

GAVI's Vaccine Investment Strategy

Background

In recent years GAVI has made decisions about its new programmatic investments based on an investment case framework. At previous meetings, the GAVI boards have received a range of investment cases¹ and at this meeting, the Board is being presented with investment cases for Yellow Fever and Meningococcal A. Reviewing investment cases as they are presented ensures an evidence-based, carefully considered decision on new programmatic investments but it does not provide an overall strategic framework for decision making. Investment opportunities are evaluated on their own merits, rather than with each other, or in light of any resource envelope. The challenge is that vaccines available in the near-term would come before the Board first, potentially exhausting GAVI's resources by the time possibly more critical vaccines – are ready for decision.

In order to make best use of the available resources – and to ensure maximum impact, the Boards recognised the need for a comprehensive vaccine investment strategy that would define which new vaccines GAVI will consider supporting over the next five years. This strategy also provides costing of the chosen option and will consider implications for fundraising with an implementation plan to be presented in October. The Board was initially presented with the proposal for a vaccine strategy at its meeting in May of 2007. At a subsequent Alliance Executive Committee meeting in July 2007, the Alliance EC endorsed a two-step process for defining the Vaccine Investment Strategy:

1. WHO develops an initial list of priority vaccines, based on an independent review of global public health priorities. The preliminary outcome of this evaluation was presented for information to the GAVI Boards in November 2007. This list represents a starting point for the GAVI Alliance to develop its vaccine strategy and determine which investments best meet the objectives of the Alliance. 18 vaccines were identified in this process.
2. A GAVI Alliance process, supported by the Secretariat, would define the specifics of the new strategy, considering which vaccines were most consistent with the GAVI goals and mission and in line with country priorities.

WHO Priority list

After conducting a landscape analysis in which information on all vaccine-preventable diseases and candidate vaccines was collected, WHO consulted a series of experts to provide input on what they felt were the most important criteria to guide vaccine-preventable disease prioritisation. The experts indicated the 10 criteria in relative importance are as follows: mortality; epidemic/pandemic potential; economic impact; case fatality rate; disease incidence in the highest burden regions; long term sequelae; morbidity; inequity; lack of other alternative treatment or prevention measures; and severity of symptoms. Experts were then asked to compare against these criteria diseases for which vaccines are currently available (and not routinely recommended or widely used) or are expected to be available by the year 2012.

¹ measles mortality reduction (two separate cases); polio stockpile; maternal and neonatal tetanus; health systems strengthening, yellow fever stockpile and preventive campaigns; rotavirus vaccine; and pneumococcal vaccine

In this preliminary ranking, 18 diseases were clustered into three groups: 1) "Very High Priority" (Malaria and Pneumococcal Disease); 2) "High Priority" (Cervical Cancer (HPV), Cholera, Dengue, Japanese Encephalitis, Meningococcal ACWY, Rabies, Rotavirus, Seasonal influenza, Typhoid Fever, and Yellow Fever); and, 3) "Medium Priority" (Hepatitis A, Hepatitis E, Meningococcal B, Mumps, Rubella, and Varicella). The result of the categorization represents the overall global picture, and is a starting point in the overall decision-making process.

In addition to the vaccines included in the WHO priority list, the issue of injectable polio vaccine (IPV) has been highlighted as an emerging issue for GAVI countries. IPV was not considered for the Vaccine Investment Strategy because it is not in the WHO priority list. Further, the GAVI Boards have decided in the past that GAVI should not provide direct support to polio eradication, except for a one-time grant for a polio stockpile which was approved with IFFIm resources. Should polio eradication go forward as planned by 2010-2012, GAVI countries may decide to switch to IPV and the GAVI Boards should be aware that GAVI might be viewed as a potential funder of this vaccine.

Overview of the strategy development process

Following a competitive bidding process, Applied Strategies Consulting was selected to develop the strategy under the supervision of a time-limited steering committee (Craig Shapiro, WHO; Osman Mansoor, UNICEF; Steve Landry, Bill & Melinda Gates Foundation; Deo Barakmfiteye, formerly of WHO AFRO; Andrew Jones, GAVI Secretariat). Implementation of the project is divided into four phases:

1. Diagnostic: Gather relevant information from Alliance partners and stakeholders, and product development partnerships to profile each disease/vaccine under consideration and consider the types of associated activities that could be funded to ensure successful vaccine introduction (February-March)
2. Consultations: Carry out 7 in-country consultations along with online, video and phone consultations to solicit input from key stakeholders. The full consultation report of country input is available on the website. (March-April).
3. Synthesis and vaccine evaluation: Based on the outcomes of the diagnostic research and analysis and the consultations, evaluate each disease/vaccine individually and in comparison. Identify a range of scenarios, or vaccine portfolio themes, associated with packages of multiple vaccines over different timeframes. The Joint Executive Committees will provide input on the themes, and an independent review committee will validate the appropriateness of the specific vaccine packages options against the chosen themes. (April – May)
4. Strategy development and investment requirements: Present recommended vaccine investment theme to the GAVI Alliance Board (June), identifying the package of associated vaccines and activities that GAVI would support, as well as an indicative investment envelope along with long-term income projections. Following a decision by the Board, an implementation plan will be prepared considering the specific financial implications (and corresponding fundraising strategy) as well as the associated activities and timeframe for investments. (July – September)

The process described above has included inputs from multiple stakeholders, the project steering committee, the GAVI Working Group and the GAVI Joint Executive Committees. The team also carried out extensive in-country consultations and consultations with Alliance partners, product development partnerships and other key players in the field of global immunization. A

background document accompanying this paper summarized the information collected during each phase and the detailed reports can be found on the project web site (http://www.gavialliance.org/vision/strategy/vaccine_investment/index.php)

1. Diagnostic phase

Data were gathered from product development partnerships and global databases, including those of WHO to consider the mortality associated with each disease. A range of other data was also considered around morbidity although this was less reliable than mortality data. Cost-effectiveness data and DALY data was available for some but not all diseases and thus could not function effectively as a cross-disease comparator. Finally, following extensive research and verification by industry, a comprehensive list of vaccines suitable for all diseases under consideration was compiled and available on the project website.

2. Consultations

A broad range of consultations was undertaken as part of the strategy development (see Annex 1). Stakeholders in thirty-seven countries were consulted with through a combination of in-country visits, online surveys and phone interviews. In addition over 60 global stakeholders were interviewed primarily by phone, although some were conducted in person. The main questions asked through the survey instrument related to 1) the decision criteria for considering whether or not to introduce a vaccine and 2) the relative importance of the vaccines under consideration.

Local disease burden and safety and effectiveness generally came out on top when country stakeholders were asked about decision criteria for introducing a new vaccine (see Annex 1, Table 3). (While rotavirus and pneumococcal vaccines have already been approved by the GAVI Board, they were included on the list of vaccines used during the interviews given that many countries have not yet introduced them.) Country preferences for the vaccines under consideration resulted in differing responses across different regions: malaria, pneumococcal and meningococcal vaccines were top priorities in Africa; Japanese Encephalitis, pneumococcal and dengue vaccines were top priorities in Asia; and other vaccines, such as rotavirus and HPV, were top priorities in other regions.

Global stakeholders felt that GAVI should focus its strategy on those diseases with the highest mortality and on the most cost-effective vaccines, taking into account country preferences (see Annex 1, table 4). When asked about disease priorities, global stakeholders ranked malaria, meningitis, HPV and JE on top, provided an effective vaccine will be available to address these diseases.

3. Synthesis and Evaluation

The first step of the synthesis was to review the 18 diseases identified by WHO to see if any should be excluded from consideration for the GAVI Vaccine Investment Strategy. Based on this review, meningococcal B and varicella were removed because of the particularly low prevalence of these diseases in GAVI-eligible countries and seasonal influenza was removed because of a decision by the Board in May 2007 not to support routine immunization against seasonal flu as a strategy to protect against pandemic flu. Pneumococcal, rotavirus and yellow fever vaccines were removed as they are already supported by GAVI.

A detailed characterisation across the 12 remaining diseases and vaccines was carried out using the data gathered in the diagnostic phase. Each disease and associated vaccine was evaluated against the different strategic themes based on their characteristics (e.g. the impact of the disease

on mortality and morbidity and on different age groups, the age at which the vaccine would be administered, etc.) leading to a number of different vaccine portfolio options guided by different policy objectives.

Six strategic themes and associated vaccine portfolios were presented to the GAVI Alliance and Fund Executive Committees on 6 May, portfolios which ranged from one that included all of the potential 12 vaccines (a total cost of \$6.8 billion over 2009-20) to one that included only the three existing vaccines (ie, no new vaccines). Following synthesis of all input – stakeholder interviews, consultations with the Project Steering Committee, the GAVI Working Group and the GAVI Executive Committees, two themes with associated vaccine portfolios were identified as the most appropriate for consideration by the IRC: *Focus on child mortality only* with an associated vaccine portfolio of 6 vaccines: Cholera, Dengue, Malaria, Japanese Encephalitis, Typhoid, and Meningitis A; and *Reduce overall mortality* with an associated vaccine portfolio of 8 vaccines: Cholera, Dengue, Malaria, HPV, Japanese Encephalitis, Rabies, Typhoid, and Meningitis A.

Independent Review Committee

An Independent Review Committee (IRC) met under the chairmanship of Dr. Robert Black (Johns Hopkins University) to review the draft vaccine strategy (See Annex 2 for the full IRC report and list of IRC members). The IRC emphasized mortality and disease burden as important assessment criteria and concluded that the data gathered as part of the analysis was sufficient to consider the relative rankings of the various diseases and vaccines in terms of potential impact. The Committee reviewed all 12 diseases and related vaccines to assess whether the categorization of vaccines into the two portfolio options was appropriate.

- The IRC endorsed the elimination of mumps and hepatitis A and E from the list of vaccines under consideration in line with the analysis of available data and outcomes from the stakeholder consultations.
- The IRC recommended differentiating between diseases for which there are currently licensed vaccines, or soon to be licensed, and diseases for which a vaccine will not be available in the short term and for which key vaccine characteristics such as efficacy and safety are still unknown. Vaccines against malaria and dengue are in earlier stages of development and evaluation; hence their availability within the next 5 years is highly uncertain. Therefore, the IRC recommended not to include malaria and dengue vaccines as part of the consideration of GAVI support for future vaccine procurement at this point in time. However, the IRC recommended that some pre-introduction activities could be supported if not addressed by other donors.
- The IRC concluded that the two portfolios under consideration focused exclusively on mortality. In reviewing the stakeholder and country consultations, they noted that disease burden and morbidity were highlighted as important criteria yet the portfolios did not adequately capture severe morbidity, and in particular, long-term disability, burden on health services, secondary impact on women as caregivers and economic impact. Therefore, the IRC modified the “overall mortality” portfolio, adding rubella vaccine given its impact on overall disease burden but not on mortality, and renaming the portfolio *Reduce Overall Disease Burden*.

Based on the above considerations, the following are the options recommended by the IRC for consideration by the GAVI Alliance and Fund Boards:

| Portfolio options: | <u>Reduce Overall Disease Burden</u> | <u>Focus only on Child Mortality</u> |
|-----------------------------|---|---|
| Vaccines considered: | | |
| 1. Cholera | 1. Cholera | 1. Cholera |
| 2. Japanese Encephalitis | 2. Japanese Encephalitis | 2. Japanese Encephalitis |
| 3. Typhoid | 3. Typhoid | 3. Typhoid |
| 4. Meningitis A | 4. Meningitis A | 4. Meningitis A |
| 5. HPV | 5. HPV | |
| 6. Rabies | 6. Rabies | |
| 7. Rubella | 7. Rubella | |
| 8. Malaria | | |
| 9. Dengue | | |
| 10. Hepatitis A | | |
| 11. Hepatitis E | | |
| 12. Mumps | | |

4. Strategy and Financial Requirements

The two recommended portfolios were then analysed against a range of quantitative and qualitative criteria. The quantitative criteria looked at the potential cost of the full portfolio should it be introduced gradually across all relevant GAVI countries and the impact such an investment would have on deaths averted, cases averted and treatment costs averted. Summary data are provided below..

As noted previously, a decision to support all 12 vaccines under consideration would cost \$6.6 billion and save just over 2 million lives. If fully funded, approximately \$3.5 billion would be required to finance the *Reduce Overall Disease Burden* portfolio from 2009 - 2020, whereas approximately \$1.7 billion would be required to finance the *Focus only on Child Mortality* portfolio. Note that this is a maximum projection because 1) it assumes full financing of both routine and catch up campaigns for all vaccines (as appropriate); 2) it assumes that there is no drop in price of vaccines over time 3) it assumes that all vaccines are taken up by countries for which they are appropriate and, 4) that the rate of uptake, although phased (in terms of fast, medium and slow adopters) and sequenced (in that one vaccine is adopted by a country before the next) is aggressive. In reality, country uptake is likely to be more limited, and slower. Once the Boards choose their preferred vaccine portfolio, projections will be further refined as part of the development of options for implementation, for example whether to include support for both routine immunisation and campaigns, and the number of countries to be targeted.

Table 1: Impact of portfolios under consideration over 2009-2020

| VACCINE STRATEGY (includes routine immunisation and catch-up campaigns) | DEATHS AVERTED | < 5yo DEATHS AVERTED | CASES AVERTED |
|---|-----------------------|--------------------------------|----------------------|
| Reduce Overall Disease Burden | 1,991,000 | 593,000 | 27 million |
| Focus only on Child Mortality | 764,000 | 532,000 | 23 million |

Table 2: Costs of portfolios under consideration over 2009-2020

| VACCINE STRATEGY (includes routine immunisation and catch-up campaigns) | Peak annual cost to GAVI | Cost to GAVI Per Death Averted | Cost to GAVI Per <5yo Death Averted | Cost to GAVI Per Case Averted |
|--|--------------------------|--------------------------------|-------------------------------------|-------------------------------|
| Reduce Overall Disease Burden | \$300 million | \$1,286 | \$ 4,317 | \$ 102 |
| Focus only on Child Mortality | \$160 million | \$1,285 | \$ 1,846 | \$ 41 |

A range of qualitative criteria were also considered by the IRC. These included potential for strengthening health systems through promoting service integration, availability of adequate treatment, whether or not the disease would affect gender inequity or inequity for poor. A complete list can be found in the Annex 3, which shows that the *Reduce Overall Disease Burden* portfolio scores better across the range of criteria than the *Focus only on Child Mortality*.

5. Recommendations

If GAVI were to support *all² vaccines for diseases identified by the strategy process*, an investment of approximately \$6.6 billion over 2009-20 would be required to buy the vaccine for GAVI countries. Although this would ensure maximum access to all available vaccines for GAVI countries, it would lack strategic focus and not be the best use of GAVI's and countries' resources given the limited impact some of these vaccines would have. Moreover, countries would likely be unable to take up multiple vaccines simultaneously in the context of weak health systems and country decision-making processes are likely to be challenged if presented with 12 new vaccine options.

The portfolio entitled *Reduce overall disease burden* has the potential to avert approximately 2 million deaths across different age groups and all GAVI countries within 10 years. The vaccines included in this portfolio broadly correspond to the priorities as expressed in the consultations by different regions and include vaccines of global and regional importance. In considering morbidity as well as mortality, this portfolio values the additional impact illness and disability places on the health system and the country at large. Moreover, with HPV and rubella vaccines, GAVI would have an opportunity to protect vulnerable women against a serious and fatal disease and congenital anomalies of their newborns.

The portfolio titled *Focus only on Child Mortality*, is expected to avert approximately 750,000 deaths in 10 years, mostly in children under 5. The four vaccines in this portfolio are less responsive to the preferences expressed by country and global stakeholders in the consultations. Because of its exclusive focus on children and on mortality (rather than morbidity), this portfolio choice would exclude HPV, rubella and rabies vaccines. Moreover, this portfolio would not make a significant contribution to MDG 4 as compared to other non-vaccine interventions such as bed nets and oral rehydration therapy, because the vaccines do not address major causes of under-5 mortality. Finally, the vaccines in this portfolio are highly regionally specific; of the four vaccines offered, only 2 (typhoid and cholera) would be applicable to GAVI countries in all regions of the world.

Given the analysis presented above, the evaluation conducted by the IRC, and feedback from consultations with a broad range of stakeholders it is recommended that *Reduce overall disease burden* be chosen as the strategy theme for GAVI's vaccine investment strategy. This portfolio

² As noted earlier, of the 18 WHO priority vaccines, three diseases were eliminated from consideration as they are not relevant for GAVI and three vaccines are already being supported, leaving 12 for consideration.

provides a balance between ‘doing everything’ on the one hand (in terms of supporting all 12 vaccines identified in this strategy process) and an exclusive focus on child mortality on the other hand. The *Reduce overall disease burden* has the potential to avert a significant number of deaths and prevent morbidity both in children and in adults. It is therefore consistent with GAVI’s overall mission of saving children’s lives *and* protecting people’s health and it provides countries with more options to apply for the vaccines that meet their individual needs. Lastly, with a strategic focus on overall mortality and morbidity, and additional advantages such as the impact on gender inequity, this portfolio provides a powerful fundraising tool for GAVI to secure the funds necessary for successful implementation.

6. Board decision

Based on comprehensive analyses and a broad consultation including review by an Independent Review Committee and the GAVI Working Group, the GAVI Alliance and Fund Boards are requested to:

- Endorse the Reduce Overall Disease Burden portfolio theme and associated vaccines (Cholera, Japanese Encephalitis, Typhoid, Meningitis A, HPV, Rabies, Rubella) for the years 2009-2013. Vaccines not included in this portfolio would not be considered within this time period.

7. Next Steps

The Board is not being asked to make a financial commitment at this time, but rather to endorse a strategic theme and associated vaccines for consideration of support in the coming five years. Vaccines not included in this portfolio would not be considered within this time period.

At this meeting, the Board is also being presented with a detailed implementation plan in the form of an investment case for meningococcal A which includes both the vaccine and program support costs. Should the Board decide to fund this investment case it would be the first step in the implementation plan for the strategy. The implementation plan for other vaccines will be presented in October.

Based on the decision take by the Board, the Secretariat will work on an implementation plan that will detail financial implications, resource needs, and timing and nature of proposed future investments, for different implementation scenarios for that portfolio.

ANNEX 1**Consultation Summary****Table 1: Countries Consulted**

| AFRO (19 OF 36) | | AMRO (5 OF 6) | EMRO (3 OF 6) | EURO (3 OF 8) | SEARO (4 OF 9) | WPRO (3 OF 7) |
|--|--|---|---|---|---|---------------------------------|
| Benin Cameroon Chad Congo Cote d'Ivoire DRC Ethiopia Ghana Guinea Kenya | Lesotho Madagascar Mozambique Nigeria Rwanda Senegal Tanzania Uganda ¹ Zambia | Bolivia ¹ Cuba Haiti ¹ Honduras Nicaragua | Afghanistan Pakistan ¹ Yemen | Armenia Kyrgyzstan Moldova Ukraine | Bangladesh India Indonesia Nepal | Cambodia Mongolia Vietnam |
| Live: 209 Online: 81 | Live: 3 Online: 9 | Live: 1 Online: 20 | Live: 15 Online: 4 | Live: 0 Online: 24 | Live: 10 Online: 8 | |

Table 2: Global Stakeholders consulted

| Affiliation | No. of Participants |
|--------------|---------------------|
| Donor | 4 |
| GAVI Board | 6 |
| GAVI WG | 10 |
| GAVI Staff | 3 |
| Key Partner | 20 |
| Other | 14 |
| PDP | 10 |
| Supplier | 9 |
| TOTAL | 61 |

ANNEX 1**Table 3: Country decision criteria by region**

| Priority | AFRO (n=264) | AMRO (n=20) | EMRO (n=7) | EURO (n=19) | SEARO (n=15) | WPRO (n=12) |
|----------------------|--|--|--|---|--|--|
| 1 st Tier | Safety & effectiveness Disease burden | Disease burden Safety & effectiveness | Disease burden Sustainability | Disease Burden | Disease burden Safety & effectiveness | Disease burden |
| 2 nd Tier | Sustainability | Sustainability Burden on immunization program | Outside support Burden on immunization program | Sustainability | Sustainability Burden on immunization program Epidemic potential | Safety & effectiveness Sustainability WHO recommendation |
| 3 rd Tier | Epidemic potential WHO recommendation | Cost to procure | Safety & effectiveness WHO recommendation Epidemic potential | Safety & effectiveness Outside support | WHO recommendation Cost to procure | Cost to procure Cost to administer |
| 4 th Tier | Burden on immunization program Cost to procure Outside support Cost to administer | WHO recommendation Epidemic potential | Cost to procure | Epidemic potential Burden on immunization program Public opinion Cost to procure | | Epidemic potential |

ANNEX 1**Table 4: Global Stakeholder criteria for decision-making**

| Factors | No. of Responses | | |
|-------------------------------|---------------------|-------------------|----------------|
| | Definitely Consider | Consider Somewhat | Don't Consider |
| Mortality | 56 | 2 | 0 |
| Cost Effectiveness of Vaccine | 47 | 12 | 0 |
| Country Preference | 44 | 7 | 2 |
| Morbidity | 43 | 14 | 1 |
| Children Most Affected | 38 | 17 | 3 |
| Cost of Vaccine Procurement | 34 | 15 | 5 |
| Epidemic Potential | 31 | 21 | 2 |
| Country Sustainability | 30 | 20 | 5 |
| Duration of Severe Symptoms | 29 | 24 | 4 |
| Cost of Administration | 29 | 28 | 2 |
| Integration Potential | 28 | 27 | 4 |
| Potential for Global Impact | 28 | 23 | 3 |
| Cost of Vaccination | 27 | 25 | 6 |
| Alt. Intervention Available | 25 | 27 | 6 |
| Packaging & Presentation | 19 | 23 | 12 |
| Impact on Gender Issues | 16 | 27 | 15 |
| Co-morbidity Vulnerability | 15 | 33 | 10 |

ANNEX 2

Vaccine Investment Strategy
Independent Review Committee Report
May 28th to 30th, 2008

The IRC met over the course of two and a half days in Amsterdam to review the vaccine investment strategy and make recommendations. Overall, the IRC commended the process to date, particularly the volume and scope of information presented to the IRC at the meeting and in advance of the meeting. Furthermore, the IRC felt the evidence and data and levels of analysis presented at the meeting, were a sufficient quality for GAVI to enable GAVI to make a decision on a vaccine investment strategy. The IRC was chaired by Dr. Bob Black (Johns Hopkins University) and consisted of the following members:

- Dr. Claire Broom, Independent Epidemiology Expert, USA
- Prof. Helen Rees, University of Witwatersrand, South Africa
- Dr. Penelope Kalesha, Government of Zambia
- Dr. Raj Bahn, Government of India
- Dr. Roland Dobbelaer, independent vaccine expert, Belgium

Terms of Reference

The IRC was asked to review the investment strategy work in line with four objectives:

1. To examine the data (morbidity, mortality, cost-effectiveness, etc.) on each of the diseases / vaccines and highlight areas of uncertainty and ensure relative comparability.
2. To review the outputs of the country and stakeholder consultation
3. To consider the application of the criteria set out by the project steering committee
4. To consider the proposed approach and options for vaccine portfolios

1. Disease and vaccines data

The IRC discussed that while the absolute numbers gathered as part of the analysis³ are subject to debate within the global community given the varying sources of data and time frames used, the data which referenced WHO sources for all diseases was considered to be acceptable by the IRC for their task of considering the relative rankings of the various diseases and vaccines in terms of potential impact. The IRC considered estimated mortality

³ WHO participated by phone on the second day and noted specific concerns on the country level data, which was often extrapolated from global and regional data. For the purposes of this project, only summaries of all GAVI countries will be used.

ANNEX 2

data or - more generally - overall disease burden (including cases and sequelae as well as mortality) over data less certain (ie. savings from cases averted). It thus emphasized the importance of mortality and disease burden as very important comparison points. The IRC reviewed preliminary cost-effectiveness data on the portfolios considered, but could not make definitive statements because it did not have time to consider all the assumptions that had been included and because not all elements e.g. deaths averted in adults from cervical cancer⁴, or the cost savings from avoided emergency response campaigns (Group A meningococcus), had been included at the time of the meeting. It also felt that the cost to countries of the delivery of the vaccine and not only the cost of the vaccine and related supplies should be considered in a future economic analysis. This is particularly important because most of the vaccines evaluated would be delivered outside the usual immunization schedule in the first year of life. Economic aspects will clearly be important in choosing between the portfolios recommended and perhaps prioritizing vaccines within the portfolios.

2. Consultation results

The IRC reviewed the information gathered from both country and global stakeholder interviews. The IRC noted that the broad range of interviewees provided a strong basis for considering which criteria should guide development of the portfolio options.

With regard to disease prioritization, the IRC noted that the small sample size for many of the countries and regions made it difficult to draw region-specific conclusions. Further, there was a lack of consistency between the prioritization criteria and the diseases chosen. In light of this, the IRC felt that, although the outputs from the country consultations regarding vaccine choice should be regarded with caution.

3. Application of criteria in creating portfolio options

Taking into account the country consultations, the stakeholder consultations, and the GAVI principals and mission statement, the IRC endorsed the criteria used to define the portfolio options. However, with regard to data on morbidity and mortality, they modified the rating from absolute numbers to a relative ranking of high, medium, low and very low, to account for the inherent uncertainty around some of these data. They then reviewed each of the 12 disease and related vaccines against the following criteria to assess if the portfolio options were appropriate (see annex 1):

- Disease Burden
 - Mortality: High, Moderate, Low or Very Low
 - Morbidity: High, Moderate, Low or Very Low
 - Long term sequelae: High, Very Low, Low, No
 - Under Five mortality: Yes, Yes_{low}, No
 - Epidemic potential: Yes/ No; as well as health system impact of an epidemic (Yes/No)
- Vaccine Assessment

⁴ In light of the varying prevalence of different oncogenic HPV types in GAVI regions

ANNEX 2

- Safety: Yes/ ? (uncertain because vaccine not yet registered or still in clinical trials)
- Effectiveness/efficacy of the vaccine: High, Moderate or Low or ? (uncertain because vaccine not yet registered or still in clinical trials)
- Impact of vaccine if successful: High, Moderate or Low or ? (uncertain because vaccine not yet registered or still in clinical trials)
- Any programmatic challenges associated with the vaccine
- Other challenges
- Special considerations

The IRC's evaluation of the diseases / vaccines, considering the criteria described above, and their assessment of the proposed portfolios resulted in the following:

1. *Hepatitis A, E and Mumps*: in line with analysis to date, three diseases were eliminated from consideration in the strategy:
 - Hepatitis A and E: Disease burden data (both mortality and morbidity) is very limited although the IRC considered it to be likely very low in GAVI countries.
 - Mumps: Disease burden data, while likely under-reported suggested that mortality is very low with cases resulting in few significant long-term sequelae.
2. *Dengue and Malaria*: IRC members noted the significant disease burden in GAVI countries of dengue and malaria and recommended differentiating between diseases for which there are currently licensed vaccines or vaccines that are soon to be licensed and diseases for which the vaccine characteristics e.g. efficacy and safety are currently still unknown. Members of the IRC felt it was not possible to compare current vaccines with those still early in development. Vaccines against malaria and dengue are in earlier stages of development and evaluation; hence their availability within the next 5 years is highly uncertain. The IRC noted that using the year 2013 as a cut-off point for future vaccines is somewhat arbitrary. The IRC concluded these vaccines should be considered separately from others in the list which are available or very close to market entry and could realistically be introduced in the 2008 – 2013 timeframe. Therefore, a recommendation to support future procurement of malaria and dengue vaccines at this point in time was not considered appropriate. Nonetheless, the IRC felt that both these diseases represented a significant burden of disease in GAVI countries and were of critical importance. Thus they noted that it would be important for GAVI to consider funding pre-introduction activities and that these types of activities should be considered in light of support from other funders for these vaccines as to where GAVI can best add its value. In light of the above, the IRC recommends that malaria and dengue be considered for alternative investments but that no decision on investment in the procurement and introduction of these vaccines be taken at this time.
3. Based on the results of the disease evaluation process described above, the IRC felt that the two portfolios in initial discussion i.e. based on child mortality (MDG 4 focused) and total mortality, did not adequately capture severe morbidity, and in particular, long-term disability, burden on health services, secondary impact on women as caregivers and economic impact. Specifically, severe long term sequelae from diseases such as congenital rubella syndrome and Japanese encephalitis and meningococcal disease could not be adequately reflected in the two mortality-based

ANNEX 2

portfolios that omitted morbidity. Therefore, the IRC created a third portfolio of vaccines which it classified as *Reduce Overall Disease Burden Through Investment in 'Licensed' Vaccines*. This included seven vaccines: Cholera, HPV, JE, Rabies, Rubella, Typhoid Fever and Men A.

4. Consideration of vaccine portfolios

In order to evaluate the three resulting portfolios, the IRC considered the following criteria:

1. Prioritise potential integration with EPI schedule (<12 months)
2. Prioritise potential integration with an extended EPI schedule (<18 months)
3. Focus on highly effective vaccines (>75% effectiveness in GAVI-eligible countries)
4. Focus on diseases for which no adequate treatment is currently available
5. Focus on diseases for which no adequate prevention is currently available
6. Prioritise vaccines that address inequity of the poor (relating to diseases disproportionately affecting the poor, or to vaccines specifically beneficial to the poor)
7. Prioritise vaccines that address gender inequity (relating to diseases disproportionately affecting one sex, or to vaccines specifically beneficial to one sex)

The IRC considered whether these seven criteria could be used to create alternative portfolios for the IRC and Board's consideration. This possibility was explored but the IRC felt that the three portfolios already identified remained the strongest, for IRC to review as none of the seven criteria provided compelling justification as the basis for an additional portfolio. In addition, the IRC aimed to present a maximum of three portfolios to the Board for their consideration. The benefits and shortcomings in relation to the final two portfolios recommended to the Board are summarized in annex 2.

RECOMMENDATIONS

The IRC acknowledged the significant amount of work done to date and the comprehensive analysis to support their work and conclusions. The IRC recommended that:

1. Mumps, Hepatitis A and Hepatitis E be eliminated from consideration in this strategy.
2. Malaria and Dengue vaccines be considered separately and in the context of possible supportive and catalytic activities to prepare and accelerate their future entry into the market
3. That the portfolio entitled "total mortality" should be eliminated because it was similar to the newly created "overall burden of disease" portfolio and was considered redundant.
4. The IRC recommends that the GAVI Boards consider 2 vaccine portfolios (as detailed in annex 2):
 - a. "Maximise Impact on Overall Burden of Disease": 7 vaccines
 - b. "Focus on MDG 4": 4 vaccines

ANNEX 2**Annex 1: Evaluation of vaccines**

| Vaccine | Disease Burden | | | | | | Vaccine Assessment | | | | | Special Considerations |
|--------------------------------|-----------------------------------|----------------------|--------------------------|----------------|--------------------|--------|--------------------|---------------------------|---|---|----------------------------|---|
| | Total Annual Mortality (H,M,L,VL) | Morbidity (H,M,L,VL) | Long Term Sequelae (Y/N) | <5yo Mortality | Epidemic Potential | | Safety | Effective-ness (H,M,L,VL) | Impact if Implementation is Successful (H,M,L,VL) | Program-matic Challenges | Other Potential Challenges | |
| | | | | | Y/N | HS Imp | | | | | | |
| Cholera | M | L | No | Yes | Y | Y | None | M | M | 1yo cohort | Duration of Protection | None |
| Dengue | L | L/M | No | Yes | Y | Y | ? | ? | ? | 1yo cohort | ? | No Tx; Lmtd Px success |
| HepA | VL | VL | No | No | N | N | None | H | VL | 1yo cohort | None | None |
| HepE | VL | VL | No | No | N | N | ? | ? | ? | ? | ? | None |
| HPV for Cervical cancer | H | M | Yes - H | No | N | N | None | M (unknown in HIV pts) | H | In & out of school-based delivery for adolescent ♀s | Cultural challenges; | Targets ♀s only (screening barriers); country preference for 4-valent (i.e., genital warts) |
| JE | H _{Regional} | L | Yes - H | Yes | Y | Y | None | H | H | 1yo cohort | China Reg/WHO PQ issues | Earthquake impact |

ANNEX 2

| Vaccine | Disease Burden | | | | | | Vaccine Assessment | | | | | Special Considerations |
|------------------------------------|-----------------------------------|----------------------|--------------------|----------------|--------------------|--------|--------------------|--------------------------|---|----------------------------------|----------------------------|--|
| | Total Annual Mortality (H,M,L,VL) | Morbidity (H,M,L,VL) | Long Term Sequelae | <5yo Mortality | Epidemic Potential | | Safety | Effectiveness (H,M,L,VL) | Impact if Implementation is Successful (H,M,L,VL) | Programmatic Challenges | Other Potential Challenges | |
| | | | | | Y/N | HS Imp | | | | | | |
| Malaria | VH | VH | Yes - L | Yes | N | N | ? | ? | ? | ? | ? | Monitor vaccine develop. |
| Mening (conjugate) | M _{Regional} | L | Yes - H | Yes | Y | Y | None | H | H | Unlikely (EPI schedule) | Campaigns 1-29yo | Investment case under review |
| Mumps | VL | L | Yes - VL | No | N | N | None | H | L | None | None | MMR exists |
| Rabies | M | L | No | N | N | N | None | H | H | Post-exp access, esp rural areas | | |
| Rubella for CRS | VL | M | Yes - H | No | No | No | None | H | H | Need ≥ 70% coverage rate | | Would “no” decision from GAVI send wrong message to countries using R/MR/MMR |
| Typhoid (licensed vaccines) | H | H | No | Yes | N | N | None | M | M | 2yo cohort | Catch-up in 3-15yo | Monitor conjugate vaccine development |

ANNEX 2**Annex 2: Evaluation of portfolios**

| Reduce Overall Disease Burden* | Benefits | Shortcomings |
|---------------------------------------|--|--|
| Cholera | <ul style="list-style-type: none"> • Addresses the greatest overall disease burden (morbidity and mortality) • More inclusive portfolio supports a broader range of country choices • Provides opportunities for integration with other services • Innovative compared to past approaches • Catalyzes new definitions of vaccination administration strategies • Represents a new era in immunization programs supported by GAVI • Promotes innovation related to vaccine delivery • Contributes to both MDG 4 and 5 • Greatest potential economic impact • Greatest potential savings to health systems • Rubella (not in MDG 4 portfolio) requires little investment relative to magnitude of impact of CRS prevention on impact on health services, social costs, gender impact, long-term disability; no other treatments or preventions available, leverages existing delivery systems • Rabies mortality is addressed (not in MDG 4 portfolio) • Can use second dose of measles to deliver MR which would motivate increase in MCV2 coverage rate; second dose of measles may be supported by GAVI, if WHO recommends | <ul style="list-style-type: none"> • Extends beyond EPI - greatest implications for delivery systems • HPV has only moderate effectiveness against oncogenic HPV types that are prevalent in GAVI-eligible countries • Cholera and typhoid have lower efficacy than desired and shorter durations of protection • Expensive relative to MDG4 portfolio |
| HPV | | |
| JE | | |
| MenA | | |
| Rabies | | |
| Rubella | | |
| Typhoid | | |

ANNEX 2

| Focus on MDG 4 Goals | Benefits | Shortcomings |
|----------------------|---|--|
| Cholera | <ul style="list-style-type: none"> • Fit with expanded EPI program • More favorable on cost per death averted • Contributes to MDG4 • Focuses on earlier impact • Increases opportunity for 2nd year immunization • With 2nd year, increase chance of 2nd dose of measles, DTP booster doses, etc. • Potential to impact availability of vaccine • Good potential economic impact • Good potential savings to health systems • Provides clear focus for GAVI investments | <ul style="list-style-type: none"> • Largely limited to MDG 4, but does not have large impact on <5yo mortality • Missed opportunity to impact greater mortality and disease burden • Missed opportunity for additional vaccine approach innovation and health services integration • Missed opportunity to determine how to introduce adolescent vaccines and enhance reproductive health package • Not addressing rabies mortality • Cholera and typhoid have lower efficacy than desired and shorter durations of protection • Largely regional diseases -- lacks global feel |
| Typhoid | | |
| JE | | |
| MenA | | |
| | | |
| | | |

ANNEX 3

Qualitative criteria assessment**Table 1: Vaccine Portfolios relative to service integration**

| Portfolio Option (# vaccines) | # of Portfolio Vaccines that Support Service Integration * | | | | | | |
|--|--|----------------|------------|----------------------------------|---|------------------------------|----------------|
| | MDG4 | MDG5 | EPI | | IMCI | IMAI | Other Programs |
| | | | <1yo | <18mo | | | |
| Reduce Overall Disease Burden (n=7) | 5 | 2 | 2 | 4 | 5 | 4 | 2 |
| Focus on MDG4 Goals (n=4) | 4 | 0 | 2 | 3 | 4 | 3 | 0 |
| Vaccines in Each Category Given Vaccines Under Consideration | Cholera JE MenA Rabies Typhoid | HPV Rubella | JE MenA | Cholera JE MenA Rubella | Cholera JE MenA Rubella Typhoid | HPV JE MenA Typhoid | HPV Rubella |

- * *EPI – Expanded Program on Immunization; IMCI = Integrated Management of Childhood Illness (WHO); IMAI = Integrated Management of Adolescent and Adult Illness (WHO)*

Table 2: Vaccine Portfolios relative to long term sequelae

| Portfolio Option (# vaccines) | # of Portfolio Vaccines Addressing Long-Term Sequelae * | | |
|--|---|----------|------------------------------|
| | Mild-None | Moderate | Severe |
| Reduce Overall Disease Burden (n=7) | 3 | - | 4 |
| Focus on MDG 4 Goals (n=4) | 2 | - | 2 |
| Vaccines in Each Category Given Vaccines Under Consideration | Cholera Rabies Typhoid | | HPV JE MenA Rubella |

- * *Categorization Guidelines*
 - Mild-None: rare severe cases or mild long-term effects (e.g., reduced fertility)*
 - Moderate: less impact but long-term (> 1yr; e.g., deafness)*
 - Severe: > 5% of cases result in neurological or congenital complications (e.g., meningitis, CRS)*

ANNEX 3**Table 3: Vaccine Portfolios relative to gender inequities**

| Portfolio Option (# vaccines) | # of Portfolio Vaccines Addressing Gender Inequities | | |
|-------------------------------------|--|--|-------------------------------------|
| | Men & Women Suffer Differently | Prevalence Greater in Men or Women | Adversely Affects Pregnant Women |
| Reduce Overall Disease Burden (n=7) | 1 | 2 | 2 |
| Focus on MDG4 Goals (n=4) | 0 | 0 | 1 |
| | HPV | HPV Rabies | Cholera Rubella |

Vaccines in Each Category
Given Vaccines Under
Consideration

Table 4: Vaccine Portfolios relative to country preferences

| Portfolio Option | # of Overall GAVI Portfolio Vaccines that Support Country Preferences* | | | | | |
|---|--|---------------------|---------------------|---------------------|---------------------|------------------|
| | AFRO | EMRO | EURO | SEARO | WPRO | AMRO |
| Reduce Overall Disease Burden | 3 | 3 | 4 | 4 | 4 | 3 |
| Reduce Childhood Mortality | 2 | 3 | 4 | 2 | 2 | 2 |
| 1 st Tier Vaccine Priorities | Malaria | Malaria (Rotavirus) | Mening | Malaria | JE | Malaria HPV |
| 2 nd Tier Vaccine Priorities | (Pneumo) | (Pneumo) | Mumps HepA (Pneumo) | Rubella HPV | Dengue (Pneumo) | (Pneumo) Typhoid |
| 3 rd Tier Vaccine Priorities | HPV Mening | Mening | (Rotavirus) Typhoid | (Rotavirus) Cholera | Malaria HPV Rubella | Dengue HepA |

*** Based on Country Consultation results**

Vaccines not under IRC consideration
() vaccines already in GAVI portfolio