

# Hexavalent IPV-based combination vaccines for public-sector markets of low-resource countries

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**Keywords:** Hexavalent vaccine, Inactivated polio vaccine (IPV), whole cell/acellular Pertussis

**Abbreviations:** D, diphtheria; T, tetanus; wP, whole cell pertussis; aP, acellular pertussis; HBV, Hepatitis B; Hib, Haemophilus influenzae B; IPV, Inactivated polio vaccine; WHO, World Health Organization; OPV, oral polio vaccine; tOPV, trivalent oral polio vaccine; bOPV, bivalent oral polio vaccine; mOPV, monovalent oral polio vaccine; WPV, wild poliovirus; BMGF, Bill and Melinda Gates Foundation; GPEI, Global Polio Eradication Initiative; SAGE, Strategic Advisory Group of Experts on Immunization; CHMP, Committee on Medicinal Products for Human Use; EMA, European Medicines Agency; DCVMs, developing country vaccine manufacturers; UNICEF, United Nations Children Funds; GAVI, Global Alliance for Vaccine Initiative; IM, intramuscular; EPI, Expanded Programme on Immunization; COGS, cost of goods sold; EU, European Union; CDC, US Centers for Disease Control and Prevention; PRP, polyribosyl ribitol phosphate, capsular polysaccharide of Hib

In anticipation of the successful eradication of wild polio virus, alternative vaccination strategies for public-sector markets of low-resource countries are extremely important, but are still under development. Following polio eradication, inactivated polio vaccine (IPV) would be the only polio vaccine available, and would be needed for early childhood immunization for several years, as maintenance of herd immunity will be important for sustaining polio eradication. Low-cost combination vaccines containing IPV could provide reliable and continuous immunization in the post-polio eradication period. Combination vaccines can potentially simplify complex pediatric routine immunization schedules, improve compliance, and reduce costs. Hexavalent vaccines containing Diphtheria (D), Tetanus (T), whole cell pertussis (wP), Hepatitis B (HBV), Haemophilus b (Hib) and the three IPV serotype antigens have been considered as the ultimate combination vaccine for routine immunization. This product review evaluates potential hexavalent vaccine candidates by composition, probable time to market, expected cost of goods, presentation, and technical feasibility and offers suggestions for development of low-cost hexavalent combination vaccines. Because there are significant technical challenges facing wP-based hexavalent vaccine development, this review also discusses other alternative approaches to hexavalent that could also ensure a timely and reliable supply of low-cost IPV based combination vaccines.

## Introduction

Polio eradication is an extraordinary and ambitious goal that has been intensely pursued for over 20 years, since the World Health Assembly first committed to global eradication efforts in the year 1988.<sup>1</sup> Subsequently, eradication of type 2 wild polio virus (WPV) and significant progress toward eradication of types 1 and

3 have successfully placed polio global eradication within reach. In preparation for the successful eradication of wild-type polio, vaccination strategies for the post-eradication era are extremely important, but are still under development. Recently, WHO's Strategic Advisory Group of Experts (SAGE) recommended at least one dose of IPV along with Oral Polio Vaccine (OPV) in those countries currently using OPV.<sup>2</sup> Although there is no fixed timeline for discontinuing the use of live OPV, the switch from trivalent OPV to bivalent OPV and the eventual cessation of use of the live virus vaccine is predicated on the success of global polio eradication efforts. Following eradication, trivalent IPV would be the only vaccine available, and would be needed for sustained immunization for several years, since maintenance of herd immunity will be essential for maintaining polio eradication.<sup>3</sup> Successful implementation of IPV, particularly in developing countries, will depend upon the availability of an effective and affordable vaccine. IPV-containing hexavalent vaccine represents one potential approach to global IPV access. A hexavalent combination vaccine could simplify complex pediatric routine immunization schedules, improve compliance, and reduce delivery costs. However, IPV-containing hexavalent vaccines have been a technical challenge for vaccine manufacturers since work began in the early 1990s to combine pediatric vaccines. Numerous technical challenges must be addressed and overcome in order to achieve widespread availability and adoption of hexavalent vaccines as part of the global polio immunization efforts.

Currently, GSK's *Infanrix Hexa*<sup>®</sup> is the only globally marketed hexavalent pediatric combination vaccine containing IPV. This vaccine contains an acellular pertussis (aP) component and is presented in a syringe-plus-lyophilized vial format because of instability of the Hib component.<sup>4</sup> A second hexavalent vaccine, *Hexyon*<sup>®</sup> (also called *Hexacima*<sup>®</sup> and *Hexaxim*<sup>®</sup>) from Sanofi Pasteur, also with aP, has received a positive opinion from the Committee on Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) and has been approved for marketing by EMA. This vaccine is likely to be targeted for

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Submitted: 04/12/2013; Revised: 06/03/2013; Accepted: 06/14/2013  
<http://dx.doi.org/10.4161/hv.25407>

private markets in Europe and worldwide.<sup>5</sup> Another hexavalent vaccine, also with aP, which is being jointly developed by Merck and Sanofi Pasteur, is currently in Phase III clinical studies. However, no hexavalent combinations with whole cell pertussis (wP) are commercially available or in late-stage development. The use of wP in hexavalent vaccines intended for developing countries is important both because of cost and emerging concerns about the long-term effectiveness of aP vaccines, especially in developing-country settings. Recent reports suggest that immunity to pertussis wanes in adolescence and that this is responsible for an increase in cases in infants under six months of age, before they are fully vaccinated.<sup>6</sup> Vaccine efficacy was estimated to be 24 percent in eight- to 12-y-olds immunized in infancy with aP. An observational study in Australia also showed higher case rates among adolescents given aP vaccine in infancy than among those given wP vaccine (relative risk of 3.3, 95 percent confidence interval 2.4–4.5).<sup>7</sup> In high-income countries, waning immunity to pertussis is being addressed by additional booster immunizations through the use of DTaP to replace DT in older age groups. However due to the higher cost this is not considered to be a viable option for lower- and lower-middle-income countries. Thus, hexavalent combination vaccines containing both types of pertussis vaccines are likely to be used in the coming decades.

The use and life cycle of an IPV-containing hexavalent vaccine will evolve during the peri- and post-eradication period as polio immunization practices are refined. Thus, the timeline for polio eradication can greatly affect the commercial viability of combination vaccines, including hexavalent products that may arrive on the market at different times. This review outlines current and potential future hexavalent products, particularly those that are relevant for public-sector markets of low-resource countries. This review assesses progress and prognosis for development of such IPV-based combination vaccines, and presents alternatives to hexavalent vaccines for IPV availability and to overcome major challenges in the development of such vaccines.

### Current and Potential Future Hexavalent Vaccine Products

The discussion of the various vaccine candidates uses the following nomenclature system:

- All of the combinations contain D and T and those letters will be listed first, followed by the pertussis composition.
- The code “aP” indicates an acellular pertussis vaccine followed by a number indicating the number of pertussis antigens.<sup>8,9</sup>
  - The 2-component aP (“aP<sub>2</sub>”) contains pertussis toxin (PT) and filamentous hemagglutinin (FHA), in vaccines made by Biken, and by Sanofi Pasteur for European and global markets.
  - The 3-component aP (aP<sub>3</sub>) contains PT, FHA and pertactin (PRN) sold by GSK, and
  - The 5-component aP (aP<sub>5</sub>) contains PT, FHA, PRN and fimbriae 2 and 3 (FIM) by Sanofi Pasteur in the USA and Canada.

- Whole cell pertussis vaccine will be indicated with the code “wP.”

- IPV stands for the three inactivated polio antigens, types 1, 2, and 3, derived from wild (Salk) strains unless otherwise noted; HBV for hepatitis surface antigen; and Hib for protein-conjugated capsular polysaccharide of *Haemophilus influenzae* type b.

- If the Hib component is preceded by a “//” then it is presented in lyophilized form in a separate vial. If there is only a dash before the Hib component then the combination product is a fully liquid presentation.

Current options for combination vaccines containing IPV (both the conventional Salk IPV which is made using wild polio strains, and the newer Sabin IPV which is made from the same attenuated Sabin strains as those used in the live attenuated OPV) are based on the use of the aP vaccine component. Because there are currently only four licensed producers of Salk IPV and one licensed producer of Sabin IPV worldwide, the supply options for potential producers of combinations containing IPV are limited. These include the licensed quadravalent vaccine (DTaP-Sabin IPV) for the Japanese market supplied by Biken and Kaketsuken, with trivalent Sabin IPV from Japan Polio Research Institute. There are other quadravalent and pentavalent combinations containing Salk-IPV in the developed countries markets including GSK’s Kinrix®, (DTaP-Salk IPV), and Pediarix® (DTaP-HepB-Salk IPV), and Sanofi-Pasteur’s Pentacel® (DTaP-Hib-Salk IPV). Infanrix Hexa® (GSK) is presently the only globally marketed hexavalent pediatric combination vaccine containing Salk IPV.<sup>1</sup> This product (DTaP<sub>3</sub>-IPV-HBV//Hib) is sold as a prefilled syringe of the pentavalent product co-packaged with a lyophilized Hib antigen PRP-T conjugate in a separate vial to be reconstituted with the rest of the vaccine before use. The Hib component is lyophilized to assure shelf life of the vaccine product as the PRP antigen may be destabilized in certain formulations containing aluminum adjuvant.<sup>10</sup> This hexavalent vaccine with aP is likely to remain a premium product with limited global supply. However, because of numerous technical and logistical issues, hexavalent vaccines with wP would not likely be available until 2020 or later.

For the analysis of potential future hexavalent vaccine products, we divided the manufacturers and products into vaccines containing aP or wP, and into three groups delineated by the theoretical time to market for each: near term (targeted approval dates of 2015–16), intermediate term (approval expected by 2020), and long-term (approval expected by 2025 or later). There are many issues and unknown pitfalls in developing combination vaccines, and those vaccines that are further into development or licensure timeline have presumably mastered these issues and are more likely to be available in the projected time frame.

**Near-term products.** Hexavalent vaccine combinations with aP newly approved or in Phase III studies and expected to be in the market by 2015–2016.

These products containing aP have a high probability of becoming available in the near term because they have presumably overcome the many technical and any logistical and clinical issues associated with their development. This encompasses developing acceptable and stable formulations as well as securing

reliable release and stability testing technology and a reliable source of all of the required bulks.

Hexaxim<sup>®</sup> (Sanofi Pasteur) DTaP<sub>2</sub>-IPV-HBV-Hib.<sup>11,12</sup> Sanofi Pasteur has independently developed an all-liquid hexavalent with a two-component aP. This product is an all-liquid formulation where the PRP antigen is stable for the indicated shelf life. It does not require reconstitution. Hexaxim<sup>®</sup> replaces a previous product, Hexavac<sup>®</sup> which was withdrawn from the market due to low immunogenicity of the hepatitis B component. In 2012, Sanofi presented their clinical data to the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) and received a favorable scientific opinion from the CHMP for use outside of the European Union (EU), presumably in private markets outside the US and EU.<sup>5</sup> The same product has recently been approved by EMA for marketing within Europe and will be marketed by the Sanofi Pasteur-MSD joint venture in Western Europe as Hexyon<sup>®</sup> and by Sanofi Pasteur in Eastern Europe as Hexacima<sup>®</sup>. It is unclear whether Sanofi is planning to provide this vaccine also to other public markets.

Sanofi Pasteur MSD: DTaP<sub>5</sub>-IPV-HBV-Hib. Merck (MSD) and Sanofi Pasteur have collaborated on a hexavalent all-liquid combination containing a five-component aP vaccine in Phase III evaluation.<sup>13</sup> This development product is also an all-liquid formulation where the PRP antigen (Pedvax HIB<sup>®</sup>) is stable for the indicated shelf life. It does not require reconstitution. This product is not expected to be marketed in Europe by the Sanofi Pasteur-MSD joint venture, which has selected Hexyon (above), but may be marketed in the US and other countries.

**Intermediate term: Expected to be marketed by 2020.** Several hexavalents with wP are under development and expected to be in low-cost markets by 2020. However, the wP bulk process practiced by many manufacturers uses thimerosal<sup>14</sup> both to kill the *B. pertussis* bacteria and to inactivate the pertussis toxin. Thimerosal also causes loss of antigenicity of IPV, and therefore IPV may need to be presented in a separate vial from thimerosal-containing wP to retain its potency over time. GSK's whole-cell combination DTwP-IPV-HBV//Hib is reported to be in several early clinical trials.<sup>15</sup> While this vaccine has the potential cost advantages of a whole-cell vaccine, it still has the lyophilized Hib component, adding to its financial complexity in that it would require double filling capacity. In the studies that were published, the polio immunogenicity of this product was not as good as a comparator vaccine, and it was clear from the data that the IPV dose would minimally need to be the same as the current vaccine and may need to be increased. There was no evidence for potential IPV dose sparing provided by this study. An all-liquid hexavalent combination would require redeveloping the pertussis bulk process.

There are several wP-based hexavalent vaccine combinations in very early development from developing country vaccine manufacturers (DCVMs), including Serum Institute of India, Limited (SIIIL), Shantha, Biological E (Bio E), and others. As these are based on classic wP vaccine with thimerosal, they face the familiar, major challenge of incompatibility with IPV antigens. Development of hexavalent vaccines would require

separate vials or changing the source pertussis bulk inactivation, e.g., to a process using formalin,<sup>16</sup> in which case clinical trials may be needed to ensure performance of the pertussis component. Furthermore, some of these combination vaccines also have mixed aluminum chemistries which might adversely affect the immunogenicity of HBV and/or Hib antigens or the stability of the final product. Important hexavalent combinations that fall within this time frame are products in the works from the SIIIL/Bilthoven, and Shantha/Sanofi acquisitions, and the BioE/GSK alliance. These partnerships already have individually marketed pentavalent products and have assured access to Salk IPV through acquisition or collaboration. All of these programs still face the issue of the incompatibility of thimerosal in the wP component with formulations containing IPV.

**Long-term: Expected to be available by 2025.** This time frame includes future hexavalent combinations that are in early development stages, some of which may be based on Sabin IPV, including hexavalent candidates from Crucell, Panacea Biotec, Bharat Biotech International Limited (BBIL), Takeda,<sup>17</sup> Bio Farma, BioVac, and Minhai Biotechnology. These companies have access to most if not all the hexavalent components. Crucell (Berna Biotech Korea Corporation, a Crucell Company) also markets Quinvaxem, which contains DTwP and Hib, provided by Novartis, and HBV.<sup>18</sup>

### Design of IPV Containing Hexavalent Vaccine— Target Product Profile

**For the public sector in low-resource countries.** The concept of developing a hexavalent combination vaccine would at first appear to be very straightforward, but, in reality, it has been a challenge for the major vaccine manufacturers since the early 1990s. No hexavalent combinations with wP are commercially available or in late-stage development at this time. One issue is uncertainty about what the useful life cycle of a hexavalent vaccine containing IPV will be in light of evolving polio immunization practices during the peri- and post-eradication period. No fixed timelines have been established for stopping use of OPV, and because herd immunity plays a critical role in maintaining successful eradication, IPV vaccination will need to be sustained for some time. Hexavalent vaccines reaching the market by 2020 could expect widespread use in both developed and developing countries, while those vaccines reaching the market in 2025 might experience only a brief period of widespread use unless the period of post-eradication IPV use was extended. If polio eradication is delayed beyond 2015, the life cycle of the hexavalent vaccines could be further extended. Eradication later on, e.g., in 2018 or 2020, would also bring hexavalent combinations from other manufacturers into play. Table 1 details the Target Product Profile (TPP) for a proposed hexavalent vaccine for developing world use. The TPP summarizes the preferred features of the hexavalent vaccine. The assessment of the desired features of the hexavalent vaccine is based on previous experience with pentavalent vaccines (containing wP) in the developing world.

**Table 1.** Target product profile (TPP) for a IPV based hexavalent vaccine for developing world markets

Product profile		Hexavalent pediatric combination vaccine for public market in developing world		
Disease area	Pediatric infectious diseases			
Possible Franchise	EPI routine immunizations			
Possible concomitant vaccinations	EPI schedule (BCG, measles), MenAfrivac, Quadrivalent Meningococcal conjugate, pneumococcal conjugate or common protein pneumococcal vaccine, measles, mumps, rubella, rotavirus			
Indication	Prevention of diseases caused by <i>C. diphtheriae</i> , <i>B. pertussis</i> , <i>C. tetani</i> , <i>H. influenzae</i> type b, Hepatitis B virus, polio viruses type 1, 2, 3			
Targeted segments of population	Immunization of infants under 1 y of age with primary series, may be followed by booster in second year of life			
Business case	Worst case	Acceptable	Best	
Claim 1	D, T, Hib, HBV responses inferior to current pentavalent vaccine (wP or aP as appropriate) plus separate IPV only after booster	D, T, Hib, HBV responses after 3 dose primary series not inferior to current pentavalent vaccine (wP or aP as appropriate) plus separate IPV	D, T, Hib, HBV responses after two dose primary series not inferior to current pentavalent vaccine (wP or aP as appropriate) plus separate IPV	
Claim 2	PT, FHA, pertactin response inferior to current pentavalent vaccine (wP or aP as appropriate) plus separate IPV only after booster	PT, FHA, pertactin response after 3 dose primary series not inferior to current pentavalent vaccine (wP or aP as appropriate) plus separate IPV	PT, FHA, pertactin response after two dose primary series not inferior to current pentavalent vaccine (wP or aP as appropriate) plus separate IPV	
Claim 3	Polio response inferior to current pentavalent vaccine (wP or aP as appropriate) plus separate IPV only after booster	Polio response after 3 dose primary series not inferior to current pentavalent vaccine (wP or aP as appropriate) plus separate IPV	Polio response after two dose primary series not inferior to current pentavalent vaccine (wP or aP as appropriate) plus separate IPV	
Safety/contra-indications	Serious AE's more frequent than individual components given together	Serious AE's no more frequent than components given together	Serious AE's less frequent than components given together	
Tolerability	Mild to moderate AE's more frequent than individual components given together	Mild to moderate AE's no more frequent than individual components given together	Mild to moderate AE's less frequent than individual components given together	
Delivery route	IM	IM	IM	
Dosing regimen	6, 10, 14 weeks of age with more booster(s) required in second year of life	6, 10, 14 weeks of age with optional booster in second year of life	6, 10, weeks of age with optional booster in second year of life	
Presentation	1 mL, dual chamber syringe	0.5 mL full liquid or liquid/lyo, pre-filled syringe, single dose vial	0.5 mL full liquid, pre-filled syringe, Uniject®, or multi dose vial, can use jet injector	
Stability storage	≤ 2 y, 2–8°C	2 y, 2–8°C	≥ 3 y, 2–8°C + 2–25°C last 1–3 mo	
Use setting	Same as EPI	Same as EPI	Same as EPI	

### Key Technical Issues in the Development of Hexavalent Vaccines

The major barriers for use of Infanrix Hexa® (GSK), in a developing-country setting are the price of the vaccine product, the requirement for reconstitution of a lyophilized form, and concerns regarding effectiveness of an aP vaccine in the developing world.<sup>7</sup> From a cost perspective, aP antigens have historically exceeded the cost of wP antigens by a factor of ten to more than 30 due to manufacturing differences and royalty costs.<sup>19</sup> As a result, the cost of wP-based hexavalent vaccines would be better suited for use in the public sector of low-resource countries. As reviewed above, hexavalent vaccines containing wP and suitable for the public market in the developing world are not likely to be available until 2018–2020 or later. The primary reasons for the long timeline for hexavalent combinations containing wP are mostly technical in nature as discussed below.

- IPV antigens are not compatible with the common vaccine preservative thimerosal, a mercury-containing compound with antibacterial activity, which causes the polio capsid to lose its antigenicity.<sup>20</sup> Thimerosal is also used by many vaccine manufacturers in the inactivation of live *B. pertussis* organisms to make wP vaccine bulks, and is carried through into the final product.<sup>21</sup> Thus a vaccine manufacturer of a hexavalent combination vaccine containing wP would have to modify its bulk process for inactivation of the pertussis bacteria. Implementation of these changes may result in significant vaccine product development issues as well as new clinical trials to prove in the clinic that the pertussis component of the new product is still effective. Moreover, there are no established serologic correlates of protection for pertussis vaccines, raising the possibility that regulatory agencies may require large, complex, and very expensive clinical efficacy trials if the production method for wP is substantially altered. Such trials may not be feasible to conduct at all as they would need to be

designed to compare the efficacy of current product and the new product, necessitating prohibitively large sample sizes.

- Thimerosal also is widely used as a vaccine preservative for multi-dose vial presentations of vaccines. Because the World Health Organization (WHO) has designated continued use of multi-dose vials as a priority,<sup>22</sup> an alternative effective and IPV-compatible vaccine preservative would be needed for IPV-containing combinations. Alternatively, effective ways of stabilization of IPV in the presence of thimerosal would have to be investigated.

- The other major key technical issue is the instability of the Hib antigen, particularly in the presence of aluminum adjuvants.<sup>10</sup> GSK's Infanrix Hexa<sup>®</sup> has the Hib component in a separate lyophilized form to avoid this issue.<sup>4</sup> It is possible to develop an all-liquid Hib-containing combination vaccine, but this requires the use of aluminum phosphate adjuvant instead of aluminum hydroxide, as well as additional formulation excipients. Hexavac<sup>®</sup> (now withdrawn from the market) and Hexyon/Hexacima/Hexaxim<sup>®</sup> are examples of all liquid hexavalent formulations containing a Hib conjugate antigen PRP-T.<sup>23</sup> Crucell, Sanofi Pasteur, SIIL, Bio E, Shantha Biotech (acquired by Sanofi Pasteur), and BBIL all produce fully liquid pentavalent combinations that contain Hib. While it is possible for developing world manufacturers to overcome the stability problems of liquid formulations of Hib, to do so requires know-how that is not currently available to the majority of smaller vaccine producers. Thus the technical challenge that a manufacturer would need to resolve would be the avoidance of different aluminum adjuvants, if the vaccine bulks going into the combination already had been on different aluminum chemistries. Mixing of incompatible adjuvants can lead to undesired physical appearances for the final product (such as extra precipitates and difficulty in re-suspension).

- The access to all components of the hexavalent vaccine is another key issue. A would-be developing country vaccine manufacturer of hexavalent combinations would need access to all of the individual antigens, which could be an issue if several companies were involved in the supply chain. A supply issue with any one of the eight monovalent bulks—Diphtheria, Tetanus, Pertussis, Hib, Hepatitis B, and IPV (types 1, 2, and 3) would interfere with the supply of the final hexavalent product. Unless the use of alternative suppliers was planned for and tested in the vaccine development process, including generating real time stability data on all of the possible alternative combinations, the vaccine bulks from different suppliers would not be inter-changeable. Moreover, the vaccine bulks would have to be available in concentrated form so that the final dose volume after formulation would still be 0.5 mL or less.

- Another important caveat to hexavalent vaccines has been the access of DCVMs to the Salk IPV component, a situation that has become more complex with the recent acquisition of the former Netherland Vaccine Institute (NVI) Salk IPV facility by SIIL.<sup>24</sup> As a result, among the DCVMs, only SIIL, Shantha (through Sanofi) and BioE (through their GSK alliance) have guaranteed access to Salk IPV before the 2015–17 timeframe, when Sabin IPV may become more widely available. Furthermore, the production of IPV vaccines containing

wild-type polio virus, is currently unfeasible in developing countries because of bio-containment requirements. As a result, the start of hexavalent vaccine formulation work by other DCVMs could be delayed by at least three to five years. While it is possible that other companies may be able to negotiate for a supply of Salk IPV from one of the four established producers, success can be achieved by partnership with any of the major IPV manufacturers. For example, Bio E and GSK recently entered into a joint venture for development of hexavalent, with GSK supplying the IPV for the Bio E pentavalent vaccine and funding 50 percent of the costs.<sup>25</sup> With regard to the Sabin IPV, although some DCVMs have access to the Sabin strains (for OPV product), further effort and time would be needed to develop an inactivated form that is compatible for combination vaccine development.

### Commercial Issues for Developing-Country Public-Sector Markets

Rough estimates using birth cohort data, Expanded Programme on Immunization (EPI) coverage surveys, and current utilization of pentavalent vaccine indicate that demand for a hexavalent vaccine for GAVI-eligible and GAVI-graduate countries alone could generate close to US\$600 million in peak sales assuming relatively low public-market prices (Table 2).

### Cost of Goods, Drivers

According to a report from Oliver Wyman, commissioned by Bill and Melinda Gates Foundation and published in 2010, the cost of aP antigens have historically exceeded the cost of wP antigens by a factor of ten to more than 30 due to manufacturing differences and royalty costs.<sup>19</sup> Current estimates put the cost of goods for aP antigens produced with traditional methods at about US\$0.25 to \$1 per dose, compared with about US\$0.10 per dose for wP, as a result of process improvements and changes in the marketplace.<sup>19</sup> Although new production methods that could significantly reduce the cost of aP antigens are being explored, the likelihood of success and timing for these potential process improvements is unclear. Therefore, while aP products would be available before 2018, their prices may not be ideal for broad adoption in the developing world.

Of all the antigens, IPV is the largest cost driver for wP-containing hexavalent vaccines. Suppliers with access to IPV produced in manufacturing plants with high capacities are better positioned to reduce production costs for this antigen. No public sources are available with Cost of Goods Sold (COGS) information for IPV.

### Pricing Benchmarks

Table 3 below includes pricing benchmarks in US dollars, for pentavalent and IPV vaccines. This is provided as a framework for relating the price of a hexavalent to the individual vaccine prices.

There is a strong desire on the part of UNICEF and others to bring the price of stand-alone IPV down to the US\$1 range. If

**Table 2.** Hexavalent vaccine market potential

Business case scenarios	Downside	Base	Upside
Key driver of value for each case	Ease of use	Ease of use, cost of administration	Two dose primary series
Product launch window	2026	2021	2016
GAVI-eligible/GAVI-graduates <sup>2</sup>			
Price/dose assumption (US\$)	\$3.50–5.00	\$2.50–4.50	\$2.25–4.25
GAVI-eligible/GAVI-graduates			
Market potential peak year (Number of subjects in millions)	20	60 <sup>3</sup>	80
GAVI-eligible/GAVI-graduates			
Peak potential sales US\$millions	\$255	\$630 <sup>1,4</sup>	\$520
GAVI-eligible/GAVI-graduates			

<sup>1</sup>60M subjects (based on pentavalent demand forecast) receiving 3 doses of hexavalent vaccine with an assumed mid-price of US\$3.50 per dose.<sup>2</sup> Seventy-three countries.<sup>3</sup> Based on pentavalent demand forecast estimates for GAVI and GAVI Graduate countries. Assumes a subset of countries that adopted a pentavalent vaccine would switch to a hexavalent.<sup>4</sup> (birth cohort × mid-point price × # of doses).

**Table 3.** Published pricing benchmarks for pentavalent and IPV vaccines (US\$) per dose

Vaccine	Low	High
Single dose pentavalent	2.25	3.20
10- dose pentavalent	1.75	2.11
Single dose IPV	3.27	4.14
10-dose IPV	2.25	2.70

Pentavalent prices shown from (2011/UNICEF).<sup>26</sup> IPV prices shown for vials from November 2012 IPV tender results.<sup>27</sup> Prices quoted in Euros were converted to US dollars based on the approximate exchange rate on 2/16/2013.

this was to occur, the lower end of a hypothetical price range for a hexavalent vaccine could be further reduced, to nearer US\$2.75, by the time the hexavalent vaccines became available.

### Relevance of Product-Development Efforts to GAVI Markets

In order to assess the relevance of hexavalent product development to GAVI markets, it is necessary to evaluate potential product availability scenarios in the context of the Global Polio Eradication Initiative (GPEI) Strategic Plan timeline for the IPV introduction, and for the period of the tOPV-bOPV switch and longer-term IPV uptake after OPV cessation.<sup>28</sup> Based on the technical assessment in this review, only aP-based hexavalent products from multinational pharmaceutical companies are likely to be available by 2018, within the OPV-cessation timeline in the GPEI Strategic Plan/Budget. SIIILs, Shantha's and BioE's wP-based hexavalent vaccines could be available by 2020, if no unforeseen difficulties occur in development and clinical studies. Therefore, in a scenario where bOPV cessation occurs before 2018, combinations with IPV and wP are not likely to play a role in the first few years. The following questions then arise: what role can a hexavalent vaccine realistically play in GAVI markets in the context of the polio endgame? If the expectation is to have eventual widespread adoption of a hexavalent vaccine in the developing world as part of a post-OPV cessation strategy,

in what time frame could this realistically become a strategically sound option? Our analysis indicates that an IPV-based hexavalent vaccine could be relied upon as the linchpin of a post-OPV cessation strategy for the developing world under the following inter-dependent conditions:

1. If the hexavalent vaccine product is available at a sufficiently low price: an obvious condition for GAVI markets is that the product is offered at a price that is acceptable to GAVI countries. From a COGS perspective, this is more likely to be achieved after 2020 with multi-dose product presentations, with products that include wP rather than aP antigens, and by suppliers with access to IPV produced in manufacturing plants with high capacities. From an implementation perspective, however, factors such as wastage rates for single-dose vs. multi-dose presentations should also be considered.

2. If the hexavalent vaccine market has multiple, highly reliable suppliers with overlapping capacities: given the complexity of manufacturing and sourcing of vaccine components for a hexavalent vaccine, this condition would allow for increased reliability of vaccine supply. This condition does not presently exist and may also not exist by 2020. The risk and potential impact of a stock-out in the context of polio eradication efforts should be evaluated upfront and should be proactively managed.

### Reliability of Combination Vaccines Supply

A UNICEF presentation from January 2012 describes the pentavalent market supplier base as “volatile.”<sup>29</sup> This assessment was made more than ten years after UNICEF procured the first doses of pentavalent vaccine in 2001. Between 2010 and 2011, two of the pentavalent vaccine products (Shan-5 from Shantha Biotechnics and Easy-5 from Panacea) were removed from the WHO's list of prequalified vaccines. Even if a manufacturer can obtain licensure and prequalification for a hexavalent vaccine, the recent de-listings raise the question of manufacturing reliability for these complex products.

Based on the technical assessment in this review, there is not just one complex step in the manufacturing processes required for the production of a hexavalent vaccine. Instead, potential issues could arise with any one of the vaccine components—from

**Table 4.** Hexavalent demand and supply

Hexavalent Demand (Mil doses)	2018	2020	2025 and beyond
Maximum demand scenario	380	380	380
GAVI demand scenario <sup>y</sup>	230	235	240
<b>Estimated Total Hexavalent Capacity (Mil doses)</b>	<b>130–170</b>	<b>280–320</b>	<b>500–770</b>
<b>Total Hexavalent Capacity Potentially Targeted to GAVI-markets</b>	<b>0</b>	<b>130–170</b>	<b>300–570</b>

Assumes developing country IPV supply and technical issues resolved to allow for 2025 launch of multiple suppliers. Assumes manufacturer's pentavalent capacity switches to hexavalent. <sup>y</sup>Based on pentavalent demand within the original 73 GAVI-eligible countries.<sup>29,30</sup>

an antigen sourcing standpoint as well as from a manufacturing and quality perspective. For a manufacturer with average lot passing rates for the 8 individual components of 90 percent each, the probability of manufacturing a hexavalent vaccine with all passing lots is only 43 percent (0.90<sup>8</sup>), considering the cumulative pass rates for D, T, P, HepB, Hib, and the three IPV serotypes. To ensure reliable supply, average lot-passing rates for the individual release assays would need to be much higher, in the range of 95 to 98% (cumulative probability 66–85%) or greater.

Identifying a back-up strategy for potential supply failures in advance is critical in a scenario where a hexavalent vaccine is relied upon as the linchpin of a post-eradication strategy and is expected to be adopted widely, replacing existing combination vaccines. The impact of having a gap in supply is not as high in a scenario where hexavalent vaccines are used more selectively.

The **Table 4** below compares potential supply with demand. One demand scenario assumes widespread adoption of hexavalent vaccines (three doses of IPV). Another scenario displays the forecasted demand for GAVI-eligible and GAVI-graduating countries, based on pentavalent vaccine demand forecasts.

Although potential manufacturing capacity for wP-based hexavalent vaccines could reach 170 million doses in 2020, only a limited number of doses would have a comparably priced back-up hexavalent in the event that one supplier experiences product manufacturing issues. If overlapping capacities are not achievable by 2020, another potential back-up strategy in the event of a hexavalent stock-out could include planning ahead to revert to pentavalent + IPV, while hexavalent manufacturing issues are being resolved. This approach is only viable if pentavalent vaccine continues to be used in some markets after hexavalent vaccine becomes available. This scenario is more likely in the situation of an uncertain supply of hexavalent.

### Potential Alternatives to Hexavalent Vaccines in Public-Sector Markets of Low-Resource Countries

It is expected that in 2013, most GAVI-eligible countries will have introduced pentavalent vaccines, the majority by procurement through UNICEF.<sup>29</sup> Given the widespread adoption of pentavalent vaccines in GAVI markets, the most feasible alternative approach to a hexavalent vaccine is a “5 plus 1” strategy with a liquid IPV to complement DTwP-Hib-HBV. This is the current default and is available now as liquid pentavalent vaccines already exist and do not need further development. There are other advantages as well. Both vaccines can be multi-dose as the incompatible preservatives are separated and there would be

freedom to down-dose or use an intradermal injection for the IPV. This approach is under consideration by WHO-SAGE for recommendation and can be implemented relatively quickly. In the long-term there could be lower development costs, and faster uptake in new markets. An evaluation of three potential “5 + 1” sub-strategies is as follows:

1. Pentavalent vaccine + stand-alone full-dose IPV delivered intra-muscularly: The cost-of-goods difference between the hexavalent vaccine strategy and this strategy is modest, when considering ten-dose vials, but more significant when comparing single-dose vial presentations.

2. Pentavalent vaccine + stand-alone IPV delivered intradermally (ID): ID delivery of IPV could allow for a reduction in the amount of vaccine antigen required to induce a protective immune response. Based on feasibility studies conducted recently in Oman<sup>31</sup> and Cuba,<sup>32,33</sup> among others, it appears that delivering one fifth of the usual dose of IPV intradermally could be a successful strategy. In these two studies, inactivated poliovirus vaccine was administered ID using a needle-free device (Biojector 2000, Bioject).

3. Pentavalent vaccine + stand-alone alum-adsorbed IPV: This strategy could allow for a reduction in the amount of vaccine antigen required to induce a protective immune response. This option will take longer to develop and appears to be feasible in the three- to four-year time frame. Because of the minimal cost of aluminum adjuvants, the modeled vaccine costs for this option are similar to the second strategy, without the additional cost of the needle-free intradermal injection device.

Alternative paths to introducing IPV into routine immunization, e.g., in non-GAVI-eligible countries, would be to use multiple combinations with fewer antigens, which would be easier to develop and have a much higher probability of success, or development of stand-alone IPV, potentially with dose sparing through use of adjuvants. Of all the antigens, IPV is the most expensive, and therefore is the largest cost driver for wP-containing hexavalent vaccines. The cost savings that could be achieved by reducing the dose of IPV to one fifth in these stand-alone presentations would be difficult to match with a hexavalent formulation, at least in the short to medium term. In the long-term, other strategies, technologies, or market shifts could change the landscape. A 5 + 1 strategy could also provide an opportunity to add new adjuvants to the IPV to enhance its immunogenicity and lower the dose, although this might be harder to implement in pediatric populations. The probability of success of this approach would need to be balanced against the difficulty of introducing new adjuvanted vaccines for infant use.

In conclusion, it is unlikely that a hexavalent vaccine can be commercially competitive with a pentavalent vaccine co-administered with a reduced-dose IPV vaccine such as an adjuvanted formulation or one given by the intradermal (ID) route. This results not only from lower utilization of the relatively more expensive IPV component, but also from lower risk of lot failures in testing, and greater diversity of potential suppliers for the pentavalent vaccine worldwide than for the hexavalent. On the plus side, use of IPV-based hexavalent could reasonably be expected to reduce costs of administration (disposables, packaging, and cold chain space) and improve patient compliance. Because of cost considerations, hexavalent vaccine combinations are more likely to be commercially successful in private markets where constraints on vaccine cost are less severe. It should be noted that the COGS for IPV are subject to change as market volume increases from its present low level, and economies of scale are realized.

### Alternative Combinations

In the event that pentavalent vaccines cease to be the combination of choice in lower-income markets due to supply or funding constraints in the future, other options could also be considered, including a HBV-Hib-IPV liquid formulation to complement existing DTwP, a Hib-IPV liquid or lyophilized formulation to complement a DTwP-HBV, a HBV-IPV to complement a DTwP-Hib and lyophilized IPV to complement DTwP-Hib-HBV. These approaches may be adopted by manufacturers seeking a faster path to market by producing less complex combinations. In addition, meningococcal or pneumococcal conjugates optionally may be added to any of the above vaccine combinations in theory, however given the complexity of adding a four component (meningococcal vaccine) or 10–13 components (pneumococcal vaccine), such products will be very challenging technically. Each of these strategies would be a potentially time-consuming independent vaccine development program, which carries potential benefits and challenges and could require additional clinical studies. The COGS implications of these alternative strategies have not been assessed in this review.

### Conclusions

While combination vaccines can help to simplify complex pediatric immunization schedules, improve compliance, and reduce

handling costs of immunization programs, their development for new applications is limited by their technical complexity. High technical complexity increases production costs and therefore many manufacturers target them as premium products. For this reason, the hexavalent vaccines that are most likely to be available now or in the very near future are primarily intended and priced for private markets. Hexavalent combinations intended for public markets are likely to take significantly longer time to develop, primarily due to the need to re-engineer the wP component to make it compatible with IPV. The acquisition of one of the two independent makers of IPV by a leading developing world vaccine company (SIIL) will limit the availability of Salk IPV to other DCVMs, with the result that only SIIL, Shantha (with access to Sanofi IPV), and BioE (with access to GSK IPV) have a realistic chance to produce combinations containing IPV in the intermediate term (between 2016 and 2020). Because other developing world producers will likely have to wait until Sabin IPV or other alternatives become available (which may not be until after 2015), alternative hexavalent vaccines for the public market likely would not be available until nearer 2025. An interim approach to make IPV more available at low cost between now and 2020 could be the use of stand-alone IPV with one of several dose-sparing strategies, or of combinations containing IPV but blended with fewer additional vaccine components. Although hexavalent vaccines may reach public markets at reasonable prices during the post-polio eradication period, they are much less likely to become the exclusive form of pediatric vaccine unless their inherent technical and pricing disadvantages can be successfully resolved.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### Acknowledgments

The authors thank Lisa Anderson and Eileen Quinn for expert editorial assistance and Harkesh Dabas from the Clinton Health Access Initiative (CHAI) for helpful discussions. Supported by a grant from the Bill and Melinda Gates Foundation to PATH Vaccine Solutions, Inc.

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