

SCIENTIFIC ADVISORY BOARD REPORT

Monday 30 April 2018 | 58 Princes Gate, Imperial College London, London, SW7 2PG, UK

Attendees:

Scientific Advisory Board (SAB) members:

Martin Friede* (WHO), Patrick Gerland (UN Population Division, Demographic Analysis Branch), Bryan Grenfell* (Princeton University), Ulla Griffiths (UNICEF), Gagandeep Kang (Christian Medical College, Vellore), Kate O'Brien (Johns Hopkins University)

Vaccine Impact Modelling Consortium (VIMC) Management Group members: Tini Garske** (Consortium Director), Lesong Conteh**, Emily Dansereau (Bill & Melinda Gates Foundation - BMGF), Neil Ferguson**, Azra Ghani**, Nick Grassly**, Tim Hallett**, Dan Hogan (Gavi), Mark Jit (London School of Hygiene & Tropical Medicine), Holly Prudden (Gavi), Tove Ryman (BMGF)

Additional attendees: Hope Johnson (Gavi), Kim Woodruff (Imperial College London)

Apologies: None

* attended remotely

** Imperial College London

Key messages from this report (based on summing up session):

Governance:

- SAB congratulated the secretariat on progress in the last year, and looks forward to seeing impact numbers being published.
- SAB welcomed the clarification that the secretariat has an RfP (Request for Proposals) standard operating procedure.
- SAB recommended publicising RfPs widely and giving applicants at least 6-8 weeks.
- Secretariat clarified the RfP application process for existing models does not require new estimates; instead this is based on groups' recent estimates and model review.

Research focus:

- Consensus that upcoming publication should include country-specific estimates. This requires careful planning and communication, including with VIMC members (and PINE countries: Pakistan, India, Nigeria, Ethiopia).
- Secretariat agreed with SAB recommendation to consult consortium-wide about what level of detail to publish, and then engage with PINE countries.
- SAB strongly recommended developing a broader publication strategy.

Prioritising data/research gaps:

- SAB stressed the need to ensure modellers are incentivised and paid well.
- SAB suggested two different approaches for engaging with Wellcome on its data gaps agenda:
 - o Get Wellcome to follow up directly with VIMC modellers
 - o Wellcome to fund Secretariat to produce a fine-grained analysis
- SAB welcomed the Secretariat proposal to send Wellcome an initial summary of our priorities (combined with our uncertainty estimates) and offer to do further work if paid.

Country engagement:

- SAB emphasised the need to start quickly and have a narrow focus; country-specific work will be time-consuming. It will also take longer to publish papers containing country-specific numbers.

- SAB asked about plans for engaging with specific contacts in PINE countries, including technical country counterparts, data collection leads and academic partners. Secretariat will get a steer from NITAG (National Immunization Technical Advisory Groups) and EPI about who to engage with and will use initial kick-off workshop to help identify key contacts in countries.
- Gagandeep Kang and Ulla Griffiths offered to help with country engagement on India and Nigeria respectively.

Other:

- General consensus that Consortium's bandwidth is limited. Secretariat's main priority is to publish estimates; will delegate to modelling groups where possible.
- SAB reiterated the need to communicate subtleties of main impact estimates.
- Ulla happy to be interlink with DoVE (Decade of Vaccine Economics); Ulla warned against using 'return on investment' measures (i.e. GDP/capita).
- SAB recommended developing a policy on who has access to Consortium's full dataset; currently DoVE has access to this and has a memorandum of understanding with Gavi.
- Coordination on publication strategies is important.

Session 1- 3: VIMC progress update, and funders' priorities

VIMC Progress Update

VIMC aims to provide vaccine impact estimates to Gavi and BMGF, focusing on quality, consistency, and efficiency. The VIMC secretariat is based at Imperial College London, and acts as the focal point between the funders and modelling groups. VIMC is growing; many new members over the last year, and staff changes.

Core outputs are cases, deaths, DALYs (disability adjusted life years) averted, from 2000-2100, disaggregated by country and age.

Output datasets are large (around 1.5Tb for each major update). Montagu is our online delivery platform that provides infrastructure for this and ensures modellers' uploads are standardised.

SAB discussed graphs showing our overall vaccine impact estimates, and a comparison of measles burden estimates (from our two measles models).

Discussion about 'total impact' bar chart (y axis: deaths averted, x axis: year of vaccination)

SAB stressed the need to present this carefully to avoid misinterpretation and poor investment decisions by policy makers. This may be wrongly interpreted as deaths that would have happened in 2026-2030, but in fact the years shown are the year of vaccination. Specific suggestions included changing the title to clarify we mean lifetime deaths averted, adding text to explain the graph, and showing other supplementary graphs.

SAB queried the relatively high impact of Hepatitis B vaccine. One factor is the prevalence of Hep B in China and India. Total impact would look very different for deaths and DALYs. For example, Hep B vaccine shows greater impact than PCV3 (pneumococcal conjugate vaccine 3rd dose) when considering deaths averted, but this may not be the case when considering DALYs. This is partly because PCV averts deaths in children under 5, whereas Hep B vaccine averts adult deaths. In addition, the uncertainty around the impact of Hep B outweighs that of PCV.

The current 'total impact' graph is designed to show the impact of vaccine investments. Figures presented to Gavi's board show deaths averted per fully vaccinated person (FVP).

Only one VIMC model (LiST) assumes an overall mortality envelope; a query was raised about whether this model may be producing over-estimates.

VIMC is modelling 98 countries: 73 Gavi-eligible countries, 23 additional countries modelled by DoVE, and two others requested by BMFG.

Update on Bill & Melinda Gates Foundation priorities

BMGF's team-wide strategic goal: "By 2020, prevent 11 million deaths, 3.8 million disabilities, and 230 million illnesses through high, equitable, sustainable vaccine coverage and supporting polio eradication."

SAB members discussed the graph 'Cumulative impact of vaccination, 2011-2020'. The blue line shows BMGF's long-term strategic goal (based on previous coverage assumptions); the red line tracks what is actually happening (based on updated coverage assumptions, and using the most accurate new models).

SAB felt we should not assume that coverage will continue to increase in future. It would be interesting to consider a scenario where coverage slipped.

Careful messaging may be needed, as the graph suggests that vaccines were all introduced in 2011. WHO would welcome graphs showing how many lives have been saved by vaccines since 1960 or 1970. This may not be within VIMC's remit, but BMGF may be interested. BMGF has data allowing us to go back to 2000.

There was agreement that VIMC's vaccine impact estimates will be very useful to many people, as these kinds of numbers are not readily available at present. We will need to think strategically about which numbers to publish, how to communicate these, and how they could influence policy.

This is a key priority for VIMC in the coming year, and we are aiming for a publication in a leading journal (e.g. the Lancet). Providing different cuts of the data could clarify some of these issues. This first publication would be coordinated with other agencies, and include infographics.

Update on Gavi priorities

Gavi provides three types of support to countries: new vaccines, health systems and immunisation strengthening, and technical assistance.

Gavi uses VIMC's impact estimates in three ways: for target-setting and performance reporting; to inform decision-making on strategies, investments and policies; and to inform advocacy and communication.

Gavi's Programme and Policy Committee will meet twice in 2018 and twice in 2019; the same applies for the Gavi Board. Gavi's Vaccine Investment Strategy is conducted every five years and is ongoing throughout 2018.

Session 4: Governance, model review & standards, continuity vs scientific robustness

Issues and questions presented to SAB:

- Trade-off continuity vs scientific quality

- Handling conflicts of interest in the review process
- To what extent should we take operational issues into account when selecting modelling groups?
- To what extent should we prioritize cost of proposals?
- Should we specify disease-specific standards, and who should define these?

Discussion

SAB asked about our capacity to re-run combinations of old/new models and old/new data, in order to show the effect of using new data. Montagu is designed to support this. Our interim updates use old model runs and new coverage data; in future we aim to run the models more automatically, which will simplify the interim updates.

The interim update deals only with vaccine coverage. Updates to other inputs (e.g. case fatality ratios) and model validation would fall in the realm of group-specific model improvements. Modellers also provide uncertainty runs, but there may be scope to ask modellers for re-runs based on changes in assumptions, on a per-disease basis. Working out how to assess uncertainty is a model-by-model process and therefore time-consuming.

Our review panels have a clear aim: to consider model documentation (e.g. published papers), model outputs, and subject matter (for the RfPs), and assess whether the model in question is suitable for VIMC's purposes. VIMC review panels consist of Consortium members with no conflicts of interest (i.e. not based at the same institution or modelling the same disease). Conflicted individuals are excluded from funding decisions.

There is potential to share our review process with IVIR-AC for information only. Given our specific purposes and the large number of models in VIMC, it is not feasible to merge our review process with IVIR-AC's.

Our January 2018 RfP resulted in three new models joining the consortium, for Japanese encephalitis (Notre Dame), yellow fever (Notre Dame) and rubella (Johns Hopkins University). As we previously had only one model for these diseases, we have now achieved our target of two groups per antigen across the Consortium.

SAB discussed the factors behind our groups being based primarily in the US and Europe, and urged the secretariat to allow more time for the RfPs to optimise opportunities for new applicants. The aim of our RfPs is not to commission the building of models from scratch, but to take on existing models that can be easily adapted for VIMC's purposes.

Model validation is the responsibility of each group; this is difficult to do due to limited disease-specific data. However, we encourage model comparison workshops, such as the Hep B workshop to be held in May 2018.

One suggestion from SAB was to have more than two models per antigen, if funding allows.

SAB emphasised the need to be clear in our RfP about the strategic purpose of model outputs, and suggested we switch to a new model only if there is a compelling reason. Another important consideration is whether groups want to pursue our quality agenda.

Most models have been published already, but these publications do not necessarily allow the two models for each antigen to be easily compared.

One question for the funders is 'how good is good enough?', given the strategic decisions that the model outputs are being used for, and given that some antigens contribute much more to the burden than others. The greatest uncertainties relate to geographic heterogeneity for

disease burden, and demography. Sub-national estimates would only be useful if they help us capture heterogeneity; it will be important to clarify if this is heterogeneity of coverage or of disease risk.

Through the model review process, we are gaining a better sense of the key parameters for each model. Our upcoming analyses of the uncertainty runs and potential model comparison workshops will also help with this.

SAB agreed that diversity among models is helpful, and we should avoid being so prescriptive that the two models converge. However, it will be important to understand the causes of differences between the two models.

Session 5: Research focus

As noted above, a priority for VIMC is to have a summary publication on 2018 impact estimates. While modelling groups within the Consortium will likely have their own papers, the aim of this overarching paper would be to show what vaccination has achieved since 2000.

Overall scope

There is an “envelope issue”, around how the number of lives saved by vaccination fits with other modelling work on different interventions. We expect vaccination will be a second order effect. There is also an issue around whether the paper focuses solely on the impact of Gavi. Ideally, we would want to take a broader view.

Forward look

This was felt to be the most interesting issue but high risk, as there may be resistance to us revealing future coverage assumptions at country level. One solution may be to present past estimates, future estimates using current trajectories, and future estimates with higher than expected trajectories. For routine coverage (rather than campaigns), we may also be able to avoid references to Gavi’s SDF/OP (strategic demand forecast / operational forecast) and instead define a future scenario as all countries achieving a specific coverage of all Gavi vaccines.

Health economics aspects

Whether or not to include this in the main publication is an open question. We may want to leave this to DoVE, to avoid mission drift. Alternatively, we may want to publish a separate detailed health economics paper focusing on heterogeneity. This could be positioned as detailing the impact of vaccine investments, without mentioning Gavi.

Countries and Gavi/non-Gavi distinction

We are aiming to include all 98 countries modelled by VIMC. (One view was that the most important issue is to get just the Gavi-73 countries.) There were mixed views on the importance of country grouping distinctions. The Gavi/non-Gavi distinction may be unimportant for the wider world but very important for Gavi donor countries. The DoVE/non-DoVE distinction may be of interest only for WHO.

Authorship

There were mixed views about funders’ involvement, and group authorship vs. individual named authorship. One view was that group authorship would be cleaner. Another view was

that we would always have to state Gavi & BMGF involvement, so we might as well be transparent in naming them.

We plan to assemble a 'writing group' of more intensive contributors. We would be transparent with all VIMC members throughout (e.g. presenting a publication strategy to them) and open the writing group opportunity to all VIMC members.

SAB members recommended drawing on examples from other consortia. It will be important to establish authorship principles and a list of planned publications at the outset. As our results come from many groups (not just Imperial), it may be hard to argue there should be a first and last author. If we opt for group authorship, Tini would be the corresponding author.

Broader scope / supplementary papers

SAB recommended against publishing a paper simply to announce the existence of the consortium. One specific suggestion was for a separate publication on Montagu; however, it was felt it may be better to incorporate that into the main publication.

We anticipate modelling groups would potentially be interested in contributing to a special issue journal supplement (e.g. one paper per group per antigen). However, this could be a lengthy process, and BMGF/Chronos will not pay for supplements (only for individual papers). Therefore, SAB endorsed the suggestion to have a single establishment paper on our new impact estimates, followed by further separate individual papers.

Individual modelling groups will be planning their own papers. At the same time, Consortium-level research outputs have been part of the VIMC proposal from the outset, and these will be by definition cross-antigen. Kate O'Brien stressed the importance of laying out principles in order to reassure VIMC members, and offered to share what her team has done.

Clustering of coverage

At present, we assume that coverage against one disease has no correlation with coverage against another, which is unlikely to be the case in reality. Data needed to get to analyse this would need to come from survey data such as DHS (Demographic and Health Surveys). SAB members felt this would be substantial, important new work. This may tie in with work by Andy Clark (rotavirus in India), Stephane Verguet, and IHME (Institute for Health Metrics and Evaluation) – which has Gates funding to look at sub-national coverage. Our starting point would be the EPI schedule. Costs may also look different if we consider clustering of coverage. Gavi is interested to know to what extent accounting for heterogeneity in coverage would change the overall vaccine impact estimates.

Disease interactions

Largest interaction is likely to be between non-Gavi pathogens (e.g. HIV) and Gavi pathogens. This is more speculative than the issue of heterogeneity of coverage. Funders may be better placed than VIMC secretariat to tackle this issue. The cost of increasing coverage is greater for harder-to-reach children. This issue relates also to herd immunity. Sub-national stratification could help address the issue of disease interactions, although this presents various challenges. PINE countries have the biggest impact, so sub-national stratification would be of high interest to Gavi.

Given disease interactions, we may wish to focus on years of life saved rather than deaths averted, but this would require careful communication.

Gavi and BMGF consider the total envelope of disease averted (by generating counterfactual scenarios).

SAB suggested Gavi 5.0 and the risk of back-sliding in fragile countries as an additional research agenda. Gavi is thinking about this and may ask VIMC to model an additional scenario where some countries' coverage slips.

VIMC funding and resources are stretched. We could consider funding small working group of interested modellers to look at issues such as heterogeneity in coverage. Important to treat our modellers as equal research partners, bearing in mind that addressing these research issues is likely to be more interesting to them than simply generating new estimates.

SAB recommended that all modellers have the chance to be involved, and we avoid perceptions that all benefits accrue to Imperial. It will be important to lay out principles in writing and have modellers to agree to this. The review/RfP process may result in more engaged groups who take a keen interest in our research agenda.

Session 6: Prioritising data gaps to fill

As discussed at the 2017 SAB meeting, we want to help modellers gain access to the best available data sources. We provide demographic data via Montagu and check the validity of modellers' demographic projections. The model review process gives feedback on other data sources, but we are not prescriptive. Following a discussion with the Wellcome Trust and Gavi, we have now reviewed disease-specific data gaps across the Consortium. Priorities identified by our modellers included sentinel surveillance, serology, (more in-depth) vaccination coverage, vaccine effectiveness and contact patterns.

Questions for SAB:

- Should we abandon the role of trying to speak for 'the field' on data collection priorities?
- Should we generate a process for the independent scientific review of those priorities?
- Can we use the VIMC results to help guide an objective and transparent prioritization?

As part of its nascent strategy on vaccines, the Wellcome Trust is interested in filling the most critical data gaps in order to improve vaccine impact estimates.

Discussion

SAB stressed the value of having an early and ongoing dialogue between modellers, field-based data collectors, and those designing impact surveillance programmes. This is crucial but has not been done well in the past. Wellcome, not VIMC, should generate a process for the independent scientific review of these priorities. VIMC could then use its results to help guide this prioritisation.

SAB discussed the potential to work more efficiently on filling data gaps, by taking a multi-antigen approach, rather than setting up more disease-specific data-gathering programmes. VIMC's multi-antigen focus may allow us to help with this.

Although groups may find it difficult to quantify the value of additional data (i.e. before it exists and they start to use it), it may be worth asking groups to justify the data gaps they have noted.

The model review process gives some sense of the key parameters for each model and priorities for research; in some cases these differ from the modellers' expectations.

Our upcoming analysis of stochastic (uncertainty) runs has some potential to reveal which data gaps are most important and start a dialogue with modellers around this. Management Group members could share the burden of this work.

Session 7: Country Engagement

Our primary aim of engaging with countries is to improve the quality of the VIMC modelling results for the most important countries; a secondary aim is to contribute modelling expertise to answer questions from country programme teams.

Our priorities are Pakistan, India, Nigeria, Ethiopia – the 'PINE' countries – given their high burden. We will focus on just four countries, due to our limited resources.

Our one-page country engagement strategy sets out our rationale and processes. We have consulted extensively with funders, SCMs (Senior Country Managers) at Gavi and BMGF, and modelling groups, and are now ready to implement this plan. Modelling groups are now enthusiastic and engaged, and many have existing links with countries.

Our next step is to approach EPI programmes (and others) via a formal request from either Gavi or BMGF, depending on which is best placed. We will liaise with SCMs to clarify the best contacts in each country; SAB members agreed this will be important.

We will then need to coordinate with modelling groups and work with countries to refine their questions. This will generate outputs, and we will then hold in-country workshops.

Questions for SAB:

1. What (other) scientific questions would be most interesting to pursue in this process?
2. How do ensure we add value for all parties (EPI programmes, modellers, VIMC)?
3. How do we avoid over-committing?

Discussion

Additional country engagement work by modelling groups could be written into their scopes of work, but no additional funds are available for this at present.

Possible measures of success for country engagement work:

- evidence that our work has helped change/support country-level policy decisions
- improvements to our modelling
- continued engagement with PINE countries
- sub-national (admin 1 level) estimates leading to sub-national introduction of new vaccines

(Whether countries provide helpful data is unlikely to be a good measure of success.)

SAB recommended that our approach targets NITAGs as well as EPI programme contacts (the latter group may have less interest in the underlying science). Our engagement could also help strengthen NITAGs. For India, it may be more effective to approach via Gavi than BMGF.

Gagandeep Kang suggested additional key contacts in India – in addition to EPI and NITAG – and offered to help liaise with them:

- public health expert on India's former Planning Commission (who may be able to convene a meeting of vaccine stakeholders)
- Medical Technology Assessment Board

SAB recommended taking a narrow approach and setting out 2-3 well-defined questions, to avoid us becoming over-burdened by requests from countries. We already have clear questions from the SCMs which we can feed back to our modellers, while acknowledging these may change in future.

SAB discussed to what extent we should link to studies on the impact of investments. Azra clarified we will not focus on 'return on investment'; instead, we will focus on 'cost per life saved' (in line with Gavi). BMGF has some information on intersecting investments in PINE countries and could get more detailed information. Stephane Verguet's ECEA (Extended Cost-Effectiveness Analysis) group may also be well placed to help.

We will need to talk to each country about its sub-national data, to be confident about the data quality. (Sub-national data is not provided by the UN.) It will be important to compare our estimates with countries' surveillance data. In some cases, a country's EPI lead may have no link to the surveillance data lead; input from BMGF and/or WHO may be helpful here.

VIMC's remit does not include the impact of vaccines on health systems, but Gavi is interested in commissioning work on this. (VIMC could potentially focus on costs of treatment averted.)

Session 8: Opportunities and external interactions

Questions for SAB:

- What kind of users may be interested in VIMC outputs?
- What should the 'rules of engagement' be in the use of VIMC outputs?
- Should VIMC pro-actively publicise the availability of model results to other groups to encourage collaborations?
- How should VIMC work with other groups already involved in generating inputs or using outputs?
- What is the best way of liaising with the modelling groups in using their outputs in wider collaborations beyond Gavi/BMGF?
- Are there any funding opportunities to extend the work of VIMC?

Discussion

Imperial owns the results produced by the modelling groups. One key issue is what level of aggregation to use when we publish our impact estimates; IHME offers an interesting case study. We will aim for a high level of disaggregation and transparency, while ensuring we comply with both BMGF's open access policy, Gavi's requirements for using its confidential data, and get buy-in from modelling groups. One solution may be to generate hypothetical vaccine coverage scenarios for our first major publication.

SAB suggested getting clarity on the purpose of external groups' requests for our results and developing a basic policy on how they access and use our data, particularly for country-level estimates. Whether our publication includes country-level numbers will require careful discussion; these will be in high-demand but could be contentious.

SAB acknowledged that setting out a carefully curated list of VIMC outputs will be an important but substantial piece of work.

VIMC results are likely to become increasingly important for Gavi as it approaches replenishment in 2020; SAB anticipate that Gavi and BMGF will require further specific analyses from VIMC. SAB urged Gavi and BMGF to continue funding VIMC generously.