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Conference report

Report from the World Health Organization's third Product Development for Vaccines Advisory Committee (PDVAC) meeting, Geneva, 8–10th June 2016

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ABSTRACT

The third meeting of WHO's Product Development for Vaccines Advisory Committee (PDVAC) was held in June 2016, with a remit to revisit the pathogen areas for which significant progress has occurred since recommendations from the 2015 meeting, as well as to consider new advances in the development of vaccines against other pathogens. Since the previous meeting, significant progress has been made with regulatory approvals of the first malaria and dengue vaccines, and the first phase III trials of a respiratory syncytial virus (RSV) vaccine candidate has started in the elderly and pregnant women. In addition, PDVAC has also supported vaccine development efforts against important emerging pathogens, including Middle Eastern Coronavirus (MERS CoV) and Zika virus. Trials of HIV and tuberculosis vaccine candidates are steadily progressing towards pivotal data points, and the leading norovirus vaccine candidate has entered a phase IIb efficacy study. WHO's Immunization, Vaccine and Biologicals (IVB) department is actively working in several pathogen areas on the recommendation of PDVAC, as well as continuing horizon scanning for advances in the development of vaccines that may benefit low and middle income countries (LMICs), such as the recent licensure of the enterovirus 71 (EV71) vaccine in China. Following on from discussions with WHO's Strategic Advisory Group of Experts (SAGE) on Immunization, PDVAC will also look beyond licensure and consider data needs for vaccine recommendation and implementation to reduce the delay between vaccine approval and vaccine impact.

1. Context

WHO's PDVAC was established by the Department of Immunization, Vaccines and Biologicals (IVB) in 2014, following a review of WHO's process for strategic priority setting for vaccines. The need for a group to advise WHO specifically on vaccine product development was highlighted, to accelerate vaccine availability and ensure accessibility of vaccines to low and middle income countries (LMICs). PDVAC's remit is to advise on the product development strategy of vaccine candidates at phase II of clinical evaluation or earlier, and to report its proceedings to the WHO's principal committee on immunization policy recommendations: the Strategic Advisory Group of Experts on Immunization (SAGE). The PDVAC committee has a critical role in assessing the evolving vaccine development landscape and in helping to define where and how WHO can be most impactful, according to three criteria:

- Unmet public health need for a vaccine, focusing on the LMIC perspective,

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- Likelihood of a product emerging from the pipeline, as defined by probability of technical and regulatory success, and the extent of awareness, activity and investment in a given area,
- A clear role for WHO with perceived added value for engagement in the pathogen area.

Typically, WHO engages in a pathogen area by working with a broad set of key vaccine development stakeholders to develop consensus on pivotal clinical trial design, vaccine roadmaps, or guidance documents on desired vaccine properties, referred to as Preferred Product Characteristics (PPCs). PPCs define WHO preferences for the properties of vaccines to be used in LMICs that are 5–10 years from licensure, and inform target product profiles in use by manufacturers and funders for vaccines. PDVAC also encourages developers to be aware of the process and requirements for WHO prequalification (PQ). WHO Prequalification is a service to UNICEF and other UN agencies that purchase vaccines once they have been licensed, to determine the acceptability, in principle, of vaccines from different sources for supply to these agencies. It aims to ensure that diagnostics, medicines, vaccines and immunization-related equipment and devices for high burden diseases meet global standards of quality, safety and efficacy, and are appropriate for use in LMICs contexts in order to optimize the potential benefit of these interventions [1].

2. Vaccine product development milestones since the 2015 PDVAC meeting

The third PDVAC meeting was held in Geneva from 8–10th June 2016. Dr. Jean-Marie Okwo-Bele, director of IVB, opened proceedings with a synopsis of the significant milestones in vaccine development in the nine months since the previous meeting in September 2015:

- the first dengue and malaria vaccines have been licensed or achieved the equivalent of licensure, respectively,
- the first RSV vaccine candidate has entered phase III studies in the elderly and pregnant women,
- the most advanced HIV vaccine candidate has met its endpoints in the interim analysis of a phase II study, and preparations to commence an efficacy study are underway,
- WHO convened the MERS-Coronavirus R&D community, and a phase I clinical study is now underway (NCT02670187),
- Ebola virus vaccines are under review and have progressed to the point of consideration for licensure in record time,
- There are co-ordinated efforts to develop a Zika virus vaccine as expeditiously as possible. A PDVAC working group has overseen the development of a Zika virus vaccine target product profile (TPP), and developed regulatory considerations towards phase I and emergency use authorization.

In addition to these significant advances in vaccine development, the UK government published in May 2016 the report on 'Tackling Drug-Resistant Infections Globally' that it commissioned in collaboration with the Welcome Trust [2]. The report highlights the urgent need to reduce reliance on currently available antimicrobials, without which today's 700,000 deaths per year from drug resistant microbes is forecasted to increase to 10 million, by 2050. The cost in terms of lost global production due to infections that are not controllable due to antimicrobial resistance (AMR) is estimated to be $100 trillion by 2050 if no action is taken [2]. The development of vaccines against pathogens that are currently controlled by antimicrobials has become an imperative, as they have the potential to reduce the prevalence and spread of drug resistance, as well as to reduce the use of antimicrobials more broadly [3].

The Decade for Vaccines' Global Vaccine Action Plan (GVAP) mid-term review, required an assessment of progress against objectives since its inception in 2011, and strategic planning to achieve the stated targets within the remaining 5 years. Part of PDVAC's remit is to review the vaccine development pipeline and consider the priority activities for IVB, within this context. During the remaining timeframe of GVAP, a number of vaccines could reach licensure, and WHO needs to ensure early engagement with policy makers regarding potential vaccine implementation, as well as alignment with GAVI's Vaccine Investment Strategy.

To facilitate information sharing, and tracking of progress within the global vaccine development community, the WHO has established and maintains an online 'Vaccine Pipeline Tracker' in which information regarding all current clinical studies in several different pathogen areas can be found [4]. In addition, landscape analyses for 25 pathogens from the 2015 meeting have been collated within a special issue of the journal 'Vaccine' and all are available through open access [5]. These documents are authored by independent subject matter experts and review the status of vaccine candidate development, as well as assessing possible pathways to regulatory approval.

3. Recommendations for PDVAC following Oct 2015 and April 2016 SAGE meetings

PDVAC reports progress on the global vaccine development pipeline to WHO's Strategic Advisory Group of Experts (SAGE) on Immunization. At the meeting in April 2016, advances in the development of interventions (vaccines and monoclonal antibodies) for Respiratory Syncytial Virus (RSV) were presented for information. The reports from the October 2015 and April 2016 SAGE meetings are available online [6,7].

Much of the discussion focused on the need to better understand the key factors for early for implementation, as well as safety and efficacy data to support the assessment of a vaccine for policy recommendation. As emerging vaccines are likely to require new vaccination platforms, such as maternal immunization, or visits outside of the current vaccination schedule, such as for the recently licensed malaria vaccine RTS,S, cost-effectiveness data informing their optimal use and potential impact must be generated in line with conventional clinical data required for regulatory approval, to minimise the delay between vaccine licensure and uptake [8].

4. The scope and objectives of the 2016 PDVAC meeting

The goals of this third PDVAC meeting were to revisit the pathogen areas where there has been significant progress to report since recommendations from the 2015 meeting, as well as to:

- Review status of vaccine development in 7 new pathogen areas where there has been significant vaccine development progress, or where there is significant disease burden but R&D has stalled,
- Refine the workplan and strategic directions for IVB in specific pathogen areas,
- Identify cross-cutting issues that accelerate vaccine development or prepare for policy decisions,
- Where appropriate, consider how to better align PDVAC's vaccine development activities and strategies with other areas of research,
- To inform the vaccine development community regarding steps to be considered beyond vaccine licensure, and WHO processes for vaccine policy recommendation.

5. Vaccine development status and PDVAC recommendations, by pathogen

5.1. The Global Vaccine Action Plan (GVAP): progress towards malaria, HIV, tuberculosis and improved influenza vaccines

The GVAP is a 10-year strategic framework derived from the Decade of Vaccines Collaboration [9] to prevent millions of deaths by 2020 through more equitable access to existing vaccines for people in all communities. Within this framework is a specific objective that supports research and development of innovations that will maximise the benefits of immunization, with indicators for progress towards development of HIV, malaria, tuberculosis and influenza vaccines. The GVAP has just completed its mid-term review stage, and following the 2015 recommendation from SAGE [10], the 2016 GVAP assessment will highlight advances made in these areas. These four pathogen areas are standing agenda items for discussion at PDVAC.

5.1.1. Tuberculosis

In 2014, *Mycobacterium tuberculosis* (Mtb) killed 1.5 million people (0.4 million of whom were co-infected with HIV) and is now the world's most deadly infectious disease [11]. Approximately 480,000 cases/annum are multi-drug resistant (MDR) or extensively drug resistant (XDR) and some strains are untreatable. In 2014, six million new cases of Mtb were reported to WHO, fewer than two-thirds (63%) of the 9.6 million people estimated to have contracted the disease. This means that 37% of new cases were not detected or reported. A vaccine is imperative to achieving the End TB goals [12], particularly through reaching the population who are undiagnosed and continue to transmit disease. As such, the TB vaccine development community has turned its focus to the development of vaccines targeted to adolescents and adults as the age-groups with highest burden of active disease and the source of Mtb transmission. Modelling studies suggest that prevention of pulmonary disease in this population from primary infection and from reinfection or reactivation of existing infections is the most effective strategy to prevent Mtb infection and disease in infants and children [13]. The most advanced vaccine candidates are targeting this indication, including current neonatal BCG replacement candidate vaccines that are also undergoing evaluation as a booster in later life. Several of these candidates are in proof-of-concept clinical studies and are approaching key endpoints through prevention of infection or disease, or prevention of disease due to reinfection in this these target populations in the next 12–24 months [14]. With this in mind, PDVAC recommended that WHO prioritize and facilitate consensus building with respect to the development of strategic goal(s) and PPC(s) for vaccines targeted to adolescents and adults, in the first instance. There are several candidates and platforms in the pipeline that target this goal in this population, as well as other important target populations [4]. PDVAC acknowledged the significant need for development for these vaccines in parallel, as well as continued efforts to understand the biological mechanism of disease to support the immunological rationalization of candidates.

5.1.2. HIV

The Pox-Protein Public Private Partnership (P5) consisting of Sanofi, GlaxoSmithKline (GSK), Bill & Melinda Gates Foundation, the US Military HIV Research Program (MHRP), and the HIV Vaccine Trials Network (HVTN) have been collaborating with the US National Institutes of Allergy and Infectious Disease (NIAID) to optimize and assess the efficacy of the ALVAC/heterologous prime boost approach, following the demonstration of partial efficacy in the RV144 trial in Thailand [15]. The interim data from a phase I/II study (HVTN 100) met its humoral and cellular immunological 'go' criteria, exceeding the RV144 responses against sub-Saharan clade C antigens. Extrapolation of these responses to those observed with RV144, suggest that the optimised vaccine could offer at least 50% protection following a 12 month booster. Based on these data, a randomised placebo controlled phase IIb/III efficacy trial (HVTN702) enrolling 5400 subjects was initiated in late 2016 in South Africa, and will evaluate ALVAC (clade C) prime/bivalent recombinant gp120 protein with MF59 adjuvant as a heterologous boost, as well as the effect of a booster at 12 months [16]. Futility analyses will be undertaken early in the 2 year follow-up period. Correlate of protection studies and assessment of cross-reactivity to other regional clades are included in the study design. Discussions with the South African Medicines Control Council (MCC) are ongoing, and licensure in South Africa could be as early as 2021.

Other vaccine candidates are in development, including Janssen's heterologous prime boost approach with Ad26/gp140, currently undergoing dose regimen selection in phase I/IIa trials.

Antibody-mediated prevention using broadly neutralizing, potent monoclonal antibody (bnMAbs) approaches are also undergoing phase I/IIa clinical evaluation. The NIAID/Vaccine Research Centre's VRC01 broadly neutralising MAb is the most advanced candidate which has been shown to neutralise CD4 binding of 90% of viral isolates. HVTN 703/HPTN 081 and HVTN 704/HPTN 085 are phase IIb studies to evaluate the efficacy of VRC01 in reducing acquisition of HIV-1 infection in high risk populations in the Americas and sub-Saharan Africa, and started enrolment in 2016. If shown to be effective, administration of VRC01 could be positioned as a long-acting supplement to increase effectiveness of anti-retrovirals.

PDVAC commended the advances in HIV vaccine development, and requested to be kept informed about progress with HVTN702. Currently, there are no known intentions for global studies with the P5 candidate vaccine, or to seek WHO prequalification. PDVAC encourages the P5 partners and the South African HIV vaccine development community to keep WHO fully informed about progress with the trial. Concerns were expressed regarding the lack of follow-on studies in Thailand, given that the initial landmark RV144 trial was performed there.

5.1.3. Malaria

Despite the substantial reduction over the last 15 years (over 50% for global malaria mortality in children aged <5 years), mainly due to greater investments in malaria control, the WHO estimates there were 214 million malaria cases in 2015, 88% of which were in Africa. Of the 438,000 people who died from the disease in 2015, 90% reside in Africa [17]. Given the increase in multi-drug and insecticide resistance, there remains an urgent need for a vaccine to combat malaria.

As reported in the 2015 PDVAC meeting summary [18], the European Medicine's Agency (EMA) provided a positive scientific opinion, indicating a favorable assessment of the risk-benefit balance of RTS,S/AS01 from a regulatory perspective. In October 2015, two advisory bodies to WHO, namely SAGE and the Malaria Policy Advisory Committee (MPAC), recommended pilot implementation studies of the 4-dose schedule of the RTS,S/AS01 vaccine in 3–5 distinct epidemiological settings in sub-Saharan Africa, at sub-national level, covering moderate-to-high transmission settings, with three doses administered to children between 5 and 9 months of age, followed by a fourth dose 15–18 months later. The intent of these pilot studies is to assess:

- the feasibility of providing all four doses of RTS,S to the target age group through existing health services;
- the impact of RTS,S on child mortality;

- whether there are any safety issues, particularly evidence of any causal relationships between RTS,S administration and either meningitis or cerebral malaria (both signalled in the phase III trials),
- whether introduction of the vaccine impacts positively or negatively on existing country immunization programs and on the use of currently recommended malaria control measures.

In 2013, the Malaria Vaccine Technology Roadmap was updated to include licensure of vaccines targeting *Plasmodium falciparum* and *Plasmodium vivax* by 2030, with protective efficacy of at least 75% against clinical malaria, and that reduce transmission of the parasite and thereby substantially reduce the incidence of human malaria parasite infection [19]. The vaccine candidate pipeline is robust, and includes novel antigens and platforms [4]. Second generation vaccines are expected to provide higher protection than RTS,S in the longer term. Optimised tools are needed to measure incremental improvements and predict potential cost effectiveness of new candidates. The development of controlled human malaria infection (CHMI) models, efforts to harmonize elements of clinical trial design and standardization of various assays continue.

PDVAC stressed the importance of the development of 2nd generation malaria vaccines in parallel to the pilot implementation Program for RTS,S, and proposed that the current version of the vaccine roadmap be updated, potentially in 2018, in light of the RTS,S pilot implementation.

5.1.4. Improved influenza vaccines

In 2015, PDVAC noted that development of universal influenza vaccines will be challenging and protracted, particularly due to the lack of a regulatory pathway for novel antigens that operate through induction of T-cell immunity. Rather, PDVAC recommended that there be a focus on the definition of, and the collection of data to support implementation of 'improved' seasonal flu vaccines that would offer more immediate impact in LMICs. PDVAC advised WHO to develop strategic public health goals and PPCs for improved seasonal influenza vaccines, and to provide guidance on data requirements that would be needed to establish improved performance of such vaccines.

A working group has been established, and has proposed a draft statement of unmet public health need: 'Safe and well-tolerated influenza vaccines that are effective at preventing severe influenza illness, that provide protection beyond a single year, and that are programmatically suitable for use, are needed for low- and middle-income countries.' Draft 5- and 10-year strategic goals for development of influenza vaccines that induce broader and more durable protection against severe illness caused by influenza A strains have been developed. These strategic goals and the draft PPC for next-generation influenza vaccines were presented at the upcoming Eighth WHO meeting on development of influenza vaccines [20].

PDVAC reaffirmed the value of PPCs based on the two different approaches. There is a public health need to develop improved performance of currently available seasonal vaccines to offer protection over multiple seasons, and against drifted strains, with a view to generating shorter timelines to achieving availability and access in LMICs. As part of this effort, it will be necessary to define the criteria needed to demonstrate clinical benefit, and additional data requirements to support policy recommendations. Efforts to develop 'universal' vaccines that target conserved antigens, or conserved components of antigens, should continue in parallel, with a focus on identifying correlates of protection to support a regulatory pathway for this novel class of vaccines.

5.2. Enteric vaccine candidates

Diarrheal disease remains the second leading cause of death in children under 5 years of age. Although mortality has declined over the past four decades, morbidity has not declined significantly, despite improvements in water and sanitation and benefits from oral rehydration therapy. There are nearly 2.7 billion cases of diarrheal disease every year, many with acute and chronic effects such as growth stunting and cognitive impairment. These long term sequelae significantly impact quality of life and economic potential, and are estimated to affect one-fifth of children globally. In 2015, PDVAC recommended that WHO expand its remit to include support for enteric vaccine development, particularly against Enterotoxigenic *Escherichia coli* (ETEC) and *Shigella*.

5.2.1. Enterotoxigenic Escherichia coli (ETEC) and Shigella

One of the main objectives of the planned WHO engagement in this area will be to ensure that the design of the phase III efficacy study, including definition of primary/secondary endpoints and long-term follow up, and the data generated, will be relevant to support a policy recommendation from SAGE. Another key objective is to develop a WHO Preferred Product Characteristics document which outlines WHO preferences, including considerations for development towards a potential combined vaccine.

Several vaccines are in development, with two ETEC candidates and seven *Shigella* candidates currently in clinical studies. For ETEC, the most advanced vaccine is ETVAX adjuvanted with dmLT, which is being developed for both a pediatric and traveller's indication. A phase I/II dose escalation, age de-escalation study in children is currently ongoing in Bangladesh, with intent to further age de-escalate into 6 week-old infants in late 2016. In parallel, a phase IIb study in travellers is planned to begin in 2017. Based on an encouraging phase IIb immunization and challenge study and additional positive protection studies in non-human primates (NHPs), an adhesin–based subunit ETEC vaccine (FTA) is moving forward with an accelerated clinical program designed to move a complete multi-valent vaccine into descending age field trials in 2020.

The most advanced *Shigella* candidate is Trivalent *Shigella* killed whole cell (TSWC) composed of formalin-inactivated *S. flexneri* 2a, *S. flexneri* 3a, and *S. sonnei*, expected to offer coverage across about 80% of isolates. A phase I study has been completed and a challenge trial with *S. flexneri* 2a prototype will begin in 2017, followed by a study that will assess co-administration with ETVAX. Both ETVAX and TSWC are being developed for oral administration.

Other promising *Shigella* vaccines in early stage clinical testing include two live attenuated vaccines, WRRS1 and ShigETEC. WRRS1 is in a descending age study in Bangladesh, while ShigETEC, which is a combination Shigella-ETEC combination vaccine, will begin a phase I study in early 2017. Three subunit approaches for *Shigella* are also in phase I/II studies; the prototype *S. flexneri* 2a bioconjugate vaccine (Flexyn2a), InvaPLex and the Generalized Module for Membrane Antigens (GMMA).

One of the critical strategic issues is whether to prioritize the licensure and approval of an ETEC vaccine, or to focus on the development of a combination with *Shigella* that will likely delay the timeline to vaccine availability. Epidemiologic data suggest that both intra- and inter-country disease heterogeneity is likely to exist and this may drive vaccine preferences, and presentation optimization. These data are critical to inform decision-making by country policymakers. For this reason, development of WHO derived preferred product characteristics for ETEC and *Shigella* vaccines, alone and in combination is needed.

5.2.2. Norovirus

In April 2016, PLOS released a collection on 'The Global Burden of Norovirus & Prospects for Vaccine Development' [21], which includes the most current estimates on global norovirus disease burden of over 200,000 deaths in low resource countries, and a global economic burden of more than $60 billion [22]. Recent

molecular analyses of samples from the community based longitudinal birth cohort MAL-ED study suggest that norovirus is the most common diarrheal pathogen in the first year of life, and the second most common in the second year of life.

There are 5 vaccine candidates in development, including three strategies to develop a combination vaccine against other enteric pathogens. However, only one candidate, which is composed of two VLPs based on the GI.I and GII.4 norovirus genotypes, has entered clinical studies, a Phase IIb study began recently [23]. The advent of cell culture methods for norovirus will facilitate many advancements, including the optimization of a neutralization assay and enable the assessment of antisera against this vaccine to block binding of a diverse genotypes. In addition, in response to the 2015 PDVAC recommendation to consider incorporating norovirus surveillance within the WHO Global Rotavirus Surveillance Network, a survey of the capability and capacity at representative global sites has been performed to support a pilot study proposal.

The recently published epidemiology and burden of disease data indicate that norovirus fulfils the PDVAC criterion of unmet public health for a vaccine in LMICs. However, the ability of the candidates in the pipeline to offer protection over the range of circulating and emerging viral genotypes, and therefore the duration of protection of these vaccines, is currently unknown. It is conceivable that the vaccine will need to be periodically re-formulated, to include emerging genotypes. In addition to infants as a priority target population, adults and particularly the elderly are at risk, requiring the potential need for two vaccine formulations and/or presentations. Fortunately, at the current time, development of a norovirus vaccine that may offer efficacy in the context of low and middle income countries is proceeding with investment from the private sector, however an assessment of vaccine programmatic suitability and applicability to prequalification is needed, prior to Phase III trials to ensure the vaccine is appropriate for use in LMICs, assuming it is demonstrated to offer coverage over circulating genotypes within LMICs.

5.2.3. Second generation rotavirus

Rotavirus is the leading cause of severe diarrhea among all children below 5 years of age worldwide, causing 20–40% of severe diarrheal hospitalisations, and is associated with significant mortality, with the latest mortality estimates at 215,000 deaths in 2013 [24]. The introduction of the live-attenuated oral rotavirus vaccines, RotaTeq and Rotarix, in 2008 has had significant direct and indirect impact in countries where they are in use, including saving lives and reducing hospitalizations. However, in GAVI-eligible and LMIC countries in Asia and Africa the vaccine effectiveness is lower, with protective efficacy observed from 40 to 70% against severe rotavirus diarrhea over the first year of life. Waning of protection has also been observed in these settings, with lower protection rates (25–50%) in the second year of life. In comparison, in high-income countries protection is higher (70–90%) and persists into the second year of life.

Thus, despite the enormous success of the live oral rotavirus vaccines, several challenges and issues remain such as the lower protection in GAVI-eligible and LMIC countries in Africa and Asia, together with the high cost of available vaccines. Despite an overall acceptable safety profile, the intussusception rate seems to be slightly increased by vaccination (occurrence 1–3/100 000 oral Rotavirus vaccine recipients) in high income countries.

Several new oral, live-attenuated vaccines, composed of alternative strains, are in mid- to late-stage clinical development. The current WHO guidance document for the quality, safety and efficacy of oral live attenuated rotavirus vaccines [25] would be applicable for these next generation oral, live-attenuated vaccines. Of these new oral rotavirus vaccines, Rotavac 20C (developed by BBIL) is the only vaccine currently licensed for use in children, having been approved for use in India in 2014. This vaccine is available on the private market in India and staged roll out in public health system is planned in four states in India. Another live rotavirus vaccine is being evaluated in a randomised placebo controlled trials in India (NCT02133690) and in Niger (NCT02145000).

Efforts are underway to develop non-replicating rotavirus vaccines (NRRV) as second generation rotavirus vaccines, which may avoid the risk of intusseseption. The most advanced candidate is P2-VP8*, a trivalent truncated VP8* of rotavirus genotypes P[8], P[4] and P[6], currently in phase II clinical testing with a parenteral route of administration (NCT02646891).

For both NRRVs and additional oral, live-attenuated vaccines in development, PDVAC encouraged the rationalization of target product profiles for these new candidates, to clearly articulate the distinguishing/advantageous features over the existing vaccines, i.e. cost, safety, efficacy in LMIC, stability, breath of protection, etc. The potential for any of these vaccine candidates to be included in combination with other emerging enteric vaccines will clearly be advantageous and should be encouraged and explorations of combination with IPV could be considered.

5.2.4. Clostridium difficile

Clostridium difficile is the leading cause of healthcare-associated diarrhoeal disease in the high-income countries, and is strongly associated with increasing age and frailty, immunodeficiency and in particular, modification of the normal flora through antibiotic use. The results of infection range from asymptomatic carriage through mild infection to severe diarrheal disease, with complications including pseudomembraneous colitis and toxic megacolon. In the US alone, it is believed to have caused approximately 0.5 million infections and 29,000 deaths in 2012 [26]. Current interventions include antibiotic treatments, but their use can trigger relapse on withdrawal. Data on the burden of disease in LMICs is lacking, however hospital based studies in India, Thailand and South Korea suggest that the *C. difficile* infection is widespread, and global (Douce, manuscript in preparation).

There is a correlation between toxin neutralising antibody in human serum and disease protection; antibodies against toxin A are associated with protection against acute diarrhea, whilst immune responses to toxin B appear to be effective against severe disease and relapse. Toxin-mediated disease is recapitulated in the syrian golden hamster, which is the standard preclinical model for demonstration of proof of concept. Currently there are three vaccines in clinical development. A toxoid vaccine candidate (containing toxins A and B) recently completed a phase II study in healthy adults and demonstrated induction of high levels of neutralizing antibodies [27] and a phase III study has been initiated. A genetically modified, detoxified whole cell vaccine has also completed phase II, alhough results have not yet been reported. In phase I, the vaccine was shown to be safe and induced toxin-specific neutralizing antibodies that were sustained for 12 months [28]. The third candidate is an adjuvanted recombinant protein encoding binding domains of both toxins, and the results of a phase I trial has been reported [29], and a phase II study has been completed. Passive immunity by administration of a monoclonal antibody is also in phase III evaluation (NCT01513239 and NCT01241552).

PDVAC agreed that the role for WHO in facilitating *C. difficile* vaccine development is not clear given the lack of data regarding the disease burden in LMICs. However, it would be useful to understand the potential effectiveness of a vaccine in low resource contexts, and PDVAC raised the possibility of testing existing samples from the GEMS and MAL-ED studies for the presence of *C. difficile*. In addition, it would be helpful to assess the impact that these vaccines many have on reducing the use, and cost of antibiotics, and to consider this in the value proposition for vaccine decision-making.

5.2.5. Heliobacter pylori (H. pylori)

H. pylori is a highly motile, Gram-negative bacterium that infects the mucus layer lining the stomach. Infection typically occurs in childhood, although symptoms and clinical disease develop in only a minority of infected individuals during their lifetime. *H. pylori* is associated with gastritis, which causes several pathologies including gastric peptic and duodenal ulcer disease. Most significantly, long term infection can result in gastric adenocarcinoma (GA) in later years of life; ~65–90% of GA cases are due to *H. pylori* infection. GA is the 3rd leading cause of death due to cancer, globally (~723,000 deaths in 2012, 8.8% of all cancers) [30]. The global prevalence of *H. pylori* is believed to be approximately 50% with the highest mortality rates in East Asia and Eastern Europe.

The route of transmission is poorly characterised but the oral-oral route appears to be a common mechanism, as well as vertical transmission from mother to child. If untreated, most *H. pylori* infections are sustained for life, and ~15% of those infected are thought to develop an associated pathology. If diagnosed, *H. pylori* infections are currently treatable with combination antimicrobial therapies. However antibiotic resistance is increasing, with ~20% of patients in some countries currently failing first treatment and 5% failing two rounds of therapy. Antimicrobial treatment offers no protection against reinfection.

The choice of indication for an *H. pylori* vaccine is challenging: a prophylactic vaccine would likely need to be given to children in the first few years of life (to reach the maximum number of the target group while uninfected) but would need to offer long term protection to demonstrate clinical benefit against GA. An effective therapeutic vaccine however could be given at almost any age and would ideally be given by the 4th decade of life, prior to the peak of GA development which typically occurs from 50 years of age. The most advanced candidate is a urease toxin fusion approach and has completed phase III trials in children, in China, and demonstrated 71.8% efficacy against natural acquisition of infection [31]. However, protection appeared to wane to 55% over 2–3 years and next steps for this vaccine are not clear. Several other candidates are in preclinical development with one close to phase I studies.

PDVAC concluded that the burden of *H. pylori* is significant, and that a vaccine that is able to protect against infection, with sufficiently long duration of protection, would be of public health benefit. Therapeutic candidates are currently too upstream in development for there to be a role for PDVAC.

5.3. Vaccines to be administered by maternal immunization

Maternal immunization is increasingly considered as a strategy to prevent maternal and/or neonatal disease. This approach has been proven to protect against maternal and neonatal tetanus and has been in place for decades. WHO recommends influenza and pertussis vaccination of pregnant women to prevent disease in mothers and newborns, respectively. However, for the first time there are now vaccines in development, specifically indicated for immunization of pregnant women as the target population. Respiratory Syncytial Virus vaccines are most advanced in this area followed by Group B Streptococcal vaccines.

Since the 2015 PDVAC meeting, a special journal issue dedicated to the issues regarding the maternal immunization vaccination strategy has been published and a great deal of work is underway to strengthen the maternal immunization platform [32].

5.3.1. Respiratory Syncytial Virus (RSV)

Due to the advanced stage of RSV vaccine and monoclonal antibody development, RSV was presented to SAGE for information in April 2016. RSV causes 33.8 million episodes of lower respiratory infection (LRI) annually in children and approximately 200,000 deaths, 99% of which are in LMICs [33]. Recently updated estimates for RSV acute and severe LRI (community based and hospitalized) disease and deaths will be published by the RSV Global Epidemiology Network (RSV-GEN) in early 2017. In addition, the pneumonia etiology research for child health (PERCH) study will present and publish results on the etiology of severe and very severe pneumonia in hospitalized infants and children in 9 sites in Africa and Asia. Preliminary data analyses indicate that RSV was the leading pathogen in infants with severe pneumonia in this study.

There are four RSV intervention strategies currently in development: (1) maternal immunization to enable passive transfer of maternal antibodies to the foetus *in utero*, (2) birth or early infant passive immunization with a long-acting monoclonal antibody, (3) active pediatric immunization and (4) vaccination of the elderly. The most advanced maternal immunization candidate begun phase III efficacy testing in late 2015 following the demonstration of induction of palivizumab-competing antibodies (measured by ELISA) in women of childbearing age (PMID: 26259809) and pregnant women. This efficacy trial has a group sequential design and will enroll 5000–8255 participants in a randomised placebo controlled trial across multiple sites in both the Northern and Southern hemispheres, and is expected to take 2–4 years to complete.

Monoclonal antibody development for the prevention of RSV in pediatrics is the next most advanced, with an extended half–life candidate (MEDI8897) that has been shown to be more potent in vitro than the currently licensed palivizumab. One dose may offer protection for up to 6 months. A phase IIb clinical study in infants born at 29–35 week gestation is planned, and the FDA recently granted fast-track designation for this product. Since the palivizumab patent recently expired, WHO in collaboration with the University of Utrecht will develop a 'biosimilar' of palivizumab and reduce costs for LMIC markets through high yield production and a novel financing plan [34]. The estimated price is $US 250 per child for the full 5 month dose series and the first market authorization is expected in late 2017.

Pediatric RSV vaccine candidates are the least advanced, however two adenovirus-based approaches have entered the clinic since the last PDVAC meeting. A chimp adenovirus (ChAd) candidate is currently in phase I testing in adults, to be followed by age de-escalation into seropositive, and ultimately seronegative infants. Ad26 is also being evaluated as a heterologous prime-boost regimen, currently in phase I testing in adults. A number of pediatric vaccine candidates developed by the Laboratory of Infectious Diseases, NIH are in phase I trials in infants and children. Of note, a vaccine containing a deletion of the M2-2 gene showed evidence of diminished replication, enhanced immunogenicity, and asymptomatic 'boosting' (anamnestic response) following naturally acquired RSV infection (PMID: 26537255).

Two vaccine candidates are in clinical development for the elderly with a post-fusion F-based adjuvanted nanoparticle in phase III efficacy testing, with data expected in early 2017.

PDVAC fully supported the following SAGE recommendations and called for WHO and partners to develop plans to support global policy-making for RSV maternal immunization as well as passive immunization with long-acting mAb, following licensure. Particular areas of emphasis include: (1) RSV surveillance to determine seasonality and age-stratified RSV disease burden and community morbidity and mortality, especially in Africa and south-east Asia (2) assessment of the long term effects of RSV interventions and the potential impact of vaccination on reducing recurrent wheeze, which, if demonstrated, would substantially increase the cost-effectiveness and impact of RSV preventive interventions (3) generation of cost-effectiveness and impact data. SAGE also emphasized the need for strengthening of the maternal immunization platform in collaboration with the influenza, tetanus and pertussis

vaccine communities, along with preparations for potential country introductions of RSV vaccine.

There is an urgent need to establish a WHO prequalification pathway for monoclonal antibodies, which does not currently exist. As a RSV vaccine or extended half-life monoclonal Ab may become available in the next 5 years, it will also be imperative to initiate early discussions with financing bodies, and to align with the GAVI Vaccine Investment Strategy (VIS) to avoid delay in achieving the potential major public health impact of RSV immunization if recommended for use by WHO.

5.3.2. Group B Streptococcus (GBS)

Globally, GBS remains the leading cause of sepsis and meningitis in young infants, with its greatest burden in the first 90 days of life. Intrapartum antibiotic prophylaxis (IAP) for women at risk of transmitting GBS to their newborns has been effective in reducing the young infant GBS disease burden in many high income countries, but IAP uptake is limited and difficult to implement in LMICs. Immunization of pregnant women with a GBS vaccine represents an alternative pathway to protecting newborns and young infants from GBS disease, through prevention of GBS colonization and transplacental antibody transfer to the fetus *in utero*.

PDVAC prioritized GBS in 2015 and encouraged WHO to engage on developing guidance on the development pathway for GBS vaccines, including development of a PPC guidance document and a vaccine roadmap. In April 2016, WHO convened its first consultation on GBS vaccine development [35]. The focus was on GBS maternal immunization development programs targeting LMIC with the ultimate goal of reducing global newborn and young infant deaths. The major knowledge gaps about the disease burden characterization were identified. Recent data suggesting that GBS is an under-reported cause of stillbirth may have profound implications on the estimate of the global public health impact of a future GBS vaccine. The relationship between GBS colonization and prematurity should also be clarified. Disease surveillance in HIC also suggest an important residual unmet medical need, despite implementation of IAP.

Two major pharmaceutical companies are currently developing a multivalent polysaccharide conjugate vaccine, based on the available evidence of an association between trans-placental maternal-foetal transfer of antibodies targeting polysaccharides of the GBS envelope, acquired as a consequence of natural exposure, and a reduced risk of invasive infant disease. A vaccine incorporating five of the eleven described GBS serotypes is predicted to cover over 95% of the global circulating serotypes, but the risk of serotype replacement is unknown. An alternative approach is targeting surface expressed proteins, in an attempt to confer broad protection across all serotypes.

Epidemiological studies evaluating the role of maternal antibodies acquired following natural exposure will determine whether a protective threshold at birth can serve as an acceptable vaccine-induced correlate of protection. Until additional epidemiological and immunological data are available, estimating vaccine efficacy against invasive GBS disease in neonates and young infants in a double blind placebo-controlled vaccine trial remains the gold standard for generating the evidence required to determine potential public health impact and inform policy decision-making.

PDVAC endorsed the consensus-based prioritization of future activities including the development of a PPC and vaccine development technology roadmap. Efforts should be made to raise awareness of the burden of GBS disease and potential public health value of a GBS vaccine, particularly in countries that lack local epidemiological data. As with RSV, efforts must be made to leverage and strengthen the maternal immunization platform by alignment with other vaccines that are administered in pregnancy, including the Brighton Collaboration's considerations for safety monitoring through the Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) [36].

5.4. Vaccines that may reduce antimicrobial drug resistance (AMR)

Antimicrobial-resistant infections currently claim at least 50,000 lives each year across Europe and the US alone, but AMR affects many hundreds of thousands in other areas of the world [2]. In 15 European countries, more than 10% of bloodstream *Staphylococcus aureus* infections are caused by methicillin-resistant strains (MRSA), with several of these countries seeing resistance rates closer to 50%. Emerging resistance to treatments for other diseases, such as TB, malaria and HIV, have enormous impacts in lower-income settings, and by 2050, the death toll due to AMR infections in Africa is predicted to be approx. 4,000,000 per year. As mentioned above, each year almost 0.5 million cases of drug-resistant TB are reported, and these are extremely costly to treat; an MDR case costs 8–15-fold more to treat than drug a sensitive case, while an XDR case is 25–32-fold more expensive [37]. The WHO estimates that approximately $8 billion per year is required to support TB care and control efforts in LMICs. This is significantly more than the current investment in TB vaccine development programs. The O'Neill review on Antimicrobial resistance estimated that by 2050 drug-resistant infections could be claiming 10 million lives per year and at an economic cost to the global GDP in excess of $100 trillion.

At the Sixty-eighth World Health Assembly in May 2015, a global action plan to tackle antimicrobial resistance, including antibiotic resistance, was adopted [38]. Its goal is to ensure continuity of successful treatment and prevention of infectious diseases with effective and safe medicines – including vaccines – that are quality-assured, used in a responsible way, and accessible to all who need them. The AMR Global Action Plan (GAP) is based on 10 work streams ranging from national plans, stewardship of antibiotics, encouraging R&D through developing new business plans and assessing environmental drivers. One work stream focuses on vaccines to prevent AMR.

The WHO GAP workstream on vaccines to prevent AMR is based on three complementary approaches: increasing the use of existing vaccines; developing vaccines against high burden diseases currently treated systematically with antibiotics; and prioritizing the development of vaccines for diseases where antibiotic resistance is significant. These three approaches, and the challenges associated with implementing them are summarised below:

a). Increasing use of existing vaccines: While it is logical that increasing the use of existing vaccines would reduce infections and result in reduced use of antibiotics, it is not always clear which vaccines, in which populations, would have the greatest impact on reducing antibiotic use and potentially AMR, and should therefore be prioritized. For example, it has been shown that the use of PCV-7 in children results in a roughly 50% reduction in antibiotic-resistant strains of *S. pneumonia*, and the use of PCV-10 reduces outpatient antibiotic purchase, leading to the suggestion that global pediatric coverage with PCV could prevent 11 million days of antibiotic use in children annually. However, it is thought that the bulk of pneumonia, and antibiotic use for *S. pneumonia* infections, is in older adults. This would suggest that demonstrating efficacy of pneumonia vaccines to reduce antibiotic use in older adults and an expanded use of these vaccines in that population group where very few countries have a vaccination policy may have a substantial impact on reducing AMR. Other existing vaccines which could impact antibiotic use include pertussis, *Haemophilus influenza, Neisseria meningitides*, typhoid, as well as influenza which, although not directly susceptible to antibiotic treatment, does

result in bacterial super-infections and accounts for up to 30% of excess (winter-related) antibiotic prescriptions in some countries.

In order for a rational evidence-based policy on expanding the use of existing vaccines a prioritization exercise needs to be performed, taking into account the disease burden in different populations, the antibiotic use associated with that disease burden, and an evaluation of how many days of antibiotic use would be avoided with each dose of vaccine administered. This exercise is particularly challenging since in most of the world antibiotics are taken in response to a symptom, rather than an identified infection. This means that, for example, preventing *Salmonella typhi*-induced infection with vaccines may have minimal impact on antibiotic use for severe diarrhea. The prioritization exercise therefore needs to consider not only the disease burden, but the symptom burden and the proportion of that burden due to the vaccine-preventable infection.

b). Developing vaccines for diseases that are consistently treated with antibiotics, where AMR is not currently an issue, but where the vaccine could reduce antibiotic use. One such example is Group A Streptococcus (GAS). While GAS is not directly associated with antibiotic resistance (there is little evidence of resistance to date) it has a high disease burden and is a source of extensive antibiotic use. In addition, it is thought that vaccine development is feasible. However to date there has been no significant effort from industry, possibly because of the weak market assessment since it can be treated with antibiotics, and such treatment is cheap. However the indirect costs from such antibiotic use, increased environmental exposure to antibiotics and expansion of AMR have not been considered. Taking these costs into account may contribute to the value proposition for developing and using such a vaccine. Other such candidates could include Group B streptococcus, and *M. catarhalis* and non-typeable *Haemophilus influenza*, both responsible for otitis media which is another source of significant antibiotic prescription. While including potential impact on reduction of antibiotic use, prioritization of these candidate vaccines also needs to consider technical feasibility, whether the antibiotic use is appropriate, and whether alternative non-antibiotic approaches may make vaccine use less attractive. For example: while there are over 700 million cases of otitis media per year in under - 5 year olds, for which antibiotic treatment is usually prescribed which could justify development of a vaccine, most otitis media resolves and new guidelines recommend limiting antibiotic treatment. Another example is urinary tract infections which are frequent in elderly patients and a cause of significant antibiotic use, yet there is little supporting evidence that these infections could be effectively reduced by vaccination.

A prioritization exercise is therefore required for vaccines that are considered technically feasible, takes into account the potential AMR impact, and therefore could contribute to the cost effectiveness of the vaccine if they were developed. To achieve this, the evaluation of impact on AMR is recommended to be included in the review of vaccine conducted by PDVAC.

c). The third and most challenging approach is developing vaccines against pathogens that are frequently antibiotic resistant and becoming increasingly difficult to treat, the so-called ESKAPE pathogens [39]. This list includes *Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumonia,* as well as *Clostridium difficile* and tuberculosis.

There are numerous challenges in this approach. The first is that although infection with these may result in significant morbidity, the current global disease burden of many of these infections remains relatively low so prophylactic vaccination of the entire population would not be cost-effective. Tuberculosis is however an example with significant disease burden and rapidly expanding multi-drug resistance. Secondly many of these infections are associated with ageing, where immune decline may make immune interventions poorly effective, or are associated with penetrative medical interventions where the time available to induce a protective immune response may be insufficient. And finally, despite significant efforts to make effective vaccines against some of these has so far proven to be difficult. Of these, tuberculosis appears to have the greatest global burden and public health impact, and TB vaccines are also the subject of extensive research.

The AMR GAP activity in this area, to be conducted by IVR is firstly to promote TB vaccine research and development through facilitation of Preferred Product Characteristics and the establishment of a roadmap for vaccine use, and highlighting the impact that the vaccine will have on antibiotic use and antibiotic resistance. Additional activities involve monitoring the state of development of vaccines against the pathogens that are becoming antibiotic resistance, and facilitating their development.

5.4.1. Group A Streptococcus (GAS)

GAS is a ubiquitous human pathogen that causes a broad disease spectrum, from mild to severe, the most serious of which is rheumatic heart disease (RHD). RHD affects approximately 30 million people globally, of whom 1 million experience heart failure and an estimated 300,000 die. GAS is also a major cause of invasive disease, with a case fatality rate of 10–15% in high income countries, and as high as 38% in LMICs [40]. On the milder end of the spectrum, GAS causes approx. 615 million cases of pharyngitis per year, resulting in 60–70% of cases being treated with broad spectrum antibiotics, rather than penicillin (9% of cases), to which GAS is universally susceptible. This extensive use of unnecessary and inappropriate antibiotics increases the likelihood of AMR emergence against antibiotics that are used to treat a range of pathogens.

Previous human challenge studies, as well as preclinical animal models suggest that it is feasible to develop a vaccine against GAS, and since the previous PDVAC meeting, phase I studies for one candidate has been initiated in adults, and two additional candidates are expected to enter phase I studies in the next 12 months. Despite this encouraging progress, significant debate remains as to the appropriate indication and optimal clinical endpoints, and the regulatory pathway for a vaccine to prevent or reduce RHD is unclear. In addition, there is a perception that increased prescription of penicillin would be an equally as effective and a significantly more cost effective method of reducing conditions that result from GAS infection. These issues are likely major stumbling blocks in incentivising investment in GAS vaccine development.

GAS has been prioritized by PDVAC previously, with a recommendation to develop a business case for both a global market, and also specifically for LMICs which would focus on prevention of severe outcomes in resource poor settings. Despite significant effort, it has been very difficult to engage stakeholders in this activity. On the recommendation of PDVAC, WHO convened a consultation in December 2016 to examine the value proposition for GAS vaccines, considering its potential impact across both high income and lower income settings – including the consideration of how current antibiotic treatment practices may increase AMR, as well as to investigate the perceived regulatory obstacles.

5.4.2. Staphylococcus aureus (S. aureus)

S. aureus is a bacterium that is found as both an asymptomatic colonizer of the skin and nares of human hosts, as well as a frequent cause of human disease. It causes a spectrum of clinical manifestations of varying severity, and is the most commonly isolated pathogen from skin and soft-tissue infections, septic arthritis,

pneumonia, endovascular infections, osteomyelitis, catheter/other foreign-body infections, septicaemia, and toxic shock syndrome. Methicillin-resistant *S. aureus* (MRSA) has been documented to be emerging at a rapid and increasing rate since the antibiotic was first introduced in 1959, and hospital-associated MRSA (HA-MRSA) clones are now recognized to be the leading cause of nosocomial infections both in the United States and around the world, in high income as well as LMICs. The emergence of community-associated MRSA (CA-MRSA) in the past several decades is of concern, as is the emergence of highly resistant vancomycin-resistant *S. aureus* (VRSA).

To date, active and passive immunization approaches have been based on increasing the concentration of opsonic antibodies to single surface antigens, and all have failed to demonstrate protection. Antigenic variation, the multiple invasion pathways and lack of a surrogate of protection all present significant obstacles to vaccine development. Following the failure of single antigen vaccine approaches, most development efforts are now focused on multiple antigens, and a number of candidates are in preclinical development. One multi antigen approach, comprised of 4 antigens including two capsule polysaccharides, clumping factor A and a manganese transport protein, is the most advanced [41]. Current efforts are also focused on further characterizing the immunopathology and immunity of *S. aureus* infections to identify new antigenic targets, and developing more representative preclinical models in which opsonising and/or neutralising immune responses are measured.

To date, none of the vaccine candidates in development have contemplated target populations or indications that are prevalent in LMICs. Focus has been on development of a vaccine that will protect against life-threatening *S. aureus* infections in high income countries, but it is hoped that such a vaccine would also protect against all *S. aureus* infections including more commonly encountered skin and soft tissue infections, and therefore be applicable in LMIC contexts.

5.5. Sexually transmitted infections (STIs)

Since the 2015 PDVAC meeting, a new Global Health Sector Strategy on Sexually Transmitted Infections has been developed for 2016–2021 and adopted by WHO member states at the 69th World Health Assembly. Within this strategic framework, STI vaccine development was highlighted as key need for future STI control [42]. In addition, the global roadmap for vaccines against STIs has been updated and included in the WHO Special Issue on pipeline vaccines published in Vaccine [43]. Currently, the only STI vaccine candidates that are undergoing or approaching clinical development are against herpes simplex virus (HSV) and *Chlamydia trachomatis*, and as such discussion was limited to these pathogens.

5.5.1. Herpes simplex virus

HSV is the leading cause of genital ulcer disease, and a particular concern for LMICs as it increases both acquisition and transmission of HIV infection. HSV type 2 and type 1 disease burden estimates were recently updated [44,45], and it is estimated more than half a billion people live with genital HSV infection, worldwide. PDVAC previously recommended that improved global estimates of neonatal herpes burden be generated, and assessment of available data has recently been completed with preliminary estimates of >14,000 new cases globally, an incidence rate of approx. 10/100,000 births, which is concerning because of a case fatality rate of 60% (Looker, submitted). The incidence is likely to be under-estimated in LMICs where HSV infection rates are highest and poor healthcare infrastructure means that neonatal herpes cases are likely to be undetected, but primary data are lacking. Ongoing evaluation of HSV infection as part of the Child Health and Mortality Prevention Surveillance (CHAMPS) network will help to address this burden gap.

At the 2015 meeting, the advance of therapeutic vaccine candidates for HSV-2 was highlighted, and the role of these types of vaccines in modulating the interaction between HSV and HIV acquisition was discussed as an important consideration for these vaccines in LMICs. In consideration of this, and with WHO support, a systematic review/meta-analysis of HSV-2 and risk of HIV acquisition including 54 studies will inform modelling of the potential impact of an HSV-2 vaccine on HIV incidence, and is expected to be published in late 2016. A review of biological mechanisms of HSV-HIV interaction and implications for vaccine development has also been drafted. The pipeline for therapeutic vaccines remains robust, with 5 candidates in clinical development, the most advanced of which now has data demonstrating significant reductions in HSV2 shedding (55%) and days with genital lesions (60%) over 12 months [46]. In response to these positive data, NIAID has formed an HSV working group to propose desired characteristics for therapeutic and prophylactic vaccines for HSV, including indication, priority target populations, clinical trial endpoints, and safety and efficacy criteria. This document could form the foundation for a WHO consultative process to generate a guidance document on Preferred Product Characteristics (PPC). PDVAC encouraged WHO to actively collaborate and support development of PPCs for HSV vaccines.

5.5.2. Chlamydia

Chlamydia trachomatis is a Gram-negative bacterium that can infect genital, ocular and lung epithelium. It includes three sets of serovars:

- Serovars Ab, B, Ba, or C — cause ocular trachoma, which can lead to blindness
- Serovars D-K — cause sexually transmitted infection resulting in urethritis, cervicitis, pelvic inflammatory disease (PID) (and associated infertility, ectopic pregnancy, and chronic pelvic pain), neonatal pneumonia, and neonatal conjunctivitis
- Serovars L1, L2 and L3 — cause lymphogranuloma venereum

C. trachomatis can ascend to the upper genital tract and cause pelvic inflammatory disease (PID), which can in turn lead to long-term sequelae including tubal factor infertility, ectopic pregnancy, and chronic pelvic pain. Other adverse outcomes of chlamydia include preterm birth, neonatal conjunctivitis and pneumonia, and increased HIV risk. Currently management is through screening programs in some high income countries that are not feasible in resource constrained settings, where most cases are likely never diagnosed. WHO estimates that there were 131 million new cases of chlamydia in 2012 [47] with most cases among adolescents and young adults. The global burden of chlamydia-associated PID, infertility and other sequelae has not been well characterised and estimates of the proportion of infertility presumed to be associated with genital infection (e.g., have a Fallopian tube etiology) in Africa are outdated [48], but are thought to be approx. 65–85% in women seeking fertility care.

There are several vaccine candidates currently in preclinical development, with a subunit vaccine based on the chlamydial major outer membrane protein (MOMP) and live-attenuated (plasmid-deficient) approaches being the most advanced. The MOMP candidate entered phase I clinical testing in late 2016, and a phase I study with the live attenuated candidate will commence in 2017. The intended goal of a chlamydia vaccine is to decrease upper genital tract sequelae, however PID is challenging to use as clinical endpoint as it is difficult to definitively diagnose and the causes of PID are multi-factorial (typically the result of *C.*

trachomatis in 1/3 of cases). The chlamydia vaccine community is seeking guidance and consensus building on clinical endpoints for clinical studies, including evaluating the potential role of biomarkers, radiologic, and other measures of upper tract ascension, infection, inflammation and damage. Improved global burden of disease data and vaccine impact modelling on long term sequelae are also needed to define the investment case for these vaccines. PDVAC commended the progress towards the first vaccine study against chlamydia since the 1960s and look forward to discussing the path ahead once the early clinical data are available.

5.6. Currently under-utilised licensed vaccines

This section refers to vaccines that have been licensed, or are approaching licensure in some areas of the world, but are currently limited in their use outside any single WHO region. In some instances, the vaccines may have the potential of offering broader public health impact by expanding approval and use in other geographical regions, and PDVAC is seeking to understand the perspective in this regard.

5.6.1. Enterovirus 71 (EV71)

EV71 is one of the most common causes of hand-foot-and-mouth disease (HFMD). Sporadic EV71 outbreaks have occurred globally since it was first isolated in 1969, but from the late 1990s a series of large HFMD epidemics caused by EV71 have been reported in the Asia-Pacific region. In China alone, 7.2 million cases were reported between 2008 and 2012, of which 2457 (0.03%) were fatal [49]. Children less than 5 years of age have the highest risk of disease, and although infection is unusually mild and self-limiting, severe infections can result in neurological and cardiopulmonary complications, and death.

Several EV71 vaccine candidates are in development, and it was stated at the meeting that the Chinese national regulatory authority has licensed two EV71 vaccines, with another in progress. The first licensed vaccine was developed by the Institute of Medical Biology, Chinese Academy of Medical Science, and has been approved for use to prevent EV71 disease in 6–71 month olds, based on a phase III study that demonstrated 95% efficacy over 12 month [50]. Sinovac has also licensed in activated vaccine, with supportive phase III data in 6–35 month olds [51]. Beijing Vigoo is in the process of licensing its inactivated EV71 vaccines in China (NCT01508247). All three vaccines are adjuvanted with aluminum hydroxide.

Given that EV71 outbreaks occur in other areas of the world (recently reported in Spain [52]), further discussions are warranted in the international health community about how to assess the role of the Chinese vaccines during outbreaks outside China.

5.7. Emerging pathogens and the WHO R&D Blueprint

In the wake of the 2014–15 Ebola outbreak, various strategies were proposed to avoid such crises from reoccurring. Key to improving R&D preparedness and response is determining which pathogens are likely to be the greatest threat, creating consensus with respect to product development strategies and co-ordinating global funding for complementary R&D efforts going forward. To tackle these questions, and at the request of its 194 Member States, WHO convened a broad global coalition to develop the R&D Blueprint [53] as a sustainable platform for accelerated R&D, with two complementary objectives:

- to develop (and implement) a roadmap for R&D preparedness for known priority pathogens, and
- to enable roll-out of an emergency R&D response as early and as efficiently as possible

The main approaches underpinning the improvement of preparedness within the R&D Blueprint include:

1. Assessing epidemic threats & defining priority pathogens
2. Developing R&D roadmaps to accelerate evaluation of diagnostics, therapeutics & vaccines
3. Outlining appropriate regulatory & ethical pathways

WHO has defined its priority list of pathogens within the published Blueprint. PDVAC has a contributory role within this framework, and when WHO declares a Public Health Emergency of International Concern (PHEIC), PDVAC may be tasked with forming a working group to facilitate development of guidance tools for the vaccine development community in the context of the emergency. For example, the current status of Ebola virus vaccine and Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV) vaccine development was reviewed by PDVAC at this and previous meetings, and a PDVAC Working Group has developed a WHO Zika vaccine Target Product Profile [56].

5.7.1. MERS-CoV

As reported in the 2015 meeting summary, a consultation to initiate work towards a MERS CoV roadmap was held in December 2015 with aims of defining the key basic and applied research activities, identifying the priority technologies and capacities to support vaccine development, and finally understanding the financing/procurement opportunities. Following this meeting, a draft roadmap was developed and underwent public consultation prior to finalisation and publication [54].

5.7.2. Ebola virus

It is well accepted that the extraordinary rate of Ebola virus vaccine development was as a result of unprecedented collaboration and co-ordination of global vaccine R&D activities, and the availability of a number of candidate vaccines that could enter clinical phase evaluation [55]. In the face of another PHEIC so soon following Ebola virus disease (EVD) outbreak, the global vaccine community is rallying, and reflecting on lessons learned from the experience in West Africa only 2 years ago. At the time of responding to the EVD emergency, the availability of well-characterised pre-clinical models and robust data was essential for the comparative evaluation and selection of candidates to move into clinical studies. Novel recombinant viral vector platforms, in combination with recombination proteins have been validated by EVD experience and it could be argued are now less risky for development of vaccine against future pathogens, but manufacturing feasibility and scale-up capabilities still need to be confirmed for the most novel platforms. Critically, sustainable public sector push and pull investment mechanisms beyond the initial emergency response phase need to be created, to incentivise manufacturers to engage in the long term commitment to developing and licensing vaccines that may only be used in outbreak or emergency scenarios.

PDVAC noted that a target product profile for a second generation Ebola virus vaccine is under development that will likely cover Ebola Zaire, Ebola Sudan, and Marburg filoviruses, and will need to demonstrate longer duration of protection. This TPP will provide guidance about WHOs preferences and minimally acceptable criteria for vaccines in this area. During the discussion it was clarified that WHO TPPs include minimally acceptable criteria, whereas Preferred Product Characteristics specify only preferences.

5.7.3. Zika virus (ZIKV)

The status of Zika virus epidemiology and the understanding of its pathogenesis and associated sequelae are evolving so rapidly that publications on these issues are almost immediately out of

date. PDVAC's role has been to oversee a working group that has developed a target product profile (TPP) for use *in an emergency*, or future outbreak scenario. The TPP was made available for public consultation, after which subject matter experts, global regulators, developers and manufacturers were convened to discuss the regulatory considerations for developing a vaccine with the characteristics described in the TPP. The finalised TPP and position paper are publically available [57].

5.8. Cross-cutting product development and implementation issues

In addition to reviewing the status of vaccine development against pathogens, PDVAC considered a number of cross-cutting issues that could better integrate and therefore facilitate product development efforts for vaccines and other interventions.

5.8.1. Novel vaccine delivery technologies

In addition to the significant morbidity and mortality that drives the development of vaccines against pathogens for which vaccines are currently not available, the WHO estimates that there are approximately 1.5 million deaths per year in children under 5 from vaccine preventable diseases [58,59]. One of the reasons for this striking immunization gap is the cost and logistical challenges of delivery of these vaccines, over and above the cost of their manufacture. The remit of WHO's Immunization Practices Advisory Committee (IPAC) is to provide strategic advice on immunization practices, tools, and technologies intended to improve the delivery of immunization programs at the country level. It oversees the recently formed delivery technologies working group (DTWG) composed of public health organizations, funders and procurement agencies as well as vaccine developers to evaluate R&D in novel delivery technologies and devices, for example the microarray patch, and compact, pre-filled auto-disable injection technologies (cPAD). Of particular focus for this group is the development and evaluation of a framework to analyze high-level trade-offs between important variables such as development, procurement and supply chain costs, coverage, efficacy, and safety in order to facilitate investment decisions by product developers, vaccine manufacturers, global policy makers, in-country decision makers and procurement agencies. This framework is referred to as total systems effectiveness (TSE). The intent of this delivery technology working group is to offer a platform for discussion and guidance regarding vaccine preferences for LMICs, early on in development, so that ultimately the vaccine is suitable for programmatic use. The DTWG reports directly to IPAC, but has potential overlap with activities that are overseen by PDVAC, particularly in consideration of second generation vaccines or new vaccines that may be developed with an alternative presentation to that of a needle and syringe.

PDVAC was supportive of the DTWG and encouraged continued communication between vaccine development and device/delivery technology development to identify potential opportunities for novel combination product development.

5.8.2. The need for a WHO monoclonal antibody (MAb) prequalification pathway

There are several pathogen areas where MAb are being developed as vaccine-like interventions, as their single dose regimen and long half-life render them amenable for LMICs contexts, where they could offer significant public health benefit. Candidates for RSV and rabies are approaching licensure within the next 5 years, and a WHO procedure for WHO prequalification is urgently needed to avoid delay implementation. This gap has been recognized and will be addressed.

5.8.3. PDVAC's role in and coordination with other vaccine/intervention development efforts

The scope of PDVAC overlaps with several other research agendas such as GVAP, AMR, new delivery technologies and development and consolidation of maternal immunization platforms. The PDVAC research agenda needs to be clearly communicated, and PDVAC and IVB will strive to be well-informed of efforts in other research areas, to help shape and align strategy where appropriate. Future PDVAC meetings will consider these potential overlaps in more detail, as well as how PDVAC and IVB can facilitate development of integrated product development approaches.

5.9. PDVAC going forward

Since its inception in 2014, PDVAC has reviewed the pipeline and vaccine development status of 33 different pathogens. PDVAC will continue to review new pathogen areas as candidates progress into clinical studies, providing that WHO engagement will likely facilitate the use of vaccines to reduce disease burden in LMICs. One such pathogen is Cytomegalovirus (CMV), which is a leading cause of congenital infections worldwide, resulting in 17–20% of infants developing permanent sequelae including hearing loss and neurodevelopmental disabilities. There are little data on CMV infection in LMICs, but a recent systemic review suggests that birth prevalence ranges are higher in LMICs than in Europe and North America [60], and several clinical trials of vaccine candidates are ongoing. As such, an assessment of CMV vaccine development will be undertaken by PDVAC 2017.

With RSV, TB, HIV and enteric candidates approaching pivotal data points, understanding what data are needed to support earlier policy implementation and outcomes will be key, as well as understanding the potential impact of vaccines within the broader control strategy – including diagnostics and other preventatives - for these pathogens. Vaccine impact modelling, and understanding the composite set of cost drivers through to vaccine delivery will be important. Interaction with WHO's IPAC and PQ teams will increase going forward, to strengthen the link between product development and programmatic requirements.

Under the recommendation of PDVAC, WHO will seek to broaden its role to support development of value propositions for vaccines against pathogens for which there is a poorly defined business case, for example GAS and HSV. Raising awareness of LMIC disease burden and requirements/procedures for access to LMICs markets may help to incentivise financing development of these vaccines. Of key consideration may be the potential for these vaccines to reduce the emergence of AMR, and PDVAC recommended that this be considered as a criterion in future landscape analyses and PPC guidance documents.

PDVAC and WHO will continue to align activities with the priorities within the WHO R&D Blueprint. PDVAC is aware that several other organizations which are responsible for emergency preparedness have been through a process to prioritize their R&D agendas, with some commonality and some complementarity to the pathogens listed in the WHO Blueprint. In this arena, PDVAC will continue its horizon scanning role, and will advocate for commitment to product development of vaccines for emerging diseases to progress through robust preclinical proof of concept to generation of phase I data, as a minimum. PDVAC strongly recommends the collaboration with other groups to co-ordinate advocacy and funding for vaccine development to prepare for the inevitable future emergencies.

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