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Vaccines to prevent pneumonia in children – a developing country perspective

Jacquie N. Oliwa[1,*], **Ben J. Marais**[2]

[1]KEMRI Wellcome Trust Research Programme, Department of Public Health Research, Health Services Unit, Nairobi, Kenya

[2]Marie Bashir Institute for Infectious Diseases and Biosecurity and The Children's Hospital at Westmead, Sydney Medical School, University of Sydney, Sydney, NSW, Australia

Summary

Pneumonia accounted for 15% of the 6.3 million deaths among children younger than five years in 2013, a total of approximately 935,000 deaths worldwide. Routine vaccination against common childhood illnesses has been identified as one of the most cost-effective strategies to prevent death from pneumonia. Vaccine-preventable or potentially preventable diseases commonly linked with respiratory tract infections include Streptococcus pneumoniae, *Haemophilus influenza* type-b (Hib), pertussis, influenza, measles, and tuberculosis. Although here have been great strides in the development and administration of effective vaccines, the countries that carry the largest disease burdens still struggle to vaccinate their children and newer conjugated vaccines remain out of reach for many. The Global Vaccine Action Plan (GVAP) has identified priority areas for innovation in research in all aspects of immunisation development and delivery to ensure equitable access to vaccines for all.

Keywords

Vaccines; Pneumonia; Children; Developing countries

Background

Globally, acute respiratory tract infections are the most common cause of both illness and mortality in children. In developing countries, there are approximately 0.22 episodes of pneumonia per child-year with 11.5% progressing to severe disease [1]. Pneumonia accounted for 15% of the 6.3 million deaths among children younger than five years in 2013, a total of approximately 935,000 deaths worldwide (Figure 1) [2,3]. This translates to a young child dying from an acute respiratory infection every 30 seconds, yet most of these deaths are preventable [3].

[*]Corresponding author. KEMRI Wellcome Trust Research Programme, Department of Public, Health Research, 197 Lenana Place, Lenana Road, Nairobi, Kenya. Tel.: +254722854812; fax: +254 (0)20 2711673. joliwa@kemri-wellcome.org (J.N. Oliwa).

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Outside the neonatal period, pneumonia and diarrhoea account for approximately 40% of all deaths in young children (Figure 1), [2] which motivated the World Health Organisation (WHO) and the United Nations Children's Fund (UNICEF) to develop the Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD) in 2013 [4]. GAPPD aims to ensure access to proven and appropriate preventive and treatment measures for pneumonia and diarrhoea, especially in resource-limited settings where most of these deaths occur [3,4].

Five simple interventions have been recommended to reduce severe pneumonia in childhood: i) exclusive breastfeeding for six months and continued breastfeeding complemented by nutritious solid foods up to age two years; ii) routine vaccination against pertussis, measles, *Haemophilus influenzae* type B (HiB) and pneumococcus; iii) safe drinking water, sanitation and hand washing facilities; iv) improved cooking stoves to reduce indoor air pollution; and v) effective treatment including amoxicillin dispersible tablets and oxygen [4]. We provide an overview of vaccine preventable respiratory infections, current implementation status and novel developments, with a specific focus on the developing world.

Currently Available Vaccines

The first vaccine was developed against smallpox in 1796, but it was not widely used until the 20th century (Figure 2) [5]. Since then vaccination has proven to be one of the most cost-effective health interventions available, leading to the global eradication of small pox in 1980. It is also a key intervention to reduce the unacceptably high mortality associated with childhood pneumonia [6,7]. Uptake of vaccination against important childhood infections, especially in the developing world, increased greatly after the creation of the Expanded Programme of Immunisation (EPI) and the Global Alliance for Vaccination and Immunisation (GAVI) [8]. It is estimated that by 2013, GAVI-led immunisation efforts had averted six million deaths from vaccine preventable diseases [6]. However, progress beyond the core EPI set of vaccines has been relatively slow and the "Expanded Programme of Immunisation (EPI)" term has become a bit of a misnomer with the exclusion of key conjugate vaccines. The WHO estimates that 1.5 million children continue to die every year from vaccine-preventable diseases, accounting for 17% of all under-5 deaths [9]. Delayed introduction of conjugated vaccines against *Haemophilus influenza* type-b (Hib) and pneumococcus in developing countries is mostly attributed to high cost and lack of political will; resulting in widening vaccine schedule gaps in developed and developing countries (Figure 3) [10].

The WHO lists 27 vaccine-preventable or potentially preventable diseases; [11] those commonly linked with respiratory tract infections include *Streptococcus pneumoniae*, Hib, pertussis, influenza, measles, and tuberculosis. *Streptococcus pneumonia* and Hib are considered to be the leading causes of child pneumonia deaths worldwide and universal use of conjugated Hib and pneumococcal vaccines should prevent approximately 1 million child deaths per year [12]. It has been argued that with the expected decline of bacterial causes of pneumonia due to increasing vaccine coverage, viral causes may be emerging as commoner causes of pneumonia in children. A study done in Pakistan found that of children admitted

with WHO-defined severe pneumonia, up to 36% had at least a viral cause identified; human metapneumovirus was detected in 24 (14.2%), influenza A virus in 9 (5.3%) and respiratory syncytial virus (RSV) in 30 (17.8%) [13].

Pneumococcal disease

Pneumococcal disease is caused by the gram-positive encapsulated bacterium *Streptococcus pneumonia*; over 90 different strain types have been recognized [14]. *Streptococcus pneumonia* is a common coloniser of the nasopharynx, but clinical disease mainly presents as pneumonia, sinusitis, otitis media and invasive pneumococcal disease (IPD). IPD occurs when the infection spreads into the bloodstream or to a normally sterile site such as the brain, resulting in bacteraemia and/or bacterial meningitis that are associated with significant morbidity and mortality. Global estimates indicate that pneumococcal disease is responsible for approximately 500, 000 deaths in children annually [15].

The first pneumococcal vaccine was licensed in 1977. This polysaccharide vaccine protected against 14 different strains and expanded to protect against 23 strains in 1984 [16]. The vaccine was found to be effective in adults, but did not generate adequate protective immunity in children younger than two years of age [16]. An enhanced conjugate vaccine for young children (PCV-7) was licensed in 2000. The 7 strains included in this vaccine represented those causing the highest disease burden in the United States of America (USA) and other developed countries, with little consideration of common strains in resource-limited settings. Initial studies demonstrated that PCV-7 was highly effective, reducing IPD caused by vaccine serotypes by more than 90% in young children; with a median all serotype IPD reduction of 45%. [17] However, IPD caused by non-vaccine serotypes increased over time. Many countries have since replaced PCV-7 with higher valency vaccines (PCV-10 or PCV-13) to cover the most common emergent serotypes. A recent study reported vaccine effectiveness against IPD of 90% for the PCV-7 serotypes and 75% for the six additional serotypes included in PCV-13 [18]. Pneumococcal vaccine impact is measured by a decrease in the incidence of IPD and reduction in hospitalisation rather than a direct impact on under-5 mortality [7].

In 2007, WHO recommended the inclusion of pneumococcal vaccines in childhood immunisation programmes worldwide with the hope that international scale-up will reduce annual deaths in children under 5 years of age by 1.5 million in 2020 [6]. Several studies are already reporting declining incidence of childhood pneumonia with rising vaccine coverage even in resource-limited settings [16,19–22], but progress is frustratingly slow and the commitment of national governments to fund fully inclusive vaccination programs limited. Pneumococcal vaccine was introduced in 103 countries (including Pakistan, the Philippines and Uganda where the vaccine was partially introduced) by the end of 2013, up from 87 countries in 2012. However, global coverage was estimated at only 25% in 2013 [9].

It is important to not only ensure adequate vaccine uptake, but also the quality of these programmes. A recent publication from South Africa showed a high incidence of pneumonia in the first year of life despite good PCV coverage, emphasising the potential detrimental influence of human immune-deficiency virus (HIV) infection, malnutrition and the need for completion of the full primary series for optimal protection [23]. However, despite relatively

high disease rates, the pneumonia case fatality rate in this cohort was quite low (1.4%), presumably due to reduced pneumonia severity from partial vaccine coverage and well-functioning primary care services [23].

Haemophilus influenzae type b (Hib)

*Haemophilus influenza*e type b is a gram negative bacterium transmitted by droplets. It is a common cause of meningitis, pneumonia, epiglottitis, septic arthritis, osteomyelitis and sepsis in unvaccinated children [24]. Hib is thought to be responsible for approximately 20% of acute lower respiratory infection deaths in the absence of immunisation and is the second most common cause of pneumonia in children [3]. In the absence of universal vaccination, Hib continues to cause more than 350 000 deaths and more than 8 million cases of severe disease annually [25].

Hib conjugate vaccine is available as a monovalent preparation or in combination as one of the routine childhood pentavalent vaccines. The vaccine is safe and efficacious if used appropriately; efficacy of two doses of Hib vaccine is reported as 94%, but only 38% for a single dose [26]. The revised EPI guidelines recommend three primary doses of HiB conjugate vaccine administered with the diphtheria, tetanus and pertussis vaccine, starting at 6 weeks of age, with 4–8 weeks between doses. The WHO reported coverage of 52% with three doses of Hib in 189 countries where it had been introduced by 2013 [9].

Studies from resource-limited settings demonstrate declining incidence of Hib disease, with greater effect seen with increased coverage and increase in number of years since introduction of the vaccine into national programmes [26–30]. Declining disease rates, in both vaccinated and unvaccinated children, may be explained by the indirect effect of Hib vaccination to reduce Hib nasal carriage within the general community [26]. Studies also report reduced all-cause radiologically confirmed pneumonia; in Vietnam the adjusted annual incidence of “all cause pneumonia” declined by 39% after introduction of Hib vaccine [31]. Cases of vaccine failure have been reported, which suggests that some non-type b *Haemophilus influenza*e strains are becoming more virulent, while there may also be a need for a booster Hib vaccine beyond infancy [32–35].

Pertussis

Pertussis (whooping cough) is a highly contagious bacterial disease caused by *Bordetella pertussis* and is typically associated with a paroxysmal cough followed by a characteristic whoop. Bronchopneumonia is the most common complication associated with high mortality [36]. WHO estimates that 16 million cases occur worldwide, mostly in developing countries, and that close to 200, 000 children die from the disease annually [12,36]. Two types of pertussis vaccines are available: whole-cell vaccines based on killed *B. pertussis* organisms, and acellular vaccines based on highly purified, selected components of the bacteria. The vaccines are usually offered in combination with diphtheria toxoid and tetanus toxoid (or additionally with poliomyelitis, hepatitis B and *Haemophilus influenza* type b). The whole-cell vaccines are effective and inexpensive but have been associated with adverse events related to local swelling, pain and high fever, which led to the development of more expensive acellular vaccines that are widely used in developed countries [10].

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Pertussis vaccines have been associated with a greater than 90% reduction in pertussis incidence and mortality [12]. WHO estimates that global vaccination averts nearly 700, 000 deaths from pertussis annually [36,37]. There have been systematic reviews of pertussis vaccine effectiveness including a recent Cochrane review [38]; but most studies are old and were conducted in high income countries with limited data from resource-limited settings. A clinical trial from Senegal reported 96% vaccine efficacy for whole cell compared to 85% for the acellular pertussis vaccines respectively [39]. WHO recommends that the first dose of pertussis vaccine should be administered at six weeks of age and subsequent doses 4-8 weeks apart, with the last dose of the primary series delivered by 6 months and a booster during the second year of life. This should confer protection for at least six years, but waning immunity beyond adolescence is a major concern [37]. It has been estimated that more than 90% coverage with at least three doses of the vaccine is required to eliminate the risk of severe pertussis in infancy [37], although this is highly dependent on the duration of protection provided. In 2013, an estimated 84% (112 million) of infants worldwide were vaccinated with three doses of diphtheriatetanus-pertussis (DTP3) containing vaccine [9]. Despite good coverage rates, a resurgence of pertussis has been observed in several developed countries, also affecting infants too young to be vaccinated; this is possibly due to disease among the aged (grandfathers and mothers), inadequate coverage among certain pockets of the population and early waning of immunity with the use of acellular vaccines [7,40]. To mitigate this, some developed countries have developed a cocooning strategy with the vaccination of mothers and other contacts of newborns and infants in order to prevent the transmission of pertussis to infants who may not have completed their primary vaccination series [41].

Measles

Measles virus belongs to the Paramyxoviridae family. Measles is a highly contagious viral disease and remains a leading killer among vaccine-preventable diseases. It is responsible for approximately 44% of the 1.7 million vaccine-preventable deaths among children annually [42]. In 2013, there were 145, 700 measles deaths globally; mostly among children under 5 years of age [43]. Bacterial pneumonia is a common complication of measles, occurring in 2-27% of children in community-based studies and in 16-77% of hospitalised children [12,44]. Pneumonia is estimated to contribute to 56-86% of all deaths attributed to measles, and the most commonly identified causative organism is Streptococcus pneumoniae [12,42,44].

Measles vaccine, in use since the 1960s, is safe, inexpensive and effective in preventing disease in young children (1-5 years of age) [45,46]. Measles vaccination coverage has been used as a marker of access to child health services and is thought to be one of the most effective public health strategies in mitigating child deaths [43,46]. It has been estimated that from 2000 to 2010, the annual measles incidence aggregated across all countries fell 66%, from 4·6 to 1·6 cases per 1000 population [47]. During the same period, global measles vaccine coverage increased from 72% to 85%, the reported number of measles cases declined 62% from 853 480 (140 per million total population) to 327 305 and measles mortality decreased 74%, from approximately 535 300 deaths to 139 300 [47]. The WHO estimates that between 2000-2013 measles vaccination prevented approximately 15·6

million deaths globally [43]. Increased measles vaccine coverage has made a key contribution to reduced under-5 mortality and achieving millennium development goal number 4 [6]. However, frequent disease outbreaks among unvaccinated pockets of the population remain a serious concern, due to measles exceptional infectiousness and high morbidity.

Influenza

Influenza viruses belong to the Orthomyxoviridae family. There are three types of seasonal influenza viruses that cause epidemics: A, B and C, with C occurring less frequently [48]. Some animal influenza strains e.g. avian (H5N1 & H7N9) and swine (H1&H3) strains have caused serious infections in human beings, but so far limited person-to-person transmission restricted pandemic potential [49]. In the very young, as well as in the elderly or immune-compromised, influenza infection can lead to severe pneumonia and death [48]. The WHO estimates that flu epidemics cause 3-5 million cases of severe illness and 250 000-500 000 deaths annually [48].

The most effective way to prevent common influenza is seasonal vaccination. Changes in circulating virus subtypes (due to antigenic shift and antigenic drift) require frequent reformulation of influenza vaccines. The WHO Global Influenza Surveillance and Response System monitors and provides recommendations for choice of vaccines for each season [48]. The currently circulating subtypes are: influenza A (H1N1); A (H3N2); the influenza B Victoria and Yamagata lineages. Influenza C cause milder sporadic infections and are not included in seasonal influenza vaccines [50]. There are trivalent and newer quadrivalent vaccines available as well, as a live attenuated influenza vaccine (LAIV) administered as a nasal spray. Studies suggest that LAIV is easy and safe to administer and offers good protection; it is recommended in some developed countries for use in children aged 2-8yr [51,52].

The WHO recommends annual seasonal vaccination of all risk groups. A review of influenza vaccines used in middle and high-income countries found pooled efficacy of 72-81% [53]. In the US influenza vaccination was associated with a 75% reduction in life-threatening illness with admission to a paediatric intensive care unit [54]. Use of the flu vaccine in children with mild persistent asthma has been associated with reduced episodes of acute respiratory tract illnesses and asthma exacerbations in Asia [55]. However, there is paucity of data from developing countries on the effect of influenza vaccine due to poor vaccine uptake and inadequate surveillance systems [53,56].

Respiratory Syncytial Virus (RSV)

Respiratory syncytial virus (RSV) belongs to the Paramyxoviridae family, and is transmitted by contact with nasal or oral secretions from infected persons [57]. It occurs seasonally in temperate countries while in tropical countries the virus is detectible year round [57]. RSV is thought to be the leading cause of pneumonia in children especially infants younger than 1yr of age [57,58]. Primary RSV infection increases the risk of secondary bacterial pneumonia, and co-infection is thought to occur in up to a third of pneumonia cases in children in developing countries [59]. A review of the burden of RSV found that there were more than

30 million episodes of RSV-associated respiratory tract infections in children in 2005 [58,60]. This is likely an underestimate especially for developing countries due to lack of proper surveillance and reporting. Mortality was estimated at close to 200, 000 deaths with 99% of these RSV-associated deaths occurring in developing countries [58,60].

There is currently no licensed vaccine for RSV, but there are over 50 vaccine candidates in development, majority in pre-clinical stages and four in clinical stage [61] The first 6 months of life are associated with the highest burden of severe RSV disease [60]. This group however is difficult to target for vaccines because of their immunological immaturity and varying levels of transferred maternal antibodies interfering with the immunogenicity of live vaccines [58]. There are additional challenges RSV vaccine development for children in developing countries due to high rate of HIV infection, malnutrition and other competing public health priorities. A maternal immunisation strategy is considered a viable strategy to protect young infants. One modelling study found that administration of an RSV vaccine to pregnant women able to boost natural maternal antibodies to 8 months of protection would reduce RSV infant incidence by over 30% [62]. The other priority strategy for developing countries is active paediatric immunisation to target to older infants and young children after maternal protection has waned off [61].

Tuberculosis

Mycobacterium tuberculosis (*M. tuberculosis*), the aetiological agent of tuberculosis (TB), is a leading cause of human disease and death, particularly in developing countries. According to WHO estimates, 80 000 children die from TB each year worldwide with over half a million new cases annually [63]. Bacille Calmette-Guérin (BCG) developed in 1921 from a strain of attenuated live *Mycobacterium bovis* is the only available vaccine against tuberculosis [64]. Given to newborns, it provides protection against severe forms of paediatric TB with 60-80% protective efficacy [65]. BCG also offers some protection against *M. tuberculosis* infection, with a risk reduction of 19-27% [65], however, it offers no protection against adult-type disease which is essential to improve epidemic control. A more effective TB vaccine is essential to achieve the ambitious target of global TB elimination by 2050. Results from initial trials have been disappointing, but current efforts are exploring multiple potential applications.

There are around 20 new TB vaccine candidates in various stages of research and development [66]. The various strategies being explored include: i) prevention of infection (pre-exposure vaccines); ii) prevention of disease after exposure (post-exposure vaccines); iii) prevention of recurrence after treatment [64,66]. The candidate vaccines are being designed to be primers that are efficacious for a longer period of time, preventing TB infection as well as disease in infants who have not been infected with *M. tuberculosis.* Additional candidates are in research for booster vaccines delivered during adolescence to prevent infection and/or progression to active disease for those who are latently infected, as BCG immunity wanes [64]. Host-directed therapies are being developed that could be beneficial for drug resistant tuberculosis by shortening the duration of treatment, restricting inflammatory damage and reducing risk of reinfection [66].

Indirect Vaccine Effects and Economic Impact

Herd immunity occurs when vaccination of a critical number of a population provides protection for non-immune, unvaccinated individuals, with less circulation of the disease and reduced risk of transmission between infected and susceptible subjects [7]. A good example of this is seen from the Gambia where Hib vaccine coverage of less than 70% resulted in dramatic reduction of incidence of meningitis in infants from 200 per 100, 000 to zero in the fifth year after introduction of the vaccine [26]. Other examples of herd immunity are seen in the cocooning strategy for pertussis where young unvaccinated infants are protected once their mothers and other close contacts have been vaccinated and conversely in the case of pneumococcal vaccine where older contacts of vaccinated children are protected from invasive disease [14,41].

Vaccination also has wider pathogen selection consequences and non-specific effects such as: i) serotype replacement; ii) prevention of antibiotic resistance; iii) protection against unrelated pathogens. Serotype replacement with an increase in the incidence of disease caused by non-vaccine serotypes has been observed with pneumococcal vaccines [67]. A meta-analysis of four randomised control trials of PCV vaccination in Sub-Saharan Africa found that nasopharyngeal carriage of vaccine type serotypes was reduced by PCV vaccination while carriage of non-vaccine type serotypes was higher among vaccinated children [68]. Immunisation programmes for pneumococcal disease have also been associated with reduction in antibiotic utilisation, presumably due to less severe disease. Vaccination may therefore reduce the selection of antibiotic resistant bacteria by decreasing antimicrobial exposure within the community which is a wider benefit beyond the target pathogen [7,69]. A South African study illustrated greater than 80% reduction in prevalence of invasive disease caused by antibiotic-resistant pneumococcal serotypes among children younger than 2 years of age after PCV introduction [21].

Live vaccines may increase protection against non-target pathogens through immune priming, for instance, tuberculosis and measles vaccines have been associated with a substantial reduction in overall child mortality, which cannot be explained solely by prevention of the target disease [70–73]. Conversely, inactivated vaccines such as diphtheria-pertussis-tetanus, inactivated polio vaccine and hepatitis B vaccine have been associated with increased morbidity and mortality from other infections [71,72]. Influenza vaccines have been associated with a reduction in acute otitis media in children as well as reductions in the use of antibiotics to treat secondary bacterial infections [74].

Economic impact of vaccines

A review on economic benefits of vaccines found that ecological externalities and productivity gains due to reduced disease risk were an indirect effect of vaccines [75]. Developing countries often have to grapple with competing priorities for limited resources and may fail to appreciate the full economic benefit of a well-functioning vaccination program. Factors contributing to limited uptake of new vaccines include: poor recognition of disease burden and costs; low political commitment; cost of the vaccines relative to national income; civil unrest; and weak health service delivery systems [10].

Commonly reported economic benefits of immunisation include: i) health effects due to morbidity and mortality averted; ii) health treatment costs saved; and short term productivity losses averted due to being unwell or caring for someone who is unwell [75]. There are also broader economic benefits benefitting the wider community. These include: i) long term productivity gains due to reduced cognitive or educational deficits caused by to childhood illness; ii) ecological externalities like herd immunity and reduced antibiotic resistance; iii) equity due to more equal distribution of health outcomes; iv) improved financial stability of health care programmes due to synergies created by vaccination programmes; v) macroeconomic impact due to improved gross domestic product [75].

Conclusion

The Global Vaccine Action Plan (GVAP) was approved by the World Health Assembly in May 2012 to prevent millions of deaths through more equitable access to vaccines [76]. GVAP identified the need for innovation and research across all aspects of immunisation development and delivery, as well as key research priorities (summarised in Table 1).

Routine vaccination against common childhood illnesses is one of the most cost-effective strategies to prevent death from pneumonia, the leading cause of death in young children. Although there have been great strides in the development and administration of effective vaccines globally, the countries that carry the greatest burden of pneumonia and other infectious diseases still struggle with vaccinating their children. Gaps in immunisation coverage results from many health system problems and low levels of vaccine research in the developing world, which can be addressed by securing the necessary political will and focussing on key priorities identified by the Global Vaccine Action Plan [76].

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Educational Aims

1. To describe the burden of disease caused by pneumonia and review efforts to reduce this
2. To identify discrepancies in vaccine availability in the developed and developing worlds
3. To review key pulmonary pathogens and assess the evidence base for vaccine prevention
4. To explore indirect effects and economic impact of vaccines
5. To identify priorities for pneumonia research in the developing world

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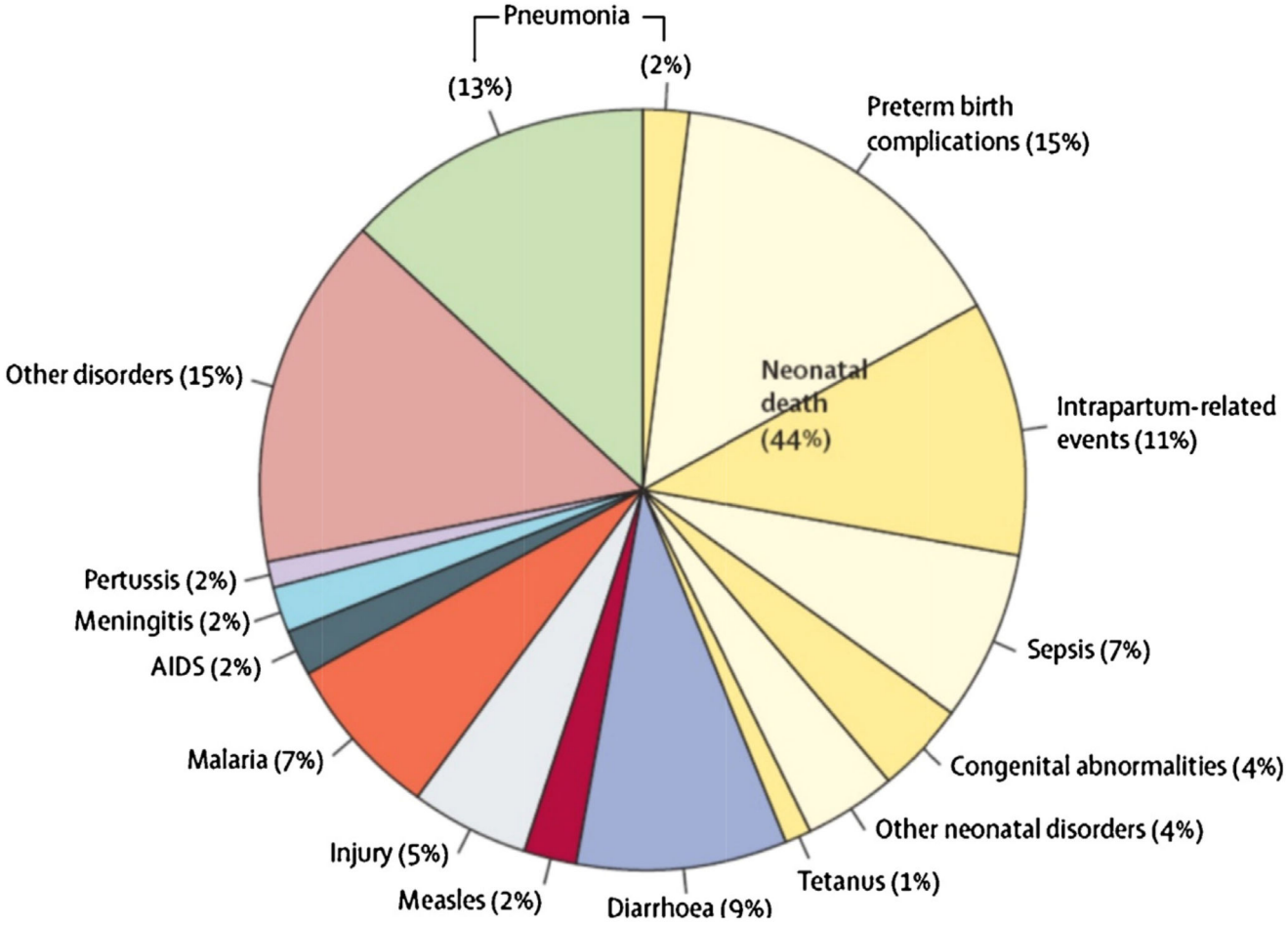

Figure 1. Causes of death in children under 5 years of age (2013)

'Reproduced by kind permission of Elsevier from Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis' [2]

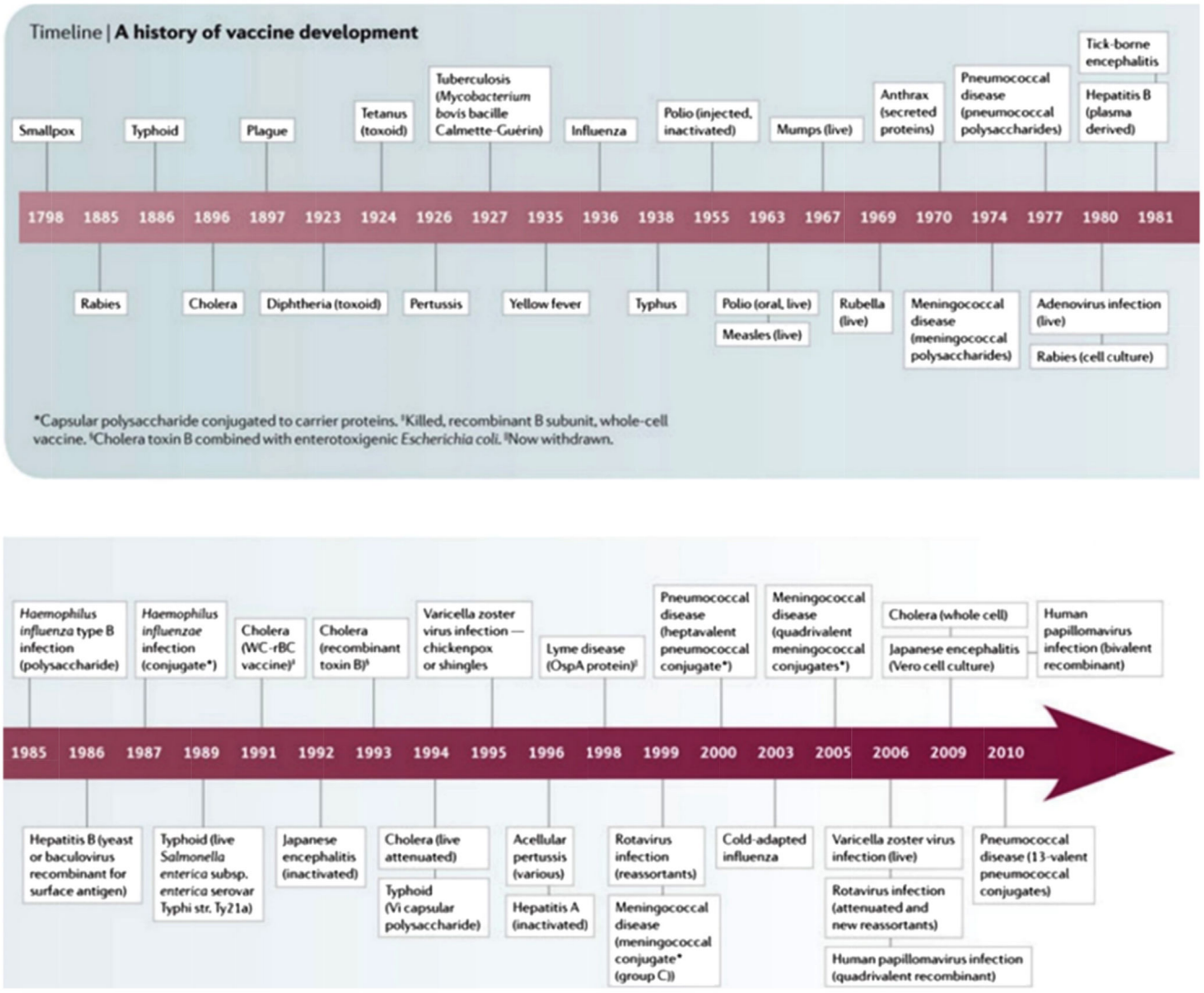

Figure 2. Timeline of vaccine development against major vaccine preventable diseases

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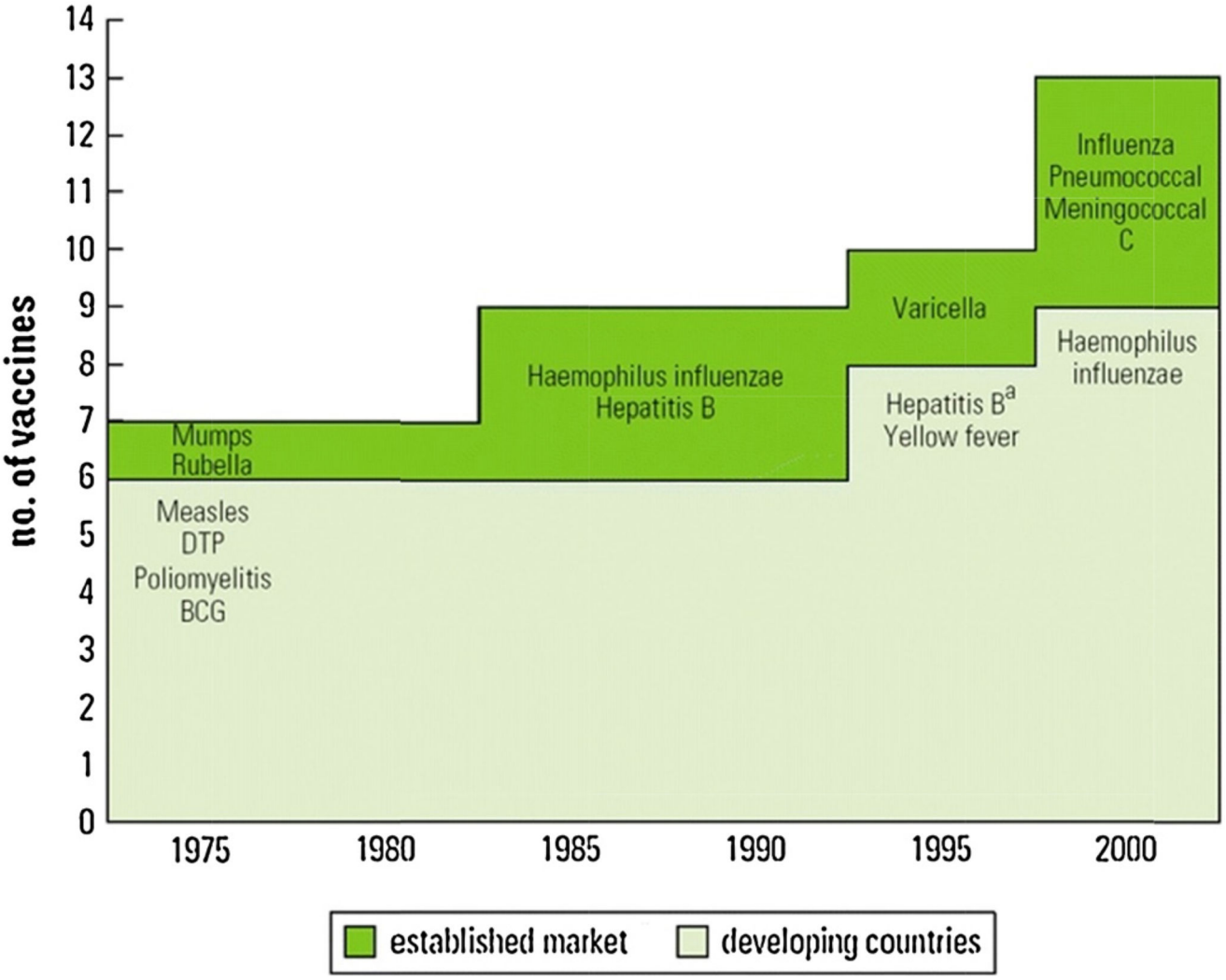

Figure 3. Childhood vaccines included in routine vaccination schedules in Developing and Established-Market Countries

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Table 1

Research needs and future directions

1	Establish platforms for exchange of information on immunisation research and consensus building among decision makers, as well as relevant end user information, using modern communication technologies
2	Continue research on the fundamentals of innate and adaptive immune responses in various populations, as well as immunological and molecular characteristics of microbes to better understand variation in pathogen and human populations' responses to vaccines
3	Expand operational research in improved delivery approaches and optimum delivery schedules considering potential interference effects and vaccination in humanitarian emergencies
4	Conduct representative epidemiological, immunological, social and operational studies and investigations of vaccine impact to guide health economics analyses
5	Develop improved diagnostic tools for conducting surveillance in low-income countries, as well as optimising aetiological identification and detection of changes in pathogen prevalence using advanced molecular techniques.