Third International Symposium on Vaccinology for Asia Pacific Experts

Organized by Fondation Mérieux

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Meeting Report

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The third symposium on vaccinology for Asia Pacific Experts took place in Vietnam-Hanoi on October 16-18th 2017. The meeting was organized by Fondation Mérieux in collaboration with the Vietnam Ministry of Health and included formal presentations, discussions and round tables on progress and challenges of current vaccines, state of art of vaccine development for emerging and re-emerging diseases and the Asian perspectives from vaccine to vaccination. A summary of main issues is reported.

1. Current vaccines: progress and challenges

Despite impressive achievements in vaccine uptake, there are still challenges with regard to coverage rate of marketed vaccines. The following sections provides an overview of issues raised by participants.

Enteric vaccines

Prequalified, whole cell oral cholera vaccine (OCV) are available, and have been shown to be safe and efficacious, even a single dose has been shown to be effective for at least 6 months [Azman 2015]. However, an estimated 2.86 million cholera cases (uncertainty range: 1.3m-4.0m) and 95,000 deaths (uncertainty range: 21,000-143,000) occur annually in 69 endemic countries, the Democratic Republic of the Congo (DRC), Haiti, Somalia, the United Republic of Tanzania and Yemen accounting for 80% of all reported cases [Ali 2015]. Yemen faced the worst cholera outbreak in the world with over 250,000 suspected cases by July 2017. These figures are probably underestimated due to the limitation of surveillance systems and the fear of impact on tourism and trade. Vaccine availability remains a major barrier limiting mass vaccination interventions. The dynamic creation by the establishment of stockpile has played a key role in increased use of OCV. From 2013 to October 2017, a total of 16,201,050 doses of OCV stockpile have been shipped to 18 affected countries. The OCV campaign in Bangladesh in October 2017 allowed 555,619 individuals to be vaccinated. The global cholera roadmap aims at reducing the number of deaths by 90% and eliminating cholera in 20 affected countries by 2030.

Rotavirus is the causal pathogen of two out of every 5 diarrhoea-related hospitalizations among children under age five, causing 200,000 deaths globally each year. Currently, two WHO-prequalified, orally administered rotavirus vaccines (Rotarix and RotaTeq) are available

and more are being licenced or developed in several countries including Vietnam, India and China. They have been shown to be highly cost-effective and to provide broad protection even against strains not included in the vaccine. However, despite the WHO recommendation, still 94 million infants do not have access to these life-saving vaccines.

Typhoid fever is endemic in Asia, Africa, Latin America, the Caribbean, and Oceania, but 80% of cases come from Bangladesh, China, India, Indonesia, Laos, Nepal, Pakistan, or Vietnam, the highest burden being reported in young children 6 months to 2 years old. The global estimate of typhoid burden ranges between 11 and 12 million cases; leading to 145000 to 161000 deaths annually. The treatment is further complicated by the emergence of multidrug-resistant (MDR) strains of *S. typhi*. Currently, three vaccines, Live attenuated oral Ty21a (Vivotif), Vi capsular polysaccharide vaccine (for children> 5 years old) and Conjugated Vi PS (TCV) are available. Furthermore, two new vaccines, Vi conjugate vaccine: Vi-rEPA and Vi-DT conjugate vaccine are undergoing licensure review by national regulatory authorities.

Pertussis

Pertussis is a highly infectious but vaccine preventable disease. In Vietnam, national surveillance data suggests that up to 5.7 million diseases cases and 26,000 deaths may have been prevented since 1980 by pertussis vaccination [Jit 2015]. Available vaccines include the whole cell (Wc) and the acellular (DTaP) pertussis vaccine. The Wc vaccine was replaced by the DTaP in many countries due to its potential reactogenic effects [Pichichero 2000]. However, despite high vaccine coverage with DTaP, pertussis incidence has increased substantially since 2012 in many countries specially among adolescents 7-10 years old. The observed upsurge has been suggested to be likely attributable in part to waning immunity to pertussis following 5 doses of DTaP [Tartof 2013]. Longer duration of immunity following natural infection (10-20 years) as compared to Wc vaccine (almost 10 years) and DTaP (4-6 years) has been reported [Wendelboe 2005]. Recent studies suggest that priming with the Wc vaccine confers better and longer protection [Schwartz 2016, Liko 2013, Klein 2013, Sheridan 2012, Vickers 2006]. Other risk factors that could explain the observed increased incidence in adolescents are loss of herd immunity, presence of new strains without pertactin/pertussis toxins [Queenan 2013, Barkoff 2012], changes in the alleles of the vaccine [Mooi 2013], and cyclical nature of pertussis epidemics [Clark 2014]. Studies in

Baboon showed that acellular vaccine protects against disease but fails to prevent infection and transmission [Eberhardt 2017, Warfel 2013], while a new live attenuated vaccine provided protection against both pertussis disease and B. pertussis infection [Locht 2017]. The new options to decrease the incidence of pertussis are cocoon strategy [Abu Raya 2015], keeping the Wc vaccination in countries that did not yet switch to DTaP, and revaccination of adolescents and adults who are considered as reservoirs.

Pneumococcus and meningococcus

Pneumococcal disease caused by *Streptococcus pneumoniae* leads to 700,000 to 1 million deaths / year in children <5years of age with over 90% of deaths attributable to pneumonia. [O'Brien 2009]. In Asia, substantial disease burden was reported in Indonesia and India.
The 23-valent pneumococcal capsular polysaccharide vaccine licenced in 1998 has shown poor immune memory, poor booster effect and poorly immunogenic in children less than 2 years [Pollard 2009]. Pneumococcal conjugate vaccines (PCV) are immunogenic and have more immune memory and booster effect. The introduction of PCV-7 vaccine has led to substantial reduction in the number of invasive pneumococcal disease in the target population i.e. children <5 years old and conferred also herd protection in older individuals [Tan 2012]. Significant reductions in the number of otitis media [Tamir 2015], sinusitis [Lindstrand 2014], resistance to *S. pneumoniae* [Kyaw 2006] and nasal carriage of PCV-7 serotypes [Spijkerman 2012] have also been observed. The observed reduction of nasal carriage was concomitant to increase in non PCV-7 serotypes [Spijkerman 2012], serotype 19A emerging as a cause of invasive pneumococcal disease in in the US [Moore 2008] and Asia Pacific [Kim 2012]. Addition of new serotypes in PCV-10 and PCV-13 vaccines improved the situation.

Neisseria meningitidis is the leading cause of bacterial meningitis with high morbidity (11-19%) and mortality in developed and developing countries (10 and >20% respectively) [Mandel 2015]. Serogroup B is the most prevalent type of the 13 known serogoroups [Papaevangelou 2012]. In Thailand, the highest burden of meningococcal invasive disease has been reported in <1 years old followed by adolescents (11 years) and young adults (21 years).
Currently, several polysaccharide and conjugate meningococcal vaccines are available and have been introduced in routine immunization programs in 21 countries [Ali 2014].

Influenza

Globally, influenza affects 10-20% of the population and cause 250,000-500,000 deaths [Luliano 2017]. Antigenic shifts and antigenic drifts [Bedford 2014] are responsible for unpredictable changes that leads to epidemics and global pandemics. In addition, the seasonality of influenza varies according to the geographical zones [Bloom-Feshbach 2013]. During the 2009-2010 influenzas season, extreme ages (<5 years and > 75 years) experienced the highest rates of hospitalization, A(H1N1)pdm09 and A(H3N2) being the most prevalent strains [Baggett 2012]. In China, the H7N9 strain led to 1507 human cases with a fatality rate of 39% since 2013. An increase in rural cases, due to mobile poultry vendors in some provinces was reported. There were no significant differences in age, sex and clinical severity, and no sustained inter-human transmission.

Current influenza vaccines are moderately effective i.e. 60% efficacy in seasons with a good antigenic match. To date, manufacturing capacity is unable to match timing and volume required for pandemic control.

Estimation of influenzas vaccine effectiveness (VE) is usually based on randomized-controlled trials, cohort or case-control studies. The test negative design (TND) is a new approach that is now being widely [Feng 2016, Foppa 2013]. Meta-analysis of TND studies showed high protection against A(H1N1)pdm09 and B in all age groups, and reduced protection against A(H3N2) in particular in elderly [Belongia 2016]. Twice-annual vaccination for this population has been considered. However, there results regarding the impact of repeated vaccination are conflicting [Ramsay 2017].

Measles and Rubella

Measles, mumps, and rubella (MMR) are highly contagious viral infections that can be prevented by MMR vaccine, first licensed in 1971. Immunosuppression triggered following measles infection is thought to increase the overall childhood infectious disease mortality [Mina 2015]. Since the beginning of the century, vaccination led to 15.6 million deaths averted [WHO 2012]. The herd immunity threshold to eradicate the infection is estimated to be 55% [Wallinga 2005]. However, measles remains a global public health problem. Since 2008, major outbreaks have been reported in Africa, Europe and in countries certified as measles free

(Brazil and Mongolia). Global control in all areas with high coverage is needed, followed by co-ordinated “final push”.

Rubella is rather a mild febrile illness with fever and rash. The main public health importance is congenital rubella syndrome (CRS). Partial vaccination of a community can result in an increase in susceptibility among women of childbearing age that may increase the risk of CRS. Strong, co-ordinated national vaccination programs are therefore needed to virtually eliminate CRS.

Yellow fever

Yellow fever (YF) is an arthropod-borne infection caused by a flavivirus belonging to Flaviviridae family. *Aedes* aegypti is the main vector involved in human to human transmission. The haemorrhagic fever represents only 10% of cases but other forms of the disease are not distinguishable from dengue or other arbovirus diseases. South America and Africa are the main transmission areas of YF.

A single dose of YF confers life-long immunity against YF disease [WHO report, add the ref]. However, the available doses and stock are not satisfactory. The use of novel technologies for new vaccines are under consideration [Maciel 2015, Monath 2011, Gaspar 2008].

2. Novel vaccines: emerging and re-emerging infectious diseases

Urbanization, industrialization, climate change, international trade, poverty, and evolution of pathogenic agents are among factors that could explain the emergence or re-emergence of some infectious diseases [McMichel 2004]. These global drivers are currently increasing, and consequently risk from emerging and re-emerging infectious diseases (E&RID) with epidemic potential will likely continue or increase. Up to now, response to E&RID have been rather reactive, ineffective, and un-sustained [Bloom 2017]. Incentivizing vaccine and the set-up of a global vaccine development fund are among proactive strategies for response these disease [Bloom 2017, Plotkin 2015].

Challenges for E&RID vaccine development include the weakness of pipeline due to the lack of market incentives, unilateral, uncoordinated government efforts to fund research and

development preparedness and difficulties to adapt clinical and regulatory pathways to epidemic context.

The state of art of some of these infectious diseases and the status of their vaccine development as presented during the meeting are summarized.

Mosquitos-borne diseases

The development of resistance to pesticides contributed to the spread of mosquito-borne diseases.

Globally, 3.9 billion people, representing half of the world's population live in dengue-endemic countries. Overall, 96 million symptomatic infections and 500,000 people with severe dengue requiring hospitalization are reported each year [WER 2016].

Dengue disease cost more than US$6 billion annually worldwide [Selck 2014]. The relative incidence ratio of symptomatic/asymptomatic infection is estimate to be 1:4 [Olivera-Botello 2016], asymptomatic individuals being reservoir for dengue transmission. Several studies in South-East Asia reported a shift of dengue cases towards adolescents and adults [Thisyakorn 2017, Tangsathapornpong 2017, Lawtongkum 2017].

Currently, several dengue vaccines are in different phase of development pipeline. The WHO SAGE recommends countries consider introduction of the marketed vaccine, CYD-, in geographic settings where dengue is highly prevalent, together with vector control, surveillance and communication strategy [WER 2016].

Zika is mainly transmitted by the bite of *Aedes Aegypti* but cases transmitted by sexual intercourse and blood transmissions have also been reported [Rodriguez-Morales 2016]. Zika virus is neurotopic and can cause Guillain-Barre syndrome [Cao-Lormeau 2016] and congenital microcephaly [Rasmussen 2016]. The 2015–16 global emergence of Zika virus infection was marked in Brazil by a total of 231,725 suspected cases, 137,288 confirmed cases and 2,869 confirmed cases of Zika virus congenital syndrome.

Development of safe and efficacious vaccines designed to prevent clinically relevant disease appears feasible. Zika vaccine development is progressing rapidly. WHO reported more than 40 Zika vaccine candidates under development. Overall, 12 phase-1 clinical trials including 6 candidates are near completion. Fast-track development of vaccine can be possible if

preclinical studies continue in parallel with human trials with an evolving target product profile [Thomas 2016].

Chikungunya has spread throughout the Caribbean and into much of Central America. Subclinical infections are reported in the majority of chikungunya infections [Yoon 2015], but approximately 5% of infected individuals will have prolonged manifestation of the disease. The development of vaccine faces several challenges that could hamper the set-up of clinical trials. This includes the sporadic character of chikungunya outbreaks, unclear clinical attack rate ratio, clinical disease phenotypes, incomplete understanding of disease pathogenesis and no known correlate of protection.

Chikungunya vaccine pipeline includes line attenuated, inactivated, subunit, DNA, virus-like particles/subunit and recombinant vectors vaccines [Smalley 2016].

Malaria

The spread of antimalarial drug- and insecticide-resistance continue to hamper malaria control efforts. RTS,S/ AS01, from GSK, is the only malaria vaccine candidate against *P. falciparum* to receive a positive opinion from the EMA so far, and provides modest protection in the first year but this wanes rapidly during subsequent years [RTS,S Clinical Trials 2015]. Studies are evaluating the development of a blood-stage malaria vaccine which could be used in conjunction with vaccines like RTS,S that target the preceding infectious liver-stage. *P. falciparum* reticulocyte-binding protein homologue 5 (PfRH5) has been shown to be susceptible to vaccine-induced broadly neutralising polyclonal antibody [Douglas 2011] and forms an essential interaction with basigin (CD147) on the erythrocyte surface [Crosnier 2011]. Detection of antibody with *in vitro* activity in assays of growth inhibition activity (GIA), the most common strategy for the selection of antigen candidates, showed that vaccine-induced GIA associates with *in vivo* protection in non-human primates [Douglas 2015]. First-generation PfRH5 vaccines are now in Phase I/IIa clinical trials with efficacy assessment by controlled human malaria infection. The first vaccine elicited strain-transcending antibodies in UK adults [Payne 2017]. A vaccine against *P. vivax* malaria is also required for use in Asia and South America, but few candidates are in the pipeline.

Tuberculosis

Tuberculosis (TB) has killed more than any other infectious disease [Paulson 2013] and has re-emerged due to evolution of the causative bacteria. The currently available vaccine, BCG, provides protection against disseminated forms of the disease [Roy 2014] and reduces all-cause mortality through beneficial non-specific (heterologous) effects on the immune system [Arts 2018]. However, the vaccine is not effective against the respiratory form, calling for the development of new vaccine. Currently, 13 vaccines, including also therapeutic vaccines are in the pipeline. Two strategies for new preventive TB vaccines are i) development of new vaccines based on recombinant BCG or based on attenuated *M. tuberculosis* as MTBVAC, and (ii) prime-boost strategy with BCG given to neonates, and a booster with the new subunit vaccine. Pre-clinical studies showed improved safety and efficacy of MTBVAC as compared to BCG [Marinova 2017], and this was associated with T-cell mediated response to CFP10/ESAT6 [Aguilo 2017]. Human phase 1 clinical studies reported robust safety, reactogenicity and immunogenicity similar to BCG [Spertini 2015] The primary objective for MTBVAC clinical development plan is a vaccine for new-borns and as a secondary objective to explore MTBVAC as vaccine for adolescent/adults.

Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

The emergence of MERS-CoV in 2012 was the second episode of the introduction of a highly pathogenic coronavirus into the human population. As of 1 Sep 2017, 2081 cases with 722 deaths (CFR 35%) have been reported in 27 countries. Dromedary camels are the primary host to humans and ongoing transmission from camels to humans is likely to continue, with consequent continuous epidemic risk. MERS-CoV epidemic potential was evidenced by the Korean outbreak where 3 index cases accounted for 136/186 reported cases [Kim 2016].

The development of effective therapeutic and preventive vaccine for this emerging disease is a research priority due to the absence of clinically approved vaccines or antiviral drugs. The WHO roadmap is to develop vaccine for reactive use during outbreaks, vaccine with long-term protection for high-risk population and dromedary camel vaccine in order to prevent transmission from the animal to humans [Modjarrad 2016]. Currently, several types of vaccine are in different phases of development. The most advanced candidate in development is the GeneOneMERS DNA vaccine (GLS-5300) that entered phase 1 first in human clinical trial (NCT02670187).

3. Vaccines for adults

Adult immunization is more complex due to several reasons including wide variety of target population (healthy young adults, adults and elderly people with chronic conditions, pregnant women, etc.), and diverse network of health-care providers. Barriers to adolescent and adult immunization are multiple ranging from lack of provider recommendation to lack of public knowledge, financial impediments and concerns about adverse events. As a consequence, challenges for increasing adult immunization should consider all the above-mentioned barriers.

Pregnant women

Maternal immunization confers i) direct protection to pregnant women who may be unimmunized, under-immunized, or have waning immunity; ii) reduces maternal carriage or transmission of pathogens from mother to foetus/new-born and iii) leads to passive immunity for the neonates through transplacental transfer of maternal antibodies [Sobanjo-Ter Meulen 2015]. However, comparison of vaccine safety data across studies is currently challenging due to the heterogeneity of definition used. The Global Alignment of Immunization safety Assessment in pregnancy (GAIA) project is a collaborative project that aims at improving the quality of outcome data from clinical vaccine trials in pregnant women by standardization of definitions and methods to conduct safety trials. Specific attention is given to needs and requirements for safety monitoring in low and middle-income countries [Bonhoeffer 2016].

Currently, influenza inactivated vaccine, acellular pertussis containing vaccine (Tdap) and the booster vaccine for tetanus and diphtheria (Td) are routinely recommended for all pregnant women in many countries [Perrett 2017]. The number of countries with policies for maternal influenza immunization increased from 15 in 2006 to 84 in 2014 [WHO-UNICEF joint reporting forms 2014], most probably as a result of concerns during 2009 H1N1 pandemic, reassuring results from studies that assessed the safety of influenza vaccine in pregnant women [Fell 2015, McMillan 2015, Bratton 2015], and recent data from clinical trials demonstrating the efficacy of maternal influenza immunization for preventing both maternal as well as infant influenza disease [Madhi 2014, Tapia 2016, Steinhoff 2017]. Maternal Tdap is recommended in the United States, several European countries, New-Zealand, Australia and some Latin

American countries [Gkentzi 2017]. As with influenza vaccination, studies of maternal Tdap immunization have not identified safety concerns [Gkentzi 2017, McMillan 2017], with the exception of an increased risk of chorioamnionitis reported by two studies [Layton 2017, Kharbanda 2015]. Increased concentrations of maternal pertussis antibodies induced by maternal immunization in infants have been shown to interfere with infant immune responses. However, the blunting effect resolved after the booster dose at 12 months in RCTs from the US [Munoz 2014] and Vietnam [Maertenset 2016]. The clinical implications of this phenomenon are unclear; however, effectiveness studies to date have found maternal pertussis immunization resulted in reduced infant pertussis disease [Amirthalingam 2014, Baxter 2017].

New vaccines under development for future implementation in the obstetrical population include Group B Streptococcus [Heath 2016, Madhi 2017], and respiratory syncytial virus (RSV) [Path 2017, August 2017]. RSV clinical trials show promising results so far: RSV vaccine was well-tolerated and immunogenic in Phase I and II studies in human adults (including women of reproductive age), and no infant adverse health effects resulted from maternal RSV vaccination [Karron 2017, Heath 2017, Munoz 2013, Omer 2017]. A Phase III international trial in pregnant women is currently ongoing until 2020 [www.clinicaltrials.gov: NCT02624947]. Evidence of protection against serologically-detected RSV infection in women of childbearing age has been reported [August 2017], however, there are still knowledge gaps on the optimal timing of vaccination, and interaction of maternal immunogenicity with other disease (e.g. malaria, HIV) [Heath 2017].

Travellers

The highest incidence rates of vaccine preventable disease among western travellers have been reported for influenza (1%) [Belderok 2013], followed by animal bits with risk of rabies (0.4%), latent tuberculosis (0.1%), typhoid, measles, pertussis, hepatitis A and B and tick-borne diseases [Steffen 2016, Steffen 2015].

Legally required travel vaccines are yellow fever, meningococcal required for haji and poliomyelitis for haji arriving from vulnerable states or people existing Pakistan and Afghanistan. However, routine vaccines (EPI catch-up) and recommended vaccines should also

be discussed during pre-travel consultations that be considered as an opportunity for adult immunization.

4. From vaccine to vaccination: the Asian perspectives

Thailand

In Thailand, the Expanded Program on Immunization (EPI) involves several partners in charge of financing, vaccine logistics, vaccine policy and disease surveillance. Vaccination coverage is monitored in 30-clusters every five years by health data centre. The results of the last survey showed high vaccine coverage for vaccines included in the EPI.

With regard to adults, priorities for vaccine introduction depend on age, health status (pregnant, elderly, medical morbidity, etc.), occupation and travel. Adult vaccine centres are available in private and public hospitals and adolescents can be vaccinated through school-based vaccination programs. Active call to vaccination, reminders, feedback to health care providers and evaluation of immunization activities are among action with evidence of efficacy to increase vaccine uptake. An adult immunization demonstration clinic has been established in 2017 in 4 districts in 4 provinces. The evaluation is ongoing and the scale up plan is 12 provinces in 2018.

HPV has been introduced nationwide in 2017 and will be evaluated for coverage rate in 2018. Rotavirus vaccine is recommended since 2015 but there are still some challenges for the introduction of this vaccine. Burden of disease, perception of diarrhoea, competing priorities, perception on disease prevention, lengthy new vaccines decision chain and financing for immunization are among these challenges. The national health security office has spent 1.29 billion Bahat for financing EPI vaccines. The budget impact for HPV and rotavirus vaccine is estimated to be 300 million and 420 million Bahat respectively.

Vaccines with highest prioritization are Tdap and influenza vaccine in pregnant women, MR in health professionals, DTwP-HB-HIB and DTwP-HB-HIB-IPV in children <5 years old.

Indonesia

According to the 1945 Constitution of the Republic of Indonesia on child protection, child immunization is compulsory. National immunization coverage has reached the target;

however, gaps are still found in some districts. Vaccine delivery and cold chain maintenance have been applied throughout the country (34 provinces, 514 districts and 9.705 Health Centres) and >90% is functioning. The national immunization plan targets for 2015-2019 are to i) maintain status of poliomyelitis free, maintain status of neonatal and maternal tetanus elimination, iii) meet global and regional targets for measles elimination and rubella control and iv) introduce new vaccines (MR, HPV, PCV and JE). To achieve each of the above-mentioned targets, innovative national strategies have been set-up. However, vaccine coverage is still various throughout the country due to many hard-reach areas, lack of community's awareness and knowledge of immunization and anti-vaccine movements. Introduction of new vaccines could face difficulties due to high prices and limited local budget. Technology transfer of new vaccines could assure access to affordable vaccines.

Malaysia

Immunization program in Malaysia has been included in the Maternal and Child Health program since 1950s. Vaccination is given free for all children. For non-Malaysian, vaccines are given free during outreach programs, mopping-up activities and supplementary immunization activities. MR, DT, tOPV, HPV and tetanus vaccines are delivered through school health services. Vaccines for adults include hepatitis B (health care professionals), influenza (health care professional frontline), typhoid (food handlers), meningococcal (pilgrims), yellow fever (travellers) and cholera (outbreaks in Sabah). Immunization coverage is quite high in Malaysia, however, vaccine hesitancy started in 2012-2013 in a small group and spread across social media. According to the data from governmental clinics and hospitals, main reasons for refusal are religious reasons, doubt of content and homeopathy practices. The consequences of drop in uptake resulted in increased outbreaks of vaccine preventable diseases. To face the anti-vaccine movements the ministry of health launched several initiatives by Provisioning Immunization Kit to aid the efforts in educating the public, training of Vaccine Advocators among the Family Health Specialist/Doctors/Paramedics, ongoing forums and seminars conducted by states in collaboration with other agencies at the local level and by promotion through mass media and social media. In addition, an initiative spearheaded by the Ministry of Health has started to address the issue of vaccine refusal in the community and to strengthen the National Immunisation Program in Malaysia. The campaign aims to empower the community by pro-vaccine messages to reach all. MOH needs to continue the

collaborative effort with other agencies and religious bodies and the social media, given the complexity of vaccine hesitancy and the limited evidence available on how it can be addressed. Identified strategies should be carefully tailored according to the target population, their reasons for hesitancy, and the specific context.

Sri Lanka

The National Immunization Programme(NIP) established in 1987 included measles and rubella vaccine and has been extended to 6 more vaccines after 2000. This has led to significant reduction in the incidence of several vaccine preventable diseases such as poliomyelitis and tetanus. Total health care service is free of charge in Sri Lanka where the government is totally funding for all vaccines except GAVI funded vaccines. The country has been certified as a GAVI graduated country in 2015. Private sector contribution in immunization service is minimum (5%). Sri Lanka has been declared free of neonatal tetanus and poliomyelitis in 2009 and 2014 respectively. Congenital rubella syndrome is near elimination.

The ministry of health plays the central role in the organisation of NIP that also include regional, district, and divisional levels. A home-based “child development record” issued at birth allow to record all immunization. Pre-vaccination screening in health offices are organised in order to educate parents, to perform vaccination and to observe for potential adverse effects. A web-based software is used to gather information on immunization, to perform regular monitoring and to provide feedback to health care professionals by epidemiological reports and bulletin. Decisions on schedule changes and the introduction of new vaccines are based on evidences from monitoring, serosurveys and disease burden studies.

5. Today’s immunization programs: challenges and strategies to move forward

Today’s immunization program faces several challenges at individual and policymaker level.

At individual level, misinformation and the subsequent misperception about safety concerns is one of the drivers of extensive growth of antivaccine movements, vaccine hesitancy and vaccine refusal. Indeed, poor understanding and false assumptions of causal associations based solely on temporal relationships, errors in vaccine reconstitution and vaccine supply has

led to the launch of unfounded safety concerns [Gessner 2017; Ueda 2015; Colafrancesco 2013, Wijnans 2013; Atanasoff 2010]. Vaccine refusal can be the start of outbreaks [Phadke 2016] and social media play a key role in providing misinformation to the public. This causes irreversible damage on public health and can take years to repair. It has been shown that once installed, correction of myths about vaccines may not be an effective approach to promoting immunization [Nyhan 2015]. The belief caused by a previously published and retracted paper on the relationship between MMR vaccine and autism led to a sharp drop in vaccination coverage and consequently an increase of measles outbreaks in several parts of the world. To address serious adverse effects (SAEs), Journal editors should institute standard criteria for accepting causality assessments in case reports, all countries should have a standing committee to review SAEs and methods for assessing SAEs should be standardized. An algorithm can help in assessing SAEs in a standardized and transparent way which can be reconsidered in case of additional information [Hasley 2012].

The format in which providers initiated vaccine discussion has been shown to be a predictor of decision. A presumptive approach [Opel 2013] or cognitively-based approach led to vaccine acceptance among initially hesitant individuals. Talking about the disease risk salience, anticipating regrets about the consequences of making the wrong decision and ending with vaccine efficacy has also been shown to positively impact vaccine's behaviour [Horne 2015, Sadique 2013]

At policymaker level, the major challenge for vaccine community is to conceptualize the full benefits value of vaccines and to accurately communicate this value. Assessment of full public health value of vaccines should include measures beyond efficacy and a broader economic evaluation of vaccines

The benefits of vaccines are usually evaluated based on risk: benefit ratios, as measured only by vaccine safety and efficacy against etiologically confirmed disease. However, more robust approach is needed to measure the full public health value of preventive vaccines. Measures such as vaccine preventable disease incidence (VPDI) [Gessner 2017, Wilder-Smith 2017, Gessner 2014], number needed to vaccinate (NNV), the use of vaccine probes studies [Feikin 2014] and modelling may provide further information to inform economic assessment of vaccines. As an example, randomized-placebo controlled trial showed lower rotavirus vaccine

effectiveness in Malawi than in South Africa (49.4% vs. 72%); while the number of prevented episodes of severe rotavirus gastroenteritis was greater in Malawi than in South Africa (67 vs. 42 per 1000 infants vaccinated per year) [Madhi 2010]. Moreover, VPDI value in these African countries was greater than those estimated in high and middle-income countries where vaccine effectiveness was higher. Test-negative design studies and enhanced active surveillance are also valuable tools to assess vaccine benefits and risk [Ali 2013, Brotherton 2016, Blyth 2016, Blyth 2016b]. The SMAT vaccines 2.0 is a software being developed to support decision-making among stockholders [Knobler 2017].

Monetizing the impact of vaccination provides policymakers with sufficient information to make well-informed decisions about including other new vaccines in national immunization programs. Until recently, economic evaluations of vaccines were focused on a narrow view of benefits (i.e., avoided medical costs). A broader perspective includes outcome-related productivity gains, behaviour-related productivity gains, herd effect, and utilitarian value of health gains [Barnighausen 2014]. In a randomized controlled trial in Bangladesh, antenatal tetanus immunization led to an increase of 0.25 years of schooling among children whose parents had no schooling and a population-wide average gain of 1.2% [Canning 2011]. By taking into account reduced spending on outbreak control, averted losses in tourism flows, and avoided productivity losses due to long-term dengue sequel, introducing dengue vaccine in national immunization programs in Brazil would more than double the narrow benefit calculation, allowing twofold return on the investment [Bärnighausen 2013]. Similar conclusions can be drawn for human papilloma virus (HPV) vaccination if the full benefits of vaccination are captured [Bärnighausen 2012]. Analysis of immunization programs in low and middle-income countries provided evidence of positive return on investments for 10 child vaccine preventable diseases [Ozawa 2016].

6. Conclusions

Vaccines are the most inexpensive means of improving health and lowering morbidity and mortality caused by infectious diseases. In spite of significant advances in science and technology, the implementation of global vaccination coverage remains a pipe dream because many obstacles and challenges remain. The nature of challenges varies and can be medical

and scientific (e.g. concerns about safety), structural and demographic (e.g. poor infrastructure), economic and political (e.g. limited resources and high cost) or societal and cultural (e.g. anti-vaccine sentiments).

Country's capacity to introduce new vaccines face the following challenges:

- Extensive involvement of policy makers and technical experts
- Updating guidelines, National and district level advocacy meetings, trainings etc.
- Effective vaccine management
- Cold chain capacity
- Budget allocation for new vaccine introduction
- Gavi support and post Gavi era

The universal immunization programs can be extensively improved by taking into consideration all the above-mentioned issues and by providing policymakers measures beyond vaccine efficacy and a broader economic evaluation of vaccines.

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