Vaccine Impact Modelling Consortium

Annual Meeting 2019 - Summary Report

Windsor, UK
6-7 March 2019

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 third VIMC annual meeting took place in Windsor, UK, on 6-7 March 2019. 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 second 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 new Consortium members and provide networking opportunities for all Consortium members and affiliates.

The annual meeting was preceded by a day of model comparison meetings (4 March) and a day of model reviews (5 March). The model reviews involved modellers from different disease areas peer-reviewing other models in the Consortium. Reviewers were encouraged to act as 'critical friends' and focus on understanding whether differences in the models reflected scientific uncertainty.

Meeting summary

Day 1: Wednesday 6 March 2019

Welcome and Consortium update

Neil Ferguson opened the annual meeting as the Consortium's acting director, in Tini Garske's absence. Neil welcomed 15 new Consortium members, as well as

representatives from external organisations, and gave an overview of the Consortium's goals and set-up.

Since the last annual meeting, the Consortium has formally taken on four new models, and now has its full complement of models (two per antigen), and collated model documentation. We are working towards publishing our first full set of vaccine impact estimates (working title: *Estimating the health impact of vaccination against 10 pathogens in 98 low- and middle-income countries*). The Consortium science team has improved its 'interim update' methodology, which allows us to update our vaccine impact estimates based on latest vaccine coverage estimates from WUENIC and Gavi. Modelling groups have been focused on model improvements, and this work will continue. We have also improved our software platform (Montagu) and started country engagement work in India.

Consortium goals for 2019 include submitting the first publication, making further model improvements, and carrying out full model runs. The secretariat will also carry out a WUENIC-based interim update and import new UNWPP demographic data. Country engagement work in India will continue. We will gauge modellers' appetite for exploring uncertainty through a technical working group, and examine the feasibility of subnational estimates. (Modellers will not be required to provide subnational estimates.) Priority countries are those with the highest disease burden: Pakistan, India, Nigeria and Ethiopia (the 'PINE' countries).

Small scale runs and interim update*

Xiang Li and Christinah Mukandavire (Consortium science team, Imperial College London) explained how they used the small-scale runs provided by modellers in late 2018 to determine the efficiency of the 'interim update' method, for standard, high, low and best-case vaccine coverage scenarios. The interim update method involves linear interpolation of vaccine impact estimates.

Discussion points:

The science team has not yet used the interim update method to analyse static vs. dynamic models but has looked at how different coverage assumptions change impact metrics. Knowing the expected shape of the burden and impact curves would be helpful for both modellers and the science team. The focus of the interim update method is impact by year of vaccination, rather than by birth cohort. One modeller suggested caveating this method, as it assumes impact metrics do not vary by year.

Modelling group presentations*

All modelling groups were invited to present their ongoing work. Presenters included Allison Portnoy (Harvard, HPV), Sean Moore (University of Notre Dame, JE), Katy Gaythorpe (Imperial, YF), Ben Lopman (Emory University, rotavirus), Kaja Abbas (LSHTM, Hib), Emilia Vynnycky and Timos Papadopoulos (PHE, rubella), Shaun Truelove

* Abstract provided in appendix 2

(JHU, rubella), Emily Carter (JHU, PCV/Hib/rotavirus), Hannah Clapham (OUCRU, JE), and Laura Cooper (Cambridge, meningitis A).

Assessing the global value of new health technologies*

Guest speaker Karl Claxton (University of York) spoke about methods and challenges for estimating health opportunity costs, and application of this to HPV vaccination. Discussion points included how to define development costs and the counter-factual scenario, how this framework can help countries transitioning out of Gavi support, and timescales for the analysis to affect policy decisions.

Update on BMGF priorities

Emily Dansereau explained that BMGF uses vaccine impact estimates to track progress against targets, for advocacy, and to inform its strategy. The Consortium's outputs help BMGF prioritise across antigens, geographies and delivery mechanisms and are thus critical to inform post-2020 strategies. The Foundation's top priority in 2019 is Gavi replenishment. Discussion points included plans for transition, standardising the modelling of background interventions for chronic infections, and inequity especially around gender.

Micro:bit-epidemic

All attendees were given wearable 'micro:bits', and participated in an interactive game simulating the spread of an infectious disease. This encouraged networking during the breaks.

Keynote talk – New malaria vaccines†

The day was concluded by a guest keynote talk by Professor Adrian Hill (Jenner Institute, University of Oxford) on aspects of developing malaria vaccines. Discussion points included time-scales, over-dosing, recent changes in non-vaccine interventions, and the potential for trialling combination vaccines.

Day 2: Thursday 7 March 2019

Research agenda

Neil Ferguson emphasised that cross-cutting research across the vaccine portfolio aims to add value to individual groups' work and improve our understanding of the overall program impact. The first Consortium-wide publication is aiming to be a high-impact paper that will establish the Consortium as a collaborative initiative. We intend to present underlying burden estimates and focus on deaths averted by past coverage and the potential for future gains. Potential research topics for future papers include uncertainty (parametric, structural, cross-cutting, etc.), clustering of coverage, subnational modelling, disease interactions, and competing hazards of mortality.

† Abstract provided in appendix 2

Discussion:

Modellers would welcome advice on which datasets to use for model calibration. There was no consensus on whether data sources on disease burden should be standardised, but meetings with data collectors (IHME, MCEE, CDC) could help guide this decision. Going forward, modellers will need to label their uncertainty runs (e.g. by CFR, transmission rates, etc.) to allow us to explore sources of uncertainty systematically. For some diseases (hepatitis B), truncating cohort projections at 2100 makes a difference.

For the first Consortium publication, key issues are what level of granularity to present, how much data to make available (and how much to hold back for later publications), and how to represent uncertainty appropriately. Looking at the uncertainty could help us decide whether to include (non-age-stratified) country-specific estimates.

The secretariat will share with modellers how it reproduced UNWPP age structure, although this does not account for demographic uncertainty.

To generate parameters, some groups use random sampling. Modellers questioned whether it would be appropriate to combine these outputs with those of models using a different process.

Modellers recommended taking a focused look at uncertainty. Sources of uncertainty into the future vary by disease, but include climate, urban/rural, CFR, historical vaccination coverage, expected duration of protection, and demography.

There may be a tension between Gavi's desire for consistent communication, and the evolving science. Gavi is keen to support technical and methodological papers, in addition to main publication of estimates and policy papers.

Modellers are keen to know our approach to model averaging as early as possible. Where out-of-sample validation data is not available, modellers suggested that groups compare using in-sample validation, with the models then weighted rigorously.

In order to explore the issues of double-counting and competing hazards, we will look at what proportion of UNWPP mortality is averted according to our estimates.

Decade of Vaccines Return on Investment (DOVE-ROI) Analysis

Elizabeth Watts (JHU) shared the DOVE team's analysis of the Consortium's vaccine impact estimates, including estimates of productivity loss averted by vaccination, and the economic benefits of vaccines from 2011 to 2030. Two key factors affecting the analysis are the base value for productivity, and growth rates for GDP per capita. Attendees were interested in assumptions around labour force participation rates and cut-off points.

R Client on Montagu

Montagu is the Consortium's software platform. Alex Hill (Consortium technical team, Imperial College London) demonstrated the new R client, which is part of Montagu. Modellers working programmatically in R can use the client to access model inputs and upload central estimates of disease burden. The technical team is happy to help modellers working programmatically in other languages to write their own client and interface with the API directly. The API is available as open-source on GitHub.

Small-group discussions

Feasibility of additional scenarios and countries

Additional scenarios and countries would be feasible for most groups but would require more time. There may be budget implications for calibrating countries. There may be data gaps for middle-income countries not covered by EPI programmes, if data is held in private sources. It was suggested that the 2019 estimates for middle-income countries are seen as 'test runs' Another suggestion was for the 'realistic' scenario to take into account supply/demand side constraints and delivery realities.

Uncertainty

Modellers suggested working with data producers to test data quality. It is important to understand the drivers of uncertainty in models, e.g. demography, burden, structural model differences. Adding in uncertainty may take time. Attendees would like to know which models are carrying out model validation, how, and whether data exists.

Counter-factual scenarios

Modellers had differing views on whether we should have an alternative counter-factual scenario with all vaccination stopping in the present year. (Yellow fever modellers were keen; meningitis A were not as the impact would take some time to show.) It is important to define the counter-factual scenario, and whether to assume current vaccine coverage is fixed, or follow projected coverage increases. Attendees were interested in the question of potential backsliding of routine immunisation; it may be more realistic to specify this using the 2021 model runs (not 2019). Some modellers may want to revisit their assumption of a constant CFR in the no-vaccination scenario. A no-vaccination scenario means pressure on health systems for certain diseases. Some modellers would welcome a 'pessimistic' scenario, showing no change in coverage.

Subnational estimates

In order to provide subnational estimates, modellers would need demography and coverage to be provided at a subnational level. Better quality subnational data may be needed for deeper insights; this links to country engagement work. The level of implementation (admin 1?) is important. Incorporating subnational levels and stochastic runs could be a computational burden, and for most diseases feasibility of subnational estimates varies between countries.

For hepatitis B, the main data input is prevalence by age (gathered by household surveys), and birth dose coverage. For rubella, modellers would not assume subnational transmission; instead it would be run by coverage and demography. Rubella modellers questioned the added value of subnational estimates if the estimates will be aggregated in any case. Both Japanese encephalitis groups will move to subnational transmission. For meningitis A groups, information on vaccine distribution would be important. Rotavirus groups can incorporate differences in vaccination coverage if data are provided, but were unclear if disease transmission would change.

Cross-cutting research topics

Suggestions included:

- Approaches to model averaging
- Comparisons with test data, even if not true model fitting
- Differences and value of subnational levels
- Disease interactions
- Double counting deaths (methods paper) – Mike Jackson to lead
- Contact patterns
- Quantifying importance of structuring of age groups (building on model comparisons)
- Methods for capturing uncertainty in a standardised way
- Impact of underlying changes in health systems, and the impact on vaccination as an intervention

Other points raised

Attendees felt it important to ensure future serology datasets can be used for vaccine modelling. The secretariat could create a repository of groups' data sources, to facilitate fitting and estimation. IHME already brings together data providers. Some modelling groups generate de novo estimates, others constrain their estimates by using IHME estimates. Attendees suggested more representation from WUENIC and IHME at VIMC meetings. For IHME and more broadly, it is crucial to understand the data inputs, their limitations and whether they are fit-for-purpose.

For advocacy purposes it is more useful to consider all vaccines together (rather than one vaccine against another), but the DOVE team could look further into opportunity costs of vaccines compared to other interventions. Analysing this well would require a good understanding of the benefits of scale, co-delivery of vaccines, and direct costs of vaccines compared to other vaccine delivery costs.

Gavi is open to modellers' requests to be more involved in how Consortium outputs are used by countries at a policy/strategy level; these conversations are already underway with measles.

Combining uncertainty across models may be possible if data sources are captured consistently across models (even if not all models use likelihoods). The secretariat will discuss this with modellers in coming months. The first Consortium publication will

represent uncertainty in a basic way, by tagging stochastic runs with parameters (demography, CFRs). Where both models for a disease area agree on which common parameters are key and should be aligned, we will focus on the top parameters driving uncertainty.

One suggestion was for all models to vary each input by +/- 10% to understand what the model is more sensitive to and identify the drivers for each model. The secretariat encourages modellers to look into this if it is of interest. It may be best to run this analysis on a disease specific basis. Demography will also vary by disease in terms of its importance as a driver.

The Consortium would like to encourage more model comparisons and should be able to provide some additional funding for this.

Attendees discussed the issue of aggregating impact, longer-term interactions between antigens, and competing hazards. One approach is to add up deaths averted across pathogens; alternatively, deaths averted could be calculated based on survival probability. Although the 'additive' approach seems more prone to double-counting effects than the 'survival' approach, there may be limited difference between the results of the two approaches. Under-5 mortality from vaccine-preventable disease is still a small proportion of overall mortality in this age group. This also relates to clustering of vaccine coverage and disease burden.

Update on Gavi priorities

Todi Mengistu and Dan Hogan clarified Gavi's uses of vaccine impact estimates (target-setting and performance reporting; informing decision-making, advocacy and communication messages). Gavi's vaccine investment strategy (VIS) is informed by modelling and aims to identify and guide future immunisation investments for Gavi in the next five years and beyond. Development of Gavi's 2021-2015 strategy ('Gavi 5.0') and associated investment case ahead of replenishment in 2020 is a key activity in 2019. Other priorities in 2019 are performance-reporting and gathering additional evidence for specific vaccines/areas of interest. Discussion points included countries transitioning out of Gavi support, and trade-offs between regression modelling (i.e. the interim update method) and full model runs.

Country engagement work

Nick Grassly presented the Consortium's country engagement plans and gave feedback from his recent meetings in Delhi with India's Ministry of Health and Family Welfare (MoHFW) and National Technical Advisory Group on Immunisation (NTAGI). The Consortium's measles and Hep B modelling groups currently have some engagement in India. There was consensus that the Consortium should engage with country partners, and that sustained engagement is key. The Consortium must avoid simply extracting data from country partners without being responsive to countries' needs. Country engagement will lead to better quality data, and potentially access to 'hidden' datasets. The Consortium may have some additional budget for modellers to get involved in country engagement.

There is much appetite in India for evidence-based and model-based estimates of vaccine impact; assessing how to respond to this is a challenge. Country engagement is not the Consortium's key focus, but it should be done well. Meaningful capacity building is an important part of this.

Two recent examples of country engagement by Consortium modellers:

- Amy Winter ran a measles workshop in India (supported by Hannah Clapham), analysing serology data; this generated much interest. It was facilitated via a BMGF grant to Bill Moss, who has contacts with Indian Council of Medical Research. Many at ICMR have technical expertise.

- Homie Razavi collaborated with WPRO and ministries of health in Nigeria and Mongolia. Local PhD students were trained to use and populate models (not build them), and ministries facilitated data collection. Having two face-to-face meetings and six months of data collection (to get best data available in advance of meetings) was key.

Attendees were keen for representatives from PINE countries to be invited to future annual meetings. Other key stakeholders to be aware of include country partners who transfer knowledge into policy. In India, the National Institute for Economics and Institute for Economic Growth may offer a good interface for modelling and quantitative econometrics.

In terms of capacity building, it is crucial to have higher-level support and coordination to ensure that in-country modellers are listened to. This can be facilitated by Gavi and BMGF's in-country presence, the Consortium's links, and links via WHO.

India is keen to invest in human capital in terms of fellowships. At least four modellers (Homie Razavi, Sean Moore, Hannah Clapham, Mark Jit) would be interested in hosting an ICMR fellow in their research team for training in mathematical modelling.

BMGF is keen to move to subnational estimates, but aware of the need to balance this with countries' needs and feasibility for modellers. Subnational estimates will also be useful to countries themselves. Modellers would likely only carry out subnational estimates if required to do so, and feasibility of this depends on access to data. For larger countries, some subnational data may already be in the public domain.

Summary of the meeting outcomes and next steps

Neil Ferguson thanked all participants for their attendance. As immediate priorities, the secretariat will share the draft of the first Consortium publication with all Consortium members and give them access to the Montagu reporting portal, and finalise scopes of work and extend contracts. The 2019 full model runs will be based on a publishable default coverage scenario, not on Gavi forecasts. In order to reflect Gavi's latest operational forecast, the secretariat will then run an interim update. The

workstream on subnational estimates will continue but these will not be part of the 2019 model runs. We will gauge modellers' interest in a technical working group on uncertainty and may fund a small workshop on competing hazards (i.e. double-counting deaths).

There will be some information requirements for modellers, especially around baseline assumptions in different models, e.g. around standards of care and health trends. Modellers will continue to work on model improvements but will then pause this work before starting on the full model runs in autumn 2019.

Appendix

1. Annual meeting agenda
2. Modelling group presentation abstracts and plenary lecture abstract
3. List of acronyms

Appendix 1

Agenda

Pre-meetings for VIMC modellers only:
Monday 4th March – Model comparison meetings (self-arranged)
Tuesday 5th March – Model review day

Wednesday 6 March

08:00 – 09:00	Breakfast/Registration	
09:00 – 09:35	Neil Ferguson	Welcome & Consortium Update
09:35 – 09:45	Wes Hinsley	Micro:bit-epidemic
09:45 – 10:10	Xiang Li & Christinah Mukandavire	Small scale runs and interim update
10:10 – 10:35	Coffee/tea break	
10:35 – 11:00	Allison Portnoy	Leveraging multiple models to estimate human papillomavirus (HPV) vaccination impact: strengths and limitations
11:00 – 11:25	Sean Moore	Estimating the size of the population at risk from Japanese encephalitis virus
11:25 – 11:50	Katy Gaythorpe	Comparing and averaging model predictions for yellow fever
11.50 – 12.15	Ben Lopman	Emory Rotavirus Vaccine model
12:15 – 12:30	Karl Claxton	Assessing the global value of new health technologies
12:30 – 13:30	Lunch	
13:30 – 13:55	Emily Dansereau	Update on BMGF priorities
13:55 – 14:20	Kaja Abbas	Efficacy and waning of Haemophilus influenzae type b vaccine
14:20 – 14:45	Timos Papadopoulos & Emilia Vynnycky	Estimates of the basic reproduction number for rubella and indicators for the epidemiology of rubella
14:45 – 15:10	Shaun Truelove & Emilia Vynnycky	Comparison of rubella models and results: The effects of small variations in methods and assumptions
15:10 – 15:35	Coffee/tea break	
15:35 – 16:00	Emily Carter	Comparative effect of PCV, Hib, and rotavirus vaccination delay on under-five mortality
16:00 – 16.25	Hannah Clapham	How to pick a spatial scale for burden and vaccine impact estimates
16:25 – 16.45	Wes Hinsley	Micro:bit-epidemic debrief
16:45 – 17:30	Adrian Hill	Keynote Talk: New Malaria Vaccines
17:30 – 19:00	Wine tasting / Informal networking	
19:00 – 21:30	Consortium dinner – Gloucester Suite, Oakley Court	

Thursday 7 March

08:00 – 09:00	Breakfast	
09:00 – 09:45	Neil Ferguson	Research agenda:
	1st VIMC publication and future publications (25 mins)	
	Group discussions on publications (20 mins)	
09:45 – 10:10	Elizabeth Watts	Methods for Estimating Productivity Loss Averted due to Vaccination for the DOVE Return on Investment Analysis
10:10 – 10:30	Coffee/tea break	
10:30 – 10:45	Rich Fitzjohn & Alex Hill	R Client on Montagu
10:45 – 12:35	Group discussions:	
	1st topic: Scenarios for autumn 2019 model runs	
	2nd topic: Subnational and other heterogeneity in vaccine coverage	
	3rd topic: Uncertainty and model validation	
12:35 – 13:35	Lunch	
13:35 – 14:00	Laura Cooper	Exploring Contact Matrices in Models of Meningococcal Carriage and Disease
14:00 – 14:30	Dan Hogan & Todi Mengistu	Update on Gavi priorities
14:30 – 15:00	Nick Grassly	Country engagement work
15:00 – 15:30	Coffee/tea break	
15:30 – 15:45	Neil Ferguson	Closing of the meeting
18:00 – 20:00	Dinner (optional)	

Appendix 2

Abstracts of Presentations – 6 March

Xiang Li and Christinah Mukandavire

Small scale runs and interim update

Modelling groups have recently submitted estimates for the 201810 runs for up to five countries, following Gavi's Operational Forecast 16 (OP16) which we received in autumn 2018. The models used for 201810 runs were frozen in the state used for the 201710 runs. Compared to OP15, three additional types of scenarios were included. These were (a) 10% above OP – where routine coverage was assumed to be 10% above the OP16 coverage (b) 10% below OP – where routine was assumed to be 10% below OP16 coverage and (c) best estimate, best case – where routine coverage from 2018 was assumed to be 90% (or historical highest routine coverage if greater than 90%) and a one-off campaign with 90% coverage for diseases with both routine and campaign activities, except for measles. The runs that modellers provided in 201710 using OP15 were also updated with the 201810 (OP16) coverage to get 201710-201810 estimates by using linear interpolation referred to as the interim update (IU) method, whose accuracy in impact estimation had not previously been tested. In addition to showing burden and impact estimates from the 201810 runs, we determined the efficiency of the IU method by comparing the impact estimates from 201710-201810 and 201810.

Allison Portnoy, Emily A. Burger, Stephen Sy, Catherine Regan, Nicole G. Campos, Steven Sweet, Stephen Resch, Jane J. Kim

Leveraging multiple models to estimate human papillomavirus (HPV) vaccination impact: strengths and limitations

Mathematical models that estimate the health and economic impacts of HPV vaccination must capture complex disease processes, including HPV transmission, cervical cancer natural history, screening practice, and changing population demographics in settings of interest. The extent and quality of available data from specific countries varies considerably, creating challenges to evaluating HPV vaccination strategies at the global level. We developed a framework involving multiple models to leverage available data on sexual behaviour and burden of HPV from a subset of countries to extrapolate vaccine impact to countries with limited data.

Methods: Three distinct models were developed and linked to capture important behavioural, epidemiological, and demographic information in order to estimate the health and economic outcomes associated with HPV vaccination. We linked a dynamic agent-based model of HPV transmission to a static individual-based model of cervical carcinogenesis in order to capture both the direct and indirect "herd immunity" benefits of HPV vaccination, as well as the complex natural history of cervical cancer and impacts of screening. Finally, we used a companion

population-based model to project the health and economic consequences for populations of women in various low- and middle-income country (LMIC) settings over time.

Results: Using a model-based approach that incorporates HPV transmission dynamics, cervical cancer natural history, and population demographics, we can evaluate HPV vaccination strategies at the global level, including extrapolation to countries with limited data. This analytic approach includes several limitations, including linkages between the models, extrapolation methods, and uncertainty analysis. For example, to the extent that sexual behaviours are different across settings, the herd immunity benefits we project according to dynamic models calibrated in a subset of LMIC settings may not be generalizable across all LMIC settings.

Conclusion: This multi-modelling framework can help inform stakeholder decision-making in light of data gaps and uncertainties.

Sean Moore

Estimating the size of the population at risk from Japanese encephalitis virus

Japanese encephalitis virus (JEV) is a major cause of neurological disability in Asia and causes an estimated 68,000 severe encephalitis cases and over 13,000 deaths annually. Cases and deaths are significantly underreported, and the true burden of the disease is not well understood. Targeting vaccination campaigns to the most vulnerable populations requires a better understanding of both the magnitude and spatial distribution of the disease. We determined the transmission intensity within different JE-endemic countries by estimating the force of infection from existing studies of age-specific seroprevalence or incidence. Because JEV is not transmissible from humans to mosquitoes, a zoonotic reservoir is a necessary component of the transmission cycle and JE is believed to be largely a rural disease. To identify the areas suitable for sustained JEV transmission and the size of the population living in at-risk areas we conducted a spatial analysis of the risk factors associated with JEV. First, we demarcated potential JEV-endemic areas using large-scale spatiotemporal datasets related to suitable climate conditions for the vector species, suitable habitat conditions (rice cultivation or nearby wetlands), and the presence of potential zoonotic hosts (domestic pigs or fowl). Seroprevalence studies (in both humans and domestic animals) from several different countries were then used to refine these associations and calculate the size of the population-at-risk throughout Asia. Finally, estimates of the susceptible population size and the current force of infection in each country were used to estimate the annual JE burden.

Katy Gaythorpe

Comparing and averaging model predictions for yellow fever

Yellow fever (YF) is a vector-borne disease causing approximately 78,000 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. There are further complications as a result of the complex transmission cycle involving the potential for explosive urban outbreaks as well as a constant infection pressure resulting from a sylvatic reservoir. The relative roles of these transmission routes have never been assessed and as a result, predictions of burden, particularly in Africa, are highly uncertain.

We present an approach to address this using two established models of yellow fever transmission estimated within a Bayesian model averaging framework. One model assumes a static force of infection, approximating a constant infection pressure from the sylvatic reservoir; the other approximates the potential effect of herd immunity through dynamic force of infection determined by R_0. Our methods allow us to assess the evidence for each model and thus, their assumptions surrounding transmission. We find strong support for the static force of infection model. However, the comparison highlights key data gaps across the African endemic region which have differing effects on the two models. As such, our method illustrates the potential benefits of model averaging whilst highlighting that, even if the compared models have similar structures, they may be respond to the data in different ways.

Within the VIMC, an aim is to assess structural uncertainty by comparing two models for each disease type. Our work illustrates one way in which this may be formalised and highlights some of the benefits and pitfalls of such a method.

Ben Lopman and Molly Steele

Emory Rotavirus Vaccine Model

The Emory Rotavirus Vaccine Model uses a deterministic, age-structured compartmental model of rotavirus transmission and disease. The model follows a Susceptible–Infected–Recovered-Susceptible (SIRS) structure, with complexity added to capture rotavirus natural history. Infants are born into the model with maternal immunity. As maternal immunity wanes, infants become susceptible to a primary rotavirus infection, which has a certain probability of causing rotavirus gastroenteritis. The model structure is built on the understanding that previous infections incrementally confer protection against both subsequent rotavirus infections and disease. Primary infections are assumed to be more infectiousness than subsequent ones. Primary, secondary and tertiary infections have different probabilities for developing gastroenteritis for the probability that disease is severe. We assume that only severe rotavirus gastroenteritis cases progress to death. We assume that vaccine-induced immunity is similar to natural immunity. Values and ranges for natural history parameters are informed by cohort and vaccine studies. The model is fit to data on the age distribution of severe rotavirus cases and deaths are calibrated to national Global Burden of Disease estimates.

Karl Claxton

Assessing the global value of new health technologies

Ensuring global access to proven interventions and prioritising the development of new health technologies (including vaccines) requires an assessment of whether the improvement in health outcomes they offer exceeds the improvement in health that would have been possible if the resources required had, instead, been made available for other health care activities. Therefore, some assessment of these health opportunity costs is required. Recent evidence of the health opportunity costs faced by different LMICs (Ochalek et al 2018) make it possible to report measures that reflect the value of providing access to an existing intervention, as well as investing in the discovery and development of new ones.

Value in each LMIC can be expressed as the scale of the potential net health impact (net DALYs averted), which is the difference between DALYs averted by an intervention and DALYs that could have been averted with any additional resources required to implement it. The global value and how the scale of net health impact is distributed (by country, GAVI eligible, LIC, MIC etc.) can also be reported. Value can also be expressed as the amount of additional health care resources which would be required to deliver similar net health impacts. These metrics of value are illustrated using country specific estimates of the health benefits and costs of HPV vaccination (Jit et al 2014). These measures of value, founded on an assessment of health opportunity cost, are not only useful to global bodies which make recommendations, purchase health technologies or prioritise the development of new ones (e.g., WHO, Global Fund, GAVI and BMGF), but also for decision makers in LMICs and their negotiations with donor agencies and ministries of finance.

Kaja Abbas, Kevin van Zandvoort, Mark Jit, Andrew Clark

Efficacy and waning of Haemophilus influenzae type b vaccine

Randomised controlled trials of Hib vaccine provide evidence on efficacy but have not been synthesised to obtain robust estimates of vaccine waning over time. This study addresses this evidence gap and estimates the efficacy of Hib vaccination and vaccine waning by time since administration of the last dose. We collected the efficacy of Hib vaccination by time since administration of the last dose from multiple randomised controlled trials and fit curves to the data to estimate vaccine waning over time.

Timos Papadopoulos, Emilia Vynnycky

Estimates of the basic reproduction number for rubella and indicators for the epidemiology of rubella

In the rubella modelling to date, the pre-vaccination epidemiology of rubella has been based on seroprevalence data collected before the introduction of vaccination, for countries for which such data are available. For countries without

such data, assumptions about the prevaccination epidemiology of rubella are obtained by pooling together bootstrap-derived force of infection estimates from countries in the same WHO region. The extent to which the epidemiology of rubella differs between countries or can be predicted by other factors is unclear.

Methods: We calculated the basic reproduction number (R0) for rubella for 100 settings using seroprevalence data predating the introduction of vaccination and correlated its value to 62 demographic, economic and health-related indicators, using the Pearson, Spearman correlation coefficients and the Maximum Information Coeffiicient (MIC). 95% confidence intervals were obtained by bootstrapping.

Results: The basic reproduction number was <5, 5-10 and >10 for 83, 14 and 3 settings respectively. For most of the settings for which data were available for both urban and rural areas from the same year, R0 was lower for urban than for rural areas. Preliminary results suggest that for the Pearson and Spearman correlation coefficients, the greatest correlation was obtained between R0 and housing indicators. Considering the MIC, R0 had the greatest correlation with the life expectancy at birth (0.37, 95% CI: 0.2,0.34), followed by poverty-related indicators.

Conclusions: The transmissibility of rubella is typically low. Our preliminary findings of the correlation between R0 and other indicators is consistent with those from the only other related study to date, which considered varicella zoster in Europe. Future work will explore the sensitivity of our findings to assumptions about age-dependent contact and the year from which several indicators were drawn.

Rubella modelling groups: Justin Lessler, Amy Winter, Shaun Truelove, Jessica Metcalf, Emilia Vynnycky, Timos Papadopoulos

Comparison of rubella models and results: The effects of small variations in methods and assumptions

The 201810 synthetic touchstone was the first time two rubella models were used to assess the impact of rubella-containing vaccine. We compare the absolute differences in the total annual numbers of rubella infections, cases of Congenital Rubella Syndrome (CRS), CRS deaths and the numbers of infections per capita for China, and Ethiopia, India, Nigeria, Pakistan for the no-vaccination and best-case scenarios, after standardising the output to the population provided in Montagu.

Results: For each country, relatively small differences in the number of infections per capita were observed from the two models, with the highest median difference found for China, at 20% over 100 years. For each country and scenario, the greatest percent difference in the output between the two models occurred for the annual number of CRS deaths, for which the median was 6800% (95% range: 5400-8400%), 65% (95% range: 48-73%), 45% (95% range: 32-56%), 73% (95% range: 61-76%) and 19% (95% range 3-40%) for China, Ethiopia, India, Nigeria and Pakistan respectively. For both scenarios, the greatest absolute differences in the outcomes between the two models occurred for China, for which the median range of the difference between the numbers of infections, CRS cases, and deaths was 20% (95% range: 14-37%),

12100% (95%: 9500-13000%), 6800% (95% range: 5400-8400%) respectively. Both models predicted that the numbers of infections, cases and deaths would drop to zero following the introduction of vaccination at best-estimate levels, although for China the speed of this reduction differed between the two models, occurring over 10 years and within a year for the Johns Hopkins and PHE models respectively.

Discussion: The similar values for the number of new infections per capita suggests that the baseline epidemiological assumptions in the two models are consistent. Most of the differences between the numbers of cases and deaths for the two models are probably attributable to differences in the assumed risk of a child infected during pregnancy being born with CRS and the CRS-related case-fatality rate. The reason for differences in the rate at which rubella incidence drops after vaccination starts in two countries is unclear and may be related to differences in how aging is implemented in the two models. We will discuss comparisons in the underlying demographic and epidemiological assumptions in the two models and discuss future work to identify improvements for each model.

Emily Carter

Comparative effect of PCV, Hib, and rotavirus vaccination delay on under-five mortality

Delay in vaccination from schedule has been frequently documented and varies by vaccine, dose, and setting. Vaccination delay may result in the failure to prevent deaths that would have been averted by on-schedule vaccination.

We constructed a model to assess the impact of delay in vaccination with pneumococcal conjugate vaccine (PCV), Haemophilus influenzae type B vaccine (Hib vaccine), and rotavirus vaccine on under-five mortality. The model accounted for the week of age-specific risk of vaccine-preventable mortality, direct effect of vaccination, and herd protection. For each model run, a cohort of children were exposed to the risk of mortality and protective effect of each vaccine for each week of age from birth to age five. The model was run with and without vaccination delay and difference in number of deaths averted was calculated. We applied the model to eight country-specific vaccination scenarios, reflecting variations in observed vaccination delay, vaccination coverage, herd effect, mortality risk, and vaccination schedule.

We found deaths averted by vaccination with and without delay to be comparable in all of the country scenarios when accounting for herd protection. The greatest relative difference in deaths averted was observed at low coverage levels and greatest absolute difference was observed around 60% vaccination coverage. Under moderate delay scenarios, vaccination delay had modest impact on deaths averted by vaccination across levels of coverage or vaccination schedule. Without accounting for herd protection, vaccination delay resulted in much greater failure to avert deaths.

Our model suggests that realistic vaccination delay has a minimal impact on the number of deaths averted by PCV, Hib, and rotavirus vaccination when accounting for herd effect. High population coverage can largely over-ride the deleterious effect of vaccination delay through herd protection.

Hannah Clapham

How to pick a spatial scale for burden and vaccine impact estimates

There are an increasing number of global estimates for disease burden or transmission intensity of infectious diseases. At the forefront of making these estimates are the Institute for Health Metrics and Evaluation (IHME) and Malaria Atlas Project (MAP) teams, both of whom have made decisions about the spatial scale on which to make and present estimates. There is also an increasing amount of work estimating of global impact of interventions, including the work of the VIMC. Though most researchers working on this area would agree that the same model with the same parameters cannot be used for the whole world, there are differing approaches to choosing spatial scales on which to make estimates of transmission, burden and intervention impact.

There are different factors that influence the choice of spatial scale: what are the drivers of transmission variation and how these vary spatially, the spatial scale of data availability for both cases and the information on the drivers of transmission, and the spatial variation in, and the spatial scale of information about, the intervention.

In this presentation I will review the methods that have been used to generate these estimates on different scales (from GBD to countrywide estimates) and how that varies by disease type. I will then review the pros and cons of estimates on smaller and larger scales. Finally, I will talk about our current work on estimating Japanese Encephalitis burden and vaccine impact at subnational levels, and the factors that are influencing our decisions about the spatial scale on which to make these estimates.

Keynote talk – 6 March

Adrian Hill, Jenner Institute, Oxford University

New Malaria Vaccines

Abstract:

110 years have passed since the first efforts on malaria vaccine development were published and the most “advanced” malaria vaccine is now said to be targeting licensure in 2024. This is an unacceptable rate of progress. I will discuss some of the challenges that RTS,S/AS01 has faced and describe much newer vaccines that now

aim to provide greater efficacy with much lower costs and reach licensure in the next five years. This saga points to some general lessons in the development of vaccines for primary use in resource poor settings.

Biography:

Adrian Hill trained at Trinity College Dublin and Oxford and is now Professor of Human Genetics and Director of the Jenner Institute at Oxford University, one of the largest non-profit vaccine institutes globally. He leads a research programme on genetic susceptibility to major infectious diseases as well as vaccine design and development. His group discovered the ability of heterologous prime-boost immunisation to induce potent T cell responses pre-clinically and has developed this approach to phase II clinical trials in Africa. He has also pioneered the use of small rapid clinical trials to provide initial safety and immunogenicity with a range of novel vaccine concepts. To date he has led over 50 clinical trials on new malaria vaccines, almost all designed by his laboratory research team.

In 2005 he founded the Jenner Institute which aims to accelerate public sector vaccine development for infectious diseases and links human and veterinary vaccine development, and since 2007 has led or co-led the Vaccines Theme of the NIHR Oxford Biomedical Research Centre. In 2014 he initiated the first trials of new Ebola vaccines targeting the West Africa strain of the virus and moved these rapidly to field testing. He also chairs the management committees of the Centre for Clinical Vaccinology and Tropical Medicine and the Clinical Biomanufacturing Facility at Oxford.

His research contributions are reflected in over 500 publications with over 50,000 citations and an h-index (Google Scholar) of 119. He has raised over £90m in grant funding for his genetics and vaccinology research groups. He is a named inventor on numerous patents and patent filings and has co-founded four university spin-off companies. He is currently an NIHR Senior Investigator and Wellcome Trust Senior investigator and a fellow of the Academy of Medical Sciences and the Royal College of Physicians.

Abstracts of Presentations – 7 March

Elizabeth Watts

Methods for Estimating Productivity Loss Averted due to Vaccination for the DOVE Return on Investment Analysis

In advance of the Gavi 2020 replenishment meeting, the Decade of Vaccine Economics (DOVE) team will update their estimate of the return-on-investment (ROI) of vaccines, originally published in 2016 for the decade 2021-2030. This project will extend the analysis through the next decade, 2021-2030, and revisit assumptions and data sources for the cost and benefit models used to calculate ROI. Past estimates of the economic benefits attributed over 99% of the benefits of vaccination to long-

term productivity loss averted. Previous methods assumed constant value of productivity, which may have underestimated the true value of vaccination in future years. This presentation will discuss changes to the methods for estimating productivity loss, as well as the impact these methods may have on the estimated economic benefits and ROI of vaccines.

Laura Cooper

Exploring Contact Matrices in Models of Meningococcal Carriage and Disease

Contact patterns influence infectious disease transmission. The growing number of studies on contact patterns in African populations has now made it possible for empirical data to inform assumptions about contact in dynamic models of disease transmission. We used age-specific contact patterns from a range of empirical studies in African populations in an age-structured compartmental model of meningococcal transmission and investigated how these influenced other model parameters and assumptions. In particular we examined the age-distribution of carriage and disease compared to evidence from carriage studies and routine meningitis surveillance. To our knowledge, there are no studies of contact patterns in core countries of the African meningitis belt and further research may be necessary to accurately characterise meningococcal transmission in this high incidence area.

Appendix 3

List of acronyms

API	application programming interface
CDC	Centers for Disease Control and Prevention
CFR	case fatality rate
CRS	congenital rubella syndrome
DALY	disability-adjusted life year
DOVE	Decade of Vaccine Economics
GBD	Global Burden of Disease
GDP	gross domestic product
Hib	haemophilus influenzae type B
HPV	human papillomavirus
ICMR	Indian Council of Medical Research
IHME	Institute for Health Metrics and Evaluation
JE	Japanese encephalitis
JEV	Japanese encephalitis virus
JHU	Johns Hopkins University
LIC	low income country
LMIC	low and middle-income countries
LSHTM	London School of Hygiene & Tropical Medicine
MIC	middle income country
NIHR	National Institute for Health Research
OP	operational forecast
OUCRU	Oxford University Clinical Research Unit (Vietnam)
PCV	pneumococcal conjugate vaccine
PHE	Public Health England
PINE (countries)	Pakistan, India, Nigeria, Ethiopia
RoI	return on investment
UNWPP	United Nations World Population Prospects
VIMC	Vaccine Impact Modelling Consortium
WHO	World Health Organization
WPRO	Western Pacific (WHO Region)
WUENIC	WHO-UNICEF estimates of national immunization coverage
YF	yellow fever