



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 analysis¹ 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 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

¹ 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.

assumptions that had been included and because not all elements e.g. deaths averted in adults from cervical cancer², 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
 - 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

² In light of the varying prevalence of different oncogenic HPV types in GAVI regions

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 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 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	

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					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 \geq 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: 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 efficacy 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		

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 	<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		