Global Post-eradication IPV Supply and Demand Assessment: Integrated Findings

Commissioned by the Bill & Melinda Gates Foundation

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Introduction

The Bill & Melinda Gates Foundation (BMGF), in discussion with The World Health Organization (WHO), commissioned Oliver Wyman to conduct a global post-eradication inactivated polio vaccine (IPV) supply and demand assessment. A preliminary report, summarizing the interim findings and remaining open research questions was released in August 2008. From August through November 2008, additional research and analysis was conducted and the following report represents the comprehensive findings from the year-long effort.

Project Charter and Objectives

Launched in 1988, the Global Polio Eradication Initiative (GPEI) had by end-2005 led to the interruption of indigenous wild poliovirus transmission in all but four countries in the world. Through the expanded use of new eradication tools and tactics coupled with heightened political advocacy, the eradication effort is on track to interrupt wild poliovirus in Asia and most of Africa by 2010. The major exception has been in Nigeria where vaccine coverage lapses due to low quality polio immunization campaigns have led to several wild poliovirus outbreaks and a vaccine-derived poliovirus outbreak.

In concert with the effort to interrupt wild poliovirus, the GPEI has continued to prepare for the 'post-eradication' era. In May 2008, the World Health Assembly (WHA) endorsed in principle the eventual cessation of routine immunization with OPV following confirmation of global eradication and containment of wild polioviruses. Recognizing that IPV would be the only option for countries wishing to maintain polio immunity through vaccination after OPV cessation, the WHA also called for intensification of the GPEI's work to develop (a) affordable options for routine IPV use in low income settings, and (b) safer IPV production processes to facilitate IPV manufacturing in tropical, developing country settings.

The GPEI continues to work towards the interruption of all wild poliovirus transmission by end-2010, in which case the containment of all wild polioviruses would need to be complete by mid-2012. Certification of WPV interruption and containment could then take place as early as end-2013. If these milestones are achieved, the cessation of all OPV use in routine immunization could potentially take place in 2014-15, depending on the status of the other pre-requisites for eventual OPV cessation.

As such, many countries, global health bodies, and key opinion leaders are now discussing the merits, costs and feasibility of wider IPV use post-eradication. While many higher income countries use or are exploring the use of IPV today, IPV has historically seen limited use in lower income countries given IPV's limited mucosal immunity, high price and significant programmatic requirements as compared to OPV. To inform ongoing IPV discussions and potential policy development for the post-eradication era, a better

understanding of potential IPV supply, demand, and economics was needed. To that end, the Bill & Melinda Gates Foundation commissioned Oliver Wyman to conduct a global IPV supply and demand assessment, focused on identifying supply strategy implications for developing world populations.

Specifically the foundation asked Oliver Wyman to answer four questions concerning IPV:

1. What range of demand could exist post-eradication?
2. What are the current and potential sources of supply, including new technologies?
3. What are the tradeoffs between these supply sources, including differences in IPV economics?
4. Within the context of global demand and supply, what are the implications for developing world supply strategies and what are the major next steps?

The insights and conclusions from this project are intended to help inform policy and aid country decision making. To date, the material has been presented in some form to the Strategic Advisory Group of Experts (SAGE) Working Group on IPV, Advisory Committee on Polio Eradication (ACPE), World Health Organization Regional Offices, the Global Polio Eradication Initiative, The United Nations Children's Fund (UNICEF), all major IPV manufacturers, and BMGF.

Approach and methodology

The effort was conducted from December 2007 through November 2008 and consisted of four high-level activities.

Activity 1: Assess current and potential supply – The project team first conducted a full literature review to identify all existing and potential sources of supply for IPV. Then, direct discussions were pursued with all of the current manufacturers to identify existing capacity levels and investments currently planned to expand capacity. In addition, discussions were held with a range of manufacturers and research institutes working on alternative IPV technologies to determine the status of those development activities and potential capacity plans.

Activity 2: Evaluate tradeoffs and economics of IPV – In parallel with activity 1, additional secondary and primary research was conducted to evaluate the full set of tradeoffs across the various sources of supply, including timing, costs, and key risks. As part of this assessment, the team modeled the economics of IPV manufacturing for both Salk / wild-type IPV (wtIPV) and Sabin-based production and evaluated how the economics may change over time. In addition, the team analyzed the economic implications of using IPV as a stand-alone vaccine or in combination with other antigens to determine the "breakeven" point between the two options. The breakeven analysis was developed to present a complete picture of the

economics, including vaccine price, shipping cost, vaccine wastage, and programmatic/administration costs.

Activity 3: Develop alternative demand scenarios – A set of activities were pursued to identify key drivers of demand and potential demand scenarios to bound the amount of supply that may be needed. To develop the alternative demand scenarios, the team conducted a primary research effort, soliciting input from approximately 20 experts from academia and global health bodies with a wealth of experience in polio eradication field work and polio-related research. The experts were asked to provide their insights and opinions through a series of one-on-one interviews. Specifically, each expert was asked a series of questions meant to identify the key drivers of demand, determine when and why countries may choose to adopt IPV, and evaluate the polio vaccination schedule they might use (i.e., dosing level and timing). Based on these responses, a series of demand scenarios were developed and quantified using WHO and UN population data.

Activity 4: Synthesize findings and identify implications – This activity was conducted in an iterative fashion to synthesize findings from the diagnostic, identify the implications for potential supply strategies, seek feedback on the findings / implications, and then continue to refine the findings and implications. During this phase of work, the team continued to interact with the set of global experts from the earlier phase, current and potential IPV manufacturers, and select country government officials.

Summary of key findings

The following eight key findings emerged from the effort:

1. Post-eradication IPV demand is still uncertain, with clear policy guidance being highlighted as one of the keys to resolving the uncertainty, which in turn requires additional research

2. Given the uncertainty, annual post-eradication demand could rise from the “as is” of 80 million doses to between 190 and 425 million doses following OPV cessation, with the potential for subsequent demand to taper over time

3. Existing Salk / wild-type IPV capacity is concentrated with a small set of manufacturers, but these suppliers have the ability to satisfy even the highest demand scenarios with moderate investments, clear demand signals, and lead times in the range of three-to-five years

4. Several factors can provide an indication of potential IPV pricing, but manufacturers will need to be engaged in a dialogue around indicative pricing to obtain more definitive estimates: manufacturing costs will decline as wtIPV manufacturers expand; given the nature of wtIPV manufacturing, IPV will,

however, never reach a price equal to that of OPV; pricing will be determined by a small set of manufacturers

5. Given their potential capacity and proven track-record with wtIPV, existing wtIPV manufacturers will have a significant role in any post-eradication supply strategy

6. Dosage-sparing approaches have an important role in further expanding capacity and reducing costs for some sources of supply

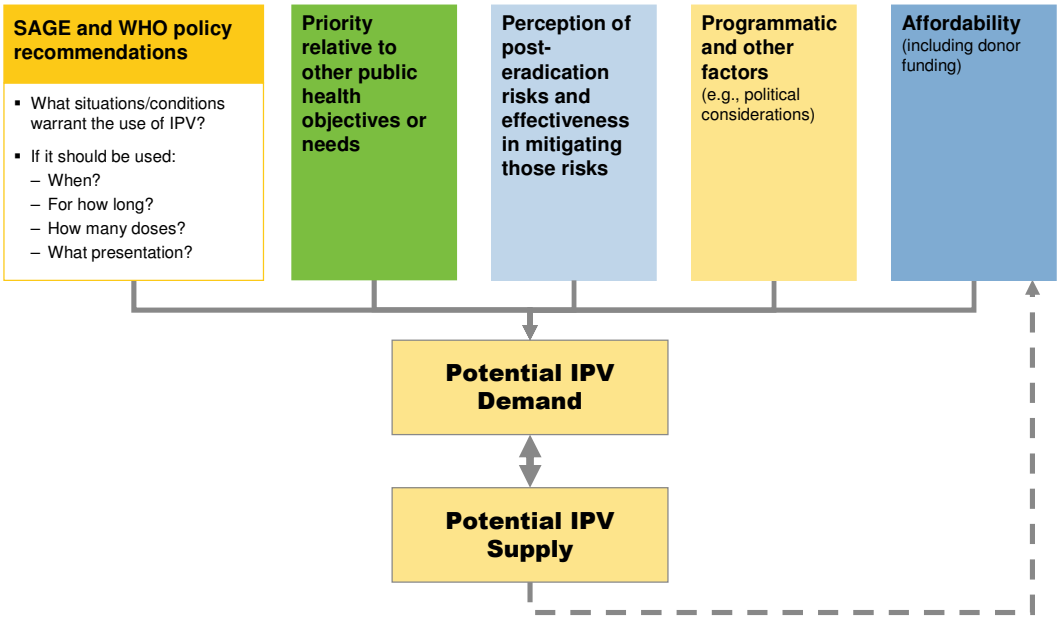
7. Sabin IPV (sIPV) may have a role to play as a complementary technology to wtIPV by meeting specific customer requirements, complying with containment guidelines, and diversifying supply; however, clear risks exist that need to be managed given the early stage nature of the technology

8. Guidance must be provided around the use of IPV in stand-alone form vs. in a combination, which needs to be informed by supply and demand considerations for stand-alone IPV, pentavalent combinations without IPV, and IPV-containing combinations (with whole-cell and acellular pertussis)

Finding #1 – Post-eradication IPV demand is still uncertain, with clear policy guidance being highlighted as one of the keys to resolving the uncertainty, which in turn requires additional research

The overall demand equation is complex and will be driven by a range of intertwined factors as illustrated in Figure 1. Although substantial hurdles to eradication remain, many countries are beginning to discuss the post-eradication role and use of IPV as well as the appropriate timeframe for adoption. Their

Figure 1: Drivers of Demand



decision-making process is still evolving and will be informed by the policy guidance they receive, indications around vaccine affordability, their perception of post-eradication risks and the effectiveness of IPV in mitigating those risks, and the priority of IPV relative to other public health objectives or needs. The aggregation of these individual country decisions will determine the overall demand for IPV.

During the consultation process, clear policy guidance from SAGE and WHO was highlighted as one of the keys to resolving uncertainty around demand and setting in motion a set of critical decisions. First, it will solidify an important input in the country decision-making process. Second, it will provide a signal to manufacturers around potential demand, enabling supply investment decisions. The magnitude of these investments will ultimately impact manufacturing cost and pricing given the scale sensitivity of IPV manufacturing (discussed further in Finding 4), possibly making the vaccine more affordable from the perspective of at least middle income countries and perhaps others. All that said, the 2008 deliberations of the SAGE IPV Working Group and Regional IPV Working Groups have highlighted the need for additional research, particularly in the areas of post-eradication risks and IPV schedule and dose reduction strategies, to facilitate policy development[1].

Finding #2 – Given the uncertainty, annual post-eradication demand could rise from the "as is" of 80 million doses to between 190 and 425 million doses following OPV cessation, with the potential for subsequent demand to taper over time

Given the uncertainty in the country decision-making process, various scenarios may still emerge with different levels of peak demand and demand patterns (i.e., specific demand over time). These scenarios will be impacted by four main decisions by the countries – do they adopt, when, for how long, and with how many doses. Based on our initial consultations, we developed four main scenarios to "bound" the supply requirements, but recognize that actual demand may fall somewhere between these scenarios:

- "As is" or status quo – At one extreme, a scenario was developed where IPV use is limited to high income countries and select middle income countries – this includes countries that use IPV today as well as other countries who are likely to adopt. This scenario results in the need to vaccinate 23 million infants annually at its peak. This relatively low level of global demand continues indefinitely.
- "Universal long-term use" - At the other extreme, a scenario exists where IPV is used universally by all countries for an extended period of time. Specifically, during the period between wild virus eradication and OPV cessation, countries would rapidly shift to IPV based on strong policy recommendations for IPV use and the availability of donor funding for lower income countries. This

[1] SAGE IPV Working Group Report; AFRO working group.

scenario results in the need to vaccinate 109 million infants annually at its peak. In this aggressive scenario, this high level of IPV use continues indefinitely.

- "Sovereign Capacity" – This scenario is similar to the "as is" scenario, but also includes adoption by the remainder of upper middle income countries and the few large developing countries with a history of locally producing the vaccines used in their country ("self-producing countries"). The birth cohorts of three of these countries – China, India and Indonesia – are projected to total 47 million by 2014, or 36% of the total global birth cohort and 42% of the birth cohort of countries currently using OPV. Total demand in this scenario peaks at 66 million infants annually. These new adopters are assumed to use IPV for only 10 years.

- "Finite Use" - This scenario is similar to the "universal long-term use" scenario, but assumes lower income countries only utilize IPV for a limited period of time (ranging from 5 to 10 years), due to policy preferences and/or funding limitations. While this change does not impact peak demand – still 109 million infants annually – it does substantially modify the shape of the demand curve over time. The implications of this demand "spike" on the supply base are an important consideration in supply strategy formulation.

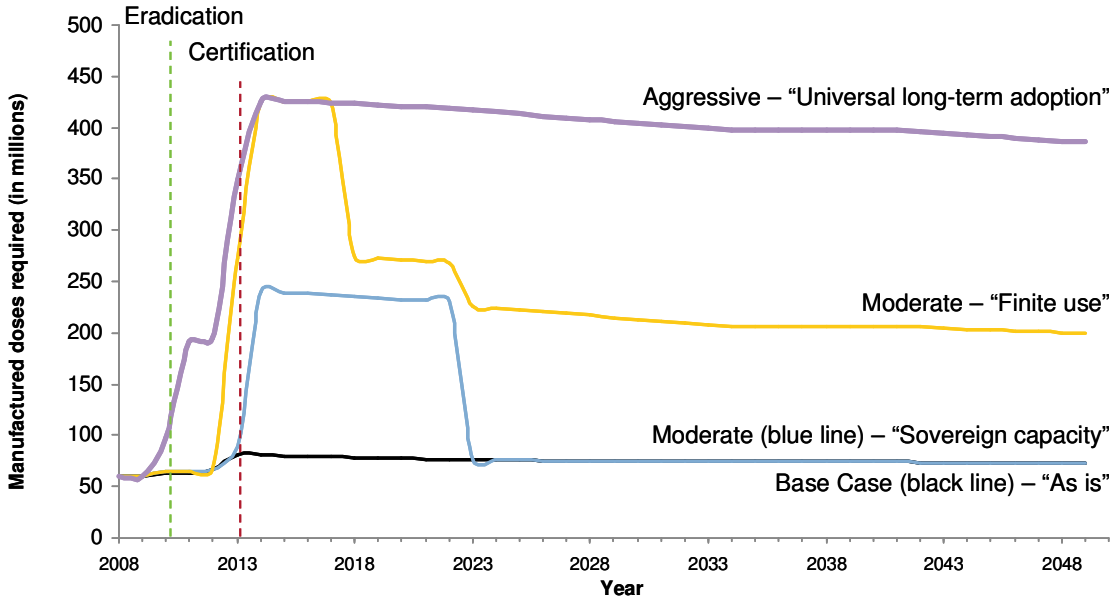
As the dosing schedule for new adopters is also an uncertainty, we have translated the demand scenarios into specific dose estimates for both a 3-dose schedule and a 2-dose schedule[2]. Annual demand can range from the "as-is" peak of 81M doses to as high as 313M doses with a 2-dose schedule and 426M doses in a 3-dose schedule (as summarized in Figure 2). In addition, the patterns of demand vary dramatically as shown in Figures 3 and 4.

Figure 2: Peak doses needed[3]

	3-dose	2-dose
"As is"	81 M	81 M
"Sovereign capacity"	241 M	190 M
"Finite use"	426 M	313 M
"Universal long-term use"	426 M	313 M

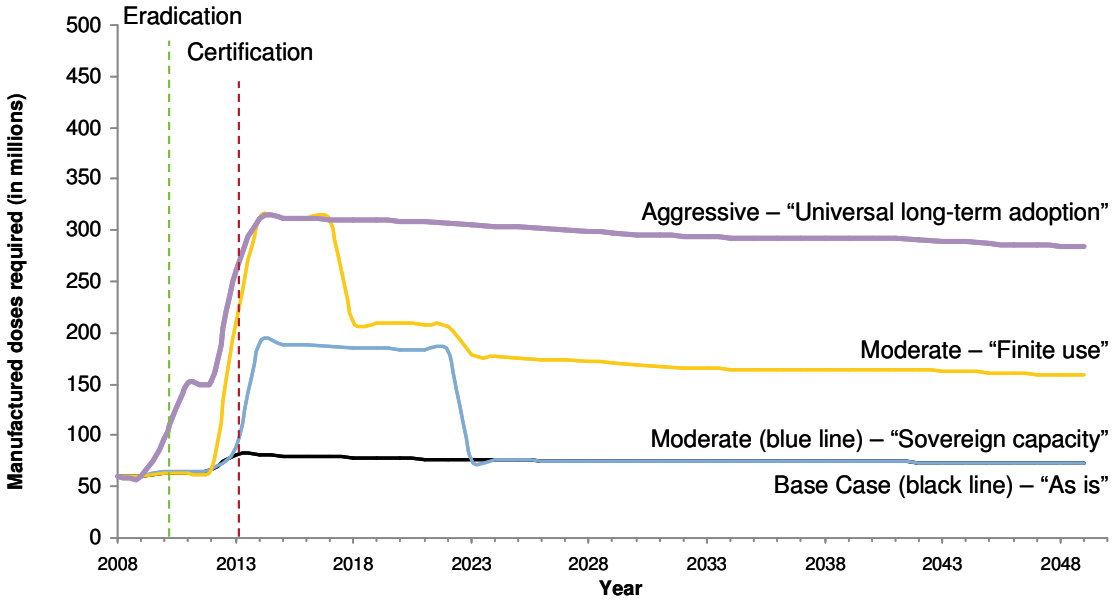
[2] Analysis assumes those countries that already use IPV continue with their existing vaccination schedule (i.e., 4+ doses)
[3] Based on Oliver Wyman analysis. Country economic and regional classification data from WHO, UNDP, GAVI, and World Bank. Birth cohort data from UNDP (utilized medium fertility projections) and includes 99.5% of the world's population. Coverage rates based on 2013 WHO ICE-T country-by-country projections. Wastage rates assumed to be 5% in higher income countries and 25% in lower income countries (Source: "Projected vaccine wastage." WHO website.)

Figure 3: Potential demand over time[3] – 3 dose schedule assumption



Source: Oliver Wyman analysis.

Figure 3: Potential demand over time[3] – 2 dose schedule assumption



Source: Oliver Wyman analysis.

Finding #3 – Existing Salk / wild-type IPV capacity is concentrated with a small set of manufacturers, but these suppliers have the ability to satisfy even the highest demand scenarios with moderate investments, clear demand signals, and lead times in the range of three-to-five years

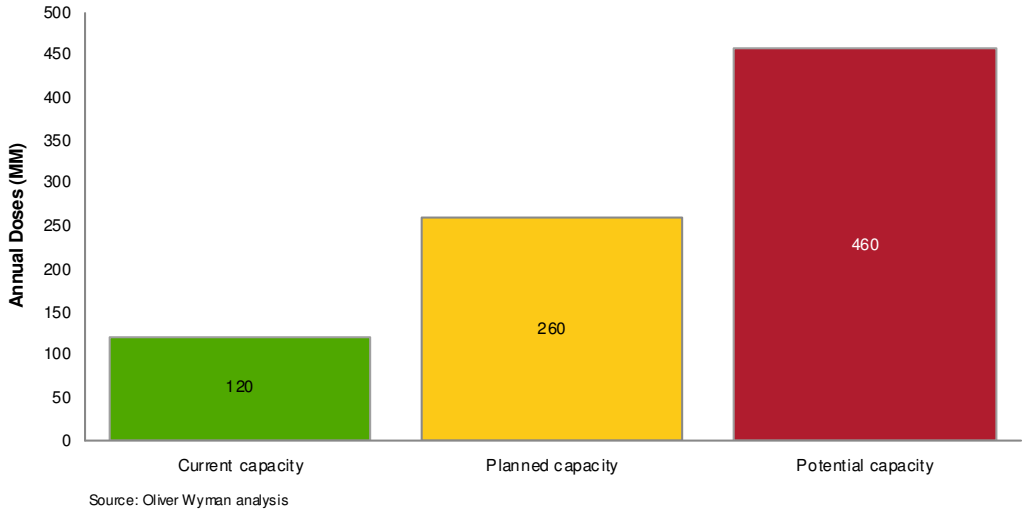
The production of IPV, currently based on the Salk or wild type strains (wtIPV), is concentrated within four manufacturers today. GlaxoSmithKline (GSK) and Sanofi-Aventis are currently the largest wtIPV bulk producers, with the Netherlands Vaccine Institute (NVI) and Statens Serum Institute (SSI) also producing wtIPV vaccine bulk in smaller quantities. Other manufacturers, such as Biological E, Panacea and Novartis, have bulk purchases agreements in place to fill and finish stand-alone IPV.

Based on our estimates, approximately 120 million doses[4] of annual production capacity exists today amongst the four wtIPV bulk manufacturers. Recognizing the potential for increased global demand both pre- and post-eradication, several of these existing manufacturers are investing or plan to invest in capacity expansions - for example, adding an additional fermentation vessel, changing the operating schedule of their production facility, or bringing a new facility online. These planned expansions are estimated to increase annual wtIPV capacity by approximately 140 million doses to a total of approximately 260 million doses, most of which would still reside with two suppliers. While capital has already been committed and several of these planned expansions are underway, the wtIPV manufacturers have indicated that two to three years will be required to ramp-up production to achieve these levels once they have further clarity around demand. In addition, the manufacturers have voiced that alternative uses exist for some of this capacity and that they will consider diverting the capacity if demand does not materialize.

Lastly, some of the existing manufacturers have the potential to expand their capacity even further. For example, some manufacturers designed their current facilities to accommodate fermenter upgrades and others have discussed constructing new facilities. These potential expansions could further increase capacity by approximately 200 million doses. Such capacity expansion will require new, currently uncommitted capital, and thus is contingent on manufacturers' expectations of future demand for their products. The wtIPV manufacturers have indicated that a lead-time of three-to-five years will be required to ramp-up production to these levels. All told, with potential expansions, existing wtIPV manufacturers have the flexibility to expand supply to approximately 460 million doses annually (as shown in figure 5), with the majority of capacity residing with a single supplier.

[4] Capacity estimated assuming 10% overfill (i.e., multi-dose vial) and a 40-8-32 DU formulation ("full dosage"). Current suppliers use a mix of pre-filled syringes (5% overfill), single dose vials (30% overfill), and multi-dose vials (10% overfill). The exact allocation was unavailable.

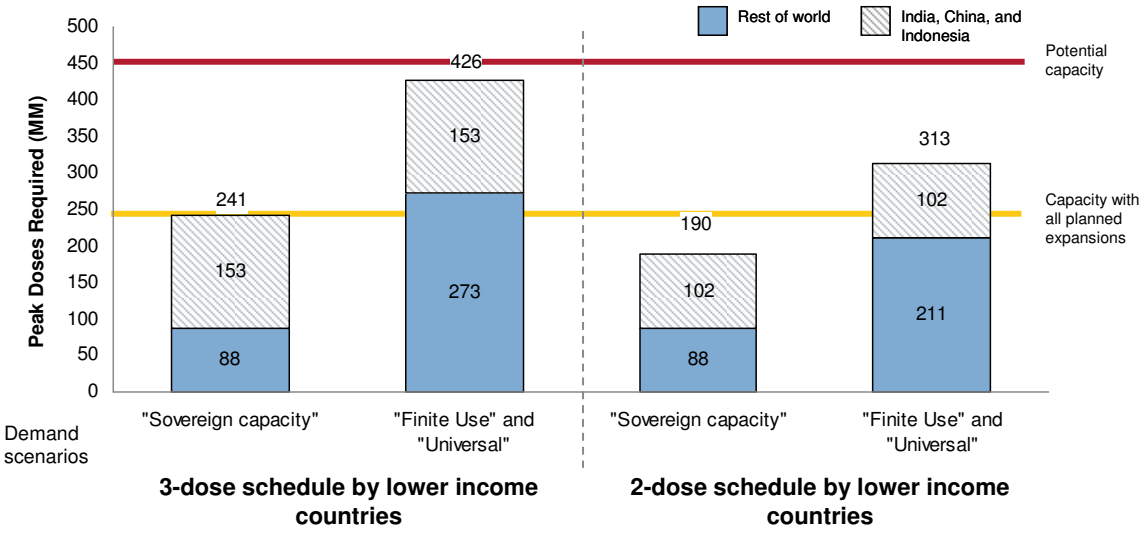
Figure 5: Global bulk wtIPV capacity (assuming 10% overfill and full dosage product)



Source: Oliver Wyman analysis

Comparing supply with potential demand (Figure 6), the current wtIPV manufacturers have the ability to meet global needs, even in the most aggressive scenario. Assuming countries with an interest in self production are able to source their demand through new local capacity, enough wtIPV-based capacity will be available from the planned infrastructure (current + planned expansions) to meet the rest of the world's demand even in the most aggressive case. With the further potential expansion of capacity (to ~460 M doses), enough capacity would exist to cover the entire global demand for all countries even if they pursue 3-dose full dosage schedules.

Figure 6: wtIPV supply – demand map (assuming 10% overfill and full dosage product)



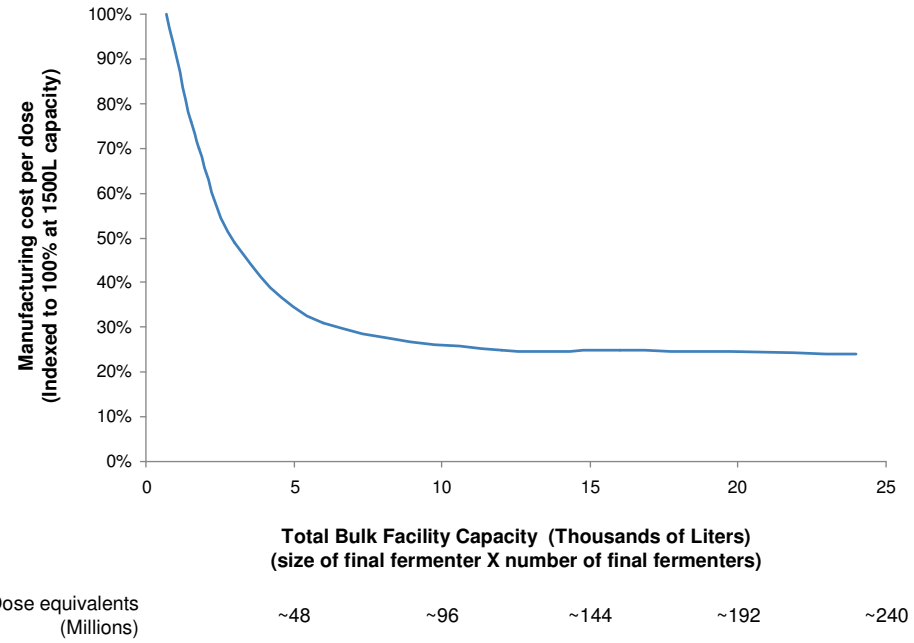
Source: Oliver Wyman analysis

While this supply situation is possible, it is important to stress that it will require clear demand signals to the manufacturers with lead times of up to five years if the full capacity is required.

Finding #4 – Several factors can provide an indication of potential IPV pricing, but manufacturers will need to be engaged in a dialogue around indicative pricing to obtain more definitive estimates: manufacturing costs will decline as wtIPV manufacturers expand; given the nature of wtIPV manufacturing, IPV will, however, never reach a price equal to that of OPV; pricing will be determined by a small set of manufacturers

As wtIPV manufacturers expand their capacity and utilize their facilities, wtIPV manufacturing economics will improve. The manufacturing of IPV is scale-sensitive (i.e., costs decline as volumes rise), similar to many other vaccines produced in fixed bioreactors. Given the technical challenges historically associated with utilizing large volume bioreactors with a mammalian cell-based microcarrier platform, high scale wtIPV production facilities have traditionally been built around multiple medium size bioreactors paired with one or more downstream purification suites. While this is not as scale sensitive as utilizing fewer large bioreactors, such a construction philosophy still results in meaningful scale economics (figure 7).

Figure 7: Scale economics of IPV production (assuming 10% overfill and full dosage)



Source: Oliver Wyman analysis
Note: Calculated based on 10-dose presentation. Assumes full facility utilization and optimal facility configuration. Manufacturer-specific costs may vary based on facility and operational choices

With the product in its current form, if scale increases and facilities are highly utilized, future manufacturing costs have the potential to decline by 30% to 50%, reaching a range of €0.40 - €1.50 per dose. While cost is only one input into the pricing decisions made by manufacturers, we would expect

pricing to decline from the current UNICEF tendered price of €2.30[5] as manufacturing costs decline. In its current form IPV will, however, never achieve pricing equal to that of OPV. IPV manufacturing costs in the future will still be four to fifteen times the current price of OPV (~€0.11 per dose). In addition, supply will remain concentrated in the hands of two major suppliers and pricing decisions will be driven by those suppliers.

While these factors provide an indication of potential pricing ranges, the manufacturers should be engaged in a direct dialogue around indicative pricing. Given the concentration of supply, long-term contracting mechanisms could be explored to guarantee sustained affordability.

Finding #5 – Given their potential capacity and proven track-record with wtIPV, existing wtIPV manufacturers will have a significant role in any post-eradication supply strategy

We envision the wtIPV manufacturers playing a critical role in any post-eradication supply strategy. wtIPV is an established technology with a proven track record of successful use, providing two benefits. First, some countries may value the proven nature and long clinical history associated with the product as they make their adoption decisions. Second, the development path and timing risks associated with alternative technologies (discussed further in Finding 6) do not exist for wtIPV. With the appropriate demand signals and lead times, the primary infrastructure already exists to produce appropriate quantities of wtIPV with only moderate additional investments. In addition, the larger wtIPV manufacturers have voiced that they are not interested in using their capacity to produce alternative products (e.g., Sabin-based) give the considerable product development and regulatory investments that would be required.

Finding #6 – Dosage-sparing approaches have an important role in further expanding capacity and reducing costs for some sources of supply

Several members of the community are actively researching dosage-sparing approaches (i.e., reducing the required antigen content), such as adjuvants and intradermal administration, as a means of improving the supply and economics of wtIPV. Historical data and ongoing trials indicate that such dosage-sparing approaches might reduce antigen requirements 50% to 80% per dose. These approaches have the potential to increase the "effective" capacity of manufacturing facilities as more doses can be produced with the same level of fixed infrastructure. This can bring two important benefits: (1) Extending the capacity of existing and/or new facilities; (2) Reducing manufacturing cost per dose (if the facility remains fully utilized).

[5] UNICEF tenders (1-dose IPV: $3.00) converted at 1.30 USD/EUR [avg. 2006])

Manufacturers' interest in dosage-sparing approaches will vary. Some manufacturers, expecting IPV demand to rise dramatically at eradication and OPV cessation, have already invested significant capital in the infrastructure and facilities needed to support planned and potential capacities. These investments allow the manufacturers to meet growing global demand without using dosage-sparing approaches. Pursuing a dosage-sparing approach would only lead to over-capacity for those manufacturers and would not be expected to reduce costs.

Dosage-sparing approaches will provide greater value for other manufacturers who have not planned for significant surplus capacity. For those manufacturers, dosage-sparing approaches would extend the production capacity of their existing facilities (or new facilities envisioned) and position them to serve growing demand. These approaches would reduce their cost structures and may also improve the competitive dynamics within the marketplace by further diversifying supply. At least one manufacturer has voiced an interest in developing a dosage-sparing product.

While dosage-sparing approaches do have an important role to play in the aggregate market, several cautions should be noted. First, dosage-sparing approaches will not simply double to quintuple the capacity available (for 50% to 80% reduced antigen products) in existing facilities. Many of the wtIPV manufacturers currently provide full dosage product to established markets and are unlikely to switch these markets to reduced-dosage products given the re-development and re-approval expense. So, only the surplus capacity in those facilities (or new capacity) would be eligible. Second, the manufacturing cost reductions associated with dosage-sparing approaches may not translate one-for-one into vaccine price reductions. The impact on pricing will be driven by a complex set of factors beyond manufacturing cost, including the competitive dynamics in the market and required R&D investments. At a minimum, the price will reflect the R&D costs associated with developing these new approaches.

Finding #7 – Sabin IPV (sIPV) may have a role to play as a complementary technology to wtIPV by meeting specific customer requirements, complying with containment guidelines, and diversifying supply; however, clear risks exist that need to be managed given the early stage nature of the technology

IPV manufactured using Sabin strain virus seeds (sIPV) is seen as the primary near-term alternative IPV technology platform. A range of manufacturers and research institutes have active programs at various stages of development, including NVI, Panacea and JPRI/Takeda. While other alternative technologies exist (primarily from non-pathogenic strains), these technologies are mostly in pre-clinical development and at their current pace of development are not expected to be available at a commercial-scale to meet near-term eradication milestones (e.g., OPV cessation). Therefore, these alternative technologies were not evaluated as part of this work. These technologies may have a role to play in the longer-term, for

example, in response to stronger virus containment requirements, but additional evaluation would be required.

In considering the potential role for the sIPV technology, we evaluated a range of tradeoffs relative to wtIPV. We evaluated the potential advantages in several categories as well as the key risks associated with this technology.

As background, sIPV is seen to address some of the perceived risks of post-eradication IPV production. sIPV proponents argue that Sabin polio viruses pose less of a threat to the population in the event of an intentional or unintentional virus release from the production facility. This is a particular concern in tropical, low income settings where the transmissibility of polio viruses is high and was one of the impetuses for the Global Action Plan III (GAP-III) guidelines restricting IPV production to just sIPV in these settings[6].

As a result, the greatest near-term potential benefit of sIPV is that it would satisfy the unique requirements of a sizable and influential demand segment – the "self producers." These countries, such as China, India, and Indonesia, have a long history of locally producing critical vaccines and it appears likely that they will have similar requirements around IPV. It is not clear what form of local production would be required – various models have been pursued for other vaccines, with full production for some (e.g., Hep B), import and then fill / finish for others (e.g., OPV), and transitioning models for yet others (e.g., Rotavirus). At least one self-producing country, however, has publicly stated that without full local production of IPV, it might not adopt IPV and cease the use of OPV, which would be a major roadblock in the global eradication effort[7]. wtIPV is unlikely be a viable solution for countries such as this one since current Global Action Plan III (GAP-III) guidelines prevent wtIPV production in such settings. Therefore, alternative technologies that comply with GAP-III (like sIPV) may have an important role to play for these self-producing countries. In addition, sIPV would bring new vaccine suppliers to the market, improving supplier diversity and reducing risk.

In order to fulfill these roles, sIPV development and commercialization must be managed carefully as it faces several key risks.

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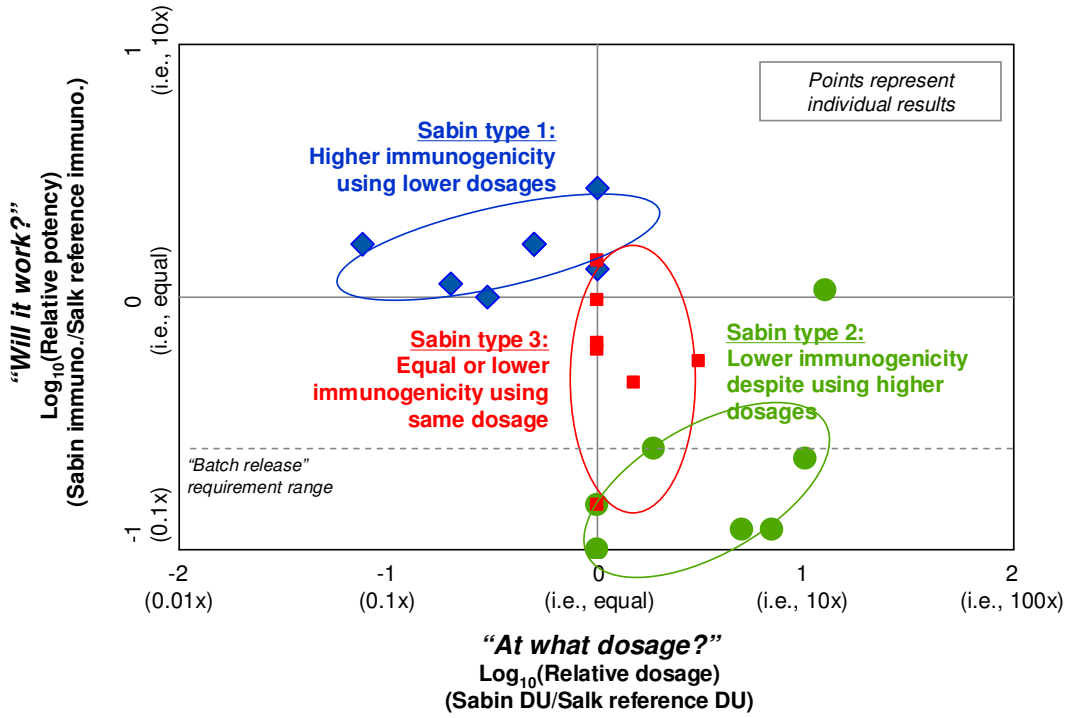
[6] Global Action Plan III (GAP-III) guidelines include primary, secondary and tertiary safeguards, all of which would apply to IPV production from WPVs in the VAPP/VDPV elimination phase, and the first two of which would apply to IPV production from Sabin PVs

[7] 2008 WHO Executive Board meeting

Risk #1 - The risk exists that a sufficiently immunogenic sIPV vaccine (relative to wtIPV) may not be possible – sIPV development is still in early stages and the results have been mixed. In almost all initial rat studies, sIPV serotype 2 immunogenicity was found to be considerably lower than wtIPV with equivalent or even higher doses. Serotype 3 immunogenicity was found to be slightly lower with an equivalent dose. Positively, serotype 1 immunogenicity was found to be higher than that of wtIPV in similar experiments. A summary of this research is presented in Figure 9.

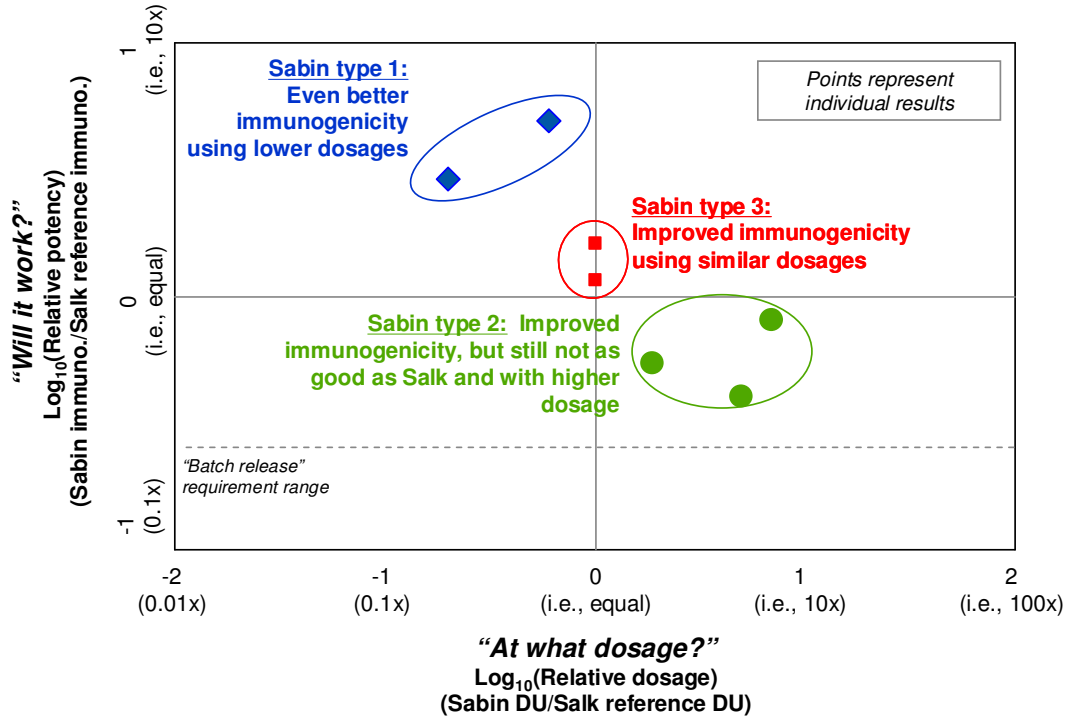
Figure 9: Sabin IPV immunogenicity



Source: G. Kersten et al. "Antigenic and immunogenic properties of inactivated polio." Vaccine 17(1999): 2059-2066; B. Simizu et al. "Development of inactivated poliovirus vaccine derived from Sabin strains." Biologicals 34(2006): 151-154; I. Pierard and M. Duchêne, "GSK Biologicals perspectives on the future IPV." Presented at the polio immunization meeting held at NIH, September 2007; W. Bakker et al. (in preparation); J. Martin et al. (in preparation); Oliver Wyman analysis

Encouragingly, some manufacturers and research institutes have found that sIPV immunogenicity improved when basic adjuvant strategies (e.g., alum) were employed (Figure 10). With an adjuvant, sIPV serotype 3 rat immunogenicity was found to be equal or slightly better that wtIPV. In the same experiments, sIPV serotype 2 immunogenicity also improved and was within wtIPV QA/QC "batch release" requirements, but was still below that of wtIPV and may not be sufficient to prove non-inferiority in humans. This group of researchers is hopeful that additional improvement in immunogenicity will be possible through production process changes (e.g., change in inactivation agent) and/or through the use of more novel adjuvants (e.g., oil in water emulsion), and/or the use of product specific analytical methods, all of which are being explored but will require time and resources to complete.

Figure 10: Sabin IPV immunogenicity using adjuvants



Source: W. Bakker et al. (in preparation); J. Martin et al. (in preparation); Oliver Wyman analysis

Risk #2 - There is a risk that sIPV could ultimately cost more to manufacture than full-dosage wtIPV. At similar scale points and dosages, sIPV manufacturing costs are expected to be slightly below full-dosage wtIPV if produced in low-cost locations. However, both the dosage and the scale point are still uncertainties, which could result in a wide range of costs.

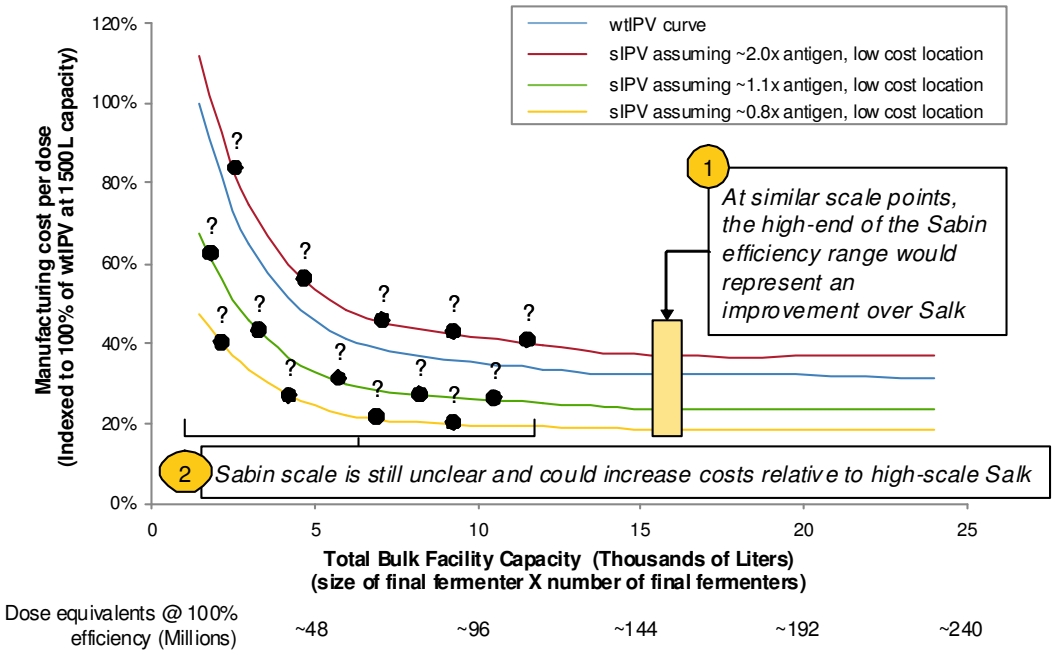
We will discuss dosage first. The best evidence to-date on adjuvanted sIPV indicates that a dosage of ~1.1x to ~2.0x the antigen content of wtIPV (weighted across serotypes) will be required to prove non-inferiority. This range assumes the immunogenicity challenges with sIPV serotype 2 can be overcome by using an alum adjuvant and ~5.0-7.0x the antigen content of wtIPV serotype 2 (this adjuvant and dosage resulted in near equivalence in one study). However, given the early stage nature of this technology, the actual dosage range is uncertain – it may be lower, but it may be higher. On the positive-side, one study produced potency results within wtIPV batch release standards using an alum adjuvant and 2.0x the antigen content of wtIPV serotype 2, with a weighted average across serotypes of ~0.8x. Dosage studies are on-going and further improvements in the required antigen content are still possible.

The second uncertainty impacting the economics is the scale point. Since IPV manufacturing is highly scale-sensitive, it is critical that large-scale facilities are built and utilized. The major wtIPV facilities

operate at high-scale, so uncertainty does not exist for those products. For sIPV facilities, however, the scale points are yet to be determined. If each self-producing country procures vaccine from several local manufacturers, the resulting scale points could be considerably below wtIPV and drive up manufacturing costs.

Figure 11 shows the comparison of wtIPV and sIPV at multiples dosage ranges and scale points. At scale points similar to wtIPV facilities and within a dosage range of ~1.1x to ~2.0x, sIPV manufacturing costs would be consistent with wtIPV (slightly higher to slightly lower depending on the position in the required dosage range). At lower dosage, sIPV could be less costly to manufacture. However, the major risk then lies in the scale points. At scale points below 5,000 liters of fermenter capacity (approximately 48 million annual doses at wtIPV dosage levels), sIPV would reach a steep portion of the scale curve and could be considerably more expensive than wtIPV.

Figure 11: Relative economics of wtIPV versus adjuvanted sIPV



Source: Oliver Wyman analysis
Note: Calculated based on 10-dose presentation. Assumes full facility utilization and optimal facility configuration. Manufacturer-specific costs may vary based on facility and operational choices. Modeled Salk location as Europe, Sabin location as India

Risk #3 - There is the risk that sufficient sIPV capacity will not be available when required given current wild polio virus eradication and OPV cessation goals. The timing is quite tight and would need to be aggressively managed. Due to the early-stage nature of the product and the need to use adjuvants and/or process changes to achieve target immunogenicity, considerable development, regulatory, and licensure activities still need to occur. While some of the manufacturers are currently operating on a

timeline consistent with eradication goals, timeline risks always exist in vaccine development. In addition, new local production capacity would need to be built and would need to begin prior to the completion of product development, requiring advanced planning and carefully staging of technology transfers for many of the developers.

Finding #8 – Guidance must be provided around the use of IPV in stand-alone form vs. in a combination, which needs to be informed by supply and demand considerations for stand-alone IPV, pentavalent combinations without IPV, and IPV-containing combinations (with whole-cell and acellular pertussis)

In making the stand-alone versus combination decision, countries, global health bodies, and donors need to carefully evaluate the economic and non-economic considerations of a combination vaccine (which would contain IPV) versus the alternative of stand-alone IPV used in conjunction with a pentavalent combination without IPV (i.e., DTwP-HepB-Hib, which is rapidly being adopted by the countries using OPV today)

To help frame the economic elements, we can analyze the price of a combination vaccine that would make it economically equivalent to the stand-alone option, referred to as the "breakeven price." For the purpose of this analysis, we have assumed the combination vaccine would be a hexavalent, which would replace the need for a stand-alone IPV vaccine and current pentavalent. The current average low income, public market price for stand-alone IPV and the non-IPV containing pentavalent combination (fully liquid form) are €2.30 per dose and €2.69 per dose respectively[8]. Programmatically, the use of a hexavalent combination would result in, on average, €0.60 in savings per child vaccinated[9]. This savings results from the need to administer less injections, reducing the cost associated with syringes, safety/disposal, cold chain transportation, etc. Combining these inputs with assumptions on wastage and shipping cost[10], a hypothetical hexavalent vaccine would have to be priced at €5.19 per dose to be economically equivalent to the stand-alone option.

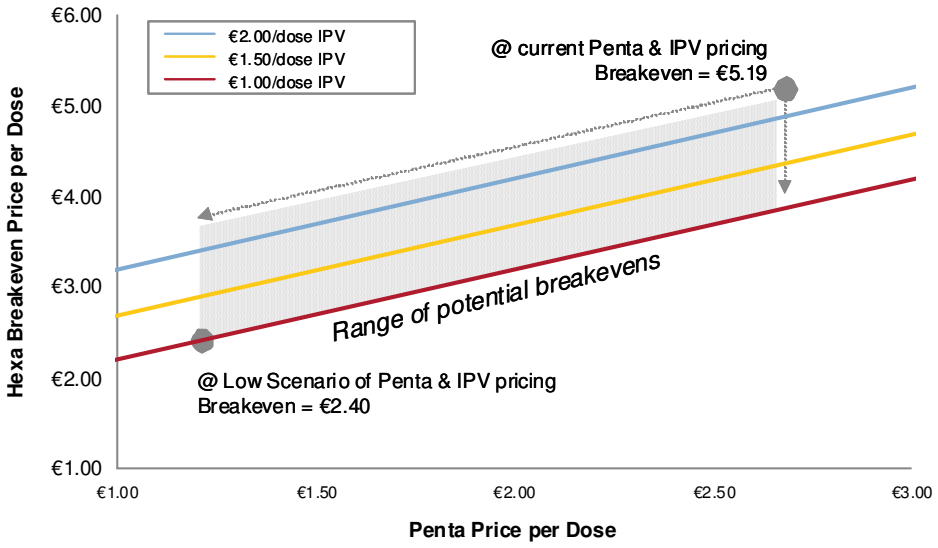
[8] UNICEF tenders (2-dose penta: $3.50 and 1-dose IPV: $3.00) converted at 1.30 USD/EUR [avg. 2006])

[9] Based on Oliver Wyman analysis of WHO Global Immunization Vision and Strategy (GIVS) programmatic cost data and projections. The €0.60 figure is a global weighted average; specific savings varied from country to country

[10] Vaccine wastage, which is driven by presentation, was assumed to be 15% (2-dose presentation). Shipping was assumed to be €0.03 per dose

This breakeven, however, is extremely sensitive to the price of the pentavalent and stand-alone IPV vaccines. Pentavalent pricing is expected to decline to €1.20[11] as more developing country manufacturers enter the market. Similarly, we would expect stand-alone IPV pricing to decline in the future (consistent with Finding 4). Hypothetically, if we assume a low-end price of stand-alone IPV at €1.00, the breakeven price would decline to €2.40 per dose. Since the actual decline in IPV and pentavalent prices is unknown, we have shown the full range of potential breakeven prices in Figure 12. It is important to note that if stand-alone IPV was used in a two dose rather than three dose schedule, the breakeven range would decrease to €2.00 - €4.36 (as the combination option would remain as a 3-dose schedule given the schedules for the other antigens).

Figure 12: Combination breakeven pricing (assuming 3 doses of IPV)



Sources: Oliver Wyman analysis, WHO GIVS cost model, WHO expert interviews
Note: Calculations based on 2-dose presentation;15% wastage; exchange rate 1.30 USD/EUR; analysis accounts for price, shipping, wastage, and administration/programmatic costs. Administration cost savings amount to ~€0.60

While this analysis establishes the break-even price, a full assessment of the potential economics and supply of combination vaccine options needs to be conducted to determine whether combinations can be supplied at appropriate volumes within the break-even range. It is critical that guidance around stand-alone vs. combination vaccines be established soon and communicated to manufacturers. This guidance should address the broader question of stand-alone vs. combination vaccines, which pertussis antigen to include (acellular or whole-cell pertussis), and which other antigens to include in the vaccine (e.g., is a hexavalent desired?). In the absence of guidance, manufacturers will make decisions based on incomplete information and supply is likely to be mismatched to demand in the future. For example, all

[11] GAVI long-term target of $1.85, using projected exchange rate of 1.54 USD/EUR (1 year currency forward as of July 2007)

IPV-containing combination vaccines today contain acellular, not whole cell pertussis, partially due to the incompatibility of existing wtIPV manufacturers' whole cell pertussis production process with IPV. Only one manufacturer produces a hexavalent combination, and supply for combination vaccines is considerably more limited than stand-alone vaccines. In addition, existing and new manufacturers are considering a range of new products, including various combinations with acellular and whole cell pertussis.

Overall, this guidance will be key and needs to be informed by various economic (e.g., vaccine price, administration costs, available supply) and non-economic tradeoffs. Further, as this decision involves different pertussis antigens, it needs to be informed by policy guidance on the merits of wP vs. aP from SAGE and WHO.

Summary implications

In summary, both wtIPV and sIPV have roles to play in satisfying the demand for different country segments. It is important to distinguish between the needs of two clear demand segments – (1) The self-producing countries, which have set a historical precedent of desiring local production; (2) All other new adopter countries, open to importing vaccine. Satisfying the needs of both of these segments will be critical to gaining global agreement around OPV cessation, a key step in the eradication process.

It is clear that wtIPV has a strong role to play for the non-self-producing countries, representing ~60% of total global birth cohort. wtIPV is an established technology, has significant planned and potential capacity, and has economics that are expected to improve as facilities scale-up. Given the lead times associated with scaling-up capacity (and ensuring that capacity is not repurposed for other uses), the decision to use planned and potential wtIPV capacity must be made soon, potentially before some of the uncertainties around sIPV are resolved (e.g., sIPV manufacturing scale). In addition, the ongoing dialogue on dosage-sparing approaches with the manufacturers should continue to better define their interest in investing in those technologies.

sIPV may have a role to play for the self-producing countries, and therefore continued development is important. It is not clear what form of local production (i.e. complete bulk through finishing, importing bulk and finishing locally) would be required, although many countries have already begun to express their preferences. If some countries will require local bulk IPV production in the long-term as they have done for other vaccines, then wtIPV will not be a viable solution for those countries. Current Global Action Plan III (GAP-III) guidelines prevent wtIPV production in such settings given concerns over the high transmissibility of wtPVs.

In the short-term, a clear dialogue with the self-producing countries must continue to explore their flexibility in their self-production requirements. Two elements of that dialogue will be critical: (1) Determination of how their decisions would change if vaccine could be imported at a price similar or lower than what would be available from local production; and (2) determination of whether in exchange for continued support of sIPV development, they would cease OPV use even if sIPV is not available in the targeted cessation timeframe. Given the risks associated with sIPV development, these countries would need to make advanced arrangements to import wtIPV post-cessation for a period of time – either in bulk or finished form – to ensure an IPV product is available if sIPV development is delayed.

Under this hybrid supply strategy, dosage-sparing approaches could play a further role in helping satisfy the short-term demand spike if self producers' only import for a period of time. The use of dosage-sparing approaches would allow wtIPV manufacturers to extend their "effective" capacity without investing in physical infrastructure that would become idle once self producers transitioned to sIPV. A summary of this hybrid supply strategy is presented in Figure 13.

Figure 13: Hybrid supply strategy

Which demand segment?	What technology platform?	What capacity?	When?	
▪ Self-producers	▪ wtIPV (transitional)	▪ Planned / potential wtIPV additions ▪ Potential dosage-sparing approaches	▪ At cessation (or earlier)	*Short-term (if needed)*
	▪ sIPV	▪ New	▪ When sIPV available	*Medium-term*
▪ Remaining middle and low income countries (i.e. non-self producers)	▪ wtIPV	▪ Planned / potential wtIPV additions ▪ Potential dosage-sparing approaches	▪ At cessation (or earlier)	

Path forward

We recommend several key next steps for the community based on these findings.

Seek indicative vaccine pricing from wtIPV manufacturers

It is important to engage the wtIPV manufacturers to understand potential vaccine pricing before making a conclusive assessment on the affordability of wtIPV. Ideally wtIPV manufacturers would provide the community price estimates across a range of different demand levels. This would allow the community to evaluate the trade-offs associated with different supply strategies as well as inform the program's future research activities. In addition, given the concentration of wtIPV supply, the community might consider long-term contracting mechanisms that would guarantee sustained affordability.

Rapidly complete the evaluation of schedule and dosage-sparing options

The community should rapidly complete the ongoing evaluation of the wide range of potential schedule (i.e., number of doses) and dosing-sparing options within the context of expected supply and demand. This evaluation should include a heightened dialogue with the manufacturers (particularly the more constrained players with an interest in dosage-sparing approaches) to optimize their participation.

Incorporate the research on IPV schedule and dose-reduction into the development of clear policy guidance for countries on the use of IPV post-eradication and assist countries in their decision making

Global health policy bodies should move towards issuing definitive guidance on the use of IPV. This guidance should address which situations / conditions warrant the use of IPV, when it should be adopted, for how long, and with what schedule. To that end, SAGE has recently established an IPV working group, which conducted its first meeting in early October. Under current timelines, this working group will deliver its initial recommendation to SAGE by 2011. In addition, it will be critical for GPEI stakeholders to work closely with the countries to help them make timely decisions around the introduction of IPV – this would include assessing the local situation in the context of the broader policy guidance.

Clarify the intentions of the "self-producers" concerning IPV

The flexibility of the "self-producing" countries should be further explored as their perspectives will impact decisions around technology / supplier choice. It will be critical to determine how their decisions would change if vaccine could be imported for similar or lower price than local production. In addition, it will be important to understand whether these countries would cease the use of OPV even if sIPV is not available at the time of global cessation. Depending on the models pursued, it may be necessary for

these countries to enter into supply agreements with wtIPV manufacturers to import product for a transitional timeframe until sIPV is available.

Refine demand estimates and communicate to manufacturers / donors in accordance with key eradication milestones

A more refined demand estimate should be developed based on the research on potential IPV schedules/dose and an understanding of specific country decision making, particularly that of the self-producers. This demand should be communicated to existing and new IPV manufacturers given the three-to-five years of lead time associated with the build out and validation of new production capacity. A consolidated view of low-income country IPV demand should also be shared with potential donors so they can further define their post-OPV cessation role in co-financing arrangements for IPV use in such settings.

Aggressively manage the risks of sIPV as development continues

With support from the community, public and private-sector manufacturers should continue to carefully monitor and manage each of the key risks associated with sIPV. As obstacles arise in development that impact the immunogenicity profile and/or timing, the community will need to continue to reassess the role of sIPV and identify potential measures (e.g., development assistance) that can be pursued. In addition, if it is important that sIPV is economically competitive with wtIPV, manufacturers need to carefully consider the implications of facility and scale point decisions.

Further evaluate key elements of the stand-alone versus combination decision and incorporate into demand projections shared with manufacturers

Several additional elements need to be evaluated to appropriately make the stand-alone vs. combination decision. First, the economic and supply situation around combination vaccines should be evaluated to determine whether these vaccines can be supplied at appropriate volumes within the economic breakeven range by key eradication milestones. Second, a better understanding of country perspectives (economic and non-economic) should be developed around the value of combination vaccines. Third, as SAGE continues to review its current guidance on the pertussis component of combination vaccines, any changes to its current policy on wP vs. aP should be incorporated into decisions regarding IPV stand-alone vs. hexavalent products. It is critical that the perspective on stand-alone vs. combination vaccines be incorporated into demand projections that are shared with manufacturers. Current and potential manufacturers are pursuing a range of different products and without clarity on this issue, supply is likely to be mismatched to demand in the future.

Credits

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