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Commentary

Prioritizing vaccines for developing world diseases

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ABSTRACT

A major disparity in the burden of health will need to be addressed to achieve the "Grand Convergence" by 2035. In particular people living in low and middle income countries have a much higher burden of infectious diseases. Although vaccines have been very effective in reducing the global burden of infectious disease, there are no registered vaccines to address 60% of the current burden of infectious disease, especially in developing countries. Thus there is a pressing need for new vaccines and for prioritizing vaccine development given that resources for developing new vaccines are strictly limited. As part of the GLOBAL HEALTH 2035: Mission Grand Convergence meeting one working group assessed the SMART vaccine algorithm as a mechanism for prioritizing vaccine development for diseases of priority in the developing world. In particular, the working group considered which criteria in the standard SMART set were considered "key" criteria and whether other criteria should be considered, when prioritizing vaccines for this important set of countries.

Report from the Working Group on Developing Country Priority Setting from the GLOBAL HEALTH 2035: Mission Grand Convergence 25 meeting, Siena 17–18th 26 July 2015

Chair: Katherine O'Brien; Co-Chair: Allan Saul

Participants: Seth Berkley, Ralf Clemens, Akira Homma, Andrew Pollard, Orin Levine, Steve Black, Walter Goycochea, Isabelle Munyangaju, Monica Moschioni,

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1. Background

Although vaccines have been highly successful in reducing the impact of infectious diseases on individuals and societies, there is room for substantial improvement. Vaccine development for most vaccines has been driven by the needs of the developed world and then the products have been adapted to those of the developing world. Consequently, vaccine introduction and use in the communities that will most benefit has often been delayed by many years following that of developed countries. Furthermore the vaccine design (strain coverage, product presentation, and delivery infrastructure including cold chain considerations) has not usually been undertaken with the developing country setting as the priority, and as a result further vaccine development has often been necessary. Our focus in the workshop and here in the report was on vaccine preventable infectious diseases, notwithstanding the future needs for vaccines against non-infectious diseases, including cancers.

Importantly, as judged from the 2010 global burden of disease (GBD2010) estimates [1,2], there remains a major burden of infectious disease for which there are no vaccines. Based on deaths, approximately 60% of the current all age global burden of infectious disease is from diseases which have no registered vaccine for their prevention. The death toll for these infectious diseases is 6.8 million per year (Fig. 1). This graph shows the total all age annual deaths for the infectious diseases with the major impact according to the GBD2010 data. Within each column in green the proportion of that disease for which there is a registered vaccine and in red diseases for which there are no registered vaccines. This diagram is quite conservative. For many of the diseases for which there are registered vaccines, the available vaccines may not be effective or suitable for the populations greatest at risk. For example, we regard TB as having a registered vaccine (BCG) although the efficacy of that vaccine is low. Almost all of these deaths occurs in low and middle income countries [3]. Not shown on this figure, but again derived from the country/region specific data in GBD2010, 91% of the mortality shown on this figure is in low and middle income countries. As shown in MacLennan and Saul [3], using DALYS instead of deaths as a measure of the burden of disease makes little difference.

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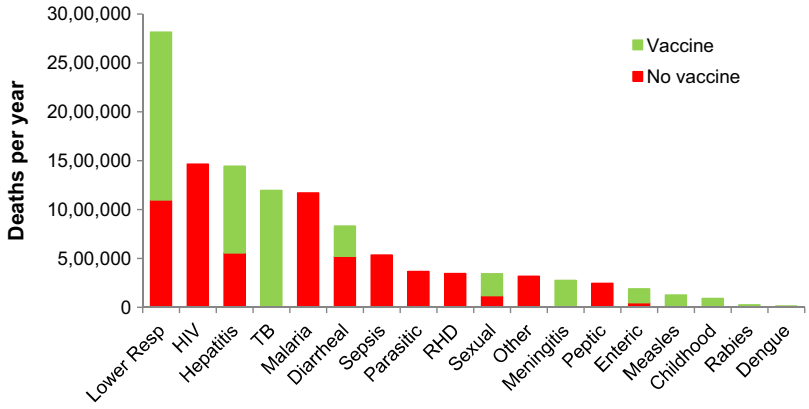

Fig. 1. Global, all-age deaths per year from infectious diseases according to the 2010 Global Burden of Disease data for different disease categories. Green bars: deaths for which there is at least one registered vaccine. Red bars: deaths from diseases for which there are no registered vaccines. Deaths include deaths from consequences of infectious disease, e.g. Hepatitis includes "cirrhosis of the liver secondary to hepatitis B and C" and "liver cancer secondary to hepatitis B and C"; sexual includes "cervical cancer" (the only disease with a vaccine in the sexual disease category) but does not include HIV for which there is a separate category; Peptic deaths we assume are largely due to infection with helicobacter. Childhood diseases are diphtheria, tetanus, varicella and whooping cough, but exclude measles for which we use a separate category. RHD is rheumatic heart disease but excludes other deaths from infections with group A streptococcus that are not categorized in the GBD2010 data.

To make progress on this infectious disease burden and narrow the mortality gap between low and higher income settings will require improving existing vaccines and developing new vaccines. Part of the challenge lies in the technical barriers to develop vaccines for these diseases. However, a related substantial barrier is finding the resources required for vaccine development. Each year since 2008, the G-Finder Report estimated the total amount of money from all sources, public and private, spent on developing vaccines for neglected diseases. In the latest report [4], expenditures on vaccines directed against 31 individual pathogens or combinations were tracked. In 2014, an estimated US$1.24 billion was spent globally on vaccines for these neglected diseases. By far the largest amount, US$937 million (75%) was spent on three diseases: HIV, malaria and TB. Half of the remaining funds ($143 million, 12% of the total) was spend on improved vaccines and vaccine uptake for pathogens causing meningitis, pneumonia, rotavirus and typhoid fever. Spending on Ebola ($69 million) was a new category in the G-Finder 2015 Report. For the 21 other diseases and disease combinations for which there are no registered vaccines at all, only $92 million was spent. This is not a trivial set of diseases – between them they cause approximately 25% of the total GBD measured in DALYs and one of these, Group A Streptococcus, alone causes >500,000 deaths per year [5].

Put in the context of the cost of developing a vaccine (estimated at $500 to million to $1 billion per vaccine registered [6,7]), an annual expenditure of $92 million for 21 vaccines suggests a substantial underinvestment in vaccine development and a failure of the vaccine and public health community to adequately communicate the slow pace and missed opportunity this represents.

There are three possible solutions:

1. We need more **resources** [7]. The value of vaccines are substantially under-appreciated [8–10], especially vaccines for neglected diseases of low and middle income countries. Recent analyses have shown that the current portfolio of childhood vaccines confers a return on investment between 16 and 44-fold, depending on the returns considered [11]. There is a pressing need for better tools to estimate and communicate the total value of vaccines and inform resource mobilization efforts.
2. We need more **efficient** ways of making vaccines so that they don't cost $1 billion for each vaccine registered. Unfortunately while most developers hope this is the case, many of the vaccines of the future are going to be difficult to design and successfully bring to licensure. For example, G-Finder estimates that the expenditure from 2008 to 2014 for developing world applications on 3 high priority vaccines (HIV, malaria and TB) has been $5 billion, $1.1 billion and $800 million, respectively. The first malaria vaccine is nearing licensure, but even for this vaccine there will be further expenditures before it can be deployed widely, since the evidence needed to develop sound implementation policies that would assure the health gains promised from the clinical trials requires evidence beyond that required for licensure. The further development costs for an HIV vaccine and a replacement for BCG are likely to also be appreciable.
3. As a global community, we need to **prioritize** vaccine development within the portfolio of global health investments. Even if global expenditure on new or improved vaccines rises substantially, and ways are found to reduce vaccine development costs, there is a substantial funding shortfall to simultaneously develop all of the vaccines that may be needed, especially for vaccines that do not have a strong commercial driver. We suggest there is a strong rationale for putting sufficient resources into a few vaccines to enable their deployment (and start having an impact on public health) as soon as possible rather than trying to slowly advance a large number of vaccines. There have been a number of recent proposals for prioritizing vaccines for public health use such as the Global Vaccine Action Plan for the Global Decade of Vaccines 2011–2020 [12] and the WHO Innovations for Vaccine Research strategic plan 2010–2020 [13] but the criteria for assigning such priorities remain unclear.

Global, regional and national policy decision-makers who must assess where on the priority list a specific vaccine will feature, have largely focused on cost effectiveness analyses. However, it is clear that other vaccine and disease characteristics are important [10]. Recently the USA Institute of Medicine developed a new tool, the Strategic Multi-Attribute Ranking Tool for Vaccines—SMART Vaccines [14] designed especially for making prioritization decisions about vaccine development. This tool considers 28 priority attributes, with potential within the tool for adding further criteria, to rank vaccine priorities.

A subset of these ranking attributes was tested by a panel of vaccine experts as part of the conference "Global Health 2035: Mission Grand Convergence" held in Siena, Italy on 18 July 2015.

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