At the same time, the very large number of uncomplicated infections means that chickenpox is overwhelmingly viewed as a benign infection by the general public and those medical professionals who don't deal with the severe cases. In addition, varicella infection in childhood can lead to reactivated disease later in life (zoster) which has a high risk of severe disease; but the temporal gap between varicella infection in childhood and zoster in retirement means that the visceral, obvious link between vaccination and reduction of disease, based on personal experience, is lost.

To build the case that immunisation is an effective and worthwhile intervention against infection where the most serious consequences may be long delayed after infection (human papillomavirus [HPV], hepatitis B virus [HBV], varicella, etc.) or where serious illness is rare (meningococcal infection, varicella) impact data is required. Ironically, in the developed world, where once-common infections such as tetanus, diphtheria and measles have been essentially eliminated by immunisation, impact data is also required to retain public support for continued immunisation. This is discussed in detail in the following sections.

3. Efficacy, effectiveness and impact

Vaccine efficacy corresponds to the direct protection to vaccinated individuals provided by the vaccine under optimal conditions, and usually focuses on the prevention of clinically apparent outcomes (e.g., meningitis, hospitalisation, death). When an infectious agent is able to cause a range of different clinical manifestations, the primary analysis will focus on one specific clinical manifestation (e.g., invasive pneumococcal disease during a pneumococcal vaccine study) while secondary analyses may include other clinical manifestations as endpoints (e.g., pneumonia, bronchiolitis, otitis media). For some vaccine studies, primary endpoints may not always correspond to clinically apparent disease at the time because the goal is to prevent a disease that may only appear later in life (such as cancer after HPV infection). Surrogate endpoints (e.g., immunological monitoring or isolation of the infectious agent) can then be used in order to shorten and reduce the costs of phase 3 trials. In some instances the primary analysis may look only at the prevention of the infection in relation to the microorganism types contained in the vaccine. Because of the cross-protection conferred e.g., by pneumococcal conjugated vaccines, HPV vaccines, and rotavirus vaccines, secondary analyses may include non-vaccine-type related infections. Adequate choice of primary endpoint is extremely important as it directly impacts on the selection of the most appropriate study design. However, because vaccine efficacy does not consider the background incidence of the disease, it may not reflect the full public health impact of the vaccine [5].

Vaccine effectiveness refers to the protection conferred by immunisation in a defined population. It measures both direct (vaccine-induced) and indirect (population-related) protection. The effectiveness of a vaccine is proportional to its efficacy but is also affected by vaccine coverage, access to health centres, costs and other factors not directly related to the vaccine itself.

Defining the impact of a vaccine is more complicated. International agencies like the World Health Organization (WHO), the European Medicines Agency and the Centers for Disease Control and Prevention have no consensus on what defines impact. For example one can estimate vaccine impact by comparing the incidence of a disease in the same population before and after the introduction of the vaccine or, in theory, by comparing one vaccinated and one similar unvaccinated population at the same time (see Box 2).

Box 2 Measuring efficacy, effectiveness and impact.

Vaccine efficacy is usually measured during pre-licensure randomised, controlled clinical trials, where the difference in disease incidence between the vaccinated and non-vaccinated participants can be considered as the result of the direct effect of the vaccine [9,66–68]. Vaccine effectiveness is usually estimated from observational post-licensure studies and reflects the ability to protect against disease under real-life conditions when the vaccine is in routine use [9,66–68].

Both vaccine efficacy and vaccine effectiveness are measured by the formula:

$VE = \frac{R_{unvaccinated} - R_{vaccinated}}{R_{vaccinated}}$ where R = risk or rate

and differ primarily in the populations where the vaccine is used, and whether indirect effects are included.

Measuring the impact of a vaccine requires defining what the term means, as 'impact' may or may not include long-term downstream effects. For example, if impact is only assessed by measuring changes in disease outcomes, healthcare use, and the proportion of samples testing positive for a disease [9] a relatively simple analysis such as the one below can be used.

$\text{Impact} = \frac{IR_{pre-vaccine} - IR_{post-vaccine}}{IR_{pre-vaccine}} = 1 - \text{IRR}$ where IR = incidence rate, IRR = incidence rate ratio

If a more complete assessment of impact is required, a complex model including the economic effect of lost educational or work time, will be needed.

As for any intervention in infectious diseases, four types of effects can be observed following immunisation: direct, indirect, total, and overall [6]. The *direct effect* is the reduction in the probability of developing the disease, which is determined by comparing vaccinated and unvaccinated persons belonging to the same population and exposed to the same immunisation programme, in order to eliminate programme-specific effects. To estimate the indirect, total and overall effects, the comparison is made between the vaccinated population (which will include both vaccinated and unvaccinated) and a reference population that contains only unvaccinated people.

The *indirect effect* is the difference between the outcome in an unvaccinated individual in a population where the immunisation programme is in place, and what the outcome would have been in the same individual in a comparable population without the immunisation programme. In other words, it is how much an immunisation programme reduces the risk of disease for an individual who did not receive the vaccine. This population-level effect resulting from reduced transmission of the infection is called herd protection. The magnitude of the indirect effect essentially depends on the immunity of the population, and on other factors such as the nature of the immunity provided, the transmissibility and pattern of transmission of the infectious agent [7]. The basic reproduction number (R_0, i.e., the average number of other individuals that each infected individual will infect in a population that has no immunity) is one of the key determinants of herd protection (Table 1). When the prevalence of protected individuals in a population against a person-to-person transmissible disease is higher than the herd protection threshold, the number of secondary cases per infected case is lower than one and the spread of disease is, in theory, blocked [8].

The total effect of immunisation is the sum of the direct and indirect effects for the vaccinated individual that result from being vaccinated and being in a population with an immunisation programme. The overall effect is the effect of the immunisation programme in the entire population that includes vaccinated and unvaccinated individuals [9] (see Box 3).

Box 3 Case studies.

Direct effects – hepatitis B: For a baby born to a mother positive for both the hepatitis B virus (HBV) surface antigen and the HBV e antigen, the risk of developing a chronic HBV infection is 70–90% [69,70]. Approximately 25% of these children may develop severe liver disease later in life, including hepatocellular carcinoma [71]. A longitudinal study conducted in Thailand over a 20-year period demonstrated that none of the children born to mothers at high risk for HBV transmission developed chronic liver disease after being vaccinated at birth and at 1, 2 and 12 months with a recombinant hepatitis B vaccine, essentially reducing their risk by 100% [72].

Indirect effects – poliomyelitis and rotavirus: For poliomyelitis, the R_0 (between 5 and 7) is associated with a herd protection threshold of 80–86%. Given the known vaccine effectiveness of OPV, the critical vaccine coverage required to interrupt transmission in the population can be determined: in this case: 84–90%. In Japan, where vaccine coverage was 90–97% with a 2-dose OPV schedule, the number of poliomyelitis cases has fallen from 1000 to 5000 per year to zero for more than two decades [73].

In Austria, rotavirus vaccine coverage reached 87% in the vaccine-eligible age group (children between 3 and 20 weeks of age) one year after the vaccine was implemented via universal mass vaccination (UMV) and a reduction of 74% in rotavirus gastroenteritis hospitalisations was observed in this age group. Interestingly, a 22% decrease in hospitalisations was also observed in older children (32–60 months of age) and a 47% decrease in younger children (below 3 months of age); two age groups that were not vaccinated [74]. Similar observations were made in other countries [75–78]. Unlike the case of poliovirus, this effect was detectable even though rotavirus continues to circulate in these populations. The impact of rotavirus vaccination is also seen in changes in the epidemiology (e.g., age-specific incidence) and the seasonality (e.g., delay in the peak epidemiologic activity) of the disease [74,79–82].

Total effects: Introduction of measles UMV had a huge impact on childhood mortality (up to 90% in most resource-limited countries) that cannot be explained by the prevention of measles infections alone [61,83–85]. It is believed that measles virus infection decreases the immunity of the population against other infections (e.g., bacterial pneumonia, dysentery) by creating a polymicrobial ''immune memory loss" that can be efficiently prevented by measles vaccination [86,87].

4. Health economics

The systematic health economic evaluation of new vaccines is a relatively recent development [10], in contrast with other new therapies where it has been used for half a century [11]. This reflects the difficulty of assessing impact, and the fact that vaccine development was often pursued as a public good by a limited

Table 1
Herd immunity thresholds for selected vaccine-preventable diseases (adapted from Fine [62]).

Disease	R_0[a]	Herd immunity threshold[b] (%)
Diphtheria	6–7	85
Measles	12–18	83–94
Mumps	4–7	75–86
Pertussis	12–17	92–94
Polio	5–7	80–86
Rubella	6–7	83–85
Smallpox	5–7	80–85

[a] R_0 – Basic reproduction number, or the average number of other individuals that each infected individual will infect in a population that has no immunity.
[b] The minimum proportion of the population that needs to be immunised to eliminate infection ($=1 - 1/R_0$). This is dependent on both the R_0 and the effectiveness of the vaccine.

number of producers, rendering price comparisons meaningless. However, over the last two decades as pressure on public health budgets has mounted and new, more sophisticated (and expensive) vaccines have become available, health economic assessment has become an essential aspect of immunisation programme planning [12–14].

Because formal health economic analysis for vaccines is a newer discipline than that for drugs, the same methodologies used for drugs were initially applied to evaluate the economic implications of immunisation [15]. This is starting to change as new tools are being developed that include the fixed budget within which health authorities operate, allowing optimisation modelling using objective function criteria and model constraints [16,17] and including assessments such as return on investment considered from a government perspective; for example, the better economic results when a population remains healthy [18,19]. In other words if a new vaccine reduces the risk of disease per at-risk individual as compared with the existing situation, how much do we want to pay for that extra benefit? Is there a maximum price to pay, or do we let the free market decide?

To help make these assessments, decision makers define upfront a standard unit of health benefit; usually defined as QALYs (Quality Adjusted Life Years), the average value of a single disease-free year for one individual. This value varies from region-to-region [20], and WHO recommends that any new medical intervention can be considered as being very cost-effective if its incremental cost-effectiveness result when compared with the existing situation is below the threshold of one times the Gross Domestic Product (GDP) per capita [21]. That is, the value of one "unit" of health gain (the QALY) in a country is usually considered to be equal to the GDP per capita of a country. This definition remains controversial, particularly for developing countries where the cost of new interventions may outstrip the available health budget [22–24]. It has been argued that for situations where resources and money are scarce, avoiding extra cost may be as critical as gaining additional health [25]. Equitable access to healthcare is also an important factor in many countries. These are all outcome measures that are relevant for vaccines. However, there are other factors to consider.

5. Vaccines, population and society

The type of cost-effectiveness analysis discussed above is very sensitive to the health evaluation of the individual, as this is what most treatment interventions specifically do: they alleviate the suffering of an individual patient who is already ill [26]. Preventive activities are different because they are initiated before disease onset: healthy people are at risk of infection and would therefore benefit from prevention. Which individuals will actually get a disease is unpredictable, and so the benefits of vaccines are most accurately measured at the population instead of the individual level. Even those who remain unvaccinated benefit from the reduction in transmission after the vaccine has been introduced (herd protection) [27]. This is very different from treatments for non-infectious disease, and conventional cost-effectiveness analyses do not easily capture the additional benefits of immunisation [28].

Additionally, infectious diseases can vary from mild to very severe. As the focus is often on a single, most severe manifestation, much of the disease prevented will not necessarily show up in an economic assessment if a narrow evaluation perspective is considered. A typical example is rotavirus immunisation which prevents many cases of infant diarrhoea for which no medical advice is sought, but where a parent must be absent from work in order to stay home and care for the child. For rotavirus, this benefit can be huge, because the total frequency of the disease can be as high as 40% of children <5 years old during epidemic winter periods in temperate countries [29].

Another example is pneumococcal immunisation, where the focus has been on preventing invasive disease such as meningitis or sepsis, which has a high mortality, but where the reduction in acute otitis media and of antibiotic use after immunisation provides a very substantial additional health and economic benefit [30]. Much of the benefit when introducing new vaccines is thus to be found at societal level affecting not just patients, but parents, employers, and the economy as a whole.

Vaccines may have a critical impact in the prevention of epidemics at times where healthcare utilisation is already very high. In temperate regions, rotavirus infections normally peak during winter periods when the incidence of other infections (such as influenza) is also peaking, potentially adding to workload at what is already a period of high demand for healthcare in hospitals [31]. Introduction of the rotavirus vaccine can therefore result in improvement in the overall quality of healthcare delivery, through better hospital bed-day management and personnel working conditions [31].

Finally, many of the benefits of immunisation are realised over decades, and may not be immediately obvious; for example, preventing disease in childhood is linked to better educational performance and higher earnings later in life [32,33]. Some of the potential benefits identified through modelling may appear years or even decades later, as for HPV and HBV vaccines, and only when the vaccine has achieved high coverage within the target population [34,35]. So, substantial investment may be needed to introduce and maintain an immunisation programme before the full return on investment can be defined. All of these aspects of vaccine impact are difficult to capture in an economic assessment using conventional methodological approaches.

The links between individual prevention through immunisation and societal benefits that may improve the overall economy have been highlighted for infectious diseases that affect all levels of society, such as tuberculosis, malaria, and pandemic influenza [36,37]. Recognising this, WHO has recently issued an overall scheme of evaluation of vaccines by which the benefit is highlighted from different angles, not only focussing on health gains. WHO concludes that vaccines have the ability to achieve broad societal or community gains more easily than any other medical intervention [38].

6. Remaining challenges

A few specific challenges remain that are unique for vaccines. One is the discounting factor that heavily affects the benefit of vaccines, since that benefit doesn't occur instantaneously after administration, but is spread over time [39]. Discounting is based on the concept that a benefit today is worth more than a benefit

tomorrow, but what discount rate, and whether it should be constant or flexible remains controversial [40].

A recent review on the value of vaccines categorised the intangible benefits of immunisation into three groups; outcome-related, behaviour-related productivity gains and community externalities [41]. The process of categorisation helps to define what to measure, when, and how. Estimating the intangible and long-term benefits of immunisation requires a credible model with transparency in structure, data input and data output, validated against observed data [42,43].

Finally, economic assessments of vaccines in the developed world are different from that in the developing world [44], where immunisation is more likely to be challenged on its priority rather than its value, given that resources are scarce. Budget optimisation or disease portfolio management are tools to specify the economic value of the new intervention.

In conclusion, immunisation is a perfect example of Adam Smith's theory on the invisible hand in the market: a "selfish desire" to remain healthy by getting vaccinated will increase overall community welfare by reducing the spread of disease [45].

7. Other ways of assessing the value of vaccines

It has long been known that measures of average IQ at the national level correlate well with GDP and educational achievement [46]. Additionally, in both developing and developed economies it has been noted that average IQ has risen significantly over the last century (the so-called "Flynn effect") with particularly sharp rises in average national IQ in the periods of rapid increase in national GDP associated with industrialisation; even when improved access to education is controlled for [47]. The reasons have been much debated, but immunisation in early childhood is associated with significantly better test results at school, which are linked with subsequent improved employment prospects [4]. That this is not purely a socioeconomic effect reflecting access to healthcare or education in resource-limited settings, is shown by a study where Danish children surviving bacterial meningitis subsequently had lower rates of educational achievement and poorer employment prospects than their peers, an effect that persisted years or even decades after their illness [32]. More recent work [33] suggests that the burden of disease in the population (drawn from WHO statistics) can explain much, if not all, of the observed IQ differences. The hypothesis is that the energy used in fighting off infections, and the nutrition lost through common infectious diseases, such as diarrhoea during childhood, can harm the developing brain, with potential long-term consequences. If correct, this suggests that improving child health through better sanitation and immunisation may ultimately provide benefits far in excess of the obvious health gains by also improving educational and employment outcomes; ultimately contributing to national economic growth. Analysis of the gains seen from the GAVI immunisation programme suggest that the increase in earnings by vaccinated children when they reach adulthood will exceed the entire cost of the immunisation programme; even before the obvious benefits such as decreased death and suffering, and reduced medical costs, are figured into the equation [4].

8. Adherence to immunisation programmes and impact

The introduction of immunisation dramatically reduced the incidence of infectious diseases. Despite this success, vaccine-preventable diseases are still endemic in different parts of the world. Several factors may be involved in the re-emergence and persistence of vaccine-preventable diseases: the rise of more virulent clones, international travel, compromised immunisation coverage in developing countries or in war areas, parents choosing not to vaccinate due to concerns about safety, lack of good immunisation programmes for elderly people, and suboptimal responses to vaccines in certain populations. These are some reasons why the herd immunity threshold needed to control the diseases is not always achieved [48].

Herd protection is related to coverage. When a high level of vaccine uptake takes place in a community, the chances of acquiring a disease may get close to zero. From the point of view of certain individuals, the ideal (selfish) strategy is that everyone else should be directly protected by immunisation, while they benefit from the indirect protection without costs (side effects, time, money, inconvenience). As the number of these "freeloaders" increase, herd immunity decreases, with the outcome that disease incidence rises [7].

Although coverage is important, other factors that may impact herd protection include "imperfect immunity": if immunisation does not confer solid immunity to all, the threshold level of immunisation required to protect a population increases. Waning vaccine-induced immunity will also require higher levels of coverage [7].

While the re-emergence of vaccine-preventable diseases is related to several factors, it is not by chance that two of the most problematic infections involved in recent outbreaks, measles and pertussis, are diseases with a high reproduction number [49–51 and Table 1]. These outbreaks represent a threat to return to a situation where measles and other preventable diseases were endemic in many countries of the world. Therefore, the implications of herd protection cannot be underestimated, because for certain diseases, it only takes a small number of unimmunised individuals in a community to facilitate the spread of illness.

9. Immunisation strategies and surveillance

The choice of the immunisation strategy depends on the epidemiology of the disease, on the biological characteristics of the natural infection, and on the vaccine. Some diseases (e.g., rotavirus, respiratory syncytial virus) have highest incidence or mortality in very young children, but the immaturity of the immune system and the negative effects of antibodies of maternal origin constitute challenges for effective immunisation early in life (see Box 4).

Box 4 The complex interplay between epidemiology, natural disease, vaccine properties and vaccine policies.

Rubella infection during pregnancy can cause congenital malformation of the foetus. Rubella vaccination is highly effective against disease and transmission but is less effective against re-infection. UMV targeting young children of both sexes may provide some indirect protection by preventing pregnant women being exposed to the virus, but this does not eliminate the risk of congenital rubella syndrome. The vaccination programme could also target only girls and adult women who will be immune to rubella at the time they enter pregnancy. In that case, low vaccine coverage or waning immunity could lead to infections during pregnancy [60]. A decision in Poland to selectively vaccinate only girls until 2004 saw a widespread rubella outbreak in 2013 (>38,000 cases) with >80% of cases in young men, and two recorded cases of congenital rubella syndrome [88].

To accurately measure the impact of a vaccine, it is essential to understand the incidence, prevalence, duration, and natural course of the infectious disease prevented. Efficient epidemiological

surveillance systems provide essential data on disease burden and help define the target population, i.e., the population that will gain most from the vaccine. After vaccine implementation, surveillance is required to measure both the vaccine uptake and the epidemiological impact [52] (see Box 5).

Box 5

After recommending hepatitis A vaccination for only some ethnic and high-risk groups of the population, in 1999 the Advisory Committee on Immunization Practices in United States (US) recommended 2 doses of hepatitis A vaccine for all children ⩾2 years living in 17 states where the incidence of hepatitis A was the highest. Since 2005, a 2-dose vaccination schedule is recommended to children 1–2 years of age in all states. Between 1996 and 1997 and 2004, a 41.5% overall decline of hepatitis A-related ambulatory visits was observed, while hospitalisations declined by 69% [89]. Interestingly, using a large medical insurance database, Zhou et al. demonstrated that all age groups and all states (although to a lesser extent in the states where the vaccine was not recommended) benefited from the hepatitis A incidence reduction, suggesting a strong herd effect [89]. Based on the excellent epidemiological data describing the natural variation in hepatitis A incidence a mathematical model allowing for herd protection confirmed that the observed decline in hepatitis A incidence can indeed be attributed to immunisation [90]. Israel adopted a different strategy and in 1999 elected to implement UMV hepatitis A vaccine for children aged 18–24 months. The passive national surveillance of hepatitis A reinforced by an active surveillance programme over a 4 year period (1999–2003) in one district demonstrated a >95% reduction in hepatitis A during the post-vaccination era. As in the US, a strong herd effect was observed and a reduction in hepatitis A incidence was documented in all age groups [91].

North Queensland, Australia, experienced 18 outbreaks of hepatitis A between 1998 and 1999. Following the report in 1999 of a severe hepatitis A outbreak in an Indigenous children population in North Queensland, hepatitis A vaccine was recommended for those children and led to a rapid 12-fold decline in the number of infections in both Indigenous and non-Indigenous children, as well as in non-vaccinated age groups, probably by simply interrupting the chain of transmission [92].

Nevertheless, only continued surveillance of the disease can confirm the real impact of these programmes, since in the absence of strong long-term protection, the hepatitis A vaccination programme could potentially shift the disease from a young age group where the infection is often asymptomatic, to an older adult age group where the disease is more often symptomatic [93].

The lessons learned from the surveillance of the epidemiological impact of a disease may in return justify changes in the immunisation programme. For instance, in the 1980s it was believed that a single dose of measles vaccine at the time of school entry would eliminate measles in US. After a prolonged period of low incidence (honeymoon period), a resurgence of measles occurred, in particular in children <5 years who were not yet attending school. Following this experience, a two-dose immunisation policy commencing at the youngest age possible was adopted by many countries [53].

Surveillance strategies focus not only on the epidemiological aspects of the diseases but also sometimes include laboratory surveillance. The introduction of the monovalent rotavirus vaccine for young children in Brazil in 2006 was rapidly followed by a decline in severe rotavirus gastroenteritis and in all-cause hospitalisation for diarrhoea [54,55]. Early concerns that protection might be lower against fully heterotypic strains have not been borne out by clinical trials and post-licensure surveillance studies [56]. A increased relative incidence of G2[P4] in Brazil seen post-immunisation turned out to be transient, and was also observed in neighbouring countries without rotavirus immunisation suggesting natural year-to-year variation [54]. Epidemiological surveillance is therefore important to describe the burden of disease, identify the target group and then measure all the aspects of the impact of the immunisation programme. Post-licensure epidemiological surveillance should ideally continue indefinitely, since it may continue to provide important insights and eventually lead to significant adjustments in the immunisation strategy.

Despite all of the developments in vaccine technology, no vaccine can provide life-long absolute protection of all individuals vaccinated. Herd protection may prevent people who are not fully protected, or not vaccinated at all, from developing disease, but the magnitude of the herd effect depends on numerous factors, and in particular on vaccine coverage. Immunisation coverage may be influenced by public health cuts following financial crises, social inequalities, intensification of travel and global trade, migration, population aging, scepticism towards public health programmes in general and distrust of prevention efforts (e.g., childhood immunisation programmes) by a portion of the population, and reticence of individuals to get vaccinated or to vaccinate their children (called "vaccine hesitancy") [57]. Vaccine hesitancy may lead to a significant increase in risk for unvaccinated individuals (e.g., parental refusal is associated with a 23-fold increase risk of pertussis compared to vaccinated individuals [58]) and it is believed that even small groups of unvaccinated people can reduce the chances of success of immunisation programmes [58,59].

10. Conclusions

Recent outbreaks of pertussis and measles in countries in which these diseases were previously controlled show that the success of immunisation programmes cannot be taken for granted. Changes that occur over decades, such as decreased compliance with immunisation or changing epidemiology of disease can overturn initial assumptions about vaccine impact [48,50,60]. At the same time, benefits flowing from immunisation, such as non-disease-specific health benefits, improved educational achievement and more efficient healthcare utilisation are difficult to predict and may also take many years to accurately assess [21,26,33,61]. From this, it is clear that while the direct benefits of immunisation can be accurately predicted, these form only a baseline; assessing the total impact of immunisation should be seen as an ongoing process, requiring modelling ahead of implementation and long-term surveillance afterwards. In addition, since so many of the benefits of immunisation rely on achieving a high level of coverage to interrupt disease transmission, frontline healthcare workers play an especially crucial role by ensuring that all age groups receive the recommended immunisations, and by contributing to educating the public on the importance of high coverage immunisation (see [94]).

Contributorship

All authors were involved in the development of this manuscript and gave final approval before submission.

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MD, PB, BS and DP-C are employees of the GSK group of companies. MD, PB and BS additionally report ownership of stock/restricted shares/shares in the GSK group of companies. CG has nothing to disclose.

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