Vaccine Impact Modelling Consortium

Annual meeting 2018 - Summary meeting report

Boston, USA

March 20 – 22, 2018

The Vaccine Impact Modelling Consortium overview

The Vaccine Impact Modelling Consortium (VIMC) coordinates the work of several research groups modelling the impact of vaccination programmes worldwide. The Consortium was established in 2016 for a period of five years, and is led by a secretariat based at Imperial College London.

The Consortium aims to deliver a more sustainable, efficient, and transparent approach to generating disease burden and vaccine impact estimates. The Consortium works on aggregating the estimates across a portfolio of ten vaccine-preventable diseases and further advancing the research agenda in the field of vaccine impact modelling.

The Consortium is funded by Gavi, the Vaccine Alliance, and the Bill & Melinda Gates Foundation. The data generated by the Consortium support the evaluation of the two organisations' existing vaccination programmes and inform potential future investments and vaccine scale-up opportunities.

Meeting objectives

The VIMC second annual meeting took place in Boston, USA on 20-22 March 2018. The Consortium will continue to alternate between European and US annual meeting locations as approximately half of its members are currently based in the US and the other half in Europe.

The key objectives of the meeting were a) to update all members on Consortium-wide progress, b) to present secretariat's work accomplished during the first year of Consortium operations, c) to provide the participating modelling groups with an opportunity to present an update on their ongoing work and d) to introduce the new groups to the Consortium as well as to provide networking opportunities for all Consortium members and affiliates.

Meeting summary

Day 1: Tuesday, 20 March 2018

Welcome and Consortium update

The first day of the annual meeting was opened by the Consortium Director, Dr Tini Garske, who welcomed the meeting participants and presented an overview of the Consortium structure and operations. Dr Garske provided broader context for the outputs generated by the modelling groups as well as their influence on Gavi and Gates Foundation internal strategy and beyond. She also outlined the key processes that the secretariat put in place during the first year.

The secretariat defined model minimum standards to ensure comparability and quality across the disease models employed for the Consortium purposes. Furthermore, the secretariat instituted the model review process to ensure that all models meet the agreed standards. In future years, the annual review committees will also include the modellers themselves as a way to engage more Consortium members, beyond the management group. This will possibly generate new ideas and methodological cross-pollination between modellers from different disease areas.

The secretariat has also successfully conducted the first Request for Proposals (RfP) round to attract new modelling groups for yellow fever, rubella and Japanese encephalitis where only one model has originally been in use. While rubella and Japanese encephalitis have received one strong application each, yellow fever received two quality applications in addition to the existing Consortium model and,

therefore, the management group reached out to a group of external reviewers for objective selection recommendations. As an outcome of the first RfP round, the Consortium invited three new groups to join, two of which attended the annual meeting. During 2018 the secretariat will continue to issue further RfPs for the remaining Consortium disease areas. The existing groups will be required to apply, although the application process will entail minimum effort.

Dr Garske also discussed the standardisation of the Consortium inputs and outputs that the secretariat embarked on during the first year. Generally, the modellers supported the idea and agreed to the standardisation of inputs, where possible, in order to ensure basic comparability between models. Some Consortium modellers, however, expressed a concern that post-hoc adjustments of demographic inputs might be problematic, especially for dynamical models.

Montagu overview and future development plans

While the management group placed a lot of focus on the set-up of processes, the technical team worked on the development of the Consortium delivery platform, Montagu. Dr Alex Hill presented more details on progress to date. Most of the Consortium modellers are relatively familiar with Montagu's interface, but not the modular structure of its implementation, comprising a number of packages (such as Jenner, Phipps, bb8, Kodiak), each enabling various functionalities under the Montagu umbrella. A SQL relational database was set-up for storing the generated disease burden estimates provided by the groups as well as the input data supplied to them. Each release of an updated input data is now recorded under a distinct "touchstone" allowing for strict version control while making it easy to trace back the demography and coverage data fed into generating specific burden estimate sets.

The next big piece of work that the technical team plans to undertake involves processing and storing the stochastic estimates and introducing API integration for the models. The technical team organised several sessions throughout the annual meeting to solicit the modelling groups' feedback and input towards further development and prioritisation of the Montagu features.

Modelling group presentations

All modelling groups were invited to present their ongoing work. These presentations on Day 1 included Professor Matt Ferrari (Pennsylvania State University, measles), Dr Emily Carter (John Hopkins University, Hib, rotavirus and PCV) and Dr Allison Portnoy (Harvard University, measles). The abstracts for these presentations can be found in the appendix of this report.

Impact estimates 2017

The second half of the day focused on reviewing the preliminary impact estimates produced on the basis of the data generated by the Consortium modelling groups. The Consortium science team, consisting of three postdoctoral researchers, Dr Zulma Cucunubá, Dr Nick Letchford and Dr Xiang Li, presented an overview of the methods implemented for aggregated burden estimates. In particular, the process of updating the estimates to account for proportional distribution of impact to the year in which vaccination activities occurred was highlighted. The modelling groups also received printed materials describing the implemented methodology and were invited to provide feedback and comments. No particular concerns were raised during this session.

Health economics

The health economics session was opened by Dr Libby Watts (Johns Hopkins University) and Dr Stéphane Verguet (Harvard School of Public Health), followed by a panel discussion on possible opportunities for Consortium modellers within the area of health economics and systems research. The discussion was facilitated by Dr Lesong Conteh (Imperial College London) and Professor Mark Jit (London School of Hygiene & Tropical Medicine).

Dr Libby Watts presented on behalf of the Decade of Vaccine Economics (DOVE) team at Johns Hopkins University. The DOVE team has collaborated with individual modellers since 2011 and this collaboration will be further enhanced with the establishment of the Vaccine Impact Modelling Consortium. Using the impact estimates, the DOVE team has generated evidence for the economic value of vaccines using Cost of Illness (COI), Value of Saved Lives (VSL), Disability-adjusted Life Years (DALYs), Return on Investment (ROI), Costing, Financing & Funding Gap (CFF) models. For the specific interest of the attending modellers, the presentation further elaborated on how the impact estimates are used in the COI models. The DOVE Modelling Team and the Consortium communicate to ensure that epidemiologic parameters in the health impact estimates are consistent with parameters in the DOVE economic models. Overall, the DOVE economic models expand on health impact estimates to provide economic evidence for vaccine decision-making, for example, supporting vaccine introduction decisions at country level.

Dr Stéphane Verguet from the Harvard School of Public Health, Department of Global Health and Population, presented on "Poverty reduction & equity benefits from vaccines in low- and middle-income countries". Similarly to the DOVE team, among other data sources, the research is relying on the outputs generated by the Consortium modellers for a restricted subset of Gavi-eligible countries. Some of the key messages highlighted by Dr Verguet were 1) more data is needed on distribution of burden of disease by key population subgroups, 2) vaccine benefits (both health and economic) seem to primarily accrue among the poor, but merely ensuring equal access to vaccines will not reduce outcome gaps across income quintiles, and 3) vaccines seem to bring large financial protection in all countries investigations needed to compare traditional/child vaccines (e.g. measles, RV, PCV) with new/adult vaccines (HepB, HPV). The presentation demonstrated another potential application of the vaccine impact estimates for further health economics analysis.

Dr Lesong Conteh opened the discussion by highlighting that, although the meeting participants might have varying level of interest in health economics and systems, there are several cross-cutting themes relevant to all diseases often asked by the economists that could be further explored in the context of impact estimates generated by the Consortium. These themes could be broadly defined as costs, cost effectiveness, health systems strengthening, equity, externalities, and financing.

While mathematical models generate important global information, it would be important to also explore how they relate to local decisions, i.e. how specific countries take up the modelling results in terms of their policies and practises. For instance, the Consortium interest in working more closely with specific countries (Pakistan, India, Nigeria, and Ethiopia) could be used as a means to conduct case studies to also address some of the economics relevant questions.

The group feedback in terms of interest to be further involved with health economics and systems work was mixed – some are already incorporating this into their modelling and are eager to explore the health economics avenue further, whilst others see this as rather separate from their current work. The discussion facilitators invited those keen to be engaged with the topic to have further

conversations separately. One of the additional points that was brought up is whether there is need to calculate DALYs twice – currently both the Consortium and the DOVE team produce these estimates based on the disease burden data. Possibly, it would be worth consolidating DALY calculations to either the Consortium/modellers or the DOVE team.

Team building

In the late afternoon, the meeting participants were split into smaller groups for a team building exercise. The activity involved each group building a miniature bridge from provided crafts supplies. A further challenge was introduced when half of the group was asked to create one half of the bridge in one room, while the other half of the team was executing the other half in a different room. At the end of the activity, the two parts were connected, and the facilitators tested the structures in terms of their ability to hold certain weight limits and to meet the requirements listed in the initial instructions. All groups enjoyed the change of pace from the general meeting and the opportunity to get to know each other in an informal context.

Plenary lecture

The day was concluded by a guest plenary lecture entitled "Vaccine efficacy/ effectiveness as an input into vaccine impact modeling: Beyond the confidence intervals" by Professor Marc Lipsitch from Harvard School of Public Health. The lecture abstract is available in the appendix of this report.

Day 2: Wednesday, 21 March 2018

Modelling group presentations

The second meeting day was opened by modelling group presentations, including Dr Emilia Vynnycky (Public Health England, rubella), Dr Katy Gaythorpe (Imperial College London, yellow fever), Dr Hannah Clapham (Oxford University Clinical Research Unit in Vietnam, Japanese encephalitis), and the meningitis A modellers (Dr Lucy McNamara (US Centres for Disease Control), Dr Caroline Trotter (Cambridge University), and Dr Mike Jackson (Kaiser Permanente Washington)). The abstracts of these presentations are available in this report appendix.

Interim update methodology

Dr Tini Garske presented in more detail the methodology implemented for the interim updates of impact estimates performed by the secretariat twice a year and described at a high-level on Day 1 by Dr Xiang Li. Dr Garske explained that Gavi's original motivation behind implementing the "modified update" (or "interim update") was to perform an update of impact estimates to take into account new vaccination coverage information post-hoc since the re-running all models frequently presented a significant effort. Using the most updated figures was and continues to be important for funders' planning and progress tracking purposes. The legacy updates from 2012, 2014 and 2015 have been handed over to the Consortium secretariat, and these data sets are now stored on Montagu. For future interim updates, the secretariat would like to conduct some quality checks by requesting the modelling groups to produce new estimates for a small sub-set of countries, in order to compare how these differ from the interim update based on previous model runs updated with the latest coverage.

The methodology proposed by the science team for the purposes of the interim update did not raise any major queries from the participating modelling groups. However, the modellers expressed some concern that any changes in models (given that the secretariat is promoting continuous model

development) would affect comparability with the past modelled results. Hence, ideally the modellers would keep older versions of their model's implementation used to generate estimates for the Consortium. This could be facilitated by providing an archiving feature via Montagu.

From the Gavi perspective, it would be important to understand any changes between previous and the updated estimates, in order to correctly message these shifts in earlier predicted outcomes. It was suggested that for larger countries (for example, Nigeria) where changes in coverage could imply significant alterations to impact estimates, the secretariat could request the modellers to re-run their original models. As a follow-up, it would be useful to have a "curve of coverage" that would ideally illustrate to the funders at which point the changes in coverage data would be significant enough to make a request for an updated model re-run.

The modellers also suggested that it would be helpful to have more visibility into the types of decisions (at Gates and Gavi) that Consortium-generated estimates are supporting. Depending on the type of question/decision (for example, introduction dates, vaccine scale-up, or country graduation date from Gavi support), the modelling group could determine whether there is enough confidence in data and whether a possible adjustment to their model could produce more useful/reliable results. Similarly, Gavi and Gates representatives agreed that a "decision matrix", where scenarios and questions are outlined, could be helpful as an indication when using certain country-specific estimates would be acceptable. If the previous estimates largely varied from the interim update estimates, it would serve as an indication to reach out to the modelling groups for additional support. Both funders use the impact estimates to report against targets (retrospectively) and set new goals (prospectively).

Research Agenda

Following the methodology discussion, Professor Neil Ferguson introduced a session aimed at generating discussion and ideas for furthering cross-cutting research across the Consortium vaccine portfolio. Potential topics of interest could include clustering of vaccine coverage (geographic, individual), disease interactions, clustering of infection risk, competing hazards of mortality and sub-national modelling. The participants were invited to brainstorm challenges and opportunities in smaller groups relating to the proposed research topics.

Participants discussed advancing the Consortium's understanding of the possible over-counting of vaccination impact due to different vaccines that may be given to the same children while other children miss out completely. It appears, however, that if the mortality risks are small across the portfolio, then consequently, the chances that mortality would be aggregated in the same children, would also be also smaller. Others pointed out that looking at "deaths averted" perhaps is not the best measure as one child's death in fact could be averted more than once from various diseases, and, thus, it would better captured by "cases averted" measure and DALY calculations.

Another topic that was raised related to the correlations in coverage (for example, the children who receive the measles vaccine are also likely to receive the rubella vaccine). These would matter more in low-coverage scenarios rather than high-coverage, and some of these effects might cancel out. In general, heterogeneity in vaccination in many cases would affect more the stochastic persistence of infection than the endemic force of infection, and might not affect the vaccine impact on mortality at a large scale.

One group suggested that for correlation of coverage between different vaccines, one could look at the DHS surveys. It would be expected to observe some geographic correlation, but cultural or climatic

factors affecting additional correlation patters could also be discovered. In addition, it was suggested that it could be useful to share the various sources underpinning the mapping exercises for different disease areas to identify possible correlations.

One group brought up the challenge of national boundaries when looking at any coverage data sets. As the borders are often porous, the national-level coverage data used across the consortium may therefore be a poor reflection of reality. Separately, another topic of interest would be looking at system-wide interactions and understanding the knock-on effects of the programmatic investments in vaccines yielding further improvements in health systems not captured by the Consortium-generated metrics of deaths, cases and DALYs averted due to vaccines.

In terms of cross-cutting topics relevant to all groups, looking at data extrapolation methods was suggested, case fatality ratio calculations for additional disease areas as well as general data sharing for disease areas that incorporate a lot of input data.

Gavi Vaccine Investment Strategy (VIS)

Dr Hope Johnson, Monitoring and Evaluation Director at Gavi, presented an overview of the Vaccine Investment Strategy (VIS). The VIS involves an assessment of potential impact of new vaccines undertaken by Gavi every 5 years to enable upfront, evidence-based decisions about future vaccine investments it has evolved and become more systematic over the years. The objectives of the VIS are to identify future vaccine investments for inclusion in Gavi's portfolio in the next 5 years and to potentially start to send also some signals for priorities beyond the next 5 years. The VIS also supports predictable programming for partners, manufacturers and Gavi-supported countries with key information to support planning.

Some of the Consortium members were involved in the modelling work for the VIS in early 2018. These results were then used for populating a decision framework to narrow-down a short list of vaccines for the next phase. During the VIS process, Gavi look across the entire vaccine investment value chain and also use the modelled estimates for benchmarking, i.e. considering how the potential new investments would compare to others within the whole of Gavi portfolio.

Dr Holly Prudden then presented further details on the steps of the VIS process this year with final board decisions expected in November 2018.

Data gaps

Dr Holly Prudden, consultant at Gavi Monitoring and Evaluation team, led a session focusing on data and research gaps critical for the Consortium modelling groups. The main goal of the session was to identify the priorities and cross-cutting (and disease-specific) issues regarding the quality, access and availability of data. Given Wellcome Trust's interest in generating evidence for decision making in the field of vaccines, there is an opportunity to influence their priority setting by demonstrating how data gaps affect decision making and the estimates that the modellers are able to generate. The meeting participants split into groups by disease area to discuss this topic and review a list of data gaps that has been previously compiled. The main comments from the groups by disease area were as follows:

Yellow fever: awaiting serology survey results from Guinea-Bissau; looking whether new information could be available based on deep frozen samples from West African countries dating prior to any vaccination campaigns; improving general data access through WHO data sharing agreements via Gavi would be valuable;

Japanese encephalitis: similarly to yellow fever, looking at serological survey data from various parts of the world, also considering surveys for other diseases that are present in the same geographic areas as Japanese encephalitis;

HPV: although incidence data is available, the source is dependent on data of varying quality, hence, it would be helpful to identify countries where data could be more generalizable and use them as a starting point for improving national registry data;

Hepatitis B: the most important studies would be to evaluate mother to child transmission rates with/without birth dose (particularly in African countries) and studies to identify the proportion of mothers with high viral load and the risk of transmission among the stratification of high viral load; an "easy fix" that would provide more data would be integrating Hepatitis B into DHS surveys;

Measles: from a practical stand point, SIA coverage/post campaign coverage surveys, more data on "non-campaign" doses to infer information about routine coverage (i.e. how often the campaign doses are actually the first doses that children are getting?); improving general data access through WHO data sharing agreements via Gavi would be valuable;

Rubella: better seroprevalence data would be a priority and would not necessarily be costly to obtain; possibly starting anonymous serum banks in countries of interest as this would provide a better idea of transmission and coverage (for example, in the UK this was instrumental for measles); not much data available on how many cases of congenital rubella syndrome (CRS) occur, so challenging to validate the modelled predictions; case fatality rate assumptions are based on data from three studies and short follow-up periods, so revisiting that would be useful; voluntary abortion rates due to rubella infection are also not available;

Meningitis A: some data that would be very useful is historic at this point, hence, would not be feasible to obtain/improve; might be possible to dig deeper into WHO data and other literature to ensure all sources are pooled together; rate of waning of vaccine protection studies would be useful (some work done by CDC but is a large scale undertaking); better contact survey data (possible synergies with other disease areas); duration of protection data;

Cross-disease: having a good listing of what key information would be needed for each of the models could be helpful to facilitate data sharing when it becomes available; economic outcomes/some additional empirical data could be collected in conjunction with other surveys; getting mixing patters data.

Rotating small group discussions (i.e. "world café" sessions):

1. *Correlation between vaccine doses and heterogeneity discussion*

The aim of this discussion was to gain an understanding of the different approaches the Consortium modellers have taken for combining multiple vaccine doses in their models, what justifications or additional data sources are being used to support their assumptions, and how far it would be sensible to assume the same or different processes for different diseases. In addition to multiple vaccine doses, groups touched on the topic of geographic heterogeneity, for instance relating to sub-national vaccination campaigns. Also, routine coverage heterogeneity was discussed as based on the multiple existing data sources (WHO, IHME, MICS, DHS) and the challenge of using these in relation to one another.

Based on the discussions, it appeared that the general approach has been to model the vaccine doses separately as not correlated. However, as best practice, the model would then have built-in structural uncertainty given that there is no knowledge of what happens on the ground. In terms of equity and access to vaccination, for various countries the model could provide several scenarios from optimistic, pessimistic to empirically supported estimate based on best available data. While the group mostly discussed the correlation of multiple doses for the same antigen, a question of multiple vaccines within the entire immunisation programme was also raised. Are there any children being continuously missed, and how to account for the "zero dose" cases? Furthermore, modellers expressed concern over the year-on-year improvements reported in coverage for some countries, which are likely to still be far away from the "real" coverage on the ground.

2. Country engagement discussion

The country engagement discussions were chaired by Professor Tim Hallett and Dr Homie Razavi. Overall, the discussions focused on running regional analysis and getting access to regional data for the PINE (Pakistan, India, Nigeria, and Ethiopia) countries, with much interest in the latter, both for different regions, and also urban/rural areas. Understanding spatial variation of burden and vaccine coverage would be important for decision making and to improve and prioritise scale-up in high-burden areas. From modellers' point of view, there is also interest in outbreak data as it would allow for further model improvements. The DoVE team at Johns Hopkins University would be interested in the economic side, for example, understanding the catastrophic health expenditure in PINE countries and by region, as well as cost of interest, in order to help improve economic modelling and analysis. Several groups expressed enthusiasm in being involved in possible country workshops and some groups already have established links with in-country representatives. Among the four PINE countries, India appeared to generate most interest (large, varied, data-rich).

The suggested next steps for the secretariat included engaging directly with relevant individuals in countries to introduce the Consortium and its remit, to establish possible needs and opportunities for collaboration.

3. Montagu features discussion

The Montagu discussion tables provided an opportunity for modellers to offer feedback on their experience using the platform. During the first year, the technical team built out the foundation of the delivery platform, started to support sharing of input data (demographic and coverage data) with the modellers via Montagu as well as rolled-out the upload capabilities for the newly generated burden estimates. Short surveys were shared with the participants to capture their comments for later reference. Key features requested by the modellers were 1) ability to receive more immediate and useful feedback based on the burden data sets they uploaded, 2) ability to view the name of the most recently uploaded file and to re-download it, 3) ability to start using the R-client for integration with Montagu API (most modellers are keen to start translating their models into programming language that would allow for this compatibility).

As next steps, the technical team will integrate these and further comments received from the Montagu users in their work plans for the upcoming months.

Uncertainty

Professor Neil Ferguson opened the discussion on the topic of uncertainty in the Consortium models. Currently, there are several approaches implemented: 1) rigorous likelihood-based representations (e.g. Bayesian posterior distributions), 2) semi-rigorous sampling of 'posterior' uncertainty (e.g. in country-specific R0), or 3) Monte-Carlo sampling of 'prior' uncertainty in key model parameters. The principle sources of uncertainty in the impact estimates could be defined as parametric (i.e. either in estimated parameters (posterior distribution) or assumed parameters (prior distributions)) or structural (i.e. natural history, representation of population structure). At this time, only the default model is used by the funders, but ideally the Consortium would be able to take advantage of all modelled estimates by averaging the results. Furthermore, there are certain cross-cutting sources of uncertainty for all models resulting from demography (currently using fixed demography) and coverage data. Ideally this type of uncertainty would be also represented in total burden/impact, however, this would require probabilistic uncertainty runs to be consistently generated and labelled across all models. The participants were then invited to discuss how uncertainty could be best incorporated across the Consortium models. Some of the points from the discussion groups are presented below.

In general, the modellers are supportive of working towards continuously improving the quality of the models. The only reservation about representing uncertainty in the most rigorous way is that it requires a significant effort. The modellers would like to know that the results would indeed be used by the funders. Currently Gavi and Gates do not use it, but there is a strong interest to better understand uncertainty. Hence, it would be important that it would be presented in a more "user-friendly" way to avoid "decision paralysis". If uncertainty is going to be used for decision making, then it needs to be standardised. Additionally, it would be extremely helpful for the modellers to have more insight/transparency into the decisions at stake to better tailor the representation of uncertainty in their models. However, there is always a danger of being too prescriptive dictating how uncertainty should be reflected in the models, thus losing out on the diversity of approaches. More systematic representation of uncertainty across models could also be difficult as every disease area has its own data set that they can fit their model to and able to understand the sources of uncertainty.

Some groups discussed whether parametric and structural uncertainty could be assessed separately or together. Uncertainty relating to coverage could be addressed by the modellers or received as input from the secretariat (latter being preferred). The modellers agreed that there would be great value in conducting model comparison workshops.

Transparency about areas where uncertainty is stemming from is important. As one of the first steps, the secretariat suggest that it would be useful to catalogue systematically all the parameters that go into the models and how modellers are approaching these, and then think of what would be the best way to standardise these.

Modelling group presentations

Final modelling group presentations were given by Dr Devin Razavi-Shearer (Center for Disease Analysis), Dr Kaja Abbas (London School of Hygiene & Tropical Medicine), and Dr Petra Klepac (London School of Hygiene & Tropical Medicine). The abstracts of these presentations are available in this report appendix.

Day 3: Thursday, 22 March 2018

The third meeting day was dedicated to small group meetings which were organised on ad-hoc basis on any topics of interest that arose from the previous meeting days. Some participants took this as an

opportunity to meet with their colleagues working in the same disease area. In addition, there were follow-up meetings on country engagement and data gaps. Some modellers also participated in one-on-one/user design experience sessions with the technical team, which were aimed at testing some of the new prototype features for Montagu.

Summary of the meeting outcomes and next steps

The meeting objectives were successfully met as proven by a high number of attendees (total of 59 participants) and the positive feedback received through a post-meeting survey. The presentations covered a range of topics from general Consortium update to more technical issues such as incorporating uncertainty and methodology for performing interim updates of the impact estimates. The presentations by modelling groups were well received as they touched on some of the cross-disease issues and provided new ideas for participating groups. Two of the three new modelling groups were able to attend and the third group was represented by a colleague, hence the meeting also served as an effective onboarding of the new Consortium members. The secretariat was able to solicit feedback on the first year of the Consortium operations and received input for future plans.

Appendix

1. Annual meeting agenda
2. Modelling group presentation abstracts and plenary lecture abstract

Agenda

Tuesday, March 20th (Meeting Day 1)

Time	Speaker & Topic		Location
From 7:30	*Breakfast (for overnight guests)*		*Dante**
From 8:30	Registration		Parkview (East Tower Level 2)
9:00 - 9:45	Tini Garske	Welcome & Consortium Update	Parkview
9:45 - 10:15	Martin Eden & Alex Hill	Montagu overview & future development plans	Parkview
10:15 - 10:45	*Coffee/tea break*		*Parkview*
10:45 - 11:10	Matt Ferrari	Heterogeneity in vaccination	Parkview
11:10 - 11:35	Emily Carter	Effect of Vaccination Delay on Deaths Averted by PCV	Parkview
11:35 - 12:00	Margaret de Villiers & Shevanthi Nayagam	The impact of birth-dose vaccination as an intervention against HBV	Parkview
12:00 - 12:25	Allison Portnoy	Estimating Case Fatality Ratios of Measles in Low- and Middle-Income Countries	Parkview
12:25 - 1:30	*Lunch*		*Dante**
1:30 - 2:15	Zulma Cucunuba, Nick Letchford & Xiang Li	Overview of vaccine impact estimates 2017	Parkview
2:15 – 3:00	Stephane Verguet, Dagna Constenla, Libby Watts, Lesong Conteh & Mark Jit	Health Economics and Health Systems	Parkview
3:00 - 3:15	*Coffee/tea break*		*Charles Foyer*
3:15 - 5:15	Team Building Activity		Charles A & B
5:15 - 6:15	Marc Lipsitch	Plenary lecture: Vaccine efficacy/ effectiveness as an input into vaccine impact modeling: Beyond the confidence intervals	Parkview
7:15 - 9:30	*Consortium dinner*		*Legal Sea Foods Kendall Square (355 Main St, Cambridge)*

Wednesday, March 21st (Meeting Day 2)

Time	Speaker & Topic		Location
From 7:00	*Breakfast (for overnight guests)*		*Dante**
8:30 - 8:55	Emilia Vynnycky & Timos Papadopoulos	Inferring the pre-vaccination epidemiology of rubella for countries lacking seroprevalence data	Parkview
8:55 - 9:20	Katy Gaythorpe	Capturing geographic variability in the Yellow Fever burden through the use of environmental covariates	Parkview
9:20 - 9:45	Quan Tran Minh & Hannah Clapham	Geographic variability: the case of Japanese Encephalitis	Parkview
9:45 - 10:10	Mike Jackson, Andromachi Karachaliou, Lucy McNamara & Caroline Trotter	Dealing with uncertainty in the factors driving epidemic periodicity of Meningitis A	Parkview
10:10 - 10:30	*Coffee/tea break & group photo*		*Charles Foyer*
10:30 - 11:00	Tini Garske	Modified update method	Parkview
11:00 - 12:00	Neil Ferguson	Research Agenda	Parkview
12:00 - 1:00	*Lunch*		*Dante**
1:00 - 1:25	Hope Johnson & Holly Prudden	Gavi Vaccine Investment Strategy	Parkview
1:25 - 2:00	Holly Prudden	Data gaps	Parkview
2:00 - 3:05	Rotating discussion groups ("World Café"):		Parkview & Charles B
	Facilitators:	*Topic:*	
	Tim Hallett & Homie Razavi	1) Country engagement work in Pakistan, India, Nigeria, Ethiopia	
	Tini Garske & Matt Ferrari	2) Correlation between vaccine doses and heterogeneity	
	Martin Eden & Alex Hill	3) Montagu	
3:05 - 3:20	*Coffee/tea break*		*Charles Foyer*
3:20 - 3:35	Wrap up from discussion groups		Parkview
3:35 - 4:35	Neil Ferguson	Incorporating uncertainty and aggregating estimates from different models	Parkview
4:35 - 5:00	Devin Razavi-Shearer & Homie Razavi	Delphi Method and Availability of HBV Data Globally	Parkview
5:00 - 5:25	Kaja Abbas & Petra Klepac	Waning efficacy and fitting age distributions: Rotavirus vaccine	Parkview
5:25 - 5:30	Tini Garske	AOB	Parkview
6:00 - 9:00	*Dinner*		*ArtBar**

Thursday, March 22nd (Meeting Day 3) – Optional half-day

Time	Topic	Location
From 7:00	*Breakfast (for overnight guests)*	*Dante*
8:30 - 10:00	One-to-one Montagu user feedback sessions	Charles A
	Continued group discussions on data gaps	Charles B
	Other collaborative group meetings, including follow-on discussions arising from Days 1 & 2	Parkview
10:00 - 10:15	*Coffee/tea break*	*Charles Foyer*
10:15 - 12:00	One-to-one Montagu user feedback sessions	Charles A
	Continued group discussions on data gaps	Charles B
	Other collaborative group meetings, including follow-on discussions arising from Days 1 & 2	Parkview
12:00 - 1:00	*Lunch*	*Dante*

Abstracts of Presentations by Modelling Groups – Day 1

Matt Ferrari
Heterogeneity in vaccination

Vaccination coverage has classically been reported as a scalar value aggregated at administrative units. This representation obscures the fine-scale variation in vaccination over age and across space. We have been developing methods to estimate subnational variation in measles vaccination rates, as a function of age from vaccination coverage surveys conducted as a part of the Demographic and Health Surveys program of USAID. Failing to account for this variation can lead to significant biases in interpretation of patterns of measles incidence. We illustrate application of these estimates, in combination with case surveillance, for identifying sub-national targets for program improvements.

Emily Carter
Effect of Vaccination Delay on Deaths Averted by PCV

Delay in receiving vaccines can reduce the impact of vaccination on child mortality reduction, particularly for diseases that peak in early infancy. Research suggests delayed vaccination is common, although the extent of delay varies by population.

We developed a model in Stata (v14) to evaluate the effect of pneumococcal conjugate vaccine (PCV) vaccination delay on under-5 pneumococcal pneumonia mortality reduction under various vaccination timing scenarios and country situations. Timing scenarios were developed from country-specific estimates of vaccination delay calculated by Clark and colleagues from population-based survey data. Country-specific vaccination schedules, pneumonia mortality rates, and final vaccination coverage estimates were used. The direct and indirect protective effects of PCV were estimated from existing literature. We modeled pneumococcal pneumonia deaths prevented directly and indirectly by PCV based on the mortality risk and vaccination coverage experienced at each week of age from birth to five years. We compared estimates of total deaths prevented and residual mortality under delayed vaccination scenarios against estimates of on-schedule vaccination. We calculated the absolute and relative difference in under-5 pneumococcal pneumonia deaths averted.

Vaccination delay had minimal impact on the number of deaths averted by PCV when accounting for herd effect. The greatest relative differences in deaths averted were observed at low final vaccination coverage levels where no herd effect was assumed. Under the most extreme delay scenarios, the largest relative differences in number of deaths averted were <10% and occurred at low levels of final vaccination coverage corresponding to small absolute differences in deaths. Under more moderate delay scenarios, the relative difference in deaths averted was less <5%, and

fell with increasing coverage levels consistent with increasing herd effect. This model suggests that realistic vaccination delay has a minimal impact on the number of deaths averted by PCV when accounting for the indirect effect of PCV.

Margaret de Villiers & Shevanthi Nayagam
The impact of birth-dose vaccination as an intervention against HBV

Chronic HBV infection is a leading cause of liver cirrhosis and liver cancer worldwide[1]. Global scale-up of HBV infant vaccination has been successful in reducing prevalence of childhood HBV infection. However, reaching the WHO elimination targets of 90% reduction of new hepatitis B related infections by 2030 will require a large scale-up of PMTCT interventions, as infant vaccination alone does not prevent mother to child transmission of HBV. The current cornerstone of HBV PMTCT is birth dose vaccination within 24 hours of birth. However, the global coverage is low at 39% despite birth dose vaccination being a WHO recommended policy since 2009 and evidence that it is effective, cheap (<$1 per dose) and cost effective. Furthermore, in Africa, where the burden of HBV is high (*under 5-year-old prevalence of HBV infection is 3%[2] and there are an estimated 370 000 estimated new infants infected with HBV at birth[3]*), only 9 countries have included this recommendation in their national strategies to date. The need for vaccine administration within 24 hours of birth poses logistical difficulties in many high burden, low income countries given the large percentage of out of hospital births. Additionally, the lack of funding support to these low-income countries for introduction of this vaccine contributes to its low coverage.

We will discuss the evidence for the efficacy of HBV birth dose vaccination, country examples where successful implementation has had a significant impact and the projected impact that scale-up could achieve. We will then discuss the key financial, logistical and political challenges to successful implementation of birth dose vaccination and some opportunities to overcome them.

References
1. The Burden of Primary Liver Cancer and Underlying Etiologies From 1990 to 2015 at the Global, Regional, and National Level: Results From the Global Burden of Disease Study 2015. *JAMA oncology* 2017; **3**(12): 1683-91.
2. World Health Organization. HBV country profiles. http://whohbsagdashboard.com/ - hbv-country-profiles.
3. Keane E, Funk AL, Shimakawa Y. Systematic review with meta-analysis: the risk of mother-to-child transmission of hepatitis B virus infection in sub-Saharan Africa. *Alimentary pharmacology & therapeutics* 2016; **44**(10): 1005-17.

Allison Portnoy
Estimating Case Fatality Ratios of Measles in Low- and Middle-Income Countries

Background: In the 21st century, increasing immunization coverage and decreasing measles case fatality ratios (CFRs) have substantially reduced the global burden of measles mortality. However, the assessment of measles mortality burden is highly dependent on estimates of measles CFRs, which vary according to geography, health systems infrastructure, prevalence of underlying risk factors, and measles endemicity. With imprecise measles CFRs, there is continued uncertainty about the current burden of measles mortality and the impact of measles vaccination.

Methods: We first conducted a systematic review of the literature to identify studies examining measles cases and deaths in low- and middle-income countries for all age groups from 1980–2016. We extracted data on measles CFRs overall and by age, where possible. Second, we developed a model to estimate measles CFRs from 1990–2015 and then a restricted model to project future measles CFRs through 2030.

Results: A total of 124 peer-reviewed journal articles were selected for inclusion in the final review – 85 community-based studies and 39 hospital-based studies. The use of a log-linear predictive model resulted in a mean CFR of 2.1% (95% CI: 0.7–3.5%) across 1990–2015. For community-based settings, the mean CFR was 1.4% (0.3–2.5%) compared to 2.7% (1.7–5.5%) for hospital-based settings. The mean projected CFR for 2016–2030 was 1.1% (0.4–1.8%).

Conclusions: Measles CFRs have seen substantial declines since the 1990s. Our study provides the most complete estimation of measles CFRs which can help refine evaluation of the mortality impact of measles control and elimination programs.

Plenary Lecture – Day 1

Marc Lipsitch
Vaccine efficacy/ effectiveness as an input into vaccine impact modeling: Beyond the confidence intervals

Abstract:

This talk will describe some of the factors influencing the estimation of vaccine efficacy or effectiveness and the challenges of integrating them into models of vaccine impact. It will argue that beyond the inherent statistical uncertainty in any model, a number of untested and often false assumptions underlie standard approaches to estimating vaccine efficacy and translating these estimates into model parameters. I will discuss some of these, first for the randomized controlled trial setting and then for the setting of observational studies, especially the case-control and test-negative designs. I will describe work, much but not all from our group, on ways to identify and alleviate these biases and conclude by describing the use of simulation to enhance the design and efficiency of randomized vaccine trials.

Biography:

Marc Lipsitch is Professor of Epidemiology and Director of the Center for Communicable Disease Dynamics at the Harvard T.H. Chan School of Public Health. His research concerns the impact of immunity, vaccination, and antimicrobial use on pathogen populations and the consequences for human health. Recent work has focused on topics of vaccine evaluation through randomized and nonrandomized designs, especially in infectious disease emergencies; the role of vaccines in controlling antimicrobial resistance; and the processes responsible for geographic and other patterns of antimicrobial resistance.

Abstracts of Presentations by Modelling Groups – Day 2

Emilia Vynnycky & Timos Papadopoulos
Inferring the pre-vaccination epidemiology of rubella for countries lacking seroprevalence data

Estimates of the burden of Congenital Rubella Syndrome for each country currently use seroprevalence data collected from before the introduction of vaccination to assign the pre-vaccination force of infection and contact parameters to model the transmission dynamics of rubella in the country. Country-specific data are currently available for approximately a third of the countries for which GAVI requires estimates of the impact of vaccination. For the remaining countries, the force of infection is based on bootstrap-derived estimates, compiled from seroprevalence data collected from the same WHO region. In this presentation, we will discuss preliminary analyses of alternative methods to infer the pre-vaccination epidemiology of rubella, based on demographic and socio-economic data and country-specific data rubella seroprevalence identified through a systematic review.

Katy Gaythorpe
Capturing geographic variability in the Yellow Fever burden through the use of environmental covariates

Yellow fever (YF) is a vector-borne disease causing 180,000 deaths annually in Africa alone. However, epidemiological data within the African endemic zone is limited due to challenges in surveillance which stem from the broad spectrum of disease severity, fairly non-specific symptoms and complex lab-testing required to confirm YF infection. To address the unquantified differences in reporting we limit the dataset of case reports to simply capture presence/ absence of cases, and use serological surveys from a subset of countries. As such, there are substantial gaps in information across the region as well as differences in data resolution between countries.

YF occurrence varies geographically and is influenced by environmental factors such as land cover, temperature and vegetation. We utilise these factors as a baseline of expected epidemiological dynamics across the African endemic zone through a regression model which allows us to harness additional information and extrapolate estimates to areas where no surveillance data are available. Onto this basis, we consider vaccination coverages, resolved at the subnational level, to account for differences in human susceptibility across the endemic region. Finally, through estimation using a Bayesian framework, we rationalise the different epidemiological data sources and quantify some of the uncertainty in surveillance quality and transmission intensity estimates.

This methodology allows the extrapolation of limited and patchy data to countries with little or no information using environmental variables and a robust estimation framework. We find that whilst surveillance quality uncertainty varies substantially across the region, areas of high transmission intensity have well resolved burden

estimates at subnational level. The methods also highlight knowledge gaps and priority areas for data collection in the region. The development of frameworks for rigorous estimation of disease burden at the subnational level will allow greater resolution in control strategies such as vaccination which promote the more effective and efficient use of limited resources.

Quan Tran Minh & Hannah Clapham
Geographic variability: the case of Japanese Encephalitis

Japanese Encephalitis (JE) is a zoonotic, vector-borne disease. There are multiple animal reservoirs, including birds and pigs, and the virus is spread to humans via the Culex mosquito. The Culex mosquito breeds well in rice paddies and under certain climatic conditions. There is therefore great geographic variation in the distribution of JE infection risk. In order to estimate variation in disease burden it is therefore important to be able to understand and quantify the drivers of this geographic variability.

We are using machine-learning and statistical models to predict JE force of infection (FOI) estimates using relevant covariates. After a literature review we have around 90 geo-located estimates of FOI estimated from age-stratified cases. We have also collated available data on the relevant variables such as climate, land-use, mosquito distribution and pig distribution. After building models to predict FOI, we use these models to extrapolate the FOI estimates to locations for which we did not have such information. From this FOI, we will then estimate the disease burden in each location.

For some countries, there is not a great amount of variation across the country, as the whole country has a similar climate and landscape. However for other countries, for example China and Vietnam, this variation is great. In these places, to accurately estimate vaccination impact, it is also important that we have information on where vaccination was used. For many countries, even routine vaccination was introduced in phases depending on perceived risk, and campaigns regularly occur in specific locations. Therefore to fully quantify geographic variation in disease risk, spatially explicit data on vaccination must also be available. We currently have this data for Vietnam, which we will include in the modelling framework and we are working on acquiring it for other countries.

In conclusion, to estimate the impact of JE vaccination, estimates should be extended to include geographic variation in both disease risk and vaccination use.

Mike Jackson, Andromachi Karachaliou, Lucy McNamara & Caroline Trotter
Dealing with uncertainty in the factors driving epidemic periodicity of Meningitis A

Prior to MenAfriVac introduction in the so-called "African Meningitis Belt", serogroup A meningococcal (MenA) disease was characterized by dry season epidemics that occurred every 5-10 years. Major epidemics often spanned two or three dry seasons, with incidence fading during the rainy season and rising again in the dry season. Between major epidemics, MenA incidence fell markedly (although still remaining higher than in many other parts of the world). Although the seasonality and periodicity of these epidemics is well-described, the factors that drive this epidemic periodicity are still unclear. In particular, the relative importance of host factors (e.g. waning

immunity), pathogen factors (e.g. appearance of novel strains) and environmental factors (e.g. dust) is uncertain.

Uncertainty regarding the factors that drive epidemic periodicity creates challenges for predicting the impact of meningococcal vaccination programs. In this talk, we will review the approaches used by the MenA modelling teams to simulate epidemic periodicity, the assumptions involved, and potential limitations to these approaches. We discuss the potential epidemic drivers and how these might be studied or quantified further. Despite the success of MenAfriVac, this is still of importance given the ongoing risk of epidemic meningitis due to other meningococcal serogroups.

Devin Razavi-Shearer & Homie Razavi
Delphi Method and Availability of HBV Data Globally

The Center for Disease Analysis utilizes a Delphi Method for collecting the data that is reported in the Polaris Observatory and used in our models. This method combines a literature review with interviews of country experts to confirm estimates and fill data gaps. Through this method we have collected data for 128 countries and produced 120 country level models with 75 of them having been validated by experts to date. Each estimate is then scored using a multi-objective decision analysis approach on a scale of 1-3. When data is not available roll-ups are created with the country level models available by Global Burden of Disease region. The age and sex specific prevalence from this roll-up are then input into a country specific model with the background data sets.

When weighted by total population, Sub-Saharan Africa Central and Sub-Saharan Africa Southern have the least amount of data. We will discuss the Delphi Method along with the specific data that we collect. We will then examine the HBsAg prevalence estimates in the Polaris Observatory, the quality of this data, and where robust serosurveys are most needed.

Kaja Abbas & Petra Klepac
Waning efficacy and fitting age distributions: Rotavirus vaccine

Correct estimates of waning efficacy and of the granular age distribution of rotavirus disease in children are important to inform a detailed assessment of the benefits of rotavirus vaccination schedules and estimating vaccine impact. Often, vaccine waning is not accounted for and reported age bands are too broad to allow such detailed impact assessment.

Waning efficacy:
We estimate the efficacy of rotavirus vaccine since administration of last dose by extracting estimates from 26 randomised placebo-controlled trials for reported periods of follow-up. Using likelihood-based methods to fit curves, we estimate vaccine efficacy after 6, 12 and 24 months of follow-up as respectively 95%, 93% and 90% in low/very low mortality settings; 78%, 75% and 71% in medium mortality settings; and 50%, 31% and 5% in high/very high mortality settings. Rotavirus vaccines provide important protection against severe disease in the first year of life but this vaccine-induced protection wanes considerably in settings with high/very high under-five mortality.

Fitting age distributions:

To estimate age distribution of rotavirus disease in children by country, child mortality stratum and type of presentation, we use a standard statistical approach to fit parametric age distributions to each country dataset. The datasets include the WHO Global Rotavirus Surveillance Network database, and data obtained by contacting the investigators of all studies published between January 1990 and February 2017 to obtain more granular rotavirus age information. The data includes pre-vaccination age distributions of rotavirus-positive community cases, clinic visits, hospital admissions, emergency visits and deaths aged <5 years. The median age of rotavirus-positive hospital admissions was 38 weeks in countries with very high child mortality, 43 weeks in countries with high child mortality, 46 weeks in countries with medium child mortality and 65 weeks in countries with low/very low child mortality. In countries with very high child mortality 69% of rotavirus-positive admissions <5 years were in the first year of life, with 3% by 10 weeks, 8% by 15 weeks and 27% by 26 weeks. The median age of rotavirus disease varies between and within countries but tends to occur at a much younger age in higher mortality settings.

Conclusions:

While rotavirus vaccine efficacy is lower and wanes more rapidly in high mortality settings, the earlier peak age of disease in these settings means that rotavirus vaccines are still likely to provide important protection to infants. The reproducible parametric age distributions can be used to assess the benefits of alternative rotavirus vaccination schedules, and assist countries to design context-specific rotavirus vaccination programmes. The methods presented here can be adapted for analysis of other vaccines in the portfolio of the Vaccine Impact Modelling Consortium.