access to medicine FOUNDATION

Rapid access to investigational vaccines: an analysis of access provisions

Vaccine pipeline analysis

30 September, 2015

Promise in the pipeline – how quickly can affordable new vaccines reach the global poor?

The world's largest pharmaceutical companies are developing promising new vaccines to tackle some of the world's highest-burden diseases. This pipeline includes a group of first-ever vaccines, which, if successful, will finally make it possible to immunise children against diseases such as dengue, HIV/AIDS, malaria and tuberculosis. Yet, at least one key question remains: how soon will these vaccines be accessible and affordable in the countries that shoulder the largest burdens from these global killers?

For the majority of the pipeline, it is not clear whether companies are taking measures to ensure future vaccines will be affordable and available in sufficient quantities to low- and middle-income countries. To help payers and procurers plan ahead, companies are strongly encouraged to put access strategies and access provisions in place early in the R&D process for vaccines, and to offer details of these provisions and their planned implementation.

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Rapid access to investigational vaccines: an analysis of access provisions

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About the Access to Medicine Foundation

This pipeline analysis examines data for the 2014 Access to Medicine Index. The Access to Medicine Index is published by the Access to Medicine Foundation, a non-profit organisation based in the Netherlands that aims to advance access to medicine by encouraging the pharmaceutical industry to play a greater role in improving access to medicine in less developed countries. The Index methodology was developed, and is continually refined, in consultation with multiple stakeholders including the World Health Organization, NGOs, governments, universities and institutional investors.

The Index is funded by the Bill & Melinda Gates Foundation, the Dutch Ministry of Foreign Affairs, and the UK Department for International Development. The Access to Medicine Foundation is now developing a second Index of healthcare companies, the Access to Vaccines Index, with funding from the Dutch Nationale Postcode Loterij.

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Executive Summary

The world's largest pharmaceutical companies are developing promising new vaccines for some of the world's highest-burden diseases. However, it is unclear whether measures are in place to ensure they will quickly be accessible soon after they reach the market.

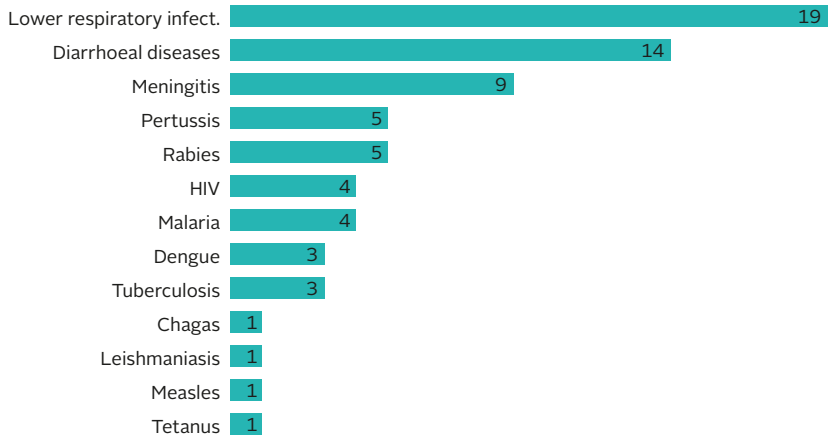
Immunisation is one of the most successful and cost-effective health interventions that exists today, preventing an estimated 2.5 million deaths each year. Access to vaccines, however, is unequally divided across the world, particularly when it comes to new vaccines.

Ensuring access to vaccines depends on a multi-stakeholder framework in which the developers and manufacturers of vaccines have an integral role to play. Starting with R&D, companies are expected to develop new vaccines to address high-burden diseases, and to adapt existing vaccines to make them more suitable for distribution and use in low-resource settings. Once successful vaccine candidates leave pipelines, they need to quickly be made as available and affordable as possible in low- and middle-income countries, which carry a major proportion of global disease burdens. To facilitate rapid access to new vaccines, companies can put measures in place (access provisions) to ensure future vaccines will be affordable, and that supplies will be sufficient.

This study investigates which vaccines are being developed by large pharmaceutical companies for high-burden diseases, using data submitted to the 2014 Access to Medicine Index by 20 of the world's largest research-based pharmaceutical companies. It also assesses the extent to which these companies are using access provisions, and looks at the types of access provisions being used.

Figure 1: 70 vaccines in development, targeting 13 high-burden diseases

Out of the 70 vaccines in development, 16 are for diseases for which no vaccines are currently on the market: dengue, HIV/AIDS, malaria, tuberculoisis, leishmaniasis and Chagas disease.



These 70 vaccines include 8 combination vaccines.

Findings

On analysis of pharmaceutical company R&D pipelines, this study finds that vaccines for high-burden diseases are indeed being developed. However, it is unclear whether measures are being systematically put in place, during the development process, to ensure that new vaccines will quickly be accessible soon after they reach the market.

1. High-burden diseases are being addressed.
There are 70 potential vaccines in pipelines that address 13 high-burden diseases. The largest proportion target lower respiratory infections, such as influenza and pneumococcal disease. Of these 70 vaccines, more than half were in development by either GSK, Novartis or Sanofi. This level of consolidation raises questions about security of supply and a lack of healthy competition in the vaccine market.

2. The 1st-ever vaccines for dengue and malaria have almost reached the end of the development process.
There are currently no vaccines on the market for these two deadly diseases. Encouragingly, the 'RTS,S' malaria vaccine (GSK and others) recently gained positive scientific approval from a key regulatory body, and the CYD-TDV dengue vaccine (Sanofi) is expected to reach the same milestone shortly. Nevertheless, gaps remain: neither of the vaccine candidates targeting Chagas disease or leishmaniasis have reached clinical development stages; only a few candidates for tuberculosis and HIV/AIDS have progressed to this point.

3. Major causes of childhood death are being targeted, with companies developing improved versions of existing vaccines.
The majority of vaccine R&D projects (54 out of 70) aim to adapt or improve existing vaccines (for example to improve their efficacy or give longer-lasting immunisation), or to create the next generations of existing vaccines. Many of these projects target leading causes of child death including diarrhoea and pneumonia.

4. Companies are developing combination vaccines that target multiple diseases, which will help optimise immunisation coverage.
Eight vaccines are being developed that consist of multiple antigens – up to six in one vaccine. This type of combination vaccine traditionally targets childhood diseases such as diphtheria, tetanus and pertussis, with newer ones in development also targeting meningitis and hepatitis B.

5. Whether companies consider vaccines' future accessibility is unclear.
Out of 70 vaccine projects, there is evidence that 12 projects are supported by provisions for supporting their accessibility (access provisions). For the majority of vaccine projects, however, it is not clear whether companies are taking measures to rapidly ensure vaccines will be affordable and available in sufficient quantities in low- and middle-income countries.

Conclusion: Promise in the pipeline, but how quickly can affordable new vaccines reach the global poor?

The research-based pharmaceutical industry is addressing high-burden diseases through R&D to develop both new and improved vaccines. With the first-ever vaccines for malaria and dengue so close to the end of the pipeline, it is clear that major milestones in immunization are approaching. It is also very encouraging to see that major causes of child deaths are being targeted, notably diarrhoea and pneumonia, and that improved vaccines for these diseases may soon be available. However, key product gaps remain, particularly for tropical diseases. Contingent on cooperation, support and incentives from other vaccine stakeholders, we urge those companies to investigate vaccines for this group of diseases, and be ready to contribute to others' R&D efforts. In addition, we also highlight the need for specific vaccine attributes to be adapted to suit the needs, capacities and resource-levels of communities living in low- and middle-income countries – notably the need for thermostable versions of existing vaccines.

How quickly will new vaccines be accessible?

The use of access provisions does not appear to be consistent or widespread. Further study is needed to fully illuminate how companies are working to facilitate rapid access to new vaccines. We strongly encourage vaccine companies to systematically consider the future accessibility of their investigational vaccines as early as possible in the R&D process, preferably by phase II. Furthermore, to help payers and procurers to plan ahead, companies are prompted to offer details of their access provisions and planned implementation.

Table 1: A guide to access provisions and their potential impact

Access provisions broadly fall into two categories: pricing commitments and licensing commitments.

What could access provisions look like?	What could their potential impact be?
Pricing Commitments	
Tiered pricing arrangements / Equitable pricing strategies	Increased affordability to poorer market segments / countries.
Price caps	Limits on mark-ups by third parties, aligning final price more closely with intended price, and improving affordability.
Price–volume arrangements	Provides incentives and predictability for arrangements and ensures supply of vaccines for purchaser.
Discounts	Increased affordability.
Licensing commitments	
Royalty-free	Ensures that vaccine manufacturers are able to manufacture at lower cost, with cost savings potentially being passed on to consumers.
Non exclusivity	Ensures fair market competition by allowing multiple manufacturers to produce a product, potentially leading to more sustainably lower prices.
Broad territorial commitments	Helps to ensure supply through the definition of a wide range of countries in which vaccine manufacturer(s) can freely operate and distribute their versions of products that remain under patent.
Supply commitments	Helps to facilitate predictability of supply of vaccines to meet forecast global demands.
Other commitments	
Supply commitment, outside of licensing	Helps to facilitate predictability of supply of vaccines to meet forecast global demands.
Local manufacturing commitments	Ensures that products/vaccines are produced regionally/locally, potentially reducing costs.
Registration commitments	Helps to ensure early access to new products in markets.

Rapid access to investigational vaccines: an analysis of access provisions

Introduction

Immunisation is considered one of the most successful and cost-effective health interventions.[1] Between 2000 and 2010, immunisation against pertussis, tetanus, diphtheria, measles and polio led the childhood mortality rate to drop from 0.9 million deaths per year to 0.4 million.[1] Overall mortality estimates show an even bigger drop of 2.5 million deaths annually as a result of immunisation. Mass immunisation has led to the eradication of smallpox and reduction of polio incidence by 99% globally.[1] In 2010, Gavi estimated that approximately 5 million deaths had been prevented by immunising children against hepatitis B, measles and pertussis over a ten-year period,[2] demonstrating powerful health outcomes when immunisation coverage is high.

Unequal access to vaccines

However, access to vaccines is unequally divided across the world, and differs per disease. While coverage of traditional vaccines can go beyond 80% – for example for the hepatitis B, measles and diphtheria-tetanus-pertussis 3 vaccines mentioned above[3] – coverage of newer vaccines, which have large potential health impacts, remains relatively low. For example, in 2013, global coverage of the pneumococcal vaccine and rotavirus vaccine were estimated at 25% and 14% respectively.[3] Pneumonia and diarrhoeal disease (which is also caused by the rotavirus) cause the deaths of 1.5 million children under the age of five each year.[4,5]

In 2010, Gavi anticipated being able to avert one million deaths through immunisation with pneumococcal and rotavirus vaccines by 2015, if sufficient funding for increasing coverage was made available.[2] In Gavi-supported countries at least, coverage of these two vaccines is increasing, although both vaccines are behind annual coverage targets, due to supply issues (pneumococcal vaccine), and delayed introductions in countries with large populations (pneumoccocal and rotavirus vaccines). The most recent coverage estimate, from 2014, for the pneumococcal (3rd dose) vaccine in these countries is 28%; for the rotavirus (last dose) vaccine, it stands at 15%.[6] Both vaccines have been introduced in more countries in 2014 than the original targets set in 2010.[6,7] This shows that immunisation coverage and access can be increased where good vaccines, solid funding, and strong global partnerships come together.

Multiple stakeholders share responsibility

In order for all people to benefit equally from the potential of immunisation, the Global Vaccine Action Plan (GVAP) was endorsed by the WHO's 65th World Health Assembly in 2012. GVAP targets are divided into separate categories: 1) The eradication of polio; 2) Global and regional elimination targets; 3) Coverage targets in every region, country, and community; 4) The reduction of child mortality beyond Millennium Development Goal 4; and 5) The development and introduction of new and improved vaccines.[1] First-ever vaccines are prioritised for malaria, dengue and

HIV/AIDS.[8] Improved versions of a number of existing vaccines are also prioritised, including thermostable measles and rotavirus vaccines and a universal influenza vaccine.[1]

Ensuring access to vaccines depends on a multi-stakeholder framework. Civil society and non-governmental organizations, such as Médecins Sans Frontières (MSF), implement immunisation programmes on the ground and routinely challenge access barriers. Philanthropic organisations such as the Bill & Melinda Gates Foundation and the Clinton Health Access Initiative (CHAI) play an important role in priority setting, market shaping and the funding of global agencies such as Gavi.[9] However, it is argued that a functional immunisation system is the primary responsibility of national governments.[1] Policies, implementation and oversight are indeed crucial, and must be supported with adequate and reliable financing. Those countries deemed not to have sufficient funds for effective national immunisation schedules can use the pooled procurement systems of global agencies such as Gavi, the UN Children's Fund (UNICEF) and the Pan American Health Organisation (PAHO).

The developers and manufacturers of vaccines also have a key role to play, due to their technical expertise, know-how and production capacities.

The vaccine market

The vaccine market has grown substantially over the past ten years, partly due to the introduction of new vaccines.[1] There has also been a growing acceptance of immunisation in general and of the targeting of underserved age segments. The global market was worth USD25 billion in 2013 and is expected to grow at a Compound Annual Growth Rate (CAGR) greater than 8% through 2018, a higher growth rate than for the pharmaceutical sector.[10] While influenza and paediatric vaccines dominate most vaccine portfolios, market growth is expected to be driven by new therapeutic areas. During the past decade, several large pharmaceutical companies acquired biotechnology companies with promising vaccine pipelines. In 2013, five large pharmaceutical companies (GSK, Merck & Co., Novartis, Pfizer and Sanofi) accounted for more than 80% of global vaccine revenues.[10–12]

Recent developments have led to some key changes in the vaccine market, with important alliances and acquisitions, including:

- In 2014, Novartis announced it would transfer its influenza vaccine division to Australia's CSL[13] and its entire remaining vaccines business to GSK.[14] Novartis has since confirmed completion of these transfers.[15,16]
- GSK also acquired GlycoVaxyn AG, in February 2015[17], and Okairos, in 2013[18].
- Pfizer acquired Baxter's marketed vaccines in 2014[19], as well as Redvax, a small biopharmaceutical company with a vaccine pipeline, in 2015.[20] In the same year, Pfizer also acquired two meningitis vaccines from GSK.[21]
- Takeda has strengthened its pipeline with the acquisition of two US vaccine companies: LigoCyte Pharmaceuticals in 2012[22] and Inviragen in 2013[23].
- In 2011, Johnson & Johnson moved into the vaccine space with the acquisition of Crucell.[24] In 2014 and 2015, Johnson & Johnson divested its cholera vaccine to Valneva[25] and its typhoid vaccine to PaxVax[26].

Even though 80% of global vaccine revenue is generated by large pharmaceutical companies, only 14% of the vaccines they produce (by volume) goes to low- and middle-income countries.[12] That so little of their vaccine business is directed toward these countries paints a concerning picture: particularly regarding the incentives for these companies to develop vaccines that meet the needs of these countries.

The bulk of the vaccine volume currently sold to low- and middle-income countries is manufactured by vaccine manufacturers based in those countries (often manufacturers of traditional childhood vaccines).[11,12]

The role for pharmaceutical companies

Barriers to access to vaccines

Although many life-saving vaccines now exist, there remains a high need for certain vaccines to be developed, including for malaria, HIV/AIDS, tuberculosis and dengue, as well as a need for existing vaccines to be adapted for use in low-resource settings. Plus, although all countries have national immunisation programmes, they are not always effective, efficient or financially secure. Among others factors, the lack of affordability and supply are delaying the targets set out in the Global Vaccine Action Plan.[27]

R&D that meets public health needs

Historically, the traditional R&D model of the pharmaceutical industry focused on recouping investments in developed countries. For high-burden diseases in low- and middle-income countries, health needs in terms of priority product development have been overlooked. As a consequence, high-priority vaccines, for example for malaria and dengue, are not yet available.

To drive strategic R&D decisions that meet public health needs, particularly for low- and middle-income countries, the WHO develops Preferred Product Characteristics (PPCs). A PPC starts with a review of an unmet public health need for which vaccine development is needed. This includes a review of priority indications, target groups, possible immunisation strategies and desired clinical data. These PPCs are reviewed and updated regularly.[28]

The WHO also sets out recommendations for vaccine presentation and packaging to help vaccine manufacturers design their products with specific constraints in mind, such as the remoteness of certain populations, weak infrastructure and unreliable roads. Together these PPCs and presentation and packaging recommendations form an essential part of vaccine developers' Target Product Profiles (TPPs).[28] Companies can use these TPPs to assist in defining target product characteristics, such as dosage, target price, target population, route of administration. Companies are expected to continuously innovate through R&D towards the goals defined in the TPP.

Affordability of new vaccines

Newly developed vaccines have increased costs for pooled procurers such as Gavi,

UNICEF and PAHO. Compared to 2000, the cost to immunise a child at the lowest available price to Gavi and UNICEF is now 68 times higher: during the same period, the WHO Expanded Programme on Immunization has only increased from six to 12 vaccines. These newly added vaccines target hepatitis B, *H. influenza* type b, pneumococcal diseases, rotavirus, and human papillomavirus (for adolescent girls only).[29] A recent MSF campaign urged GSK and Pfizer to lower the prices of their newly introduced pneumococcal vaccines for children in low-income countries.[30] Gavi in particular is focused on accelerating access to newer vaccines in low- and lower-income countries. However, only certain countries can apply for support from Gavi: those with a *per capita* Gross National Income that is equal to or below USD1,570, as identified by the World Bank. Currently, only 49 countries qualify for this support.[31]

National governments that fall outside of such pooled-procurement systems often have to pay much higher prices for their vaccines, especially for the newer human papilloma virus (HPV), rotavirus and pneumococcal vaccines. Typically, this affects those countries moving from LMIC to MIC World Bank status. Worryingly, it is argued that middle-income countries do not view these vaccines as being cost-effective enough to include in national immunisation schedules,[29] and that they would put too much pressure on national immunisation budgets. Countries need to make cost-effectiveness and budgetary decisions prior to deciding whether to include a vaccine in national immunisation programmes. A lack of transparency here can obscure and slow down decision making.[29] Vaccine companies can support this process by increasing the transparency of information on both the price and the different product characteristics of vaccines. Companies are also encouraged to take affordability for different national governments into account when pricing their vaccines.

Matching supply and demand

Vaccine shortages disrupt or delay vaccination programmes. They can be the result of inaccurate demand forecasting, interruptions in production or supply, or a lack of funds for purchasing vaccines. Due to the biological nature of vaccines, production is a complex and lengthy process. It can take up to three years to produce a finished vaccine.[32–34] As supply is often fully committed to specific purchasers, it can take up to one year between the confirmation of demand and actual delivery. Communication among public sector organisations, countries and vaccine manufacturers is crucial to ensure appropriate and adequate vaccine supply.

For example, a recent outbreak of meningitis in Niger proved difficult to curb due to shortages of the vaccine against *Neisseria meningitidis* bacteria types A, C, W135 and Y. The International Coordinating Group on Vaccine Provision for Epidemic Meningitis (ICG) ordered vaccines for their emergency stockpile from three private-sector manufacturers. When one manufacturer faced production problems, the other two could not increase their production quickly enough to deliver vaccines to Niger. As of May 31 2015, the epidemic has caused nearly 7,000 cases and more than 400 deaths.[35]

To prevent shortages and delays in vaccine delivery, it is crucial that companies and vaccine procurers (e.g., governments, international procurement agencies) align their planning processes, implement accurate forecasting tools and engage in dialogue about the types of new vaccines that are needed (both innovative and adaptive).

Access provisions: Putting measures in place to address access barriers

In summary, there are three key areas where vaccine developers and manufacturers can address barriers to access to vaccines:

1 **R&D:** By developing new and adapted vaccines, particularly for meeting high-priority needs, and needs specific to low-resource settings;
2 **Affordability:** By taking measures to ensure that these new vaccines are affordable in low- to middle-income markets, such as equitable pricing strategies that take the payer's ability to pay into account; and
3 **Supply**: By putting measures in place to ensure sufficient continuity and scale of supply to meet large demand in terms of production capacity. This could include manufacturing commitments and/or royalty-free licensing arrangements and non-exclusive field or territory rights (especially where developed in partnerships).

Defining access provisions

Measures that are put in place to improve affordability and/or supply are referred to in this paper as access provisions. Access provisions are particularly important for facilitating rapid access to new vaccines, as soon as possible after market entry. By planning for, or by putting such measures in place while a vaccine is under development, a company can significantly accelerate the speed at which a new vaccine is available at prices that are affordable for payers, and at volumes that can support multiple national immunisation programmes. Table 1 provides an overview of such provisions and their potential impact on access to vaccines.

Table 1: A guide to access provisions and their potential impact

Access provisions broadly fall into two categories: pricing commitments and licensing commitments.

What could access provisions look like?	What could their potential impact be?
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Tiered pricing arrangements / Equitable pricing strategies	Increased affordability to poorer market segments / countries.
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Local manufacturing commitments	Ensures that products/vaccines are produced regionally/locally, potentially reducing costs.
Registration commitments	Helps to ensure early access to new products in markets.

The research question

This paper aims to illuminate companies' behaviour when bringing new vaccines to developing country markets, in particular with regard to access strategies that include affordability and supply arrangements (access provisions). First, it investigates which vaccines for high-burden diseases are being developed by large pharmaceutical companies. Second, it assesses the extent to which companies are making use of access provisions, putting measures in place during the R&D phase to accelerate and facilitate access to vaccines in developing countries on market entry.

Methods and approach

Extracting and re-analysing data from the 2014 Access to Medicine Index

Data collection for this paper was conducted through an online survey designed by the Access to Medicine Foundation for the 2014 Access to Medicine Index.[36] This biennial Index ranks 20 of the largest research-based pharmaceutical companies on their policies and practices for increasing access to medicine in developing countries. The 2014 Access to Medicine Index covers 106 low- and middle-income countries and 47 high-burden diseases across several disease areas, including infectious diseases. Its methodology measures key access to medicine aspects across 95 indicators. From this database, information on investigational vaccines was extracted and re-analysed for this study. The period of analysis for all data presented here is from June 2012 until May 2014. Due to this period of analysis, vaccines submitted by Novartis are reported as such despite a completion of transactions, largely to GSK, that occurred in 2015.[15] It is not known if GSK has since made changes to the Novartis' former vaccine business that would alter the results of this study.

All companies and diseases covered by the 2014 Access to Medicine Index were included in this vaccine analysis. The targeted age population of investigational vaccines in this paper was restricted to children, adolescents or adults, excluding those vaccines developed exclusively for neonatal health, maternal immunisation or the elderly. The latter group of vaccines are generally not under development for use in routine immunisation schedules, and as such, they are not directly comparable for analysis in this paper.

Disease covered by this study

The diseases covered by the 2014 Access to Medicine Index that are considered vaccine-preventable were separated into two categories: 1) diseases for which no vaccine is currently available; and 2) diseases for which vaccines are currently available. To make this distinction, summaries of available vaccines and WHO policy recommendations were used.[8]

Tuberculosis was included as a disease for which no vaccine is currently available, as the only available tuberculosis vaccine is recommended exclusively for neonates and is only partially effective for non-pulmonary forms of tuberculosis.[37] Vaccines with a high R&D priority were identified and analysed separately from other investigational vaccines. R&D priorities were identified using the WHO policy recommendations[8] and the GVAP[1].

Table 2: Analysis scope: high-burden diseases

This table shows the analysis scope of this study: vaccine-preventable diseases covered by the 2014 Access to Medicine Index. High R&D priorities are indicated, with specific needs given in brackets.

Diseases in scope, with identified priority status for vaccine R&D	
Diseases for which vaccines are not available on the market*	
Chagas disease	
Dengue	High-priority
HIV/AIDS	High-priority
Leishmaniasis	
Malaria	High-priority
Tuberculosis	High-priority (for broad age range)
Other neglected tropical diseases	
Diseases for which vaccines are available – improvements/adaptations needed	
Diarrhoeal diseases • Cholera • Rotavirus • Typhoid	High priority (for thermostability)
Hepatitis B	
H. influenzae type B disease	
Lower respiratory diseases • Influenza • Pneumococcal disease	High priority (for universal protection)
Measles	High priority (for thermostability)
Meningitis (meningococcal)	
Pertussis	
Rabies	
Tetanus	

* GSK's RTS,S malaria vaccine was approved for use by European Regulators in July 2015. It is not yet available on the market.

This study does not address other diseases that may be vaccine-preventable, such as human papillomavirus, Japanese encephalitis, mumps, polio, rubella, tick-borne encephalitis, varicella and yellow fever[8], and Ebola. Data on these diseases is not included in this paper because they are out of the scope of the 2014 Access to Medicine Index and thus no data was collected.[36] The disease scope of the Index is limited to diseases with the highest burden, as indicated by their related Disability Adjusted Life Years (DALYs).

Mapping R&D projects

This paper examines data on all vaccine R&D projects for the diseases in scope submitted by the 20 companies measured to the 2014 Access to Medicine Index, whether they are being developed in-house solely by the pharmaceutical company, or in a partnership with others.

It includes projects for developing new vaccines, projects that aim to adapt certain product attributes, and studies that specifically aim to meet needs of people living in developing countries. This includes projects that aim for thermostability, easier administration routes, fewer doses, more flexible dosing schedules, reduced volume of administration, improved efficacy of oral vaccines and more efficacious antigen combinations. Phase of development is taken into account to be able to distinguish between non-clinical and clinical development.

Examining access provisions

Per vaccine project, the authors examined supporting evidence for access provisions provided by pharmaceutical companies to the 2014 Access to Medicine Index. These provisions could include pricing considerations, arrangements to ensure sufficient supply, royalty-free terms and non-exclusivity of field or territory rights, or others.[36] Access provisions were used to determine for which diseases pharmaceutical companies take access into account during in-house and collaborative vaccine development.

To illustrate examples of vaccine projects of public health significance and the use of access provisions, three examples of vaccine projects identified in this paper are described in more detail in the results section in Tables 3-5. These vaccines are all: (1) of high priority, or newer vaccines that are included in the WHO Expanded Programme on Immunization;[8] (2) in phase II or III clinical studies (where access provisions are more likely to be used), and (3) were supported by sufficient data submitted to the 2014 Access to Medicine Index. The developers of these three vaccines were approached for this study after the launch of the 2014 Access to Medicine Index to verify and update this information.

Findings: Promise in the pipeline – how quickly can affordable new vaccines reach the global poor?

1 High-burden diseases are being addressed

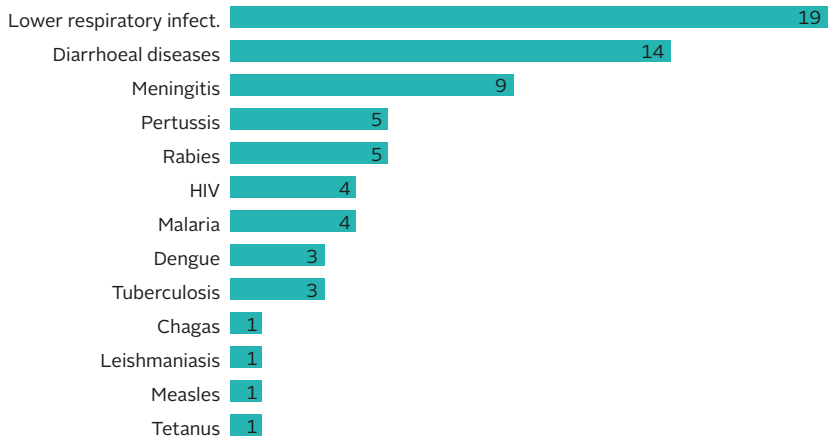
There are 70 potential vaccines in pipelines that address 13 high-burden diseases identified by the 2014 Access to Medicine Index that are considered vaccine preventable. Most vaccines in development are for lower respiratory infections, such as influenza and pneumococcal disease.

Of these 70 vaccines, more than half were in development by either GSK, Novartis or Sanofi. At the time of analysis, these three companies were the only ones with dedicated vaccine divisions.[36] Novartis has since divested its vaccine business, largely to GSK. This level of consolidation raises questions about security of supply and a lack of healthy competition in the vaccine market. This analysis also identified seven other companies that are developing vaccines for diseases in scope: AstraZeneca, Daiichi Sankyo, Eisai, Johnson & Johnson, Merck & Co., Pfizer and Takeda.

Out of the 70 vaccines in development, 16 are for diseases for which no vaccines are currently on the market (6 diseases), and the remaining 54 target diseases for which vaccines already exist.

Figure 1: 70 vaccines in development, targeting 13 high-burden diseases

Out of the 70 vaccines in development, 16 are for diseases for which no vaccines are currently on the market: dengue, HIV/AIDS, malaria, tuberculoisis, leishmaniasis and Chagas disease.



These 70 vaccines include 8 combination vaccines.

2 The first ever vaccines for dengue and malaria have almost reached the end of the development process.

Looking across the disease scope of this analysis, there are six diseases without vaccines on the market: Chagas disease, dengue, HIV/AIDS, leishmaniasis, malaria, and tuberculosis. In total, 16 vaccines are in development for these diseases. Encouragingly, vaccines for malaria and dengue have almost reached the end of the development process: malaria vaccine 'RTS,S' recently gained market approval from key regulatory bodies, and the dengue vaccine is expected to reach the same milestone shortly. For the remaining first-ever vaccine candidates, if they prove to have sufficient efficacy and safety profiles, they could reach the market and the people who need them in the near future.

Half of these 16 first-ever vaccines are in clinical development including five in clinical phases II or III. Out of these 16 vaccines, 14 target four high-priority diseases: dengue, HIV/AIDS, malaria and tuberculosis (see Figure 1).

- **Dengue:** Sanofi and Takeda each have a preventive vaccine for dengue in late-stage development, a disease for which only general medical care is available, but no specific treatment. Sanofi's vaccine is most advanced (in phase III – see Table 4).
- **HIV/AIDS:** One HIV/AIDS-preventative vaccine has reached phase II clinical development, and is being developed under a public/private partnership (between Sanofi, Novartis, Bill & Melinda Gates Foundation, U.S. National Institute of Health, HIV Vaccine Trials Network, and the U.S. Military HIV Research Program).

Figure 2: First-ever vaccines in the pipeline

	Stage of development				
	Pre-clinical	Phase I	Phase II	Phase III	Market Approval
Disease					
Chagas disease	1	0	0	0	0
Dengue	1	0	1	1	0
HIV/AIDS	2	1	1	0	0
Leishmaniasis	1	0	0	0	0
Malaria	2	1	0	0	1
Tuberculosis	0	1	2	0	0

There are 16 first-ever vaccines currently under development, including for malaria and dengue. Nevertheless, gaps remain. For example, the pre-clinical phase is the fullest. Considering the high project attrition rate in pharmaceutical R&D, there is still a chance that none of the vaccines in this earliest phase will reach the people who need them.

- **Malaria:** GSK is partnering with PATH, which could bring the first vaccine for malaria to the market in 2015, as this has now received a positive scientific opinion by the EMA.[38] However, efficacy is moderate in young children and infants (see Table 3).[39]
- **Tuberculosis:** GSK and Johnson & Johnson are both involved in the late-stage clinical development of tuberculosis vaccines that potentially offer better protection for a wider age range compared to the BCG vaccine.

Nevertheless, there are significant worrying gaps in the development pipeline for vaccines, with no vaccines in clinical development for Chagas disease or leishmaniasis, and only a few vaccines in clinical stages for tuberculosis and HIV/AIDS (Figure 2). Considering the high project attrition rates in vaccine R&D, there is still a relatively high chance that none of these candidates will reach people. Furthermore, there is little sign that the next generations of vaccines for these diseases are under development, which will be crucial for supporting eradication and elimination goals.

Table 3: Most advanced vaccine candidate in development for Malaria: RTS,S/AS01 (GSK and PATH/MVI)

Product profile	RTS,S is a a hybrid polypeptide consisting of a portion of the CSP (circumsporozoite protein of P. Falciparum) antigen and the surface antigen S of Hepatitis B virus (HBsAg), combined with a GSK proprietary Adjuvant System.[40]
Phase of development	Received a positive EMA Article 58 scientific opinion in July 2015.
Disease prevalence	Malaria is a high-burden disease that affects many regions worldwide. It is estimated that 3.2 billion people are at risk of malarial infection, with 1.2 billion people facing a high risk. Mortality rates due to malaria are highest in Africa.[41] It is the third largest cause of death among children under the age of five in low-income countries, following pneumonia and diarrhoea.[42] A vaccine for malaria would offer potentially one of the most powerful preventive interventions in global health, especially considering the backdrop of increasing microbial resistance against artemisinin-based malaria treatment[41].
Current availability of vaccines	None.
Clinical trial results	RTS,S has been proven to reduce the number of malaria cases, in use alongside established interventions. The first phase III results were obtained after a 12-month follow-up period at first vaccination. RTS,S was shown to reduce clinical malaria by 56% in children aged 5 to 12 months.[43] In infants aged 6 to 12 weeks, clinical malaria was reduced by 31%.[44] However, the latest available data show that clinical efficacy wanes over time. Vaccine efficacy in children in the age group of 5–17 months was reduced, to 16.8% after a four-year follow-up period.[40] Although this vaccine appears to provide moderate efficacy, without full protection against malaria, other control measures will remain critical in order to reduce the burden of this disease.
Access provisions covered by this project:	GSK has committed to setting not-for-profit prices.[45] GSK indicates that the RTS,S pricing model will only cover manufacturing costs and it will reinvest small returns into R&D for second-generation malaria vaccines.[46] The parties involved in the R&D partnership commits to ensuring that price will not be a barrier to access.

Expected next steps	Following the positive opinion by the EMA under Article 58 in July 2015, GSK will be able to apply for market authorisation from African regulatory authorities. If the required public health information and clinical trial results are satisfactory, the WHO estimates that it can make policy recommendations by the end of 2015.[47] This would clear the way for large-scale implementation by African governments.
Expected time to market	GSK anticipates that the vaccine will be ready for implementation in the first African countries in 2017.

Table 4: Most advanced vaccine candidate in development for dengue: CYD-TDV (Sanofi)

Product profile	Recombinant, live, attenuated, tetravalent vaccine (DEN1-4 serotypes)[48]
Phase of development	Phase III
Disease prevalence	Dengue incidence has increased enormously over the last 50 years. The WHO estimates that 50-100 million infections occur every year, including in areas that were previously unaffected. All four serotypes have spread from Asia to Latin-America, Africa and Eastern Mediterranean regions. As there is no treatment available, a vaccine is an important intervention that could contribute to the WHO's goals to reduce dengue morbidity rates by 25% and dengue mortality rates by 50% by 2020.[49]
Current availability of vaccines	None.
Clinical trial results	The CYD-TDV vaccine has been tested in two phase III trials. The most recent study shows a vaccine efficacy of 60.8% in children between 9 and 16 years old at 25 months after vaccination. For severe dengue (dengue haemorrhagic fever), vaccine efficacy was estimated at 95%.[50] These results are supported with findings from an earlier phase III study. An efficacy of 56.5% was shown in children aged 2 to 14 years old following the same immunisation schedule and follow up period.[51] No pattern of serious adverse events has been observed so far. Final results of the phase III trial in Latin America will be made available after a four-year follow up period.[48]
Access provisions covered by this project	Sanofi commits to large scale production once the vaccine has been approved by using its new vaccine manufacturing site in France.[52] Sanofi indicates that this will enable endemic countries to start immunisation programmes soon after approval without delays. Pricing is reported to be tiered for low-income countries, but affordability is unknown.[53,54]
Expected next steps	Submission for registration and approvals are expected in 2015.[54] Sanofi expects the vaccine to be licensed in 20 endemic countries by the end of 2015. It will prioritize these countries over registration in the US and EU.[55]
Expected time to market	The first launch could take place before the end of 2015.[54]

3 Major causes of childhood death are being targeted, with companies developing improved versions of existing vaccines.

The majority of vaccine R&D projects (54 out of 70) aim to adapt or improve existing vaccines (for example to improve their efficacy or give longer-lasting immunisation), or to create the next generations of vaccines already on the market. Many of these projects target leading causes of child deaths including diarrhoea and pneumonia (see Figure 1).[4,5]

These projects aim to achieve one or more of the following benefits: improved efficacy, broader coverage, longer-term immunisation, greater ease of administration, or to reduce volumes (e.g. individual vials and large shipments). For example, GSK is conducting a study to confirm the safety and efficacy of its measles vaccine when used in the WHO Expanded Programme on Immunization; Pfizer is increasing the number of doses in each vial of its pneumococcal vaccine in order to reduce volumes and relieve pressure on supply chains. Among vaccines in the pipeline, there is limited evidence of projects for developing thermostable vaccines and no studies that aim to develop more flexible immunisation schemes.

There are substantial numbers of seasonal influenza vaccines (13) and pneumococcal vaccines (5). Vaccines for diarrhoeal diseases target a variety of pathogens including rotavirus (e.g., see Table 5), cholera and several species of bacteria that can cause typhoid, among other diseases. Other causes of diarrhoeal diseases are also targeted by investigational vaccines, including norovirus and shigella, *E. coli* and enterotoxigenic *E. coli* bacteria, among others. These vaccines are mostly in early development phases.

Table 5: Most advanced vaccine candidate in development for rotavirus: BRV-TV (Led by Shantha Biotechnics, supported by Sanofi)

Product profile	Oral live-attenuated bovine-human reassortant rotavirus vaccine comprising four serotypes (G1-4)[56]
Phase of development	Phase III
Disease prevalence	Rotavirus is one of the main causes of child mortality in developing countries.[4] Infants and young children in particular are at risk for rotavirus-induced severe diarrhoea. Annually, 450,000 children under the age of five die due to rotavirus infection, and millions more are hospitalized. Most of these deaths occur in Gavi-eligible countries (95%). Implementation of rotavirus vaccine in these countries is expected to prevent 0.8 million deaths between 2011 and 2020.[57]
Current availability of vaccines	To date, two vaccines for rotavirus are available, Rotarix® (GSK) and RotaTeq® (Merck & Co.). However, prices are relatively high compared to other vaccines in the WHO Expanded Programme on Immunization. Moreover, there is a shortage of supply and global demand is expected to increase. New rotavirus vaccines are needed to ensure sufficient supply, reduce prices, and to establish a sustainable market.[57] In 2014, another rotavirus vaccine developed by an Indian biotech and several public partners, Rotavax®, obtained licensure in India.[58] Vaccine efficacy against severe diarrhoea was shown to be around 55%.[59] Its developers have announced that the vaccine will be priced at US$1/dose.[60]

Clinical trial results	Safety and efficacy of the BRV-TV vaccine was illustrated in a phase I/II trial that was conducted in India.[56] After safety had been determined in healthy adults, efficacy in infants was measured according to the anti-rotavirus IgA antibody response. Results were compared to vaccination with RotaTeq® and a placebo. BRV-TV induced a dose-response immune response, which was superior to RotaTeq®'s immune response in healthy infants. These results will need to be confirmed in a larger number of trial subjects in order to determine the vaccine's efficacy. Sanofi Pasteur announced that the vaccine has entered a phase III trial.[61] Phase III trial results are expected in 2016.
Access provisions covered by this project	Sanofi indicates that it aims to provide an affordable rotavirus vaccine to meet the demand in emerging markets through partnerships with organizations like UNICEF/Gavi. The affordability of eventual pricing is to be ensured by its subsidiary Shantha Biotechnics. At the time of writing, the company states that the details of the vaccine price are still to be determined.
Expected next steps	Sanofi is expecting to file for registration in India in 2016 based on favourable phase III study results. Sanofi also plans to submit its rotavirus vaccine through a WHO pre-qualification procedure for addressing UNICEF/Gavi and PAHO countries needs in Asia, Africa, and Latin America.
Expected time to market	Sanofi is targeting a licensure in India by end of 2016 based on favourable phase III study results and regulatory reviews.

4 Companies are developing combination vaccines that target multiple diseases, which will help optimise immunisation coverage.

Eight vaccines are being developed that consist of multiple antigens – up to six in one vaccine. This type of combination vaccine traditionally targets childhood diseases such as diphtheria, tetanus and pertussis, with newer ones in development also targeting meningitis and hepatitis B. These combination vaccines mean children need to make fewer visits to healthcare centres, and can reduce the cost and complexity of stocking, storing and administering multiple separate vaccines.[62]

Five companies (Johnson & Johnson, Merck & Co., Novartis, Sanofi and Takeda) are developing combination vaccines that include multiple antigens. For example, Johnson & Johnson and Novartis partnered with other organizations such as PATH to develop a combination vaccine that targets meningitis, *H. influenza* type b, pertussis, tetanus and hepatitis B, plus diphtheria. It uses a new delivery device that eases administration, making it suited for use with reduced risk of errors by community workers in more remote areas.

There are also combination vaccines in development that target multiple serotypes that cause the same disease. This approach helps to ensure broader suitability and efficacy. It is most evident for influenza and meningitis. Most vaccines for meningitis are quadrivalent conjugates targeting the A, C, W135 and Y serotypes. For influenza, there are also multiple vaccines in development that target both A and B serotypes.

5 Whether companies consider vaccines' future accessibility is unclear.

The WHO Strategic Advisory Group of Experts for Immunization has identified vaccine affordability and supply as a key area that is delaying progress toward global immunisation targets. Once a vaccine has gained regulatory approval, it is important that it is made widely available and affordable as soon as possible. To facilitate this rapid access to new vaccines, pharmaceutical companies need to think about vaccines' future accessibility while they are still under development, usually expected by stage 2 clinical trials, but preferably before.

Access provisions for 12 projects

Out of 70 vaccine projects identified, companies provided evidence that 12 (17%) are supported by measures for facilitating accessibility (called access provisions). This includes:

- Tiered pricing strategies aimed at ensuring affordability;
- A subsidiary with manufacturing capacity based in a developing country, aimed at greater affordability and supply;
- An advanced market commitment with Gavi, including discounted prices; and
- A manufacturing commitment designed to ensure large volumes of the vaccine are available at the point of market entry.

The 12 vaccine projects supported by access provisions target malaria, dengue, diarrhoeal diseases, lower respiratory infections, combination vaccines, and meningitis. The majority (8) of them were in clinical development (phase I, II, III or IV). Two first-ever vaccines are explicitly supported by access provisions: GSK has pledged to sell its potential vaccine for malaria at not-for-profit prices; Sanofi has made a large-scale manufacturing commitment for its potential vaccine for dengue, and a recent registration commitment (see Tables 3 & 4 on pages 16-17)

There is no clear correlation between access provisions and vaccine development for a particular disease.

Lack of evidence

It is not clear whether access provisions are truly lacking, or whether low transparency accounts for the gap. For some vaccines under development (7), it was specified that access provisions had not been taken into consideration. For some collaborative projects (11), it was specified that companies were unable to disclose information about access provisions due to confidentiality clauses. An intent to develop project specific access strategies was provided for 14 projects, mainly in discovery and pre-clinical development phases. For the remaining projects (26), no information was provided. It is a limitation that the survey did not specifically include 'intent to develop access strategies', for projects in earlier development phases.

When taking only clinical projects into consideration results show that later stage development does not impact these transparency findings: out of 42 clinical stage projects, evidence of access provisions in place was provided for 8 projects (20%).

Further study is needed to explore whether and how companies are systematically considering the future accessibility of their vaccine candidates.

Discussion

Progress: the vaccine pipeline is targeting high-need diseases

There are 70 potential vaccines in pipelines that address the high-burden diseases identified by the 2014 Access to Medicine Index. Pharmaceutical companies are using their technical expertise and know-how to develop innovative, high priority vaccines, including for diseases where there is no vaccine currently available. Of these, it is likely that the first-ever malaria and dengue vaccines will reach the market in the near future. With high project attrition rates, this number is low and more needs to be done to incentivize fuller pipelines. There is also a strong need for next generation vaccines to serve specific populations and gear towards elimination and eradiation targets rather than preventing disease.

Combination vaccines reduce the number of times a child needs to be injected, making them useful for improving the timeliness of immunisation, as well as public acceptance of and adherence to immunisation schedules. Combination vaccines also help cover multiple disease serotypes, protecting people from several diseases at the same time. The trivalent DTP vaccine (developed in the 1950s) was the first combination vaccine, and is considered the cornerstone of the Expanded Program on Immunization (which began in 1974). Pentavalent vaccines have been introduced in 170 countries so far, indicating the level of immunisation that innovative combination vaccines can bring. Considering the large numbers of people in need of immunisation, it is of concern that a decrease in the number of manufacturers producing pentavalent vaccines could potentially adversely constrain vaccine supply. To combat this scenario, more companies can invest in creating multivalent vaccines, licensing them to multiple manufacturers. In combination with adequate and accurate demand forecasts, such steps would help guarantee supply and prevent shortages.

Vaccines for dengue will be important tools for counteracting rising prevalence of the disease across multiple regions. For malaria, the complicated life cycle of the malaria parasite, with different cell-surface protein expression,[63] points to a need for a next-generation of malaria vaccines. To date, developing a vaccine for HIV/AIDS with sufficient protection has been a challenge due to the rapidly mutating HIV retrovirus.

Other vaccines are being adapted or improved in order to enhance efficacy, ensure broader coverage for different diseases or serotypes, provide longer-term immunisation, ease administration routes, or reduce shipping volumes. These adaptations target product characteristics that can form barriers to access to vaccines, depending on the local circumstances of the receiving country. All vaccines in development presented here have the potential to further reduce mortality rates and to indirectly stimulate economic growth in developing countries. Even those that are broadly similar to existing vaccines have potential to facilitate access: the availability of multiple similar vaccines, for example pneumococcal vaccines or rotavirus vaccines (see Table 5), could stimulate competition in the future and help bring prices down.

Key R&D gaps remain

Critical developing-country needs continue to be overlooked. Most vaccines in development target universal medical needs, with only a few examples of projects that only target developing country access barriers. One notable exception is from GSK, which has entered a partnership with the Bill & Melinda Gates Foundation under which GSK will focus on the development of thermostable adjuvants.[64] None of the companies analysed are currently developing thermostable vaccines for diseases within scope, including high-priority vaccines for measles and rotavirus.[1] None are performing studies that aim to achieve more flexible immunisation schemes. This suggests that incentives for such vaccine R&D projects remain poor.

Thermostable vaccines in particular would offer a powerful solution to current cold chain difficulties. With the continued absence of such innovations, strong government oversight and accountability will remain critical for rolling out efficient national immunisation programmes.[65] Other organisations are playing an important role in developing and investigating new cold chain technologies. For example, PATH works on the development of technologies that can be used to adapt vaccines to extend heat stability and prevent freeze damage.[65,66]

It is also concerning that there are not more pipeline candidates for diseases with no vaccine currently available. While first-ever vaccines bring real hope for reducing disease and death, eradication and elimination targets are best supported with multiple vaccines per disease.

Key product gaps remain: certain diseases unaddressed

The 20 companies analysed have no vaccines in clinical development for parasitic neglected tropical diseases, which indicates that it will take considerable time before these diseases can be prevented or treated with vaccines, as appropriate. Small market sizes may continue to form a limitation and to disincentivize the profit-driven pharmaceutical industry when it comes to investing in these R&D projects. In addition, depending on the price of any new vaccine, current treatment, albeit far from ideal, may be more cost-effective than immunisation.

Nevertheless, it is important that pharmaceutical companies continue to invest in vaccine development. Companies' technological expertise and know-how may offer innovative solutions to such issues, or maximize the efficacy and safety of vaccines that target diseases such as HIV/AIDS, influenza, malaria, and parasitic neglected tropical diseases. R&D partnerships with non-profit organizations active in this space could offer an opportunity for pharmaceutical companies to share risks and combine knowledge and expertise.

Access provisions: not widespread

A number of vaccine R&D projects (12) are clearly supported by access provisions designed to make the vaccines more affordable, and/or to make vaccine supplies more reliable, once the development phase is over. This includes not-for-profit prices for a potential first-ever vaccine for malaria (see Table 4), and a large-scale manufacturing commitment for a potential first-ever vaccine for dengue. For the majority of vaccine projects, it is not clear whether access provisions are truly lacking, or whether low transparency accounts for the gap.

Market access strategies are typically not organized before vaccines have reached at least phase III clinical trials. An intent to develop project specific access strategies was provided for 14 projects, mainly in discovery and pre-clinical development phases.

It is important that companies develop a profile of suitability for each product in development as soon as possible in the research phase. The authors of this paper would also encourage companies and other research partners to compare these profiles and other suitability data on their respective, relevant projects. Such comparisons would enable all parties to identify technology and invention hurdles, whether Target Product Profiles are being developed, and whether suitable access provisions are being put in place.

The vaccine market and the case for access provisions

As reported in the 2014 Access to Medicine Index, there is less evidence of access provisions for vaccines than for all products in development (17% vs. 39%), most of which are medicines.[36] In contrast with the medicine market, the vaccine market is concentrated among a few companies[10–12]; vaccines are sold mainly in large volumes, especially if incorporated into national immunisation schemes; and a limited number of manufacturers have the technical expertise for guaranteeing sufficient supply and lowering prices. For newer vaccines, these market circumstances combined can enable single vaccines to generate large revenues, particularly where few other vaccines have similar characteristics.

Without access provisions, traditional pharmaceutical business models can lead to a number of access barriers for patients in developing countries: most acutely, high prices can prevent governments from being able to incorporate certain vaccines into national immunisation programmes. Equitable pricing is an important approach for ensuring accessibility in low income countries and for lower middle income countries. Furthermore, considering the often complicated and lengthy production processes for vaccines, it is critical that companies systematically take measures to ensure supply is consistently sufficient to meet demand. By putting implementation strategies in place before products gain market approval, companies can accelerate the roll-out of new vaccines in developing countries and prevent unaffordability and vaccine shortages.

Access provisions for first-ever vaccines

Competition between multiple, relatively similar vaccines will have a natural downward pressure on prices and thereby increase accessibility. Where a vaccine in development will be the first-ever for the targeted disease, this downward pressure on prices will not be present. Therefore, it is concerning that access provisions were almost exclusively linked only to diseases for which vaccines are already available (see Figure 2). Without access provisions for new, high-priority vaccines, many patients in developing countries will likely continue to face delays in vaccine accessibility due to a lack of affordability or limited supplies, and hence they will face a continued high risk of diseases such as malaria, HIV/AIDS, tuberculosis and dengue infection.

It must not be seen as a given that companies or others will put access provisions in place simply because the disease in question has high prevalence in low- or

middle-income countries. Transparent and concrete guarantees (for example, concerning demand) from funders and other market shapers, are also important for building the confidence needed by manufacturers before they will invest in supply.

Measures to promote affordability

As more vaccines become available, pooled procurement systems and national immunisation programmes can come under additional pressure. Many countries are still struggling to implement the GVAP.[27] Addition of new vaccines to the WHO's Expanded Programme for Immunization will further increase the cost of vaccinating a child. As important new, lifesaving vaccines are introduced, pooled procurement systems, such as Gavi and PAHO, and countries that purchase vaccines bilaterally may face large financing gaps.

Currently, there is already significant pressure on pharmaceutical companies to improve the affordability of vaccines, in particular pneumococcal and rotavirus vaccines. Médecins Sans Frontières has directly challenged pneumococcal vaccine producers GSK and Pfizer to lower their prices for low-income countries.[30] The Clinton Foundation negotiated a price reduction of US$1 billion in total for low-income countries and is providing support to accelerate the implementation of pneumococcal, rotavirus, meningitis and other vaccines.[67]

However, lower middle income country governments that are non-eligible or are transitioning from eligibility for Gavi support may not be able to afford new vaccines at all. Countries with a relatively higher Gross National Income (GNI) per capita, but with large socio-economic inequalities, may face hurdles to purchase sufficient volume for their entire populations if inequality within the country is not taken into account in price negotiations. New high-priority vaccines may only be available through the private sector, if at all. Companies can act to prevent this future crisis by exploring and implementing access strategies further to enable rapid rolling out of large volumes of upcoming high priority vaccines across lower-middle and middle-income countries.

The recent Ebola outbreak reminds us that the pharmaceutical industry can respond to an acute public health crisis.[68] While, it is important to prioritize vaccines to need, companies are apparently deterred by the lack of sufficient incentives for engagement. Pooled procurement systems can influence the development of needs-based vaccines, for example by giving advanced market commitments to provide companies with assurances of large sales volumes once a successful vaccine is approved. Gavi negotiated an advance market commitment for Pfizer's pneumococcal vaccine, which allowed its fast introduction in low income countries following initial approval. Currently, the vaccine is adapted into a multi-dose formulation to overcome supply chain issues associated with low income countries. This is a good example of how a market-pull mechanism can be used to negotiate discounted prices, overcome supply chain issues and stimulate needs-based product development.

Conclusion

Promise in the pipeline

Based on this analysis of vaccine pipelines, the research-based pharmaceutical industry is addressing high-burden diseases through R&D targeting new and improved vaccines. In total, 70 vaccine R&D projects were identified, and it is clear that major milestones in immunology are approaching: the first-ever vaccine for malaria recently received approval and a first-ever vaccine for dengue is close to the end of the pipeline. It is also very encouraging to see that major causes of child deaths are being targeted, notably diarrhoea and pneumonia, and that improved vaccines may soon be available.

Key product gaps remain

Key product gaps remain, particularly for tropical diseases. Considering the consolidated nature of the vaccine industry, there are only a handful of pharmaceutical companies with the expertise and know-how to continue and expand research into vaccines. With cooperation, support and incentives from other vaccine stakeholders, we urge those companies to begin investigating vaccines for this group of diseases. We also seek to highlight the need for specific product attributes to be adapted to suit the needs of low- and middle-income countries, notably the need for thermo-stable versions of existing vaccines.

Role for access provisions

Once successful vaccine candidates leave pipelines, they need to quickly be made as accessible as possible in low- and middle-income countries, which carry a major portion of global disease burdens. There is a risk that new vaccines will put additional pressure on funding for immunisation systems, or that vaccine shortages will occur if supply and demand are not adequately aligned. The pharmaceutical industry has a key role to play in ensuring rapid access to new vaccines in low- and middle-income countries: including putting in place measures to ensure future vaccines are affordable, and that supplies are sufficient, as early as possible in the R&D phase, preferably by phase II. Funders and other market shapers also play a key role by providing the transparent, concrete guarantees concerning vaccine demand that manufacturers need before they can invest in development and scale up of production.

A number of vaccine R&D projects (12 out of 70) are clearly supported by such measures, called access provisions. This includes not-for-profit prices for a first-ever vaccine for malaria, and a large-scale manufacturing commitment for a potential first-ever vaccine for dengue.

Are access provisions being systematically applied?

The early use of access provisions does not appear to be consistent or widespread, which raises questions about how soon promising new vaccines will be available to people living in low- and middle-income countries. For the majority of vaccine projects, it is not clear whether access provisions are truly lacking, or whether low transparency accounts for the gap. To help payers and procurers to plan ahead, companies are strongly encouraged to be transparent about their access strate-

gies. Further study is needed to fully illuminate how companies are working to facilitate rapid access to new vaccines.

Looking ahead

Knowing that immunisation is a cornerstone of public health, and that effective vaccines are going to be in substantial demand, there must be greater international support for stocking and accelerating pipelines. Specifically, we need clear incentives for companies to invest in vaccine pipelines, to put access provisions in place early in the R&D process and to develop vaccine candidates with poor, rural and isolated populations in mind.

As the WHO will continue to assess progress of the vaccination coverage targets set out in GVAP, the world will be looking for pharmaceutical companies and other vaccine manufacturers to continue to develop the next generation of vaccines and to produce and supply these vaccines to the countries in need. Reporting on how they fulfil this role will encourage support from public donors and provide an incentive to companies to take action.

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Appendix

About the 2014 Access to Medicine Index

This findings in this report are based on the analysis of data submitted by pharmaceutical companies to the 2014 Access to Medicine Index. The Access to Medicine Index independently ranks 20 of the world's largest pharmaceutical companies by revenue on their efforts to improve access to medicine for people living in developing countries. Funded by the Bill & Melinda Gates Foundation and the UK and Dutch governments, the Index has been published every two years since 2008.

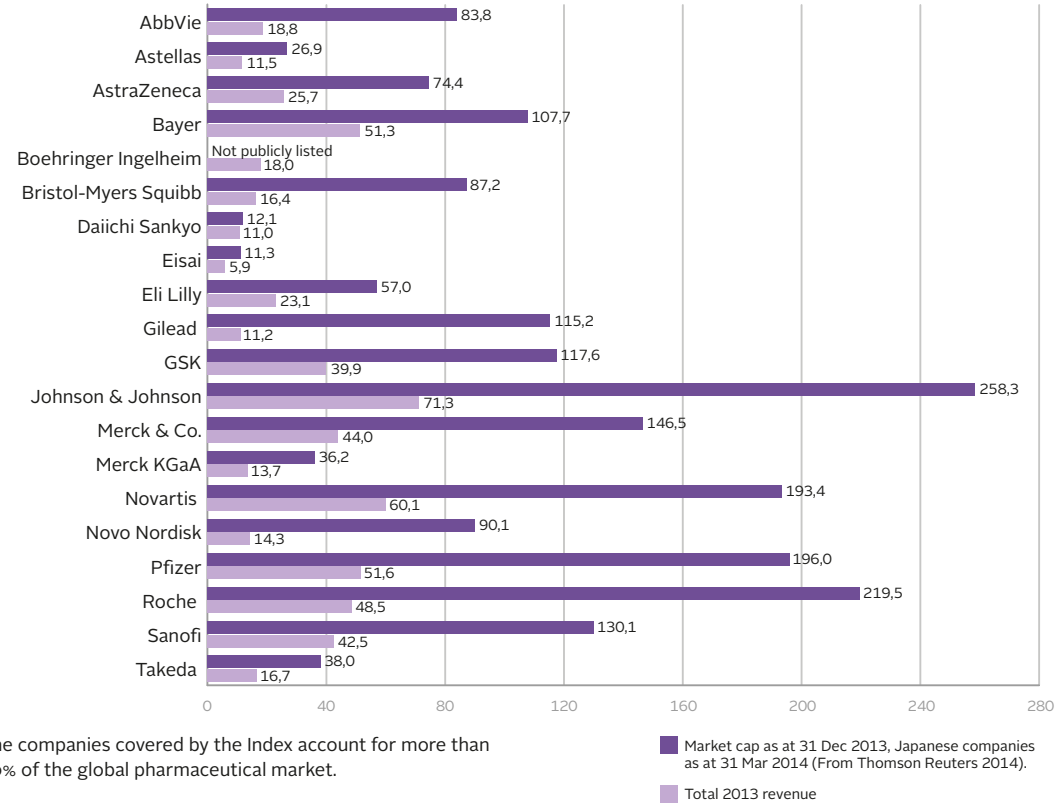
By publicly recognising companies' access-related policies and practices, the Index raises awareness of relevant issues within pharmaceutical companies and provides them with a transparent means of assessing, monitoring and improving their own performances as well as their public and investment profiles. Consistent iterations of the Index highlight industry trends and provide a basis for multi-stakeholder dialogue and solution building.

The Access to Medicine Index uses a weighted analytical framework to consistently capture and compare data from the top 20 research-based pharmaceutical companies across a set of countries, diseases and product types. For each successive Index, the Index research team works with independent representatives of relevant stakeholder groups to refine this framework, to confirm the robustness and usefulness of our analysis, and align it with developments in the access-to-medicine landscape and pharmaceutical industry. The framework is constructed along seven areas of focus, which cover the range of company business activities that experts consider most relevant to access to medicine. Within each area, the Index assesses four aspects of company action: commitment, transparency, performance and innovation.

Analysis scopes for the 2014 Access to Medicine Index

Company scope

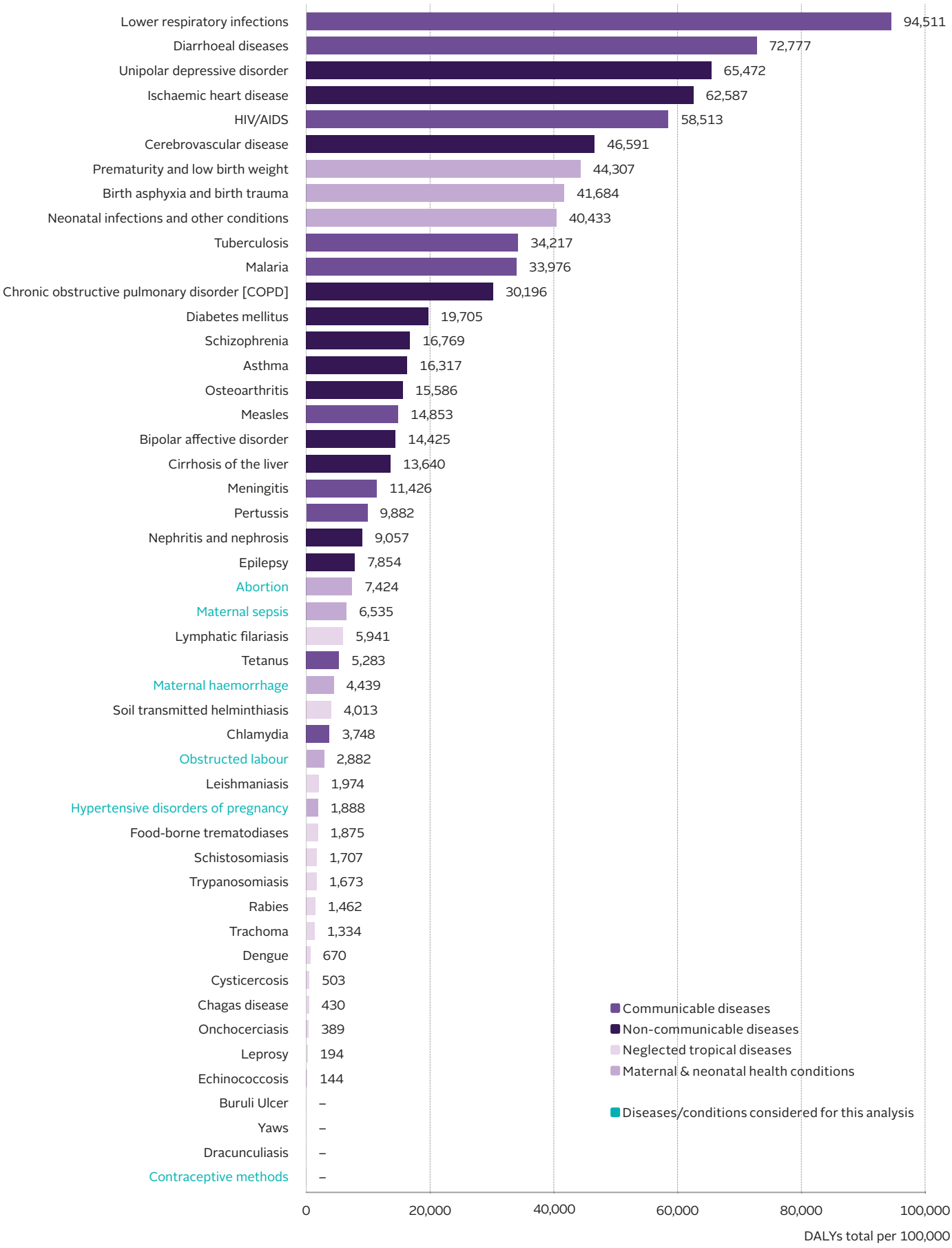
Figure 3: **2014 Index company scope**



The companies covered by the Index account for more than 50% of the global pharmaceutical market.

Disease scope

Figure 4: **DALYs of diseases in the 2014 Access to Medicine Index**



Country scope

Table 7: **List of countries included in the 2014 Access to Medicine Index – 106 countries**

Country	Classification
East Asia & Pacific	
Cambodia	LIC*
China	MHDC
Fiji	MHDC
Indonesia	LMIC
Kiribati	LMIC
Korea, Dem. Rep.	LIC
Lao PDR	LMIC*
Micronesia, Fed. Sts.	LMIC
Mongolia	LMIC
Myanmar	LIC*
Papua New Guinea	LMIC
Philippines	LMIC
Samoa	LMIC*
Solomon Islands	LMIC*
Thailand	MHDC
Timor-Leste	LMIC
Tonga	MHDC
Tuvalu	LDC
Vanuatu	LMIC*
Vietnam	LMIC
Europe & Central Asia	
Armenia	LMIC
Georgia	LMIC
Kosovo	LMIC
Kyrgyz Rep.	LIC
Moldova	LMIC
Tajikistan	LIC
Turkmenistan	MHDC
Ukraine	LMIC
Uzbekistan	LMIC
Latin America & Caribbean	
Belize	MHDC
Bolivia	LMIC
Brazil	HiHDI
Colombia	HiHDI
Dominican Rep.	MHDC
Ecuador	HiHDI
El Salvador	LMIC
Guatemala	LMIC
Guyana	LMIC
Haiti	LIC*
Honduras	LMIC
Nicaragua	LMIC
Paraguay	LMIC
Suriname	MHDC
Venezuela, RB	HiHDI
Middle East & North Africa	
Djibouti	LMIC*
Egypt, Arab Rep.	LMIC
Iraq	MHDC
Jordan	MHDC
Morocco	LMIC
Syrian Arab Rep.	LMIC
West Bank and Gaza	LMIC
Yemen, Rep.	LMIC
South Asia	
Afghanistan	LIC
Bangladesh	LIC*
Bhutan	LMIC
India	LMIC
Maldives	MHDC
Nepal	LIC*
Pakistan	LMIC
Sri Lanka	LMIC
Sub-Saharan Africa	
Angola	LHDC*
Benin	LIC*
Botswana	MHDC
Burkina Faso	LIC*
Burundi	LIC*
Cameroon	LMIC
Cape Verde	LMIC
Central African Rep.	LIC*
Chad	LIC*
Comoros	LIC
Congo, Dem. Rep.	LIC*
Congo, Rep.	LMIC
Côte d'Ivoire	LMIC
Equatorial Guinea	MHDC
Eritrea	LIC
Ethiopia	LIC
Gabon	MHDC
Gambia, The	LIC*
Ghana	LMIC
Guinea	LIC*
Guinea-Bissau	LIC*
Kenya	LIC
Lesotho	LMIC*
Liberia	LIC
Madagascar	LIC*
Malawi	LIC*
Mali	LIC*
Mauritania	LMIC*
Mozambique	LIC*
Namibia	MHDC
Niger	LIC*
Nigeria	LMIC
Rwanda	LIC*
São Tomé and Principe	LMIC
Senegal	LMIC*
Sierra Leone	LIC*
Somalia	LIC
South Africa	MHDC
South Sudan	LIC
Sudan	LMIC
Swaziland	LMIC
Tanzania	LIC*
Togo	LIC*
Uganda	LIC*
Zambia	LMIC*
Zimbabwe	LIC
Countries removed since 2012 Index	
Algeria	HHDC
Marshall Islands	UMIC

LIC: Low-income Country
World Bank income classification

LMIC: Lower-middle-income Country
World Bank income classification

LDC: Least Developed Country
UN Human Development Index

LHDC: Low Human Development Country
UN Human Development Index

MHDC: Medium Human Development Country
UN Human Development Index

HiHDI: High Human Development Country with high inequality
UN Inequality-Adjusted Human Development Index

* LDC with WTO membership

5 Countries newly included countries in the 2014 Index scope

2 Countries removed from the Index scope

Product scope

The product type scope for Index 2014 remains necessarily broad to capture the wide-ranging product types available to support prevention, diagnosis and treatment of Index Diseases in the Index countries.

It draws closely from the definitions provided by the G-Finder 2012 Neglected Disease Research and Development: A Five Year Review,[5] and remains unchanged from the 2012 and 2010 Indices.

Medicines
All innovative and adaptive medicines, branded generics and generic medicines used to directly treat the target pathogen or disease process, regardless of formulation, are included. Medicines used only for symptomatic relief are not included.

Microbicides
These include topical microbicides intended to prevent HIV.

Therapeutic vaccines
This covers vaccines intended to treat infection.

Preventive vaccines
This covers vaccines intended to prevent infection.

Diagnostics
Diagnostic tests designed for use in resource-limited settings (cheaper, faster, more reliable, greater ease of use in the field) are included.

Vector control products
These include pesticides, biological control compounds and vaccines targeting animal reservoirs. Only chemical pesticides intended for global public health use and which specifically aim to inhibit and kill vectors that transmit diseases relevant to the Index are included. Likewise, only biological control interventions that specifically aim to kill or control vectors that transmit Index-relevant diseases are included. Only veterinary vaccines specifically designed to prevent animal-to-human transmission of diseases covered by the Index are included.

Platform technologies
Only those products directed specifically at meeting the needs of countries covered by the Index are included. These comprise general diagnostic platforms, adjuvants and immunomodulators, and delivery technologies and devices.

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Funders
The Access to Medicine Foundation is independently funded by the Bill & Melinda Gates Foundation, the UK Department for International Development (DFID), and the Dutch Ministry of Foreign Affairs.

Bill & Melinda Gates foundation

Department for International Development

Ministry of Foreign Affairs of the Netherlands