

The supply landscape and economics of IPV-containing combination vaccines: Key findings

Commissioned by the Bill & Melinda Gates Foundation

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Project context and objectives

In fall 2008, the Bill & Melinda Gates Foundation (BMGF), in close discussion with the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF), commissioned Oliver Wyman (OW) to assess potential supply and demand for inactivated polio vaccine (IPV) in the impending post-polio eradication era, with a focus on supply strategy implications for developing world populations. One of the assessment's findings was that there was a need for further guidance on the use of stand-alone IPV versus combination vaccines containing IPV, as well as additional evidence about IPV-containing combinations. The current study was designed to fill part of that need, focusing on the supply of IPV-containing combination vaccines, primarily for the low-income public sector market. It can be used along with the 2008 assessment of stand-alone IPV to create an integrated supply picture, though there is still need for an assessment of demand of stand-alone versus combination vaccines. With that as context, this assessment had two objectives:

1. Develop a fact base on IPV-containing combination vaccines, including current and potential economics and supply landscape
2. Identify the implications of these facts for low-income countries, policy bodies, and donors

The key findings of the assessment, summarized in this document, are intended to assist in global, regional, and country-level decisions on policy. The findings have been, or will be, discussed with the Strategic Advisory Group of Experts (SAGE) Working Group on IPV, the SAGE Working Group on Pertussis, the Global Polio Eradication Initiative (GPEI), UNICEF, all major vaccine manufacturers, and BMGF.

Approach and methodology

The assessment was conducted by OW from June to September 2009 and consisted of the three activities summarized below. Because low-income countries are increasingly turning to pentavalent vaccines (i.e., DTwP-HepB-Hib), and because it seemed reasonable to assume they would prefer to add IPV antigen to that combination rather than replace one of the combination's antigens with IPV, the decision was made to focus on IPV-containing hexavalent vaccines (i.e., DTP-HepB-IPV-Hib).

Activity 1: Assess current and potential supply landscape. OW identified current manufacturers of IPV-containing combination vaccines and manufacturers with the greatest potential to develop them. Ten companies were selected in all, representing a large majority of the total number. OW held discussions with each manufacturer covering their current and/or potential programs for developing IPV-containing hexavalent vaccines, their manufacturing capacities, and their development and commercialization timelines.

Activity 2: Evaluate manufacturing economics. In parallel with Activity 1, OW conducted extensive primary and secondary research to determine which antigens contribute most to the overall cost of combination vaccines. For more costly antigens, OW developed detailed economic models of upstream and downstream production processes, in order to understand the cost impact of various

manufacturing configurations. A similar model was developed for formulation and filling (including lyophilization). Available market pricing data were used to check model outputs as well as to estimate the cost of some antigens.

Activity 3: Synthesize findings and identify implications. OW identified key implications from the research and analysis conducted as part of Activities 1 and 2 and shared them with project sponsors and contributors for feedback and commentary.

Key findings

Finding #1 – While IPV-containing combination vaccine is in limited supply globally today, several manufacturers are developing, or are interested in developing, new hexavalent vaccines for public-sector use in low-income countries.

The existing IPV-containing combination supply landscape currently focuses on high- and middle-income markets. Two manufacturers offer advanced IPV-containing combinations to the global market today: (1) GlaxoSmithKline (GSK), which produces the only licensed IPV-containing hexavalent vaccine (DTaP-HepB-IPV-Hib[lyo]) as well as two pentavalent vaccines (DTaP-IPV-Hib[lyo]), and (2) Sanofi-Pasteur (Sanofi), with two IPV-containing pentavalent vaccines (DTaP-IPV-Hib[lyo]). Sanofi currently has a hexavalent vaccine in Phase II clinical trials, which means the product will not reach the market for several years. GSK's and Sanofi's products are primarily sold into high-income countries, though demand is rapidly increasing in middle-income countries. As a result, both manufacturers are making investments to meet increasing demand. These existing products have been designed and are produced in a manner that targets high- and middle-income countries and thus will remain primarily appropriate and destined for those markets. Low-income markets will require new products specifically designed for their needs; these could be developed by existing or new manufacturers of IPV-containing vaccines.

Several manufacturers are developing, or are interested in developing, new IPV-containing hexavalent vaccines for low-income countries. The assessment of the future supply landscape focused on three manufacturer segments, whose existing knowledge, capabilities, and lines of business made them the most logical potential suppliers for low-income countries. (See Exhibit A.) In conversations with a sample of ten manufacturers across these segments, four said they are developing, or are interested in developing, new hexavalent vaccines for low-income countries. Three others said they are still evaluating the business case for IPV-containing hexavalent vaccines and might initiate development at a later date.

Manufacturers are developing, or are interested in developing, both new wP-based and aP-based hexavalent vaccines. Existing IPV-containing combinations all contain acellular pertussis antigen (aP)—mainly because high-income countries prefer lower-reactogenic vaccines and are willing to pay more for them. IPV-containing combinations based on whole-cell pertussis antigen (wP) did exist in the past, but were withdrawn from the market because of changing customer preferences

Exhibit A: Potential future IPV-containing hexavalent vaccine manufacturers (sample)

Current IPV-containing combination vaccine suppliers	Other combination vaccine suppliers	Other IPV vaccine suppliers
<ul style="list-style-type: none"> ▪ GSK (BE) ▪ Sanofi-Pasteur (FR/US) 	<ul style="list-style-type: none"> ▪ Current pentavalent (DTwP-HepB-Hib) manufacturers <ul style="list-style-type: none"> – Crucell (NL) – Panacea Biotech (IN) – Shantha Biotech (IN) – Serum Institute of India (IN) ▪ Manufacturers with pentavalents in development <ul style="list-style-type: none"> – Bharat Biotech (IN) – BiologicalE (IN) 	<ul style="list-style-type: none"> ▪ Current manufacturers <ul style="list-style-type: none"> – Netherlands Vaccine Institute (NL) – Staten Serum Institute (DE) ▪ Manufacturers with IPV in development <ul style="list-style-type: none"> – Kunming Institute (CN) – Takeda (JP)

and the technical challenges associated with maintaining the immunogenicity of IPV in the presence of thimerosal-inactivated wP. That said, the four manufacturers currently developing or interested in developing hexavalent vaccines for low-income countries are focused on wP-based combinations. They believe that low-income countries are already familiar with wP and will want to keep the price of the vaccine as low as possible, and will thus prefer wP-based combinations, at least in the short to medium term. To overcome the technical challenges associated with IPV-wP combinations, these manufacturers plan to utilize alternative wP inactivation methods (such as heat-only or heat plus formaldehyde). Several manufacturers are also developing or interested in developing new aP-based hexavalents. At first these products would target middle-income countries and the private market in low-income countries. But depending on their nature and cost structure, these products could eventually serve both private and public markets in low-income countries.

If they initiate development and are successful, some manufacturers believe their new hexavalent vaccines could be available between 2012 and 2014. Two potential manufacturers of hexavalent vaccines for low-income countries say they are aiming at regulatory approval and market entry by 2013–2014. Both envision lengthy product development activities and/or extensive clinical trial requirements. In comparison, two other potential manufacturers optimistically target regulatory approval by early 2012—a rapid, compressed development program. Based on recent communication, one manufacturer will begin a Phase III trial by the summer of 2010 and is targeting licensure in the fourth quarter of 2011. The second manufacturer anticipated its thimerosal-free trivalent vaccine (DTwP) would receive regulatory approval by the end of 2009.¹ This manufacturer believed this approval would enable its IPV-containing hexavalent vaccine to proceed straight into Phase III, possibly as soon as early 2010. This potential availability of new products with a cost structure suitable for low-income countries could enable at least some low-income countries to transition their routine immunization programs from oral polio vaccine (OPV) to hexavalent vaccine by the scheduled date for OPV cessation (2016–2017, under current timelines).

¹ Manufacturer-provided information as of summer 2009. No further updates were available at the time this report was released.

If fully realized, the potential manufacturing capacity of new, low-cost hexavalent vaccines could be sufficient to provide three doses of the vaccine to the annual birth cohort of low-income countries. All told, the four manufacturers developing or interested in developing hexavalent vaccine for low-income countries could bring online manufacturing capacity equivalent to 280 million doses a year by 2014. If all three manufacturers still evaluating their business case were also to enter, capacity would increase by at least another 50 million doses. It is important to note that a significant portion of the additional doses would come from bulk and fill/finish facilities used today to manufacture pentavalent vaccine and would likely reduce pentavalent capacity. Setting aside questions of affordability, this level of capacity would be more than enough to provide three doses of hexavalent vaccine to each of the approximately 70 million children born annually in low-income countries.² Achieving this level of capacity, however, is contingent on many factors—including manufacturers' access to IPV antigen—discussed later in this paper.

Finding #2 - Manufacturers are pursuing several developments that if successful, would lower the ongoing manufacturing cost of IPV-containing hexavalent vaccines potentially available to low-income countries

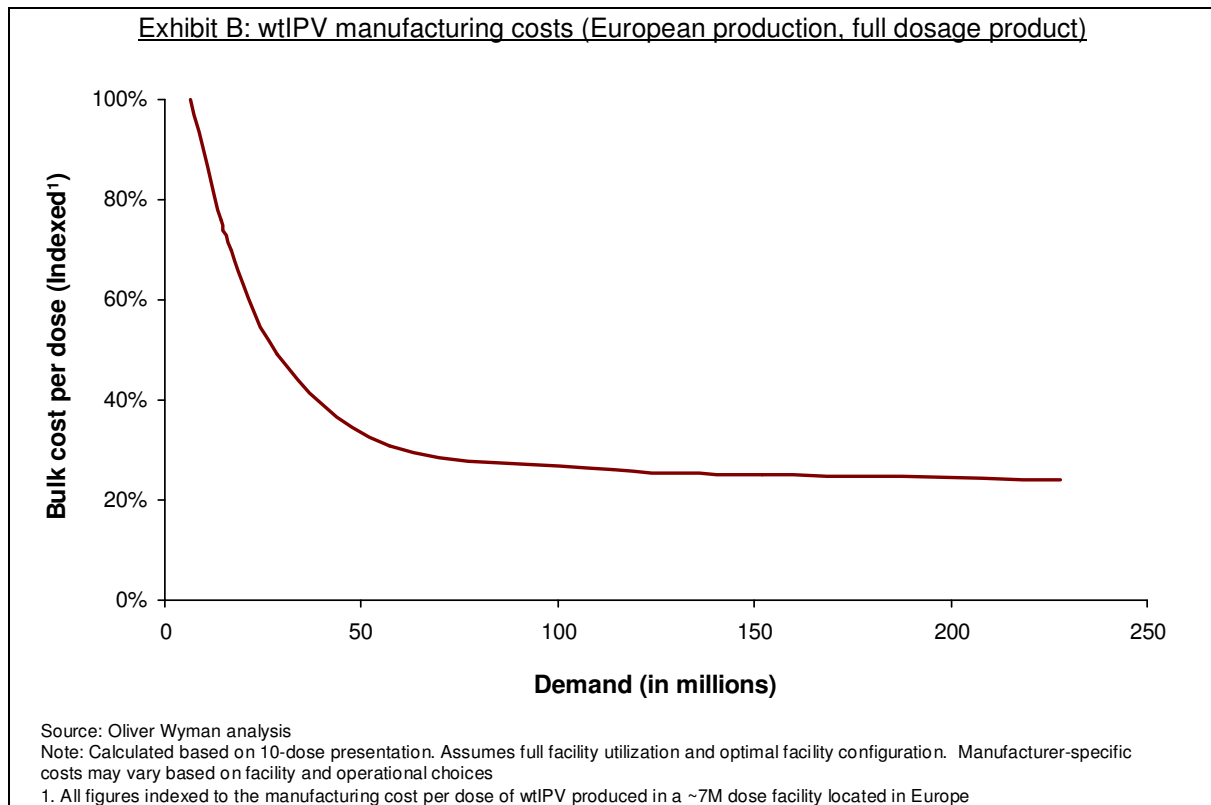
Manufacturer activity is focused on IPV, acellular pertussis, and haemophilus influenza type B conjugate vaccines. Manufacturers are collectively pursuing a range of developments around IPV, acellular pertussis, and haemophilus influenza type B (Hib) conjugate vaccines. These antigens have historically been very expensive to manufacture and have contributed significantly to the overall cost of combination vaccines. The new developments include changes to the scale of manufacturing facilities, the efficiency of production processes, antigen dosage, and product formulation. Manufacturers vary in the scope and approach of their development projects, with some undertaking a broad program of work across several antigens and others focused on just one. This situation could lead to a fairly wide difference in what it costs different manufacturers to produce the same antigen, particularly given other differences, for example, location of production.

IPV manufacturing costs could come down for some manufacturers through increases in scale and/or reductions in dosage. As outlined in a previous report,³ three major developments have the potential to lower ongoing manufacturing costs for IPV.

1. Because IPV requires a high-fixed-cost production infrastructure, its costs are very sensitive to scale. (See exhibit B.) One manufacturer has built high-scale facilities to manufacture wtIPV (wild-type or Salk IPV) with the expectation of increased demand. If the average scale of manufacturing increases and facilities are highly utilized, the cost of manufacturing wtIPV could decline by 30 to 50 percent, reaching the range of \$0.50 to \$2.00 per dose.
2. Some manufacturers are exploring the use of adjuvants to reduce the amount of wtIPV required per dose, increasing effective capacity and reducing cost. Historical data and trials indicate that antigen requirements could be reduced by 50 percent to 90 percent per dose,

² Population estimate for 2014 from UNPD; low-income country designation based on World Bank classifications.

³ More detail is available in the report entitled "Global Post-eradication IPV Supply and Demand Assessment: Integrated Findings" posted on the Global Polio Eradication Initiative Web site (<http://www.polioeradication.org/content/general/March 2009 OW IPV Effort Report.pdf>).



although the high end of the range has been achieved only with stand-alone wtIPV, not wtIPV-containing combination vaccines. If the approach succeeds, the combination of adjuvants and full utilization of manufacturing facilities could reduce wtIPV manufacturing costs below \$0.50 per dose while expanding effective manufacturing capacity. Some research groups are exploring the use of intradermal administration of IPV to reduce dosage, although this is only applicable to stand-alone IPV.

3. Manufacturers and research institutes continue to develop alternative IPV technologies with the goal of eventually enabling low-cost manufacturing of IPV in developing countries. The use of Sabin IPV (sIPV) is a particular area of focus, with encouraging results recently reported. There are still uncertainties, however, about required dosage and the likely scale of production, which lead to uncertainties about the potential cost of manufacturing. At similar scale in a location with low labor costs, sIPV could cost more or less to manufacture than wtIPV, depending on the dosage of sIPV required and whether adjuvants are used to reduce wtIPV content.

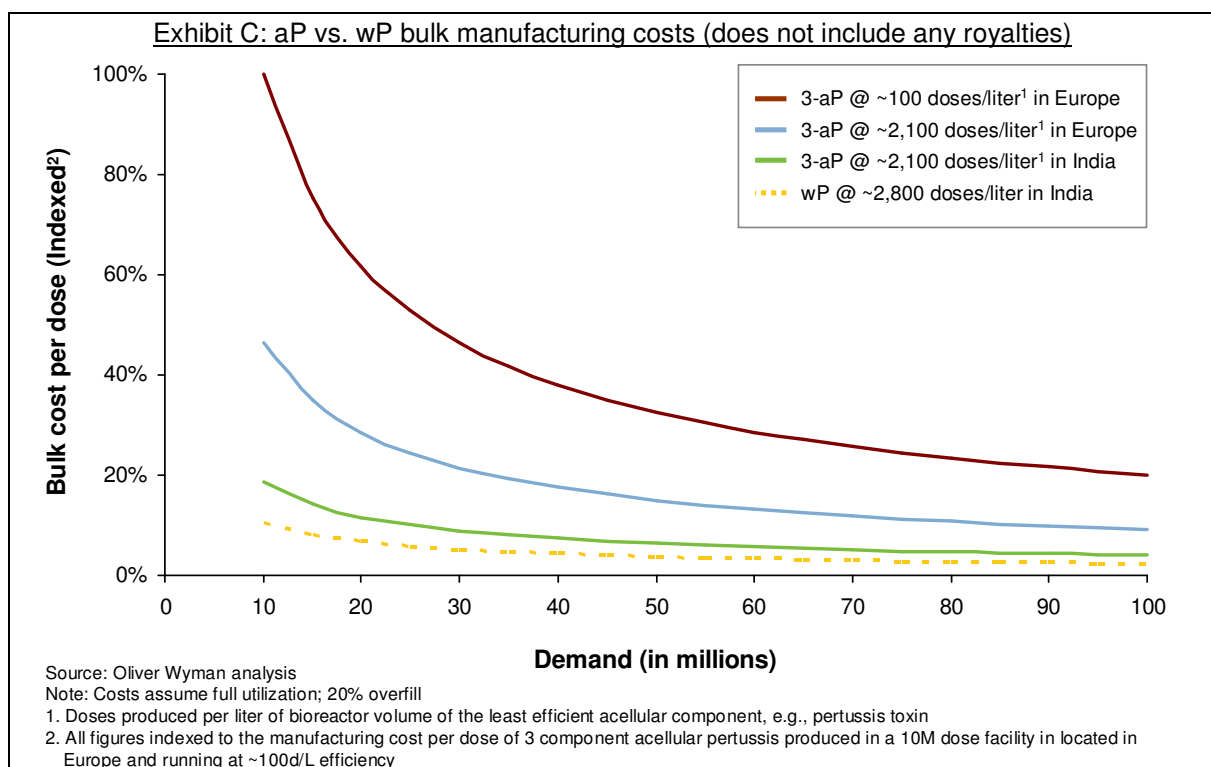
All told, future IPV manufacturing costs could range, manufacturer to manufacturer, from below \$0.50 to well over \$2.00 per dose, as a result of each manufacturer’s unique configuration of products and production processes.

The cost difference between acellular pertussis and whole-cell pertussis could narrow considerably as some manufacturers improve manufacturing efficiency and patents expire.

The underlying cost of acellular pertussis (aP) has historically exceeded that of whole-cell pertussis (wP) by a factor of 10 to more than 30 due to inherent differences in the manufacturing efficiency,

differences in the scale of production, and royalties paid to holders of intellectual property. Today, however, some manufacturers are taking steps to improve the efficiency of producing aP. Some are seeking to further optimize “traditional” production methods, while others are in the early stage of exploring entirely new methods—for example, using genetically-modified *B. pertussis* to improve toxin expression and potency or using *E. coli* or baculovirus systems to express pertactin/69k. As a result, some manufacturers could reduce the cost of producing aP by 50 to 80 percent or more below current levels, reaching approximately \$0.25 per dose, assuming (1) the use of high-efficiency production methods at medium to high scale and (2) the absence of royalties, which should disappear as patents expire. (See Exhibit C.) For these manufacturers the cost differential between aP and wP would narrow considerably.

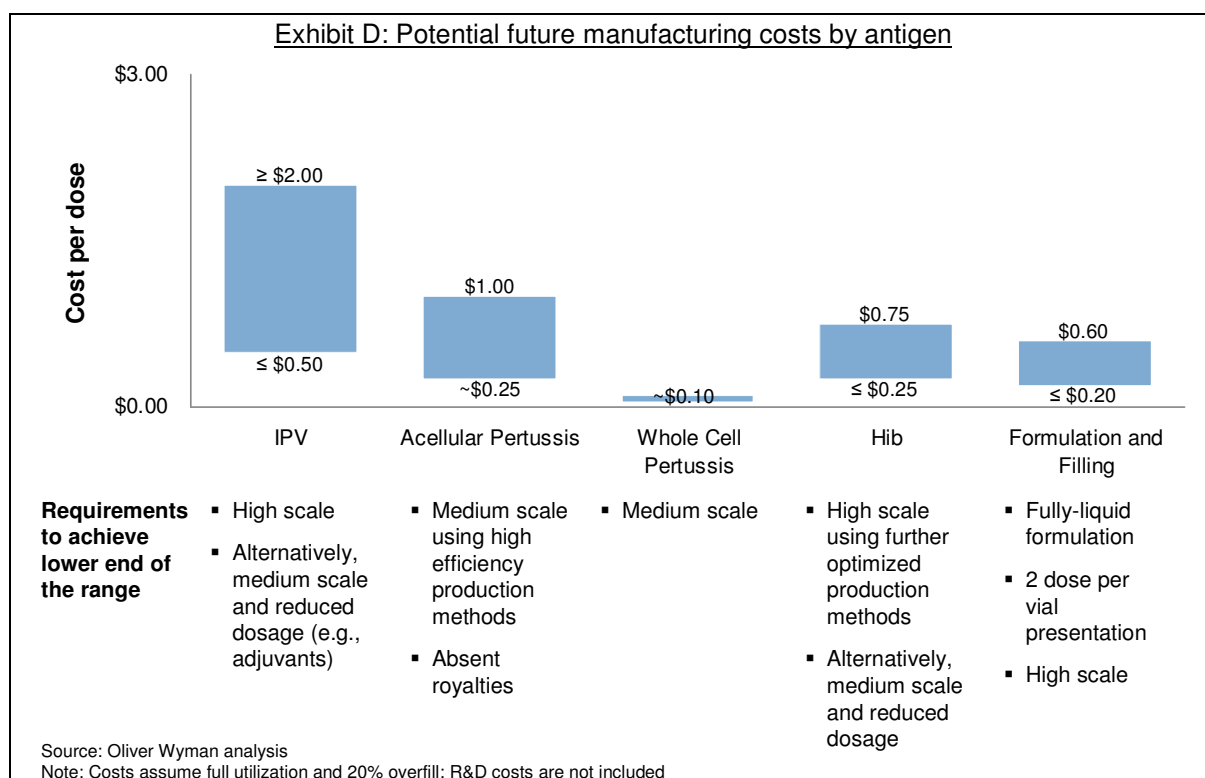
Hib costs for many manufacturers decreased with their move to fully liquid formulations; manufacturing cost for some manufacturers could further decrease with process improvements. All manufacturers consulted either have introduced a liquid Hib formulation or are in the process of developing one. This has a significant impact on cost. In the past, liquid Hib formulations had stability problems, leading manufacturers to lyophilize the vaccine—and adding \$0.30 to \$0.70 of costs per dose, depending on the presentation and the scale of the form/fill operation. Since then, several successful liquid formulations have been developed, eliminating the cost of lyophilization and creating programmatic benefits (e.g., reducing the number of vials to move in the cold chain). Several Hib manufacturers are already operating fairly efficient processes at high scale. A few are pursuing additional process improvements as well as improvements in conjugation chemistry (e.g., further optimization of cyanylating chemistries, application of hydrazone chemistries). Together these changes could reduce ongoing manufacturing cost by 15 to 20 percent. One



manufacturer has developed a reduced-dosage formulation (2.5 µg PRP, 5-10 µg carrier protein), which represents a reduction of approximately 75 percent from the antigen content of other approved Hib products. All told, depending on the manufacturer’s unique product and production process configuration, the future cost of manufacturing Hib could range from less than \$0.25 to nearly \$0.75 per dose.

Developments being pursued by some manufacturers could substantially decrease the overall cost of manufacturing IPV-containing combination vaccine, especially if a number of these developments are combined in a single product. If manufacturers’ ongoing or planned development activities are successful, the total ongoing cost of manufacturing IPV-containing combination vaccine could decrease by 25 to 60 percent or more, eventually reaching a range of \$1.00 to \$4.00 per dose. Such developments could also bring the cost of aP-based vaccines in line with those of wP-based vaccines. (All this assumes that vaccines are in vial-based presentation and production facilities fully utilized.) The potential range of manufacturing costs for several important antigens is summarized in Exhibit D.

With such developments, the price of IPV-containing combination vaccine would be expected to decline, although not proportionately to cost and not necessarily to the “break-even” price of pentavalent vaccine plus stand-alone IPV due to factors such as development costs, capital investments, etc. While the savings described above are significant, it is important to note that ongoing manufacturing costs are only one input in pricing. For example, a significant investment is required to enter a new market, realize savings in ongoing costs, or boost capacity. One manufacturer indicated that to develop a hexavalent vaccine and build production capacity of 50 million doses a



year could cost more than \$100 million—on top of what the manufacturer has already spent to develop trivalent, quadrivalent, and pentavalent combination vaccines. A useful way to look at the potential price of an IPV-containing hexavalent vaccine is to compare it to the price of a similar antigen load delivered as two vaccines—that is, stand-alone IPV plus pentavalent combination vaccine (DTwP-HepB-Hib). Our 2008 analysis, which considered UNICEF vaccine prices⁴ plus estimates of the cost associated with vaccine distribution and administration, found that a hexavalent vaccine priced at \$6.75 per dose would be economically equivalent to stand-alone IPV plus pentavalent.⁵ But as the prices of pentavalent combination vaccine and stand-alone IPV decrease, the economic equivalence or “break-even” price for a hexavalent vaccine decreases as well. The 2008 analysis considered projections that the price of stand-alone IPV could approach \$1.30 and pentavalent vaccine \$1.85 per dose and estimated that the hexavalent break-even price could approach \$3.00 per dose—or even lower if dosage-sparing approaches such as adjuvants, intradermal administration, or two dose schedule are successfully developed for stand-alone IPV dosage. Given the manufacturing cost range described earlier—\$1.00 to \$4.00—it seems possible for a manufacturer to offer a hexavalent vaccine priced at or below this break-even point, depending on development costs, capital investments, and other factors. It is important to note that this comparison is strictly economic. It does not consider the potential non-economic, programmatic, and other benefits of a hexavalent vaccine, as well as the additional potential benefits of an acellular pertussis component.

Finding #3 – The potential manufacturing developments have varying degrees of technical risk, which could substantially affect the availability and affordability of hexavalent vaccines for low-income countries

There are two primary risks in developing new vaccines. First, manufacturers’ efforts around some or all of these potential developments could fail outright, leading to a reduction in the number of products in the market and negatively affecting the supply landscape. Second, manufacturers’ efforts could fall short of anticipated levels of scale, efficiency, dosage, etc., impairing their cost-effectiveness. Both types of risk need to be carefully managed.

Degree of risk varies by manufacturer, antigen, and approach taken. Some developments rely more on the optimization of existing processes or facilities and should have a lower degree of risk. The regulatory requirements should also present relatively low risk. For example, some IPV facilities are already configured for fermenter upgrades, making it straightforward to make planned increases in facility scale. The degree of risk does increase when considering some of the other potential developments. For example, manufacturers have failed in past attempts to develop liquid Hib formulations, particularly when attempting to combine a liquid Hib component with the other antigens

⁴ 2006 UNICEF tenders (2-dose penta: \$3.50 and 1-dose IPV: \$3.00) converted at 1.30 USD/EUR [avg. 2006]).

⁵ More detail is available in the report entitled “Global Post-eradication IPV Supply and Demand Assessment: Integrated Findings” posted on the Global Polio Eradication Initiative website (<http://www.polioeradication.org/content/general/March 2009 OW IPV Effort Report.pdf>).

found in combination vaccines. As another example, some manufacturers are pursuing novel approaches to aP production, which rely on new expression systems (e.g., baculovirus).

Finding #4 – Manufacturers currently without captive IPV capacity may be unable to gain sufficient and cost-effective access to the antigen, which could also impact the availability and affordability of hexavalent vaccines for low-income countries

Most potential hexavalent manufacturers cannot produce their own wtIPV locally. The potential changes to the supply landscape and economics of IPV-containing hexavalent vaccines detailed above can have a significant impact on low-income countries. But to realize this potential, manufacturers need access to IPV. Manufacturers that currently produce IPV-containing combination vaccine have all built their own captive wtIPV capacity and intend to leverage it to support future hexavalent vaccine programs. In contrast, other potential manufacturers of hexavalent vaccine—most of them based in developing countries—lack such capacity and will find it difficult to develop. Post-eradication, wtIPV production would not be feasible in developing countries, given the high transmissibility of wild polio viruses in such settings in the event of a virus reintroduction from the production facility.⁶ Would-be manufacturers in these countries need to secure sufficient and cost-effective supplies of antigen through alternative means. If they cannot, the amount of hexavalent vaccine capacity potentially available for low-income countries would decrease from more than 280 million doses to approximately 100 million.

Potential manufacturers are considering three IPV access strategies and their trade-offs and risks; two of the strategies would involve wild-type IPV. One option is for manufacturers to purchase IPV from existing manufacturers. In fact, some potential manufacturers already have wtIPV bulk supply agreements. But the total wtIPV capacity currently available through existing agreements is insufficient for them to achieve their full envisioned hexavalent vaccine capacity. While other, larger sources of wtIPV bulk capacity exist, these sources have their own hexavalent vaccine programs, making them less likely to be interested in supplying wtIPV bulk to potential competitors. The long-term viability of this access strategy will also depend on the underlying cost structure of the bulk supplier (e.g., scale) and the margin or mark-up applied. The current supply agreements of many manufacturers will prevent them from achieving the low end of their potential hexavalent manufacturing cost range. A second option: Potential manufacturers could build or buy their own wtIPV capacity in a different geography. For example, GAP-III policy would allow for new wtIPV capacity to be built in cold or temperate climates with very high routine IPV coverage rates. The viability of this access strategy will depend on the manufacturers' ability to manage the additional operational and managerial complexity of having multiple production sites as well as their access to capital to build the required infrastructure. Two manufacturers are evaluating building facilities in Europe, but these evaluations are in the very early stages.

⁶ Further detail and rationale is available in the Global Action Plan III (GAP-III), which outlines post-eradication polio virus containment guidelines. GAP-III defines primary, secondary and tertiary safeguards for IPV production, all of which would apply to wtIPV production in the VAPP/VDPV elimination phase.

The third strategy would involve Sabin IPV, which would allow bulk IPV production in low-income settings, though substantial development challenges remain. Potential manufacturers could build their own local capacity using sIPV or another alternative technology. For such an option to be viable, one or more of these alternative IPV technologies needs to be fully commercialized in time to meet demand (i.e., by the post-eradication era) and be competitive in cost with wtIPV. As outlined in finding #2, the manufacturing cost of sIPV could be above or below that of wtIPV depending on the scale of production and required dosage. Currently, only one of the potential hexavalent manufacturers consulted has an active sIPV program, with the others instead focusing on wtIPV-based combinations. If sIPV is to be used, manufacturers have to complete internal development quickly, or more likely, in-license it or receive a tech transfer from another manufacturer, such as the WHO-NVI collaborative project established for this purpose.

Finding #5 – There is a risk that future hexavalent vaccine and/or stand-alone IPV supply will be mismatched or ill-suited for low-income country demand

Both the supply landscape and the manufacturing economics of hexavalent vaccines will be shaped by manufacturers’ perceptions of demand. Some manufacturers are seeking assurances of future demand before initiating development. Without such assurances, these manufacturers may choose not to pursue development, reducing the total capacity available and possibly preventing some of the manufacturing cost improvements from being realized. Others plan to move forward without such assurances and are designing their development programs and target product profiles using their own hypotheses and assumptions about future demand—which may or may not be correct. Given the long lead time required to develop and build manufacturing capacity, enhanced collaboration and communications with manufacturers around IPV demand (from the side of the global health community) and price (from the side of the manufacturers) is essential to ensure sufficient, well-utilized capacity. Misinformed decision making by some manufacturers and/or lack of entry by others could result in a supply/demand imbalance.

Risk of a supply/demand imbalance exists in two areas: the relative focus on stand-alone IPV versus hexavalent vaccines; for hexavalent vaccines, the relative focus on wP-based versus aP-based versions. Most manufacturers assume some level of IPV will be used by low-income countries post-eradication. Manufacturers, however, differ on whether these countries will prefer stand-alone IPV or hexavalent vaccines containing IPV. Several manufacturers, considering the increasing use of pentavalent vaccine and the programmatic benefits of a single injection, have judged that hexavalent vaccines will be preferred and are focusing on them. Others are focusing on stand-alone IPV, recognizing that some countries may want to (1) integrate IPV into the immunization program only as part of a temporary transitional post-eradication strategy, (2) utilize a reduced dosing schedule (i.e., one or two doses of IPV versus the three required for a hexavalent), (3) achieve higher seroconversion rates by using later contacts (i.e. if their pentavalent schedule follows the classic EPI schedule of 6, 10, and 14 weeks), or (4) use a combination of these strategies. Given the uncertainty over how stand-alone and combination vaccines will be priced in low-income countries, these parallel

approaches can be viewed as offering the community short-term advantages. But because manufacturers differ significantly in their planned or potential capacity, it is important to periodically reassess whether the mix of capacity is sufficient for demand. In addition, several of the manufacturers pursuing combination vaccines are developing both aP- and wP-based versions, or considering it as an option. Many of these manufacturers, however, would prefer to focus on wP-based hexavalent vaccines, which would allow them to leverage existing knowledge and infrastructure. If a different sequence or mix of product is required, it will be important for the procurement agencies and the countries themselves to communicate this requirement to manufacturers in a timely manner to avoid potentially duplicative development efforts, which would negatively impact pricing.

Summary and implications

The potential exists for a significant improvement in the supply landscape and manufacturing economics of IPV-containing hexavalent combinations for low-income countries. While existing IPV-containing products will probably continue to be used only in high- and middle-income countries, manufacturers are interested in producing new hexavalent vaccines for low-income countries, and several have products in development. If these development programs succeed and manufacturers are able to secure adequate supplies of bulk IPV, manufacturing capacity for these new vaccines could rise to more than 280 million doses annually by 2014, enough to provide three doses to each of the 70 million children born annually in low-income countries. Collectively, manufacturers are pursuing or considering product and process improvements that could lower the ongoing manufacturing cost of these vaccines by 25 percent to more than 60 percent. If this happens, the ongoing manufacturing cost of hexavalent vaccines could eventually reach a range of one to four dollars a dose and the cost of aP-based and wP-based vaccines could be similar. However, several challenges would need to be overcome to achieve such manufacturing costs and ultimately cost-effective pricing for low income countries, especially given the investments required in R&D and facilities. Further effort is required to fully evaluate these challenges and where necessary, develop potential mitigating solutions, which could include roles for the international public health community. A sample of potential mitigating solutions is discussed here to illustrate the range of what can be done by the community.

First, manufacturers may experience technical challenges during development. Several are pursuing innovative technologies and approaches, which are inherently risky. Failure, or even delay in development, could have an unfavorable impact on costs and capacity. To diminish this possibility, the community could, for example, expand its current work on IPV with manufacturers to include tracking key developmental milestones, or directly supporting research in technologies critical to reducing the manufacturing cost of other antigens in hexavalent vaccines.

Second, it is possible some potential manufacturers will be unable to secure adequate, cost-effective access to bulk IPV antigen; some may respond by significantly scaling back or halting their development programs. To diminish this possibility, the community could, for example, expand the work it is doing to facilitate dialogue among manufacturers to develop new or alternative sources of

IPV capacity (e.g., sIPV) or help advance measures like adjuvants, which would expand the effective capacity of existing sources.

Third, supply and demand could become imbalanced. On the one hand, if manufacturers build insufficient capacity, or the wrong type of capacity, some demand segments could be left underserved. On the other hand, if manufacturers build too much capacity, average facility utilization would decrease, preventing manufacturers from achieving their lowest possible ongoing cost—and therefore price. To diminish this possibility, the community should continue to provide demand indications and forecasts to manufacturers as far in advance as possible. Manufacturers can improve the accuracy of these inputs by providing the community with indications of potential vaccine pricing at different levels of demand. This indicative pricing information will allow the community to engage countries and donors such as GAVI to understand their relative interest in stand-alone IPV versus IPV-containing hexavalent vaccines or wP-based versus aP-based combinations. These country- and donor-level insights could bring great focus to manufacturers' development efforts, possibly increasing the pace of development and reducing cost further. In parallel, WHO and regional policy discussions should continue and be accelerated as early as eradication progress allows, as these are important inputs for both country and manufacturer decision-making. Particularly important is the work of the SAGE Working Group on IPV, which is charged with developing by April 2011 for the consideration of SAGE options on the role of IPV for low-income settings in the post-eradication era. Further, SAGE's work to coordinate the deliberations, decisions, and recommendations of its various antigen-specific policy bodies should be even more closely aligned, since policy recommendations around one antigen impact the availability and affordability of combination vaccines as a whole. Since all these activities will take time to complete, it is important to continue to keep manufacturers up to date on the latest developments so they can most effectively manage their own internal timelines.

Finally, reductions in the ongoing manufacturing cost of hexavalent vaccines may not translate into product pricing low enough to drive large-scale public-sector use in low-income countries. To diminish this possibility, the community could, for example, improve the investment case for manufacturers by co-funding the investments in R&D or facilities or ensuring long-term demand for the vaccine. Such measures should help promote the development of a diverse supply base.

Credits

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