TECHNICAL CONSULTATION ON THE MODELLING OF HEPATITIS B

9-10 MAY 2018

LONDON, UK

VACCINE IMPACT MODELLING CONSORTIUM

This meeting was organised by the Vaccine Impact Modelling Consortium, managed at Imperial College London. An agenda and list of participants can be found at the end of this document.

Soraya Rusmaully, June 2018

Following the "elimination" targets of viral hepatitis and the goals enshrined within the Sustainable Development Goals, there is now increasing attention on the mathematical modelling of Hepatitis B. Among the questions being tackled, of greatest priority are the estimates of the historic and potential future impact of hepatitis B virus (HBV) vaccination, the marginal impact of a birth dose vaccine and the health impact that could result from an expanded programme of vaccination and treatment.

Consequently, The Vaccine Impact Modelling Consortium (VIMC), based in the Department of Infectious Disease Epidemiology at Imperial College London (ICL), convened a technical consultation to bring together groups with expertise in the field of hepatitis B epidemiology and mathematical modelling to discuss these topics, to compare results and to share insights and learnings.

OBJECTIVES OF THE CONSULTATION

- To review all methods being used to generate estimates of age-specific HBV prevalence (HBsAg & HBeAg)
- To review all methods being used to generate other metrics of HBV impact (HBV-related deaths)
- To review estimates and come to shared understanding of differences
- To discuss how these estimates can be used in modelling and economic evaluation work
- To compare and discuss estimates of the impact of birth dose in specific countries
- To compare and discuss assumptions regarding the economic impact of HBV interventions (cost of treating advanced liver disease, cost of providing care, cost of screening and treatment, etc.)

INTRODUCTORY REMARKS

Mark Thursz and Tim Hallett welcomed all participants and outlined the objectives of the meeting (detailed above).

Although viral hepatitis accounts for almost as many deaths as diseases such as malaria, HIV and tuberculosis, it receives comparatively little funding and attention from global health policy makers and donors. Furthermore, countries lack of necessary surveillance and data collection systems to quantify the burden of disease has inhibited them from accurately determining the impact and prioritisation of necessary interventions. It remains clear that country programme managers need technical guidance to generate strategic information to make the case for national plans to adequately support efforts for hepatitis elimination at the country level. Mathematical models can complement empirically collected data in areas where epidemiological parameters cannot be measured directly and economic analyses can be used evaluate cost–effectiveness and cost–benefit for various intervention options for prevention and treatment.

SESSION 1: METHODS AND RESULTS OF ALTERNATIVE HBV BURDEN ESTIMATES

A comparative analysis of global, regional and country-level point estimates of HBV prevalence produced by the World Health Organization (WHO), the Polaris Observatory in the Center for Disease Aanalysis (CDA) Foundation, the Institute for Health Metrics and Evaluation (IHME) and Ott et al. and Schweitzer et al. was presented by Nora Schmit.

Across all sources, except for IHME, HBsAg prevalence was found to be between 3.5-4.5%. Of the 195 countries covered by IHME, the global estimation of HBsAg was calculated to be substantially higher than other groups at 6.4%. Further discrepancy between sources were shown in the global estimation of HBsAg among children. WHO and CDA estimates were both found to be approximately 1.3%, whereas estimates from IHME and Ott et al, were shown to be three times higher than this.

Largest absolute variability between sources was most apparent in the intermediate-high prevalence regions, Oceania, Central, East and West Africa. Variability across regions was often shown to be driven by an outlier – where higher estimates tend to be from IHME and Ott sources, and lower estimates from WHO data. Overall regional prevalence estimates were shown to be most similar between WHO and CDA data, and CDA-Schweitzer data, with half of their estimates within 0.5% prevalence points of each other. Similar trends were observed in children under five years. However, Nora Schmit highlighted that when compared with estimates of prevalence in the general population estimates were more variable in younger years.

Further comparison at the country-level showed relatively little variation but, large differences between data sources were observed in some high-endemicity countries and in comparisons with the consistently higher estimates from the IHME group. In addition, there was high discrepancy in estimates of prevalence in children under 5 years of age, highlighting a lack of good-quality data on this indicator of new infections and vaccination impact particularly in sub-Saharan Africa.

Given these findings, Nora Schmit recommended that further research be undertaken to calculate prevalence in children under the age of five years, specifically in sub Saharan Africa. She also noted that it would useful to examine differences in the age patterns of HBsAg prevalence and predictions of HBV-related mortality.

In response to the comparative review, each of the modelling groups presented their respective models and methods. It was acknowledged that similarities between estimates produced by WHO and CDA could be attributed to their comparable methodologies. It was noted that the observed divergence between WHO and CDA among children under five – could be associated with the fact that WHO conducted a systematic review and extrapolated their inputs using age-specific data, whereas CDA appeared to impose a regional pattern scaled accordingly. The reason why IHME appears to be an outlier at global, regional and country levels remains unclear but, it appears that updates outlined by Nick Walsh to GBD 2017 could rectify the overestimation of HBV burden.

The group acknowledged that estimates of the worldwide incidence and mortality curated by the International Agency for Research on Cancer in the GLOBOCAN series was an excellent resource and underused. Furthermore, it was noted that given the availability of such data it is surprising that there are no mechanistic models currently available to assess the prevalence of HBV.

Recommendations

- *It was recommended that the various literature reviews conducted between groups be shared.*
- *It was suggested that more mechanistic models may be useful for data integration.*

SESSION 2: THE IMPACT OF BIRTH DOSE

As of 2009, the WHO recommends the administration of a first dose of monovalent HBV vaccine within twenty-four hours of birth to prevent mother-to-child transmission. However, without Gavi's financing or promotion, many developing countries have done little to promote the birth dose, despite high rates of hepatitis B. Maya Malarski confirmed that Gavi seeks to reconsider potential support for the hepatitis B birth dose for the 2018 Vaccine Investment Strategy (VIS). The CDA, Imperial and Goldstein models have all contributed to the VIS analyses. During the next phase of analysis Maya Malarski confirmed that Gavi aims to better understand the operational implementation barriers that may lower the impact of a birth dose program.

A comparative review of the birth dose estimates was presented by Mark Thursz and Tim Hallett. Given the range of HBV models in use, Mark Thursz reminded the group that differences in model structure

and assumptions can yield variation in results. Comparative modelling therefore serves as an opportunity to pool resources and strengthen estimates.

Tim Hallett informed the group that the aim of comparative model analysis was to determine whether the Imperial, CDA and Goldstein models come to similar conclusions about the likely impact of scaling up birth dose. Each model simulated the impact of birth dose under standardised scenarios for scale-up. Models were then successively constrained to identify where original differences may have resulted in a divergence in the outputs.

This yielded two tentative findings:

- The Imperial/CDA comparison shows that assumptions of '*Probability of Chronic Infection*' and 'Survivorship of Chronic HBV Cases' are particularly important parameters. Increased risk among younger age groups underlies the higher impact of birth dose in the Imperial Model. The somewhat higher mortality rates of the CDA model contributed to the higher impact of birth dose; fitting to death data as well as prevalence data would likely ameliorate this difference.

- For the Goldstein to ICL/CDA comparison: Results seem uniform across countries, although unusually low which may be due to the Goldstein's underlying mortality estimates.

Based on these analyses, Tim Hallett confirmed the impact of the scale-up of birth dose remains clear, despite the different approaches adopted (data inputs and calibration/ assumptions on probability of chronic infection / survivorship assumptions) by each respective model.

In response to these findings, each of the modelling groups presented methods (structure and assumptions) used to estimate birth dose impact.

Devin Razavi-Shearer provided an overview of the mother-to-child transmission rates of HBsAg used in the ProGReSs Model. He confirmed that various characteristics are used to determine the probability of transmission in accordance to the mother's viral load: no vaccination, birth dose of HBV vaccine, complete HBV vaccine series with birth dose with and without hepatitis B Immunoglobulin (HBIG) etc. He noted that in the absence of any intervention it is assumed that there is no transmission among mothers with a low viral load (20,000) and 100% transmission where viral load is high. If pre-dose is administered, transmission is assumed to be 33% and if birth dose is administered, chances of transmission is halved. The group discussed the implications of this assumption.

Xi Li highlighted that the Goldstein model captures mortality due to chronic hepatitis B both during the acute phase and in the long-term. She noted that it assumes a 70% case-fatality ratio in fulminant hepatitis cases, with long-term causes of death including liver cirrhosis, and liver cancer associated with HBV infection. She noted that the model validation was conducted by comparing empirical measurements from recent surveys to model prediction. Nationally representative surveys that sampled children born after 2000'S from China, Viet Nam, Mongolia, Papua New Guinea, Lao PDR and Nepal were used to predict HBsAg prevalence of the surveyed birth cohorts at the age when they were surveyed.

Of the six countries analyzed, the predicted HBsAg prevalence using national coverage was higher than the reported HBsAg prevalence by a median of 3.1%, and the predicted HBsAg% using sero-survey coverage was higher than the reported HBsAg prevalence by a median of 1.6%. Furthermore, among the five countries in the Western Pacific, HBsAg prevalence among pregnant women was assumed to be 11.83% and e antigen prevalence was assumed to be 30%. This is higher than that observed in the survey in China in 2006, Xi Li suggested that this could therefore be a contributor to the overestimation of mortality.

Xi Li highlighted that although the Goldstein model predications are anchored to empirical measurement, several limitations exist. Firstly, there appears to be difficulties in estimating the counterfactual anti-HBc prevalence when increasing numbers of the population have been vaccinated. Currently, the anti-HBc prevalences that are used have been taken from the pre-vaccination era. The assumption stands that if the cohort is not vaccinated, they will reach the same level of infection as those in the pre-vaccination era, which may not be true when a large proportion of the population have been vaccinated. Further, the model does not consider the impact of herd immunity. Secondly, the same HBsAg prevalence among pregnant women is used across all cohorts. But, in reality vaccinated cohorts arrive at reproductive age, the HBsAg prevalence among pregnant women appears to decline. Previous sensitivity analyses have showed that the background mortality rate had the largest impact on cases and deaths averted.

Margaret de Villiers presented results from the Imperial Model and highlighted that assumptions of risk of mother-to-child transmission are calibrated for each country for risk of transmission from an HbeAg mother to her infant and then constrained to be lower than the risk of transmission from an HbeAg+ mother. Further, birth dose vaccination is set to be less effective in the case of an HbeAg+ mother than an e- mother. For the submission of estimates to Gavi earlier this year, the Imperial group calibrated to the CDA's prevalence data and where countries were not available Ott regional data were used. She noted that as vertical transmission and horizontal transmission in young children are the only parameters that can be manipulated, the model prevalence has a limited ability to fit to the reference prevalences. However, she highlighted that the model prevalence peaks at higher age groups in later years after the start of vaccination.

The group recognised that there are various nuances between the modelling approaches – and hoped that Gavi would perceive this to be a strength. However, Tim Hallett and Mark Thursz acknowledged further analyses and discussion must be undertaken to characterise underlying elements that yield variation such that we are able to strengthen these estimates. Based on the review of the models, Tim Hallett suggested that three hypotheses may be put forward to the differences outlined above.

Recommendations

- *In order to strengthen birth dose estimates, the group agreed that further data collection should be conducted with emphasis on surveys of young children to measure risk of transmission from mothers.*
- *The model comparison should be continued, enforcing a tighter alignment in the elements that are to be controlled (e.g. matching to prevalence more closely). This was strongly encouraged by GAVI.*

SESSION 3: ECONOMIC MODELS

Robert Hecht and Shevanthi Nayagam provided an overview of the current economic evaluations of HBV testing and treatment strategies in low and middle-income countries (LMICs) which is lacking, therefore limiting the ability to provide formal recommendations on the basis of cost-effectiveness alone. Further implementation research is needed in order to help guide national policy planning. Slow action is the paucity of locally informed rigorous analyses estimating the likely cost, health impact, value and feasibility of scaling up national HBV/HCV programs. In addition, there is no immediately available source of large-scale external donor aid for HBV/HCV programs.

Ivane Gamkrelidze provided an overview of the inputs of the Economic Impact Module in the PRoGReSs model. In addition to this, he provided some examples of what the module could generate. The biggest use of this module is scenario analysis so up to seven strategies including the base case for a time horizon of up to 2050 can be run at one time. This work is yet to be published. Shevanthi

Naygam also provided an overview of the Imperial Economic Model using published case studies from The Gambia and Senegal.

Stephen Resch provided an outline of the Pharos hepatitis economic model using South Africa as a case study. In collaboration with epidemiological modellers at Imperial College London and CDA, the Pharos group used an investment case approach to develop a national hepatitis action plan for South Africa. In order to estimate the Action Plan's financial requirements, an ingredients-based costing tool was developed in Excel. The tool provides a template for program objectives, planned activities, responsible parties, scale-up targets and progress indicators and summarizes costs by objective, activity and calendar year, and breaks down capital, recurrent, fixed, variable and one-time start-up costs. The Imperial and CDA models were then adapted to assess health impact. Cost estimates and the impact analysis were then used to determine selective value-for-money measures. Case studies for Malaysia and Morocco were also used to illustrate challenges that may arise when developing the investment case.

The group also acknowledged that further understand of the human capital approach (a representation of the loss of future contribution to the national economy given that the individual dies earlier than country-specific expected age of retirement) and quantifying 'value of additional life years' should be better understood in order to quantify deaths may be due to poor health or hepatitis related illness.

Recommendations

- *The group agreed that while there is significant enthusiasm for the use of economic models in HBV policy planning key data gaps continue to frustrate these efforts but strategies for data collection were discussed.*
- *The group agreed to share published economic models.*

TECHNICAL CONSULTATION ON MODELLING OF HEPATITIS B

9 – 10 May 2018

Chandos House, London UK

Day 1: Wednesday 9th May

Time	Duration	Session	Speaker
915	20	Welcome & Introductions	Tim Hallett, Mark Thursz, Yvan Hutin
Session 1: Methods and Results of Alternative HBV Burden Estimates *Aims:* • *Review all methods being used to generate estimate of age-specific HBV prevalence (HBsAg & HBeAg);* • *Review all methods being used to generate other metrics of HBV impact (HBV-related deaths);* • *Review estimates and come to shared understanding of differences;* • *Discuss how these estimates can be used in modelling and economic evaluation work;*			
Chair: Tim Hallett			
935	5	Introduction	Tim Hallett
940	15	Comparison of Results from Different Methods	Nora Schmit
955	25	WHO Methods and Results	Yvan Hutin
1020	25	IHME Methods and Results	Nick Kassebaum and Kathryn Lau
1045	25	Globocan Methods and Results	Catherine De Martel
1110	20	*Coffee break*	
1130	25	CDA Methods and Results	Devin Razavi-Shearer
1155	25	Schweitzer Results	Jördis Ott and Johannes Horn
1220	45	Discussion	All
1305	60	*Lunch*	
Session 2: The Impact of Birth Dose *Aims:* • *Compare and discuss estimates of the impact of birth dose in specific countries* • *Come to agreement on overall model estimates for magnitude of impact from birth dose in PINE countries*			

• *Identify major gaps for data for communication to stakeholders*			
Chair: Mark Thursz			
1405	20	Introduction – and comparative review of BD model estimates	Mark Thursz
1425	10	Update on GAVI VIS process	Maya Malarski
1435	25	CDA Results	Devin Razavi-Shearer
1500	25	'Goldstein Model' results	Xi Li
1525	20	Imperial Model results	Margaret de Villiers
1545	20	*Coffee Break*	
1605	55	Discussion / Workshop	All
1700		*Adjourn*	

Day 2: Thursday 10th May

Start	Duration	Subject	Speaker
Session 3: Economic Models *Aims:* • *Compare and discuss assumptions regarding the health and economic impact of HBV interventions (averted cost of treating advanced liver disease and of providing care, incremental investments needed in expanded immunization, screening and treatment, etc.)* • *Identify priority areas for further data collection (or analysis)*			
Chair: Shevanthi Nayagam			
915	10	Introduction	Shevanthi Nayagam, Robert Hecht
925	20	Different Approaches to Economic Modelling: A Bestiary	Nick Walsh
945	20	CDA Economic Model	Ivane Gamkrelidze
1005	20	Imperial Economic Model	Shevanthi Nayagam
1025	20	Cost-Effectiveness Model of HBV Treatment	David Hutton
1045	20	Pharos Economic Model	Stephen Resch and Robert Hecht
1105	20	*Coffee Break*	
1125	45	Discussion to meet aims / Workshop	All
1205	15	Final Remarks	Mark Thursz
1300	60	*Working Lunch – The Role of Epidemiological Model in Elimination Campaigns*	Mark Thursz
1400	15	*Meeting Close*	

LIST OF PARTICIPANTS

Graham Cooke
Imperial College London
London, UK

Catherine De Martel
International Agency for Research on Cancer (IARC)
Lyon, France

Margaret de Villiers
Imperial College London
London, UK

Ivane Gamkrelidze
Center for Disease Analysis Foundation
Lafayette, CO, USA

Markus Haacker
Harvard T.H. Chan School of Public Health
Boston, MA, USA

Tim Hallett
Imperial College London
London, UK

Robert Hecht
Pharos Global Health Advisors,
Boston, MA, USA

Alastair Heffernan
Imperial College London
London, UK

Daniel Hogan
WHO
Geneva, Switzerland

Johannes Horn
Helmholtz Centre for Infection Research & Medical School
Hannover, Germany

Yvan Hutin
WHO
Geneva, Switzerland

David Hutton
University of Michigan
Ann Arbor, MI, USA

Nick Kassebaum
University of Washington/IHME
Seattle, WA, USA

Kathryn Lau
University of Washington/IHME
Seattle, WA, USA

Maud Lemoine
Imperial College London
London, UK

Maya Malarski
GAVI
Geneva, Switzerland

Shevanthi Nayagam
Imperial College London
London, UK

Jördis J Ott
Helmholtz Centre for Infection Research & Medical School
Hannover, Germany

Holly Prudden
GAVI
Geneva, Switzerland

Devin Razavi-Shearer
Center for Disease Analysis Foundation
Lafayette, CO, USA

Stephen Resch
Harvard T.H. Chan School of Public Health
Boston, MA, USA

Nora Schmit
Imperial College London
London, UK

Yusuke Shimakawa
Institut Pasteur
Paris, France

Elisa Sicuri
Imperial College London
London, UK

Mark Thursz
Imperial College London
London, UK

Nick Walsh
Pan American Health Organization/WHO
Washington DC, USA