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25-26 August 2010
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1. Introduction

1.1 Background

Dengue virus of the Flaviviridae family has for distinct serotypes (DENV 1 through 4) that are all capable of causing dengue fever. Dengue is transmitted by mosquitoes of the genus *Aedes*. Infections occur in both adults and children, and dengue is endemic in most tropical ans sub-tropical regions of the world including Central and South America, south Asia, southeast Asia, and the Pacific region countries [1-3]. More than two billion people live in these at risk areas, and it is estimated that each year there are nine million symptomatic cases [4] and 500,000 severe episodes of dengue worldwide [1] . Dengue infections can cause a range of clinical syndromes from asymptomatic infection to an incapacitating flu-like illness sometimes called "break bone" fever. Some clinically apparent cases will develop a vasculopathy, historically called dengue hemorrhagic fever (DHF), which in severe cases can result in circulatory shock (dengue shock syndrome, DSS. In clinically apparent dengue, a rapid onset of fever is usually observed four to seven days after infection, and fever can last from a few days to a week. Symptoms associated with severe disease (e.g. hemorrhage vascular leak, hypotension) typically develop after defervescence.

There are currently no licensed vaccines or drugs to prevent or treat dengue infections. Candidate drugs are years or decades away, and only one vaccine – a tetravalent chimeric yellow-fever dengue vaccine (CYD, Sanofi Pasteur) – is in an advanced stage of clinical trials, with phase III trials set to begin in 2011. As dengue immuno-epidemiology, immuno-pathology, and vector-host interactions are quite complex, their interplay requires careful analysis to guide vaccination strategy. Mathematical modeling can be a useful tool to explore the interplay of key determinants of transmission to assess the effectiveness of various introduction strategies. To meet this objective, the World Health Organization, in collaboration with the Vaccine Modeling Initiative (VMI, University of Pittsburgh) and the Pediatric Dengue Vaccine Initiative hosted a workshop on August 25-26, 2010 to bring together mathematical modelers, clinicians, vaccinologists, virologists, immunologists, entomologists and epidemiologists to examine the current state of knowledge and future needs in this area of work.

1.2 Purpose

The purpose of the August 2010 workshop was to review:

1) The current state of dengue transmission models and the main scientific challenges facing the development of future dengue models.

2) Strategies to evaluate the impact of vaccination and, in particular, the potential impacts of different vaccination strategies using representative data.

3) The potential of mathematical modeling to improve understanding of risks and to guide risk mitigation strategies, pharmacovigilance programs, and phase IV study designs.

2. Summaries of presentations and discussions

The workshop included presentation on modeling work, either completed or in process, as well as discussions on what is missing from the current dengue modeling environment. Workshop discussions centered on specifics of model structure, data needs for building accurate models of transmission and vaccination, and general dengue biology. Participants identified and discussed key questions concerning the likely impact of different vaccination strategies and discussed the epidemiological and entomological features of dengue that need to be better understood for this modeling effort.

Recognizing the complexity of modeling the transmission of a vector-borne disease like dengue with its four serotypes and associated complicated immune responses, then adding in vaccine impact, the workshop participants concluded that a multiple modeling efforts and strategies are desirable. A key component to facilitate this process will be the generation, availability, and sharing of epidemiological data. For all involved in this effort, it is critical that data sets and the analyses thereof be shared and discussed by all partners. This type of cooperative and collaborative effort ensures that we will have the best tools to begin understanding and planning future dengue vaccination efforts.

In the following section is a summary of the presentations made at the workshop.

Dr. Scott Halstead, Uniformed Services University of the Health Sciences (Bethesda, USA), provided a background on dengue viraemia, the neutralizing antibody response, antibody-dependent enhancement, and their effects on disease severity. After infection with a dengue virus (DENV) serotype, lifelong homotypic immunity is developed against the infecting serotype and a transient heterotypic protection against the other serotypes. Upon infection with a second serotype, a heterologous immune response is demonstrable using plague neutralization reduction assay. However, secondary infection with a different DENV serotype can also lead to severe disease in the presence of sub-neutralizing antibody concentrations resulting from the previous infection; this feature of dengue immuno-pathology is called antibody-dependent enhancement (ADE). The severity of secondary infections may is also be influenced by the sequence of the infecting serotypes; for example, serotype 1 followed by serotype 3 has been observed to be more severe than serotype 3 followed by serotype 1. Third and fourth infections do occur but appear less likely to be severe than secondary infections. Cohort studies, detailed population-based studies, and observational studies from non-endemic regions during with occasional outbreaks (e.g. Cuba) can yield useful information about the immune response and risks for severe disease.

Dr Pej Rohani, University of Michigan, presented a parameter inference method known as 'particle filtering' by which immunological interactions among dengue serotypes were explored to show how complex and heterogeneous data sets can be used to make inferences on biological processes. Examples of data from Mexico and Thailand were given to demonstrate simultaneous circulation of multiple DENV serotypes, immune interactions, antibody-dependent enhancement (ADE), and short-term cross immunity. The overall goal of the presented work was to use particle-filtering methods to estimate strength and duration of cross immunity and ADE. Parameters with short-term effects were more difficult to measure than those with long-term effects. Use of shorter time series did not make a difference for parameter estimates in the absence of interaction, but shorter time series resulted in less accurate estimates in when immunological interactions were present. It was found that the shape of epidemics of co-circulating DENV serotypes is more informative for parameter estimation than phase relationships or amplitude.

Dr Helen Wearing, University of New Mexico, explored the roles of temporary cross-protection immunity, antibody dependent enhancement (ADE) and vector seasonality in dengue dynamics. Epidemiological data from Thailand and mathematical models were shown to demonstrate the interaction between co-circulating serotypes and strong seasonality in DENV epidemics. The following potential determinants of observed dengue dynamic patterns were considered: short-term cross protection, antibody-dependent enhancement, variation in virulence among strains, and climate-driven vector populations. The modeling showed that a temporary period with cross-immunity is required to match observed dengue incidence patterns, and that neither ADE nor variation in virulence can be the sole drivers of dengue epidemic dynamics. The critical vaccination fraction in this model was not affected by serotype interactions; it was determined simply by the serotype with the highest basic reproductive number (R_0). It was emphasized that in future modeling exercises, we will need to differentiate between naturally-acquired and vaccine-induced immunity.

Dr Mario Recker, University of Oxford, using data from Thailand and Viet Nam modeled immune interactions between dengue serotypes and their epidemiological consequences to illustrate circulation of multiple DENV serotypes. The model included the effects of ADE during secondary infections, using effects on transmissibility and susceptibility. Model simulations and data coincided when the level of enhancement was low, and the model showed that ADE alone could explain observed patterns of dengue dynamics. The question of DENV persistence was addressed and it was hypothesized that virus persisted through asymptomatic transmission, as there are many asymptomatic cases for each hospitalized case. Third and fourth DENV infections probably occur, but are often not clinically overt.

Dr Mark E. Beatty, Pediatric Dengue Vaccine Initiative, International Vaccine Institute, discussed how the methods and accuracy of dengue surveillance vary widely by country and are prone to reporting error. Overall, dengue occurrence is severely underreported due to lack of symptoms, limited health seeking, or lack of reporting. Comparisons between national surveillance and cohort studies have revealed between 10 times and 250 times as more dengue cases as passive surveillance. In addition, national (passive) surveillance sometimes applies varying case definitions and often lacks laboratory confirmation. In cohort studies (active surveillance), one can study the short-term broad cross-reactivity against all dengue serotypes that is thought to occur immediately after a dengue infection; however, this has not been investigated thoroughly

since the Sabin study in the 1950s, which in fact only examined DENV-1 and DENV-2 [5]. Moreover, inference on immune status against DENV in general is challenging as it depends on assay validity, serotype, and the day of illness the measurement is taken.

The Pediatric Dengue Vaccine Initiative (PDVI) funded multiple field sites in Latin America, South Asia, and Southeast Asia for long-term (5-6 years) cohort studies on dengue. All studies capture clinical cases of febrile disease in clinic or community settings, with standardized data collection instruments and laboratory databases. An effort is ongoing to make these instruments available to other research sites, to pool data in one repository and to share laboratory protocols. The PDVI aims to concentrate on four early adopter countries of a dengue vaccine –Thailand, Viet Nam, Brazil and Colombia – where field studies will need to include work on demographics, collecting acute and convalescent blood samples from febrile cases, annual serosurveys to capture asymptomatic cases, health-seeking behavior, cost-of-illness and willingness-to-pay studies, and comparison of cohort data to national surveillance.

Dr Jan Medlock, Clemson University, explored the impact of vaccination on dengue virulence looking at the potential within-serotype virulence evolution. Potential ways that vaccination can protect a host are reduced susceptibility, reduced viral load and transmission, reduced pathogenicity, and slower pathogen growth. A mathematical model with one serotype was developed to explore the association between a vaccine's effects on transmission and a virus' virulence, where dengue-related mortality was used as a proxy for virulence. For different modes of vaccine protection, virulence evolution could be pressured in different directions (both up and down), and thus the expected long-term evolutionary outcome post-vaccination is very difficult to predict. Although virulence was modeled as an increase in mortality in this analysis, it was acknowledged that pathogen virulence can manifest itself in many ways and can be the product of both virus and host factors. Despite years of theoretical modeling on this topic, effects of vaccination on flavivirus virulence have not yet been observed.

Dr Jean Lang, Sanofi Pasteur, provided an update on the progress of the development of the current chimeric, live-attenuated, tetravalent vaccine (based on the 17D 204 yellow fever vaccine backbone). This vaccine will be administered subcutaneously or intramuscularly in three doses, at zero, six, and twelve months (regimen based on PRNT50 optimal CLINICAL immunogenicity). Vaccine development and production was conducted according to current standards and guidelines as established by WHO and regulatory agencies. Multiple potential risks of vaccination were addressed in clinical and non-clinical studies: reversal of the vaccine virus to a virulent form, replication in mosquito vectors, recombination with a wild-type virus, adverse events related to Yellow Fever vaccination, protection against all recent /genotypic strain variants, and possibility for antibody-dependent enhancement. Phase II staggered clinical trials were conducted in Mexico and Philippines and no severe adverse events were found. No increased reactogenicity was found in subjects with previous flavivirus infections. In non-endemic populations, three doses of vaccine provided a balanced tetravalent immune response. In endemic populations, a boosting effect was observed in previously exposed people and a two-dose schedule gave a robust immune response. A phase II/B trial is ongoing in Rachaburi Thailand among 4000 children between 4 and 11 years of age. The Phase III clinical program is on-going since October 2010 with material representative of the final manufacturing scale. Phase III clinical efficacy trials will take place in several countries of Asia and Latin America in about 10,000 and 21,000 children, respectively and are planned to start in 2011.

Dr. Katia Koelle, Duke University, showed how models can be used to explore the long-term effects of vector control and vaccination on dengue transmission rates. The rapid rise of dengue fever cases in Singapore and the inappreciable decrease in dengue hemorrhagic fever cases in Thailand over the past decades was investigated. In both places, an increase in the mean age of infection was observed. One potential explanation for the increase in dengue fever incidence in Singapore was a decrease in the transmission rate caused by effective vector control, and the increase in the age of infection that resulted from this reduction [REF- Egger, Ooi, et al. 2007]. As individuals are more likely to develop symptomatic dengue infections the older they are [REF- Egger and Coleman, 2007], this may have effectively lead to an increase in the reported number of dengue cases. Two potential explanations for the increase in the age of dengue cases in Thailand were also discussed. One explanation focused on a decrease in the transmission rate in Thailand; the number of DHF cases in this case did not decline significantly due to the effect of short-term heterologous clinical cross-protection [6]. The second explanation focused on declining birth rates [7]. A second model (age-specific, four serotypes) was developed to assess the effect of vector control and vaccination on dengue fever and dengue hemorrhagic fever incidence. It was found that if vector control were implemented first, it would reduce the basic reproduction number, leading to a higher average age of infection and, possibly, more severe clinical disease in these cases. This same effect was not observed when vaccination is implemented first.

Dr. Laurent Coudeville, Sanofi Pasteur, presented a model developed to estimate the potential impact of vaccination on DENV transmission. A deterministic model was developed that included: host-vector interactions, cross-protective immunity and ADE, age-specific incidence, age-specific DENV transmission rates, seasonality, serotype-specific impact of vaccination, and host and vector population growth. The model was calibrated with surveillance and cohort data from southern Viet Nam where possible. In these data, vector density and dengue incidence rates did not seem to correlate very well and a periodicity of 3-5 years was found. It was assumed that 1 dose of vaccine resulted in 30% reduction of infection, 2 doses in 60% reduction, and 3 doses in 80% reduction. An efficacy rate of 80% was assumed with average duration of 15 years, doses given at 12, 18 and 24 months of age, 90% population coverage, and a ramp-up period of two years. The model estimated that DENV incidence would decrease to very low levels after about 10 years of vaccination, with epidemics still occurring occasionally. When compared to a two-year ramp-up campaign, a ramp-up period of five years resulted in higher monthly cases during the first eight years, but this disparity could be reduced if catch-up vaccination were provided to 60% of children aged between two and nine.

Dr. Dana A. Focks, University of Florida, presented a simulation model of dengue for studies on epidemiology and control. Models were developed with the goal of optimizing vector control strategies. Weather and habitat parameters in the model determined reproductive rates of various mosquito developmental stages and mosquito survival; the reproduction number was determined by mosquito type and number of breeding sources per land area. This entomological model (CIMSiM) was linked to a transmission model (DENSim) [8], and the output of these models was validated by field data from Thailand, Peru, Honduras, and Indonesia. All types of breeding sites were included in the models, and data from Jakarta indicated that indoor containers cause 85-95% of overall vector production. The climate analysis in the model indicated that in the Carribbean basin, increased temperature would increase mosquito infectivity,

but would result in fewer breeding sites due to reduced rainfall; thus, conclusive results on the effects of climate change could not be made. In high-altitude locations like Mexico City, increased temperature would likely increase DENV transmission by allowing for the survival and establishment of the mosquito vector. Vector control has been unsuccessful in the past, with some exceptions observed in Cuba and Peru.

Dr. Derek Cummings, Johns Hopkins Bloomberg School of Public Health, presented an analysis of dengue epidemiology based on hospitalized cases in Thailand. The average age of symptomatic dengue infection has increased in Thailand over the last 20 years. This increase is best explained by a decrease in birth rates from 30/1000 to 10/1000 over the past 20 years [7]. A mathematical model parameterized with Thai data indicated that the optimal age of vaccination was the youngest age, except in the case when DENV transmission and/or vaccine efficacy are age-dependent; however, vaccinating older age groups may have programmatic benefits such as making the vaccination school-based. If a vaccine were to provide 75% protection to each serotype in 90% of the population, an 83% reduction in secondary cases could be achieved with vaccination at 12 months compared to a 68% reduction with vaccination at 5 years. However, comparison of multiple vaccination strategies may require multiple model formulations and validating these models with data. Spatial heterogeneity of R_0 between provinces in Thailand was observed. Since the critical vaccination fraction depends on this parameter, spatial targeting of the vaccine may be a cost-effective policy to maximize public health benefit with a limited vaccine supply.

Dr. Gerhart Knerer, GlaxoSmithKline Biologicals, presented a linear-programming model to find optimal resource allocation in a dengue vaccination scenario. As governments often face constrains on resources, interventions such as vaccination need to be both cost-effective and affordable. This model sought to minimize DHF hospitalizations given a set of resource constraints. Various interventions were tested: vaccination, larvicide, insecticide treated bed nets, and indoor residual spraying. Multiple scenarios were tested assuming varying levels of vaccine cost, efficacy, and coverage. The vaccine would be the best choice of intervention if met 90% efficacy, 1 USD per dose, and 90% coverage. With these parameters, 2000 hospitalizations would be avoided in Thailand per year by including vaccination in the disease control strategies. This model was parameterized so that model output was representative of observed dengue dynamics. It was discussed that more detailed parameterizations and non-linear processes would improve dengue cost-effectiveness analyses.

Dr Rome Buathong, Ministry of Public Health, Thailand, discussed the opportunities and challenges in translating evidence to policy stressing the importance of close interaction needed between the scientific community and the decision makers at country level. The introduction of mathematical modelling methods to Thailand in 2005 was discussed. The process of adapting computational models as tools for decision making was described, the need for reliable data sources was emphasized, and the surveillance methodology in Thailand, conducted by the Bureau of Epidemiology in the Ministry of Health, was presented. Various other organizations collect information on dengue, such as the national surveillance system, Queen Sirikit Hospital, and US Armed Forces Research Institute of Medical Sciences (AFRIMS) in Thailand. When starting collaborations with local officials in endemic countries, academic-government partnerships must be considered in the context of capacity building opportunities, data transfer agreements, potential training, and overall public health goals. In Thailand, a standard system has been developed for inclusion of new

collaborators. The specific purpose of surveillance data collection was discussed, and the lack of archiving of historical reports was noted as commonplace. Many countries would probably be interested in learning how to manage and analyze their surveillance data, and could learn from the Thai experience.

Dr. Ira Longini, University of Washington School of Public Health, demonstrated the use of an agent-based models, using cholera and H1N1 as illustrations. Two movies of epidemic simulations were shown for H1N1 in 285 million people (US; no intervention) and for cholera 200,000 people (Matlab, Bangladesh; oral vaccine) in 200,000 people. The methodology of constructing agent-based models was discussed. Most model development is concentrated on representing the structure of the population and the disease transmission parameters. The differences between agent-based models and highly-stratified compartmental models were discussed. The use of each type of model depends entirely on the research question, but in general agent-based models allow more detail and complexity and would not need to compartmentalize populations into arbitrary subgroups. Agent-based models also provide a better representation of stochasticity and spatial heterogeneity. On the other hand, their data requirement exceed those of compartmental models. It was generally agreed that maintaining multiple models for various questions would be valuable.

3. Discussion

3.1 Purpose of Mathematical Modeling

Mathematical modeling of epidemiological systems has two general purposes that are useful for evaluating dengue vaccination programs. First, modeling can be used to infer unknown parameters that may be critical to vaccination efforts. For example, modeling can be used to infer the length or strength of various types of dengue-specific immune responses. Certainly, these estimates may be only as good as the underlying model, and they may come with wide confidence intervals, but estimating such a parameter with modeling takes considerably less work than following up thousands of individuals for years and possibly decades; this is of particular use when we are trying to infer parameters for long-term processes. Second, mathematical models can be used to generate predictions of the outcomes of vaccination strategies, or equally important, predictions of disease incidence and endemicity in the absence of vaccination strategies. Again, predictions are only as good as the underlying models, and such predictive models cannot take into account unforeseen events such as unusually high rainfall or lack of compliance with vaccination recommendations. Nevertheless, these types of predictions can be useful in determining the relative value of different vaccination strategies in the absence of other unforeseen circumstances.

Mathematical modeling comes with many caveats, the most important of which is that if model assumptions are wrong or not validated, parameter estimates and predictions can be wrong. As mathematical modeling has developed over the past decades, it has produced experienced modelers. Their engagement in this dengue initiative ensures that validation and model-building are done to the highest standards. For validation to be performed properly, modelers must use available long-term data sets national surveillance systems, from cohort studies, cross-sectional studies, and/or other similar studies to determine if their models accurately represent the epidemiological behavior observed in the data. As the relationship between model output and data will never be perfect, a careful assessment must be made about how well the model represents the underlying epidemiological mechanisms generating the data and whether the model adequately captures the essential behaviors of the system; we should resist the temptation to label models as 'right' or 'wrong'. When comparing model results to data, we must be able to assess if the data are extremely variable or if there are unknown/unobserved processes generating the disparity between models and data. This type of assessment is very common in mathematical modeling exercises, and indeed, sometimes it is simply unknown why a model is not a good approximation to epidemiological observations; in these situations, an iterative process of altering model assumptions and mechanisms can be used to determine which features of the model are critical, unnecessary, or simply incorrect.

With the rise of affordable, large-scale computing power over the past two decades, mathematical modeling has evolved from a mathematical science — where models were simple and results were the fruit of detailed computations by pencil and paper — to a computational science where complex models with thousands of variables and parameters could be run thousands or millions of times. The benefit to health policy of this computational aspect of modeling is that many policy scenarios can be generated and evaluated with a mathematical model. This will be critical to the rollout of dengue vaccine, as many vaccination strategies will be evaluated, and relative benefits of one strategy over another can be discussed and weighed.

Two of the most important aspects of mathematical models that need to be understood before we can use them to support decision on dengue vaccination strategies are (1) an understanding of immunogenicity of the vaccine and (2) and understanding of the immune response to dengue.

3.2 Relationship between Immunity and Pathology

The relationship between immunity and pathogenesis is one of the most important areas of dengue vaccine research, and despite decades of work on many well-supported hypotheses, many unanswered questions still remain in this field. Pathogenesis in dengue patients is affected by age, viraemia, viral phenotype (including serotype), the cellular immune response, and antibody levels to all four dengue serotypes. The most unusual feature of dengue severity is that secondary infections are sometimes — in about 10% to 20% of cases — observed to be more severe than primary infections. The severity of secondary dengue infections is usually attributed to the presence of sub-neutralizing antibody concentrations that increase viral replication through a process called antibody-dependent enhancement (ADE). This theory is corroborated by direct evidence obtained in primate experiments and severe primary infections in human infants aged 6 to 12 months in whom maternally derived anti-dengue antibody has waned to sub-neutralizing levels [9-11]; in vitro evidence also exists supporting the theory behind ADE [12]. However, many other factors have been associated with disease severity, and observations of severity in primary infections and non-severity in secondary infections have not yet been explained by antibody levels in these patients. The complex effects of immune status on disease severity, though not yet fully understood, are critical to assessing the effects of dengue vaccine candidates.

To understand how antibody levels affect pathogenesis and susceptibility, we need to know how long heterotypic and homotypic immunity last. The challenge in measuring long-term processes is that follow-up must be done for many years, which can be financially and logistically prohibitive. Two possible solutions can remedy this problem: (1) using natural setting where dengue epidemics occur many years apart (Cuba, Chile), and (2) estimating these parameters with mathematical models given the appropriate type of long-term incidence data set. Indeed, long intervals without dengue challenge led to a very high proportion of severe cases in Cuba [13], but this is one of very few data sets available to investigate long-term immunological processes.

In general, variation in disease severity is still poorly understood. As vaccination programs are rolled out, a new confounding factor – that vaccine-induced immunity will probably differ from naturally-acquired immunity – will need to be taken into account as is likely to have an effect on the relationship between immunity and severity.

3.3 Relationship between Immunity and Disease Dynamics

In addition to affecting how individuals progress to severe disease, the immune response has a population-level effect in determining short-term and long-term dengue dynamics. Many hypotheses have been put forward, and some tested with mathematical models, on how population-wide immunity and antibody-dependent enhancement can affect dengue disease dynamics.

One modeling analysis presented at this workshop showed that observed dynamics in Thailand are consistent with either (1) ADE combined with a period of temporary cross-protection, or (2) ADE combined with variation in virulence. This study showed that seasonality in transmission and the presence of short-term cross protection are key features of the epidemiological dynamics of dengue. However, a second model showed that ADE alone can generate the multi-annual epidemic and sequential replacement of serotypes that we see in dengue, and that high levels of serotype diversity often precede seasons with peak incidence. This second model used data from southern Viet Nam to build and test model mechanisms. It is not uncommon for models to disagree in early stages of development, especially when different assumptions are used; the lesson to be learned is that the relationship between ADE and dengue dynamics is very sensitive to model assumptions, and much work remains to be done in developing a functional and accurate model of ADE.

An analysis of a longer Thai time series considered how immunity comes into play when we look at the decline in both dengue's basic reproductive number (R_0) and the birth rate in Thailand over the past decades. These processes seem to have increased the mean age at which we see DHF in Thailand and one hypothesis put forward is that an individual period of clinical cross-protection, during which infections are asymptomatic, can explain this pattern. A second hypothesis of this epidemiological trend is that a lower birth rate and changing age structure in Thailand over the past two decades have lowered incidence and increased the spacing between infections [7]. A similar increase in age of DHF was also observed in Singapore after implementation of a vector control program, but a hypothesis has not yet been developed and tested for this observation.

A key epidemiological feature highlighted by some of these modeling studies is the level of asymptomatic infection in dengue endemic areas. Most of what is known about asymptomatic infection comes from the comparisons of active surveillance at PDVI field sites with national dengue reporting in those same countries. Passive surveillance underestimates true dengue burden by one or two orders of magnitude (10-fold to 250-fold). To date, no model has been constructed to specifically look at the dynamics of asymptomatic dengue, or to test hypotheses on the determinants of asymptomatic infections.

3.4 Vectors

Vector control programs will most likely be deployed alongside vaccination campaigns, as a combined approach should yield further reductions in disease incidence. For the purposes of general dengue modeling, the most important issues to consider for vector populations are the effects of rainfall and temperature, their seasonal patterns, size estimates of mosquito population, and the effectiveness of vector control.

Effectiveness of vector control appears to vary widely from one country to another. The history of vector control in Cuba shows that it can be very effective if carried out to a high standard, however most countries have not had such success. The best way to determine the effectiveness of vector control measures and the strength of seasonality is to count pupae, as this is the best determinant of vectorial capacity for dengue transmission.

As discussed at the meeting, there are three key aspects of vector populations that could modulate transmission and therefore should be considered in mathematical model building. First, models may need to incorporate community household structure and household sizes as Aedes mosquitoes rest indoors and can spend their entire lifetime in one home. Second, the general pattern of vector population seasonality is the most important contributor to the force of infection. Vector populations do not need to be modeled explicitly, but the induced seasonality does need to be modeled. Third, for modeling that looks decades ahead, climate change scenarios may need to be modeled. Higher temperatures can reduce the gonotrophic cycle and the extrinsic incubation period (EIP), and lower rainfall can reduce the number of available breeding sites.

3.5 Epidemiological Impact of Vaccination Programs

Once vaccination programs are operational, the increased herd immunity should affect longer-term trends in dengue epidemiology. Specifically, we may expect to see changes in age distribution, the pattern of multi-year dengue cycles, and the cycling of serotypes.

After a vaccination campaign reduces the force of infection in the population, the age of first infection and the spacing between first and second infection should both increase. These epidemiological changes will affect vaccinated individuals and non-vaccinated individuals alike, in terms of the ages they can expect infections and in terms of the risks they face by facing infection with a particular antibody/immune level. Many scenarios and questions need to be investigated surrounding this potential age shift; these include (1) an age-specific investigation of (severe) disease reduction, (2) consideration of the use and timing of booster shots, and (3) age shifts if the vaccine is first introduced in urban areas where age structure differs from rural areas.

In addition to a changing age profile, vaccination induces a changed immune profile. Essentially, the vaccination campaign shifts the profile of the dengue-immune population from primarily naturally immune to primarily vaccinated, while simultaneously increasing the overall proportion of the population having some immunity. Once the differences between naturally-acquired and vaccine-acquired immunity are better understood, the long-term dynamics of this effect will also need to be investigated.

The dynamics of catch-up campaigns need to be understood in order for certain desired outcomes to be optimized, especially if there are features of catch-up campaigns that can temporarily increase risk or disease. Some preliminary analyses of the initial phases of vaccination campaigns were discussed —that faster catch up campaigns and younger ages of vaccination are more optimal — but more modeling is necessary to understand these dynamics.

Finally, long-term serotype oscillations may be affected by a vaccinated population. Currently, the four serotypes of dengue oscillate every three to six years because of the accumulation of herd immunity. These oscillations are thought to reflect the impact of cycling of immunity on incidence. A vaccinated population will not only change disease dynamics, but it may have two other effects. First, a tetravalent vaccine may dampen or prevent cycling of immune profiles in the long term since a population vaccinated with TDV should in principle have a uniform and constant immune profile, i.e. the same level of immunity to each serotype every year. Second, a vaccinated host population puts pressure on the viral population to evolve at its immunogenic sites; however, it is still completely unknown how apt dengue virus populations will be at immune-escape evolution.

3.6 Recommendations for Future Action

In creating a joint endeavor linking the expertise of two scientific communities — those with a background in biology and medicine, and those with a background in mathematics or theoretical ecology — communication will be a key to progress. Communication is a critical aspect of this collaboration as these two research communities have different knowledge bases, different habits of interpreting data, and even divergent vocabulary; e.g. 'mathematical modeling', 'virulence', and 'epidemiology' can mean different things to different researchers. The August 2010 meeting was a first step in bringing together these two groups, and creating a forum where they will be able to interact and communicate. This forum will be critical for bringing the tools available in mathematical modeling to the dengue community, and allowing the dengue community to learn how to manipulate these tools to answer pertinent questions in dengue biology. As a first step in developing this collaboration, dengue experts and modelers will be invited to collaborate on articles to be submitted to a special journal issue (as yet to be determined) focusing on the dengue modeling and the most current knowledge on dengue epidemiology

Estimating model parameters is a critical step in building mathematical models. Measuring parameters requires access to data which can then be used either to measure a parameter directly or to infer a parameter's value with a mathematical model. It is critical that modelers work closely with dengue biologists who understand the lab/field data and the parameter measurements. These data will be critical for the iterative process of model building and model validation. For all those involved — whether in epidemiology, in clinical or laboratory settings, or as modelers — it is critical that complete data sets and the analysis of that data be shared so that all the partners can come to a common understanding of the interpretation of the data. The August 2010 meeting sought to catalyze this effort by taking advantage of the participants' varied skills and experiences and by bringing together those scientists specializing in theory/modeling with those that have a detailed understanding of the data.

The most important feature to be added to the next generation of dengue models is vaccination. A set of requirements will be developed so that all models will be capable of producing some minimum set of results. The analytical capability of these models must include, but is not be limited to, (1) comparison of standard vaccination strategies across different age groups, (2) consideration of risk for severe disease during secondary infections, and (3) sensitivity analysis to vaccination coverage and vaccine efficacy.

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The World Health Organization has provided technical support to its Member States in the field of vaccine-preventable diseases since 1975. The office carrying out this function at WHO headquarters is the Department of Immunization,Vaccines and Biologicals (IVB).

IVB's mission is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. The Department covers a range of activities including research and development, standard-setting, vaccine regulation and quality, vaccine supply and immunization financing, and immunization system strengthening.

These activities are carried out by three technical units: the Initiative for Vaccine Research; the Quality, Safety and Standards team; and the Expanded Programme on Immunization.

The Initiative for Vaccine Research guides, facilitates and provides a vision for worldwide vaccine and immunization technology research and development efforts. It focuses on current and emerging diseases of global public health importance, including pandemic influenza. Its main activities cover: i) research and development of key candidate vaccines; ii) implementation research to promote evidence-based decision-making on the early introduction of new vaccines; and iii) promotion of the development, evaluation and future availability of HIV, tuberculosis and malaria vaccines.

The Quality, Safety and Standards team focuses on supporting the use of vaccines, other biological products and immunization-related equipment that meet current international norms and standards of quality and safety. Activities cover: i) setting norms and standards and establishing reference preparation materials; ii) ensuring the use of quality vaccines and immunization equipment through prequalification activities and strengthening national regulatory authorities; and iii) monitoring, assessing and responding to immunization safety issues of global concern.

The Expanded Programme on Immunization focuses on maximizing access to high quality immunization services, accelerating disease control and linking to other health interventions that can be delivered during immunization contacts. Activities cover: i) immunization systems strengthening, including expansion of immunization services beyond the infant age group; ii) accelerated control of measles and maternal and neonatal tetanus; iii) introduction of new and underutilized vaccines; iv) vaccine supply and immunization financing; and v) disease surveillance and immunization coverage monitoring for tracking global progress.

The Director's Office directs the work of these units through oversight of immunization programme policy, planning, coordination and management. It also mobilizes resources and carries out communication, advocacy and media-related work.

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