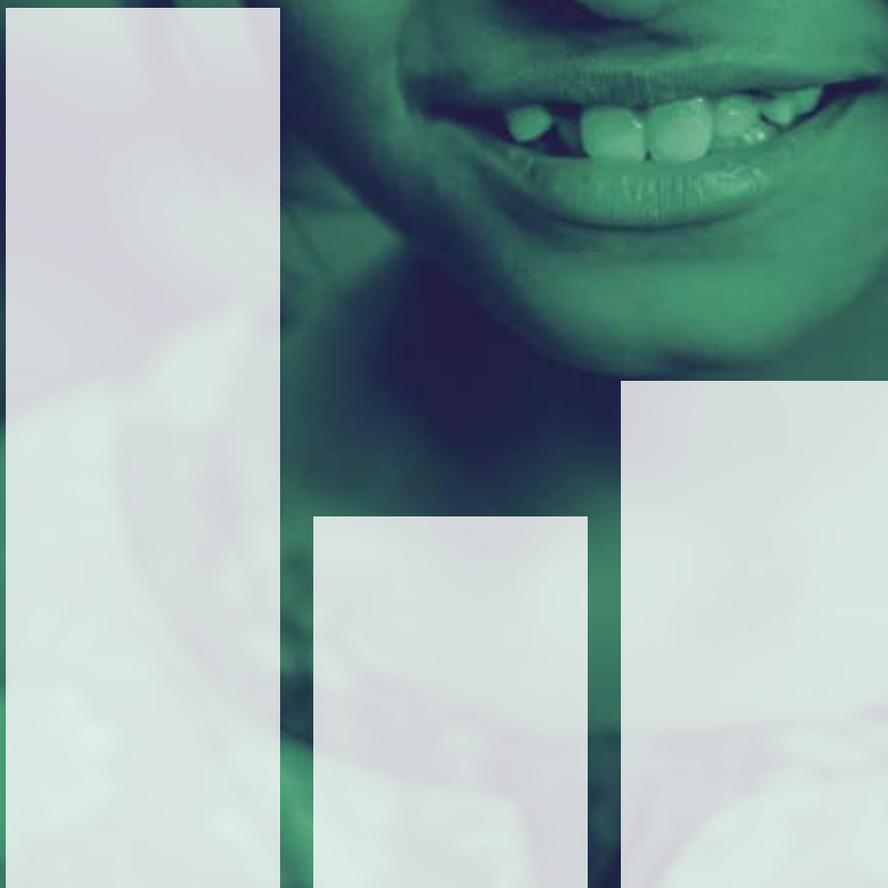


Access to Vaccines Index 2017

How vaccine companies are responding to calls
for greater immunisation coverage



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ACCESS TO MEDICINE FOUNDATION

The Access to Medicine Foundation is a non-profit organisation. It aims to advance access to medicine in low- and middle-income countries by stimulating and guiding the pharmaceutical industry to play a greater role in improving access to medicine and vaccines. For ten years, the Foundation has been building consensus on the role for the pharmaceutical industry in improving access to medicine and vaccines. It published its first benchmark of industry activity in this area in 2008, in the first Access to Medicine Index, now in its fifth iteration. In 2017, it published the first Access to Vaccines Index and is developing the first Antimicrobial Resistance Benchmark.

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FUNDERS

This report was made possible through financial support from the Dutch National Postcode Lottery. The Foundation is grateful for this support.



Access to Vaccines Index 2017

ACCESS TO MEDICINE FOUNDATION

March 2017

ACKNOWLEDGEMENTS

The 2017 Access to Vaccines Index has been made possible through collaboration with experts and specialists from across the access-to-vaccines space.¹ The Foundation is grateful for their time and expertise, and would like to thank them for providing valuable insights throughout the development of the 2017 Index.

Funders

The Dutch National Postcode Lottery

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¹ This acknowledgement is not intended to imply that the individuals and institutions mentioned above endorse the Access to Vaccines Index analyses or results. Decisions regarding inclusion of all feedback were ultimately made by the Access to Medicine Foundation.

Foreword



Vaccines are a cornerstone of modern health systems. A few shots can protect a child for life against diseases such as diphtheria and measles. While many of us take vaccines for granted, every year, nearly two million children under five die from vaccine-preventable diseases. Most unvaccinated children live in low- and middle-income countries, where health systems are often under pressure.

Many parties share responsibility for ensuring everyone can benefit from vaccines. Governments and many others are dedicated to boosting immunisation coverage or reshaping vaccine markets, to ensure safe and effective vaccines can be made available and affordable everywhere.

The role for companies

Vaccine manufacturers, the innovators and producers of vaccines, stand early in the vaccine value chain. The decisions they make to improve access to vaccines can help safeguard the health, well-being and economic potential of many millions of people. Take the decisions to develop pneumococcal, malaria, dengue and HIV vaccines. In all four cases, the technical hurdles have been immense. The benefits, when such projects prove successful, are profound. The Access to Vaccines Index has now mapped, for the first time, what vaccine companies are doing to improve access to vaccines, and what prompts them to take action.

The drivers behind company action

The Index finds that companies are responding to global calls to increase immunisation coverage, and to mechanisms put in place to ensure vaccine markets are viable long-term. We found a high level of diversity in how companies approach access. Yet overall, their actions and strategies are largely

driven by the reliability and sustainability of vaccine markets, and by political will. At least in part, this is because vaccine development and production are lengthy, complex and expensive.

Mapping the path ahead

Achieving access to vaccines is possible. Look at the progress made toward polio eradication and measles elimination, and the R&D and regulatory response to the Ebola epidemic. Vaccine companies need to be at the table as governments and others work to build resilient health systems. Several companies are already in the right conversations and poised to do something about investing in remaining vaccine R&D gaps, addressing affordability, and ensuring supply meets increasing global demand of vaccines. The map will help define next steps and chart progress. For those looking to deepen company engagement in vaccines access, the Index shows that the formula of commitment-making, market-shaping and incentivising collaborative action really works, especially as the world faces challenges to global health security.

A handwritten signature in blue ink that reads "Jayasree K. Iyer".

Jayasree K. Iyer
Executive Director
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About this report

Vaccines are one of the most powerful and cost-effective health interventions available. Yet WHO estimates that 19.4 million infants are missing out on basic vaccines. This report reveals the first landscape of industry activity to improve immunisation coverage.

Framework of analysis

The Access to Vaccines Index analyses eight key vaccine companies: the four largest companies by revenue (GSK, Merck & Co., Inc., Pfizer, Sanofi); one of the largest vaccine companies by sales volume (Serum Institute of India); and three companies with significant potential for improving access to vaccines (Daiichi Sankyo, Johnson & Johnson and Takeda).

The Index uses 13 metrics to measure company performance relating to 69 vaccine-preventable diseases in 107 countries in three areas of behaviour: Research & Development; Pricing & Registration; and Manufacturing & Supply. The Index metrics reflect stakeholders' views on how vaccine companies can contribute to global immunisation targets.

The first baseline for companies

The need to increase access to vaccines is being tackled at the global level. In the Sustainable Development Goals and the WHO's Global Vaccine Action Plan, targets have been set for driving up immunisation rates. Progress is being made, but there is more to be done.

Within this dynamic landscape, the Access to Vaccines Index provides an initial baseline of company activity on access to vaccines. It highlights where companies are taking action, as well as where action is still required. Companies and other stakeholders can use this information to inform priorities and strategies, and learn where new incentives or stronger mechanisms would spur companies towards greater engagement in access issues.

SECTIONS IN THIS REPORT The Index findings are presented at various levels in the following order.

Industry landscape and Key Findings

This section summarises how the companies in scope have performed in the three Research Areas, and looks ahead to where companies can do more. It presents an industry-level vaccine portfolio and pipeline analysis and key findings.

Cross-cutting analyses

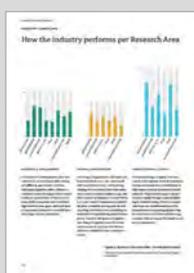
The cross-cutting analyses draw on findings from the Index's three Research Areas to examine industry responses to two current vaccine-access challenges: developing and deploying the first malaria and dengue vaccines; and responding to emerging infectious diseases.

Three Research Area analyses

The Index includes in-depth analyses of company performances in three Research Areas: Research & Development, Pricing & Registration and Manufacturing & Supply. All eight companies were evaluated in Research & Development; six were also evaluated in Pricing & Registration, and in Manufacturing & Supply. (Daiichi Sankyo and Takeda are the exceptions).

Company report cards

The 2017 Access to Vaccines Index includes eight company report cards, which each provide a detailed overview of how one company is approaching access to vaccines. Each report card includes overviews of the company's portfolio and pipeline.



INTRODUCTION

Mapping the landscape: how company behaviour influences immunisation coverage

Vaccines are one of the most successful and cost-effective ways to protect billions of people from disease. Through herd immunity, vaccines can even protect those who are not vaccinated. Vaccines have greatly reduced disease, disability, death and inequity globally, saving the lives of up to three million children each year. Immunisation has eradicated smallpox, and international stakeholders are working to eradicate polio and eliminate measles and rubella. The world's population stands to benefit from vaccines that do not yet exist, for diseases and pathogens such as HIV/AIDS and Group B streptococcus.^{1,2}

Although global immunisation coverage is increasing, nearly one in five children in 2015 did not receive basic life-saving vaccines that the World Health Organization (WHO) recommends for routine immunisation. The reasons for this are varied, including weak health systems and supply chains, insufficient vaccine supply, financing challenges, and community acceptance of vaccines. For

newer vaccines, such as for pneumococcal disease (conjugate vaccines) and rotavirus, coverage is even lower (see figure 1): affordability and production capacity are among the key issues here. The impact of these missed immunisation opportunities is profound: almost one third of deaths of children under five years – nearly two million children – are vaccine-preventable.^{2,3,4}

A global plan for action

The Global Vaccine Action Plan⁵ and Sustainable Development Goals⁶ set out clear targets to improve access to vaccines worldwide. Achieving these targets requires a coordinated framework of multiple stakeholders, including governments, multilateral organisations, purchasers, funders, vaccine developers and manufacturers. This is particularly important given the generally high level of consolidation on both the production and purchasing sides of the vaccine market (although markets for specific vaccines have different characteristics). A careful balance is required

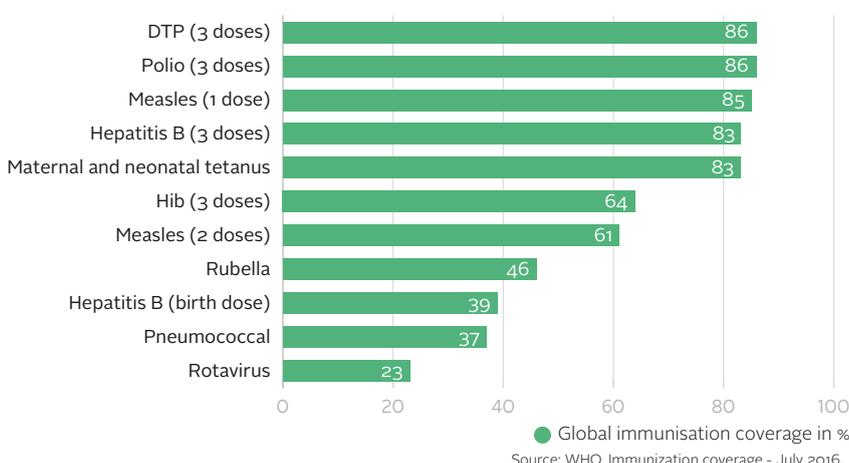
between both demand and supply, and cost and value.⁷

Balancing supply and demand

On the demand side, vaccines for routine immunisation are generally purchased by governments or, for some low- and middle-income countries, through pooled-procurement systems aiming to lower prices. There are three main multilateral organisations involved in these systems: the United Nations Children's Fund (UNICEF) and the Pan American Health Organization (PAHO) Revolving Fund procure vaccines on behalf of countries, while Gavi, the Vaccine Alliance, provides funding for immunisation in the world's poorest countries and plays a market-shaping role.^{8,9}

On the supply side, five large research-based multinational corporations have accounted for around 80% of global vaccine revenues in recent years. Following divestments and acquisitions, the "big four" remain: GSK (which acquired Novartis' vaccines business in 2015), Merck & Co., Inc.,^a Pfizer and Sanofi. There is also a growing number of private and public vaccine manufacturers based in emerging markets. Known as developing country vaccine manufacturers, they focus on manufacturing traditional, lower-cost vaccines. While these companies' revenues make up a smaller proportion of global sales, their combined supply volumes are significant (for example, contributing around 50% of doses supplied to UNICEF).¹⁰

Figure 1. Global coverage of older vaccines exceeds 80% - for newer vaccines, coverage remains relatively low



a Merck & Co., Inc. is known as MSD outside the US and Canada.



An infant is vaccinated against polio following the introduction of Sanofi's inactivated polio vaccine in Nepal.



The nation-wide distribution of polio vaccines is carefully coordinated by government staff and volunteers in the Democratic Republic of Congo.

Vaccine market dynamics

Overall, the global vaccine market is growing: between 2000 and 2014, it expanded from USD 6 bn to USD 33 bn. Sales to high-income countries represent around 65% of the total value of this market, upper middle-income countries 23%, lower middle-income countries 8%, and low-income countries 4%. The value of UNICEF vaccine procurement doubled between 2010 and 2014 to USD 1.5 bn. As national immunisation programmes expand – both boosting coverage for older vaccines and introducing new vaccines – this presents new challenges for ensuring access. This is particularly significant for countries with growing incomes that are transitioning out of Gavi support, and that increasingly finance vaccines through national government spending.¹¹

Within this context, vaccine companies have a key contribution to improving access to vaccines. Their R&D expertise and position at the start of the innovation value chain, their role in setting vaccine prices, and their management of vaccine supply planning and production make them integral to the successful development and effective supply of vaccines in the market. Due to high failure rates, vaccine development, production and access is very demand-driven: other global health stakeholders can support mechanisms to improve access.

Key examples of push and pull incentives and achievements include:

- **The Meningitis Vaccine Project** is a public-private partnership between WHO, PATH, Serum Institute of India and African public health officials to develop an affordable meningitis A vaccine for use in sub-Saharan Africa, in response to a large public health need paired with the low commercial potential of a vaccine. The resulting vaccine (MenAfriVac®) was developed rapidly and at less than one-tenth the average cost of a new vaccine. Since its introduction in 2010, more than 235 million people have been vaccinated.¹² In 2014, a lower dose of the vaccine for children under one year was approved.^b
- **The most advanced malaria vaccine candidate** (RTS,S or Mosquirix®) was also developed through a public-private partnership between GSK and the PATH Malaria Vaccine Initiative, supported by funding from the Bill & Melinda Gates Foundation.¹³ This vaccine, which targets a malaria parasite found mainly in sub-Saharan Africa and with a large burden of disease, is expected to have low commercial potential, much like MenAfriVac®.^c
- **The Advance Market Commitment (AMC) for pneumococcal conjugate vaccines** is a mechanism through which donors commit funds to guarantee the price of vaccines once they have been developed, and in turn, companies commit to providing affordable vaccines in the long term. This incentivises vaccine pro-

ducers to accelerate the development of pneumococcal vaccines that meet the needs of poorer countries, scale up production to meet demand, and encourage uptake through predictable pricing for countries and manufacturers. This AMC is also a test for how AMCs could be applied to other diseases in future.^{14,15} Based on the six supply agreements current in 2015, the pneumococcal AMC's total contracted supply amount totalled 1.46 billion doses through 2024.^{16,d}

Expectations for company behaviour

Given the critical role of vaccine companies in improving access to vaccines, it is necessary to clearly define expectations for the industry that can be translated into firm commitment and concrete action. It is also important to track progress against established goals and targets: data-driven performance management is essential in identifying what is working and why. Responding to this gap, the Access to Vaccines Index is the first publicly available tool for mapping the efforts major vaccine companies are engaging in to increase access to vaccines in low- and middle-income countries. Transparent information sharing about companies' performance will help improve accountability and share good practices: this is particularly useful given the high level of consolidation of the market. It is also the first non-financial incentive for companies to improve access to their vaccines: good practice (relative to peers and/or stakeholder expectations) is reflected and recognised publicly in the Index.

Three Research Areas

To develop the methodology for the Access to Vaccines Index, the Access to Medicine Foundation has applied its multi-stakeholder process to crystallise society's expectations of vaccine companies. It identified key standards for companies in three areas:

- **Research & Development:** companies are expected to address high-priority gaps for new and improved vaccines and delivery technologies, and support these with clear access plans.

- **Pricing & Registration:** companies are expected to ensure their vaccines are affordable for governments with limited resources, balanced with maintaining a sustainable supply.
- **Manufacturing & Supply:** companies are expected to have strong policies and processes in place to ensure sufficient quantities of high-quality vaccines are available.

Using multi-stakeholder consensus, the Foundation developed a set of metrics for tracking how companies meet these expectations. These metrics are set out in the first Access to Vaccines Index Methodology Report, published in December 2015 (also see Appendix).

Developments in 2016-2017

Since then, in a little over a year, numer-

ous important developments have taken place in the access-to-vaccines landscape. For example, the world's first dengue vaccine received marketing approval;¹⁷ the race to develop a Zika vaccine began;¹⁸ the global switch from the trivalent oral polio vaccine to the bivalent version – a critical stage in polio eradication – took place;¹⁹ the global yellow fever vaccine stockpile was twice depleted in response to the Angola-based outbreak;²⁰ the Americas was declared the first region in the world to eliminate measles;²¹ UNICEF secured an unprecedented price reduction for the pentavalent DTPHibHep vaccine, below USD 1 per dose;²² access to the most advanced malaria vaccine candidate moved one step closer, with full funding announced for large-scale implementation pilots;²³ and a new outbreak-focused global vaccine

R&D organisation – the Coalition for Epidemic Preparedness Innovations – was launched with USD 460 mn pooled funding.²⁴

A baseline of company activity

Within this dynamic landscape, the Access to Vaccines Index 2017 provides an initial baseline of company activity on access to vaccines, which is a critical first step for stimulating change and increasing accountability. It highlights good practices, and areas where action is still required. Companies and other stakeholders can use this information to inform priorities and strategies, and to learn where new incentives or stronger mechanisms would spur companies towards greater engagement in access issues. This is the first edition of the Index.

- For more information about R&D for MenAfriVac®, please see the R&D key finding on page 22 and Serum Institute of India's Report Card.
- For more information about RTS,S, please see the cross-cutting analysis on new dengue and malaria vaccines on page 26.
- For more information about the AMC for pneumococcal vaccines, please see the Pricing & Registration chapter on page 46.

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INDUSTRY LANDSCAPE

Vaccine companies take diverse approaches to improving access to vaccines

The Access to Vaccines Index assesses how key vaccine companies act to ensure access to vaccines in low- and middle-income countries. It has evaluated the performance of eight companies in Research & Development, and six in both Pricing & Registration and Manufacturing & Supply.

The companies represent a cross-section of the diverse vaccine industry: they include the four companies with the largest global vaccine revenues, one of the largest vaccine manufacturers by doses sold (based in a developing country) and three mid-sized pharmaceutical companies by revenue with an increasing focus on vaccine R&D. Several com-

panies are growing their vaccines businesses to reach global markets.

The Index has found that the companies approach access to vaccines in differing ways. In general, their approaches are linked to whether their businesses are focused more on developing new vaccines or on marketing existing ones, or on both. For example, some companies have portfolios of highly profitable vaccines and small vaccine pipelines: here, access considerations mainly relate to pricing, registration and supply. Other companies have small portfolios but larger pipelines supported by proportionally high investments in vaccine R&D. For these companies, the access-

to-vaccines focus is on ensuring vaccines in development will meet global health needs and on putting measures in place to ensure that successful vaccines will be accessible.

Of the six companies evaluated across all areas of assessment, GSK performs the best, with Sanofi also performing well across the board. Of the eight companies evaluated in Research & Development, GSK also leads, followed closely by Johnson & Johnson. The other companies demonstrate mixed performances across the different areas evaluated.

WHAT DOES THE INDUSTRY LOOK LIKE?

The companies evaluated in the Access to Vaccines Index have diverse business models, which are reflected in their vaccine pipelines, portfolios, revenues and volume of doses sold (see figures 2 and 3). This section provides context for the following analyses of company performance, and provides insight into the make-up of the vaccine industry more broadly.

The industry is highly consolidated: the “big four” – GSK, Merck & Co., Inc.,^a Pfizer and Sanofi – represent a large proportion (around 80%) of global vaccine revenues. While all companies within this group have very high vac-

cine revenues, there are also important differences between them: GSK and Sanofi have a large number of vaccines in their diverse portfolios, a relatively wide geographic spread^b and larger-than-average pipelines. Merck and Co., Inc. and Pfizer have smaller pipelines and portfolios, and sell fewer doses globally.

Serum Institute of India is also a major player of global public health importance, especially in terms of the number of vaccine doses produced and its wide geographic reach: its lower revenue reflects its high-volume, low-cost model. For Johnson & Johnson, vac-

cines currently represent a smaller part of the business – its revenue is low compared with other companies evaluated – but a promising vaccine pipeline supported by a very high proportion of R&D investments (compared to revenue) indicates an increasing focus on vaccines in the future. Daiichi Sankyo and Takeda are smaller players that are important to the domestic Japanese vaccine market, with growing vaccines businesses. Neither currently markets vaccines in other countries, but the pipelines and R&D investments of both companies show potential and interest in contributing to the global vaccines market.

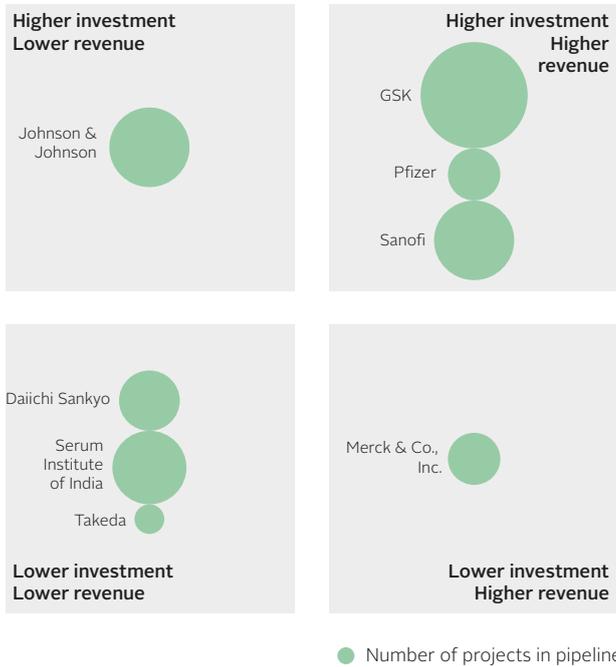
a Merck & Co., Inc. is known as MSD outside the US and Canada.

b In this section, “geographic scope” refers to the proportion of countries in scope of the Index in which the company has filed to register at least one vaccine.

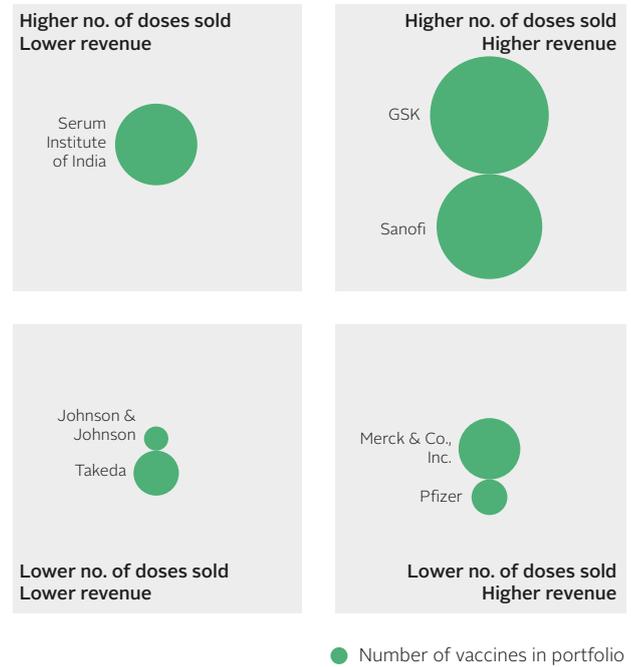
Figure 2. The vaccine industry is highly consolidated; business models are diverse.

The figure compares key characteristics of each company included in the Index scope. The companies evaluated in the Access to Vaccines Index have diverse business models, which are reflected in their vaccine pipelines, portfolios, revenues and number of doses sold globally.

Company vaccine pipelines



Company vaccine portfolios



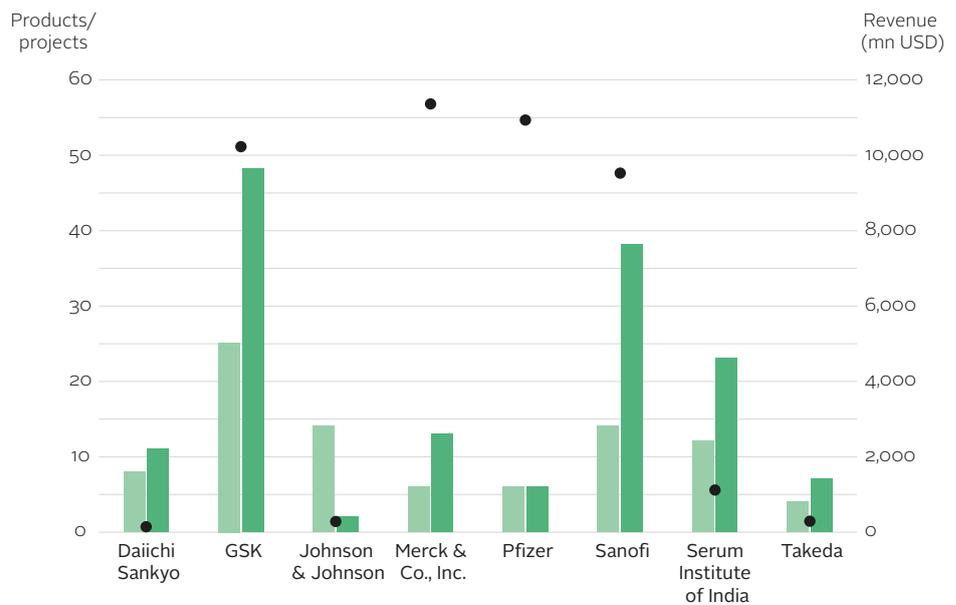
The area of each circle represents each company's number of vaccine R&D projects (left) or vaccines on the market (right). Investment represents vaccine R&D investment in USD for diseases in scope over the 2014 and 2015 fiscal years. No. of doses sold represents the number of vaccine doses sold globally in 2015.

Revenue represents global vaccine revenue in USD over the 2014 and 2015 fiscal years. Serum Institute of India's pipeline is based on publicly available sources. It has additional projects for which the data are confidential. Daiichi Sankyo did not provide data on number of doses sold globally.

Figure 3. Looking beyond revenue: variations in portfolio and pipeline size signal potential for decreasing consolidation.

Four companies account for 80% of global vaccine revenues: GSK, Merck & Co., Inc., Pfizer and Sanofi. Often collectively referred to as the "big four", they vary significantly by portfolio and pipeline size. All four have vaccines on the market that are of significant public health value.

Three of the other four companies in scope have larger pipelines than Merck & Co., Inc. or Pfizer. When their vaccine candidates leave the pipeline, there is potential for significant changes in the vaccine landscape – including increasing competition in key vaccine markets.

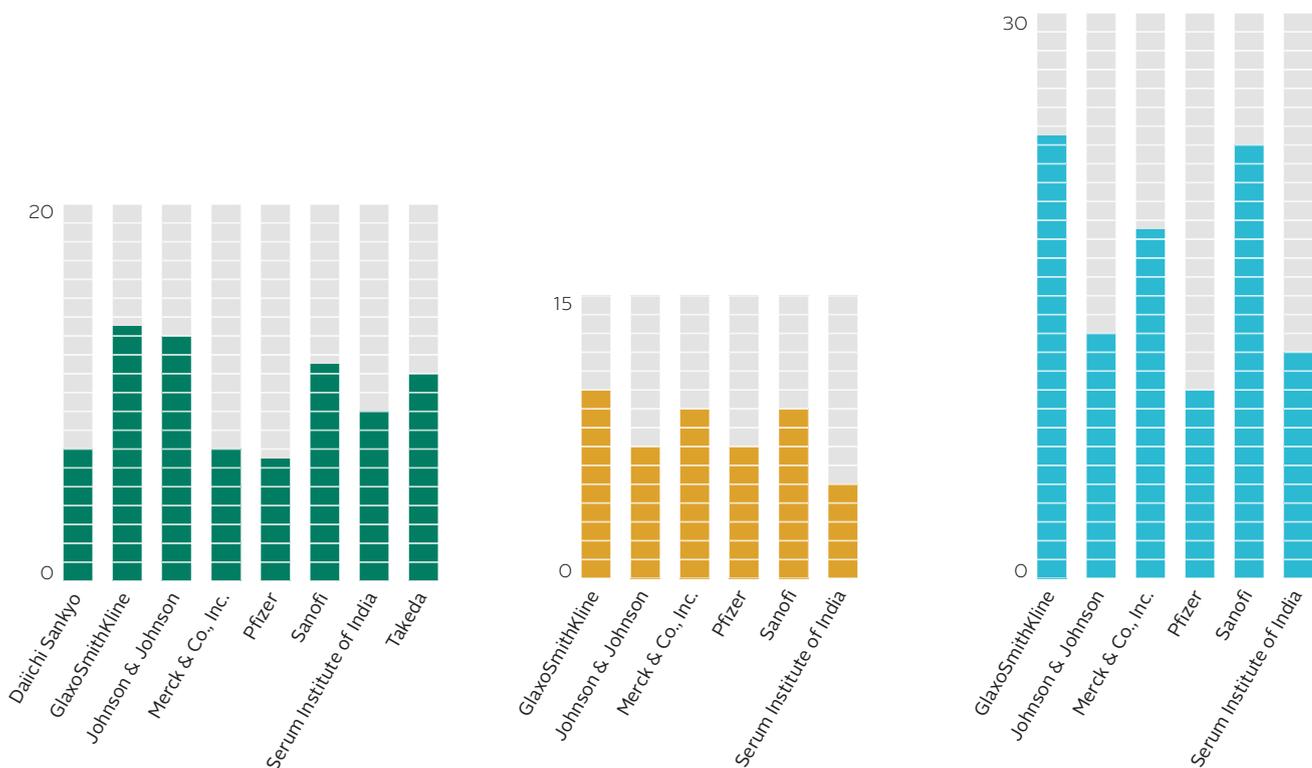


Serum Institute of India's pipeline is based on publicly available sources. It has additional projects for which the data are confidential. Vaccines that were approved during the period of analysis are counted twice: in both the number of projects in the pipeline and in the number of vaccines on the market.

● Number of projects in pipeline
 ● Number of vaccines on the market
 ● Vaccine revenue (2014 + 2015)

INDUSTRY LANDSCAPE

How the industry performs per Research Area



RESEARCH & DEVELOPMENT

In Research & Development, GSK and Johnson & Johnson lead, with strong yet differing approaches. GSK has the largest pipeline, while Johnson & Johnson makes the largest R&D investments as a proportion of vaccine revenue. Both companies aim to address high-need vaccine gaps, and both have access plans in place for over half their late-stage vaccine candidates.

PRICING & REGISTRATION

In Pricing & Registration, GSK leads, followed by Merck & Co., Inc. and Sanofi with equal total scores. GSK’s pricing strategy for vaccines is the most sensitive to each country’s ability to pay, relative to peers’ strategies. GSK and Merck & Co., Inc. lead in transparency, publishing their complete pricing strategies and reporting that they do not prohibit governments from publishing manufacturer prices. Sanofi is the leader in registration, filing to register most of its relevant vaccines in 30-50% of both low- and lower middle-income countries in scope.

MANUFACTURING & SUPPLY

In Manufacturing & Supply, GSK and Sanofi score highest. Both demonstrate strong processes and commitments to help ensure vaccine production meets demand. They further support global vaccine supply through capacity building in manufacturing. The two companies have also implemented vaccine presentations and packaging that help to overcome local access barriers (e.g., vaccines that are easier for health workers to administer).

Figure 4. Access to Vaccines Index - Overall performance

The number of cells represents the maximum possible score. Coloured cells represent points attained.

RESEARCH & DEVELOPMENT

In total, the eight companies evaluated have 89 projects in the pipeline for 35 of the 69 diseases in scope. Many of the 34 unaddressed diseases currently have no vaccines. Six diseases/pathogens receive the most attention: pneumococcal disease (9 projects), HPV and seasonal influenza (6 each), meningococcal disease and RSV (5 each), and dengue (4). Almost one-third of projects target diseases highly prioritised by WHO for vaccine R&D. The 89 projects in the pipeline are relatively evenly split between developing new vaccines on the one hand and adapting existing ones on the other (52% and 48% respectively). Both types of vaccine R&D are critical for facilitating widespread immunisation. Over half of late-stage projects have one or more measures in place to ensure the vaccine's future accessibility. Company investment in vaccine R&D varies, with investments ranging from less than 10% to 253% of a company's global vaccine revenue.

PRICING & REGISTRATION

The six companies evaluated each consider multiple factors when setting vaccine prices, the combination of which is unique to each company and dependent on their portfolio. Across all companies, the most frequently considered factor is whether a country is eligible for Gavi support. This is followed by Gross National Income per capita, which is considered by four companies for at least some low- and middle-income countries. Some companies publish their complete pricing strategies online for all vaccines, yet in general, the transparency of pricing strategies varies. Most companies state that they do not include clauses in government contracts that prevent manufacturer prices being published. Vaccines are not being filed for registration widely: for the 91 vaccines that qualify for analysis, the registration process has begun in less than a quarter of low-income countries and middle-income countries within the scope of the Index.

MANUFACTURING & SUPPLY

The six companies evaluated are taking steps to align supply and demand at a global level, increasing the likelihood that some potential vaccine shortages are being detected, mitigated or prevented. Companies generally implement multiple internal processes to improve alignment between supply and demand; many also make commitments around continuing supply of needed vaccines. Companies are building vaccine manufacturing capacity in some countries in scope: a relatively small number of middle-income countries with established vaccine production capacities. All companies take steps to ensure certain vaccines have packaging, presentations or features intended to help overcome barriers to access on the ground.

Looking ahead in R&D

To ensure the long-term relevance and sustainability of their vaccine businesses, companies must invest sufficient vaccine profits into vaccine R&D. This also entails responding to R&D gaps prioritised by global health stakeholders, designing vaccine characteristics to address specific access barriers, and making clear plans to ensure rapid uptake where needed. While commercial market incentives drive vaccine R&D for some diseases, for others – in particular those that predominantly affect populations in low- and middle-income countries – potential profitability is low: alternative external incentives may be necessary to support this work where traditional incentives are lacking.

Looking ahead in Pricing & Registration

When pricing vaccines, companies need to address affordability systematically – especially for countries that receive no support from Gavi and do not participate in pooled procurement via PAHO or UNICEF. Companies can form and share clear pricing strategies for all low- and middle-income countries. Companies should also enable global information sharing about vaccine prices to promote a more competitive environment, facilitate negotiations and help ensure that prices are fair. There is also a gap in certain countries regarding vaccine registration: companies need to file to register vaccines according to public health need. In turn, governments and procurers must invest sufficiently in national regulatory systems and immunisation programmes in low- and middle-income countries.

Looking ahead in Manufacturing & Supply

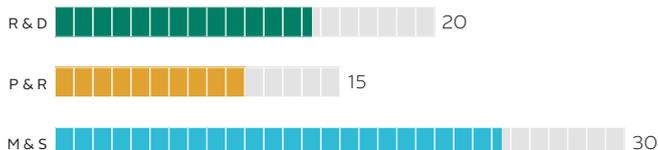
The existence of ongoing vaccine shortages shows that communication and coordination between the industry, procurers and other stakeholders can be further improved. The industry must continue to monitor demand and improve approaches for preventing shortages. This is especially important – nationally and on a global level – where demand suddenly spikes, such as with disease outbreaks. To support access on the ground, companies can also ensure that vaccine presentations pose minimal challenges to local supply chains and health systems. There is further progress to be made in this area: partnerships with stakeholders who understand local needs and can put incentives in place for private-sector involvement may be useful here.

INDUSTRY LANDSCAPE

How the companies perform

The Index has found that the eight companies approach access to vaccines in differing ways. In general, this is linked to whether they focus more on developing new vaccines or on marketing existing ones. This section shows how individual companies have performed across the three areas of assessment. Daiichi Sankyo and Takeda were evaluated in Research & Development only. The number of cells represents the maximum possible score. Coloured cells represent points attained.

GSK



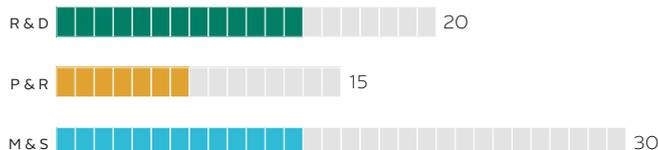
Research & Development: GSK is a leader in this area, with the largest vaccine pipeline that targets relevant diseases (25 projects). It has at least one access provision in place for around half of its late-stage R&D projects, and is one of two companies developing vaccine packaging and delivery technologies to overcome barriers to access.

Pricing & Registration: It also leads in this area, with the most structured vaccine pricing strategy. However, it has filed to register only some vaccines in low-income countries.

Manufacturing & Supply: Again, GSK leads. It has strategies to support access at a high level, strong internal supply-management processes and vaccine presentations that help overcome access barriers on the ground.

GSK is one of the largest vaccine companies in scope by revenue, portfolio size, pipeline size and geographic scope. For several key vaccines, it is one of a small number of producers, including for rotavirus (Rotarix®) and pneumococcal disease (Synflorix®). GSK performs very well overall.

JOHNSON & JOHNSON



Research & Development: Johnson & Johnson is a leader in this area, making the largest investments in vaccine R&D and with a relatively large pipeline of 14 vaccine projects. It has at least one access provision in place for three out of its four late-stage projects.

Pricing and Registration: The company has filed to register vaccines in some low-income and lower middle-income countries. It has published only a very general commitment to affordable vaccine pricing.

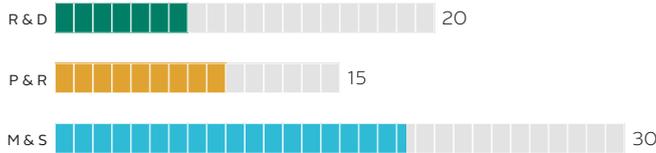
Manufacturing & Supply: Its performance is below average: while it has internal processes to align supply and demand, it is less active than peers in building manufacturing capacity, and has not implemented presentations or packaging to help overcome local access barriers for its two marketed vaccines.

Johnson & Johnson currently has relatively low vaccine revenue, reflecting its small portfolio size, volume of doses sold and geographic scope. However, its pipeline (including a HIV vaccine candidate) and R&D investments indicate a growing focus on vaccines. Overall, its performance is in the average range compared to other companies.

INDUSTRY LANDSCAPE

How the companies perform

MERCK & CO., INC.



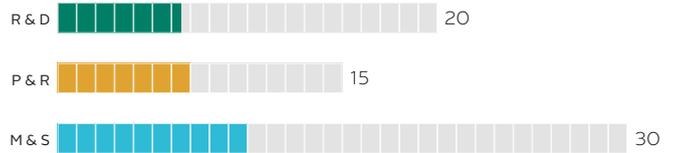
Research & Development: The company performs below average, investing a relatively small amount into vaccine R&D as a proportion of vaccine revenue, and with a relatively small pipeline (six projects). Merck & Co., Inc. has at least one access provision in place for two out of its four late-stage projects.

Pricing & Registration: Merck & Co., Inc. publishes its complete vaccine pricing strategy. It has filed to register some vaccines in only some low-income countries.

Manufacturing & Supply: Its performance is above average, with the strongest commitment to maintaining supply of vaccines as long as they are needed. It has implemented presentations and packaging to overcome local barriers for several vaccines, with a focus on cold-chain requirements.

Merck & Co., Inc. has one of the largest vaccine revenues, above-average geographic scope and a medium-sized portfolio, including key vaccines with few producers, such as for HPV (Gardasil/Gardasil 9®) and rotavirus (Rotateq®). It focuses less on vaccine R&D than peers in scope. Overall, it falls in the middle of the pack of companies.

PFIZER



Research & Development: The company performs below average, with a relatively small vaccine pipeline (six projects) and relatively low R&D investment as a proportion of vaccine revenue. Pfizer has at least one access provision in place for one of its four late-stage projects.

Pricing & Registration: Although Pfizer newly publishes its tiered pricing strategy, it is the only company that states it supports the use of price confidentiality provisions.

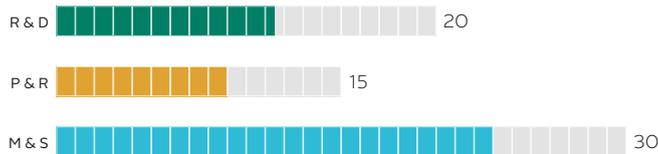
Manufacturing & Supply: Pfizer is lagging in several aspects measured in this area. For example, it makes no commitment to notify stakeholders in advance when reducing or ceasing supply of vaccines.

Pfizer has one of the largest vaccine revenues, a small portfolio and pipeline, and on-average geographic scope. It is the largest PCV producer, supplying 70% of the global market with Prevenar 13®. Overall, it falls short in multiple areas compared to peers.

INDUSTRY LANDSCAPE

How the companies perform

SANOFI



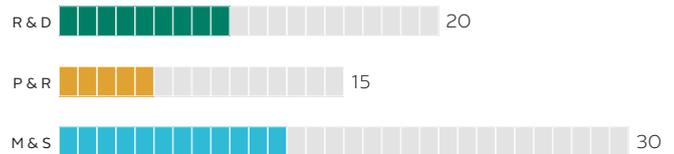
Research & Development: Sanofi performs above average, with a relatively large vaccine pipeline (14 projects). It has at least one access provision in place for 60% of its late-stage vaccine candidates, and is one of two companies developing vaccine packaging and delivery technologies to overcome barriers to access.

Pricing & Registration: Sanofi is the leader in registration, with the majority of its relevant vaccines filed to be registered in 30-50% of countries in scope. It makes a general commitment to ensuring the prices of its vaccines are sustainable and equitable.

Manufacturing & Supply: Sanofi’s performance is strong in all areas: it demonstrates strong commitments and processes to align supply and demand, and is a leader in supporting local logistics needs.

Sanofi’s vaccine pipeline, portfolio size, revenue, volume of doses sold, and geographic scope are among the largest of companies in scope. It markets the world’s first dengue vaccine (Dengvaxia®). Overall, the company’s performance in the Index is strong.

SERUM INSTITUTE OF INDIA



Research & Development: Serum Institute of India falls in the middle of the pack, with relatively low R&D investments as a proportion of its global vaccine revenue, but a relatively large pipeline (12 projects as indicated by publicly available sources) and access provisions in place for half of its late-stage vaccine candidates.

Pricing & Registration: Serum Institute of India does not publish details of its vaccine pricing strategy. The company performs well in filing vaccines for registration in low- and middle-income countries.

Manufacturing & Supply: It performs below average in this area: it has strong commitments but its processes to align supply and demand appear less structured than those of other companies.

Serum Institute of India produces the largest volume of vaccines and has the largest geographic scope of companies evaluated, with a relatively large pipeline, portfolio and revenue. Many of the vaccines it produces are for diseases recommended by WHO for routine immunisation for children. The company’s high-volume, low-cost business model is clearly access-oriented. However, its approach to providing access to vaccines is less transparent and less structured than other companies.

INDUSTRY LANDSCAPE

How the companies perform

COMPANIES EVALUATED IN R&D ONLY

DAIICHI SANKYO

R & D  20

Research & Development: Daiichi Sankyo performs below average, with a relatively small pipeline (eight projects) and no access plans in place for late-stage projects.

Daiichi Sankyo's vaccine business is currently focused on the Japanese market, and there is evidence it is increasing its focus on vaccine R&D. Its pipeline includes combination vaccines for diseases recommended by WHO for routine immunisation for children.

Daiichi Sankyo currently markets vaccines only in Japan, and not in countries in scope. It states that it has processes for preventing vaccine shortages, including coordinating supply plans with stakeholders and scaling up production capacity.

The company is partnering with the Japan International Cooperation Agency (JICA) to build the vaccine manufacturing capacity of POLYVAC in Vietnam. It is part-way through a five-year project to provide technical cooperation for the production of a measles and rubella combination vaccine (started in 2013).

TAKEDA

R & D  20

Research & Development: Takeda performs above average, with relatively large vaccine R&D investments as a proportion of its global revenue and clear access provisions for its late-stage vaccine candidate. It has a relatively small pipeline (four projects).

Takeda currently markets vaccines in Japan only and is growing its vaccine pipeline, including R&D projects for dengue and chikungunya (both neglected tropical diseases).

While it does not currently market vaccines in countries in scope, it is taking steps to support affordability and supply of vaccines in its pipeline. For example, from 2016, Takeda has been developing a low-cost IPV with support from the Bill & Melinda Gates Foundation. As part of the worldwide polio eradication strategy, Takeda will produce at least 50 million IPV doses per year for supply to more than 70 developing countries. For this vaccine, Takeda is committed to a ceiling price for Gavi countries through UNICEF, and intends to extend Gavi-level prices to Gavi transitioning countries for a number of years post-transition. Pricing for non-Gavi-eligible countries will take into account (among other criteria) the cost of goods, country GDP per capita, procurement conditions, terms and impact of competition.

INDUSTRY LANDSCAPE

Portfolios & pipelines: where is the industry focusing?

When it comes to vaccines, companies clearly concentrate on diseases with larger global markets: for example, the diseases with the most vaccines on the market are meningococcal disease, polio, seasonal influenza and viral hepatitis; the largest pipelines are for pneumococcal disease, seasonal influenza, HPV, meningococcal disease and RSV.

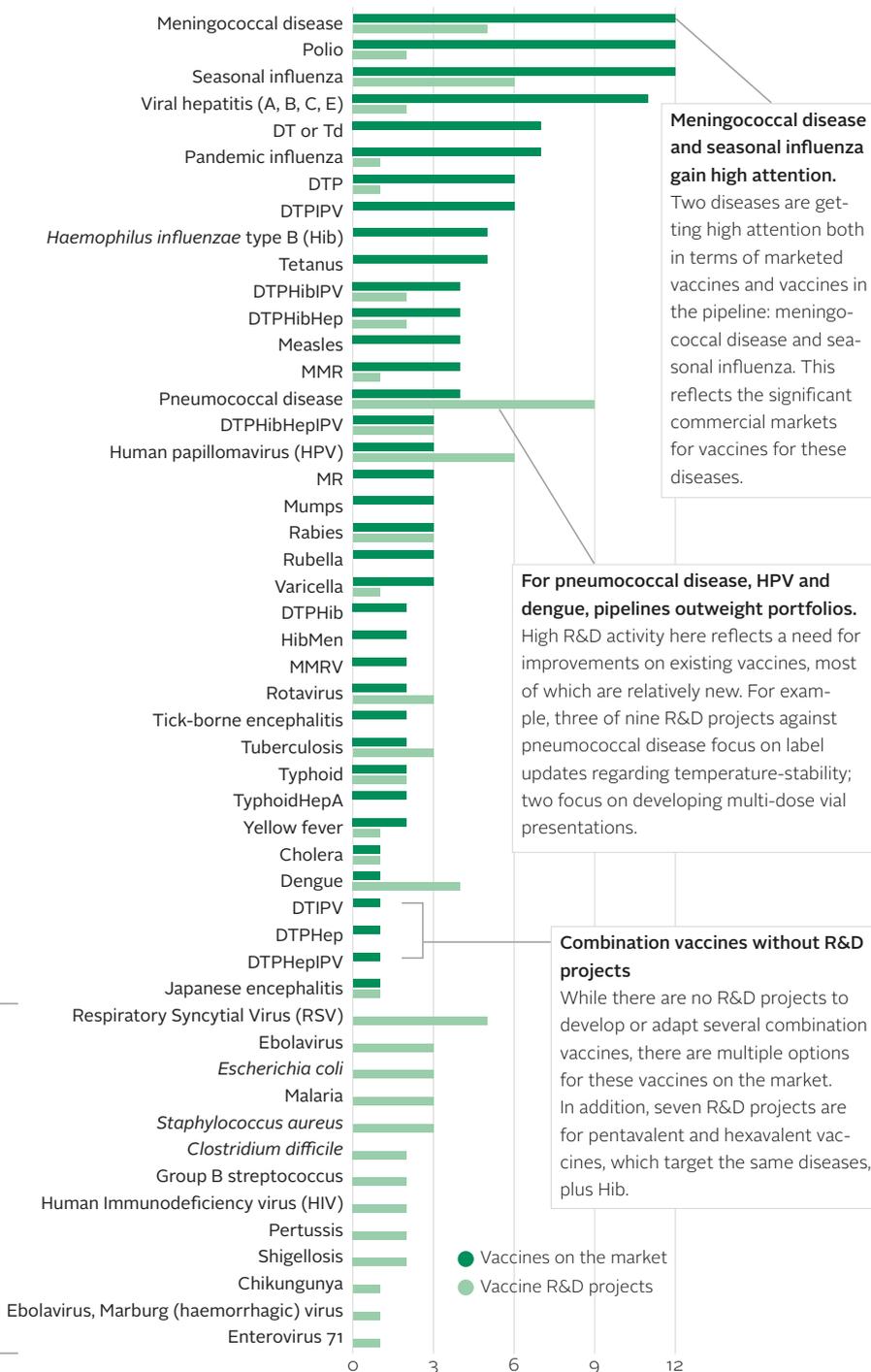
Nearly two thirds of vaccines on the market target at least one disease or pathogen for which WHO recommends routine immunisations for all children. These have large, relatively reliable global markets. Many are combination vaccines, with diphtheria and tetanus-containing vaccines being the most common (35). A further third are recommended by WHO for certain groups of children. Some of these are more likely to be used in higher income countries (e.g., for meningococcal disease and seasonal influenza).

About one fifth of the pipeline is in phase III trials. Of these, almost one quarter targets seasonal influenza. This reflects both the large commercial market for influenza vaccines and the need to develop new vaccines for each influenza season. The same proportion of projects in phase III targets diseases and pathogens without vaccines on the market: *C. difficile* (Pfizer), Ebolavirus (Johnson & Johnson and Merck & Co., Inc.) and malaria (GSK).

One third of R&D projects target diseases without vaccines on the market. These projects are promising. Yet, high attrition rates in vaccine development mean many candidates will likely not make it to market.

Figure 5. Comparing vaccine pipelines and portfolios for eight vaccine companies

The eight companies in scope have 89 vaccine R&D projects in the pipeline for 35 diseases and pathogens – and 148 vaccines on the market for an overlapping group of 24.



Meningococcal disease and seasonal influenza gain high attention.
Two diseases are getting high attention both in terms of marketed vaccines and vaccines in the pipeline: meningococcal disease and seasonal influenza. This reflects the significant commercial markets for vaccines for these diseases.

For pneumococcal disease, HPV and dengue, pipelines outweigh portfolios.
High R&D activity here reflects a need for improvements on existing vaccines, most of which are relatively new. For example, three of nine R&D projects against pneumococcal disease focus on label updates regarding temperature-stability; two focus on developing multi-dose vial presentations.

Combination vaccines without R&D projects
While there are no R&D projects to develop or adapt several combination vaccines, there are multiple options for these vaccines on the market. In addition, seven R&D projects are for pentavalent and hexavalent vaccines, which target the same diseases, plus Hib.

Figure 6. Companies have no projects in the pipeline for 32 diseases in scope with no marketed vaccines

For some diseases companies are not expected to be developing vaccines. For others, a gap reflects a lack of incentives for companies to engage in needed R&D. WHO has published lists of diseases where vaccine R&D is urgently needed. Such prioritisation can help engage companies in R&D for these diseases.

Diseases with no R&D from companies in scope and no existing vaccines

Adenovirus
 Amoebiasis
 Balantidiasis
 Buruli ulcer
 Campylobacter enteritis
 Chagas disease
 Cryptosporidiosis
 Cytomegalovirus (CMV)
 Dracunculiasis
 Echinococcosis
 Food-borne trematodiasis
 Giardiasis
 Hantavirus pneumonia
 Human African trypanosomiasis
 Human metapneumovirus
 Human monkeypox
 Isosporiasis
Klebsiella pneumoniae
 Lassa fever
 Leishmaniasis
 Leprosy
 Lymphatic filariasis
 Onchocerciasis
 Parainfluenza
Pneumocystis jiroveci
 Schistosomiasis
 Severe Acute Respiratory Syndrome (SARS)
 Soil-transmitted helminthiasis
 Taeniasis/cysticercosis
 Trachoma
 Yaws
Yersinia enterocolitica

Figure 7. Nine recent vaccine approvals

The eight companies in scope gained nine approvals for new vaccines, vaccine presentations and label updates between June 2014 and January 2017.

Vaccine	Company	Approval
Dengue (Dengvaxia®)	Sanofi	COFEPRIS, Dec 2015
DTPHibHepIPV (Vaxelis®)	Merck & Co., Inc., Sanofi	EMA, Feb 2016
HPV (Gardasil 9®)	Merck & Co., Inc.	FDA, Dec 2014
HPV (Gardasil®) Controlled Temperature Chain	Merck & Co., Inc.	EMA
Meningococcal A (MenAfriVac®) 5 µg dose for children under one year	Serum Institute of India	WHO, Dec 2014
Meningococcal B (Trumenba®)	Pfizer	FDA, Oct 2014
Pneumococcal (Prevenar 13®) four-dose vial	Pfizer	EMA, Apr 2016
Rabies	Serum Institute of India	CDSCO, Jun 2016
Seasonal influenza (VaxiGripTetra™)	Sanofi	UK, Jul 2016

KEY FINDING: R&D FOR VACCINE ADAPTATIONS

Adaptations to existing vaccines account for half of vaccine R&D projects

The characteristics of a vaccine – such as its thermostability, number of doses required, or the serotypes it targets – have a substantial impact on how immunisation programmes can be effectively implemented, particularly in low-resource settings. Often, the best combination of characteristics becomes apparent once a vaccine has been rolled out in real-world settings. Once this happens, further R&D is required to improve the vaccine.

The Access to Vaccines Index has evaluated the pipelines of eight vaccine companies: Daiichi Sankyo, GSK, Johnson & Johnson, Merck & Co., Inc., Pfizer, Sanofi, Serum Institute of India and Takeda (see figure 8). The industry is responding to cases where existing vaccines need to be adapted: such projects account for 48% of projects in the pipeline (43/89), with one project aiming for multiple adaptations (see figure 9).

Some 30% of adaptive R&D projects involve multivalent vaccines. For example, Serum Institute of India is developing a 10-valent pneumococcal conjugate vaccine (PCV). It targets the serotypes prevalent in 70% of the population affected by pneumococcal disease in Africa, Asia and Latin America. Meanwhile, 28% of adaptive R&D projects focus on either characterising or improving the temperature stability of a vaccine, and 44% target a range of other improvements, including in efficacy, immunisation schedules, yield of production, or formulations to allow for easier administration.

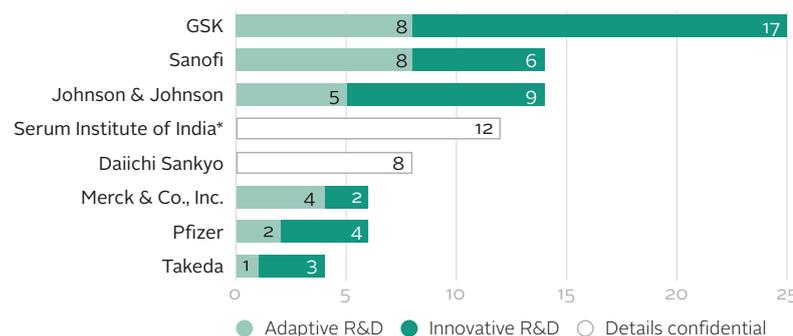
Taken as a group, the 43 adaptive R&D projects are diverse, with companies

working toward a wide variety of adaptations. For example, GSK is characterising the thermostability of its PCV Synflorix®; Sanofi is doing the same for its cholera vaccine Shanchol®; and in 2015, Merck & Co., Inc. received Controlled Temperature Chain approval for its HPV vaccine Gardasil®. Five pro-

jects focus on approving vaccines for use in lower age groups: including GSK for influenza vaccines and Sanofi for a meningococcal vaccine. Serum Institute of India received approval in late 2014 for children under one year to receive a 5 µg dose of its meningococcal A vaccine (MenAfriVac®).

Figure 8. Vaccine adaptations account for half of R&D projects; individual company pipelines vary.

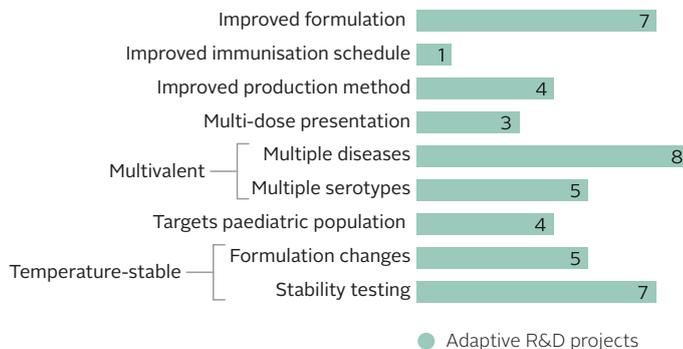
GSK and Sanofi are undertaking the most projects to adapt existing vaccines.



* Serum Institute of India's pipeline is based on publicly available sources. It has additional projects for which the data are confidential.

Figure 9. Companies are working toward a wide variety of vaccine adaptations.

Companies have 43 adaptive vaccine R&D projects for diseases in scope. Adaptive R&D projects for multivalent vaccines are the most common, followed by temperature-stability projects.



One project is counted twice: it falls into two categories of adaptation.

KEY FINDING: VACCINE PRICING

When setting prices, all companies consider countries' Gavi status – most also consider GNI per capita

Vaccines are among the most cost-effective ways of protecting people against disease, not least children, who can be safeguarded from the often debilitating impact of many childhood illnesses. Nevertheless, immunisation programmes involve considerable costs, with vaccine prices accounting for a significant proportion. Understanding how vaccine prices are determined can help shape expectations for procurers, donors, market-shapers and other companies when entering negotiations. A better understanding here can lead to more affordable vaccines, in turn enabling greater immunisation coverage and greater market sustainability. The Access to Vaccines Index asked six companies which factors they consider when setting vaccine prices: GSK, Johnson & Johnson, Merck & Co., Inc., Pfizer, Sanofi and Serum Institute of India.

Collectively, the six companies consider 18 diverse factors when setting vaccine prices, with the most attention being paid to the conditions (not least economic conditions) in a given country. Indeed, the only factor considered by all six companies is a country's eligibility for Gavi support; four companies also consider Gross National Income (GNI) per capita. Cost plays a role in vaccine pricing, including investments companies make in clinical development or in manufacturing facilities. The public health value of a vaccine to healthcare systems is also used to inform vaccine prices.

All six companies offer discounts to Gavi-eligible countries. Most also publicly commit to offer discounts for some vaccines for a set time period to the 16 countries classified in 2016 as Gavi-transitioning. Companies generally offer their lowest prices to Gavi-eligible countries. However, many middle-income countries (MICs) are not eligible for Gavi support (or PAHO's Revolving Fund).

Many also face healthcare budget constraints. The Index does not find clear evidence that companies systematically consider countries' ability to pay when setting vaccine prices in MICs. This raises concerns that many MICs may not be able to afford vaccines, thus limiting immunisation coverage, particularly of newer, more expensive vaccines.

Figure 10. Companies report considering 18 factors when setting vaccine prices.

The 18 factors can be divided into five different groups. The largest focuses on conditions in a given country, such as its Gavi status. Others look at aspects of government commitment, or the value of or need for the vaccine in question, including related costs.

Type of factor	Factor	GSK	Johnson & Johnson	Merck & Co., Inc.	Pfizer	Sanofi	Serum Institute of India
Country feature	Gavi status (eligible, transitioning)	●	●	●	●	●	●
	GNI per capita, for at least some countries	●	●		●	●	
	Humanitarian emergency discount	●			●		
	Fiscal capacity and health spending			●			
	Mechanisms & policies for procuring vaccines			●			
	Competitive environment					●	
	Existence of distinct distribution networks (e.g. public/private)					●	
Extent of government's commitment	Target population coverage	●		●			
	Covering entire birth cohort				●		
	Vaccinating catch-up cohorts	●					
	Volume to be purchased	●					
	Duration of contract	●					
Value of vaccine	Public health value to healthcare system			●	●		
	Scientific innovation vaccine represents				●		
Need for vaccine	Public health need			●			
	Disease burden & which population segments are affected by the disease					●	
Required investment	In clinical development programmes				●		
	In manufacturing facilities & workforce				●		

KEY FINDING: ALIGNING SUPPLY AND DEMAND

Companies take diverse approaches to aligning supply with demand

Vaccine demand can outstrip supply for a range of reasons, including unexpected outbreaks, inaccurate demand forecasting and manufacturing interruptions. In recent years, many countries have reported vaccine shortages. These can disrupt immunisation programmes, putting herd immunity at risk and increasing the chance of outbreaks. While coordination between stakeholders is needed to address shortages, vaccine companies can take specific actions to help prevent them (see figure 11). The Access to Vaccines Index has evaluated the approaches taken in this area by six companies: GSK, Johnson & Johnson, Merck & Co., Inc., Pfizer, Sanofi and Serum Institute of India.

Four of the companies take comparatively strong approaches to aligning vaccine supply with global demand: GSK, Johnson & Johnson, Merck & Co., Inc. and Sanofi. Their approaches are deemed strong because their internal processes for aligning supply and

demand include four or more of the eight elements the Index has identified as key to improving supply, and because they commit to staying in vaccine markets where there are few or no other suppliers and/or to communicating when they plan to reduce or cease supply of a vaccine (see figure 11).

All six companies implement a combination of the elements assessed. No particular combination is identified as best practice, but implementing more elements is expected to better prevent shortages. Each company's approach is likely to be linked to its portfolio, structure and business model. Five companies regularly review levels of supply and demand, and four have processes for scaling up production when shortages are forecast. Five also commit to continuing to supply needed vaccines, and/or to notifying stakeholders when planning to reduce supply. As vaccines for specific diseases may have few suppliers, such commitments help

to increase accountability and provide confidence around supply. Where companies do exit markets, providing stakeholders with early notice can allow other suppliers' production and distribution plans to be adjusted to minimise negative impacts on public health.

All six companies are taking action to align supply with demand, which suggests that vaccine shortages are, in some cases, being detected, mitigated and/or prevented. The existence of ongoing vaccine shortages, however, shows that more needs to be done. The industry needs to continuously monitor and improve its approaches to preventing shortages, for instance by considering how they can implement the key actions shown in figure 11. Other stakeholders also need to play their part, with clear, accurate and timely demand forecasting supported by sustainable purchasing commitments where possible.

Figure 11. Companies take diverse approaches to aligning supply with demand

Most companies implement elements and supply commitments. GSK, Johnson & Johnson, Merck & Co., Inc. and Sanofi take stronger approaches.

	GSK	Johnson & Johnson	Merck & Co., Inc.	Pfizer	Sanofi	Serum Institute of India
Key elements for preventing/responding to shortages						
Commitment to ensure access in case of shortages	●	●	●			
Regular and timely supply-and-demand review process	●	●	●	●	●	
Clear process for escalating and acting on identified issues	●				●	
Reserve stocks (not including externally managed stockpiles)		●	●	●		
Processes for scaling up production		●		●	●	●
Processes for re-allocating stocks	●				●	
Donations or affordability measures in emergency situations	●					
Consideration of other suppliers in a market when making decisions	●					
Commitments to continuing supply of vaccines						
Commitment to stay in vaccine markets where needed		●	●			●
Commitment to communicate plans to reduce supply externally	●		●		●	

● Company has a clear commitment/process

CROSS-CUTTING ANALYSIS: NEW DENGUE AND MALARIA VACCINES

The world's first dengue and malaria vaccines: what can we learn about access?

Dengue is the fastest-growing mosquito-borne disease globally; malaria is the deadliest.¹ The first-ever vaccines for these diseases are currently being rolled out. Sanofi received the first approval for its dengue vaccine (Dengvaxia® or CYD-TDV) in December 2015, while GSK's malaria vaccine candidate (Mosquirix® or RTS,S) will be rolled out in pilot projects from 2018. These inno-

ventions present important opportunities for lowering the disease burden of dengue and malaria.

The Access to Vaccines Index has examined the different approaches that Sanofi and GSK have taken to developing these vaccines and to making them accessible, as well as R&D data from all eight companies in the scope of the

Index. The aim is to provide insight into the challenges Sanofi and GSK face, specifically related to the characteristics of their vaccines; the dengue and malaria vaccine pipelines; and the next steps companies and other stakeholders need to take to fully and successfully implement new vaccines for these diseases in low- and middle-income countries.

NEW VACCINES POSE CHALLENGES IN IMPLEMENTATION

► DENGUE

Strong data-collection systems are required to maximise effectiveness

An estimated 390 million people are infected with dengue virus each year worldwide. These include 96 million cases of symptomatic dengue infection: comprising either dengue fever, which has flu-like symptoms, or the potentially fatal dengue haemorrhagic fever.² The first-ever dengue virus vaccine, used alongside current preventive measures, such as vector control, could significantly strengthen prevention strategies. This could bring us closer to reaching the World Health Organization's (WHO) goal of reducing dengue morbidity by at least 25% and mortality by at least 50% between 2012 and 2020.^{3,4}

Efficacy linked to prior infection

In phase III clinical trials, the efficacy of the dengue vaccine CYD-TDV against symptomatic dengue illness was found to be 65.6% for participants aged nine or older. However, individual-level outcomes varied on several factors, including the individual's serostatus (i.e., whether they had previously been infected with dengue). In seronegative

individuals, the vaccine's efficacy was 52.5%, whereas in seropositive individuals, it was 81.1%. This may suggest that the vaccine's efficacy is higher among those with previous dengue infection. In addition, the trials showed that vaccinating seronegative people could lead to more serious outcomes if they were infected post-vaccination.

Individual serological testing prior to vaccination would likely be challenging in most affected countries. Given this, WHO recommends that CYD-TDV should be implemented in areas with at least 70% seropositivity. Assuming immunisation coverage of 80%, modelling predicted a decrease in dengue

incidence of up to 30% over 30 years in such areas. However, in settings with low seropositivity (defined as 10%), an increase in hospitalisation rates is expected. To maximise the positive health effects of CYD-TDV, high-quality epidemiological and surveillance data is required. This means that, where strong data collection systems do not exist, governments and other global health stakeholders may need to support activities designed to strengthen such systems.^{5,6}

► MALARIA

Vaccine requires challenging dosing schedule

Malaria places a large burden on the global population, with 214 million cases annually and nearly half a million deaths.⁷ The vaccine candidate RTS,S targets *P. falciparum*, one of the five species of the malaria parasite. *P. falciparum* is found mainly in sub-Saharan Africa, where the disease burden from malaria is also highest. In 2015, 90% of global malaria deaths occurred in this region. RTS,S could ameliorate this burden substantially. WHO estimates that up to 30% of deaths in chil-



WHO estimates that GSK's RTS,S, used with other interventions such as bed nets, could avert up to 30% of deaths in under-fives.

dren younger than five could be averted by RTS,S if implemented alongside current prevention and treatment interventions.⁸ Scientifically, the development of RTS,S is also significant: not only is RTS,S the first-ever vaccine against malaria, but also the first-ever vaccine to successfully target a parasite.⁹

In a large-scale phase III trial, completed in 2014, RTS,S showed 39% efficacy against malaria after four doses in infants aged 5-17 months and 27% efficacy in infants aged 6-12 weeks. After only three doses, efficacy was lower for both groups: 28% and 18%, respectively. For the older group, the fourth “booster” dose proved critical for preventing severe malaria. Without it, there

was no protection against this most serious form of the disease.¹⁰

The vaccine currently needs to be administered in three doses at monthly intervals, followed by a fourth and final dose 18 months later. This is a challenging dosing schedule, with the risk that non-completion will lead to unprotected children and wasted resources. In addition, in the older age group, for whom the vaccine was more effective, the trial identified a potentially higher risk of febrile seizures, meningitis and cerebral malaria.^{10,11}

In 2015, RTS,S received a positive scientific opinion from the European Medicines Agency. In January 2016,

WHO recommended undertaking large-scale pilot implementation programmes to test the efficacy, safety and feasibility of implementing RTS,S in real-world settings.¹² In June 2016, Gavi, the Vaccine Alliance committed to providing up to USD 27.5 million for these pilots, on the condition that additional funding would be provided by other organisations.¹³ UNITAID provided USD 9.6 million in June, and in November 2016, The Global Fund to Fight AIDS, Tuberculosis and Malaria approved allocation of the remaining USD 15 million required for the four-year programme. The pilot is due to start in three sub-Saharan African countries (yet to be determined) in 2018.^{14,15}

REGISTRATION AND AFFORDABILITY: WIDE DIFFERENCES IN PROVISIONS FOR ENSURING ACCESS

Sanofi and GSK submitted data on R&D, registration and pricing for the CYD-TDV dengue vaccine and RTS,S malaria vaccine respectively to the Access to Vaccines Index.

► DENGUE

CYD-TDV: developed in-house, with novel registration strategy but uncertain affordability

CYD-TDV was developed and brought to the market by Sanofi in-house, investing USD 1.6 billion over 20 years in the process.¹⁶ The company's sustained interest in developing the vaccine in-house may have been due to the emergence of potentially profitable markets for a dengue vaccine, following the rapid spread of the disease, including in upper middle-income and high-income countries. This situation is in contrast with other neglected tropical diseases (NTDs), for which the potential for a commercial market is low. In this case, the lack of market incentives leads to a reliance on external mechanisms – such as product development partnerships (PDPs) – to drive vaccine R&D.¹⁷

When registering CYD-TDV for use, Sanofi pursued an innovative approach. The vaccine was first registered in Latin



Following the approval of Sanofi's Dengvaxia® in 2015, the Philippines began the first public immunisation programme against dengue in 2016.

America and Asia, where the disease burden is highest (starting in 2015 with Mexico, the Philippines and Brazil). This is different to the typical registration pathway used by major pharmaceutical companies, which prioritises registration by stringent regulatory authorities, such as those in the European Union, Japan and the US.¹⁶ By taking an innovative approach, Sanofi may have accelerated access to the vaccine in lower-income, dengue-endemic countries. CYD-TDV is now registered in 11 countries,^a including three lower middle-income countries and one low-income country.¹⁸ Sanofi has not yet applied for WHO prequalification for CYD-TDV, which is required to enable procure-

ment by United Nations agencies such as the United Nations Children's Fund (UNICEF).⁴

Public immunisation programmes with CYD-TDV have begun in the Philippines¹⁹ and Brazil (Paraná State).²⁰ Sanofi reported its pricing strategy for CYD-TDV to the Index (see page 50). It is unclear whether this strategy will lead to affordable prices for the vaccine. Affordability is important, given that Sanofi is currently the sole global supplier of the world's only dengue vaccine.

► MALARIA

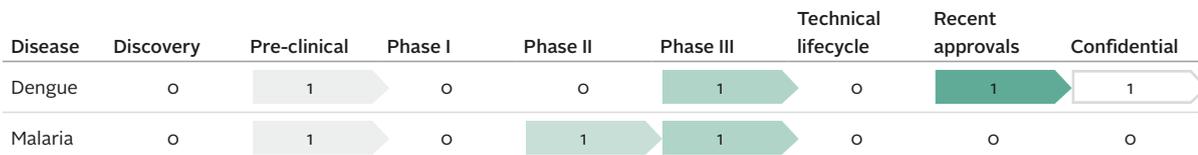
RTS,S developed collaboratively, with clear access plans in place

GSK has invested 28 years in the development of RTS,S. Unlike the dengue vaccine, RTS,S was developed through a PDP between GSK and the PATH Malaria Vaccine Initiative (MVI). The development of the vaccine cost USD 656 million, including financial support received from the Bill & Melinda Gates Foundation.²¹ Collaborative models are particularly important for accelerating R&D: they can facilitate risk- and expertise-sharing in disease areas such as malaria, where commercial incentives to drive R&D are low.²²

a Brazil, Costa Rica, El Salvador, Guatemala, Indonesia, Mexico, Paraguay, Peru, the Philippines, Singapore and Thailand.

Figure 12. R&D pipelines for dengue and malaria vaccines

GSK, Serum Institute of India and Takeda are developing dengue vaccines, and Sanofi's dengue vaccine was first approved in December 2015. In addition to RTS,S, GSK is working on a second-generation malaria vaccine (phase II) and a thermostable version of RTS,S (pre-clinical).



As with the dengue vaccine, when RTS,S receives marketing approval, it will likely have a sole global supplier, at least initially. To mitigate any concerns this may raise, the vaccine has, from the outset, been developed following a not-for-profit model. GSK plans to submit RTS,S for WHO prequalification, and has agreed to adopt pricing that will cover manufacturing costs plus 5%. In addition, GSK has agreed to reinvest the profit margin in R&D for next-generation malaria vaccines or vaccines against NTDs.²³ These arrangements are common in PDPs, where non-industry stakeholders are better able to influence decisions on access. GSK has reported that RTS,S will be priced around GBP 8.50 per child (based on demand of approximately 100 mn doses).²⁴ It is yet to be determined if this price will prove affordable in malaria-endemic countries where the vaccine is registered.

► NEXT-GENERATION VACCINES

There is a continuing need for vaccine R&D targeting dengue and malaria

Even though CYD-TDV and RTS,S have the potential to substantially ameliorate disease burden, R&D needs to continue, with a focus on improving these vaccines and providing alternatives. For example, for dengue, an important goal is greater efficacy in the absence of previous infection, while for malaria, efforts to improve efficacy should be balanced with a simplified dosing schedule.

Between June 2014 and May 2016, the Access to Vaccines Index evaluated the R&D activities of eight major vaccine companies with a focus on malaria and dengue. Three companies in scope of the Index in addition to Sanofi had dengue vaccine candidates in the pipeline: GSK, Serum Institute of India²⁵ and Takeda (see figure 12). GSK was the only company engaged in malaria vaccine development during this time. It is not yet clear if these projects will effectively address the greatest challenges presented by the current vaccines.

GSK has a dengue vaccine in pre-clinical development. The company is working in collaboration with the Walter Reed Army Institute of Research in the US and Bio-Manguinhos/Fiocruz in Brazil. GSK is planning for local clinical trial sites and WHO prequalification, as well as affordable pricing strategies. Serum Institute of India aims to launch its dengue vaccine candidate, licensed from the US National Institutes of Health, in 2018-19.^{25,26} Takeda has a dengue vaccine candidate in phase III trials. It intends to seek WHO pre-qualification for its candidate and will prioritise registration in countries where clinical trials have taken place and in countries with the highest medical need. In addition to the approval of its dengue vaccine in December 2015, Sanofi is conducting post-marketing effectiveness studies and phase III long-term follow-up studies in Latin America and Asia. These may lead to a reduced reg-

imen and/or an expanded age-range in the indications for its dengue vaccine.

In collaboration with PATH MVI, GSK is conducting further research into delaying and reducing the size of doses (i.e., fractional dosing) for RTS,S. Results of a recent phase II challenge study, comparing alternative dosing schedules of RTS,S, show greater efficacy in healthy volunteers receiving a fractional dose schedule. A further phase II study to test this hypothesis in malaria-endemic countries is planned to begin in 2017. In December 2016, the German government announced a grant of EUR 7.8 million to PATH MVI to support this trial.²⁷ If RTS,S is more effective with lower doses, this could reduce per-dose production costs and potentially improve access. The ultimate aim is to develop a second-generation vaccine that reduces malaria cases by 75%, provides immunisation for longer than two years, and targets all populations living in *P. falciparum* malaria-endemic regions.

RTS,S currently requires refrigeration throughout the supply chain, which is a considerable challenge in sub-Saharan Africa.²⁸ GSK is therefore collaborating with the Bill & Melinda Gates Foundation to render the adjuvant contained in RTS,S thermostable for three years at temperatures of up to 30°C. This project is currently in pre-clinical stages. A thermostable vaccine could have a substantial impact on coverage in low-resource populations.

b This project was not disclosed in Serum Institute of India's public pipeline during the period of analysis, and therefore may not be represented in other analyses of the 2017 Access to Vaccines Index.

LEARNING FROM THE EXPERIENCES OF DENGUE AND MALARIA

The first vaccines for dengue and malaria represents major breakthroughs in vaccine R&D, but both vaccines present implementation challenges. CYD-TDV requires strong data collection systems and greater clarity on whether its pricing will be affordable, and RTS,S has safety concerns and a challenging dosing schedule. While the introduction of these vaccines is welcome, there is still much that needs to be done to ensure their safe and effective implementation. These efforts must not compromise the sustainability of effective vector control strategies. Continued vaccine R&D targeting dengue and malaria is also needed.

At a high level, much of the “low-hanging fruit” in vaccine development has been picked, and complex technical challenges exist in developing new vaccines.²⁹ At the same time, immunisation is increasingly being recognised as an important preventive intervention, and the industry is being called on to respond accordingly. The roll-out of the new dengue and malaria vaccines suggests that the potential benefits and risk reduction offered by vaccination are increasingly being prioritised even where their efficacy is less than that of other widely used vaccines. This prioritisation reflects the heavy burden imposed by these diseases and the corresponding pressure to respond.

Where the potential benefit of immunisation is substantial, but the outcomes of vaccine candidates have so far been sub-optimal, there is a strong need for careful implementation plans that adequately test new vaccines in real-world settings. These plans must be able to respond rapidly to newly emerging data. They must also ensure new vaccines are implemented safely and cost-effectively without compromising existing interventions. The new dengue and malaria vaccines present invaluable opportunities, including for vaccine companies, to gain insights into viable models for effectively developing and implementing new vaccines that respond to contemporary global health challenges.

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CROSS-CUTTING ANALYSIS: VACCINES FOR EMERGING INFECTIOUS DISEASES

Protecting global health security from the threat of emerging infectious diseases: are vaccine companies doing enough?

Over the past 10 to 15 years, a succession of infectious diseases has emerged, with widespread effects.¹ The West African Ebola outbreak, for example, caused more than 11,000 deaths worldwide between December 2013 and March 2016.^{2,3} In February 2016, as the Ebola outbreak slowed, WHO declared that birth defects related to the Zika virus amounted to a Public Health Emergency of International Concern.⁴ Within a few months, Zika had infected over one million people.⁵ Emerging infectious diseases (EIDs) can also take a toll on economies: the Ebola crisis is estimated to have had a negative impact of USD 2.8 billion in Guinea, Liberia and Sierra Leone.⁶

Infectious diseases are considered “emerging” if they have newly appeared in a population, or are rapidly increasing in incidence or geographic range.⁷ The threat posed by EIDs differs from that

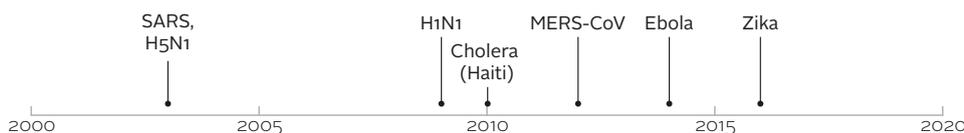
posed by other diseases: local and international health systems often have little to no experience with their prevention or control.⁸

What is more, with increased movement of people and pathogens across borders due to globalisation, threats from local infectious diseases can be quickly transformed into global problems.⁹ Urbanisation, changing patterns of contact with wild and domestic animals, and climate change further propagate vulnerability to pandemics.⁷ This means that EIDs pose a threat to the health security of all nations, regardless of where an infection first emerges. Several major outbreaks in recent years underscore this point. These include Severe Acute Respiratory Syndrome (SARS) (2003), H5N1/avian flu (2003), H1N1/swine flu (2009), Middle East Respiratory Syndrome coronavirus (MERS-CoV) (2012) and, more recently, Ebola and Zika (see figure 13).⁸

The International Health Regulations (IHR) 2005 are a key international legal instrument designed to protect global health security in response to contemporary challenges.¹⁰ The IHR recognise that vaccines are crucial to preventing the spread of EIDs.¹¹ Vaccine companies play an important role in this space, in coordination with national and international stakeholders.¹² The Coalition for Epidemic Preparedness Innovations (CEPI) is a key partnership here, aiming to accelerate R&D for new EID vaccines. This analysis examines the role of vaccine companies in protecting global health security from EID threats. While animal vaccines and other measures to control zoonotic EIDs are also important,¹³ this analysis focuses on human vaccination. Data from all eight companies in the scope of the Index was examined for this analysis.

Figure 13. Seven major outbreaks of EIDs in the 21st century

Since the beginning of the 21st century, a series of major infectious disease epidemics have occurred.



DEVELOPING AND DELIVERING VACCINES FOR EIDS

Incentives critical to driving R&D

For many EIDs, treatments are simply not available. Where treatments are available, it can be difficult to diagnose acute infections quickly enough to facilitate effective treatment and curb the spread of infection. In this context, being able to prevent and manage EIDs by vaccinating susceptible populations adds real value. This requires the rapid development of effective vaccines. However, the response of vaccine companies to the need for R&D that specifically targets EIDs has often been limited. While vaccine R&D is generally complex and lengthy, R&D targeting EID vaccines is particularly difficult and risky for a number of reasons.¹⁴

R&D targeting EIDs is most often reactive, undertaken in response to disease outbreaks. This requires flexibility, and the technologies and processes used must be consistent, highly standardised and reproducible to allow for application across diverse pathogens. In this context, traditional approaches to pharmaceutical R&D, such as random target identification, are time consuming and often fail to produce effective vaccines against EIDs.^{14,15}

Proactive vaccine R&D is more desirable than reactive R&D, but less common. Despite being undertaken before an outbreak occurs, proactive R&D may also require flexible and reproducible processes. This is due to the rapidly changing genetic make-up of some pathogens. Influenza is a case in point: due to its high mutation rate and fre-

quent genetic reassortment, WHO conducts a twice-annual identification of seasonal influenza strains in each hemisphere, to which vaccine developers must respond rapidly.^{14,15,16}

The current market-driven innovation model primarily stimulates R&D that focuses on products with a predictable market and a guaranteed return on investment. This does not provide sufficient incentive for developing new vaccines for existing or predicted EID outbreaks. Investments are likely to be deemed risky, not only due to attrition rates in vaccine R&D: because the size and severity of outbreaks can be difficult to predict, companies have little certainty with regard to the market potential of newly developed vaccines.^{17,18} While some EIDs may never lead to major epidemics, others may become widespread. For example, vaccine developers have estimated that the annual market for a Zika vaccine could exceed USD 1 billion.¹⁹

Consequently, some of the most urgently needed vaccines are not being developed.²⁰ There are some mechanisms for incentivising vaccine R&D, such as Advance Market/Purchase Commitments (AMCs/APCs), which offer funds to guarantee the price of a currently unavailable vaccine. Donor funding can help mitigate the financial risks associated with investing in technically challenging vaccine development where return on investment is uncertain. Such funding may be delivered through product development partnerships (PDPs). PDPs have additional benefits, such as accelerating vaccine development by bringing together the diverse strengths of stakeholders. Furthermore, by facilitating access to comparator products, portfolios of R&D projects can be actively managed, and resources can be directed to those projects with higher potential impact.^{21,22}

Post-development considerations for ensuring access to vaccines

While there is a clear need for development of novel EID vaccines, ensuring rapid, widespread access to vaccines with demonstrated safety and efficacy is equally important for preventing and controlling outbreaks. Regulatory approval processes for vaccines, which are often complex and lengthy, may be particularly challenging in the context of EIDs. Affordability is also critical to ensuring equitable access to vaccines across countries, as is the sustainability of vaccine markets:²³ EID vaccine pricing must be carefully considered to ensure affordable access, as well as sufficient revenues to support R&D and manufacturing costs.

Furthermore, in order to ensure rapid access to sufficient supplies of vaccines if an outbreak occurs, consideration should be given to supply and deployment strategies. National, regional and global vaccine stockpiles can help support this. Global vaccine stockpiles exist for several diseases with outbreak potential, such as cholera, meningitis, yellow fever and smallpox.²⁴ However, the 2016 yellow fever outbreak in Angola has twice depleted the global stockpile of six million doses, demonstrating that stockpiles do not guarantee sufficient supply.^{25,26} In such cases, the ability to rapidly scale up vaccine production is critical. Similar stockpiling mechanisms could be considered for EIDs. For example, Gavi has plans to create an Ebola vaccine stockpile.²⁷ Such stockpiles will require sufficient funding, as well as strong governance and cooperation between stakeholders, including the private sector.



The first clinical trial participant receives Johnson & Johnson's Ebolavirus vaccine candidate. The companies in scope have two Ebolavirus vaccine candidates in phase III trials.

CURRENT STATE OF R&D TARGETING EIDS

In December 2015, WHO prioritised R&D for vaccines, diagnostics and therapeutics for those emerging diseases that are most likely to cause major epidemics, and for which few or no medical counter-measures exist (Crimean Congo haemorrhagic fever, Ebola and Marburg virus diseases, Lassa fever, MERS and SARS coronavirus diseases, Nipah and Rift Valley fever). It also designated three additional diseases as posing serious threats (chikungunya, severe fever with thrombocytopenia

syndrome, and Zika).^{28 a} The Access to Vaccines Index examines the vaccine R&D activities undertaken between June 2014 and May 2016 by eight major vaccine companies. Five of the emerging diseases prioritised by WHO are in scope of the Index and have no existing vaccines: chikungunya, Ebola, Lassa fever, Marburg (haemorrhagic) virus disease and SARS.

Half of the eight companies evaluated are active in this area, developing five

vaccines for three of the five diseases in scope (one against chikungunya, three against Ebola and one against Ebola and Marburg; see figure 14). All five vaccines in the pipeline are being developed in partnership, suggesting that risk-sharing arrangements were important to engage the companies in these projects. The size of the pipeline for these five diseases reflects the limited incentives for major vaccine companies to engage in R&D in these areas, and for EIDs more broadly.

Figure 14. Limited pipeline of vaccines for emerging infectious diseases.

Three companies have vaccines in development for Ebola: Johnson & Johnson (pre-clinical; phase II), GSK (phase III) and Merck & Co., Inc. (phase III). Takeda has a vaccine against chikungunya in pre-clinical development. Johnson & Johnson's pre-clinical Ebolavirus candidate, which also targets Marburg virus, has moved into phase I clinical trials since the period of analysis ended.

Disease	Discovery	Pre-clinical	Phase I	Phase II	Phase III
Ebolavirus	o	1	o	1	2
Chikungunya	o	1	o	o	o
Marburg (haemorrhagic) virus	o	1	o	o	o
Lassa fever	o	o	o	o	o
SARS	o	o	o	o	o

CASE STUDY: COMPANIES HAVE FOUR EBOLA VACCINE CANDIDATES IN THE PIPELINE

WHO has identified an urgent need for vaccine, diagnostic and therapeutic R&D targeting the Ebola virus.²⁹ The Access to Vaccines Index found that three companies evaluated had Ebola vaccine candidates in the pipeline in the period of analysis: GSK, Johnson & Johnson and Merck & Co., Inc. During the period of analysis, Pfizer discontinued its discovery stage research into Ebola. Each company's approach to vaccine R&D targeting Ebola demonstrates the importance of coordinated and sustained incentives for driving R&D that focuses on EIDs, as well as for ensuring that companies plan ahead to make successful candidates accessible. This is especially important given traditional vaccine development often takes

between 5 and 15 years.^{30,31}

The case of Ebola suggests that the vaccine industry is ready to respond to incentives to engage in R&D targeting EIDs. However, it also illustrates that the established system incentivises reactive over proactive R&D. All three companies accelerated Ebola vaccine development after the West African Ebola outbreak began in 2013, in response to the global prioritisation of Ebola R&D. The scale of incentives to drive Ebola vaccine R&D was significant. All three companies collaborated with multiple stakeholders and received external funding to support vaccine development. Global health stakeholders predict that an Ebola vaccine will reach the market,

but the timeframe for this is unknown. When it does occur, stakeholders envision that the vaccine will be used as part of future outbreak responses.³² Greater global coordination is necessary to incentivise companies to engage effectively in developing and bringing to market vaccines for a full range of EID threats.

GSK

► PHASE II

Partnerships and funding: In August 2014, GSK formed an international consortium to fast-track the development of its Ebola vaccine candidate (ChAd3-EBO-Z). The vaccine is being developed in collaboration with partners such as the US National Institutes of Health.

The partners have committed approximately GBP 25 million in R&D funding. GSK entered into negotiations with Gavi for an APC, but ultimately no agreement was reached. GSK cited concerns that the USD 5 million payment offered by Gavi did not constitute appropriate risk-sharing, as it did not sufficiently cover manufacturing costs incurred by GSK.

Access provisions: GSK has committed to continuing to develop its Ebola vaccine at its own risk and to produce the vaccine for emergency use and stockpiling purposes. The company is considering partnerships to ensure cost will not be a barrier to access in low- and middle-income countries. GSK has also committed to supplying 300,000 doses of the vaccine to Gavi for use if an epidemic re-emerges before a vaccine is approved.

JOHNSON & JOHNSON

► PHASE III

Partnerships and funding: In January 2015, Johnson & Johnson announced the formation of a consortium to accelerate the development of its Ebola vaccine candidate (VAC52150), which it founded together with research institutions and non-government organisations.³³ The consortium has received EUR 102 million in Ebola R&D funding from the Innovative Medicines Initiative

(a public-private partnership). The vaccine candidate is in phase II clinical trials.

Access provisions: Johnson & Johnson will take “commercially reasonable” steps to make its vaccine available in developing countries, acting either directly or through partnerships with local authorities and international organisations (e.g., WHO, UNICEF). It applied to WHO for Emergency Use Assessment and Listing (EUAL) in September 2016, a procedure for use of vaccine candidates in the context of a public health emergency.³⁴

► PRE-CLINICAL

Partnerships and funding: Johnson & Johnson has a multivalent filovirus vaccine that moved from pre-clinical into phase I clinical development since the period of analysis ended. This project is based on AdVac® technology (prime) and Modified Vaccinia Ankara Bavarian Nordic vector (boost) and aims to protect against all filovirus strains (Ebola and Marburg). It is being developed in partnership with Bavarian Nordic and received funding from the US Department of Health and Human Services.

Access provisions: Johnson & Johnson did not disclose access provisions for this project.

MERCK & CO., INC.

► PHASE III

Partnerships and funding: In late 2014, Merck & Co., Inc. entered into an agreement with a biopharmaceutical company, NewLink Genetics Corporation, to develop and commercialise its Ebola vaccine candidate (rVSV-ZEBOV). It is now in clinical phase III. The company is collaborating with multiple partners to continue developing this vaccine, and has received R&D funding from donors, including several US government bodies and the Wellcome Trust. Results of a major trial in Guinea, published in December 2016, showed the vaccine was highly protective against Ebola. The vaccine will be fast-tracked for regulatory approval in the EU and US.³⁵

Access provisions: In January 2016, Merck & Co., Inc. agreed to the terms of Gavi’s APC, which was declined by GSK. It has pledged to make the vaccine available to Gavi-eligible countries “at the lowest possible access price to help achieve sustainable public sector access.”³⁶ It has also committed to supplying 300,000 doses for emergency use and/or broader clinical trials. It applied for EUAL in December 2015.³⁷

It is not clear how each company will ensure the affordability of its vaccine(s) in the potential absence of a viable market.

A GLOBAL APPROACH IS REQUIRED TO RESPOND TO THE THREAT OF EIDS

The response to the Ebola outbreak prompted four global commissions to evaluate the national and global responses to the epidemic. They concluded that the approach to preventing, detecting and responding to future infectious disease threats needs to be improved.³⁸ The findings of the Access to Vaccines Index support this view. The Index’s analysis of the vaccine pipelines of eight major companies for five high-priority EIDs found an insufficient level of R&D activity to ensure preparedness in preventing and controlling outbreaks of five EIDs. Ebola receives most attention, yet funding sources for

Ebola vaccine development were consolidated only after the recent outbreak was underway. What is more, some of this funding has since been redirected to the current Zika outbreak.³⁹ While R&D incentive mechanisms, such as AMCs/APCs, donor funding and PDPs, may effectively engage companies in R&D targeting specific diseases, such mechanisms are often employed reactively and are not well-coordinated across EIDs. A stronger framework is required to coordinate global responses so that they are focused on the most pressing EID threats.

CEPI, launched in January 2017, recognises these challenges. It brings together a range of stakeholders, including governments, industry, academia and civil society, to finance and coordinate the development of new vaccines to prevent and contain infectious disease epidemics.⁴⁰ Donors – including the Wellcome Trust, Bill & Melinda Gates Foundation and several governments – have provided USD 460 million in initial funding for the initiative. The first disease targets will be MERS-CoV, Nipah and Lassa fever: CEPI aims to have vaccine stockpiles for these diseases by 2021.⁴¹ GSK, Johnson

& Johnson, Merck & Co., Inc., Pfizer, Sanofi and Takeda are participating in CEPI, as well as Serum Institute of India (representing developing country manufacturers).⁴²

Similarly, GSK has proposed a dedicated, permanent Bio-Preparedness Organisation (BPO) to continuously design and develop vaccines against previously identified and newly emerging pathogens that present a threat to global health, in a “no profit/no loss” model. In late 2016, it was in discussions with interested stakeholders to assess the alignment of the BPO with global policy objectives and, if appropriate, to identify how the concept may

be funded.⁴³ GSK's latest global vaccine R&D centre in the US would serve as the site for its proposed BPO.⁴⁴ GSK has also offered CEPI the use of its R&D centre for vaccine development, at no profit to the company.⁴⁵

Vaccine companies should proactively engage with CEPI and other preparedness mechanisms to ensure their vaccine R&D expertise results in global benefits. Alongside enhanced R&D for EID vaccines, access provisions must be established early in the development process to ensure immunisation coverage is sufficient to protect populations in low- and middle-income countries and to prevent the spread of infec-

tions internationally. These challenges must be overcome to improve preparedness for the emergence of infectious diseases – which will inevitably occur – and ensure global health security for the future.

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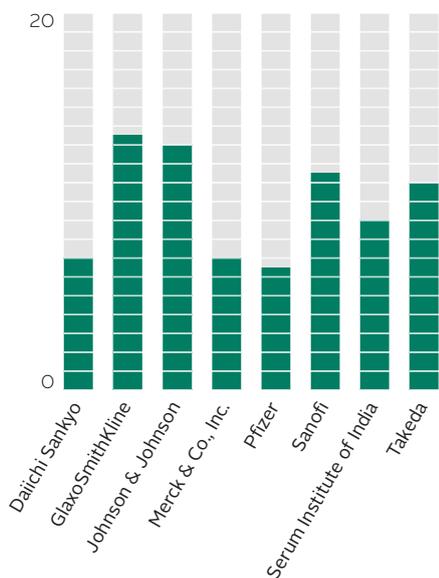
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RESEARCH AREA: RESEARCH & DEVELOPMENT

How vaccine companies engage in R&D of preventive vaccines for 69 priority diseases

COMPANY PERFORMANCES



The number of cells represents the maximum possible score. Coloured cells represent points attained.

GSK and Johnson & Johnson lead, with strong yet differing approaches. GSK has the largest pipeline, while Johnson & Johnson makes the largest R&D investments as a proportion of vaccine revenue. Both companies aim to address high-need vaccine gaps, and both have access plans in place for over half their late-stage vaccine candidates.

CONTEXT

The potential public health benefits of developing new effective vaccines are immense. Further benefits can be achieved by adapting existing vaccines to make them more suitable for resource-limited settings. Yet

vaccine R&D involves high costs, technical complexity and high risk of failure, while there are limited incentives to stimulate engagement. Without heavy investments, by companies and donors, few vaccines will make it to market.

When companies do develop vaccines, it is important they consider the future accessibility of the product.

WHAT THE INDEX MEASURES

In this chapter, the Access to Vaccines Index analyses the R&D projects for preventive vaccines of eight companies: Daiichi Sankyo, GSK, Johnson & Johnson, Merck & Co., Inc.,^a Pfizer, Sanofi, Serum Institute of India and Takeda.

The Index examines the following areas:

- 1 R&D investments:** companies' investments in vaccine R&D for the 69 diseases and pathogens in scope, compared to global vaccine revenues.
- 2 Vaccine pipelines:** where companies are focusing vaccine R&D.
- 3 Types of vaccine R&D:** whether companies are developing new vaccines, adapting existing ones, and/or developing technologies for vaccine packaging and delivery.
- 4 Access provisions:** actions companies take during vaccine R&D to ensure rapid uptake of approved vaccines by populations in need.

^a Merck & Co., Inc. is known as MSD outside the US and Canada.

INTRODUCTION

When companies develop vaccines, it is important they consider the future accessibility of the product. This means considering accessibility when making decisions about a candidate's characteristics. It also includes making plans, early in the development process, to facilitate the vaccine's rapid uptake in low- and middle-income countries, once it has been approved. To achieve these

things, companies need to engage with stakeholders on an ongoing basis.

The Access to Vaccines Index captures companies' efforts to improve access to vaccines for 69 priority diseases and pathogens (see Appendix for a full list). These include:

- 1 all diseases recommended by the World Health Organization (WHO)

for routine immunisation where a cost-effective vaccine is already available;

- 2 all diseases identified by WHO as having a high need for further vaccine R&D; and
- 3 five groups of diseases included on the basis of stakeholder recommendations.

R&D INVESTMENTS: COMPANIES VARY IN THEIR APPROACHES TO INVESTING IN VACCINE R&D

The global vaccine market is highly concentrated, with four companies making up approximately 80% of the market by sales.¹ These companies – Merck & Co., Inc., Pfizer, GSK and Sanofi – are known as the "big four".² In 2014 and 2015, they had the largest global vaccine revenues respectively. Companies' vaccine revenues vary widely: for the "big four", vaccine revenues are between nine and 79 times greater than those of the other four companies evaluated in the Index (Serum Institute of India, Takeda, Johnson & Johnson and Daiichi Sankyo, in order of descending vaccine revenue size). The size of a company's vaccine revenue reflects various factors, including the number of vaccines it has on the market, market demand for those vaccines, the share of the market the company holds and the prices it sets per vaccine.

Commercial market incentives – primarily in high-income countries – drive vaccine R&D for some diseases, such as HPV and pneumococcal disease. For other diseases – in particular those that predominantly affect populations in low- and middle-income countries – potential profitability is low, and alternative incentive systems are necessary to drive R&D.

Companies reported various reasons to the Index for being cautious when investing in vaccine R&D. These included unpredictable demand for vaccines, particularly for infectious diseases that break out sporadically, and

limited recognition of the value of new platforms and technologies for vaccine production. Companies also acknowledged the influence of incentives for engaging in vaccine R&D: including product development partnerships, Advance Market Commitments and market exclusivity arrangements.

Comparing vaccine revenue, R&D investments and pipeline size

The Access to Vaccines Index examines the financial investments companies make into vaccine R&D for 69 priority diseases and pathogens. It compares the scale of these investments to companies' overall vaccine revenues.

Figure 15. Companies take varying approaches to investing in vaccine R&D.

Johnson & Johnson stands out: it earns relatively low revenue, yet makes the largest financial investments into relevant R&D, and has a relatively large pipeline. The company has placed a high priority on vaccine R&D, in particular towards Ebola virus.



● Number of projects in pipeline

*Serum Institute of India's pipeline is based on publicly available sources. It has additional projects for which the data are confidential.

The area of each circle represents each company's number of vaccine R&D projects. Investment represents vaccine R&D investment in USD for diseases in scope over the 2014 and 2015 fiscal years. Revenue represents global vaccine revenue in USD over the 2014 and 2015 fiscal years.

It examines companies' approaches to R&D by analysing and comparing their models for investing in R&D and distributing those investments across pipeline projects.

In 2014-2015, the "big four" made small financial investments into vaccine R&D for diseases in scope – compared to other companies evaluated and when measured as a proportion of their vaccine revenues. Pfizer's investments made up 6% of its revenue, Sanofi's made up 2%, and GSK's and Merck & Co., Inc.'s are confidential. In absolute terms, the investments of GSK, Pfizer and Sanofi were high compared to all companies evaluated.

Serum Institute of India's vaccine revenue is significantly smaller than those of the "big four". As a proportion of its rev-

enue, it made low investments into vaccine R&D compared to other companies evaluated. The three companies with the smallest revenues made larger proportional investments into vaccine R&D: Johnson & Johnson's investments corresponded to 253% of its revenue, and Daiichi Sankyo's and Takeda's investments are confidential.

GSK has the largest pipeline of vaccines targeting diseases in scope: 25 projects (see figure 16). Johnson & Johnson and Sanofi follow with 14 projects each. Public sources indicate Serum Institute of India has 12 vaccine R&D projects targeting diseases in scope;^{3,4,5,6,7,8,9,10,11} however its total pipeline size is confidential. The remaining companies have markedly smaller vaccine pipelines: Daiichi Sankyo (8), Merck & Co., Inc. (6), Pfizer (6), and Takeda (4).

Taking these factors together, it is apparent that companies evaluated take varying approaches to investing in vaccine R&D (see figure 15). Johnson & Johnson stands out from the other companies evaluated: it earns relatively low revenue, yet makes the largest investments into relevant R&D in both absolute terms (USD 717.3 mn) and as a proportion of its revenue (253%). The company has placed a high priority on vaccine R&D, in particular towards Ebola virus. This is reflected in its relatively large pipeline. Of the companies with the largest revenues, GSK and Sanofi stand out for making large absolute investments into vaccine R&D and distributing them across many pipeline projects. Pfizer also makes large investments, focusing these on a smaller range of projects.

VACCINE PIPELINES: MOST VACCINE CANDIDATES ARE IN LATE STAGES OF CLINICAL DEVELOPMENT

Although many effective vaccines have already been developed, persistent product gaps remain. The disease scope of the Access to Vaccines Index comprises 69 diseases and pathogens that are vaccine preventable, and are deemed highly important in the drive to improve access to immunisation. When it comes to vaccine R&D, the importance of targeting a disease can depend on whether effective treatment is already available, or whether a new or adapted vaccine would be the leading tool against a specific disease.

89 vaccine R&D projects in pipeline

The eight companies evaluated have 89 vaccine R&D projects in the pipeline, some of which are being conducted in partnership between multiple companies measured. This comprises 81 vaccine candidates (both new vaccines and adapted versions of existing vaccines); and eight projects that aim to achieve label updates for existing vaccines. Specifically, these label updates aim to: characterise the temperature stability of a vaccine (7 projects) and gain approval for an accelerated immunisation scheme (1 project).

Pipeline movement shows promise

Most projects are in phase II or later of clinical development. This reflects the fact that many projects aim at adapting existing vaccines, and/or expanding approved uses: such projects often do not require early-stage R&D. During the period of analysis, at least ten projects moved from discovery or pre-clinical development into clinical development. Three of these projects target RSV, and the remainder target diseases and combinations of diseases that are distinct from one another. During the same time period, there were ten regulatory approvals. Some were for first-ever vaccines (e.g., Sanofi's Dengvaxia® for dengue, December 2015^{12,13}), while others offered improvements to existing vaccines (e.g., Merck & Co., Inc.'s Gardasil 9® for HPV, covering a broader range of serotypes than Gardasil®)¹⁴. During the period of analysis, five R&D projects were discontinued, and therefore are not included in the 89 vaccine R&D projects reported here. The discontinued projects include a phase III oral rotavirus vaccine discontinued by Sanofi's Indian subsidiary Shantha Biotechnics, and some discovery-stage

Ebola virus research halted by Pfizer.

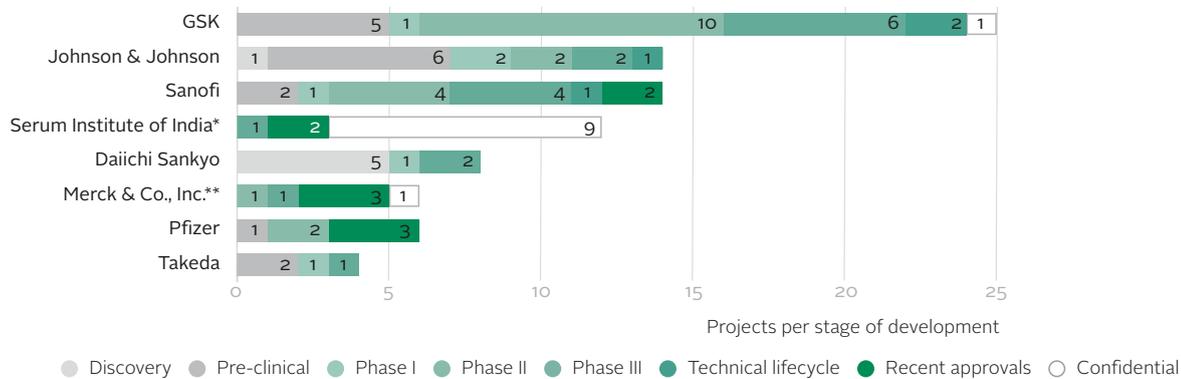
Most projects target diseases with greater market potential

Combined, the 89 projects target 35 diseases, with attention fairly evenly spread among 29 of them (see figure 17). Six diseases and pathogens receive the most attention: pneumococcal disease (9 projects), HPV and seasonal influenza (6 each), meningococcal disease and RSV (5 each), and dengue (4). High R&D activity in these areas reflects commercial incentives for additional manufacturers to enter the market, among other factors. For example, in the case of pneumococcal disease and HPV, it also reflects a need for improvements to the existing vaccines, which are relatively new. For seasonal influenza, it also reflects the need for new vaccines to protect against influenza virus strains that are most likely to spread in a given region each season.

Notably, the pipeline includes three hexavalent vaccine candidates (targeting 6 diseases) and four pentavalent vaccine candidates (targeting 5). These vaccine candidates are likely to be incorporated

Figure 16. Most vaccine candidates are in phase II or later of clinical development.

Many projects aim at adapting existing vaccines, and/or expanding approved uses: such projects often do not require early-stage R&D. GSK and Sanofi have the largest number of projects nearing potential approval; Daiichi Sankyo's and Johnson & Johnson's pipelines focus on early-stage research, reflecting an increasing shift towards the vaccine sector.



*Serum Institute of India's pipeline is based on publicly available sources. It has additional projects for which the data are confidential.

**Through its joint venture with the Wellcome trust, Merck & Co., Inc. is also developing vaccines for cholera, enterotoxigenic *E. coli*, meningococcal disease and rotavirus.

into routine immunisation schedules globally, which offer a large and predictable market for successful innovations. Importantly, they offer advantages compared to many existing DTP-based combination vaccines by targeting a wider range of diseases also recommended for routine immunisation by WHO.

Some diseases get no attention

Half of diseases in scope (34/69) are unaddressed by the vaccine R&D efforts of major global vaccine developers. For 32 of the 34 unaddressed diseases, no vaccines currently exist. The disease scope of the Access to Vaccines Index aims to capture vaccine R&D for a broad range of vaccine-preventable infections. However, it must be noted that companies are not expected by stakeholders to be active in all disease areas measured by the Index. This is in part due to the limited feasibility of including new vaccines into routine immunisation schemes for many coun-

tries in scope. To ensure relevance and uptake, companies should focus R&D activities in areas where potential public health benefit is high.

Almost one third of projects target diseases highly prioritised by WHO

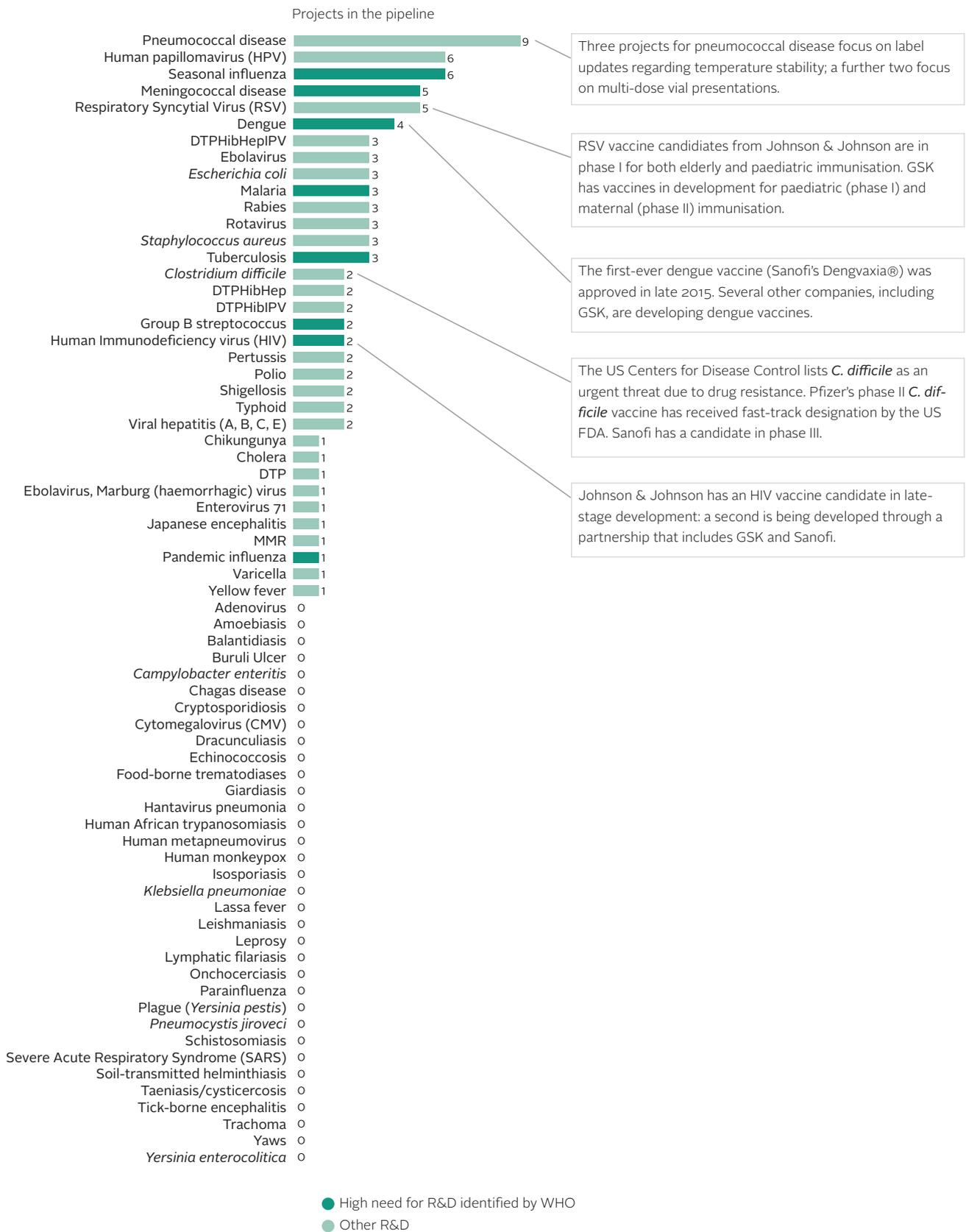
When it comes to R&D prioritisation, WHO's Initiative for Vaccine Research (IVR) identifies vaccine research gaps of particular relevance to low- and middle-income countries. The disease scope of the Index includes seven diseases for which the IVR has prioritised vaccine R&D: dengue, Group B streptococcus, HIV, influenza, malaria, meningococcal disease and tuberculosis (TB).¹⁵ Other stakeholders have identified different disease targets: for example, PATH has set 13 diseases as targets for vaccine development and delivery,¹⁶ and Policy Cures has identified a need for preventive vaccine R&D for 28 neglected diseases with a lack of commercial incentives to drive R&D.¹⁷

Almost a third of the pipeline (26/89 projects or 29%) targets one of the diseases identified by WHO as having a high need for vaccine R&D, particularly for low- and middle-income countries. Seven of these 26 projects target diseases for which no vaccines exist: Group B streptococcus (2 projects), HIV (2) and malaria (3). A further four projects target dengue, for which no vaccine existed until midway through the period of analysis. One of these is the first successful dengue vaccine, approved in December 2015. Two companies lead at targeting diseases highly prioritised by WHO for vaccine R&D: GSK (10 of its 25 projects, or 40%) and Sanofi (5 of its 14 projects or 36%). GSK is the only company that targets all seven diseases in scope prioritised by WHO. This includes malaria, which no other company targets in its vaccine R&D projects. Sanofi targets five of the six diseases.

b WHO added Group B streptococcus and Zika to this list after the development of the Access to Vaccines Index Methodology in 2015. While Group B streptococcus was already included in the disease scope on the basis of stakeholder recommendation, Zika did not meet inclusion criteria. Vaccine R&D activities targeting Zika were therefore not captured during the data collection process. Sanofi and Takeda each have Zika vaccine candidates in development. In February 2017, WHO added RSV to this list

Figure 17. Companies are targeting high-priority diseases with vaccine R&D.

Companies have 89 R&D projects to develop preventive vaccines for 35 diseases and pathogens in scope. Almost a third of the pipeline (26/89 projects or 29%) targets diseases WHO has prioritised for vaccine R&D.



TYPES OF VACCINE R&D: COMPANIES HAVE BALANCED FOCUS ON INNOVATING AND ADAPTING VACCINES

Developing a new vaccine – included here under the term innovative R&D – involves large investments and a high risk of failure. Conversely, fewer resources are typically required to adapt the formulation of an existing vaccine – referred to here as adaptive R&D. Both types of R&D have great potential for improving access to vaccines.^{18,19}

The projects in the pipeline differ substantially in terms of scientific complexity and the resources they require. Having taken these factors into consideration, the Access to Vaccines Index treats vaccine R&D projects equally when it comes to comparing pipelines.

The companies in the Index divide their

CONTEXT

Stakeholder guidance on vaccine characteristics is critical

When engaging in vaccine R&D, companies require certainty around the attributes that are suitable for major international vaccine procurers and funders (e.g., the United Nations Children's Fund [UNICEF] Supply Division, the Pan American Health Organization Revolving Fund and Gavi, the Vaccine Alliance). These vaccine-market shapers can provide guidance in this regard, for example, in the form of target product profiles (TPPs). The WHO Vaccine Presentation and Packaging Advisory Group publishes a Generic Preferred Product Profile for Vaccines, which recommends a key set of vaccine presentations and packaging standards for vaccines intended for use in low- and middle-income countries.²⁰ These recommendations relate to formulations (e.g., temperature stability) and primary container presentations, in addition to packaging and labelling considerations.²⁰ Disease-specific TPPs have also been developed by organisations such as the Malaria Vaccine Initiative, UNICEF and WHO.^{21,22,23}

focus relatively evenly between developing innovative vaccines (46/89 or 52%) and adapting existing vaccines to make them more suitable for use in resource-limited settings or by certain populations (43/89 or 48%). The composition of individual companies' pipelines varies (see figure 18).

Most innovative R&D focuses on diseases with no existing vaccines

Innovative R&D can lead to vaccines that are able to protect large populations from infection, in areas where no vaccines exist or where existing vaccines are sub-optimal. Most (28/46 or 61%) of innovative R&D projects in the pipeline target diseases that are not vaccine preventable. The diseases most often targeted by these projects are RSV (5 projects) and Ebolavirus (4). In addition to these 28 projects, four projects in the pipeline target dengue, including the first approved vaccine, Sanofi's Dengvaxia®.

The remaining innovative R&D projects (14) focus on developing vaccines that offer important alternatives to existing vaccines (e.g., extending protection to new demographic groups). For example, the traditional BCG vaccine protects infants against TB. However, a vaccine

is also needed to prevent TB in adolescents and young adults: GSK and Sanofi each have novel TB vaccines in phase II development targeting these groups. In another example, Merck & Co., Inc. received US FDA approval in December 2014 for its second-generation HPV vaccine (Gardasil 9®),¹⁴ which protects against an additional five serotypes compared to its first-generation vaccine (Gardasil®). Merck & Co., Inc. developed Gardasil 9® in response to a clear public health need to prevent cervical cancer, particularly in countries within the scope of the Index. It is not yet available in countries in scope.

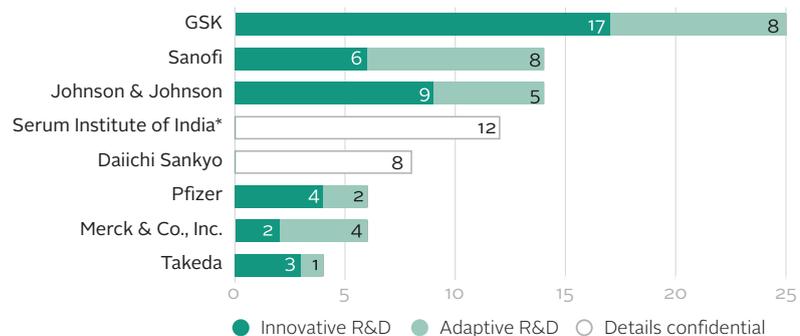
Wide variety of adaptations

Adapting product profiles to improve the suitability of vaccines for use in resource-limited settings is important for improving vaccination coverage and achieving immunisation and eradication goals. Often, the best combination of characteristics becomes apparent once a vaccine has been rolled out in real-world settings. Once this happens, further R&D is required to improve the vaccine.

Multivalent vaccines, which target multiple pathogens and/or multiple serotypes of the same pathogen, can facil-

Figure 18. Companies engage equally in innovative and adaptive vaccine projects.

The companies in the Index divide their focus relatively evenly between developing innovative vaccines (46/89 or 52%) and adapting existing vaccines to make them more suitable for use in resource-limited settings (43/89 or 48%). The balance varies by company.



*Serum Institute of India's pipeline is based on publicly available sources. It has additional projects for which the data are confidential.

itate simplified vaccine schedules for childhood immunisation programmes and reduce the costs and complexity of stocking, storing and administering multiple individual vaccines.²⁴ There are 43 adaptive R&D projects in the pipeline (including one project that aims to achieve two adaptations; see figure 19). Almost one third (30%) of adaptive R&D projects involve multivalent vaccines. For example, Serum Institute of India is developing a 10-valent pneumococcal conjugate vaccine (PCV) that targets the serotypes prevalent in 70% of people affected by pneumococcal disease in Africa, Asia and Latin America.²⁵ Meanwhile, 28% of adaptive R&D projects focus on either characterising or improving the temperature stability of a vaccine, and 44% target a range of other improvements, including in efficacy, immunisation schedules, yield of production, or formulations to allow for easier administration.

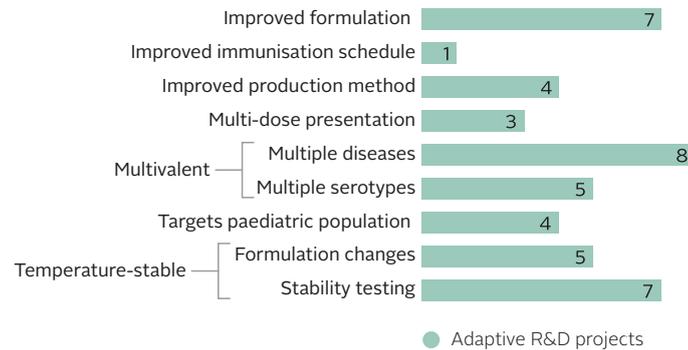
Most temperature-stability projects focus on vaccine characterisation

To maintain their efficacy, many vaccines must be transported and stored between 2 and 8°C (i.e., the cold chain). The risk of high or freezing temperatures rendering vaccines unusable poses a major barrier to access in low-resource settings. Companies are addressing this through R&D to improve or describe temperature stability, with 12 projects in total. Five of these projects focus on developing thermostable vaccine formulations. For example, GSK is working through the Vaccine Discovery Partnership to render the adjuvant of its RTS,S malaria vaccine candidate (Mosquirix®) thermostable. This project could have benefits for other vaccines containing the same adjuvant (ASo1), such as GSK’s candidate HIV and TB vaccines.²⁶

The other seven temperature stability projects focus on characterising a vaccine’s temperature-stability profile and achieving corresponding label updates. Such projects tend to be inexpensive (at least when compared to reformulating a vaccine to improve its thermostability) as they usually only require additional

Figure 19. Companies are working toward a wide variety of vaccine adaptations.

Companies have 43 adaptive vaccine R&D projects for diseases in scope. Adaptive R&D projects for multivalent vaccines are the most common, followed by temperature-stability projects.



One project is counted twice: it falls into two categories of adaptation.

stability studies.²⁷ The WHO Controlled Temperature Chain (CTC) programme requires evidence that a vaccine maintains stability when exposed once to at least 40°C for a minimum of three days just prior to administration.²⁸ Several companies are working towards CTC label updates, including GSK for its PCV (Synflorix®) and Sanofi for its cholera vaccine (Shanchol®). Notably, only one project focuses on ensuring an existing vaccine retains stability after freezing: GSK is testing the impact of sub-zero temperatures on its PCV (Synflorix®).

New dose presentations under development

Single- and multi-dose vaccine presentations support access in different ways: the former can reduce waste and support safe administration, while the latter generally sell at lower per-dose prices, and require less supply chain capacity. Companies have a role in ensuring vaccine presentations are available in dose forms appropriate to each vaccine. Changing the dose presentation of existing vaccines can require significant resources: often, the vaccine must be reformulated, requiring additional clinical trials.

Takeda has committed to developing multi-dose presentations of its candidate chikungunya vaccine, dengue vaccine and IPV to meet the expectations of individual countries and WHO. Two

companies are developing four-dose presentations of existing PCVs: GSK for Synflorix® and Pfizer for Prevenar 13®. Johnson & Johnson was working to develop a multidose vial presentation of its pentavalent vaccine (Quinvaxem®) during the period of analysis, however this project has since been discontinued.

Technologies for vaccine packaging and delivery receive less attention

In addition to the vaccines themselves, companies can also help develop new platform technologies for vaccine packaging and delivery – ones that specifically aim to overcome barriers to access in low-resource settings. Such technologies could potentially be used for multiple vaccines, and therefore should be shared with other manufacturers to maximise uptake and potential impact. However, engagement by companies in such R&D is low. One factor that could raise this level of engagement is greater clarity from global health stakeholders on R&D priorities, and the likelihood of innovations being taken up.

Two companies evaluated are actively developing such platform technologies for vaccine packaging and delivery: GSK and Sanofi. For example, Sanofi is collaborating with the Infectious Disease Research Institute on the Global Health Vaccine Center of Innovation, established in 2015. This project aims to

accelerate the development of vaccines and supporting technologies. During product development, the partners involved integrate measures to ensure R&D addresses public health needs in

low-income countries and to facilitate access to affordable products, produced at suitable volume, after market entry. Under a grant from the Bill and Melinda Gates Foundation, Sanofi is also explor-

ing the technical and regulatory feasibility of using Micropellet technology for cost-effective novel combination vaccines that are thermostable.²⁹

ACCESS PROVISIONS: COMPANIES HAVE ACCESS PLANS FOR OVER HALF OF VACCINES IN LATE-STAGE DEVELOPMENT

Companies can plan ahead during product development to ensure vaccines are made accessible in low- and middle-income countries. This type of forward planning can help ensure broad access to vaccines is rapidly achieved following approval. Such plans, referred to as access provisions, can take the form of commitments, plans and strategies to ensure successful vaccines are supplied in sufficient quantities and at affordable prices. Other stakeholders can facilitate effective forward planning by communicating what action is needed. For example, Gavi's Vaccine Investment Strategy and disease-specific roadmaps encourage dialogue and communicate population needs.^{30,31} Such clarity can be particularly useful given the uncertainty companies face regarding future demand for vaccines in development.

Access provisions should be put in place as early as possible in the development process. All vaccines in late-stage development should have access provisions in place, as these vaccines have the greatest likelihood of making it to market. Access plans can be made increasingly specific as vaccines progress through the pipeline and their characteristics and potential markets are better understood.

Almost half (43/89 or 48%) of the companies' vaccine candidates are in late stages of development. Of these, over half (24/43 or 56%) have one or more access provisions in place (see figure 20). Six companies have access provisions for at least half their late-stage pipeline candidates (GSK, Johnson & Johnson, Merck & Co., Inc., Sanofi, Serum Institute of India and Takeda). GSK and Sanofi, with the largest late-stage pipelines, also have the most late-

stage projects with one or more access provision in place (8/15 or 53% for GSK; 6/10 or 60% for Sanofi).

Access provisions can take many forms

Often, companies' access plans are directly tied to mechanisms put in place by vaccine stakeholders in order to increase access. This is the case with the WHO prequalification process, which is designed to facilitate procurement by United Nations agencies. During vaccine development, companies can commit to applying for WHO prequalification, which indicates the company's intention to supply to low- and middle-income countries. This is the most common form of access provision in the pipeline. For almost one third (13/43 or 30%) of late-stage projects, companies have received, applied for, or plan to apply for WHO prequalification:

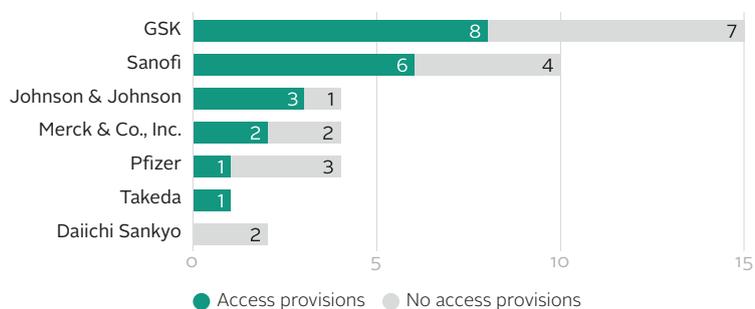
for a pentavalent combination vaccine plus 12 projects targeting ten other diseases in scope.

Twelve late-stage projects (12/43 or 28%) involve a commitment to price the vaccine affordably in low- and middle-income countries. For example, Merck & Co., Inc. has agreed to the terms of Gavi's Advance Purchase Commitment for its Ebola vaccine candidate, pledging to make the vaccine available to Gavi-eligible countries "at the lowest possible access price to help achieve sustainable public sector access."³² GSK has committed to pricing its malaria vaccine candidate, RTS,S, at manufacturing costs, plus 5% to be reinvested in R&D for next-generation malaria vaccines or vaccines against NTDs.

Overall, while commitments to affordable pricing tend to be broad, they pro-

Figure 20. Companies have access provisions in place for over half of vaccines in late-stage development.

Access provisions are the plans companies make during development to ensure vaccines are rapidly accessible, once approved. The most common provision made by companies is to commit to applying for WHO prequalification, which indicates an intention to supply to low- and middle-income countries.



Details of Serum Institute of India's pipeline are confidential. Half of its late-stage projects have at least one access provision in place. Late-stage projects refer to those in phase II and III clinical trials and those that were approved during the period of analysis. Late-stage projects that involve adaptations to existing marketed vaccines, which will not lead to a new vaccine (e.g., Controlled Temperature Chain label updates), are excluded here.

vide an important indication of a company's intent to make its vaccine affordable. GSK and Merck & Co., Inc. stand out for making more specific commitments to affordable pricing than their peers. However, until specific prices are agreed and a vaccine enters the market, it is impossible to determine a vaccine's actual affordability. For example, GSK has reported that RTS,S will be priced around GBP 8.50 per child (based on demand of approximately 100 mn doses), which may still prove unaffordable in many malaria-endemic countries.³³

Companies can also commit to registering newly approved vaccines in low- and middle-income countries, and developing registration strategies to sup-

port these commitments. For example, Johnson & Johnson, together with several partners, is testing its HIV vaccine candidate in Rwanda, South Africa, Thailand and Uganda, and commits to registering the vaccine, if approved, in all countries where trials have taken place. It has also committed to making the vaccine sufficiently affordable for the public sector in low- and middle-income countries to purchase in quantities sufficient to meet populations needs. This includes offering a preferential price to these countries. Companies can also make advance commitments to supplying their vaccines in sufficient quantities, for example for emergency and stockpiling purposes. GSK and Merck & Co., Inc. have each committed to supplying 300,000 doses of their

Ebola vaccine candidates in the case of emergencies.

No evidence of access provisions was provided for the remaining 19 late-stage projects. This includes all late-stage projects for infections with *C. difficile* (Pfizer, Sanofi), *E. coli* (Johnson & Johnson) and *S. aureus* (Pfizer), as well as GSK's candidates for hepatitis C, RSV (maternal immunisation) and varicella (shingles). In some cases, companies reported a plan to develop access provisions at a later stage. Companies that follow through on these plans, increasing their comprehensiveness as a vaccine approaches the market, will help ensure their vaccines become rapidly accessible upon approval.

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CONCLUSION

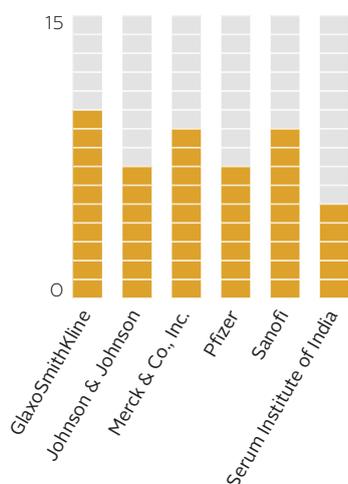
The eight companies evaluated by the Access to Vaccines Index have 89 projects in the pipeline for 35 of the 69 diseases in scope. Almost one third of projects target diseases deemed high priority by WHO for vaccine R&D. Companies focus evenly on developing new vaccines and adapting existing ones: both types of vaccine R&D are critical to facilitate widespread immunisation. While just over half of late-stage projects have one or more access provision in place, companies do not provide evidence of access provisions for the remainder of these projects. These findings indicate that, while companies are responding to the need for vaccines, substantial improvements can be gained. Sustained incentives to drive R&D are required to make this a reality. Companies must continue to invest sustainably in vaccine R&D for diseases prioritised by external stakeholders. This not only includes considering how the vaccine's characteristics can be best designed to facilitate access, but also making clear plans to ensure the rapid uptake of successful innovations in low- and middle-income countries.

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RESEARCH AREA: PRICING & REGISTRATION

How vaccine companies take steps to make vaccines affordable and available

COMPANY PERFORMANCES



GSK leads, followed by Merck & Co., Inc. and Sanofi with equal total scores. GSK’s pricing strategy for vaccines is the most sensitive to each country’s ability to pay, relative to peers’ strategies. GSK and Merck & Co., Inc. lead in transparency, publishing their complete pricing strategies and reporting that they do not prohibit governments from publishing manufacturer prices. Sanofi is the leader in registration, filing to register most of its relevant vaccines in 30-50% of both low-income countries and lower middle-income countries in scope.

CONTEXT

Vaccines for routine immunisation are generally purchased by governments or through pooled-procurement systems aiming to lower prices. There are three main organisations involved in these systems: the United Nations Children’s Fund

(UNICEF), the Pan American Health Organization (PAHO) Revolving Fund, and Gavi, the Vaccine Alliance.¹ The vaccine market is consolidated, with four companies accounting for the majority of vaccine revenues (GSK, Merck &

Co., Inc., Pfizer and Sanofi). There is also a growing number of vaccine manufacturers based in emerging markets which focus on manufacturing traditional, lower-priced vaccines.

WHAT THE INDEX MEASURES

The Access to Vaccines Index evaluates data from six companies in relation to vaccine pricing and registration: GSK, Johnson & Johnson, Merck & Co., Inc., Pfizer, Sanofi and Serum Institute of India.

The Index examines the following areas:

- 1 Vaccine pricing decisions:** whether and how companies consider affordability in pricing strategies for public sectors in low- and middle-income countries.
- 2 Price trends:** how prices of key new vaccines for Gavi-eligible countries have changed over time.^a
- 3 Transparency in pricing:** whether companies are transparent around the factors they consider in their pricing strategies and whether they support vaccine price transparency.
- 4 Availability:** how widely companies file to register vaccines in low- and middle-income countries.

^a Companies were not scored in this area.

INTRODUCTION

Ensuring sufficient vaccine coverage depends on a variety of factors, not least the availability of effective, quality, affordable vaccines. These conditions are key for enabling procurers to purchase the quantities of vaccines needed to immunise entire target populations. Supply, availability, and affordability are closely inter-linked in the vaccine ecosystem.

Market shapers, manufacturers and governments all have a role to play in facilitating the registration of vaccines where needed, and ensuring vaccines are affordable.

Registering vaccines rapidly and broadly

The registration of a vaccine is a critical step in enabling access: a vaccine cannot be made available in a given country until it has been registered for use there. It is important that companies start the registration process as the vaccine is approved, especially where there is an urgent public health need. Rapid registration is also key for securing market access and enabling a strong market share, particularly for newer vaccines with few alternatives. Registration decisions need to be informed by the range of other vaccines available and the vaccine's suitability for use in different environments.

Pricing vaccines to realise affordability

Affordability is a cornerstone for ensuring access to vaccines. High vaccine prices contribute to the high cost of immunisation programmes, alongside costs for vaccine administration, wastage and disposal.^{2,3} For low-income countries (LICs) and some middle-income countries (MICs), vaccines are commonly purchased through pooled-procurement systems, which

enable countries to purchase vaccines efficiently and at lower prices. United Nations Children's Fund (UNICEF) and the Pan American Health Organization (PAHO) serve as procurement agencies for vaccines and negotiate lower prices. Gavi, the Vaccine Alliance – a public-private global health partnership – supports certain countries via a co-financing policy.^b

Countries qualify for Gavi support based on their average Gross National Income (GNI) per capita and a number of other criteria, depending on the vaccine they are requesting support for. Fifty-four countries were eligible for Gavi support in 2016, as their average GNI per capita for the past three years was below or equal to USD 1,580.⁴ Each year, some countries begin transitioning from Gavi support – as their average GNI for the previous three years has passed the Gavi eligibility threshold.⁵ In 2016, sixteen countries were in the process of transitioning. An additional five reached the end of Gavi support and will begin to fully self-finance their immunisation programmes.

Affordability remains an issue

Despite the success of organisations such as Gavi and PAHO in negotiating lower vaccine prices for poorer countries, affordability remains an issue, particularly for newer vaccines. This is affected by the availability of financing for vaccines, as well as the actual price of vaccines. Spending on immunisation in LICs and lower middle-income countries (LMICs) is expected to more than double in the coming decade.⁶ Between 2001 and 2014, six new vaccines^c were added to the World Health Organization (WHO) Expanded Programme on Immunization (EPI), bringing the total number to 12.^{7,8} During this period, the introduction of new vaccines into

national immunisation programmes significantly raised the cost of fully immunising a child following WHO recommendations: from less than USD 1 in 2001, to USD 32.09 to immunise a boy and USD 45.59 to immunise a girl (includes the HPV vaccine), in 2014.⁹

Some newer vaccines are reportedly already viewed by governments as too costly to include in national immunisation schedules.⁹ A study from 2012 found that LMICs^d were lagging behind both low-income and high-income countries in the adoption of new vaccines, with vaccine prices being identified as one of the key factors. Few LMICs that didn't qualify for Gavi support had adopted new vaccines, including for rotavirus and pneumococcal disease.¹⁰ Even in some upper middle-income countries (UMICs) with significant vaccine markets, such as China and Thailand, people are not routinely immunised with pneumococcal conjugate vaccines (PCVs), despite it being recommended by WHO for routine immunisation.¹¹ Looking ahead, new and more complex vaccines, many offering more effective disease prevention, may put increasing pressure on immunisation budgets while governments are confronted with other competing health priorities.

Certain traditional vaccines have also become more expensive. This is typically either due to supply problems (including shortages caused by demand- or supply-side fluctuations) or reduction in competition. Suppliers have exited certain markets for traditional vaccines as industrialised countries have shifted to different vaccines;⁷ in other markets, suppliers have (temporarily) left as very low initial prices contributed to under-investment in infrastructure, resulting in technical difficulties.

b UNICEF is the world's largest supplier of vaccines to children and works with many stakeholders to increase demand for vaccines, including through pooled procurement. PAHO serves as a United Nations (UN) public-sector procurement agency for vaccines and has established a revolving fund that enables member states in the Americas to access lower vaccine prices. Gavi brings together many key organisations in a single decision-making body regarding access to vaccines, and historically has worked to accelerate the introduction of new and underused vaccines in over 70 of the poorest countries.

c Rubella, hepatitis B, *Haemophilus influenzae* type b (Hib), pneumococcal, rotavirus and human papillomavirus (HPV).

d In 2017, 52 countries are classified as LMICs: 49 of which are in the scope of the Access to Vaccines Index. These include 23 countries (44% of all LMICs) that self-finance their vaccine purchases. These 23 countries are not members of PAHO: 14 of them are also not eligible for Gavi support (including Egypt, Kosovo and Morocco); the remaining nine (including Democratic Republic of Congo, Indonesia and Vietnam) are currently transitioning from Gavi support.

For example, the weighted average price (WAP) per dose for yellow fever vaccine (YFV), used to prevent yellow fever, increased by an average of 7% a year between 2001 and 2015, from USD 0.39 to USD 1.04. An outbreak of yellow fever in Angola in 2015 led to increased demand, despite limited production capacity and a global shortage of the YFV. UNICEF anticipates the WAP of YFV to increase to USD 1.10 per dose over 2016–2017, given continued supply constraints and prior trends.^{12,13}

For BCG vaccines, used for childhood tuberculosis, UNICEF reported supply shortfalls due to manufacturer technical difficulties and certain manufacturers temporarily leaving the market since the end of 2013.¹⁴ While the supply outlook for 2016–2018 is no longer constrained and is considered to be sufficient to meet all country require-

ments,^{15,16} UNICEF anticipates the 2016–2018 BCG vaccine WAP per dose will increase by approximately 30%, compared to 2015. This increase reflects increases in overhead costs experienced by most manufacturers related to refurbishments during 2013–2015.¹⁷ The price increases allow a higher margin for manufacturers to invest in system upgrades and maintenance, which can prevent future supplier exits and technical difficulties.

Based on the inclusion of new vaccines in the EPI and predicted price rises for certain traditional vaccines, governments and other purchasers are facing financing constraints and there is growing pressure for manufacturers to address vaccine affordability, keeping in mind the sustainability of their vaccine businesses.

The Access to Vaccines Index evaluates vaccine manufacturers' strategies to make vaccines affordable and efforts to apply to register vaccines in LICs and LMICs, to encourage and enable vaccine companies to adopt or expand good practice in these areas. The Index also aims to encourage companies to publish information that can enable governments and other procurers to understand how manufacturers set prices, and also to support price transparency in their purchasing contracts with governments. This has potential to facilitate better negotiations around vaccine prices, to ensure both affordability and, eventually, improved immunisation coverage.

VACCINE PRICING DECISIONS: VACCINE PRICING IS BASED ON MULTIPLE FACTORS; ALL COMPANIES CONSIDER GAVI STATUS

The Access to Vaccines Index has examined companies' vaccine pricing strategies for the public sector, to determine whether companies consider affordability for both LICs and MICs and whether this varies according to countries' eligibility for Gavi support and/or whether they procure vaccines via PAHO or UNICEF. Companies have diverse portfolios of vaccines. The specific pricing strategy for each vaccine for any given market may be different, and thus pricing strategies were not compared by the Index per product. When reporting on vaccine pricing strategies, the Index uses the term affordability to refer to a measure of governments' and/or other procurement agencies' ability to pay for a vaccine for the public sector.

All companies consider Gavi status

Collectively, the six companies consider 18 diverse factors when setting vaccine prices, with the most attention being paid to the conditions in a given country. Indeed, the only factor considered by all six companies is a country's eligibility for Gavi support (see figure 21).

Four of the six (GSK, Johnson & Johnson, Pfizer and Sanofi) have a vaccine pricing strategy that considers GNI per capita, for at least some LICs and MICs, as a measure of different countries' affordability. The other two companies in scope (Merck & Co., Inc. and Serum Institute of India) have pricing strategies for vaccines, but do not consider GNI per capita for LICs and MICs.

In addition to GNI, companies report that they consider several other factors when setting prices. This includes demand-side factors, such as volume and time commitments. Such factors are important for enabling companies to set prices that recoup fixed costs and ensure sustainable supply. While the need to consider such factors is certainly reasonable, it should be noted that they do not ensure a given country's affordability. Similarly, where companies price vaccines based on the innovative nature of the vaccine and/or value provided by it, this may not result in affordable prices.

All six companies evaluated in this area offer discounts to Gavi-eligible countries. All companies except Serum Institute of India publicly commit to offer discounts for some vaccines for a set time period to the 16 countries classified in 2016 as Gavi-transitioning. Companies generally offer their lowest prices to Gavi-eligible countries.

Middle-income countries not systematically addressed

However, many MICs are not eligible for Gavi support (or PAHO's Revolving Fund), e.g., Ukraine and Sri Lanka. Many countries also face healthcare budget constraints. The Index does not find clear evidence that companies systematically consider countries' ability to pay when setting vaccine prices in MICs, given that several other factors influence their pricing decisions. This raises concerns that many MICs may not be able to afford vaccines, thus limiting immunisation coverage, particularly of more expensive newer vaccines.

GSK and Pfizer: the most specific strategies

GSK and Pfizer have the most specific pricing strategies for vaccines: they sort countries into the most number of pricing tiers, based on income (GNI per capita), allowing more granular price differentiation. GSK has 35 vaccines in its vaccine portfolio for diseases in scope, while Pfizer has three. Consequently, GSK's commitment has a broader potential application. However, Pfizer's three vaccines (Mencevax®, Nimenrix® and Prevenar 13®) are important, as they represent markets with few manufacturers.

► GSK

Seven pricing tiers

GSK's strategy sets out seven pricing tiers for different markets: the lowest comprises all Gavi-eligible countries. The other tiers are determined according to a combination of criteria, including: GNI per country, target population coverage, duration of contract and committed volume (see figure 21). In other words, non-Gavi countries can qualify for lower pricing tiers by committing to longer contracts and higher volumes.

Compared to its peers' strategies, GSK's pricing matrix is the most sensitive to countries' ability to pay. However, larger MICs with financing constraints may be faced with dilemmas, for example: whether they should commit to longer-term higher-volume contracts in order to secure affordable prices, or commit to contracts with feasible time-scales and volumes but less affordable per-dose prices.

► PFIZER

Six pricing tiers

Pfizer's pricing strategy includes six tiers and its strategy was published in May 2016:¹⁸ it is unclear whether Pfizer acted on these plans before this date. Pfizer's lowest tier includes Gavi-eligible countries, Gavi-transitioning countries and all other LICs. Similar to GSK, Pfizer assesses affordability using GNI per capita. It also considers the level of government commitment, the degree of innovation represented by the vaccine

and the required investments in clinical development programmes and manufacturing facilities. This cluster of factors implies new and more complex vaccines will have higher prices regardless of a country's income level.

Figure 21. Which factors do companies consider when setting vaccine prices?

The 18 factors considered across the six companies can be divided into five different groups. The largest group focuses on conditions in a given country, such as its Gavi status. Others look at aspects of government commitment, or the value of or need for the vaccine in question, including related costs.

Type of factor	Factor	GSK	Johnson & Johnson	Merck & Co., Inc.	Pfizer	Sanofi	Serum Institute of India
Country feature	Gavi status (eligible, transitioning)	●	●	●	●	●	●
	GNI per capita, for at least some countries and vaccines	●	●		●	●	
	Humanitarian emergency discount	●			●		
	Fiscal capacity and health spending			●			
	Mechanisms & policies for procuring vaccines			●			
	Competitive environment					●	
	Existence of distinct distribution networks (e.g. public/private)					●	
Extent of government's commitment	Target population coverage	●		●			
	Covering entire birth cohort				●		
	Vaccinating catch-up cohorts	●					
	Volume to be purchased	●					
	Duration of contract	●					
Value of vaccine	Public health value to healthcare system			●	●		
	Scientific innovation vaccine represents				●		
Need for vaccine	Public health need			●			
	Disease burden & which population segments are affected by the disease					●	
Required investment	In clinical development programmes				●		
	In manufacturing facilities & workforce				●		

Figure 22. Pricing for Gavi countries: product-specific commitments

Companies commit to ensuring certain vaccines are offered at discounts/low prices to Gavi countries and have specific pricing strategies for their dengue and malaria vaccines. In reality, some of these vaccines may still be unaffordable, when decisions are made regarding their inclusion in routine immunisation schedules. Countries not eligible for support from Gavi might be offered higher prices.

Disease	Product	Company	Details of commitment			
			Made in	Price per dose	Geographic scope	Notes
Dengue	Dengvaxia®	Sanofi	2016	Not specified	Endemic countries where dengue is a major public health priority	A programme-based pricing policy for public markets, regardless the size of the country, but depending on the scale of a national or sub-national immunisation programme. Sanofi will decrease the average public price with increasing number of age cohorts.
Diphtheria, <i>Haemophilus influenzae</i> type B, Pertussis, Tetanus, Viral hepatitis	Quinvaxem®	Johnson & Johnson	2015	USD 2.35*	Gavi countries	
Diphtheria, <i>Haemophilus influenzae</i> type B, Pertussis, Tetanus, Viral hepatitis	Pentavalent	Serum Institute of India	2011	USD 1.75**	World community	
Human papillomavirus (HPV)	Cervarix®	GSK	2013	USD 4.60	Four new Gavi demonstration projects	433,300 vaccine doses to be supplied between 2013-2017.
Human papillomavirus (HPV)	Gardasil®	Merck & Co., Inc.	2013	USD 4.50	Gavi countries	2.4 million doses to be supplied between 2013 and 2017.
Malaria	Mosquirix®	GSK	2015	Not specified	Not specified	A not-for-profit price covering the cost of manufacturing, plus a return of around 5% that will be reinvested in R&D for second-generation malaria vaccines, or vaccines against other neglected tropical diseases.
Pneumococcal disease	Synflorix®	GSK	2017	USD 3.05 (tail price)	Gavi countries	240 million doses to be supplied over ten years from 2013.
Pneumococcal disease	Prevenar 13®	Pfizer	2017	USD 3.05 (tail price)	Gavi countries	260 million doses to be supplied from July 2013 until 2025.
Polio	Imovax® Polio	Sanofi	2014	Euro 0.75 (approx. USD 1)	Gavi countries	Through a joint price support mechanism with BMGF (including a financial contribution from both organizations).
Rotavirus	Rotarix®	GSK	2012	USD 2.50	Gavi countries	132 million doses to be supplied over five years.
Rotavirus	Rotateq®	Merck & Co., Inc.	2013	USD 3.50	Gavi countries	
Viral hepatitis	Hepavax-Gene®	Johnson & Johnson	2015	USD 0.16	Gavi countries	

* UNICEF price database projects prices of USD 2.35 per dose in 2016 and USD 0.80 per dose in 2017.

** UNICEF price database projects prices of USD 0.75 per dose in 2017 and USD 0.69 per dose in 2018 and 2019.

PRICE TRENDS: PRICES OF THREE KEY VACCINES FOR GAVI COUNTRIES REMAINED GENERALLY STABLE OVER TIME^e

Various stakeholders, including governments, Gavi and others, have committed to achieving global immunisation goals. To achieve these goals, procurers must meet the significant challenge of financing vaccine purchases for entire populations. Many countries face funding gaps: studies estimate that national immunisation programmes across 94 LICs and MICs have funding gaps, ranging from USD 7.6 billion to USD 14.2 billion, for the period between 2016 and 2020 (assuming constant or decreasing vaccine prices).^{19,20} MICs without Gavi support, as well as Gavi-transitioning countries, are particularly at risk of funding constraints and inadequate vaccine coverage.

Analysing price dynamics

In figure 23a-c, to give insight into price dynamics, the Index has compared prices over time for three key new vaccines offered to Gavi countries (for pneumococcal disease, rotavirus and HPV). Examples of prices paid by self-procuring MICs (from WHO's Vaccine Product, Price and Procurement [V3P] database²¹) give an indication of the range of prices paid by such countries. The examples chosen were based on the availability of data for countries in regions in scope, given that country names are anonymised in the database. Figure 23 also includes key contextual information about the vaccines in question.

The aim is to determine how the prices of newer vaccines have changed in recent years, given that they constitute a large proportion of national immunisation programme costs, and are not yet adopted by all LICs and MICs. Two of these vaccines – against rotavirus and pneumococcal disease – now make up around three quarters of the total cost of vaccinating a child (with 12 required vaccines).⁹ The Index does not evaluate companies on the affordability of their vaccines' prices, as affordability cannot be judged purely on the basis of the price of vaccines. It depends on who

is paying for the vaccine and what their constraints are.

As shown in figure 23a-c, new vaccine prices for Gavi countries have either marginally fallen or have experienced no change over the past 5-7 years, given existing demand and incentive structures in place.

Volume data: a missing puzzle piece

These trends also need to be interpreted using volume data, which is not publicly available per manufacturer. Vaccine prices are demand-driven and volume-dependent, and manufacturers' willingness and ability to reduce prices may depend on reaching critical volumes. Prohibitively high prices and competing spending priorities may prevent governments from purchasing certain new vaccines.¹⁰ Yet, without sufficient demand, companies may not have sufficient incentive to lower prices. Given the high barriers to entering vaccine markets, it is common to have periods with only a few manufacturers for a new vaccine. If one company then has a significantly higher market share than its competitor(s), the latter may not have the incentive to lower prices, offering little competition to the market leader.

Innovative tendering approaches are possible

In October 2016, UNICEF reached an agreement with six manufacturers of the pentavalent vaccine against Hib, pertussis, tetanus, hepatitis B and diphtheria to offer the vaccine at an average price of USD 0.84 per dose.²² This is half what UNICEF previously paid. The agreement was reached through an innovative, multi-round tendering process, and included three manufacturers in scope: Johnson & Johnson, Sanofi and Serum Institute of India. This is an important precedent: this price can be accessed by certain governments who self-finance the procurement of this vaccine. This agreement also demonstrates the value that partnerships can

bring to affordability and price sustainability when applied in supplier discussions.

Collaboration between the industry, market shapers and governments is critical to achieving such successes, as well as to enabling a healthy market place where multiple manufacturers compete to offer lower prices and sustainable supply.

Limitations of this analysis

This analysis has not been able to take account of sales volume data per manufacturer, as this data was only available in terms of annual tenders. Further, it is important to note that certain types of vaccines are more expensive than others to develop and manufacture, due to their individual characteristics. For example, vaccines that target multiple diseases or disease strains can reduce the number of injections required to immunise.²³ This can limit the logistical cost of multiple injections²⁴ and improve adherence. Multi-dose presentations are also generally sold at lower per-dose prices than single-dose presentations. As a result, comparisons between the prices of different vaccines should be made with caution, even where they target the same disease. Figures 23a-c are not intended to provide direct price comparisons, but rather insight into price trends over time in Gavi countries, for some of the new EPI vaccines for which there are few manufacturers.

^e Companies were not scored in this area.

Figure 23. How have vaccine prices for Gavi countries changed over time?

This analysis* compares vaccine prices contracted with suppliers by UNICEF, over time and by manufacturer. These figures are intended to provide insight into price trends over time in Gavi countries, for some of the new EPI vaccines for which there are few manufacturers. New vaccine prices for Gavi countries have either marginally fallen or have experienced no change over

the past 5-7 years, given existing demand and incentive structures in place. These trends also need to be interpreted using volume data, which is not publicly available per manufacturer. Vaccine prices are demand-driven and volume-dependent, and manufacturers' willingness and ability to reduce prices may depend on reaching critical volumes.

Figure 23a. Prices for Rotavirus vaccines

The Index analysed the prices of rotavirus vaccines for 73 countries that were eligible for Gavi support (in 2009) and that procured via UNICEF. Since 2013, these prices have remained constant. Source: UNICEF Vaccine Price Data: Rota

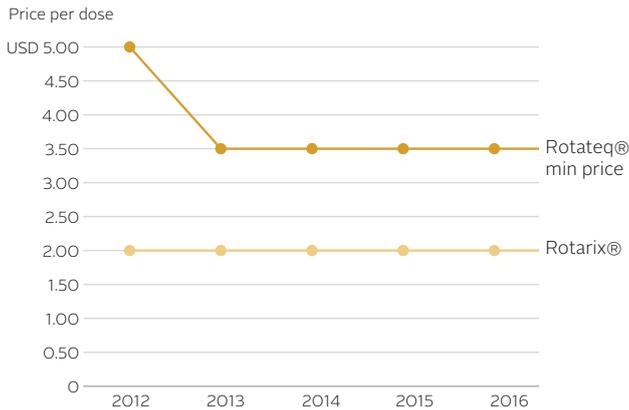
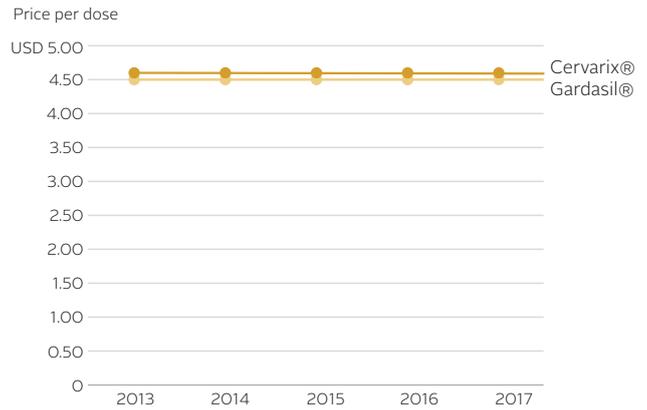


Figure 23b. Prices for human papillomavirus (HPV) vaccines

Since 2013, HPV vaccine prices have remained constant for countries eligible for Gavi support. Source: UNICEF Vaccine Price Data: HPV



Does volume demand account for difference in Gavi price for rotavirus vaccines?

Rotavirus is the leading cause of death due to diarrhoea in children under five, accounting for 37% of all diarrhoea deaths in children under five.²⁵ There are currently two manufacturers who supply rotavirus vaccines: GSK and Merck & Co., Inc. There is no evidence that one vaccine is more effective than the other.²⁶ GSK has a much higher market share, and the vast majority of Gavi's supply (via UNICEF) is of GSK's vaccine: in the 2012-2016 tender, 92% of UNICEF's awarded courses (66 million courses) were for this vaccine.²⁷ Merck & Co., Inc.'s vaccine is almost 1.5 times more expensive than GSK's. Demand for Merck & Co., Inc.'s vaccine is limited: without higher volume demand, the company has less incentive to lower its per-dose price. A 2012 study in the WHO Bulletin²⁸ and a 2015 publication by MSF⁹ suggested that, even at current, lowered prices, rotavirus vaccines are still substantially more expensive than traditional childhood vaccines and that continuing with rotavirus vaccination programmes may be unaffordable for LICs.

Discussion on HPV vaccines' costs and prices

There are currently two vaccines procured by UNICEF that protect against both HPV 16 and 18, which are known to cause at least 70% of cervical cancers. The vaccines, manufactured by GSK and Merck & Co., Inc. may also provide some cross-protection against other less common HPV types that cause cervical cancer.²⁹ Merck & Co., Inc.'s Gardasil@ had a 94% share of the global HPV vaccine market in 2015.³⁰ A recent study³¹ makes a series of estimates about manufacturing costs of both vaccines. It estimates that: (1) the "break-even" price of Gardasil@ being offered to Gavi could be USD 0.50-0.60 per dose; (2) that manufacturing costs for the first set manufactured of 15.4 million doses of Gardasil@ lie between USD 2.07 and USD 3.05; (3) that manufacturing costs for the second set (sold to Gavi and developing countries) range between USD 0.48-USD 0.59 per dose; (4) that manufacturing costs of Cervarix@ for the first set manufactured lie between USD 6.16 and USD 9.39, which is higher than the price GSK offers to Gavi. The same study notes that GSK's estimated gross profits from Cervarix@ sales between 2006 and 2015 (USD 2.6 billion) have arguably covered its past, net corporate costs for research and development.

Prices for LMICs that self-procure depend on volume and contract length

WHO V3P's price database²¹ shows the price of the single presentation plastic tube of Rotateq@ in 2015 was USD 3.7 per dose for a one year contract of 1,980,000 doses procured by a self-procuring LMIC in the WHO Eastern Mediterranean Region. The price of the single presentation plastic tube of Rotarix@ in 2015 ranged from between USD 2.1 to USD 8.0 per dose to four different self-procuring LMICs in the WHO African Region, with annual volumes procured ranging from 2,938,500 to 77,400 doses, respectively. The contract lengths vary from 1 year to 5+ years.

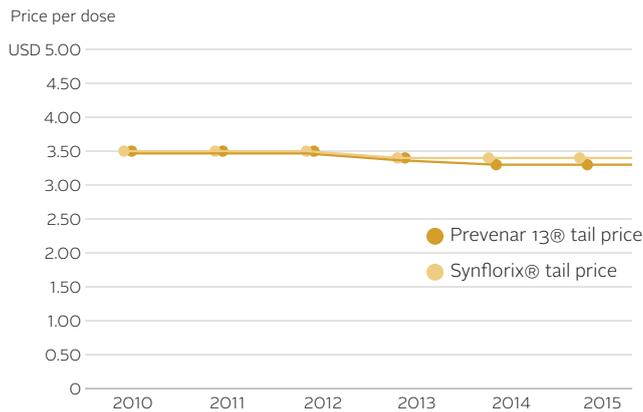
Prices for MICs that self-procure are higher: depend on volume and contract length

In 2015, MICs reported to V3P that prices they were offered by manufacturers for HPV vaccines range from USD 20.94 to USD 93.40.³² Examples available from WHO V3P's price database²¹ show the price of the single presentation vial of Cervarix@ in 2015 was USD 8.3 and USD 19.5 per dose, to two different self-procuring UMICs in the WHO African Region, with annual volumes of 19,000 and 928,400 doses procured, for one year and two year contracts, respectively. The price of the single presentation vial of Gardasil@ in 2015 was USD 14.8 per dose for 300,000 doses in a 1 year contract to a self-procuring LMIC in the WHO Western Pacific Region.

* Companies were not scored on the basis of this analysis.

Figure 23c. Prices for Pneumococcal Conjugate Vaccines (PCVs)

Since 2012, the prices offered by GSK and Pfizer to Gavi-eligible and transitioning countries for their PCVs (Synflorix® and Prevnar 13®, respectively) have marginally decreased. Source: UNICEF Vaccine Price Data: PCV



Pneumococcal vaccines pricing – a closer look

Pneumonia remains the leading infectious cause of death among children under five. In 2015, it accounted for 15% of all under-five deaths and killed 920,000 children.³⁹ Pfizer and GSK are currently the sole manufacturers of vaccines for the disease (PCVs). In 2007, WHO recommended PCVs be included in national immunisation programmes, updating this recommendation in 2012 to specify the 10-valent and 13-valent PCVs manufactured by GSK and Pfizer, respectively. Following an Advanced Market Commitment (AMC)³⁴ pilot for PCV, both companies established agreements to supply a share of the target demand of 200 million doses annually at a price no higher than USD 3.50 per dose for AMC eligible countries (paid for by Gavi with a co-financing contribution from the recipient country governments, in accordance with Gavi's standard co-financing policy). In return, each manufacturer receives a share of the committed AMC Funds of USD 1.5 billion from donors, in proportion to their supply commitment.³⁵ For countries not eligible to access prices and quantities under the AMC scheme, PCV prices can reach more than 20 times higher than AMC prices.¹¹

Both GSK and Pfizer have announced price reductions for their PCVs in recent years. In 2015, Pfizer announced a 20 cent (6%) reduction of its price for Prevnar 13®: from USD 3.30 to USD 3.10 per dose. This was expected to be introduced under the AMC scheme in 2016, and then extended to all Gavi-eligible and transitioning countries through 2025.³⁶ In 2016, GSK announced a 35 cent (10%) reduction of its price for Synflorix®: from USD 3.40 to USD 3.05 per dose. This is expected to be introduced under the AMC scheme from 2017.³⁷

Outside the period of analysis, in September 2016, GSK became the first company to commit to supplying its pneumococcal conjugate vaccine (PCV) (Synflorix®) at USD 3.05 per dose to civil society organisations that fund and

Products analysed

For rotavirus (fig. 23a):

Rotarix® - GSK

Rotateq® - Merck & Co., Inc.

For human papillomavirus (HPV)(fig 23b):

Cervarix® - GSK

Gardasil® - Merck & Co., Inc.

For pneumococcal disease (fig 23c):

Prevnar 13® - Pfizer

Synflorix® - GSK

deliver immunisation programmes for refugees and displaced persons. Pfizer reported to the Index that it has committed to providing its PCV to Gavi at USD 3.05, effective January 1st 2017, in the multi-dose vial presentation, and to specified NGOs for humanitarian emergencies.

Pfizer has made more than USD 26 billion in sales from the pneumonia market since 2009. GSK has made USD 3.5 billion in the same period.¹¹ This is in addition to their share of the committed Advance Market Commitment Funds of USD 1.5 billion, which they will receive in proportion to the scale of their supply commitment over the 10 year period.³⁵ Both companies state that the vaccines are highly complex: GSK reports that it is just covering manufacturing costs; Pfizer states that it is selling at a price below manufacturing costs – and that any price reductions would threaten their ability to supply the vaccine long-term.³⁸

Serum Institute of India has announced it will establish a dedicated manufacturing site for a PCV and intends to offer a per-dose price of USD 2 to Gavi countries. This would make it significantly cheaper than the current Pfizer and GSK products.³⁹ Serum Institute of India has received funding from the Bill & Melinda Gates Foundation for the vaccine's development costs.^{40,41,42,43}

Prices for LMICs that self-procure do not depend on volume and contract length. Examples available from WHO V3P's price database²¹ show the price of the single presentation vial of Synflorix® in 2015 was USD 13.23 per dose for 2,000,000 doses in a 1 year contract to a self-procuring LMIC in the WHO Eastern Mediterranean Region. The price of the single presentation vial of Prevnar 13® in 2015 was USD 16.63 per dose for 103,400 doses in a 2 year contract with a self-procuring LMIC in the WHO African Region and was USD 17.58 per dose for 2,008,125 doses in a 1 year contract with a self-procuring LMIC in the WHO Western Pacific Region.

** The AMC offers a legally binding commitment to support the market of targeted PCVs with US\$ 1.5 billion of funds for which vaccine manufacturers can bid. Interested manufacturers compete over successive tenders to supply a share of the annual forecasted demand of vaccines (which is expected to increase over time and reach around 200 million doses per year at peak). This "AMC price" is set with the aim to enable companies to quickly recover incremental investment costs incurred to serve the GAVI market.

TRANSPARENCY IN PRICING: INFORMATION ASYMMETRY PERSISTS

Transparency around vaccine prices can promote a more competitive supply environment,⁴⁴ facilitate supply negotiations and help ensure that prices are fair. WHO reports that vaccine pricing is considerably less transparent than pricing for other life-saving pharmaceuticals. The WHO Strategic Advisory Group of Experts (SAGE) on Immunisation has called for greater transparency on vaccine prices, especially from governments.⁴⁵ Historically, manufacturers do not report prices for all products. Plus, collective engagement in price transparency could violate antitrust laws.⁴⁶ As a result, the responsibility for ensuring transparency has increasingly fallen to purchasers.⁴⁵

UNICEF and WHO price databases

UNICEF's database⁴⁷ has near complete transparency: it includes price data over time covering vaccines procured by UNICEF. UNICEF and Gavi are both at liberty to disclose the prices they negotiate.

Governments often do not disclose the prices they pay for many reasons. Governments and manufacturers sometimes include confidentiality clauses in purchasing contracts. This hinders the development of comprehensive price databases, such as the one managed

by the V3P project.²¹ The asymmetry in information about vaccine prices limits the ability of stakeholders to assess pricing trends or market dynamics.

GSK and Merck & Co., Inc.: leaders in transparency

GSK and Merck & Co., Inc. lead in transparency in pricing, as measured by the Index, publishing their complete pricing strategies for vaccines. Further, GSK states that it does not include non-disclosure clauses on vaccine prices in its contracts with governments and other procurers, while Merck & Co., Inc. states that it does not have a policy permitting or prohibiting governments from disclosing prices: it leaves this to each government's discretion. Pfizer is the only company in scope that states that price confidentiality provisions mitigate a major risk for governments and manufacturers i.e., that a discounted price would be referenced by a purchaser, such as another country, for whom it is neither intended nor appropriate.

The Index does not evaluate companies based on whether they publish vaccine prices on their websites: but it did collect data on this aspect of company practice. None of the six companies systematically publishes all prices for its vaccines in all countries in scope where

it has sales. Company news releases sometimes contain pricing information.

UNICEF only works with manufacturers on the condition of price transparency^{48,49} and works with all companies in scope: it can be assumed that they all collaborate with the organisation on pricing transparency. Several companies referred to either Gavi's, UNICEF's and/or PAHO's websites for publicly available vaccine prices.

Transparency can improve

However, even with the growing price databases managed by WHO and UNICEF, information on vaccine prices paid by many countries not eligible for Gavi support is still not publicly available.⁵⁰ The data that is available is anonymised and not easily comparable over time.¹¹ Some MICs are known to have paid more than high-income countries for the same vaccine: in some of these countries, vaccine prices can reach more than 20 times the prices negotiated via Gavi.¹¹ Until there is more transparency around vaccine prices, the underlying issues that lead to unaffordable vaccines will be hard to understand and resolve. Improvement will require consolidated efforts by all relevant stakeholders, including governments and manufacturers.

AVAILABILITY: COMPANIES DO NOT APPLY TO REGISTER VACCINES WIDELY IN LOW- AND MIDDLE-INCOME COUNTRIES

The Access to Vaccines Index assesses whether companies apply to register vaccines in LICs and MICs, regardless of whether there is a lucrative market. This is an essential step in making sure a vaccine is available for purchase. Stakeholders consulted during the Access to Vaccines Index methodology development agreed that it is better to register vaccines in more countries, and note that each country's needs for vaccines may differ. With each additional vaccine that is registered in a country, the government and procurers gain more choice. When multiple manufac-

turers register competing vaccines in a market, it enhances the ability of the government to obtain an optimum vaccine price. It may also reduce supply chain uncertainty, both by improving access to vaccine supply (i.e., bringing in an additional company to supply a given vaccine to a specific market) and by ensuring more options are available in case of supply disruptions.⁴⁵ In turn, governments can take steps to ensure that registration processes are efficient.

The companies evaluated by the Index together are developing and market-

ing a diverse and important portfolio of vaccines. It is not expected that a company will register any given vaccine in countries where there are currently multiple manufacturers supplying similar vaccines, unless it is a more effective, more affordable or higher quality alternative.

Hurdles to registration

Companies cite multiple regulatory hurdles that provide disincentives to registering vaccines, including:

- Regulatory complexity: Certain countries require a full review of each vaccine, including additional testing and either Good Manufacturing Practice (GMP) inspections post-approval, or additional clinical studies pre-approval. These requirements are also applied to vaccines that have been approved by stringent regulatory authorities and have gained WHO prequalification status.
- Delays in regulator's approval of registration dossiers (some as long as two years).
- Varying information requirements: Different territories have varying requirements for additional information to be provided on vaccine labels: e.g., registration number, additional instructions, and local languages.
- WHO prequalification costs
- Lack of coordination of funders, purchasers and implementers
- Requirement that vaccines are first registered for use in two western European countries.

Registering vaccines is a complex pro-

cess, dependent on multiple stakeholders, including governments and manufacturers. National Regulatory Authorities (NRAs) and manufacturers would both benefit from harmonised regulatory processes for registering vaccines in LICs and LMICs, and allow faster access to vaccines. Multiple stakeholders support harmonisation and are working to improve it, including WHO, the International Federation of Pharmaceutical Manufacturers & Associations, World Bank, UNICEF, the Bill & Melinda Gates Foundation, Drugs for Neglected Diseases initiative and various governments.

Sanofi files to register vaccines most widely

Sanofi leads in filing to register vaccines in LICs and MICs: it files to register the majority (>50%) of its relevant^f vaccines in 30-50% of both the LICs and MICs in the scope of the Index. Given that the company has a large vaccine portfolio, this is a relatively good performance. Sanofi first registered its dengue vaccine, Dengvaxia®, for use in countries where it has the greatest potential to reduce dengue disease burden.^g This may become common practice for vaccines for tropical diseases.

Many vaccines not widely registered

However, the Index analysis indicates that vaccines are not being registered widely. Together, the six companies measured in this area offer 91 vaccines for the diseases in scope that are currently registered in LICs and/or MICs. Most are universally recommended for routine immunisation.

For most vaccines assessed by the Access to Vaccines Index, the registration process has begun in less than a quarter of the LICs and MICs in scope. The average is 23 countries (out of 107 in scope), across the 91 vaccines evaluated, i.e., 21%. Each vaccine is filed for registration, on average, in 58% of the PAHO countries in scope, 25% of Gavi-eligible and Gavi-transitioning countries in scope, and only 22% of non-Gavi, non-PAHO countries in scope.

The category of non-Gavi, non-PAHO countries includes self-financing MICs such as Botswana, China, Egypt, the Philippines, South Africa and Thailand. Some of these countries, for example Thailand, have local manufacturing capacity and procure traditional vaccines domestically, so registration of such vaccines may not be of value to foreign manufacturers.^{51,52}

Newer vaccines filed for registration more widely

When only considering six of the newer vaccines that are part of the EPI (those for pneumococcal disease, rotavirus and HPV), figures on registration filing are higher, but more mixed: each vaccine is filed for registration, on average, in 92% of the PAHO countries in scope, 38% of Gavi-eligible countries in scope, 43% of Gavi-transitioning countries in scope, and only 29% of non-Gavi, non-PAHO countries in scope. Of note – these new, unique, effective and important vaccines are still filed for registration in relatively few non-Gavi, and non-PAHO countries, illustrating that these coun-

CONTEXT

The facilitating role of WHO Prequalification

The WHO process of prequalifying certain eligible vaccines is an important facilitator for the swift registration of vaccines in low-income countries (LICs) and lower middle-income countries, particularly those with weak or non-existent National Regulatory Authorities (NRAs).⁵³ The prequalification process consists of a transparent assessment, which includes dossier review, testing and even site visits. This information is used by the UN and other procurement agencies to help make purchasing decisions.⁵⁴ Currently 127 vaccines are prequalified and are used in 134 countries. Approximately 64% of the global birth cohort is immunised with prequalified vaccines.⁵⁵ Three companies (GSK, Sanofi and

Merck & Co., Inc.) make explicit commitments to seek WHO prequalification for eligible vaccines in order to expedite access in LICs. All six companies in the scope of the Index have prequalified vaccines.

UNICEF only procures prequalified vaccines, in order to ensure their acceptability, quality, safety and efficacy in target populations.⁵⁶ However, the prequalification process requires funding. To ensure the mechanism remains in place, manufacturers may have to pay higher fees. Until more countries develop and/or strengthen their NRAs, prequalification remains an important mechanism.

f Relevant vaccines are preventive vaccines for diseases in the scope of the Index which have been filed to be registered in at least one country in scope.

g For more information about Dengvaxia®, see page 26.

Figure 24. Key vaccines filed for registration in 23% of countries on average

Nine diseases in scope have been adopted into the immunisation schedules of more than 90 countries. The companies evaluated have 26 vaccines for these diseases. While some are widely filed for registration (i.e., in more than 50 countries), these 26 vaccines are filed for registration in only 25 countries in scope on average.

Disease	Product	Company	No. of countries per category where vaccine is filed for registration						Total
			Gavi eligible	Gavi eligible + PAHO	Gavi transitioning	Gavi transitioning + PAHO	PAHO	Other	
Diphtheria, <i>Haemophilus influenzae</i> type B, Pertussis, Tetanus, Viral hepatitis	Quinvaxem®	GSK	1	0	2	0	0	6	9
	Quinvaxem®	Johnson & Johnson	10	0	4	0	6	8	28
	Shan5®	Sanofi	3	0	1	1	1	1	7
	Pentavalent	Serum Institute of India	29	0	4	1	11	15	60
Diphtheria, Tetanus	Td	Serum Institute of India	3	1	2	2	10	6	24
	Td-pur/ Diftetall	GSK	1	0	0	0	0	2	3
Human papillomavirus (HPV)	Cervarix®	GSK	26	1	7	1	10	8	53
	Gardasil®	Merck & Co., Inc.	24	0	8	2	12	12	58
Measles, Mumps, Rubella	M-M-R® II	Merck & Co., Inc.	0	0	2	0	4	5	11
	MMR	Serum Institute of India	12	0	5	3	14	12	46
	Priorix®	GSK	7	0	2	0	6	10	25
Pneumococcal disease	Prevenar 13®	Pfizer	2	0	1	0	2	6	11
	Synflorix®	GSK	25	1	4	2	12	8	52
Polio	BOPV	Sanofi	7	1	3	0	0	6	17
	bOPV	Serum Institute of India	18	0	1	0	0	1	20
	Imovax® Polio	Sanofi	19	1	7	1	9	13	50
	IPV	Serum Institute of India	18	0	1	0	0	2	21
	Polio Sabin	GSK	2	0	2	0	1	2	7
	Polio Sabin Mono T1	GSK	1	0	0	0	0	1	2
	Polio Sabin Mono Three	GSK	1	0	0	0	0	0	1
	Polio Sabin One and Three	GSK	1	0	0	0	0	0	1
	Poliorix	GSK	1	0	1	0	2	1	5
	tOPV	Serum Institute of India	21	0	0	1	4	2	28
Rotavirus	Rotarix®	GSK	19	1	2	0	6	6	34
	Rotateq®	Merck & Co., Inc.	19	0	7	2	12	9	49
Tuberculosis	BCG	Serum Institute of India	0	1	4	3	11	13	32
Total possible countries (in the scope of the Index)			51	1	11	3	13	28	107

● Filed for registration in at least 50 countries in scope

tries have availability and affordability gaps for new vaccines.

Key vaccines filed for registration in 23% of countries on average

The need for a specific vaccine will vary between markets, depending on the availability of alternatives, of domestic manufacturing, government preference, and demand, among other factors. Vaccines for nine diseases in scope have been adopted in the immunisation schedules of more than 90 countries. This is almost half of the 194 countries with immunisation schedules monitored by WHO. This wide adoption is a good indication of how important vaccines for these nine diseases are for safeguarding public health.

For these nine diseases, the companies evaluated have 26 vaccines filed for registration in at least one country in scope. Of these 26, the five vaccines most widely filed for registration are Serum Institute of India's Pentavalent®, Merck & Co., Inc.'s Gardasil®, GSK's Cervarix®, GSK's Synflorix®, and Sanofi's Imovax® Polio (see figure 24). While these five vaccines are each widely filed for registration, the larger group of 26 vaccines are only filed for registration in an average of 25 countries, or 23% of the countries in scope. Although comparable to the average for all 91 vaccines, this figure is particularly low, considering how important these vaccines are for national immunisation programmes. Manufacturers not in the scope of the Index also supply vaccines for some of these diseases.

CONCLUSION

The six companies evaluated each consider multiple factors when setting vaccine prices, the combination of which is unique to each company and dependent on their portfolio. Across all companies, the most frequently considered factor is whether a country is eligible for Gavi support. This is followed by GNI per capita, which is considered by four companies for at least some LICs and MICs. Some companies publish their complete pricing strategies online for all vaccines, yet in general, the transparency of pricing strategies varies. Most companies state that they do not include clauses in government contracts that prevent manufacturer prices being published. Vaccines are not being filed for registration widely: for the 91 vaccines that qualify for analysis, the registration process has begun in less than a quarter of LICs and MICs within the scope of the Index.

When pricing vaccines, companies need to address affordability systematically – especially for countries that receive no support from Gavi and do not participate in pooled procurement via PAHO or UNICEF. Companies can form and share clear pricing strategies for all LICs and MICs. Companies should also enable global information sharing about vaccine prices to promote a more competitive supply environment, facilitate negotiations and help ensure that prices are fair. There is also a gap regarding vaccine registration: companies need to file to register vaccines more broadly in LICs and MICs according to public health need. In turn, governments and procurers must invest sufficiently in national regulatory systems and immunisation programmes.

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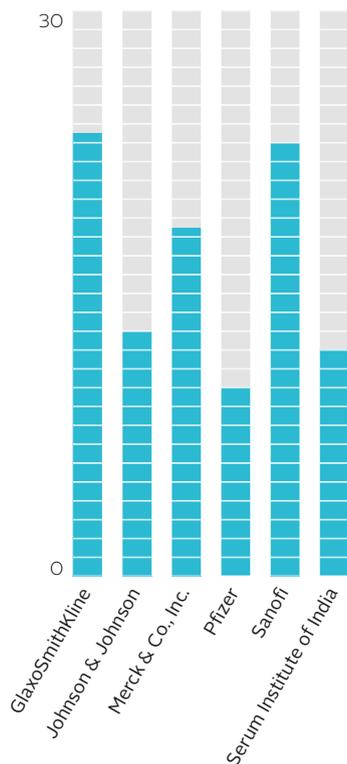
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RESEARCH AREA: MANUFACTURING & SUPPLY

How vaccine companies support access at key points in the supply chain

COMPANY PERFORMANCES



GSK and Sanofi score highest. Both demonstrate strong processes and commitments to help ensure vaccine production meets demand. They further support global vaccine supply through capacity building in manufacturing. The two companies have also implemented vaccine presentations and packaging that help to overcome local access barriers (e.g., vaccines that are easier for health workers to administer).

CONTEXT

To achieve their full potential, immunisation programmes must be effectively implemented. National as well as international stakeholders share the same goal here: an uninterrupted supply of

high-quality vaccines, from the manufacturer to the clinic, school or home.¹ This shared interest requires cooperation and coordination at each step of the vaccine supply chain:^{2,3} implementation can

be hindered by many factors, including insufficient vaccine supply, inadequate distribution systems and limited local capacity to store, handle and administer vaccines.

WHAT THE INDEX MEASURES

In this chapter, the Access to Vaccines Index examines six companies' activities in relation to the manufacture and supply of vaccines: GSK, Johnson & Johnson, Merck & Co. Inc.,^a Pfizer, Sanofi and Serum Institute of India.

The Index examines the following areas:

- 1 Aligning supply and demand:** the steps and processes companies use that help prevent vaccine shortages.
- 2 Capacity building:** companies' capacity building activities in countries in scope for vaccine manufacturing.
- 3 Distribution and administration:** how companies have adapted or developed vaccine presentations, packaging and delivery technologies that help simplify distribution and administration.

^a Merck & Co., Inc. is known as MSD outside the US and Canada.

INTRODUCTION

The main responsibility for immunisation programmes lies with national governments and, in some cases, multilateral organisations such as the World Health Organization (WHO), United Nations Children's Fund (UNICEF), Pan American Health Organization (PAHO) and Gavi, the Vaccine Alliance. Vaccine companies also have a critical role to play, in particular:

- 1 Aligning their supply plans with global demand;
- 2 Contributing to enhancing global manufacturing capacity by sharing expertise with other vaccine manufacturers; and
- 3 Ensuring product features are appropriate for resource-limited settings.

Additionally, companies can and do improve access to vaccines through other manufacturing and supply initiatives: for example, by optimising manufacturing processes, strengthening vaccine distribution systems, or building health worker capacity.^b These dimensions of company behaviour, while important, were not identified by stakeholders as critical during methodology development for the Index and are therefore beyond the scope of this analysis.

ALIGNING SUPPLY AND DEMAND: FOUR OUT OF SIX COMPANIES HAVE STRONGER APPROACHES

Immunisation programmes depend on sufficient and reliable supplies of high-quality vaccines. In recent years, many countries have reported vaccine shortages, and UNICEF has identified insufficient supply (vs. demand forecasts) of a range of vaccines for routine and emergency immunisation, including diphtheria, tetanus and pertussis (DTP) vaccines and inactivated polio vaccines.⁴

Vaccine manufacturing is complex, lengthy and highly regulated: production can often take more than a year.^{5,6} Without reliable demand from purchasers, companies face challenges in keeping their production lines available: multiple stakeholders can help to minimise this risk and incentivise ongoing production by companies. It is therefore critical that companies and other stakeholders can effectively share information and promptly respond to issues around demand forecasting, manufacturing interruptions and regulatory changes. The Access to Vaccines Index examines companies' processes, strategies and commitments for preventing and responding to shortages.

While companies are not solely responsible for aligning supply and demand, they can help to ensure sufficient vac-

cines are reliably available and minimise the risk of shortages and stock-outs by developing strong internal processes and working with external stakeholders (particularly multilateral and government vaccine purchasers). By aligning vaccine supply plans with global demand, companies help to avoid both under- and over-supply that could harm the sustainability of vaccine markets.

To prevent major supply disruptions, it is vital that companies continue manufacturing vaccines that have few or no other suppliers, as long as the vaccine is needed, and to notify stakeholders in advance, should companies plan to alter or cease production (e.g., if they are unable to bear the cost of production without a market guarantee). To minimise the risk of companies exiting markets with low profitability, procurers can support companies with, for example, accurate and sufficient demand forecasting, insight into long-term planning, purchasing commitments and prices that are sustainable for both parties.³ For example, the Pneumococcal Advance Market Commitment, through which donors commit funds to guarantee demand for pneumococcal vaccines once developed,⁷ has had a positive impact on access to vaccines.⁸ Plus,

UNICEF undertakes an annual vaccine forecasting process, with country-level input, to estimate demand for the next five years. UNICEF informs suppliers of changes to forecasts on a monthly basis, which is important for manufacturers' and procurers' planning.⁹

Strong approaches include several elements to align supply and demand

Overall, four out of six companies evaluated in this area are taking relatively strong approaches to aligning supply and demand (GSK, Johnson & Johnson, Merck & Co., Inc. and Sanofi). GSK stands out for its clear and proactive processes, both internally and in its communication with external stakeholders. For example, GSK's internal process for ensuring sufficient supply includes six of the eight key elements identified by the Access to Vaccines Index (see figure 25). Notably, these include: a monthly review of global demand; a process for escalating supply issues to senior management in order to reallocate stock; and considering prioritising supply in countries where GSK is the sole supplier of a vaccine.

Johnson & Johnson makes a strong commitment to staying in vaccine markets where its products are needed. For

^b For example: GSK's mVacciNation programme is a mobile technology-based supply chain management capacity building programme, aiming to increase childhood immunisation in Mozambique; Sanofi's EPIVAC programme trains doctors involved in implementing immunisation programmes in 11 sub-Saharan African countries.

example, on discontinuing its hepatitis A vaccine (Epaxal®), the company first evaluated the likely public health impact of exiting the market. It announced its decision in 2013, in advance of production ceasing in 2014. Hepatitis A vaccines continue to be supplied by other companies. Johnson & Johnson also has a comparatively strong internal process for preventing and responding to shortages (see figure 11). This process includes: a commitment to minimising stock-outs and their impact on customers; additional vaccine stocks held in reserve; and an inventory of the materials needed to scale up production.

Merck & Co., Inc. makes the strongest commitment to maintaining supply of its vaccines for as long as they are needed: it does not discontinue any vaccines used to prevent serious disease for which there are no alternatives on the market. Merck & Co., Inc. also engages with key stakeholders, such

as UNICEF, PAHO and national authorities, before exiting major markets and, where possible, in case of upcoming supply disruptions. It prioritises public health needs when re-allocating limited stock. Its approach is particularly important because it is one of the few producers of vaccines available for several diseases, including rotavirus and human papillomavirus (HPV).

Sanofi has clear processes for proactively engaging with purchasers to align supply and demand. The company contributes to global vaccine stockpiles for oral cholera, yellow fever (YF) and meningococcal vaccines. The funding mechanisms for these stockpiles vary. For example, the meningococcal vaccine stockpile is partly prepaid through an international revolving fund, and partly maintained by manufacturers, who share the financial risk that vaccines will expire before they are needed.¹⁰ Sanofi has worked with partners to improve

planning and stock management processes related to these stockpiles: it specifically highlights the need for improved risk sharing.

Less clear or absent processes or commitments

Serum Institute of India commits to staying in vaccine markets where there are only a few other suppliers. It has also scaled up vaccine production in response to increased demand. For example, in 2004-05, it established a new production facility to respond to increased global demand for measles vaccines. Its reported processes for aligning supply and demand are less clear and structured than other companies evaluated. This may reflect the company's status as a privately held, family-owned company: in general, publicly traded multinational vaccine companies are required or expected to have more formalised policies and processes in place, and (in some cases) to be transparent about them. Serum Institute of India is one of a small number of global suppliers for several critical vaccines, including for measles and rubella; measles, mumps and rubella; and meningococcal A.¹⁷ It is important that the company's processes are effective and reliable.

Pfizer's processes and strategies to align supply and demand are less comprehensive than other companies evaluated. It is the only company out of the six evaluated that does not state that it commits to staying in vaccine markets where there are few or no alternative suppliers, nor to communicating its plans externally when reducing or ceasing supply of a vaccine. Its other internal and external processes related to aligning supply and demand are below industry average as evaluated by the Index. This is particularly relevant given that Pfizer is currently one of only two pneumococcal conjugate vaccine (PCV) manufacturers: reliable supply of its 13-valent PCV (Prevenar 13®) is important.¹⁸

CONTEXT

Yellow fever: vaccine shortages and outbreaks

Sanofi is one of only four yellow fever (YF) vaccine manufacturers supplying the global market (the others are Bio-Manguinhos [Brazil], FSUE of Chumakov [Russia] and Institut Pasteur de Dakar [Senegal]).¹¹ In 2013, UNICEF identified that YF vaccine supply would not meet demand from 2014-2017.¹² In 2014, in order to better meet global demand, Sanofi invested in a new production unit to double its YF vaccine manufacturing capacity by 2016.¹³

Despite this and other measures, the global emergency YF vaccine stockpile – of six million doses – was depleted twice in 2016 by the YF outbreak in Angola.¹⁴ The outbreak was exacerbated by the insufficient immunisation of large cohorts. As an emergency measure, WHO has recommended administering fractional dosing (one



People in Togo queue for the yellow fever (YF) vaccine. Despite efforts to increase vaccine supply for YF, including by manufacturer Sanofi, shortages are expected to persist.

fifth of a standard dose) in at-risk populations, to partly overcome the fact that there are not enough full doses to meet the extraordinary demand.¹⁵ Although supply has been scaled up, UNICEF foresees that shortages will persist through 2017.¹¹ Further, a YF outbreak in Brazil, reported in January 2017, will put the global YF vaccine supply under even more pressure. This highlights the need for effective mechanisms for stakeholders to work together to prevent and respond to vaccine shortages.

Figure 25. Companies take diverse approaches to aligning supply with demand

Most companies implement elements and supply commitments. GSK, Johnson & Johnson, Merck & Co., Inc. and Sanofi take stronger approaches.

	GSK	Johnson & Johnson	Merck & Co., Inc.	Pfizer	Sanofi	Serum Institute of India
Key elements for preventing/responding to shortages						
Commitment to ensure access in case of shortages	●	●	●			
Regular and timely supply-and-demand review process	●	●	●	●	●	
Clear process for escalating and acting on identified issues	●				●	
Reserve stocks (not including externally managed stockpiles)		●	●	●		
Processes for scaling up production		●		●	●	●
Processes for re-allocating stocks	●				●	
Donations or affordability measures in emergency situations	●					
Consideration of other suppliers in a market when making decisions	●					
Commitments to continuing supply of vaccines						
Commitment to stay in vaccine markets where needed		●	●			●
Commitment to communicate plans to reduce supply externally	●		●		●	

● Company has a clear commitment/process

CAPACITY BUILDING: ESTABLISHED MANUFACTURERS ARE TARGET OF COMPANIES’ ACTIVITIES

Building global vaccine manufacturing capacity is important for ensuring reliable supply worldwide: local vaccine production in multiple countries can help reduce costs and make supply more secure.¹⁹ Because preventive vaccines are administered to healthy people – often children – very high manufacturing standards are required worldwide to ensure safety and quality, and improve trust in and acceptance of all vaccines.²⁰ Strategies such as the Pharmaceutical Manufacturing Plan for Africa²¹ and the related African Vaccine Manufacturing Initiative (launched in 2010) set out frameworks to build such capacity and provide support to existing and future vaccine manufacturers in Africa (e.g., in Egypt, Nigeria and Senegal).²² Key requirements for local vaccine production include: a significant amount of capital investment, economies of scale to reduce per-dose costs, and strong regulatory systems to ensure quality.¹⁹ Vaccine companies have unique expertise that is important to share to improve global manufacturing supply and quality. Companies can build capac-

ity in-house and with third-party vaccine manufacturers, both public and private, through partnerships, training and/or technology transfers. Within commercial relationships, such support can reduce production costs and facilitate market entry. Capacity building activities can also be philanthropic. Regardless, “win-win” conditions for companies and populations are needed to incentivise companies to engage: this can be facilitated by governments or other public agencies.²³ The Index examines companies’ capacity building efforts in countries in scope.



Inspecting cholera vaccines at Sanofi’s Hyderabad plant, India. Companies direct their capacity building efforts to a few MICs, including India.

Focused activity in middle-income countries

Across the six companies evaluated, capacity building activities are directed at a relatively small range of middle-income countries in scope with established vaccine production capacities: most commonly Brazil, followed by India, Mexico, South Africa and Vietnam. This reflects the need for a highly skilled workforce to produce vaccines. These are also markets in which multinational vaccine companies are generally interested in expanding their presence.²³

Sanofi engaged in the highest number of manufacturing capacity building activities in countries in scope during the period of analysis. It has undertaken long-term manufacturing technology transfers in a range of countries, including for several different vaccines in Latin America. GSK also demonstrated a relatively high number of activities in scope compared to peers: it is running several technology transfer programmes, for example, for production of its DTP vaccine (Boostrix®) in Brazil.

Johnson & Johnson, Merck & Co., Inc. and Pfizer undertake fewer capacity building activities in countries in scope, including:

- a Johnson & Johnson provides operational and technology support to Vabiotech in Vietnam, a state-owned company producing vaccines for cholera, hepatitis A and B, and Japanese encephalitis.²⁴
- b Merck & Co., Inc. is currently engaged in a technology transfer for its HPV vaccine (Gardasil®) to Instituto Butantan in Brazil, including advising on the design of the manufacturing facility. A technology transfer for its hepatitis A vaccine (Vaqta®) to Butantan was recently approved.
- c Pfizer is transferring skills and equipment to the Biovac Institute of South Africa for the manufacture of Prevenar 13®. The technology transfer will take place over five years from 2015, with local manufacturing scheduled to start in 2020.²⁵

Serum Institute of India is a member of the Developing Countries Vaccine Manufacturers Network (DCVMN). The DCVMN is a public health-focused alliance of 50 manufacturers based in “developing countries” (including Brazil, Egypt, India and Vietnam), which supports information- and expertise-sharing between its members.²⁴ The DCVMN provides a key mechanism for building vaccine manufacturing capacity in a range of countries.

DISTRIBUTION AND ADMINISTRATION: ALL COMPANIES TAILOR VACCINE PRESENTATIONS TO IMPROVE ACCESS

The ease with which a vaccine can be distributed and/or administered has a large bearing on the efficiency of immunisation programmes. Many vaccines have special storage requirements to ensure efficacy and safety: often, constant refrigeration in a specific temperature range (the “cold chain”) is required.²⁷ When vaccines reach the end of the supply chain, trained health workers are needed to administer them correctly.²⁸ The role for vaccine companies in improving distribution and administration is limited: the main responsibility for such health system strengthening lies with governments.

However, vaccine companies can support access by developing or adapting vaccines to ensure they address usage needs in resource-limited settings. Vaccines that are easier to distribute, store and administer are less likely to be compromised and/or discarded as they move through the supply chain. The result is less waste, fewer stock-outs, and improved public confidence in vaccines. Furthermore, by considering local barriers to distribution and/or administration, companies can facilitate their entry into new and growing markets. This is especially relevant since UN agencies (through the WHO prequalification process^c) and other procurers routinely consider the local programmatic suitability of vaccines.²⁸

Companies can develop or adapt suitable vaccine presentations and packaging in-house or in partnership, for example with stakeholders such as PATH and via the WHO Vaccine Presentation and Packaging Advisory Group. It is important to note that such projects can involve significant costs and other challenges such as additional regulatory approvals.^{2,28}

The Access to Vaccines Index examines how companies help to overcome local access barriers in several ways: by adapting or developing vaccine presentations, packaging and delivery technologies that help simplify distribution and administration. Such features include multi-dose presentations that reduce the burden on local supply chains; vaccines that do not require constant refrigeration; delivery technologies that allow simpler routes of administration, such as oral or intranasal; and vaccine package inserts or packaging designed to promote rational use by health workers (such as instructions tailored for people with lower literacy skills, or translated into local languages).

All companies address ease of use and distribution

All six companies evaluated have vaccines either on the market or in development^d with features designed to help overcome local barriers to access (see examples in figure 26). Overall, com-

panies are less active when it comes to implementing delivery technologies, and adapting packaging and package inserts to support rational use by health workers (beyond what is legally required).

Overall, GSK and Sanofi lead in this area of analysis. Sanofi has implemented at least one of the approaches described above for approximately a quarter of its marketed vaccines in scope: for example, the packaging of its dengue vaccine (Dengvaxia®) has several features to prevent counterfeiting. GSK has implemented a range of relevant presentation and packaging types: for example, using illustrations on the packaging of its rotavirus vaccine (Rotarix®) to help avoid errors in administering it.

Merck & Co., Inc.’s performance is also relatively strong: it has made several adaptations to its products to help overcome cold chain barriers. Pfizer and Serum Institute of India have adapted some of their products to address access barriers, and Johnson & Johnson is working toward a thermostability label update for its hepatitis B vaccine (Hepavax-Gene®).

Figure 26. Different access barriers require different solutions: companies are implementing a variety of packaging and presentations to increase access.

All six companies evaluated have vaccines either on the market or in development with features designed to help overcome local barriers to access. The figure provides a range of examples.

Barrier to access	Presentation/packaging to address barrier
Cold chain requirements	Serum Institute of India's meningococcal A vaccine (MenAfriVac®) and Merck & Co., Inc.'s Gardasil® have both been approved for Controlled Temperature Chain use. This means that they can be transported and stored without refrigeration for several days at relatively high temperatures. Both products have vaccine vial monitors that register whether the vaccine has been exposed to damaging temperatures.
Weak supply chains	Pfizer and GSK participated in a pilot project in Tanzania, with partners including PATH and Gavi, testing whether matrix (2D) barcodes on vaccine packaging could improve supply chain and stock management. GSK has extended 2D barcodes to all Rotarix® doses supplied to Gavi. Pfizer has also piloted 2D barcodes to improve vaccine distribution in Nicaragua, in partnership with PATH. 2D barcodes can hold a significant amount of information.
Vaccine wastage	The multi-dose vial of Pfizer's Prevenar 13® and Sanofi's inactivated polio vaccine (Imovax Polio®) can be used for 28 days from first use, provided they are refrigerated between 2-8°C. Because the product lasts longer after opening, there is a greater chance that all doses in the vial will be used, reducing wastage. Health workers sometimes avoid opening multi-dose vials if they can't be sure all doses will be used before expiry. The vial's longer shelf life reduces the perception that left-over doses are likely to be wasted.
Multiple barriers	Serum Institute of India provides multiple dosage options for more than two thirds of its vaccines. Single- and multi-dose vaccines offer different benefits: single-dose vaccines can be used as needed and support safe administration; while the latter generally sell at lower per-dose prices, and require less supply chain capacity. Different dosage options support purchasing decisions based on local needs. Companies should work to ensure vaccine presentations are available in dose forms appropriate to the specific vaccine.



GSK is using 2D barcodes on Rotarix® doses to help improve vaccine stock management.



An infant receives Sanofi's inactivated polio vaccine. The multi-dose vial lasts 28 days after opening, helping to reduce wastage.



The purple symbol on this cholera vaccine vial from Sanofi changes colour through exposure to heat, to indicate whether the vaccine is safe for use.

c WHO prequalification is a service for UNICEF and other UN agencies that purchase vaccines, to determine the acceptability, in principle, of vaccines from different sources for supply to these agencies.

d See R&D chapter for vaccine adaptations in development page 36.

CONCLUSION

Vaccine companies are taking an active role to align global supply and demand, and there are clear indications that potential vaccine shortages are being proactively detected, mitigated and in some cases prevented: companies generally implement multiple processes or take steps internally to improve supply and demand alignment; many also make commitments around continuing supply. Providing further support to global vaccine, companies are building vaccine manufacturing capacity in some countries in scope: a relatively small range of middle-income countries with established vaccine production capacities. This reflects the need for favourable workforce and market conditions. Looking at individual products, all companies take steps to ensure vaccines have packaging, presentations or features intended to help overcome barriers to access on the ground.

While companies are taking steps at various levels of the supply chain to help improve access to vaccines, the existence of ongoing shortages, barriers to entry to vaccine manufacturing in low- and middle-income countries, and limited consideration of local barriers for some vaccines' presentations and packaging, shows that more needs to be done. There is a role here for vaccine companies and other stakeholders to work together to continuously assess the most critical access-to-vaccines issues and respond with strategic and sustainable solutions that meet the needs of low- and middle-income country immunisation programmes.

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Company Report Cards

The 2017 Access to Vaccines Index includes eight company report cards, which each provide a contextualised analysis of one company's performance in the 2017 Index. This includes a summary of its performance (both overall and per Research Area). Each report card includes overviews of the company's portfolio and pipeline, and identifies tailored opportunities for it to increase access to vaccines. For a detailed explanation of the report card contents and data sources refer to the Appendix. The report cards are divided into five sections:

Performance

This section explains the relevance of the company for the Access to Vaccines Index and its overall performance. It covers:

- Drivers behind its scores
- Main areas where the company scores well or poorly compared to peers

Sales and Operations

This section provides a general description of the company's operations globally, including changes in its business (such as acquisitions or divestments) in recent years with a particular focus on its vaccines business.

Vaccine portfolio

This figure shows the number of vaccines the company markets globally for diseases in scope, as of January 2017. This includes, but is not limited to, vaccines included for scoring in the Research Areas Pricing & Registration and Manufacturing & Supply.

Opportunities

This section outlines tailored opportunities for the company to improve access to its vaccines, taking into account company-specific characteristics.

Research areas

This section summarises company performance per Research Area. This includes:

- Main areas within the Research Area where the company scores well or poorly
- Description of commitments, performance and/or relevant initiatives with the Research Area

The Research & Development Research Area includes an overview of the company's preventive vaccine pipeline for diseases in scope. This reflects the period of analysis, and comprises R&D projects included for analysis in this Research Area. Any changes to the pipeline as of January 2017 are noted.

GlaxoSmithKline plc

Stock Exchange: XLON
 Ticker: GSK
 HQ: Brentford, UK
 Employees: 101,255

Index performance by Research Area



The number of cells represents the maximum possible score. Coloured cells represent points attained.

PERFORMANCE

GSK is one of the largest vaccine companies in scope by revenue, portfolio size, pipeline size and geographic scope. For several key vaccines, it is one of a small number of producers, including for rotavirus and pneumococcal disease. GSK performs very well overall, leading in all three Research Areas. In Research & Development, it has the largest vaccine pipeline.

In Manufacturing & Supply, it has strategies to support access at a high level, strong internal supply-management processes and vaccine presentations that help overcome access barriers on the ground. It leads in Pricing & Registration with the most-structured vaccine pricing strategy. However, it has filed to register only some vaccines in low-income countries (LICs).

SALES AND OPERATIONS

GSK operates through three divisions: pharmaceuticals; vaccines; and consumer health-care. It has sales in 92 countries in scope (including sales of products other than vaccines); sales in emerging markets account for about 25% of total sales. Among the companies in scope, GSK's vaccines division accounts for the highest share (15%) of overall revenue. In 2014, the company acquired Novartis's vaccine business (excluding influenza vaccines), while divesting its marketed oncology portfolio to Novartis. In 2015, GSK sold two meningococcal vaccines to Pfizer (Mencevax® and Nimenrix®). GSK's vaccines division now has 48 marketed vaccines. GSK also has a joint venture with Daiichi Sankyo, Japan Vaccine Co., Ltd., through which it sells vaccines in Japan.

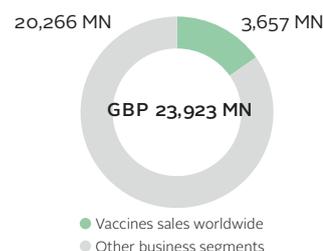
Sales in countries in scope (all product types)



Number of doses sold in 2015



Sales by segment 2015



VACCINE PORTFOLIO

GSK has 48 vaccines on the market for 19 diseases in scope, one of the largest portfolios of the companies evaluated. Its portfolio is diverse, ranging from traditional childhood vaccines (e.g., DTaP-containing combination vaccines) to newer vaccines with few other suppliers (e.g., for HPV, pneumococcal disease and rotavirus).

Marketed vaccines

DT	1	HPV	1	TBE	1
DTP	2	Meningococcal	4	Td	1
DTPHepIPV	1	MMR	1	Tetanus	1
DTPHib	1	MMRV	1	Typhoid	1
DTPHibHep	1	Pandemic influenza	3	TyphoidHepA	1
DTPHibHepIPV	1	Pneumococcal disease	1	Varicella	1
DTPHibIPV	1	Polio	6	Viral hepatitis	4
DTPIPV	2	Rabies	1		
Hib	2	Rotavirus	1		
HibMen	2	Seasonal influenza	5	Total	48

OPPORTUNITIES

Make an overarching commitment to continuing supply of vaccines where needed. While GSK commits to communicating its intentions with regard to altering its supply of vaccines, it can also make a clear commitment to continuing supply of its vaccines with few other suppliers.

Develop access provisions for all late-stage candidates. Among its peers, GSK has the largest number of late-stage projects and the most late-stage projects that are supported by plans to ensure access. GSK can, working with partners where relevant, develop similar plans for its other late-stage projects: its candidates for HIV,

hepatitis C, meningitis, pneumococcal (phase II), RSV (maternal), seasonal influenza and varicella. For those projects with access provisions in place, the company can strengthen and refine its plans as the vaccines approach market approval.

File to register vaccines more widely where they are needed. GSK can expand the availability of key vaccines in more LICs and middle-income countries (MICs), where needed, taking account of the availability of alternative products and domestic vaccine manufacturing, government demand and preferences and registration hurdles. This can provide purchasers with

more choice, create a more competitive environment and improve supply reliability.

Work with stakeholders to reduce the price of key new vaccines. GSK can continue to work with pooled procurers and self-procuring countries, e.g., with regard to its vaccines for pneumococcal disease (Synflorix®), rotavirus (Rotarix®) and HPV (Cervarix®), for all LICs and MICs, and particularly for Gavi-transitioning countries in the future and non-Gavi and non-PAHO countries at present. This can help increase the adoption of these vaccines in more MICs.

RESEARCH AREAS

RESEARCH & DEVELOPMENT

Proportionally low R&D investments. As a proportion of its global vaccine revenue, GSK made relatively low investments in vaccine R&D targeting diseases in scope in 2014 and 2015, compared to other companies in scope. In absolute terms, its investment was relatively high.

Largest vaccine pipeline. GSK has a pipeline of 25 vaccine R&D projects, targeting at least 16 diseases in scope. GSK targets all seven diseases in scope prioritised by WHO for vaccine R&D: such projects account for 40% of its pipeline.

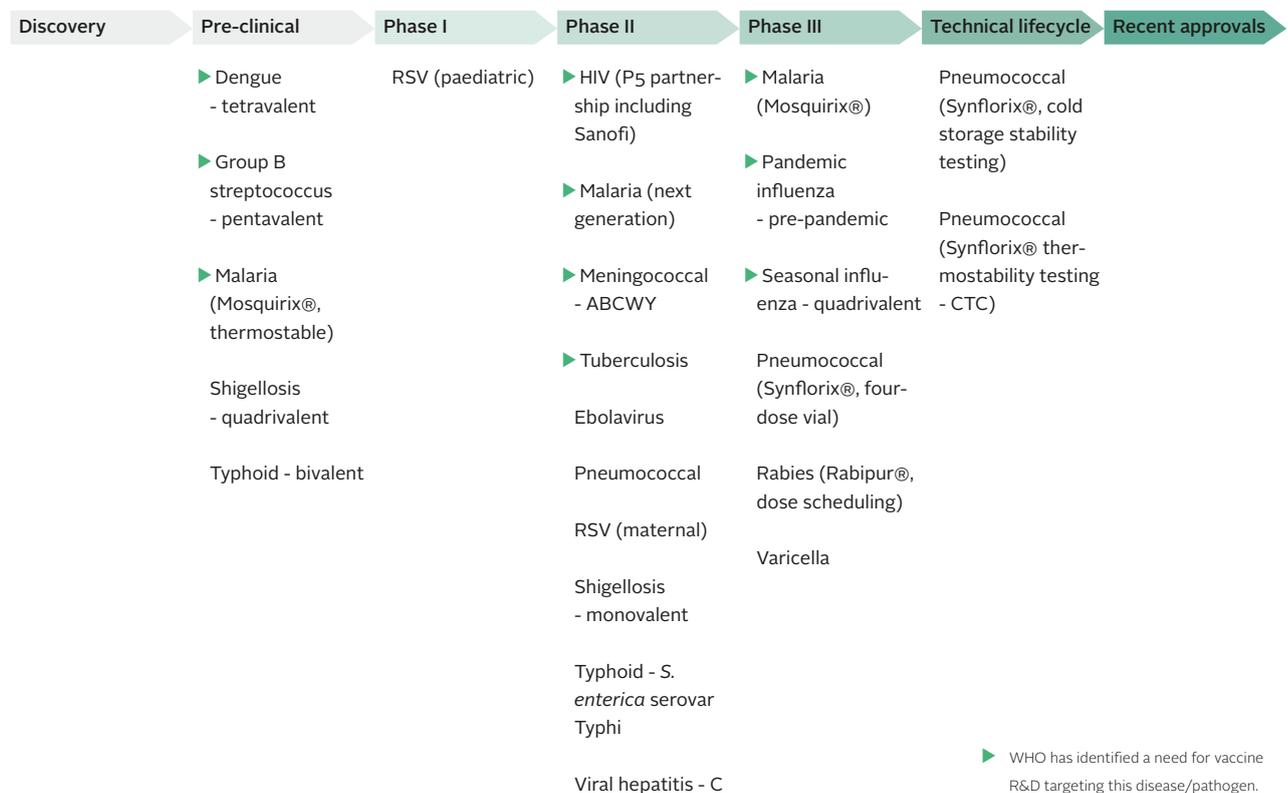
R&D projects (8/15). For example, GSK commits to making its shigellosis, TB and typhoid vaccine candidates affordable to countries in need.

Largest number of late-stage projects with access provisions. GSK has at least one access provision in place for around half of its late-stage

Researching technologies for vaccine packaging and delivery. GSK is developing technologies for vaccine packaging and delivery that aim to overcome barriers to access in low-resource settings.

Vaccine pipeline

GSK has the largest vaccine pipeline among companies evaluated, with most projects in late stages of development. In addition to the projects shown here, GSK has a project for which data are confidential.



GlaxoSmithKline plc (continued)

PRICING & REGISTRATION

Most detailed tiered pricing strategy. GSK's strategy for public sector vaccine pricing comprises seven pricing tiers covering a range of markets. The lowest tier is applied to all Gavi-eligible countries. The other tiers are applied according to a combination of gross national income per country, target population coverage, duration of contract and committed volume. The number of tiers makes this strategy the most sensitive to each country's ability to pay, compared to peers' strategies.

Commitment to offering lower prices to Gavi-transitioning countries. In early 2015, GSK committed to freezing prices it offers to countries transitioning from Gavi support, so that they can purchase vaccines for pneumococcal, rotavirus

and HPV at significantly discounted prices for a decade after graduation.

First company to make vaccine price commitment for humanitarian situations. Outside the period of analysis, in September 2016, GSK became the first company to commit to supplying its pneumococcal conjugate vaccine (PCV) (Synflorix®) at USD 3.05 per dose to civil society organisations that fund and deliver immunisation programmes for refugees and displaced persons.

Limited registration filing in LICs. GSK files the majority of its relevant vaccines for registration in some lower middle-income countries, like its peers. However, it files only some of its vaccines for registration and in only some LICs. GSK states

that its decision to file for registration is based on where vaccines are needed and depends upon the regulatory procedures of each country. GSK commits to seeking WHO prequalification of eligible vaccines to expedite access in LICs.

Above average transparency. Like its peers, GSK does not systematically publish all prices for its vaccines in all countries in scope on its website. However, unlike most of its peers, it does publish its complete vaccine pricing policy. Like most peers, it states that it does not include non-disclosure clauses on vaccine prices in its contracts with governments and other procurers.

MANUFACTURING & SUPPLY

Leader in aligning supply and demand. GSK takes a very strong approach to aligning vaccine supply and demand, implementing six of eight key practices identified by the Index in this area. Overall, it has regular processes for proactively coordinating with external stakeholders; and its internal process for ensuring sufficient supply is very comprehensive.

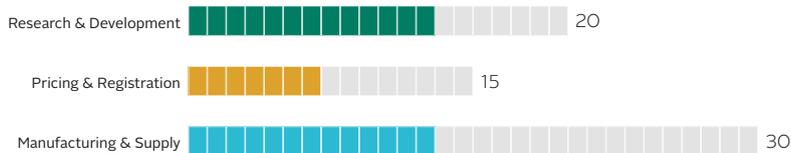
Very active in building manufacturing capacity. GSK is undertaking a relatively high number of activities to build global vaccine manufacturing capacity. It is running several technology transfer programmes with capacity building components (e.g., for the production of its diphtheria, tetanus and acellular pertussis vaccine (Boostrix®) in Brazil).

Multiple vaccine presentations support access. GSK has implemented a range of presentation and packaging types to help overcome local barriers to access. For example, the packaging of its rotavirus vaccine (Rotarix®) includes illustrations, to help avoid administration errors, as well as matrix (2D) barcodes to help improve the tracking of vaccines as they move through the supply chain.

Johnson & Johnson

Stock Exchange: XNYS
 Ticker: JNJ
 HQ: New Brunswick, NJ, US
 Number of employees: 127,100

Index performance by Research Area



The number of cells represents the maximum possible score. Coloured cells represent points attained.

PERFORMANCE

Johnson & Johnson currently has relatively low vaccine revenues, reflecting its small portfolio size, volume of doses sold and geographic scope. However, its pipeline and R&D investments indicate a growing focus on vaccines. Overall, its performance is in the average range compared to other companies. It is a leader in Research & Development, making the largest investments in vaccine R&D and with a relatively large pipeline. In Pricing & Registration, it has filed to register vac-

cines in some low-income and lower-middle-income countries (LICs; LMICs). It has published only a very general commitment to affordable vaccine pricing. In Manufacturing & Supply, its performance is below average: while it has internal processes to align supply and demand, it is less active than peers in building manufacturing capacity, and has not implemented presentations or packaging to help overcome local access barriers for its two marketed vaccines.

SALES AND OPERATIONS

Johnson & Johnson has three segments: consumer healthcare; pharmaceuticals; and medical devices. Its pharmaceuticals segment focuses on various therapeutic areas, including vaccines. Johnson & Johnson is present in 69 countries in scope. Sales in emerging and frontier markets account for 20% of total sales. Its vaccines are developed and produced by Janssen Vaccines & Prevention B.V. (part of Janssen Pharmaceutical Companies). Following the divestment of its oral typhoid and oral cholera vaccines, it now has two vaccines on the market.

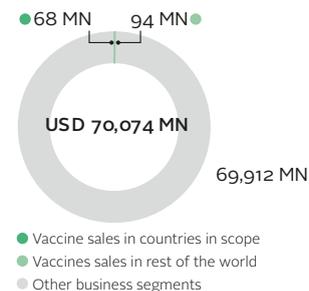
Sales in countries in scope (all product types)



Number of doses sold in 2015



Sales by segment 2015



VACCINE PORTFOLIO

Johnson & Johnson has two vaccines on the market for five diseases in scope, one of the smallest portfolios of the companies evaluated. Its portfolio is made up of a single hepatitis B vaccine (Hepavax®) and a diphtheria, tetanus,

whole-cell pertussis, hepatitis B and Hib combination vaccine (Quinvaxem®).

Marketed vaccines

DTPHibHep	1
Viral hepatitis	1
Total	2

OPPORTUNITIES

Commit to communicating supply discontinuation plans. Johnson & Johnson can commit to consistently communicating its intentions publicly when deciding to discontinue supply of a vaccine in future. This will allow stakeholders to adapt procurement and distribution plans early to minimise the risk of shortages and the potential impact on public health.

Consider barriers to access of marketed products. Johnson & Johnson can consider how

its marketed products may present barriers to access in resource-limited settings, in terms of supply chain management, storage and administration. As it expands its R&D activities, it can adapt its existing vaccines, where possible, to address these barriers. Beyond vaccine development, it can adapt vaccine packaging and package inserts to address barriers to access.

Develop and publish a more specific pricing policy. Johnson & Johnson can outline how it

defines the pricing tiers of its pricing policy, and include non-Gavi and non-PAHO country governments in its strategy, with a consideration of these countries' ability to pay. By publishing a more specific pricing policy, which applies to new and existing vaccines, Johnson & Johnson can improve its accountability and ensure that self-financing countries have a better understanding of how to negotiate prices.

RESEARCH AREAS

RESEARCH & DEVELOPMENT

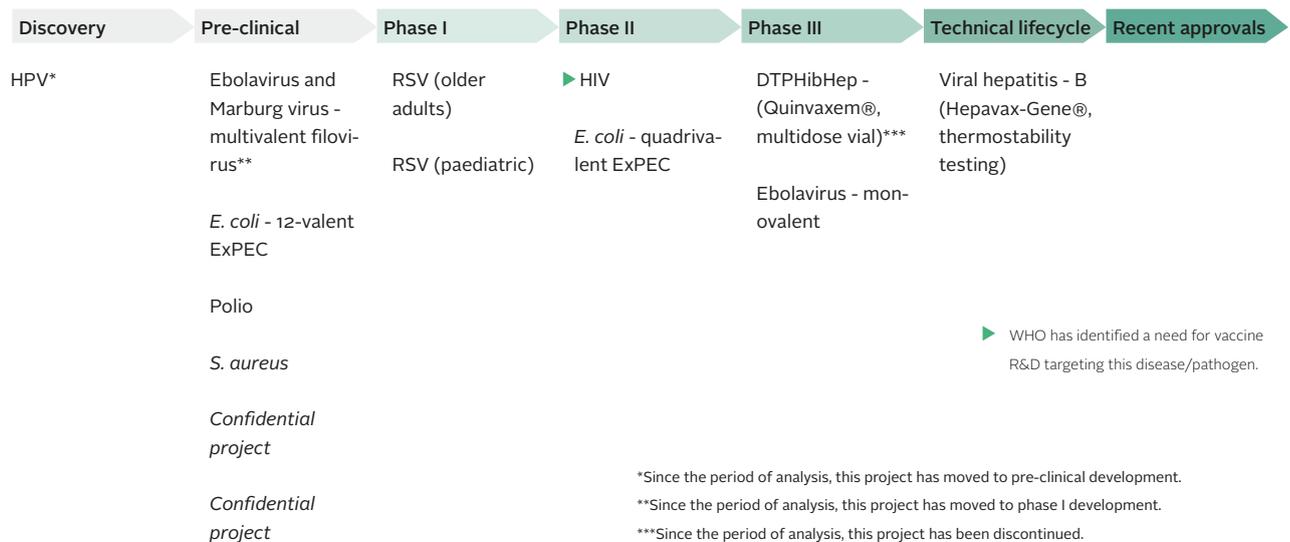
Largest R&D investments. Johnson & Johnson made the largest investments of companies evaluated in vaccine R&D targeting diseases in scope in 2014 and 2015, both in absolute terms (USD 717.3 mn) and as a proportion of its vaccine revenue (253%).

Relatively large vaccine pipeline. Johnson & Johnson has 14 R&D projects in its pipeline, targeting at least 13 diseases in scope. One of its projects targets a disease prioritised by WHO for vaccine R&D: its phase II HIV vaccine candidate.

Access provisions in place for three late-stage projects. Johnson & Johnson has at least one access provision in place for three out of its four late-stage projects. For example, it aims to register its Ebolavirus and HIV vaccine candidates in countries where clinical trials take place. These two vaccines are being trialled in six and four countries in scope respectively.

Vaccine pipeline

Johnson & Johnson has the largest number of projects in pre-clinical development.



PRICING & REGISTRATION

General pricing strategy. Johnson & Johnson makes a broad commitment to using a tiered pricing approach for key vaccines in developing countries. However, it only provides UNICEF and PAHO as examples of procurers for whom it differentiates prices (based on countries' wealth). It is not clear how the company takes affordability into account for non-Gavi, non-PAHO self-procuring countries. As part of its pricing strategy, the company states that vaccines specifically developed for poorer countries and not sold in affluent markets must stay profitable in order to sustain production, uphold quality and recoup investments.

Extends Gavi prices to Gavi-transitioning countries. In January 2015, Johnson & Johnson extended its pledge to make its pentavalent vaccine (Quinvaxem®) available at Gavi prices to transitioning countries over the next five years.

On-average performance in registration filing. Johnson & Johnson has filed to register both of its relevant vaccines in some LICs and some LMICs. Johnson & Johnson's policy is to file for registration in countries where there is a medical need, taking into account regulatory and market hurdles.

On-average transparency. Like its peers, Johnson & Johnson does not systematically publish all prices for its vaccines in all countries in scope. Unlike leaders in this area, it only discloses a high-level version of its general pricing policy, with limited detail. Like most of its peers, it states that it does not include non-disclosure clauses regarding vaccine prices in its contracts with governments and other procurers.

MANUFACTURING & SUPPLY

Above average performance in aligning supply and demand. Johnson & Johnson has an above-average approach to ensuring sufficient vaccine supply. It makes a strong commitment to staying in vaccine markets where needed, and has a relatively comprehensive internal process for preventing and responding to shortages.

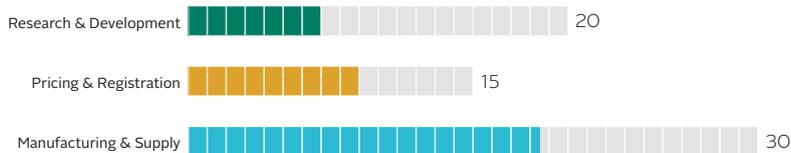
Some activity in building manufacturing capacity. Johnson & Johnson undertakes a relatively small number of activities to build vaccine manufacturing capacities in countries in scope. It provides operational and technology support to Vabiotech in Vietnam, a state-owned company producing vaccines for cholera, hepatitis A and B, and Japanese encephalitis.

Limited focus on vaccine presentations that support access. Johnson & Johnson's performance is comparatively weak when it comes to ensuring its marketed products help to support access on the ground. It has adaptations in development, but has not yet implemented relevant presentations or packaging for marketed products.

Merck & Co., Inc.

Stock Exchange: XNYS
 Ticker: MRK
 HQ: Kenilworth, NJ, US
 Employees: 68,000

Index performance by Research Area



The number of cells represents the maximum possible score. Coloured cells represent points attained.

PERFORMANCE

Merck & Co., Inc. has one of the largest vaccine revenues, above average geographic scope and a medium-sized portfolio, including key vaccines with few producers (e.g., for HPV and rotavirus). It focuses less on vaccine R&D than peers in scope. Overall, it falls in the middle of the pack of companies. Merck & Co., Inc.'s performance in Manufacturing & Supply is

above average, with the strongest commitment to maintaining supply. In Pricing & Registration, it publishes its vaccine pricing policy. It has filed to register some vaccines in only some low-income countries (LICs). It performs below average in Research & Development, with relatively low R&D investments and a relatively small vaccine pipeline.

SALES AND OPERATIONS

Merck & Co., Inc. (known as MSD outside the US and Canada) has three businesses: pharmaceuticals; vaccines; and animal health. For its entire portfolio (all products including vaccines), it has sales in 81 countries in scope. Merck & Co., Inc. had a vaccines joint venture in Europe with Sanofi Pasteur (Sanofi Pasteur MSD) which ceased operation at the end of 2016. The company will take its vaccine assets back in-house. It now has 13 marketed vaccines.

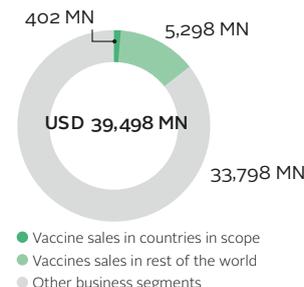
Sales in countries in scope (all product types)



Number of doses sold in 2015



Sales by segment 2015



VACCINE PORTFOLIO

Merck & Co., Inc. has 13 vaccines on the market for 14 diseases in scope, including three combination vaccines. Its portfolio is diverse, from traditional childhood vaccines (e.g., measles, mumps, rubella combination vaccines) to newer vaccines with few other suppliers, including for HPV (Gardasil®) and rotavirus (RotaTeq®).

Marketed vaccines

DTPHibHepIPV	1	Rotavirus	1
Hib	1	Tuberculosis	1
HPV	2	Varicella	2
MMR	1	Viral hepatitis	2
MMRV	1	Total	13
Pneumococcal disease	1		

OPPORTUNITIES

Strengthen internal process for aligning supply and demand. Merck & Co., Inc. can implement some or all of the strategies identified by the Index to strengthen its internal process for aligning supply and demand. For example, it could establish a clear process for escalation and action on identified supply issues; consider other suppliers when making supply allocation decisions; and set up a clear process for re-allocation of stocks in limited supply situations.

Apply a more specific pricing policy and reduce key vaccine prices. Merck & Co., Inc. can outline how it defines pricing tiers and explicitly state how it takes different countries' ability to pay

into account. In addition, it can work with stakeholders to reduce the price of key vaccines (e.g., Gardasil® for HPV and RotaTeq® for rotavirus) for all LICs and middle-income countries (MICs), particularly in the case of Gavi-transitioning countries in the future and current non-Gavi and non-PAHO countries. For this purpose, Merck & Co., Inc. can continue to work with pooled procurers and work directly with self-procuring countries. This can help increase the adoption of these vaccines in more MICs.

Invest more in R&D. Merck & Co., Inc. can invest more in vaccine R&D, and engage in new projects to develop and adapt vaccines that meet

the needs of people in countries in scope. This will help the long-term sustainability of its vaccine business.

File vaccines for registration more widely where they are needed. Merck & Co., Inc. can expand the availability of existing and future key vaccines in more LICs and MICs, where needed, taking into account the availability of alternative products and domestic vaccine manufacturing, registration hurdles, and government demand and preferences. This can provide purchasers with more choice, create a more competitive environment, and improve supply reliability.

RESEARCH AREAS

RESEARCH & DEVELOPMENT

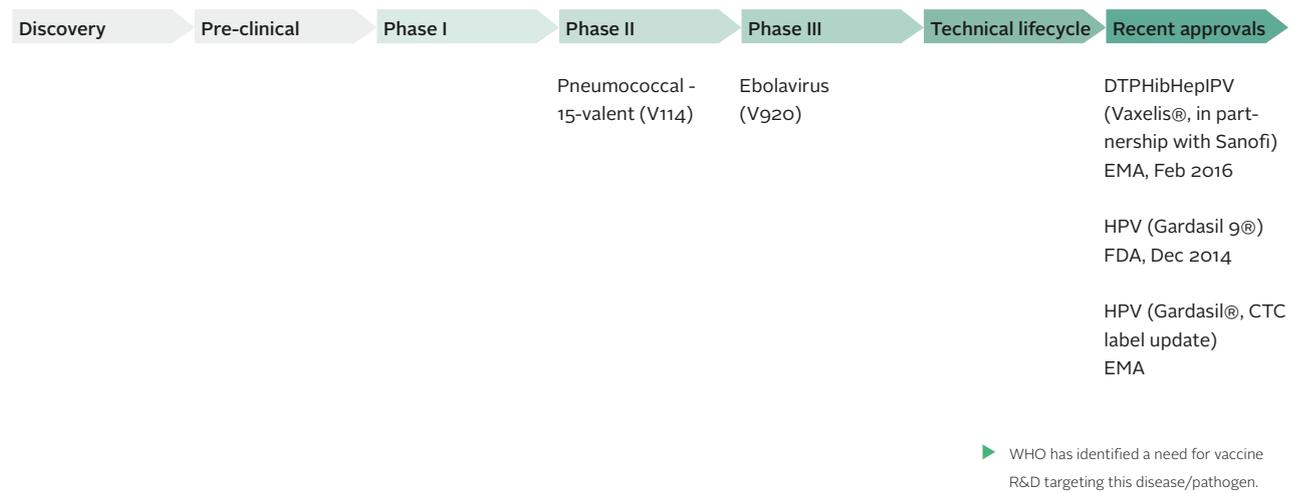
Proportionally low R&D investments. Compared to other companies measured, as a proportion of its global vaccines revenue, Merck & Co., Inc. made relatively low investments in vaccine R&D for diseases in scope in 2014 and 2015.

Relatively small vaccine pipeline. Merck & Co., Inc. has six R&D projects in its pipeline, including projects targeting Ebola virus and pneumococcal disease. It received approval for two vaccines during the period of analysis, as well as a thermostability label update for its HPV vaccine (Gardasil®).

Access provisions in place for two late-stage projects. Merck & Co., Inc. has at least one access provision in place for two out of its four late-stage projects. It applied for WHO prequalification for its HPV vaccine (Gardasil 9®), which is not yet available in countries in scope.

Vaccine pipeline

Merck & Co., Inc.'s pipeline is concentrated in late stages of development. Along with Pfizer, it received the highest number of relevant market approvals during the period of analysis. In addition to projects shown here, Merck & Co., Inc. has a further project for which data are confidential.



PRICING & REGISTRATION

Pricing strategy takes multiple factors into account. Merck & Co., Inc. states that it uses tiered pricing to (a) expand access and (b) to ensure sufficient return on its investment in R&D over time. The company does not provide details of its pricing tiers. The company's access to vaccines policy takes multiple factors into account, including the country's level of economic development, fiscal capacity for investments in health, and actual health spending, which could be seen as proxies for the country's ability to pay.

Extension of Gavi prices to Gavi-transitioning countries. Merck & Co., Inc. is extending the current Gavi prices for its quadrivalent HPV vaccine

(Gardasil®) and rotavirus vaccine (RotaTeq®) through 2025 to Gavi-transitioned countries with gross national income per capita not exceeding USD 3,200.

Above-average transparency. Like its peers, Merck & Co., Inc. does not systematically publish all prices for its vaccines in all countries in scope. Unlike most of its peers, the company publishes its detailed vaccine pricing policy. It states that it does not have a policy permitting or prohibiting governments from disclosing prices: it leaves this to each government's discretion.

Limited registration filing in LICs. Merck & Co., Inc. files the majority of its relevant vaccines for registration in some lower middle-income countries, like its peers. However, it files only some of its vaccines for registration and in only some LICs. Merck & Co., Inc. states that its decision to file for registration is based on where vaccines are needed. The company commits to seeking WHO prequalification of eligible vaccines to expedite access in LICs.

MANUFACTURING & SUPPLY

Very strong in aligning supply and demand. Merck & Co., Inc. makes the strongest commitment to maintaining supply of its vaccines as long as they are needed, and notifies stakeholders of plans to alter supply. It prioritises public health needs when re-allocating limited stock.

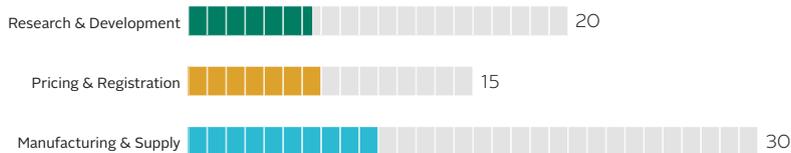
Building manufacturing capacity in Brazil. Merck & Co., Inc. undertakes some vaccine manufacturing capacity building activities. It is undertaking a technology transfer with capacity building components for its HPV vaccine (Gardasil®), and is beginning a technology transfer for its hepatitis A vaccine (Vaqta®), both to Instituto Butantan in Brazil.

Above-average performance in addressing local logistics needs. Merck & Co., Inc. has implemented presentations and packaging to overcome local barriers for several vaccines, with a focus on cold-chain requirements. For example, Gardasil® has been approved for Controlled Temperature Chain use as it does not require constant refrigeration.

Pfizer Inc.

Stock Exchange: XNYS
 Ticker: PFE
 HQ: New York, NY, US
 Number of employees: 97,900

Index performance by Research Area



The number of cells represents the maximum possible score. Coloured cells represent points attained.

PERFORMANCE

Pfizer has one of the largest vaccine revenues, a small portfolio and pipeline, and on-average geographic scope. It is the largest PCV producer, supplying 70% of the global market with Prevenar 13®. Overall, it falls short in multiple areas compared to peers. In Pricing & Registration, although Pfizer newly publishes its tiered pricing policy, it is the only company

that states it supports the use of price confidentiality provisions. The company performs below average in Research & Development, with a relatively small pipeline, and is lagging in several aspects of Manufacturing & Supply. It makes no commitment to notify stakeholders in advance when reducing or ceasing supply of vaccines.

SALES AND OPERATIONS

Pfizer has two segments: Pfizer Innovative Health (including vaccines) and Pfizer Essential Health. The company has sales in 86 countries in scope. Of all companies in scope, it has the highest vaccines revenue, largely due to its PCV (Prevenar 13®). It recently purchased three meningococcal vaccines: from GSK (Mencevax® and Nimenrix®) and Baxter (NeisVac-C®). It now has six marketed vaccines.

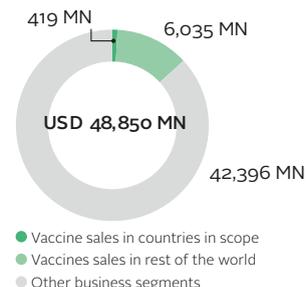
Sales in countries in scope (all product types)



Number of doses sold in 2015

Data confidential

Sales by segment 2015



VACCINE PORTFOLIO

Pfizer has six vaccines on the market for three diseases in scope. Its portfolio comprises four vaccines for meningococcal disease (Mencevax®, NeisVac-C®, Nimenrix®, Trumenba®), one for pneumococcal disease (Prevenar 13®) and one for tick-borne encephalitis (FSME-IMMUN/TicoVac®).

Marketed vaccines

Meningococcal disease	4
Pneumococcal disease	1
TBE	1
Total	6

OPPORTUNITIES

Commit to continuing supply and communicating future supply plans. Pfizer can commit to staying in vaccine markets with few or no other suppliers. It can also commit to communicating its intentions publicly when deciding to discontinue supply of a vaccine in the future, as necessary. Notifying stakeholders in advance will help them to adapt procurement and distribution plans early to minimise the risk of shortages and potential public health impact.

Limit use of price confidentiality provisions. Pfizer can limit its use of confidentiality pro-

visions to help promote a more competitive market and a clearer understanding of pricing problems.

Work with stakeholders to reduce the price of key vaccines. Pfizer can continue to work with pooled procurers and with self-procuring countries, e.g., with regard to its PCV (Prevenar 13®), for all low- and middle-income countries (LICs; MICs), particularly for Gavi-transitioning countries in the future and non-Gavi and non-PAHO countries at present. This can help increase the adoption of these vaccines in more MICs.

Expand R&D activities and pair them with access strategies. Pfizer can engage in new projects to develop and adapt vaccines that meet the needs of people in countries in scope. This will help the long-term sustainability of its vaccine business. Further, by committing to and developing strategies to ensure access to its projects targeting diseases with no existing vaccines, Pfizer has a key opportunity to address unmet needs of populations in LICs and MICs.

RESEARCH AREAS

RESEARCH & DEVELOPMENT

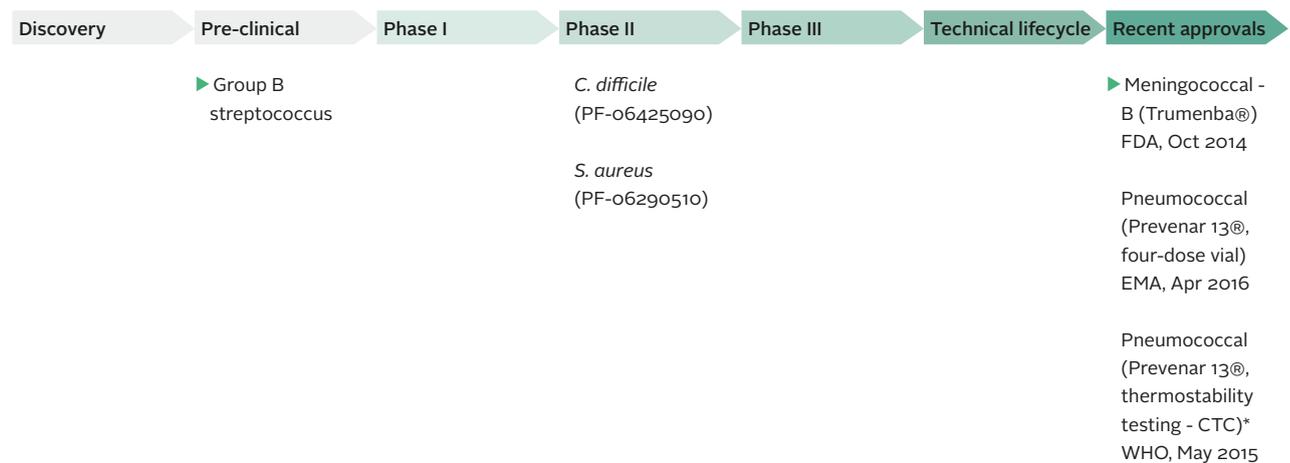
Proportionally low R&D investments. Pfizer invested USD 676.3 mn in vaccine R&D targeting diseases in scope in 2014 and 2015. Relative to other companies measured, this makes up a low proportion of its global vaccines revenue (6%). In absolute terms, the investment was relatively high.

Relatively small vaccine pipeline. Pfizer has six R&D projects, targeting *C. difficile*, Group B streptococcus and *S. aureus* infections. During the period of analysis, it received three approvals for vaccine R&D projects targeting meningococcal and pneumococcal diseases. Two of its projects target diseases prioritised by WHO for vaccine R&D.

Access provisions in place for one late-stage project. Pfizer has at least one access provision in place for one of its four late-stage projects. Prior to receiving regulatory approval, it committed to applying for WHO prequalification for a four-dose presentation of its PCV (Prevenar 13®). The presentation was approved by the EMA in April 2016 and WHO prequalification was granted in July 2016.

Vaccine pipeline

Pfizer, along with Merck & Co., Inc., had the highest number of relevant market approvals during the period of analysis.



*Since the period of analysis, the CTC claim on the single-dose vial of Prevenar 13® was withdrawn, as per request by the EMA, to ensure both vial presentations would have a harmonised label regarding CTC usage.

▶ WHO has identified a need for vaccine R&D targeting this disease/pathogen.

PRICING & REGISTRATION

Pricing strategy with one of the highest numbers of tiers. Pfizer's pricing strategy includes six tiers. The lowest tier includes Gavi-eligible, Gavi-transitioning and any other LICs. Pfizer assesses affordability on the basis of Gross National Income per capita. Its prices are also influenced by the relevant government's commitment to immunisation, the degree of innovation the vaccine represents, and the required investments in the vaccine. Relative to its peers' commitments, Pfizer's pricing strategy is one of the most sensitive to each country's ability to pay, given the number of the tiers.

New humanitarian commitment for Prevenar 13®. Outside the period of analysis, Pfizer committed to providing its PCV to Gavi at USD 3.05, effective January 1st 2017, in the multi-dose vial presentation, and to specified NGOs for humanitarian emergencies. Pfizer has also committed to providing the Gavi price to Gavi-transitioning countries through 2025.

Below average in transparency. Similar to peers, Pfizer does not systematically publish all prices for its vaccines in all countries in scope. It publishes full details of its vaccine pricing policy.

Unlike all other peers, it states that price confidentiality provisions mitigate a major risk for governments and manufacturers: i.e., that discounted prices are used as reference prices by purchasers (e.g., another country) for whom it is neither intended nor appropriate.

Average in registration filing. Pfizer files to register the majority of its relevant vaccines in some of both LICs and lower-middle income countries.

MANUFACTURING & SUPPLY

Lacking commitments to ensure supply. Pfizer's processes and strategies to align supply and demand are less comprehensive than other companies evaluated. It does not commit to staying in vaccine markets where there are few or no other suppliers, nor to communicating its plans externally when reducing or ceasing supply.

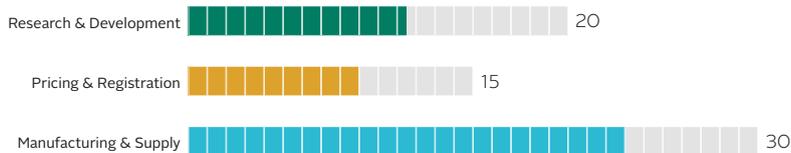
Some activity in building manufacturing capacity in countries in scope. Pfizer has a relatively small number of vaccine manufacturing capacity building activities. From 2015 to 2020, it is undertaking a technology transfer for the manufacture of its PCV (Prevenar 13®) to the Biovac Institute of South Africa.

Below average in addressing local logistics needs. Pfizer has adapted its PCV Prevenar 13® to overcome local barriers. If correctly refrigerated, the multi-dose vial can be used for 28 days after opening. The company does not adapt its products' package inserts or packaging to support rational use by health workers.

Sanofi

Stock Exchange: XPAR
 Ticker: SAN
 HQ: Paris, France
 Employees: 115,631

Index performance by Research Area



The number of cells represents the maximum possible score. Coloured cells represent points attained.

PERFORMANCE

Sanofi's vaccine portfolio size, revenue, volume of doses sold, and geographic scope are among the largest of companies in scope. It markets the world's first dengue vaccine (Dengvaxia®). Overall, the company's performance in the Index is strong. It performs above average in Research & Development, with a relatively large pipeline. Sanofi's per-

formance is strong in all areas of Manufacturing & Supply. In Pricing & Registration, Sanofi is the leader in registration, with the majority of its relevant vaccines filed to be registered in 30-50% of countries in scope. It makes a general commitment to ensuring the prices of its vaccines are sustainable and equitable.

SALES AND OPERATIONS

Sanofi consists of five business units: vaccines; diabetes and cardiovascular; general medicines and emerging markets; specialty care; and animal health. For its entire portfolio, Sanofi has sales in 96 countries in scope. About one-third of all sales are made in emerging markets. Sanofi Pasteur is the vaccines division of Sanofi, and includes the company's India-based affiliate Shantha Biotechnics. Sanofi Pasteur had a vaccines joint venture in Europe with Merck & Co., Inc. (Sanofi Pasteur MSD), which ceased operation at the end of 2016. The company will take its vaccine assets back in-house. It now has 38 marketed vaccines.

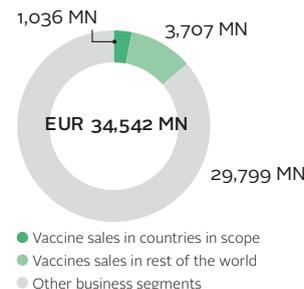
Sales in countries in scope (all product types)



Number of doses sold in 2015



Sales by segment 2015



VACCINE PORTFOLIO

Sanofi has 38 vaccines on the market for 18 diseases in scope, one of the largest portfolios of the companies measured. Its portfolio covers a wide range, including many vaccines recommended by the WHO for routine immunisation (e.g., for diphtheria, hepatitis B, Hib, pertussis, polio and tetanus).

Marketed vaccines

Cholera	1	DTP	2	MMR	1	Typhoid	1
Dengue	1	DTP/IPV	3	Pneumococcal	1	Typhoid/HepA	1
DT	1	Hib	1	disease	1	Viral hepatitis	2
DTP/Hib/Hep	1	JE	1	Polio	3	Yellow fever	2
DTP/Hib/Hep/IPV	1	Measles	1	Rabies	1		
DTP/Hib/IPV	3	Meningococcal	5	Seasonal influenza	5		
DT/IPV	1	disease	3	Tetanus	1	Total	38

OPPORTUNITIES

Strengthen internal process for aligning supply and demand. Sanofi can consider implementing some or all of the key strategies identified by the Index to further strengthen its internal process for aligning supply and demand. For example, it can commit to taking steps to ensure access to vaccines where they are needed in the event of a shortage.

Define and publish a clear pricing strategy for vaccines. Sanofi can define what its pricing strategy is for governments that do not procure vaccines through UNICEF, and ensure it takes these countries' ability to pay into account. It can also publish its pricing strategy for vaccines.

Strengthen approach to access provisions for late-stage vaccine candidates. Applying lessons learned from its dengue vaccine (Dengvaxia®),

Sanofi can consider the value of all its late-stage vaccine candidates to countries in scope and, as appropriate, develop plans to facilitate access to them in such countries. For those projects with at least one access provision in place, Sanofi can continue to strengthen and refine its access commitments and strategies to ensure the vaccines are made rapidly accessible upon approval.

RESEARCH AREAS

RESEARCH & DEVELOPMENT

Proportionally low R&D investments. Sanofi invested USD 214.7 mn in vaccine R&D targeting diseases in scope in 2014 and 2015. As a proportion of its global vaccine revenue, this is relatively low (2%) compared to other companies in scope, but comparatively high in absolute terms.

Relatively large vaccine pipeline. Sanofi has 14 R&D projects, targeting at least 15 diseases in scope. Five of these diseases have been prioritised by WHO for vaccine R&D.

Access provisions in place for over half of late-stage projects. Sanofi has the second-largest number of late-stage projects with at least one access provision in place (6/10 or 60%). For example, it plans to apply for WHO prequalification for its vaccine candidates for meningitis and rabies.

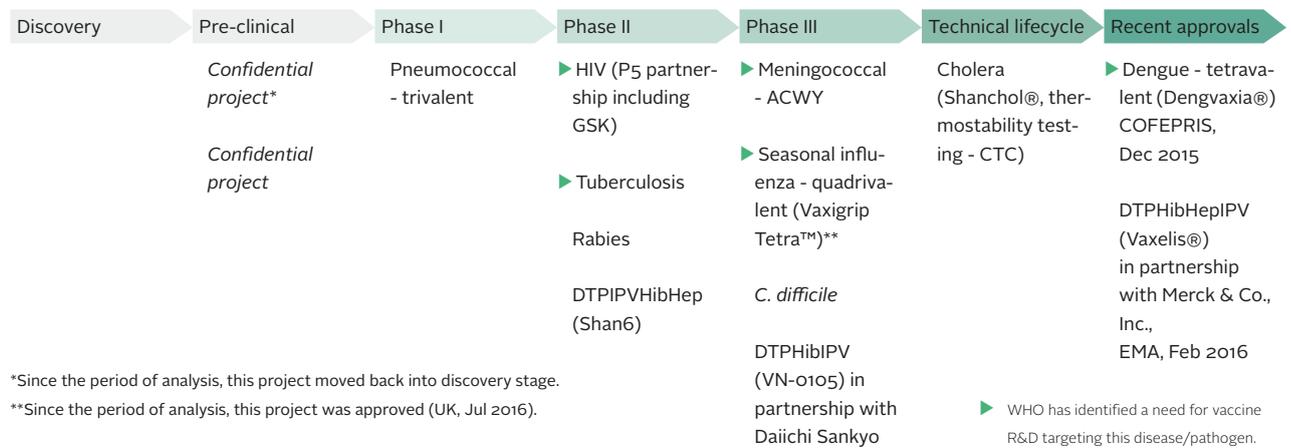
Researching Micropellet technology. Sanofi is developing technologies for vaccine delivery and packaging targeted at resource-limited set-

tings, for example by exploring Micropellet technologies for the development of thermostable vaccines. It is also collaborating on vaccine technology development for developing countries through the Global Health Vaccine Center of Innovation.

Vaccine pipeline

Sanofi has the second largest number of R&D projects nearing potential approval.

Since the period of analysis, Sanofi has a new discovery-stage project for a disease in scope.



*Since the period of analysis, this project moved back into discovery stage.

**Since the period of analysis, this project was approved (UK, Jul 2016).

PRICING & REGISTRATION

General pricing strategy. Sanofi makes a general commitment to ensuring the prices of its vaccines are sustainable and equitable. It applies a tiered pricing approach to countries that procure its inactivated polio vaccine (IPV) in a 10-dose vial through UNICEF. For its other vaccines procured through UNICEF, Sanofi complies with the Most Favored Nation Clause, through which Sanofi agrees to give UNICEF the best terms it makes available to any other buyer. However, it is not clear how Sanofi prices vaccines for non-Gavi and non-PAHO countries that self-procure, or whether it takes these countries' ability to pay into account.

Extension of Gavi prices to Gavi-transitioned countries. Sanofi commits to offering Gavi-level pricing in its UNICEF tender to Gavi-transitioned countries until the end of 2018. This applies to its yellow fever (Stamaril®) and pentavalent (Shan5®) vaccines.

Average transparency. Similar to peers, Sanofi does not systematically publish all prices for its vaccines in all countries in scope. Sanofi publicly discloses its pricing policy for one relevant marketed vaccine (its IPV, Imovax®), but does not disclose a general pricing strategy, unlike leaders in this area. Like most of its peers, it states that

it does not include non-disclosure clauses on vaccine prices in its contracts with governments and other procurers.

Leader in registration filing. Sanofi files to register the majority of its relevant vaccines in 30-50% of the low-income countries (LICs) and lower middle-income countries in scope. As the company has a large vaccine portfolio, this applies to a relatively large number of vaccines. Sanofi also commits to seeking WHO prequalification of eligible vaccines to expedite access in LICs.

MANUFACTURING & SUPPLY

Strong in aligning supply and demand. Sanofi demonstrates strong commitments and processes to align supply and demand, including clear processes for proactively engaging with purchasers. Internally, the company regularly reviews demand, has a clear process for escalating issues, and scales up production and/or reallocates stock when needed.

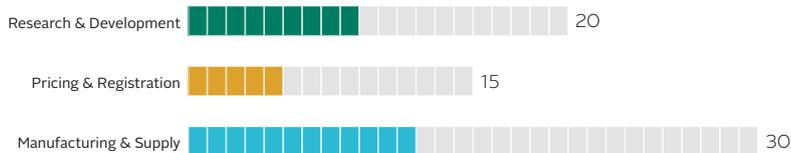
Leader in building manufacturing capacity. During the period of analysis, Sanofi had the highest number of vaccine manufacturing capacity building activities. It has undertaken long-term, manufacturing technology transfers in a range of countries in scope, including for several vaccines in Latin America.

Leader in addressing local logistics needs. Sanofi has presentations or packaging to help overcome local access challenges for approximately a quarter of its vaccines in scope. For example, to prevent waste, its inactivated polio vaccine (Imovax Polio®) can be used for 28 days once opened (if correctly refrigerated).

Serum Institute of India Pvt. Ltd.

Stock exchange: privately held
 Ticker: -
 HQ: Pune, India
 Employees: unknown

Index performance by Research Area



The number of cells represents the maximum possible score. Coloured cells represent points attained.

PERFORMANCE

Serum Institute of India produces the largest volume of vaccines and has the largest geographic scope of companies evaluated, with a relatively large pipeline and medium-sized portfolio and revenue. Many of the vaccines it produces are for diseases recommended by WHO for routine immunisation for children. The company's high-volume, low-cost business model is clearly access-oriented. However, its approach

to providing access to vaccines is less transparent and less structured than other companies. For example, in Pricing & Registration, Serum Institute of India does not publish details of its vaccine pricing strategy. The company performs well in filing vaccines for registration in low- and middle-income countries. It falls in the middle of the pack in Research & Development, and below average in Manufacturing & Supply.

SALES AND OPERATIONS

Serum Institute of India is a subsidiary of the Poonawalla Group, a privately held, family-owned business. Serum Institute of India's portfolio focuses on vaccines: it is one of the world's largest vaccine producers by number of doses. Its portfolio also includes products such as antitoxins and antivenoms, anemia and hormone treatments, and vitamin supplements. Its vaccines are sold in 84 countries in scope. In 2012, Serum Institute of India acquired Bilthoven Biologicals, a Dutch company producing several vaccines, including an IPV. Serum Institute of India now has 23 vaccines in its portfolio.

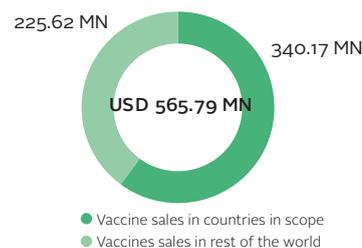
Sales in countries in scope (vaccines)



Number of doses sold in 2015



Sales by segment 2015



VACCINE PORTFOLIO

Serum Institute of India has 23 vaccines on the market for 14 diseases in scope. Its portfolio is diverse, including many vaccines recommended by WHO for routine immunisation (e.g., DTWP-containing combination vaccines, and vaccines for meningococcal A and polio).

Marketed vaccines

DT	1	Meningococcal disease	1	Rubella	1
DTP	1	MMR	1	Seasonal influenza	1
DTPHep	1	MR	1	Td	1
DTPHib	1	Mumps	1	Tetanus	1
DTPHibHep	1	Pandemic influenza	1	Tuberculosis	1
Hib	1	Polio	3	Viral hepatitis	2
Measles	1	Rabies	1		
				Total	23

OPPORTUNITIES

Strengthen its processes for aligning supply and demand. Serum Institute of India can develop – and share with stakeholders – clear and structured processes for aligning supply of their vaccines with global demand. Effective and transparent processes (including making information publicly available, where appropriate) will support stakeholders' planning and contribute to the sustainability of the company's business.

Develop and publish a pricing strategy for vaccines. Like peers, Serum Institute of India can publish what its pricing strategy is for Gavi and PAHO countries, as well as countries that procure through UNICEF. It can also specify its pricing policy for governments that self-procure, explicitly stating how it takes these countries' ability to pay into account and what other factors it considers when pricing its vaccines.

Continue to engage in strong, adaptive R&D. Serum Institute of India can continue to develop its strong and unique R&D model, which focuses on developing vaccines with characteristics aimed at improving access in low- and middle-income countries (LICs; MICs). This will help the long-term sustainability of its vaccine business.

RESEARCH AREAS

RESEARCH & DEVELOPMENT

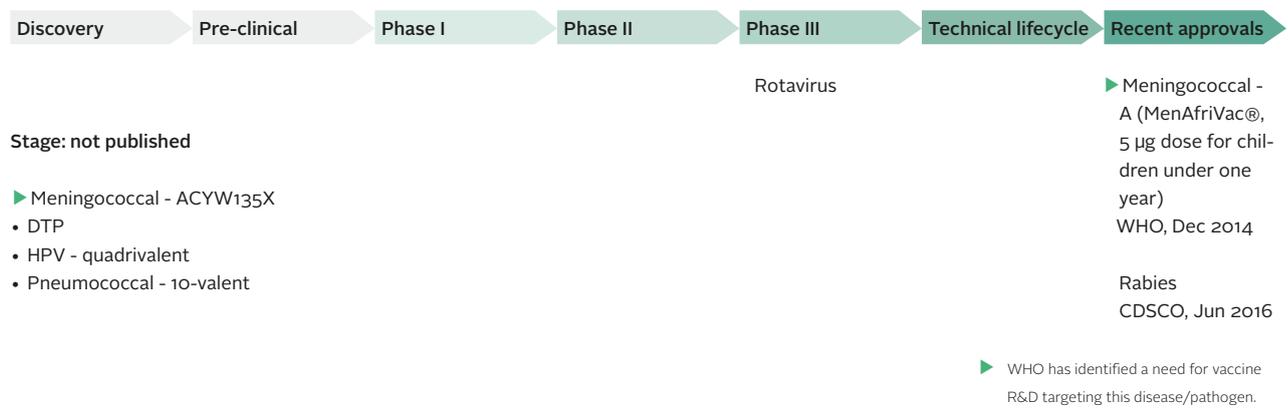
Proportionally low R&D investments. Compared to other companies measured, as a proportion of its global vaccines revenue, Serum Institute of India made relatively low investments in vaccine R&D targeting diseases in scope in 2014 and 2015.

Relatively large vaccine pipeline. Serum Institute of India has 12 R&D projects in its pipeline, as indicated by publicly available sources. Two of its projects target meningococcal disease, which is prioritised by WHO for vaccine R&D.

Access provisions in place for half of late-stage projects. For example, its meningococcal vaccine, MenAfriVac®, was developed in partnership with WHO and PATH with affordability in mind. The recently approved 5 µg dose was priced at USD 0.49 per dose in 2016. The total number of late-stage projects with at least one access provision in place is confidential.

Vaccine pipeline

Serum Institute of India has a relatively large pipeline compared to other companies evaluated. Data for this figure is based on public pipeline during the period of analysis (www.seruminstitute.com/content/prod_pipe.htm, accessed 28 April 2016), using additional public sources for recent approvals. Public sources also indicate Serum Institute of India has five additional vaccine R&D projects (not in figure): they target dengue, HPV, rotavirus, seasonal influenza and tuberculosis. Serum Institute of India has further, additional projects for which all data are confidential.



PRICING & REGISTRATION

General pricing strategy. Serum Institute of India has a general policy of making vaccines available at affordable prices and has shown evidence of proactively taking steps to ensure affordable prices in LICs and MICs. Its meningococcal A vaccine (MenAfriVac®), developed for African markets by the Meningitis Vaccine Project, is offered at USD 0.64 per dose. Serum Institute of India intends to sell its pneumococcal vaccine for USD 2 per dose to Gavi countries, if and when it is approved. While Serum Institute of India has received support from partners for

both vaccines, the company is an integral contributor, ensuring the supply of these vaccines.

Pricing strategy not published. Like its peers, Serum Institute of India does not systematically publish all prices for its vaccines in all countries in scope. Unlike its peers, however, it does not publish even a general pricing strategy for vaccines. The company's stance on price confidentiality provisions is confidential.

Above-average performance in filing for registration. Serum Institute of India files to register the majority (>50%) of its relevant vaccines in 30-50% of LICs and some lower-middle income countries. Serum Institute of India has a large vaccine portfolio, so this is a relatively good performance. The company's policy is to file to register vaccines wherever there is market potential, whether that entails supplying vaccines directly to governments, private parties or through UN agencies.

MANUFACTURING & SUPPLY

Strong commitments but processes to align supply and demand appear less structured. Serum Institute of India states that it commits to staying in vaccine markets in which there are few other suppliers. However, it is unclear whether the company has strong processes to support ongoing alignment of supply and demand.

Builds manufacturing capacity through the Developing Countries Vaccine Manufacturers Network (DCVMN). Serum Institute of India is a member of the DCVMN, an alliance of 50 manufacturers that supports capacity building through information and expertise sharing among its members.

Some vaccine presentations support access. Some of Serum Institute of India's vaccine presentations help address local access barriers. For more than two-thirds of its vaccines, it provides several dosage options. These options help to support purchasing decisions based on local needs.

Daiichi Sankyo Co., Ltd.

Stock Exchange: XTKS
 Ticker: 4568
 HQ: Tokyo, Japan
 Employees: 15,249

Index performance by Research Area



The number of cells represents the maximum possible score. Coloured cells represent points attained. Daiichi Sankyo was evaluated in one Research Area: Research & Development.

PERFORMANCE

Daiichi Sankyo's vaccine business is currently focused on the Japanese market, and there is evidence it is increasing its focus on vaccine R&D. Its pipeline includes combination vaccines for diseases recommended by WHO for routine immunisation for children. Daiichi Sankyo performs below average in Research & Development, with a relatively small pipeline and no access plans in place for late-stage projects. Daiichi Sankyo currently markets vaccines only in Japan, and not in coun-

tries in scope. It states that it has processes for preventing vaccine shortages, including coordinating supply plans with stakeholders and scaling up production capacity. The company is partnering with the Japan International Cooperation Agency (JICA) to build the vaccine manufacturing capacity of POLYVAC in Vietnam. It is part-way through a five-year project to provide technical cooperation for the production of a measles and rubella combination vaccine (started in 2013).

SALES AND OPERATIONS

Daiichi Sankyo has four business units: innovative pharmaceuticals; generics; vaccines; and over-the-counter medicines. For its entire portfolio, Daiichi Sankyo has sales in 44 countries in scope of the Index. Its vaccines business unit comprises Kitasato Daiichi Sankyo Vaccine Co., Ltd., which is responsible for R&D, production and sales, and Japan Vaccine Co., Ltd. (a joint venture with GSK), which conducts late-phase clinical development and sales. Daiichi Sankyo has 11 marketed vaccines.

Sales in countries in scope (all product types)



Sales by segment 2015



Number of doses sold in 2015



VACCINES PORTFOLIO

Daiichi Sankyo has 11 vaccines on the market for nine diseases in scope. Its portfolio focuses on traditional childhood vaccines, including for diphtheria, tetanus, pertussis, measles, mumps and rubella (including four combination vaccines). It also has a seasonal influenza vaccine and two pandemic influenza vaccines.

Marketed vaccines

DT	1	Pandemic influenza	2
DTP	1	Rubella	1
DTPIPV	1	Seasonal influenza	1
Measles	1	Tetanus	1
MR	1		
Mumps	1	Total	11

OPPORTUNITIES

Continue strong investments in R&D. As the company's vaccine business grows, Daiichi Sankyo can continue to make vaccine R&D investments that represent a high proportion of its vaccine revenue in vaccine R&D. This will help the long-term sustainability of its vaccine business.

Expand manufacturing capacity building activities. Daiichi Sankyo can build on its experience in providing technical cooperation, for example to POLYVAC in Vietnam, to undertake further vaccine manufacturing capacity building activities with manufacturers in other countries in scope of the Index.

Direct efforts towards product attributes that address key barriers to access. As its discovery-stage projects progress, factors such as cost of production, dose schedule, dose presentation and temperature stability need to be considered to address barriers to access. This process can be facilitated by working with external stakeholders to identify what product attributes are most desirable to address population needs, balanced with technical considerations.

Make investigational vaccines, if approved, accessible in countries in scope. This involves making commitments and developing strategies as early in development as possible to ensure vaccines are accessible, once on the market.

Aligning these plans with those of vaccine procurers and other stakeholders will help ensure the company meets access needs, and provide it with greater predictability regarding the future market for these vaccines.

Expand processes for responding to vaccine shortages. As Daiichi Sankyo expands its vaccines business beyond Japan, it can work with relevant national and global health stakeholders to help expand and adapt its current processes for preventing and responding to vaccine shortages. A structured and predictable process will support the company's engagement with national and global health stakeholders and help ensure sustainability.

RESEARCH AREAS

RESEARCH & DEVELOPMENT

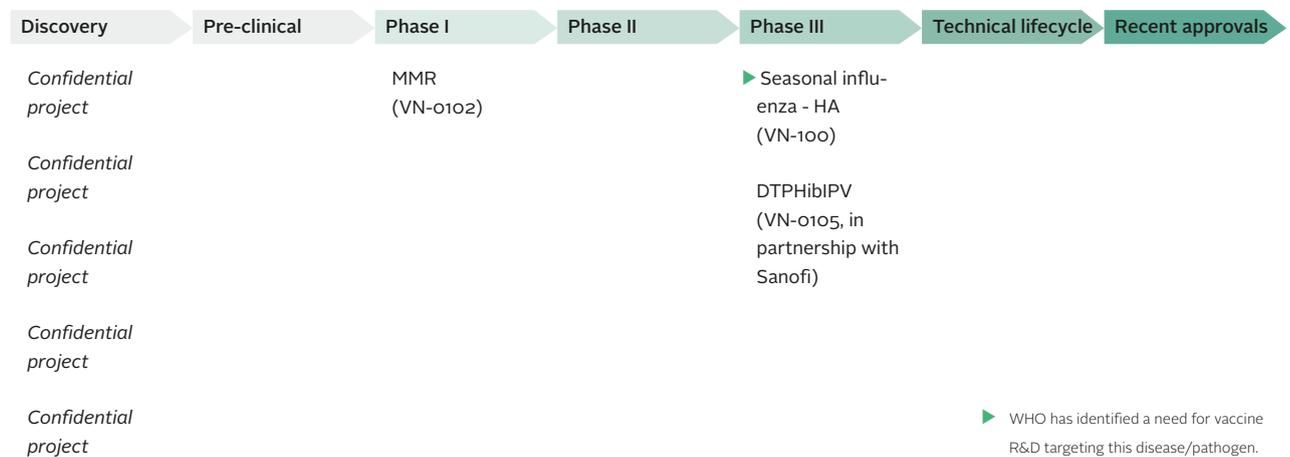
Proportionally high R&D investments. As a proportion of its global vaccine revenue, Daiichi Sankyo made relatively high investments into vaccine R&D targeting diseases in scope in 2014 and 2015, compared to other companies in scope.

Relatively small vaccine pipeline. Daiichi Sankyo has eight R&D projects, including a vaccine candidate for seasonal influenza: influenza is prioritised by WHO for vaccine R&D. It also has two combination vaccine candidates (DTPHiBPV and MMR).

No evidence of access provisions. Daiichi Sankyo does not provide evidence that it has access provisions for its two late-stage R&D projects.

Vaccine pipeline

Daiichi Sankyo has the largest number of discovery-stage vaccine R&D projects among companies evaluated.



Takeda Pharmaceutical Co., Ltd.

Stock Exchange: XTKS
 Ticker: 4502
 HQ: Osaka, Japan
 Employees: 31,168 (consolidated)

Index performance by Research Area



The number of cells represents the maximum possible score. Coloured cells represent points attained. Takeda was evaluated in one Research Area: Research & Development.

PERFORMANCE

Takeda currently markets vaccines in Japan only and is growing its vaccine pipeline, including R&D projects for dengue and chikungunya (both neglected tropical diseases). Takeda performs above average in Research & Development, and has clear access provisions for its late-stage vaccine candidate. While it does not currently market vaccines in countries in scope, it is taking steps to support affordability and supply of vaccines in its pipeline. For example, from 2016, Takeda has been developing a low-cost IPV with support from the Bill & Melinda Gates Foundation. As part of the worldwide

polio eradication strategy, Takeda will produce at least 50 million IPV doses per year for supply to more than 70 developing countries. For this vaccine, Takeda is committed to a ceiling price for Gavi countries through UNICEF, and intends to extend Gavi-level prices to Gavi transitioning countries for a number of years post-transition. Pricing for non-Gavi-eligible countries will take into account (among other criteria) the cost of goods, country GDP per capita, procurement conditions, terms and impact of competition.

SALES AND OPERATIONS

Takeda's three business segments are ethical drugs (including vaccines); consumer health care; and other (including industrial chemicals). The ethical drugs division accounts for the largest share of revenue (around 90%). For its entire portfolio, Takeda has sales in 29 countries in scope of the Index. Its vaccines business unit currently markets seven vaccines in Japan only.

Sales in countries in scope (all product types)



Sales by segment 2015



Number of doses sold in 2015



VACCINE PORTFOLIO

Takeda has seven vaccines on the market for six diseases in scope. Its portfolio comprises a diphtheria and tetanus combination vaccine, a tetanus vaccine, vaccines for measles, mumps and rubella including a MR combination vaccine, and a pandemic influenza vaccine.

Marketed vaccines

DT	1	Rubella	1
Measles	1	Tetanus	1
MR	1		
Mumps	1		
Pandemic influenza	1	Total	7

OPPORTUNITIES

Continue to make strong investments in R&D. As its vaccine business grows, Takeda can continue to make R&D investments that represent a high proportion of its vaccine revenue.

Expand processes to respond to vaccine shortages. Takeda is taking steps to support sufficient vaccine supply. As it expands its vaccine business outside Japan, it can work with relevant national and global health stakeholders to expand and adapt its processes for preventing and responding to vaccine shortages. It can also commit to continuing supply of vaccines outside Japan for which there are few or no other suppliers.

Aim toward product attributes that meet needs of populations in scope. Takeda should continue its efforts to identify what product attributes are most desirable for addressing population needs. Expanding on its commitment to develop multi-dose vials of certain vaccine candidates in response to WHO recommendations, Takeda can consider factors such as dose schedule and temperature stability for all its vaccine R&D.

Continue to share expertise with local manufacturers. As demonstrated by its partnership for chikungunya vaccine development in India, Takeda has valuable expertise that it can share

with vaccine manufacturers and developers in countries in scope. In that way, it can contribute to improving global vaccine manufacturing expertise and supply. In assessing capacity building opportunities, the company should consider how it could draw upon its expertise to assess and respond to local capacity building needs.

Put pricing strategies in place for new vaccines. Takeda is researching affordability for its future vaccines for chikungunya, dengue and enterovirus 71, and should strive to ensure that these future vaccines are affordable for both Gavi and non-Gavi low- and middle-income countries.

RESEARCH AREAS

RESEARCH & DEVELOPMENT

Proportionally high R&D investments. As a proportion of its global vaccine revenue, Takeda made relatively high investments into vaccine R&D targeting diseases in scope in 2014 and 2015, compared to other companies in scope.

Relatively small vaccine pipeline. Takeda has four R&D projects. It is working to develop vaccines against chikungunya, dengue, enterovirus 71 and polio. Dengue is prioritised by WHO for vaccine R&D.

Access provisions in place for late-stage project. Takeda intends to seek WHO prequalification for TAK-003, its phase III live-attenuated tetravalent dengue vaccine candidate. Takeda will prioritise registration in countries where clinical trials have taken place and in countries with the highest medical needs.

Vaccine pipeline

Takeda's live-attenuated tetravalent dengue vaccine candidate, TAK-003, is approaching potential regulatory approval.



▶ WHO has identified a need for vaccine R&D targeting this disease/pathogen.

Methodology scopes

PRODUCT SCOPE: PREVENTIVE VACCINES

The Access to Vaccines Index focuses on preventive vaccines, which are designed to protect against future disease, rather than therapeutic vaccines, which are designed to treat existing

disease. The Index also covers vaccine platform technologies that can be used for different vaccines and vaccine types.

COMPANY SCOPE: 8 COMPANIES

The Access to Vaccines Index measures 8 vaccine companies²: seven large research-based pharmaceutical companies based in mature markets and one vaccine manufacturer based in an emerging market. In the inclusion process, the pipelines and portfolios of 20 of the world's largest research-based pharmaceutical companies were examined to identify: 1) those with a large vaccine business or subsidiary; and 2) those with relevant, high-need vaccines on the market or

in their pipelines. This brought Daiichi Sankyo, GSK, Johnson & Johnson, Merck & Co., Pfizer, Sanofi and Takeda into scope. Advice was then sought from experts regarding other major players in the vaccine market. Experts suggested several further additions to the company scope. These were assessed for: a) suitability for measurement, looking for publicly-listed or privately-owned companies with relevant products on the market or in the pipeline and a presence in

countries in the geographic scope of the Index; and b) ability and will to participate in the Access to Vaccines Index. This brought Serum Institute of India into scope.

^a AstraZeneca was included in scope when the methodology was published, but later excluded from analysis: it has a limited vaccine pipeline and portfolio, and its future business strategy does not focus on vaccines, therefore its performance is considered not comparable to other companies evaluated.

List of companies included in the 2017 Access to Vaccines Index – 8 companies

Ticker	Company	Country	Total revenue 2014	Vaccine revenue 2014 (bn USD)* (bn USD)
4568	Daiichi Sankyo Co. Ltd.	JPN	7.6	n/a
GSK	GlaxoSmithKline plc	GBR	37.9	5.26**
JNJ	Johnson & Johnson	USA	74.3	n/a
MRK	Merck & Co. Inc.	USA	42.2	6.25**
PFZE	Pfizer Inc.	USA	49.6	4.48**
SAN	Sanofi	FRA	43.1	5.85**
n/a	Serum Institute of India Ltd.	IND	n/a	n/a
4502	Takeda Pharmaceutical Co. Ltd.	JPN	14.8	0.315***

* Data from Bloomberg Business [Accessed 9th October 2015]

** Data from EvaluatePharma [Accessed 9th October 2015]

*** Data from statista.com [Accessed 9th October 2015]

GEOGRAPHIC SCOPE: 107 COUNTRIES

The geographic scope for the Access to Vaccines Index consists of 107 countries. Out of the 107 countries in scope, 53 are eligible for support from Gavi, the Vaccine Alliance, for financing and implementing their national immunisation programmes.¹ This includes 14 countries that are currently transitioning from the Gavi system. The transition period lasts five years, after which countries can no longer access Gavi support, putting the future sustainability of their immunisation programmes at risk.² Of the

countries in scope, 18 are members of the Pan-American Health Organization (PAHO),³ three of which are also members of Gavi. Through the PAHO revolving fund, these countries have access to pooled procurement of vaccines and thus potentially lower prices.

The geographic scope covers:

- 1) All countries defined by the World Bank as low-income or lower middle-income;⁴
- 2) All countries defined by the UNDP as either

low or medium human development;⁵

- 3) All countries that receive a score of less than 0.6 on the UN Inequality-Adjusted Human Development Index.⁶ This measure takes account of how health, education and income are distributed within each country; and
- 4) All least developed countries (LDCs), as defined by the Committee for Development Policy of the UN Economic and Social Council (ECOSOC).⁷

List of countries included in the 2017 Access to Vaccines Index - 107 countries

Country	Classification			
East Asia & Pacific		Middle East & North Africa		Nigeria
Cambodia	LIC	Djibouti	LMIC	LMIC
China	HiHDI	Egypt, Arab Rep.	LMIC	Rwanda
Indonesia	LMIC	Iran, Islamic Rep.	HiHDI	LMIC
Kiribati	LMIC	Iraq	MHDC	São Tomé and Príncipe
Korea, Dem.Rep.	LIC	Morocco	LMIC	LMIC
Lao PDR	LMIC	Palestine, State of	LMIC	Senegal
Micronesia, Fed. Sts.	LMIC	Syrian Arab Rep.	LMIC	LMIC
Mongolia	MHDC	Yemen, Rep.	LMIC	Sierra Leone
Myanmar	LMIC			LIC
Papua New Guinea	LMIC	South Asia		Somalia
Philippines	LMIC	Afghanistan	LIC	LIC
Samoa	LMIC	Bangladesh	LMIC	South Africa
Solomon Islands	LMIC	Bhutan	LMIC	MHDC
Thailand	HiHDI	India	LMIC	South Sudan
Timor-Leste	LMIC	Maldives	MHDC	LIC
Tuvalu	LDC	Nepal	LIC	Sudan
Vanuatu	LMIC	Pakistan	LMIC	LMIC
Vietnam	LMIC	Sri Lanka	LMIC	Swaziland
				LMIC
				Tanzania, United Rep.
				LIC
				Togo
				LIC
				Uganda
				LIC
				Zambia
				LMIC
				Zimbabwe
				LIC
Europe & Central Asia		Sub-Saharan Africa		
Armenia	LMIC	Angola	LMIC	
Georgia	LMIC	Benin	LIC	
Kosovo	LMIC	Botswana	MHDC	
Kyrgyz Rep.	LMIC	Burkina Faso	LIC	
Moldova	LMIC	Burundi	LIC	
Tajikistan	LMIC	Cameroon	LMIC	
Turkmenistan	MHDC	Cape Verde	LMIC	
Ukraine	LMIC	Central African Rep.	LIC	
Uzbekistan	LMIC	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	LMIC	
		Lesotho	LMIC	
		Liberia	LIC	
		Madagascar	LIC	
		Malawi	LIC	
		Mali	LIC	
		Mauritania	LMIC	
		Mozambique	LIC	
		Namibia	MHDC	
		Niger	LIC	
Latin America & Caribbean				
Belize	HiHDI			
Bolivia	LMIC			
Brazil	HiHDI			
Colombia	HiHDI			
Dominican Rep.	HiHDI			
Ecuador	HiHDI			
El Salvador	LMIC			
Guatemala	LMIC			
Guyana	LMIC			
Haiti	LIC			
Honduras	LMIC			
Jamaica	HiHDI			
Mexico	HiHDI			
Nicaragua	LMIC			
Panama	HiHDI			
Paraguay	MHDC			
Peru	HiHDI			
Suriname	HiHDI			

Table legend

LIC	Low-income country <i>World Bank income classifications</i>
LMIC	Lower middle-income country <i>World Bank income classifications</i>
LDC	Least developed country <i>UN Human Development Index</i>
MHDC	Medium human development country <i>UN Human Development Index</i>
HiHDI	High human development country with high inequality <i>UN Inequality-Adjusted Human Development Index</i>

- Eligible for Gavi support
- Transitioning from Gavi support
- Not eligible for Gavi support

DISEASE SCOPE: 69 DISEASES

The disease scope of the Access to Vaccines Index consists of 69 diseases/pathogens that are vaccine preventable and have the highest priority when it comes to improving access to immunisation. Priority depends on a combination of factors that is unique to the disease in question, to the needs of the population at risk of infection, and to the nature of the market for an effective vaccine.

The disease scope covers:

- 1) All diseases recommended by the WHO for routine immunisation⁸ where a cost-effective vaccine is already available;
- 2) All diseases identified by the WHO as having a high need for further vaccine R&D⁹; and
- 3) Five groups of diseases included on the basis of stakeholder recommendations.

Diseases suitable for maternal immunisation and emerging infectious diseases were selected using the data provided by Rappuoli et al.¹⁰ Diarrhoeal diseases were included based on the 2016 Access to Medicine Index disease scope.¹¹ The most prevalent causes of lower respiratory infections among children were selected using data from Rudan et al.¹² All diseases classified by the WHO as neglected tropical diseases (NTDs) are included in scope.¹³

Diseases without existing vaccines included in the 2017 Access to Vaccines Index - 43 diseases.

Disease	Included based on WHO position		Included based on stakeholder recommendation				
	Need for routine immunisation	Need for R&D	Lower respiratory infection	Diarrhoeal disease	Neglected tropical disease	Maternal immunisation	Emerging infectious disease
Adenovirus*			●				
Amoebiasis				●			
Balantidiasis				●			
Buruli Ulcer					●		
Campylobacter enteritis				●			
Chagas disease					●		
Chikungunya					●		
<i>Clostridium difficile</i>				●			
Cryptosporidiosis				●			
Cytomegalovirus (CMV)						●	
Dracunculiasis					●		
Ebolavirus							●
Echinococcosis					●		
Enterovirus 71							●
<i>Escherichia coli</i> infections				●			●
Food-borne trematodiasis					●		
Giardiasis				●			
Group B streptococcus		●				●	
Hantavirus pneumonia							●
Human African trypanosomiasis					●		
Human Immunodeficiency virus (HIV)		●					
Human metapneumovirus			●				
Human monkeypox							●
Isosporiasis				●			
<i>Klebsiella pneumoniae</i>			●				
Lassa fever							●
Leishmaniasis					●		
Leprosy					●		
Lymphatic filariasis					●		
Marburg (haemorrhagic) virus							●
Onchocerciasis					●		
Parainfluenza			●				
<i>Pneumocystis jiroveci</i>			●				
Respiratory Syncytial Virus (RSV)**			●			●	
Schistosomiasis					●		
Severe Acute Respiratory Syndrome (SARS)							●
Shigellosis				●			
Soil-transmitted helminthiasis					●		
<i>Staphylococcus aureus</i> ***			●				●
Taeniasis/cysticercosis					●		
Trachoma					●		
Yaws					●		
<i>Yersinia enterocolitica</i>				●			

*An adenovirus vaccine has been approved for military personnel in the US.

**RSV was added to the list of diseases for which the WHO has identified a need for vaccine R&D in February 2017.

***This includes methicillin-resistant *S. aureus* (MRSA).

● Included ● Included

Diseases with existing vaccines included in the 2017 Access to Vaccines Index - 26 diseases.

Disease	Included based on WHO position		Stakeholder recommendations				
	Need for routine immunisation	Need for R&D	Lower respiratory infection	Diarrhoeal disease	Neglected tropical disease	Maternal immunisation	Emerging infectious disease
Cholera	●			●			
Dengue		●					
Diphtheria	●						
<i>Haemophilus influenzae</i> type B (Hib)	●		●				
Human papillomavirus (HPV)	●						
Japanese encephalitis	●						
Malaria*		●					
Measles	●						
Meningococcal disease	●	●				●	
Mumps	●						
Pandemic influenza		●	●			●	●
Pertussis	●					●	
Plague (<i>Yersinia pestis</i>)							●
Pneumococcal disease	●		●				
Polio	●						
Rabies	●				●		
Rotavirus	●			●			
Rubella	●						
Seasonal influenza	●	●	●			●	●
Tetanus	●					●	
Tick-borne encephalitis	●						
Tuberculosis	●	●					
Typhoid	●			●			
Varicella**	●						
Viral hepatitis (A, B, C, E)***	●					●	●
Yellow fever	●						

*A malaria vaccine received a positive scientific opinion from the European Medicines Agency (EMA) but it is currently not registered for use in countries relevant to the Index.

**Here, varicella refers to vaccines for diseases caused by varicella zoster virus, i.e., varicella ("chicken pox") and herpes zoster ("shingles").

***Vaccines exist against hepatitis viruses type A and B. A vaccine to prevent type E has been developed and is licensed in China, but is not yet available elsewhere. No vaccines exist against type C.

● Included ● Included

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Stakeholder engagement 2015

The Index team established the founding principles of the Access to Vaccines Index through an initial feasibility exercise, landscaping study and literature review. These studies used the priorities defined in the Global Vaccine Action Plan (GVAP) as a background framework, and drew on the Foundation's ten years' experience in engaging with stakeholders and tracking company behaviour to stimulate change with the Access to Medicine Index.

Challenging the founding principles

Throughout 2015, the Index team consulted on these founding principles with the major players working to improve access to immunisation. The aim of these consultations was to:

- 1 Create stakeholder consensus on the founding principles. Stakeholders also examined the parameters of the proposed methodology to see if other areas of company behaviour, such as managing intellectual property or donations, should also be included.
- 2 Determine that the Access to Vaccines Index would complement the work of other organisations active in this space.
- 3 Ensure that all stakeholders can use the Index's data and insights to inform future interventions. We spoke with many different experts and market shapers, asking which metrics would help them most in their efforts to stimulate change.

Stakeholder dialogue

The Index team gathered in-depth feedback from experts working in industry, governments, NGOs, procurers, philanthropic organisations and research organisations. The IFPMA provided consolidated feedback from companies with vaccine businesses and/or R&D units, and the Index team held individual discussions with large research-based pharmaceutical companies as well as the largest manufacturers based in emerging markets. Further critical feedback was provided by a group of Expert Advisors, from CHAI, Gavi, the Vaccine Alliance, UNICEF and the IFPMA.

Expert Advisors: 2015 Access to Vaccines Index Methodology Report

Laetitia Bigger, IFPMA
Heather Deehan, UNICEF
Melissa Malhame, Gavi, the Vaccine Alliance
Sourabh Sobti, Clinton Health Access Initiative

Additional contributors: 2015 Access to Vaccines Index Methodology Report

Gian Gandhi, UNICEF
Stephanie Mariat, WHO
Wilson Mok, Gavi, the Vaccine Alliance
Aurélia Nguyen, Gavi, the Vaccine Alliance
Nine Steensma, Clinton Health Access Initiative

Other sources of feedback

The Access to Medicine Foundation remains open to feedback from other entities willing to provide comments and suggestions. Maintaining openness through engaging and building partnerships with all the stakeholder groups is crucial to the long-term success, legitimacy and impact of the Index.

No single feedback mechanism has disproportionately affected the Index methodology. We maximised our efforts to ensure that all the stakeholders receive equal representation in the stakeholder engagement process.

Scoring and review process

SUMMARY OF THE SCORING PROCESS

1. Before inclusion for analysis, the Index team reviewed both marketed products and products in company R&D pipelines. This verification was to ensure they were within the scope of Index 2017 and met relevant inclusion criteria.

Process for R&D pipeline product inclusion

- R&D projects submitted by companies were included for analysis if they aimed to develop preventive vaccines targeting a disease/pathogen within the scope of the Index.
- Projects were excluded if they aimed to develop product types other than vaccines

(e.g., antibodies) and if they were vaccines or vaccine-like products used for therapeutic rather than preventive purposes.

- R&D projects were included if they aimed to develop new vaccines or adapt existing ones. Both in-house and collaborative R&D activities were included.
- R&D projects were included only if they were ongoing during the period of analysis. This included projects from discovery-stage research to vaccines that received first global marketing approval during the period of analysis (including label updates that were approved

during the period of analysis). Projects discontinued during the period of analysis were excluded.

- Following the first data submission, companies' submitted pipelines were verified using their publicly available pipelines. Where the nature of a vaccine (preventive or therapeutic) or its disease target was unclear, companies were asked to provide clarification. Where a discrepancy existed with a company's public pipeline, companies were asked to provide clarification.

- After final data submission, all R&D projects were evaluated for inclusion according to this standardised procedure.
- NB: Company pipelines in Company Report Cards reflect the period of analysis. Where relevant, footnotes are included to indicate movement of these projects along the pipeline since the period of analysis, as of January 2017 (including discontinuation of projects and projects new since the period of analysis). These movements did not impact scoring.

Process for registered product inclusion

- Registered products submitted by companies were included for analysis if they were preventive vaccines targeting at least one disease/pathogen within the scope of the Index.
- Products were excluded if they were not vaccines (e.g., antitoxins or other antisera) and if they were vaccines or vaccine-like products used for therapeutic rather than preventive purposes.
- Vaccines may target a pathogen which is prevalent only in specific geographic areas, and may not be relevant for other markets: products were included for scoring only if they were registered or filed to be registered in at least one country in scope, as a proxy measure of relevance for countries in scope.
- Vaccines were excluded if they were divested or withdrawn from all global markets prior to the period of analysis.
- Vaccine portfolios submitted by companies were verified using external sources. Product indications were verified using information from regulatory authorities (such as the US FDA and EMA). Where necessary following this process, the company was asked to provide clarification regarding the indication(s) of its product. External sources (e.g., company and company subsidiary websites, WHO prequalification database) were reviewed to identify any preventive vaccines marketed by companies in scope that appeared to target a disease/pathogen in scope but that were not submitted by the company for analysis. Companies were asked for clarification around vaccines identified through this process to facilitate inclusion where relevant.

- NB: Scoring for product-specific indicators in Pricing & Registration and Manufacturing & Supply were based only on products submitted by companies. In some figures, company portfolios include each company's entire global vaccine portfolio for diseases in scope: this comprises vaccines included for scoring in addition to vaccines not included for scoring, which were identified using public data and verified but not submitted by the company. These figures appear in the following sections of the Index: The Access to Vaccines Index: overall analysis, Portfolios & pipelines: where is the industry focusing? and Company Report Cards.

2. All indicators are scored from zero to five, and are weighted equally. Because the Research Areas have a different number of equally-weighted indicators (R&D: four indicators; Pricing & Registration: three indicators; Manufacturing & Supply: six indicators), the maximum possible score of each Research Area is different (R&D: zero to twenty; Pricing & Registration: zero to fifteen; Manufacturing & Supply: zero to thirty).

3. For some quantitative indicators, the scoring process took company size into account (e.g., based on revenue or size of relevant vaccine portfolio) to reflect varying expectations of companies of different sizes. Consistent with the relative ranking approach of the Access to Medicine Index, the adjusted numbers were then used to determine scoring tiers from zero to five.

Specifically, in Research & Development, the relative size of a company's vaccine R&D investments in 2014 and 2015 targeting diseases within the scope of the Index was measured as a proportion of a company's total global vaccine revenue over the same time period. The number of late-stage vaccine R&D projects for which a company has one or more access provision in place was scored as a proportion of the company's total late-stage pipeline. Product-specific indicators in Pricing & Registration and Manufacturing & Supply were scored based on

the relevant proportion of vaccines in the company's portfolio included for analysis.

4. The Index team assessed which Research Areas were relevant to each company: R&D was determined to be relevant to all companies in scope; Pricing & Registration and Manufacturing & Supply were considered relevant only to companies who during the period of analysis marketed vaccines in countries in scope. Where a Research Area was deemed relevant for a company, all indicators in that Research Area were scored for that company. Where a Research Area was not deemed relevant for a company, no indicators in that Research Area were scored for that company. Neutral scoring for individual indicators was not used.

5. Scoring was carried out based on data from companies' submissions, supported by research from a wide range of information sources including independent reports; databases from the World Health Organization (WHO), other multilateral organisations, governmental and non-governmental organisations; and news databases such as Bloomberg.

6. The final scoring of the companies is the result of a multi-tiered analysis and quality assurance process beginning with a data assessment per company by the Research Area analyst during the first round of the data collection period, followed by scoring after companies had provided further clarification in areas identified by the analyst. This was followed by verification by the Research Area analyst, including an extensive quantitative and qualitative check of each indicator for each company. The project manager performed a quality assurance check on all scores to ensure consistency.

7. A statistical analysis has been carried out on the final scores to check the distribution of scores for each indicator. Based on the analysis of every single indicator, adjustments were made to some indicators' scoring guidelines to ensure maximum variability and an appropriate distribution of scores, depending on whether the indicator has an absolute or relative scale.

REVIEW PROCESS

Following clarification and cross-check of company scores, the Index research team wrote the various sections of the Index report. These narratives are supported by additional analyses that explore company activities in supporting access to vaccines, but that do not reflect scoring. For a complete overview of indicators used for scoring, please see Appendix: Indicators and Scoring Guidelines. The Key Findings, Research Area Chapters and Cross-cutting Analyses were reviewed by Expert Advisors. In addition to this, an external editorial review of the Index was performed.

Limitations of the Methodology

Limitations exist in every study of this design. Some major limitations specific to this study are discussed here. These and other methodological limitations will be reviewed for any future iterations of the Access to Vaccines Index, as part of a multi-stakeholder Methodology Review process.

Disease and country comparability

The outputs analysed in this study and the findings generated relate only to the geographical, disease, product and company scopes, as determined in consultation with stakeholders during the methodology review process, and as published in The Access to Vaccines Index Methodology 2015.

Although the Foundation recognises that all vaccines, diseases, countries, and access and product initiatives are not the same, in general, in most Research Areas in this study they are treated equally. For example, in Research & Development, all vaccine R&D projects are treated equally if they meet the inclusion criteria, regardless of the characteristics of a candidate vaccine, or whether the R&D project aims to develop a new vaccine or adapt an existing one.

Product inclusion criteria

Preventive vaccines were included if they are registered or filed to be registered in at least one country in scope, as a proxy measure of relevance for other countries in scope. A limitation of this inclusion criteria is that it does not include vaccines that could be applicable in countries in scope of the Index, but have not yet been filed or approved for registration in any of these countries. This is particularly relevant for new vaccines that have recently entered the market.

Company comparability

One of the objectives of the Index is to produce standardised scoring of companies' access-to-vaccines performances. However, not all companies are the same. Some have large and diverse portfolios and pipelines. Some have a compar-

atively narrow scope of country operations. Developing country vaccine manufacturers generally have different business models to those of major multinational pharmaceutical companies producing vaccines.

The Index uses various methods to correct for these variations between companies, where relevant. The Index only measures companies in the Research Areas deemed relevant for them, based on their activities. In several indicators that measure quantitative elements, in general, the research team made adjustments for company size. These are made, for example, against the size of the relevant portfolio of products, or against company vaccine revenue for 2014 and 2015. Further, the Index provides key information about companies' vaccines businesses in several sections of the report (e.g., vaccine revenue, size of portfolio and pipeline, and volume of doses produced annually): this information should be considered as important context when interpreting companies' scores, and descriptions of their performance in general.

Companies of different sizes have different capacities to report information. For example, larger companies may be less likely to have all data available in a centralised repository/database, and may have more data to report on. This can be further complicated where there are vaccine-producing subsidiaries to account for. Companies have idiosyncratic systems for recording and reporting information, which can give rise to complications when comparing the performance of different companies. For example, companies may have different mechanisms for calculating the value of R&D investments.

Companies also often have individual ways of categorising information, for example, how different pricing strategies are referred to. In order to minimise the variability of information sourced from companies, all companies were provided with training on the data submission process and the questionnaire had help text to provide definitions and examples for Index jargon. In addition to this, a clarification round

in the data submission process was carried out, giving companies an opportunity to provide additional data where there were gaps, inconsistencies identified, or clarifications necessary.

Further, given the diversity of the vaccine industry more broadly, the analysis of these companies should not be seen as representative of other companies outside the scope of the Index. In particular, it should be noted that there is a growing number of private and public vaccine manufacturers based in emerging markets, known as developing country vaccine manufacturers (DCVMs). While these companies' revenues make up a smaller proportion of global sales, their supply volumes are significant. Only one DCVM is included in the company scope for the 2017 Index.

Data availability

Companies are sometimes unwilling or unable to disclose commercially sensitive data, or, if they do, may do so only partially. Occasionally, where sensitive data could be submitted and analysed, complete results could not be published due to legal constraints related to public disclosure. In other cases, collection of specific detailed data (e.g., information on specific vaccine manufacturing capacity building initiatives) was not always possible. Data availability is an obstacle to finding and reporting specific relationships and conclusions in several areas.

Measuring Outcomes and Impacts

The study as currently designed is not intended to measure the direct impact of companies' access-to-vaccines initiatives on people receiving vaccination(s) and their communities. For example, within Manufacturing & Supply, the impact of a company's adaptations to vaccine presentations or packaging on vaccination coverage is not measured.

Indicators and Scoring Guidelines

A RESEARCH & DEVELOPMENT

A.1 R&D Investments

Proportion of financial R&D investments dedicated to vaccine development for diseases relevant to the Index out of the company's total vaccine revenue.

- 5-1 Each company's vaccine R&D investments for diseases within the scope of the Index (2014 plus 2015) is divided by the total revenue (2014 plus 2015) derived from vaccines. This revenue-standardised number is scaled across all companies and scored.
 - o The company makes no disclosure in this area.

A.2 R&D projects - vaccines

Number of investigational vaccines that the company is developing for vaccine-preventable diseases in scope of the Index, including innovative and adaptive vaccines (developed in-house or through collaborative R&D).

- 5-1 The company's number of investigational preventive vaccines for diseases in the scope of the Index. This number is scaled across all companies and scored.
 - o The company has no relevant R&D activity with respect to vaccines for diseases in the scope of the Index.

A.3 R&D projects - technologies

Number of projects the company is engaged in to develop technologies for vaccine packaging and delivery in order to overcome barriers* to vaccines in countries relevant to the Index (developed in-house or through collaborative R&D).

- 5 The company is developing four or more vaccine packaging and delivery technologies that aim to overcome barriers to access to vaccines in countries within the scope of the Index.
- 2.5 The company is developing two to three vaccine packaging and delivery technologies that aim to overcome barriers to access to vaccines in countries within the scope of the Index.
- 1 The company is developing one vaccine packaging and delivery technology that aims to overcome barriers to access to vaccines in countries within the scope of the Index.
 - o The company has no relevant R&D activity related to the development of vaccine delivery or packaging technologies that aim to overcome barriers to access to vaccines in countries within the scope of the Index.

* Barriers include stock-outs, imperfect supply chains, controlled temperature chains, high manufacturing costs resulting in high prices and lack of trained healthcare professionals.

A.4 Facilitating access

Number of late-stage** vaccine R&D projects for which the company provided evidence of having access provisions in place, with the aim of ensuring future availability, affordability, and/or accessibility in Index Countries (for both in-house and collaborative R&D).

- 5 All late-stage vaccine R&D projects have access provisions in place, with the aim of ensuring future availability, affordability, and/or accessibility in countries within the scope of the Index.
- 4 50% to 99% of late-stage vaccine R&D projects have access provisions in place, with the aim of ensuring future availability, affordability, and/or accessibility in countries within the scope of the Index.
- 2.5 10% to 49% of late-stage vaccine R&D projects have access provisions in place, with the aim of ensuring future availability, affordability, and/or accessibility in countries within the scope of the Index.
- 1 1% to 9% of vaccine R&D projects have access provisions in place, with the aim of ensuring future availability, affordability, and/or accessibility in countries within the scope of the Index.
 - o The company did not provide evidence having access provisions in place for any of its late-stage vaccine R&D projects.

** Late-stage refers to projects in phase II and III clinical trials and those that were approved during the period of analysis. This indicator relates to plans to ensure access upon approval to products in the pipeline. For this reason, late-stage projects that involve adaptations to existing marketed vaccines, which will not lead to new vaccines (e.g., Controlled Temperature Chain label updates), are excluded here. Where relevant, access plans for such existing vaccines are scored elsewhere.

B PRICING & REGISTRATION

B.1 Pricing strategy

The company has a pricing strategy that takes into account income and other criteria* when selling vaccines to governments and through pooled procurement.

- 5 The company has a general pricing strategy for vaccines that takes into account country-level affordability and other criteria when setting prices for existing and future vaccines, for the public sector in low income countries (LICs) and lower middle-income countries (LMICs), whether selling to governments or through pooled procurement agencies. The company's pricing strategy is applied to all key products relevant for LICs and LMICs and is demonstrated through low prices for these products in both LICs and LMICs.
- 4 The company has a general pricing strategy for vaccines that takes into account country-level affordability and other criteria when setting prices for existing and future vaccines, for the public sector in low income countries (LICs) and lower middle-income countries (LMICs), whether selling to governments or through pooled procurement agencies. The company's pricing strategy is applied to a subset of key products relevant for LICs and LMICs.
- 3 The company has a general pricing strategy for vaccines that takes into account country-level affordability and other criteria when setting prices for the public sector in low income countries (LICs) and lower middle-income countries (LMICs), whether selling to governments or through pooled procurement agencies. The company's pricing strategy is applied to a subset of key products relevant for LICs and LMICs.
- 2 The company has a general pricing strategy for vaccines that takes into account country-level affordability when setting prices for the public sector in LICs and LMICs, whether selling to governments or through pooled procurement agencies.
- 1 The company makes a general commitment to considering affordability when pricing vaccines and has shown evidence of affordable prices for marketed vaccines.
- o The company has no relevant pricing strategy.

* This includes how the company uses Gavi classifications (eligible, transitioning and non-eligible) when setting the public price of its products.

B.2 Pricing strategy transparency

The company publicly discloses its pricing strategy for vaccines and provides evidence that it does not prevent governments from making publicly available manufacturer prices.

- 5 The company publicly discloses its complete pricing strategy and prices for all vaccines in scope, and states that it does not include non-disclosure clauses on vaccine prices in its contracts with governments and other procurers.
- 4 The company publicly discloses its complete pricing strategy for all vaccines in scope and states that it does not include non-disclosure clauses on vaccine prices in its contracts with governments and other procurers.
- 2 The company publicly discloses either its pricing strategy for a subset of vaccines in scope or a broad pricing strategy for vaccines, and states that it does not include non-disclosure clauses on vaccine prices in its contracts with governments and other procurers.
- 1 The company does not publicly disclose its pricing strategy for vaccines but states that it does not include non-disclosure clauses on vaccine prices in its contracts with governments and other procurers.
- o The company publicly discloses its pricing policy for vaccines but states that it does support the use of price confidentiality provisions in contracts with governments.

B.3 Registration

The company makes efforts to ensure vaccines are available in low-income countries and lower middle-income countries by filing for registration there.

- 5 The company files to register the majority (>50%) of its vaccines in scope in the majority (>50%) of low-income countries, lower and upper middle-income countries in scope.
- 4 The company files to register the majority (>50%) of its vaccines in scope in 30-50% of low income countries, lower and upper middle-income countries in scope.
- 3 The company files to register the majority (>50%) of its vaccines in scope in <30% of low income countries, lower and upper middle-income countries in scope.
- 2 The company files to register the majority (>50%) of its vaccines in scope in <30% of lower and upper middle-income countries in scope and some (<50%) of its vaccines in <30% of low-income countries.
- 1 The company files to register some vaccines in some lower and/or upper middle-income countries in scope.
- o The company does not file to register any vaccines in scope in any countries in scope.

MANUFACTURING & SUPPLY

C.1 Overcoming local barriers

The company is implementing vaccine packaging and delivery technologies* in order to overcome barriers to access to vaccines in Index countries (e.g., stock-outs, imperfect supply chains, manufacturing costs, lack of trained health care professionals) and ensure these vaccines are non-inferior to the standard vaccine in terms of quality.

- 5 The company has implemented vaccine packaging and delivery technologies in order to overcome barriers to access to vaccines in Index countries for >50% or ≥5 products.
- 3.5 The company has implemented vaccine packaging and delivery technologies in order to overcome barriers to access to vaccines in Index countries for 26-50% or 3-4 products.
- 2 The company has implemented vaccine packaging and delivery technologies in order to overcome barriers to access to vaccines in Index countries for 1-25% or 1-2 products.

- 1 The company makes a general commitment to or considers implementing vaccine packaging and delivery technologies in order to overcome barriers to access to vaccines in Index countries, but not yet implemented for marketed products.
- o The company does not provide evidence of implementing vaccine packaging and delivery technologies in order to overcome barriers to access to vaccines in Index countries.

* For example, reduced volume, single, or multi-doses, adapted formulations for alternative routes of administration (e.g., intradermal, intranasal, oral), delivery technologies (e.g., disposable syringes) and adaptations to packaging (e.g., vaccine vial monitors, reconstitution technologies).

C.2 Ensuring rational use

The company adapts package inserts/packaging to ensure rational use of the vaccine at the point of delivery, i.e., that the vaccine is administered appropriately.

- 5 The company has adapted package inserts or packaging to support rational use of vaccines at the point of delivery for >50% or ≥5 products.
- 3.5 The company has adapted package inserts or packaging to support rational use of vaccines at the point of delivery for 26-50% or 3-4 products.
- 2 The company has adapted package inserts or packaging to support rational use of vaccines at the point of delivery for 1-25% or 1-2 products.
- 1 The company makes a general commitment to or considers adapting package inserts or packaging to support rational use of vaccines at the point of delivery, but not yet implemented for marketed products.
- o The company does not provide evidence of adapting package inserts or packaging to support rational use of vaccines at the point of delivery.

C.3 Responding to shortages

The company has a strategy in place to help ensure sufficient or additional supplies of vaccines are made available in case of global, regional or local shortages (both for vaccines that are part of routine immunisation as well as those needed in emergency situations, such as outbreaks, natural disasters, etc.).

- 5 The company's strategy to help ensure sufficient or additional supplies of vaccines are made available in case of shortages includes ≥6 of the following elements: a) a commitment to ensure access; b) a regular and timely supply and demand review process; c) a clear process for escalating and acting on identified issues; d) buffer stocks; e) processes for scaling up production; f) processes for re-allocating stocks; g) donations or affordability measures in emergency situations; and/or h) consideration of other suppliers in a market when making decisions.
- 3.5 The company's strategy to help ensure sufficient or additional supplies of vaccines are made available in case of shortages includes 4-5 of the elements outlined above.
- 2 The company's strategy to help ensure sufficient or additional supplies of vaccines are made available in case of shortages includes 2-3 of the elements outlined above.
- 1 The company's strategy to help ensure sufficient or additional supplies of vaccines are made available in case of shortages includes 1 of the elements outlined above.
- o The company does not provide evidence of a strategy to help ensure sufficient or additional supplies of vaccines are made available in case of shortages.

C.4 Collaboration to align supply and demand

The company has a mechanism in place to engage with vaccine purchasers and partners on a regular basis to align supply and demand of its vaccines in order to identify, prevent or bridge periods of global, regional or local stockouts, for example due to supply delays, due to the company exiting a specific vaccine market or in response to urgent, unplanned or accelerated demand.

- 5 The company has a process to proactively engage with vaccine purchasers and partners on a regular basis to align supply and demand of its vaccines.
- 2.5 The company proactively engages with vaccine purchasers and partners on an ad hoc basis to align supply and demand of its vaccines.
- o The company does not provide evidence of a process to proactively engage with vaccine purchasers and partners to align supply and demand of its vaccines.

C.5 Supporting vaccine security

The company has a strategy in place that takes into account global health needs for vaccines, including a commitment to continue vaccine production for its vaccines which have either few or no other suppliers AND a commitment to proactively and clearly communicate any intentions on altering supply plans, manufacturing capacity and/or exiting a specific vaccine market, and to work with stakeholders to bridge the period when supplies would diminish or cease.

- 5 The company commits to a) continuing vaccines production for its vaccines which have either few or no other suppliers AND b) proactively and clearly communicating any intentions to change supply (including exiting a market).
- 4 The company commits to continuing vaccines production for its vaccines which have either few or no other suppliers.
- 2.5 The company commits to proactively and clearly communicating any intentions to change supply (including exiting a market).
- 1 The company makes a general commitment to considering global health needs when making decisions to change or cease supply of its vaccines.
- o The company does not provide evidence of a commitment to consider global health needs when making decisions to change or cease supply of its vaccines.

C.6 Increasing global manufacturing capacity

The company has engaged in partnerships, training and/or technology transfer that support the growth of manufacturing capabilities with the aim of increasing vaccine supply and innovation in manufacturing.

- 5 The company has provided ≥7 capacity building activities (e.g., training or technology transfers) to local vaccine manufacturers in countries in scope of the Index to support the growth of manufacturing capacities.
- 4 The company has provided 5-6 capacity building activities (e.g., training or technology transfers) to local vaccine manufacturers in countries in scope of the Index to support the growth of manufacturing capacities.
- 3 The company has provided 3-4 capacity building activities (e.g., training or technology transfers) to local vaccine manufacturers in countries in scope of the Index to support the growth of manufacturing capacities.
- 2 The company has provided 1-2 capacity building activities (e.g., training or technology transfers) to local vaccine manufacturers in countries in scope of the Index to support the growth of manufacturing capacities.
- 1 The company makes a general commitment to assisting local vaccine manufacturers in countries in scope of the Index to support the growth of manufacturing capacities.
- o The company does not provide evidence of a commitment or activities to assisting local vaccine manufacturers in countries in scope of the Index to support the growth of manufacturing capacities.

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Definitions

Access provisions

[Working definition, used for analysis]

Provisions put in place during product development to help ensure that public health needs are taken into consideration and to facilitate rapid access to affordable products after market entry. Access provisions can take the form of commitments and strategies to facilitate availability, accessibility and affordability of products for patients in countries within the scope of the Index. Access provisions can be included in R&D partnership agreements and/or developed in-house. Examples of access provisions include equitable pricing strategies, sufficient supply commitments, non-exclusivity in specified territories, waiving patent rights, royalty-free provisions and registration targets.

Adaptive R&D

[Working definition, used for analysis]

Adaptive R&D covers the adaptation of existing vaccines to make them more suitable for use in low- and middle-income countries, or to address a need relevant to those countries. This includes adaptations that address demographic segments (e.g., infants, children, pregnant women), environmental conditions (e.g., heat-stable formulations), diseases and serotypes (e.g., multivalent vaccines), programmatic suitability (e.g., dose schedule) or delivery methods (e.g. intradermal, oral, sublingual, intranasal, pulmonary delivery technologies).

Affordability

[Working definition, used for analysis]

A measure of governments' and/or other procurement agencies' ability to pay for a vaccine. The Index takes this into account when assessing companies' pricing strategies for vaccines for the public sector. Vaccine manufacturers may use many different criteria to assess affordability.

Diseases prioritised by WHO for vaccine R&D

WHO's Initiative for Vaccine Research (IVR) identifies vaccine research gaps of particular relevance to low- and middle-income countries. At the end of January 2017, WHO had identified the following diseases as priorities for vaccine R&D: dengue, Group B streptococcus, HIV, influenza, Zika, malaria, meningitis and tuberculosis. WHO added Group B streptococcus and Zika to this list after the development of the Access to Vaccines Index Methodology in 2015. While Group B streptococcus was already included in the disease scope on the basis of stakeholder recommendation, Zika did not meet inclusion criteria for the disease scope in the 2017 Index. Therefore, the diseases considered for analysis

in the Access to Vaccines Index 2017 are dengue, Group B streptococcus, HIV, influenza (seasonal and pandemic), malaria, meningitis and tuberculosis. In February 2017, WHO added respiratory syncytial virus to this list.¹

Emerging diseases prioritised by WHO for R&D

In December 2015, WHO convened a panel of experts to prioritise diseases for the WHO R&D Blueprint. The R&D Blueprint focuses on severe emerging diseases with potential to generate a public health emergency, and for which insufficient or no preventive and curative solutions exist. The panel identified the following diseases as priorities for R&D to develop vaccines, diagnostics and therapeutics: Crimean Congo haemorrhagic fever, Ebola virus disease and Marburg, Lassa fever, MERS and SARS coronavirus diseases, Nipah and Rift Valley fever. The panel identified the following additional diseases as 'serious', requiring action by WHO to promote R&D as soon as possible: chikungunya, severe fever with thrombocytopenia syndrome, and Zika.² In January 2017, WHO reviewed and updated the list of priority diseases for the WHO R&D Blueprint.³

Innovative R&D

[Working definition, used for analysis]

Innovative R&D covers the development of new vaccines for diseases that are currently not vaccine-preventable. It also includes development of new vaccines that offer important alternatives to existing ones (e.g., extending protection to new serotypes or new demographic groups).

Period of analysis

[Working definition, used for analysis]

For the 2017 Index, the time period for which data is analysed covers fiscal years 2014 and 2015, where company activities must be on-going between June 2014 and the beginning of June 2016, as this is the cycle of the Index. Programmes or activities that have ended before June 1st 2014 are not included. The Index team assesses the most recent policies, strategies and activities, up to final submission. Information since the end of the period of analysis may be included across the report, as context or to provide up to date information; such data is not included for scoring.

Research Area

The Index researches and evaluates companies in three main areas of activity, known as Research Areas. In the Access to Vaccines Index 2017, these are a) Research & Development; b) Pricing & Registration; and c) Manufacturing & Supply. These are the areas where vaccine com-

panies have the largest role to play, and where a benchmark of company behaviour could have the most impact, confirmed through stakeholder discussions. Companies can also take action in other areas, such as in licensing or to strengthen local capacities, yet their efforts here are currently seen as less likely to improve access to vaccines.

Vaccine manufacturing capacity building

Activities undertaken by companies to increase or improve the capacity of other manufacturers to produce a sufficient supply of high-quality vaccines. Such activities may be carried out directly between the two parties, or in partnership with other stakeholders (e.g., government agencies or multilateral organisations). Relevant activities include expertise-sharing arrangements, secondments, manufacturing partnerships, training exercises or technology transfers with capacity building components.

Vaccine packaging and delivery technologies

Technologies that allow for adaptations to vaccines packaging and/or administration and that will reduce barriers to vaccines in resource-limited settings. Packaging and delivery technologies are not specific to certain vaccines. Packaging technologies refer to technologies that address product presentations and primary and secondary containers, for example, reduced volume containers, single or multi-dose presentations, vaccine vial monitors and reconstitution technologies. Delivery technologies include alternative routes of administration and changes to delivery devices, for example, intradermal, intranasal, oral/sublingual, pulmonary delivery, microneedle patches and auto-disable syringes.

References

1. WHO. "Disease-specific areas of work." 2017. Accessed 14 February 2017 at <http://www.who.int/immunization/research/development/en/>
2. WHO. "WHO publishes list of top emerging diseases likely to cause major epidemics." 2015. Accessed 1 February 2017 at <http://www.who.int/medicines/ebola-treatment/WHO-list-of-top-emerging-diseases/en/>
3. WHO. "Annual review of the list of priority diseases for the WHO R&D Blueprint." 2017. Accessed 23 February 2017 at http://www.who.int/csr/research-and-development/2017_priority_disease_list_review_short_summary_25Jan.pdf?ua=1

Guide to the Report Cards

Section	Description	Source
General company information (heading)	Stock exchange, ticker, location of headquarters, number of employees	Annual report and/or the company's website
Index performance by Research Area (figure)	This graph shows the company's scores for each of the Research Areas under which companies are scored.	Index analysis
Performance (text)	This section explains the relevance of the company for the Access to Vaccines Index and its overall performance in the 2017 Index. It covers: <ul style="list-style-type: none"> • Drivers behind its scores • Main areas where the company scores well or poorly compared to peers Note: In this section, "geographic scope" refers to the proportion of countries in scope of the Index in which the company has filed to register at least one vaccine.	Index analysis
Sales and operations (text)	This section provides a general description of the company's operations globally, including changes in its business (such as acquisitions or divestments) in recent years with a particular focus on its vaccines business.	Annual reports, company website and other news sources
Sales in countries in scope (figure)	This figure shows the number of countries in scope in which the company has sales (all products, not limited to vaccines).	Data submission to the Index
Sales by segment 2015 (figure)	This figure shows the breakdown of the company's 2015 revenue for its vaccine business in countries in scope, in the rest of the world, and the total revenues.	Company financial statement, data submission to the Index
Number of doses sold in 2015 (figure)	This figure shows the number of vaccines doses sold in 2015 in countries in scope and in the rest of the world.	Data submission to the Index
Vaccine portfolio (text and figure)	This figure shows the number of vaccines the company markets globally for diseases in scope, as of January 2017. This includes, but is not limited to, vaccines included for scoring in the Research Areas Pricing & Registration and Manufacturing & Supply. Vaccines are categorised by target disease/pathogen, following the disease scope of the Index. Combination vaccines are listed according to vaccine naming conventions used by the WHO. The text describes the company's vaccine portfolio, including its size and focus.	Data sources for the vaccine portfolio are products submitted by the company for scoring and analysis in the Index, as well as any registered products identified from the EMA, FDA, PMDA, and the company's website.
Opportunities (text)	This section outlines tailored opportunities for the company to improve access to its vaccines, taking account of company-specific characteristics.	Index analysis
Performance by Research Area (text)	This section summarises company performance per Research Area. This includes: <ul style="list-style-type: none"> • Main areas within the Research Area where the company scores well or poorly • Description of commitments, performance and/or relevant initiatives with the Research Area 	Index analysis Note: In the Research & Development performance points, access provisions are analysed for late-stage projects: late-stage refers to phase II, phase III and projects approved during the period of analysis. Since this analysis relates to plans to ensure access for vaccines in the pipeline, late-stage projects that involve adaptations to existing marketed vaccines, which will not lead to a new vaccine (e.g., Controlled Temperature Chain label updates), are excluded here.
Vaccine pipeline (figure)	This figure shows the company's pipeline of R&D projects included for analysis. This comprises each company's projects to develop preventive vaccines for diseases in scope. The figure includes the following details per project, where data is available: phase of development, disease/pathogen targeted, specific pathogen(s) targeted and project code/or brand name. Where applicable, projects in partnership with another company evaluated are noted, and regulatory approvals (including label extensions) are noted, including the regulatory body/location and date of approval. Data omissions due to confidentiality agreements are noted, in addition to changes to the status of projects since the period of analysis (as of January 2017).	Data source for the vaccine pipeline is products submitted by the company for scoring and analysis in the Index, including a process of verification with companies' public pipelines. Approval data is verified using public sources.

Acronyms

AIDS	Acquired Immuno Deficiency Syndrome	LIC	Low-income country [World Bank]
AMC	Advance Market Commitment	LMIC	Lower-middle income country [World Bank]
APC	Advance Purchase Commitments	MERS-CoV	Middle East Respiratory Syndrome coronavirus
BCG	Bacille Calmette-Guérin (vaccine against tuberculosis)	MIC	Middle-income country [World Bank]
BPO	Bio-Preparedness Organisation	MR	Measles and rubella vaccine
CDD	Conserved Domain Database	MMR	Measles, mumps, and rubella vaccine
CDSCO	Central Drugs Standard Control Organization	MMRV	Measles, mumps, rubella and varicella vaccine
CEPI	The Coalition for Epidemics Preparedness Innovations	MR	Measles and rubella vaccine
CHAI	Clinton Health Access Initiative	MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
CMV	Cytomegalovirus	MSF	Médecins Sans Frontières
COFEPRIS	Comisión Federal para la Protección contra Riesgos Sanitarios	MVI	Malaria Vaccine Initiative
CTC	Controlled Temperature Chain	NGO	Non-governmental organisation
DCVM	Developing Country Vaccine Manufacturers	NRA	National Regulatory Authorities
DCVMN	The Developing Countries Vaccine Manufacturers Network	NTD	Neglected Tropical Disease
DT	Diphtheria and tetanus toxoid vaccine	P5	Pox-Protein Public-Private Partnership
DTaP	Diphtheria and tetanus toxoid with acellular pertussis vaccine	PAHO	Pan American Health Organization
DTIPV	Diphtheria and tetanus toxoids, pediatric + inactivated poliovirus vaccine	PCV	Pneumococcal conjugate vaccine
DTP	Diphtheria-tetanus-pertussis vaccine	PDP	Product Development Partnership
DTPHep	Tetravalent diphtheria and tetanus toxoid with pertussis and hepatitis B vaccine	PMDA	Pharmaceuticals and Medical Devices Agency
DTPHepIPV	Pentavalent diphtheria and tetanus toxoid with pertussis, hepatitis B and inactivated polio vaccine	R&D	Research and Development
DTPHib	Tetravalent diphtheria and tetanus toxoid with pertussis and <i>Haemophilus influenzae</i> type b vaccine	RSV	Respiratory Syncytial Virus
DTPHibHep	Pentavalent diphtheria and tetanus toxoid with pertussis, <i>Haemophilus influenzae</i> type b and hepatitis B vaccine	SAGE	The WHO Strategic Advisory Group of Experts on Immunization
DTPHibHepIPV	Hexavalent diphtheria, tetanus toxoid with pertussis, <i>Haemophilus influenzae</i> type b, hepatitis B and inactivated polio vaccine	SARS	Severe Acute Respiratory Syndrome
DTPHibIPV	Pentavalent diphtheria and tetanus toxoid with pertussis, <i>Haemophilus influenzae</i> type b and inactivated polio vaccine	TB	Tuberculosis
DTPIPV	Diphtheria and tetanus toxoids and pertussis vaccine + inactivated poliovirus vaccine	TBE	Tick-borne encephalitis
DTwP	Diphtheria and tetanus toxoid with whole cell pertussis vaccine	Td	Tetanus toxoid with reduced amount of diphtheria toxoid vaccine
ECOSOC	United Nations Economic and Social Council	TPP	Target Product Profile
EID	Emerging infectious disease	UK	United Kingdom
EMA	European Medicines Agency	UMIC	Upper-middle income country [World Bank]
EPI	Expanded Programme on Immunization	UN	United Nations
EU	European Union	UNDP	United Nations Development Programme
EUAL	Emergency use assessment and listing	UNICEF	The United Nations Children's Fund
EUR	Euro	USD	United States Dollar
FDA	Food and Drug Administration	V3P Project	The WHO Vaccine Product, Price and Procurement project
GDP	Gross Domestic Product	WAP	Weighted average price
GMP	Good Manufacturing Practices	WHO	World Health Organization
GNI	Gross National Income	YF	Yellow Fever
Hib	<i>Haemophilus influenzae</i> type b	YFV	Yellow Fever vaccine
HIV	Human Immunodeficiency Virus		
HPV	Human papillomavirus		
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations		
IHR	The International Health Regulations		
IP	Intellectual Property		
IPV	Inactivated Polio Vaccine		
IVR	WHO's Initiative for Vaccine Research		
JICA	Japan International Cooperation Agency		
LDC	Least Developed Country [United Nations]		

Report Design

Explanation Design (Klaas van der Veen)

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