



The need for new vaccines

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ABSTRACT

Advances in biotechnology and immunology are yielding exciting progress in the development of new biologics and vaccines. Yet in both the developed and developing world, we see a backlog of new vaccines that are licensed but not yet used, an “innovation pile-up”, which may prevent individuals and societies from benefiting from protection against preventable infectious diseases. What is the “need for new vaccines”? Reviewing the vaccines environment and the place of vaccination in public health, we present our business model that we use to sustainably deliver the benefits of vaccination and review potential solutions to accelerating the introduction and adoption of under-utilised and future vaccines.

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1. Introduction

Many are moved to superlatives when describing the achievements of vaccines. Bill Gates described the halving of the number of deaths among young children to 10 million a year over five decades as “one of the most amazing statistics ever” [1]. Such enthusiasm can be justified by the facts: smallpox has been eradicated; polio’s worldwide incidence has dropped by 99%, and polio has been completely eliminated from the Western Hemisphere; and measles is controlled in US and parts of Europe, while Africa has seen a 90% decrease in deaths [2].

With further scientific innovation delivering new vaccines to protect against previously unpreventable infectious diseases, the potential public health impact of vaccination is increasing continually. New diseases are becoming, or will soon become, vaccine-preventable, including prominent killers such as cervical cancer, malaria, rotavirus, and pneumococcal diseases. Additionally, the technology contained in vaccines is evolving rapidly. Advances include new combination vaccines and presentations that increase the ease and speed of delivery, and novel adjuvants that particularly help address some of the most difficult immunological challenges by enhancing the strength and duration of the protection given by vaccines. The synergy of an adjuvant with a given antigen within a vaccine can optimise the interaction of the vaccine with the immune system to obtain more targeted, broader and/or longer-lasting immune responses.

Some commentators expect the worldwide vaccine market to significantly expand, growing from €11.5bn in 2008 to €19.5bn in 2014. Growth will come from emerging markets, especially from the populous countries with dynamic economies, known as the “BRICs” (Brazil, Russia, India and China) and other middle-income countries. A fundamental challenge to this growth potential, however, lies in the beliefs and actions of policy makers, those who vaccinate and the vaccine industry. The abundance of new and often more costly vaccines requires a rethinking of traditional approaches to immunisation budgets and programming built on an appreciation of the value of prevention, which in nearly all cases confers positive health economic benefits to society. Failure to do so will result in an “innovation pile-up” (see Fig. 1), meaning that people across the world will not enjoy the full benefits of immunisation [3]. The risk has increased with the impacts of the global financial crisis on the holders of public and private purse strings. Furthermore, these new financial constraints threaten to undermine global efforts to close the historical gap of 15–20 years between introduction of new vaccines in the developed world and in the developing world, where the medical need in most instances is far greater.

This article reviews the current public health contribution of vaccines and outlines some principles on how to meet the needs for immunisation worldwide. It then discusses the challenges to achieving the highest public health benefits through immunisation and reviews potential solutions.

2. Vaccination and its place in public health

Health is exceptionally valuable. It is better to prevent disease than to allow avoidable human suffering, incur the costs of care and treatment, and suffer the economic consequences of lost work and lower productivity. Beyond its intrinsic humanitarian value, the prevention of disease contributes to a positive cycle of health

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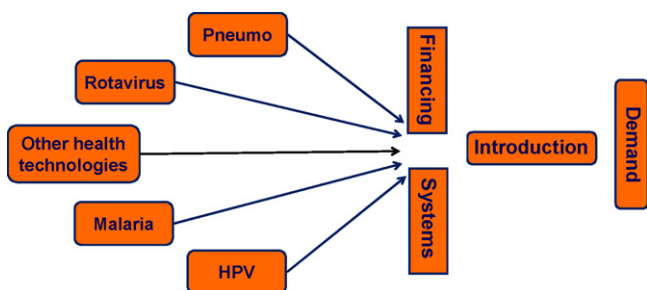


Fig. 1. “Innovation pile-up.” Scientific breakthroughs have yielded many new vaccines and promising new vaccine candidates.

and wealth gains as either is improved [4,5]. Hence, health is also an economic engine. There is a strong relationship between good health and national economic development [4]. Good health not only reduces poverty, but also accelerates a nation’s economy in both developing and industrialised economic settings [6]. A healthy population creates substantial, long-lasting economic benefits for everyone through increased productivity, an expanded number of productive working years, the enabling of reallocation of budgets to other investments, and enhanced educational and employment opportunities [7]. As a result, effective health policies and their expenditures should be viewed as an investment, not a cost. “Good health boosts economies; illness drains them.” [8].

Achieving and sustaining health gains are critical in order to move national and global health forward and to continue to realise human and economic benefits. This can be done by strengthening health systems so they intervene effectively, efficiently and equitably and provide a wide range of preventive interventions. Preventive measures include screening and vaccination, which sustain health gains through the continuation of low-cost and highly effective programmes. This facilitates vigilance against the resurgence of communicable diseases despite the public health and economic threat chronic conditions represent [9–11]. This gains in importance in the setting of global mobility and hence shared interdependence of susceptibility; to counter this shared risk, control of infectious diseases must be organised in a very systematic and organised way.

Vaccines contribute to health. It has been said that, “Vaccines represent the single greatest promise of biomedicine: disease prevention.” [12] “Each year, vaccines prevent up to 3 million deaths, and 750,000 children are saved from disabilities.” [13]. Elimination of polio now seems well within reach: in 1988 there were 350,000 reported cases and endemicity in 125 countries, yet in 2006 there were just 1997 reported cases and endemicity affected just four countries by 2008 [14,15]. Even when global eradication is not possible, global control is and disease can be reduced to very low levels if vaccination coverage is sustained. Vaccines have widespread endorsement from supranational organisations, including the World Health Organization (WHO) and the United Nations. The World Bank proposes that immunisation be among the first public health initiatives in which governments should invest, as does “the US Panel on Cost-Effectiveness in Health and Medicine.” [16]. Support is based on numerous benefits, including:

- Individuals benefit. Vaccines reduce the pain, suffering, and death from disease. They also avoid the longer term disabilities associated with diseases, such as mental impairment, blindness, hearing loss and many others. Vaccines reduce the need to pay for medical care and the loss of work due to illness or from caring for an ill family member.
- Families benefit when the main wage earners stay healthy and family members do not need to make up lost income [17], if par-

ents do not miss work caring for sick children [18]. Additionally, vaccination can serve as a ‘point of contact’ for the entire family for other interventions, health education and routine childhood examinations [19].

- Employers benefit from a healthy, more productive workforce [7], and lesser risks of transmission between workers who are exposed to vaccine-preventable diseases through their children.
- Governments benefit as vaccination compares favourably with other preventive investments [20]. Even newer, more costly vaccines compare favourably with screening for breast and colorectal cancer [21,22].
- Societies benefit from ‘herd immunity’ when a high percent of vaccination is achieved, one generation benefits the next generation when eradication or elimination is achieved [23]. ‘Herd immunity’ protects vulnerable individuals who cannot be vaccinated [16,24].

3. GlaxoSmithKline’s approach to meeting the need for vaccination worldwide

GlaxoSmithKline (GSK) aims to work with partners to deliver the benefits of vaccination to individuals and societies. To this end and over more than twenty years, GSK has constructed a business model designed to meet medical needs and achieve the public health benefits of vaccination within global economic realities. Based upon a framework of tiered pricing, the business model developed by GSK is guided by three key principles:

1. Availability—seek to make all vaccines available wherever possible to all countries that need them as early as possible and to produce quality vaccines in volumes sufficient to meet global demand.
2. Affordability—seek to set vaccine prices at levels that allow countries across all income levels to purchase, regardless of whether the payor is a government, a supranational organization or any other customer.
3. Sustainability—seek to do this in a way that allows the business to continue to supply innovative, high quality vaccines to all who need them for as long as they are needed. This requires sustained investment in the research and development required to continue to develop new vaccines that address unmet medical need as well as to maintain and continually upgrade manufacturing facilities.

The research and production of vaccines are governed by a number of economic realities. The production of vaccines is a complex process based on biological systems. This often leads to high costs of manufacture due to high direct costs associated with production inputs and processes. Indirect costs may also be substantial as biological production facilities need to be constantly maintained and updated. In addition, the depreciation costs on high capital investments must be borne for the lifetime of the facility; such capital investments being in the order of €300 and €500 million for a new production facility. Skilled staff assuring the highest level of quality in the manufacturing is also required. Due to the high costs of most new vaccines, production best achieves economies of scale and guarantees of quality when plants producing vaccines’ active ingredients are very large—often with capacities in the order of hundreds of millions of doses. This means that two or three plants worldwide can be sufficient to supply global needs. In contrast, secondary production, including filling and packaging, can be operated on smaller scales.

Another challenge faced by vaccine innovators is that it takes years to build and validate a new manufacturing facility, and each facility is typically dedicated to one specific vaccine. This means

that capital expenditure is incurred at the manufacturer's risk with the investment being made many years before it is known whether the vaccine will be approved by regulatory agencies around the world or valued and purchased by payors. The vaccines that are being developed today, such as combination vaccines and vaccines using adjuvants, are far more complicated and use much more sophisticated technologies than the vaccines of the past.

Furthermore, the standards required by regulatory authorities for the clinical trials needed to register a vaccine and the inspections to certify manufacturing facilities for continued operation are constantly being raised. For example, whereas products like *Infanrix hexa*TM (for the prevention of diphtheria, tetanus, pertussis, polio, hepatitis B and *Haemophilus influenzae* type b) made available as of the early 1990s were licensed on a clinical database required by the authorities at the time of around 5000 subjects, recent products like *Rotarix*TM (for the prevention of rotavirus) and *Cervarix*TM (for the prevention of cervical cancer) have pre-licensure clinical trial activities involving several tens of thousands of subjects and with additional post-licensure follow-up commitments involving more than 100,000 people each. Each of these elements contributes to the costs of vaccines.

When pricing its vaccines, GSK must reflect the medical, public health and health economic value of each vaccine, together with the risks shareholders take by investing in the company. At the same time, GSK seeks to address ability to pay of the rich and poor countries or individuals wherever they may be. Prices are varied across markets according to countries' income and ability to pay as measured by their Gross National Income (GNI) as defined by the World Bank, as well as by the volumes of vaccine purchased and the duration of the purchase commitment. GSK pioneered this tiered pricing approach for vaccines in the mid-1980s and has applied it ever since, with the endorsement of organisations such as the Global Alliance for Vaccines and Immunisation (GAVI) [25]. In other words, the 5 billion people who live in low- and middle-income countries are offered lower prices than the 800 million people in the wealthiest countries. The overall result is that large public vaccination programmes pay significantly less per dose for the vaccine than private payors, and poorer countries pay significantly less than wealthier ones. For example, historically vaccine prices paid in the poorest countries are 10–25% of the prices in high-income countries. This partnership between global stakeholders is a key means of addressing the healthcare needs of the world's poorest countries [26,27].

Because GSK's vaccines play such an important role in developing countries (in 2008, nearly 80% of the 1.1 billion doses GSK produced were distributed in these countries [28]), it is critical that this approach is sustainable. That is why the price in these countries typically allows for a small return to support continued investment in R&D and in ensuring the quality of manufacturing facilities, including for diseases associated with the developing world. It also allows maintenance and further provision of high quality manufacturing facilities. This model and GSK's efforts have been recognised and have been linked to wider efforts driven by international organisations to promote human rights [29].

Other vaccine companies are seeking to widen access to modern vaccines and are adopting different approaches. Some companies adopt models of not-for-profit pricing for the poorest countries. Typically, however, these companies allocate very small proportions of their vaccine output to the developing world and deliver most of their vaccines to wealthier countries [30]. GSK believes that for companies that consistently adopt a business model based on a hybrid model designed to support both innovation and access across economies of different levels of wealth, the alternative not-for-profit model does not support sufficient investment in innovation and production. A hybrid model enables both sustainability and the returns that shareholders require.

Some companies may rely on vaccine donations as their approach to the developing world. GSK's view is that donations do not constitute a sustainable response to the medical need in developing countries, with a few exceptions. One such exception is the role of donations in times of natural disaster or conflict. Such donations made under "special circumstances" such as stockpile and emergency use should be treated differently from vaccine supply for ongoing major vaccination programs such as the Expanded Program for Immunisation (EPI), clearly conforming with WHO and UNICEF guidelines on product donations as the basis of governing policy.

4. Challenges for vaccination

Ten years ago, there were just five diseases that were included in the basic EPI programs; today over two dozen diseases are preventable. Vaccines are available not only to protect infants and children, but also to protect people of all ages, including adolescents, adults (including those with heightened risk from other diseases or because of their occupation or travel activities) and the elderly.

In human impact terms, barriers to access translate to over two million children dying each year from vaccine-preventable diseases, with the risk being 10 times higher for those born in the developing world compared to their counterparts born in developed countries [31]. One quarter of infants still do not have access to basic immunisation services. These statistics are even more troubling in a context of increasing numbers of new vaccines becoming available to increase the ease of vaccination and to prevent previously unaddressed diseases.

While there are many strategic choices that individual manufacturers can make to overcome barriers to access and contribute to global health goals, there are many other factors that inhibit effective or optimal immunisation and that are beyond industry's control or influence. Many developing countries suffer from a lack of infrastructure to store and distribute vaccines (including a reliable energy supply for the cold chain) and from a lack of investment to build and to maintain health facilities, including vaccination centres. A lack of resources to train and retain healthcare professionals to deliver the vaccine where it is needed also inhibits effective vaccine delivery. Intermediaries may also engage in price mark-ups that reduce the affordability to patients.

In both developed and developing countries, sustainable and predictable levels of financing are often not in place and contribute to the "innovation pile-up" (see Fig. 1). It is estimated that a minimum of US\$ 5 per child is required for basic immunisation anywhere. In developing countries, this would have to be delivered with a suitable infrastructure level that would cost US\$ 400m to upgrade and an on-going 5–10% annual cost over a 10–20 year life cycle to maintain (personal communication—Osman Mansoor, UNICEF). Such levels of financing cannot be obtained without the highest level of buy-in from heads of states and international organisations [32]. Political will and backing is often lacking not only for allocating the necessary funding within health budgets but also to support public awareness campaigns to underline the benefits of vaccination to prevent previously controlled diseases from making dangerous come-backs. Finally, the discovery of new vaccines can suffer from not being linked to effective delivery strategies to obtain the maximum public health impact. New health interventions tend to benefit the richest segments of a society first and only much later trickle down to benefit the poorest groups [33].

5. Potential solutions

Faced with these numerous and interrelated challenges, potential solutions addressing both the supply-side of vaccine provision

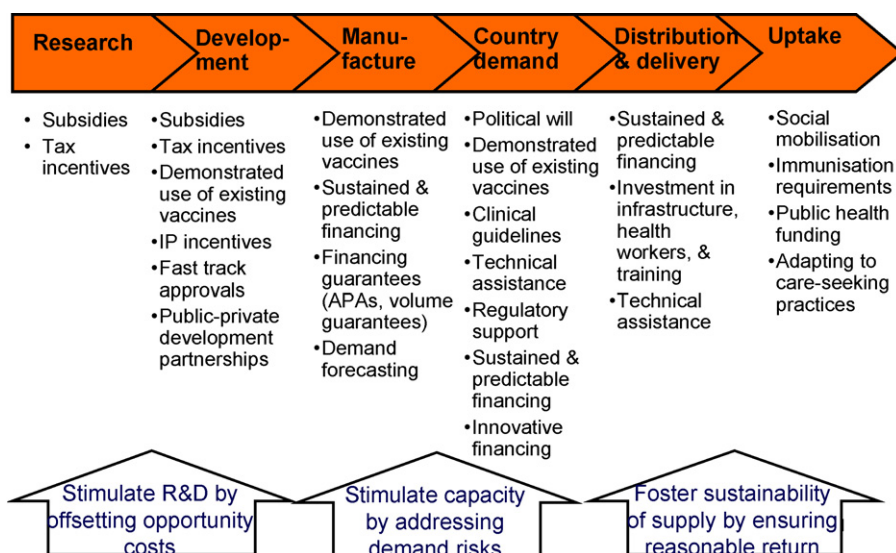


Fig. 2. Many mechanisms can speed new vaccine development and use.

(“push” mechanisms) and the demand-side (“pull” mechanisms) exist to help speed new vaccine development and use [34]. Potential solutions for tackling these challenges can be framed by looking at each stage of the vaccine development and implementation process (Fig. 2):

- Research and development for diseases mostly affecting developing countries
- Manufacture
- Country demand
- Distribution and delivery
- Uptake.

5.1. Research and development

For diseases mostly affecting developing countries, the aim is to create sufficient returns to provide a commercial justification for the necessary research and product development. This can be achieved through the incentivisation of manufacturers or through partnerships. Incentives include “push” mechanisms such as tax credits and subsidies to help stimulate research. For example, the National Institutes of Allergy and Infectious Diseases (NIAID) in the US use federally sponsored grants for projects researching the next generation anthrax vaccine, to conduct a human trial on an Ebola virus vaccine and for continued work on AIDS vaccines [35]. Such supply-side interventions aim at offsetting the opportunity costs of potential investments that could be targeted to other diseases. Once the candidate vaccine is in the development stage, these subsidies and tax credits can be supplemented or replaced by intellectual property incentives and/or fast track regulatory approvals. For example, due to the high unmet medical need for a vaccine addressing the causes of pneumococcal diseases in developing countries, WHO allowed submission of the regulatory file to its prequalification system (which is the gateway to procurement by international organisations such as UNICEF) in parallel with the submission to the European regulatory agency, instead of going through a typical process of doing these steps in sequence.

Partnerships are also a key element to reach for new and wider capabilities in R&D, as well as to share risks and resources to accelerate development of new vaccines [36,37]. Within GSK, 40% of vaccine candidates are being developed in collaboration with a variety of R&D partners. For example, public–private Product

Development Partnerships (PDPs) are critical in the work focusing on diseases of the developing world—partners include Aeras Global Tuberculosis Vaccine Foundation, the International AIDS Vaccine Initiative (IAVI), and the Malaria Vaccine Initiative (MVI) programme at PATH. In January 2001, GSK and MVI (PATH Malaria Vaccine Initiative), with support from the Bill & Melinda Gates Foundation, entered into a public–private partnership to develop a vaccine candidate for infants and children living in malaria endemic regions in sub-Saharan Africa. The clinical development of the vaccine candidate is conducted by the Clinical Trial Partnership Committee, a collaboration of leading African research institutes, Northern academic partners, MVI and GSK, with support from the Malaria Clinical Trial Alliance. To date, GSK has invested over US\$ 300 million to develop the vaccine and provides the clinical, regulatory and manufacturing expertise and resources through its global R&D and supply network. Partners help fund the cost of running clinical trials and address issues of access and distribution. The result is a candidate vaccine now entering pivotal phase III studies, which will be the world’s largest malaria vaccine trial to date, involving 16,000 participants in 11 centres in Africa.

Working with PDP partners and academic institutions across countries of all development levels to conduct clinical trials also helps to strengthen R&D capacity across the world, including in developing countries. Continued research should be encouraged into options for financing of R&D, especially in neglected diseases of developing countries, to match vaccine development with latent vaccine demand and facilitate high uptake rates.

5.2. Manufacture

Vaccine production entails the risk of high investments taken many years in advance of any potential revenue generation. Capacity development should follow public health mandates for the earlier availability of vaccines that respond to a high unmet medical need. In order to accelerate the development of capacity, it has been proposed that financing mechanisms could help to share the financial risk linked to demand not materialising for a product developed in response to a public health request. In June 2009, the first pilot Advanced Market Commitment (AMC) will be launched towards this goal. The AMC commits long term funding for a selected vaccine meeting pre-defined characteristics if it is demanded by countries in return for a guaranteed low, long term price.

5.3. Country demand

The three aspects of political will, technical capability and funding need to be aligned for country demand to translate into the purchase of vaccines. A strong political will as mentioned above driven by a true belief in the value of vaccines is the first element required [32]. This has been demonstrated by world leaders promising to do more on vaccines and the creation of the Millennium Development Goal 4 (MDG 4) that targets a reduction in the under-five mortality rate by two-thirds between 1990 and 2015. Prominent individuals such as Bill Gates and Gordon Brown have become champions for vaccines, but more are needed [38]. Most important in providing this backing is the ability to generate progressive and irreversible funding.

Secondly, the technical aspect of getting vaccines to market through clear and streamlined regulatory processes, a regular review of vaccination calendars, clinical guidelines and cost-effectiveness analyses enables country demand to translate faster into distributed vaccines. This in turn can be facilitated through technical assistance, for example, through sharing of best practice between national regulatory agencies.

Third, the aspect of financing is part of the remit of key partnerships with multilateral organisations such as GAVI, the Pan American Health Organization (PAHO) and UNICEF to facilitate vaccine financing. These organisations work to plan medium to long term, source and fund vaccination in their dedicated geographies. Significant volumes secured through purchasing commitments that are sustained and hence reliably predictable – for example by supranational organisations or other payors – enable economies of scale that can realise reduced production costs.

GAVI has experimented with a range of innovative financing mechanisms to increase the availability of their funding and to accelerate vaccine production, affordability and uptake. Two notable examples are the International Financing Facility for Immunisation (IFFIm) and the pneumococcal pilot Advance Market Commitment (AMC). The AMC is designed to promote a market for pneumococcal vaccines, assuming country demand materialises. The pneumococcal AMC is underwritten by donors composed of governments and the Bill and Melinda Gates Foundation. In exchange, manufacturers agree to bid for the sustained provision of vaccines at a pre-agreed price, which decreases in later years. The targeted result of current and hopefully future partnerships of this kind is more predictability in financing, yielding a sustainable supply of affordable quality vaccines for those in need and a sustainable return for manufacturers to reinvest in innovation.

The philosophy of these three solutions should be applicable in all parts of the world as similar hurdles also exist in higher income countries. For example, in the US, 11% of children have insurance that does not include coverage for vaccinations [39]. As Albert Sabin put it eloquently, “A vaccine that sits on the shelf is useless.” Political will must translate into the necessary financial and technical resources to enable vaccine distribution and delivery.

5.4. Distribution and delivery

Partnerships between the industry and multilateral organisations such as GAVI and PAHO also enable the supply and delivery of high quality vaccines through extensive vaccination campaigns across developing world countries. This requires a long term view through investment in infrastructure, health workers and training to ensure the sustainability of supply and demand, which will yield a suitable return for manufacturers. Achieving high and equitable coverage requires a high level of commitment and dedicated resource to suit effective interventions to the local epidemiological profiles. The private sector can play a strong part, for example in monitoring and ensuring quality and equity [33].

Creative solutions such as alternative delivery channels can complement or be a partial substitute for the public sector. For example, GSK is looking to partner with a major sexual and reproductive health NGO to distribute cervical cancer vaccination to low socio-economic groups in middle-income countries. Through this project, GSK is offering cervical cancer vaccines at an affordable level appropriate for each country and the NGO is providing access to its clinics which support women in low- and middle-socio-economic groups, thereby creating a sustainable business model for an alternative delivery channel and for tiered pricing within markets for vaccines.

5.5. Uptake

Achieving a high uptake rate will be the final hurdle to overcome to a successful introduction of a new vaccine. Indeed, vaccine refusal amongst parents is increasing, and this can have important consequences for nations' health as illustrated by the measles outbreaks in the US in 2008 [40]. The public health community has responded by measures such as immunisation requirements for school entry and social mobilisation. Further work needs to be done at the clinician level to educate clinicians to listen to parental concerns and explain the risks of non-vaccination since they are cited as the most frequent source of information for parents [41]. Furthermore, “softer” factors need to be addressed by delivering programmes according to community preferences, understanding who the unvaccinated are and suiting care-seeking practices [33,42]. A programme led by UNICEF in Laos underlined strongly that coverage rates can be sustainably high even in very vulnerable environments when parents “buy in” to the concept of vaccination [43].

There is no silver bullet. Faced with multiple levels of challenge, the answer to achieving vaccination can therefore only be through a spectrum of solutions that are well balanced across these different elements and are sensitive to the context in which vaccines are delivered.

6. Conclusion

Immunisation is one of the most effective and cost-effective of all public health interventions and fundamentally contributes to and underpins economic growth. Many challenges remain to effectively delivering an adapted response in a fast moving and complex external and internal environment. All stakeholders – governments, public health systems, international organisations and industry – need to work in partnership. This requires political commitment at the highest levels to have immunisation prioritised in health and aid budgets and to promote partnerships to enable vaccine R&D, financing mechanisms, production and delivery for everyone who needs vaccines. The globalisation of the world's economies, the rise in emerging and pandemic disease threats, and the mobility of populations mean that global policies and approaches will become increasingly important. At the same time, the science of vaccines continues to evolve, and we will see more vaccines to address new diseases or to better address diseases with safer and more effective vaccines, including through recombinant DNA and adjuvant technologies.

Industry has an established track record of being an involved actor in continually providing vaccines with demonstrated safety and efficacy profiles to the populations of developed and developing countries. We want to continue to achieve more. We believe that through our philosophy of availability, affordability and sustainability with tiered pricing and given a supportive environment for research and operations, we will deliver our contribution to improving global public health.

Conflict of Interest

A Nguyen and J Stephenne are employees of GSK, and K Taylor was employed by GSK Biologicals at the time of writing.

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