Retrospective Analysis of Volume Guarantees in the Pentavalent and Rotavirus Vaccine Markets

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Introduction

Every year, an estimated two to three million deaths and a greater burden of morbidity and disability are prevented through immunization.\(^1\) While significant progress has been made in improving global immunization coverage, an estimated 22 million children are still not reached by immunization programs.\(^2\) Global organizations and stakeholders continue to collaborate to shape the dynamics of the vaccine market so as to improve access to vaccines in low-income (LIC) and lower middle-income countries (LMIC). The vaccine market for these countries is structured such that funding and demand for vaccines are consolidated to Gavi, the Vaccine Alliance. Procurement is largely consolidated to the United Nations Children’s Fund (UNICEF)\(^3\), which uses long-term agreements (LTA) to procure vaccines for committed volumes at a negotiated price, and the Pan American Health Organization (PAHO), which operates a regional pooled procurement system for vaccines in countries of Latin American and the Caribbean.\(^3\)

When demand for a product is uncertain and the current market size is small, volume guarantees to supplier(s) can be used to improve market outcomes. Under a volume guarantee, the buyer agrees to purchase a specified quantity of product, in advance, over a specified period of time. In exchange for improved demand visibility provided by the volume guarantee, suppliers may offer reduced prices and better delivery terms, which can improve supply security.

The subject of this retrospective analysis is the volume guarantee and prepayment mechanism negotiated for Rotarix\(^*\), the rotavirus vaccine manufactured by GlaxoSmithKline (GSK), and the volume guarantee negotiated for Biological E’s (Bio E) pentavalent vaccine in late 2011. We evaluate the two vaccine markets before and after these volume guarantees, and assess the overall market impacts of the interventions. Following a description of the underlying dynamics of volume guarantees, we highlight key considerations of their use and discuss other interventions that could be used to achieve similar desired outcomes.

Rotavirus vaccine market

Background

Diarrheal disease

Diarrhea continues to be one of the two leading infectious causes of childhood morbidity and mortality globally.\(^4\) Among children less than five years of age, rotavirus is the leading cause of severe and fatal diarrhea.\(^5\) According to World Health Organization (WHO) estimates, more than 450,000 children under five die from rotavirus infection each year.\(^5\) An estimated 95% of global rotavirus deaths occur in LICs of Africa and Asia – the countries eligible for Gavi support.\(^5,6\) Rotavirus spreads rapidly among children through the fecal-oral route, and can be spread via contaminated hands, objects, food and water.\(^7\) The rotavirus vaccine is an effective preventative measure against rotavirus disease.

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\(^1\) There are six Gavi-eligible countries of PAHO who utilize the PAHO revolving fund for vaccine procurement.
Rotavirus vaccines

The first rotavirus vaccine, Rotashield®, was developed by Wyeth Ayerst Laboratories and approved for use in the United States in 1998. One year later, Wyeth withdrew Rotashield® from the market following reports of vaccine-related intussusception in some healthy infants.\(^8\) In 2000, the WHO convened a meeting to discuss future directions for rotavirus vaccine research and development, and to create an agenda for accelerating the introduction of a rotavirus vaccine into developing countries.\(^9,10\) Fifteen years later, there are two manufacturers with WHO prequalified rotavirus vaccines (Table 1).

Merck Sharp and Dohme (Merck) manufactures RotaTeq® – an oral, live attenuated and liquid pentavalent bovine-human reassortment rotavirus vaccine. RotaTeq® is administered orally on a three dose schedule with at least four weeks between doses. The vaccine is available in a single dose tube presentation, requires 138cm\(^3\) per course of cold chain capacity and is without a Vaccine Vial Monitor (VVM).\(^11\) RotaTeq® was approved by the United States Food and Drug Administration (US FDA) in 2006, and RotaTeq® obtained WHO prequalification in October 2008.\(^12\)

GSK manufactures Rotarix® – an oral, live attenuated, liquid or lyophilized monovalent vaccine derived from a human rotavirus strain most frequently found in temperate regions.\(^9\) Rotarix® has an approved shelf life of 36 months, requires 34cm\(^3\) per course of cold chain capacity, and is delivered with a VVM.\(^11\) The vaccine is administered orally to children ages 6-24 weeks of age in a two-dose schedule, with each dose at least four weeks apart.\(^9\) GSK obtained WHO prequalification for the single-dose vial presentation of Rotarix® in January 2007, and Rotarix® was approved by the US FDA in 2008.\(^12\) In 2009, GSK obtained prequalification for a single-dose plastic tube and a liquid single-dose applicator presentation of Rotarix®.\(^12\) Given the reduced number of doses, smaller cold chain footprint, multiple presentations, and inclusion of the VVM, Rotarix® is considered to be a programmatically superior product to RotaTeq® for Gavi countries. Rotarix® is also significantly less expensive than RotaTeq®, which becomes important for countries upon graduation from Gavi support.

Table 1: Comparison of RotaTeq® and Rotarix®\(^{11,12}\)

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>RotaTeq® (RV5)</th>
<th>Rotarix® (RV1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Live attenuated liquid pentavalent</td>
<td>Live attenuated liquid monovalent</td>
</tr>
<tr>
<td>Doses per course</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Presentation</td>
<td>1-dose tube</td>
<td>1-dose vial; 1-dose applicator; 1-dose plastic tube</td>
</tr>
<tr>
<td>Secondary packaging</td>
<td>10 or 25 doses per carton</td>
<td>1, 10 or 50 doses</td>
</tr>
<tr>
<td>Approved shelf life</td>
<td>24 months at 2-8°C</td>
<td>36 months at 2-8°C</td>
</tr>
<tr>
<td>Vaccine Vial Monitor</td>
<td>None</td>
<td>Delivered with Type 14 VVM</td>
</tr>
<tr>
<td>Cold chain capacity requirement (per dose)</td>
<td>10-dose carton – 75.3cm(^3) 25-dose carton – 46.3cm(^3)</td>
<td>1-dose carton – 134cm(^3) 10-dose carton – 85.3cm(^3) 50-dose carton – 17.1cm(^3)</td>
</tr>
</tbody>
</table>
Rotavirus market pre-volume guarantee

Access to rotavirus vaccines in LIC and LMIC
In 2003, Gavi created the Accelerated Development and Introduction Plans (ADIP) to ensure and accelerate the introduction of rotavirus and pneumococcal vaccines in developing countries. The two strategic objectives of the ADIP model upon inception were:

1) To provide information that enables decision-makers, the Gavi Alliance Board and its partners to make an evidence-based decision regarding rotavirus and pneumococcal vaccine use; and
2) To increase access to an affordable, sustainable supply of both vaccines for the world’s poorest countries.

Each ADIP was initially funded with $30 million over a five year period, with an additional $20 million for a one-year extension in 2008. During the seven year period between 2003 and 2009, Gavi invested $112 million into the two ADIPs. The RotaADIP, also known as the PATH Rotavirus Vaccine Program (RVP), was a partnership between PATH, the U.S. Centers for Disease Control and Prevention (CDC) and the WHO. Additional funding was committed by Gavi to support clinical trials for rotavirus. The RotaADIP helped generate demand for the rotavirus vaccine. Under the ADIP, efforts were made to characterize the disease burden of rotavirus and communicate the value of the rotavirus vaccine to multinational manufacturers. To further demonstrate the value of the rotavirus vaccine, an evaluation was done in 2007 to demonstrate the cost effectiveness as well as impact of the vaccine on the known disease burden.

The rotavirus vaccine was initially accepted for use in 14 countries in Europe and the Americas. Four countries of Latin America were the first to benefit from Gavi rotavirus funding, utilizing the PAHO revolving fund for vaccine procurement. Nicaragua became the first Gavi-supported country to introduce the rotavirus vaccine in 2006, followed by Bolivia in 2008, Honduras in 2009 and Guyana in 2010. In June of 2009, the WHO Strategic Advisory Group of Experts (SAGE) recommended the inclusion of rotavirus vaccine in all national immunization programs, which enabled the introduction of the rotavirus vaccine to Gavi-supported countries in Asia and Africa.

By 2010, four Gavi-supported countries had introduced the rotavirus vaccine and an additional six countries had approved applications for financial support from Gavi to begin rotavirus vaccine introduction. At this time, UNICEF had not yet completed a procurement round for rotavirus vaccines. In order to prioritize scaling efforts for this product, the rotavirus vaccine was placed in the Gavi New and Underused Vaccine Support (NVS) portfolio in 2010. It was added to the Gavi NVS list without an official UNICEF price, which raised the question of the expected financial sustainability (for Gavi) of widespread adoption and introduction of this relatively expensive vaccine.
Figure 1: Timeline of events in the rotavirus vaccine market

UNICEF LTA and volume guarantee to GSK
Sudan received the first doses of rotavirus vaccine (Rotarix®) procured by UNICEF in 2011\(^2\), at a price of $15 per course.\(^{11}\) The following year, UNICEF entered into LTAs with both GSK and Merck for the purchase of 71.4 million courses of the rotavirus vaccine between 2012 and 2016 (Table 2).\(^{11}\) The vast majority of the courses purchased (approximately 89%) were the preferred vaccine, Rotarix\(^{\text{®}}\). As part of these negotiations, GSK was offered a volume guarantee for Rotarix\(^{\text{®}}\) and reduced the price of Rotarix from $15.00 per course to $5.00 per course for developing countries. Under these LTAs, Merck also offered a reduction in price of RotaTeq\(^{\text{®}}\) to $15.00 per course (or $5.00 per dose), with the expectation that the price will decrease further to $3.50 per dose once the purchase volume has reached 30 million doses.\(^{11}\)

Table 2: UNICEF awards for the 2012-2016 tender \(^{11}\) (From the 2013 Supply and Demand outlook)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Manufacturer</th>
<th>Presentation</th>
<th>Duration</th>
<th>Value</th>
<th>Doses</th>
<th>Courses</th>
<th>Price/ds</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVI</td>
<td>GSK</td>
<td>1ds</td>
<td>LTA – 5 years</td>
<td>$330,000,000*</td>
<td>132,000,000</td>
<td>66,000,000</td>
<td>$2.50</td>
</tr>
<tr>
<td>RV5</td>
<td>Merck</td>
<td>1ds</td>
<td>LTA – 5 years</td>
<td>$57,162,350</td>
<td>16,332,100</td>
<td>5,444,033</td>
<td>$5-3.50</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>148,332,100</td>
<td>71,444,033</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*RVI value was calculated from the announced $2.50 USD price per dose and the number of doses awarded.

\(^2\) According to the Gavi Annual progress report submitted by the government of Sudan, the number of infants vaccinated with the first and second dose of rotavirus vaccine in 2011 was 472,507 and 328,725, respectively.\(^{50}\)
GSK’s 2012 tender award involved several components. The financial terms of the award included both prepayment of product and a volume guarantee mechanism. Prepayment for 25% of the forecasted quantity was made to GSK on an annual basis for the first three years of the contract. Out of the 68 million courses awarded to GSK, a volume guarantee was agreed upon for 45 million courses of Rotarix® over a five-year period. As part of the LTA, Gavi secured a price commitment from GSK to reduce the price of Rotarix® from $15.00 per course to $5.00 per course (or $2.50 per dose). [For reference, the price per dose of Rotarix® for the government of South Africa was $6.06 in 2013/2014, while the price per dose for the United States government was $92.15.]

**Rotavirus market post-volume guarantee**

**Demand**

Between 2006 and 2011, only five Gavi-supported countries introduced the rotavirus vaccine. Within the first two years of the Rotarix® volume guarantee (2012 and 2013), an additional 14 countries introduced the vaccine.

As of June 30th 2014, 34 countries were approved for Gavi support to introduce the rotavirus vaccine, with 24 having already introduced the vaccine into their national Expanded Programme on Immunization (EPI) lists. At that time, annual country-specific demand for the rotavirus vaccine was 19.8 million courses, while 23 countries were still eligible to apply for rotavirus vaccine introduction. As of October 2014, 32 Gavi countries had introduced the rotavirus vaccine (Figure 2). Demand is expected to reach 33.1 million courses in 2015 and 36 million courses in 2016.

*Figure 2: Number of Gavi countries that have introduced rotavirus vaccine as of October 2014 as compared to the target*

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3 2012: Ghana, Rwanda, Moldova, Yemen, Malawi, Armenia, Tanzania. 2013: Georgia, Haiti, the Gambia, Burkina Faso, Ethiopia, Zambia, and Burundi.
As mentioned above, GSK’s Rotarix® is considered by some as more programmatically suitable for Gavi-supported countries than RotaTeq®, and has been shown to be more cost effective in various settings.\textsuperscript{21,22} This preference is reflected in the differing demand for the two available rotavirus vaccines. As of August 2013, 25 of the 29 countries approved for rotavirus vaccine support had chosen to introduce Rotarix\textsuperscript{®}.\textsuperscript{11} With approximately 90% of the rotavirus vaccine demand dependent on GSK, demand for Rotarix\textsuperscript{®} continued to exceed the manufacturer’s supply capacity.\textsuperscript{11} The resulting supply shortages were expected to persist over the next three years, causing delays in country introductions of the vaccine.\textsuperscript{11}

According to publicly available Gavi global shipment data\textsuperscript{4}, 86% of the total rotavirus vaccine volume shipped in 2014 was for GSK’s Rotarix\textsuperscript{®}, while 14% of the volume was for Merck’s RotaTeq\textsuperscript{®} (Figure 3).\textsuperscript{23}

\textit{Figure 3: Gavi global shipments (units) of rotavirus 2014 by manufacturer}\textsuperscript{23}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure3.png}
\end{figure}

\textbf{Supply}

The UNICEF Rotavirus 2014 Supply and Demand Update reports that increased manufacturing capacity has improved the supply situation for rotavirus vaccine.\textsuperscript{19} Contracted rotavirus vaccine supply in 2014 was 20.2 million courses, while the actual availability of rotavirus vaccine is expected to reach 22.8 million courses, which includes 2.3 million courses carried over from 2013 and an additional 250,000 courses from GSK.\textsuperscript{19} In 2014, UNICEF expected to procure 22.65 million courses (47 million doses) of rotavirus vaccine, 22 million (41.9 million doses) of which were are Rotarix\textsuperscript{®}.\textsuperscript{18} [The previous year, UNICEF increased allocations for 2014 from 16.5 million courses to 18.6 million courses (33 million to 37.2 million doses) of Rotarix\textsuperscript{®}.\textsuperscript{18}]

\textsuperscript{4} Accessed in October 2014
Table 3: UNICEF awards for the 2012-2016 tender (from the 2014 Supply and Demand Outlook)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Manufacturer</th>
<th>Schedule</th>
<th>Presentation</th>
<th>Duration</th>
<th>Doses</th>
<th>Courses</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV1</td>
<td>GSK</td>
<td>2 doses</td>
<td>1 dose</td>
<td>4 years</td>
<td>136,200,000</td>
<td>68,100,000</td>
</tr>
<tr>
<td>RV5</td>
<td>Merck</td>
<td>3 doses</td>
<td>1 dose</td>
<td>4 years</td>
<td>16,332,100</td>
<td>5,444,033</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>152,532,100</td>
<td>73,544,033</td>
</tr>
</tbody>
</table>

Through 2016, UNICEF has 73.5 million courses (152.5 million doses) of rotavirus vaccine under contract (Table 3). However, from 2015 onward, the current contracted supply is not expected to meet total demand, and the need for new awards is being reviewed. GSK’s current maximum supply capacity is 50 million courses per year. There is also no new demand for RotaTeq®, and some countries are considering switching away from RotaTeq® to Rotarix®. Furthermore, Pakistan, Nigeria, Bangladesh and the Democratic Republic of Congo have not yet applied for rotavirus vaccine introduction support; their introduction plans and preferences will significantly impact the ability of supply to meet the potentially substantial increase in rotavirus vaccine demand in the future.

If countries select Rotarix®, GSK will not be able to satisfy the additional demand with existing capacity.

However, there are seven rotavirus vaccines currently under development. Through a unique collaborative public-private partnership under the Indo-US Vaccine Action Program, Bharat Biotech India Limited (Bharat) developed both a frozen and liquid presentation of the rotavirus vaccine, ROTAVAC®, which completed a Phase 3 efficacy study in late 2013. ROTAVAC® was recently launched in India in March of 2015, and will be made available at a price of $1 per dose to governments in LICs and United Nations (UN) procurement agencies. As stated by the manufacturer, the development of an innovative manufacturing process enabled the reduction in the cost of manufacturing and enhanced affordability. Within their newly developed manufacturing facilities, Bharat has an installed manufacturing capacity of 300 million doses of ROTAVAC® per year.

Serum Institute of India (SII) is conducting a Phase 3 efficacy trial of their oral bovine-human reassortment rotavirus vaccine which has both a lyophilized and fully liquid presentation. Both SII and Bharat are expected to obtain WHO prequalification for their rotavirus vaccines between 2016 and 2018, while a later report anticipates WHO prequalification of a new rotavirus vaccine no earlier than 2017. Although the frozen and lyophilized vaccines are less programmatically desirable, these presentations are likely to be prequalified before the fully liquid presentations.

Impacts
Prior to the 2012 UNICEF tender, affordability was a prominent issue in the duopolistic rotavirus vaccine market; the cost of a single course of Rotarix® was $15.00. This price was not only prohibitive to countries procuring their own vaccines, but also to Gavi in supporting rollout and introduction of the

5 From personal communication with Gates Foundation
6 Partners involved include the Government of India’s Department of Biotechnology (DBT), the US National Institutes of Health, US Centers for Disease Control and Prevention, Stanford University School of Medicine and PATH. The partnership was supported by the Bill and Melinda Gates Foundation, DBT, the UK Department for International Development and the Research Council of Norway.
rotavirus vaccine. Due in part to the high price, the rotavirus market was at an early stage of the adoption curve, with only five Gavi-supported countries having introduced the vaccine by 2011.\textsuperscript{16}

The volume guarantee and prepayment to GSK for Rotarix\textsuperscript{®} achieved significant price savings in the short term, as illustrated in the price per course curve below (Figure 4). The price reduction effectively spurred demand for the vaccine, and is thought to have accelerated vaccine adoption and introduction into LICs and LMICs. The rotavirus market, prior to the volume guarantee, was experiencing a volume-uptake trap, whereby high procurement prices discourage or limit demand for a product. Low demand volumes prohibit the manufacturer’s ability to achieve economies of scale, which preclude any decrease in the marginal cost of production and leaves the prohibitively high procurement price unchanged. An external factor, such as the volume guarantee, provided a way out of this trap by reducing the procurement price. Upon securing the new low price, Gavi estimated the potential cost savings to be $650 million (which is the amount of additional funding that would have been required to purchase the vaccine at the previous price).\textsuperscript{29}

Stakeholders cited that one long-term expectation (or hope) for a volume guarantee is that it is catalytic – inciting price-following (matching or reducing prices) or encouraging more competition to generate price-following. It was mentioned that the likelihood of observing price following in the rotavirus market as a result of this volume guarantee is in question because the existing rotavirus vaccines are not perfect substitutes for one another, and have widely different demand volumes.

\textit{Figure 4: Price per course of Rotarix\textsuperscript{®}, number of WHO-PQ rotavirus vaccine manufacturers 2011-2017, with duration of volume guarantee delineated by vertical dashed lines}

Significant demand uncertainty can exist for manufacturers at the early stage of the adoption curve, as the rate of country adoption and introduction is difficult to predict. Demand uncertainty affects manufacturers’ ability to plan supply capacity and production, which can lead to supply shortages of essential vaccines. The volume guarantee improved supplier confidence in medium- to long-term contributions to the rotavirus vaccine market. The long duration of the tender (2012-2016) gave GSK
visibility into volumes of demand and enabled better planning of production and capacity utilization. In committing to a specified volume over a longer period of time, buyers also conferred information to suppliers that was otherwise difficult to credibly share. A key factor in vaccine markets, for example, is sustainable donor funding as well as strategic and political commitment to long term market growth. By awarding the volume guarantee, buyers conveyed their confidence in the availability of future funding, which significantly reduced information asymmetry between the buyer and the supplier.

From the suppliers’ perspective, a reduction of demand uncertainty and information asymmetry enables better planning of production sequences and lot sizes, and allows for better informed, longer-term decisions. One stakeholder mentioned that GSK was building a fifth Rotarix® production line around the same time of the tender award. While it is uncertain whether their decision to increase capacity was influenced or driven by the volume guarantee, one stakeholder implied that the volume guarantee influenced the internal production economics of GSK such that they modified their current capacity to optimize production scale.

**Discussion**

In the absence of the volume guarantee to GSK, the rotavirus vaccine market could have remained in the volume-uptake trap until an external factor, such as the entry of additional competition, placed downward pressure on prices. The rapid introduction and adoption of the rotavirus vaccine into Gavi-supported countries may not have been possible at the higher pre-volume guarantee price. However, even if the same rate of introduction were possible at this high price point, it is uncertain whether GSK would have invested additional supply capacity to meet the increasing demand for their preferred product without the incentive of the volume guarantee. In this scenario, it is likely that the market would have adjusted to these constraints with many countries adopting the sub-optimal RotaTeq®.

Recall that the increased demand for the rotavirus vaccine, coupled with a global preference for Rotarix®, also resulted in global supply shortages of Rotarix®. According to one stakeholder, supply security was not a leading concern at the time when negotiations for the volume guarantee were taking place. Although GSK was investing in additional capacity around the time of the volume guarantee, their current maximum supply capacity of 50 million courses per year is not expected to be able to meet the
increasing demand for Rotarix® from 2015 onward, especially if/when additional high-population countries apply for Gavi support. In this respect, the volume guarantee improved availability of the rotavirus vaccine in the short term, but may not have incentivized enough capacity investment for the preferred product to meet the longer-term growth in demand.

However, this temporary supply shortfall may (eventually) be counteracted by new supplier entry to the market. The substantial uptake in demand spurred by the volume guarantee can be a signal of sustainable, long-term market growth, which may motivate manufacturer entry. In awarding the volume guarantee to GSK, Gavi also aimed to encourage other developing country manufacturers to enter the market, thus expanding the rotavirus vaccine supplier base. It remains unclear whether the volume guarantee influenced the decisions of the manufacturers of the seven rotavirus vaccines currently in the development pipeline. In the case of Bharat, for example, multiple global donors and organizations financially and technically supported the development of ROTAVAC®. ROTAVAC® is expected to enter the market early as 2017. With a supply capacity of 300 million doses per year, and a new low price of $1 per dose, we could expect to see Bharat not only meeting the demand GSK is unable to satisfy, but also taking market share from GSK if the price of Rotarix® remains unchanged or increases in the post-volume guarantee period.
Penta
vavalent vaccine market

Background

Disease
The pentavalent vaccine is a combination vaccine that protects against Diphtheria, Tetanus and Pertussis (DTP), hepatitis B (HepB) and *Haemophilus influenzae* type B (Hib). In 2013, 4,680 cases of diphtheria, 14,860 cases of tetanus, and 136,036 cases of pertussis were reported worldwide. The reported global immunization coverage of the third dose of DTP (DTP3) was 84% in 2013, and had remained stagnant since 2009. In the 73 Gavi-eligible countries, the weighted average DTP3 coverage was 76% in 2013.

Global immunization coverage of the HepB antigen increased from 74% in 2009 to 81% in 2013. Global immunization coverage of Hib antigen continues to lag behind, but increased from 39% in 2009 to 52% in 2013. Coverage of the third dose of the pentavalent vaccine in Gavi-eligible countries was 53% as of October 1, 2014.

Vaccine development history
Multiple vaccines for different combinations of these five diseases have been developed over a 60-year period, all leading up to the WHO prequalification of the first pentavalent vaccine in 2003 (Figure 6). A vaccine against DTP was first developed in the United States in 1942 and was one of the founding vaccines of the EPI list in 1974. The first HepB vaccines were developed in France and the United States and became available between 1981 and 1982. GSK’s single-dose per vial HepB vaccine was the first to be prequalified by the WHO in 1987, and the vaccine was recommended for use in all national immunization programs in 1992. The inclusion of HepB into national immunization programs (recommended by the WHO in 1992) resulted in increased global demand for the vaccine; the manufacturing technology was also easily transferrable to emerging manufacturers.

*Figure 6: Vaccine development timeline*

- **First DTP vaccine developed**: 1942
- **First HepB vaccine available**: 1974
- **First conjugated Hib vaccine licensed in US**: 1987
- **First DTP-HepB vaccine licensed by GSK**: 1992
- **WHO recommends Hib vaccine for use**: 1996
- **WHO recommends HepB vaccine for use**: 1997
- **WHO PQ of GSK’s 1-ds HepB vaccine**: 1998
- **WHO PQ of Novartis 1-ds Hib vaccine**: 2003
- **WHO PQ of GSK’s 2-ds lyophilized pentavalent vaccine**: 2003

- **Founding of Expanded Programme on Immunization**
- **WHO PQ of GSK’s 1-ds HepB vaccine**
- **WHO recommends HepB vaccine for use**
- **WHO PQ of Novartis 1-ds Hib vaccine**
- **WHO PQ of GSK’s 2-ds lyophilized pentavalent vaccine**
The first conjugated Hib vaccine was developed by Connaught Laboratories (now Pasteur Mérieux Connaught (PMC)) and licensed in the United States in 1987. The entrance of new manufacturers to the market following the development of PMC’s vaccine was much slower than for the HepB vaccine as the conjugation technology used to create the Hib vaccine was more complex and difficult to transfer. Novartis’ single-dose per vial Hib vaccine was the first to be prequalified by the WHO in 1997, and the vaccine was recommended for use by the WHO in 1998. [By 2000, there were eight monovalent Hib vaccines and five Hib combination vaccines available on the market. Between 2000 and 2005, three additional Hib vaccines were licensed, which included two new pentavalent vaccines.]

In an effort to increase the protection conferred through routine immunization, vaccines against HepB and Hib were combined with DTP vaccines in the late 1990s. The U.S. FDA approved GSK’s DTP-HepB combination vaccine in 1996, which was later combined with GSK’s Hib vaccine to create the first DTP-HepB-Hib (pentavalent) vaccine. GSK’s two-dose per vial lyophilized pentavalent vaccine was the first to be WHO prequalified in 2003.

Existing pentavalent vaccines

One course of the pentavalent vaccine requires three doses, usually administered between 4 and 14 weeks of age, at an interval of one month. The vaccine currently exists as either a “lyophilized” or liquid formulation in a one-dose per vial, two-dose per vial or ten-dose per vial presentation (Figure 7). The lyophilized formulation consists of two separate vials – one with lyophilized Hib vaccine and another with liquid DTP-HepB vaccine which serves as the diluent. The lyophilized Hib vaccine must be dissolved (reconstituted) into the liquid DTP-HepB vaccine prior to administration. While individual stakeholders may have different preferences of vaccine formulation and presentation, the fully liquid pentavalent vaccine has been found to be widely preferred over the lyophilized pentavalent vaccine.

Figure 7: Schematic of existing pentavalent vaccine formulations and presentations
Pentavalent market pre-volume guarantee

Creation and initial influence of Gavi

Gavi was founded in 2000 with the goal of improving health and saving the lives of children, particularly those in developing countries, through the widespread use of vaccines. One of Gavi’s primary objectives was to accelerate access to new and under-utilized vaccines in developing countries, including vaccines against HepB and Hib.\(^\text{13}\)

When Gavi was founded, there were 13 licensed monovalent HepB vaccines and two DTP-HepB combination vaccines.\(^\text{13}\) Manufacturers within emerging economies produced 79% of the HepB monovalent vaccines.\(^\text{13}\) Driven by Gavi’s preference for DTP combination vaccines, many manufacturers in developed countries as well as some within emerging economies began including HepB in their combination vaccines.\(^\text{13}\) By 2005, the price for HepB monovalent vaccines declined to less than $0.50 per dose, driven by competition among monovalent HepB vaccines. As a result of low prices and decreasing global demand, several monovalent HepB vaccine manufacturers exited the market.\(^\text{13}\) In contrast, the price (and demand) for DTP-HepB combination vaccines increased from $1.00 per dose in 2000 to $1.25 per dose in 2005.\(^\text{13}\)

By 2000, there were eight monovalent Hib vaccines and five DTP-Hib combination vaccines available on the market. In contrast, there was one pentavalent vaccine on the market.\(^\text{13}\) GSK’s two-dose per vial lyophilized vaccine was the only pentavalent vaccine to be WHO prequalified during Gavi’s first phase.\(^\text{13}\) Gavi’s preference for combination vaccines resulted in an increased demand for GSK’s pentavalent vaccine that exceeded their installed supply capacity. Amidst a global supply shortage, the price of the pentavalent vaccine did not drop below $3.50 per dose between 2000 and 2005.\(^\text{13}\) Although there was a readily available DTP-Hib combination vaccine, there was very little demand for it from developing countries; the greatest Gavi demand was for the DTP-HepB combination vaccine and the pentavalent vaccine, each of which relied on a single supplier (Figure 8).\(^\text{13}\)
Global pentavalent vaccine supply

In the years preceding the volume guarantee to Bio E, the global pentavalent market experienced a period of expansion, shortly followed by the exit of two manufacturers due to quality issues (Figure 9). GSK’s two-dose per vial lyophilized pentavalent vaccine was WHO prequalified in 2003 and held a monopoly over the global market until the WHO prequalification of a single-dose per vial liquid vaccine manufactured by Berna Biotech Korea Corporation’s, a Crucell Company (Berna), in 2006. Both Panacea Biotec Ltd. (Panacea) and Shantha Biotechnics Ltd. (Shantha) entered the market in 2008 with single-dose per vial liquid vaccines. Between 2007 and 2010, a 20% price decline was observed for the liquid pentavalent vaccine, driven by competition among the three liquid pentavalent vaccines suppliers. Although four pentavalent vaccine suppliers were active in the market by 2008, the global supply of the pentavalent vaccine was still considered to be “limited” through 2009.

SII entered the market with a two-dose per vial lyophilized vaccine in 2010, becoming the fifth pentavalent vaccine supplier to UNICEF. [During this year, a 16% decline in price of the lyophilized vaccine was observed, thought to be driven by a decrease in demand for the lyophilized vaccine due to an increase in the liquid vaccine supply.] Later in 2010, SII obtained WHO prequalification for their single-dose per vial, two-dose per vial and ten-dose per vial liquid pentavalent vaccines. SII was the only supplier of a ten-dose per vial liquid vaccine at this time. The weighted average UNICEF/Gavi market price for the pentavalent vaccine was $2.49 per dose, down from $3.61 per dose in 2007 (when the majority of Gavi-eligible countries transitioned to the 5-in-1 vaccine).
Also in 2010, the WHO recommended the temporary suspension of procurement and use of Shantha’s pentavalent vaccine, SHAN5, due to the presence of a white sediment sticking to the vials. Following a subsequent recall and destruction of all lots of SHAN5, the WHO removed it from the list of prequalified vaccines. In August 2011, Panacea’s Easyfive (DTwP-Hep B-Hib), Ecovac4 (DTwP-Hep B), and EnivacHB (Hepatitis B) were also removed from the list of WHO prequalified vaccines, due to deficiencies in Panacea’s quality management system. The de-listing of both Panacea’s and Shantha’s WHO prequalified pentavalent vaccines caused a disruption in the balance of supply and demand. As a result, the market was facing the risk of supply shortages.

In the same month of Panacea’s delisting, Bio E obtained WHO prequalification for both a single-dose per vial and a ten-dose per vial lyophilized pentavalent vaccine. A volume guarantee was then offered to Bio E in early 2012, the negotiations for which took place in 2011.

**Volume guarantee to Biological E**

The volume guarantee to Bio E was a Gates Foundation program related investment (PRI) aimed to reduce the cost of procuring the pentavalent vaccine for developing countries. The mechanism was also designed to fill and/or bridge the supply gap during an unstable period of supply availability, following two WHO prequalification de-listings. The stakeholders involved in the design and negotiation of the intervention wanted to ensure that Bio E would not only remain in the market, but would also be incentivized to proceed with the investments needed to achieve WHO prequalification of their liquid vaccines. At the time, Bio E had only gained WHO prequalification for lyophilized vaccines, and SII was the only supplier of a ten-dose per vial liquid vaccine (at a UNICEF-listed price range of $1.75 – $2.105 per dose).
The volume guarantee consisted of two constructs – one for 2012 and another for 2013-2017. In the 2012 construct, the volume guarantee covered a combination of both the lyophilized and liquid vaccines, as only the lyophilized vaccine was WHO prequalified at the time of the tender. There were 30 million doses available in total, and prepayment was included in the agreement. Under this construct, the price of the lyophilized vaccine was $1.80, while the price of the liquid vaccine was $1.25.

The second construct covered 30 million doses of only the liquid vaccine in 2013, followed by 50 million doses each year from 2014 to 2017. The price of the vaccine under this construct was $1.19, with prepayment made by the Gavi Secretariat to Bio E through UNICEF. [Without prepayment, the price of the vaccine under the second construct is $1.34.] However, Gavi’s access to this new low price is capped in terms of the number of doses. From 2014 onwards, under the existing volume agreement, the maximum number of doses Gavi can purchase at $1.19 is 50 million; a higher price must be paid for additional doses. [While the Gavi-funded vaccine market is Bio E’s largest market segment, Bio E also supplies to middle-income countries through the PAHO using a tiered pricing approach.] As part of these negotiations, the Gates Foundation also provided a backstop guarantee to Gavi. The prepayment agreement between Gavi and UNICEF and the backstop agreement between Gavi and the Gates Foundation are both reviewed and renewed on an annual basis.

**Pentavalent market post-volume guarantee**

**Supply**

Bio E obtained WHO prequalification for their ten-dose per vial liquid vaccine in May 2012, midway through the first construct of the volume guarantee. In the same year, LG Life Sciences (LGLS) gained WHO prequalification for a single-dose per vial and a two-dose per vial lyophilized pentavalent vaccine. In 2013, Panacea obtained WHO prequalification for a single-dose per vial and a ten-dose per vial liquid.

In May of 2013, the supply capacity of the pentavalent vaccine market was estimated to be between 290 and 320 million doses per year for an estimated demand of 200 to 260 million doses per year.  

Two of the WHO prequalified manufacturers, SII and Bio E, accounted for approximately 70% of the estimated supply capacity (Figure 10).

*Figure 10: Gavi pentavalent vaccine doses shipped in 2014 by manufacturer*
Shantha also obtained WHO prequalification for single-dose per vial and a ten-dose per vial liquid vaccine in April 2014.\textsuperscript{12}

In December of 2014, Bio Farma of Indonesia obtained WHO prequalification for a five-dose per vial and a ten-dose per vial liquid vaccine, becoming the eighth WHO prequalified pentavalent vaccine manufacturer.\textsuperscript{12} As of January 2015, UNICEF was procuring under multi-year agreements from seven of the manufacturers for three different formulation-presentation combinations (Table 5).\textsuperscript{45}

Table 5: Current pentavalent manufacturers of pentavalent vaccines under LTAs with UNICEF\textsuperscript{45}

<table>
<thead>
<tr>
<th>Formulation-Presentation</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-dose liquid</td>
<td>Bio E</td>
</tr>
<tr>
<td></td>
<td>Berna</td>
</tr>
<tr>
<td></td>
<td>SII</td>
</tr>
<tr>
<td>Ten-dose liquid</td>
<td>Bio E</td>
</tr>
<tr>
<td></td>
<td>Panacea</td>
</tr>
<tr>
<td></td>
<td>SII</td>
</tr>
<tr>
<td></td>
<td>Shantha</td>
</tr>
<tr>
<td>Two-dose lyophilized</td>
<td>GSK</td>
</tr>
<tr>
<td></td>
<td>LGLS</td>
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</tbody>
</table>

Current demand

By 2014, all 73 of the Gavi-supported countries had introduced the pentavalent vaccine.\textsuperscript{46} Gavi shipped an estimated 152.5 million doses of the pentavalent vaccine globally in 2014.\textsuperscript{23} As shown in the figure below, the ten-dose per vial liquid presentation dominates country preferences, accounting for approximately 71% of the total doses shipped by Gavi in 2014.\textsuperscript{23,47} The single-dose per vial liquid presentation accounted for an estimated 28%, followed by the two-dose per vial lyophilized presentation accounting for the remaining 1%.\textsuperscript{23}

Figure 11: Gavi pentavalent vaccine doses shipped in 2014 by presentation\textsuperscript{23}
Gavi demand for pentavalent vaccines between 2013 and 2016 was estimated to be 750 million doses, representing an approximate 84% of the global volume of pentavalent vaccines. Gavi will continue to be the major financier of pentavalent vaccine for the next three to four years until India begins scaling the vaccine and becomes the second largest purchaser.

**Impacts**

The de-listings of Shantha and Panacea from the WHO prequalification list led to supply insecurity in the pentavalent vaccine market, and brought to light the significant risk of supply disruptions within this market. The predictability of demand (and thus, revenue) conferred by the volume guarantee aimed to incentivize Bio E to remain in the pentavalent vaccine market, and to bring the ten-dose per vial liquid vaccine through the WHO prequalification process. As seen above in Figure X, (illustrating the Gavi shipments of the pentavalent vaccine by presentation in 2014), there is a strong global preference and demand for the ten-dose per vial liquid presentation. Bio’s entry as the second WHO prequalified manufacturer of this preferred presentation is thought to have improved supply security in a somewhat fragile pentavalent vaccine market.

According to stakeholders, demand visibility over an extended period of time allowed for the strong negotiation on price. Prior to the pentavalent volume guarantee, the 2011 UNICEF-listed price range for SII’s ten-dose per vial liquid pentavalent vaccine was $1.75 – $2.105 per dose. Under the first construct of the volume guarantee to Bio E, the price for this formulation was reduced to $1.25 per dose, while the second construct (2013-2017) achieved a lower price of $1.19 per dose (with prepayment). The volume guarantee is also anticipated to prove catalytic in the long-term, with stakeholders expecting price-following once the pentavalent vaccine market has stabilized and competition has increased.

*Figure 12: Market characteristics and dynamics of the pentavalent volume guarantee*

**Discussion**

Supply security was the leading concern for global stakeholders and purchasers of the pentavalent vaccine the time of the volume guarantee award to Bio E. At the time, there was a gap in supply created by the exit of two manufacturers and one other manufacturer of the preferred ten-dose presentation of the vaccine in the market. Under these conditions, one could argue that Bio E would have realized the business case for proceeding with WHO prequalification of their liquid vaccines, entered the market, and received orders for this preferred presentation without the added incentive of a volume guarantee. However, recall that the same global stakeholders value maximum vaccine coverage and incentives for
innovation above other considerations. The time-bound assurance of supply security provided by the volume guarantee may not have been achievable without intervention.

The price reduction achieved by the volume guarantee, although not as significant as for rotavirus, likely increased the number of doses of pentavalent purchased by Gavi and therefore the number of children receiving the vaccine. However, the price of the pentavalent vaccine had already decreased significantly from 2007, corresponding to an increase in the number of WHO prequalified pentavalent vaccines (Figure 13). It is uncertain whether the volume guarantee to Bio E influenced the decisions of manufacturers to enter (or re-enter) the pentavalent market. As mentioned above, pentavalent vaccines manufactured by LGLS, Panacea and Shantha all received WHO prequalification following the award of the volume guarantee. One could argue these manufacturers would have entered the pentavalent vaccine market regardless of the volume guarantee to Bio E, and in doing so, would have placed additional downward pressure on prices.

*Figure 13: Number of WHO prequalified suppliers and average awarded price per dose (across formulations) of pentavalent vaccine over time*

*Prices were last updated January 29th 2015; authors used minimum of price range where range was provided.*
**Volume guarantees**

**Underlying dynamics**
As alluded to in the cases above, the risk faced by vaccine manufacturers is driven by demand uncertainty in the market for donor funded vaccines and information asymmetry between the buyer and the manufacturer (Figure 14). This uncertainty forces the manufacturer to consider the costs of too little capacity to satisfy demand, as well as the costs of excess capacity. In some markets, the amplitudes of the variability in demand can increase as one moves up the supply chain, with each stage overreacting to changes in demand – a phenomenon known as the bullwhip effect. While we cannot assume that the bullwhip effect always takes place in vaccine markets, the phenomenon is representative of the demand uncertainty faced by manufacturers. Information asymmetry also exists between the manufacturer and the buyer in vaccine markets, as the buyer likely has more information about the sustainability of donor funding, the expected future demand for vaccines, and perhaps even the timing of country introduction and adoption (in the case of new vaccines).

High risk from demand uncertainty and information asymmetry were the likely root causes behind the shortcomings of the pentavalent and rotavirus vaccine markets prior to their respective volume guarantees (Figure 14). When faced with higher risk, few manufacturers saw the donor-funded market as an attractive business opportunity, resulting in insufficient supply capacity and/or sub-optimal competition in the market. Manufacturers that were engaged in the market may not have invested in sufficient capacity due to demand uncertainty, or limited information about the expected demand for their product. These dynamics can result in insufficient supply capacity and high procurement prices.

*Figure 14: Schematic of risk distribution, drivers of risk and market shortcomings in the pentavalent and rotavirus markets*

The redistribution or sharing of risk along the value chain is the underlying force behind the volume guarantee mechanism. Volume guarantees essentially transfer the risk from demand uncertainty and information asymmetry from the manufacturer to the buyer. By committing to purchase a specific
volume of product, the buyer is eliminating uncertainty for this portion of the demand for a period of time. As the manufacturer no longer faces the risk of demand uncertainty, he/she is more able and willing to lower the procurement prices. In a similar way, guaranteeing to purchase a specific volume over an extended period of time also reduces the information asymmetry between the buyer and the manufacturer. Under the volume guarantee, the manufacturer knows that the buyer expects to satisfy or generate at least as much demand as the guaranteed volume, and has sufficient funding to purchase it (Figure 15).

![Figure 15: Schematic of volume guarantee mechanism of action](image)

**Considerations**

In assessing the volume guarantees in these two markets, key considerations arose which either help to ensure the anticipated benefits of the mechanism or highlight potential unintended consequences of its implementation. Stakeholders specifically mentioned the importance of having adequate information on production costs to inform negotiations and the likelihood of price-following (i.e. the sustainability of price reductions) after the volume-guarantee period. The possibility of limiting competition in these markets and setting a precedent were both cited as potential unintended consequences to consider.

**Cost information**

An important precondition for the consideration of a volume guarantee (as cited by stakeholders) is a certain level of confidence in the negotiation’s ability to reset a significantly lower and sustainable price for the product. This confidence is driven by an understanding of the production economics, as well as by visibility into the technology and competition landscape. Stakeholders involved in negotiations typically start with an outside-in perspective (or informed guess) into production economics, and acquire cost of goods sold (COGS) information where available. It was mentioned that stakeholders are likely to work more closely with manufacturers who are willing to share COGS information. Although stakeholders may set an objective for the price and volumes to be guaranteed, the deal that is negotiated is dependent upon the specific manufacturer’s circumstances.

A better understanding of COGS would inform negotiations and increase the likelihood of achieving significant and sustainable price savings. However, this assumes that exact information is available about the procurement price composition. In reality, this information is difficult to acquire.
**Sustainable price reduction**

It was mentioned that the pentavalent volume guarantee could incite price following with the entry of new suppliers, whereas the likelihood of observing price following in the rotavirus market was in question. Price following can be viewed as a potential longer-term effect of demand uptake spurred by the volume guarantee, or a result of new supplier entry into the market which places downward pressure on prices. There are multiple scenarios in which the price reductions achieved by a volume guarantee could remain in the period after the volume guarantee, as well as scenarios in which the price reductions could be lost.

At the time of the pentavalent volume guarantee to Bio E, SII was the only manufacturer with a prequalified ten-dose per vial liquid formulation and there were two other lyophilized formulations (manufactured by GSK and SII) on the market. Outside of the volume guarantee period, and in the case of no new entrants to the market, it is unlikely that the other suppliers in the pentavalent market would match or go below the price set by the volume guarantee to Bio E. However, price-following could be observed if the volume guarantee spurs entry of new suppliers to the market, who then place additional competitive pressure on the incumbent suppliers.

In the case of Rotarix®, there was very little competition for GSK at the time of negotiations for the volume guarantee. [Recall the overwhelming preference for GSK’s formulation, and that Rotarix® and RotaTeq® are not considered substitutes. In this regard, Rotarix can be seen as having a monopoly over the market in which it operates.] While the price reduction achieved by these negotiations is significant, the $5.00 per course price could still be higher than it would be with significant competitive pressure. If this is the case, new manufacturers could enter the rotavirus vaccine market at a price that matches or goes below the price set by the volume guarantee. Additionally, the reduction in price of Rotarix® spurred a significant increase in demand, which could have resulted in a decrease in the marginal cost of production as GSK reached economies of scale. By this reasoning, price-following may be possible in the rotavirus market because global demand for the vaccine increased and stabilized.

**Limiting competition**

Some argue that market shaping interventions can be distorting, appearing to favor one or a few suppliers over the rest. Guaranteeing a large portion of the global demand for a product over an extended period of time to one manufacturer may be seen as competition-limiting, forcing other manufacturers to exit the market or serving as a barrier to entry of new manufacturers. The directionality and degree of a volume guarantee’s effect on competition is difficult to determine given the complexity and dynamic nature of competition itself. Each manufacturer’s vantage point in the market will determine how he/she views the competition effects of a specific intervention.

Nonetheless, the fraction of the market covered by the volume guarantee and the duration of the volume guarantee may influence the competitive effects of the intervention. The estimated Gavi demand for pentavalent vaccines between 2013 and 2016 is 750 million doses; in this time period, approximately 230 million doses (or 30% of the total demand) are covered by the volume guarantee. On the one hand, the award of a volume guarantee of this size and duration may send a positive signal to other manufacturers; if buyers are willing to take on much of the risk faced by manufacturers, it may
give other manufacturers confidence in the health and potential growth of the market, thus encouraging entry. However, we are unable to determine the fraction of the market covered by the volume guarantee after which the intervention is likely to be seen as competition-limiting. Similarly, we do not know the point at which the duration of a volume guarantee becomes so long that it discourages manufacturer entry. In the case of the Rotarix®, 45 million of the 71.4 million doses awarded under the two five-year LTAs are covered by the volume guarantee (approximately 63% of the total market) (Figure 16).

Figure 16: UNICEF rotavirus 2012-2016 tender award; share of 71.4 million course award between Merck and GSK, with portion covered by the volume guarantee to GSK

The demand covered by this volume guarantee may be seen as a positive market signal to some manufacturers, while others may view it as limiting competition and discouraging market entry. The expressed global preference for Rotarix® further complicates the discussion of competition effects of this intervention, as global demand is already skewed toward one product).

New market entries and a saturated development pipeline suggest that these volume guarantees were viewed as a positive signal to at least some manufacturers. In the two years since the initial award of the volume guarantee to Bio E, no pentavalent manufacturers have exited the market, and Panacea, Shantha and Bio Farma have all entered the market with single-dose, five-dose and ten-dose per vial liquid vaccines. Hexavalent vaccines (DTwP-Hib-HepB-IPV) may become available as soon as 2018, and it currently remains unclear as to how the adoption and uptake of hexavalent vaccines will impact the demand for pentavalent or affect the market impact of this volume guarantee.48) As mentioned, no manufacturers have exited the rotavirus vaccine market following the volume guarantee, and there are currently seven rotavirus vaccines in the development pipeline.

Setting a precedent
There is an inherent risk of setting a precedent in awarding volumes guarantees, whereby manufacturers could begin to expect a guarantee against every procurement. In response to these critiques, stakeholders cite the importance of having a large and strategic reason for facilitating this type
of intervention from the outset. They suggest volume guarantees must be used selectively to yield extraordinary value, in the form of a price point that would not have been accessible otherwise or a significant and impactful change to the market. [In the case of the pentavalent vaccine market, some believed that the volume guarantee achieved both of these extraordinary outcomes, and fit the particular void in the marketplace left by the exit of two manufacturers.]

**Appropriate use and other mechanisms**

It is difficult to determine with complete certainty whether a market intervention was necessary and whether a volume guarantee was the best or most appropriate intervention to use for the rotavirus and pentavalent vaccine markets. Stakeholders have stated that the decision to use a volume guarantee and the rationale behind their design were based on the best available information at the time. Considering the counterfactual is instructive in evaluating each volume guarantee. In the absence of a rotavirus volume guarantee, the volume-uptake trap may have persisted, likely resulting in sustained high prices and limited availability of the rotavirus vaccine in LIC and LMIC. Furthermore, without substantial global demand for the vaccine (which was seemingly spurred by the volume guarantee), manufacturers (and global stakeholders) may not have invested in the development of additional rotavirus vaccines. In the case of pentavalent, countries may have experienced (earlier) supply shortages of the preferred vaccine in the absence of the volume guarantee. However, it is possible that Bio E would have entered the market without the added incentive of the intervention, as there appeared to be sufficient surplus demand to be met by Bio E’s supply.

Regarding appropriateness of use, multiple other market shaping mechanisms exist which aim to either mitigate or reduce uncertainty in a market, diversify risks, or more equitably share risks among stakeholders. Yadav et al. argues that the global health community may be too quick to jump to risk-sharing mechanisms, before first trying to reduce uncertainty or diversify risk in the market. For example, global demand forecasts and better financial information sharing can mitigate or reduce demand uncertainty in global markets. [Forecasts may be viewed as a pre-requisite to the design and award of a volume guarantee.] Risk diversification can take place through pooled procurement mechanisms, such as vaccine procurement by UNICEF. In addition to the volume guarantee, other mechanisms which aim to more optimally share risk include price-volume negotiated schedules, quantity flexibility (QF) contracts, buy backs and revenue sharing.

As described above, volume guarantees involve the transfer of all or most of the risk faced by the manufacturer to the buyer for a defined period of time. The improved demand visibility for the manufacturers conferred by this mechanism allows for a strong negotiation on price. A QF contract is similar to a volume guarantee, in that the buyer commits to purchase a minimum amount of product at a specified price, thus transferring the majority of the risk faced by the manufacturer to the buyer. However, in a QF contract, the buyer also retains the flexibility to purchase additional units of a product in case of additional demand. The supplier agrees to make a specified quantity of product above the minimum amount at a premium price.

In contrast to volume guarantees and QF contracts, price-volume negotiated schedules (or quantity discount pricing) do not transfer the majority of risk from the manufacturer to the buyer. Instead,
quantity discount pricing provides an incentive to the buyer to consolidate and/or generate more demand. Under this mechanism, the manufacturer and the buyer would agree upon a quantity-discount schedule, whereby the unit procurement price of a product would depend on the demand quantity. Some risk is still transferred under quantity discount pricing, as the manufacturer is assured that the buyer is incentivized to purchase more units to achieve greater price savings. Two-part pricing contracts operate in a similar way, where the buyer pays an initial lump-sum to buy from the manufacturer as well as a per-unit charge for the product. In this way, the manufacturer still receives some assurance of future business from the buyer (and thus transfers some portion of the risk), and the buyer receives more favorable prices.

We cannot determine how much risk is right for each market, or how much risk must be transferred to achieve the desired outcomes. It could be that in the pentavalent and rotavirus vaccine markets, a full transfer of the risk from the manufacturer to the buyer was necessary to achieve the significant price savings and ensure sufficient supply capacity. However, it is instructive to consider whether other mechanisms that provide incentives or transfer a smaller portion of the risk could have achieved similar or better outcomes, while also preventing or reducing the likelihood of unintended consequences.
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