Vaccine update: Recent progress with novel vaccines, and new approaches to safety monitoring and vaccine shortage

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Abstract

Vaccines are increasingly based on new constructs, new technologies, and new compounds. Novel immunization programs are rapidly implemented globally. In this article, we highlight selected hot topics of this highly dynamic and broad field of scientific and public health development. A first section focusses on novel vaccines including malaria, dengue, serogroup B meningococcal, and RSV vaccines and antibodies. A second section is addressing emerging strategies and programmatic challenges including maternal immunization, integrated mother-child safety monitoring, and finally coping strategies with vaccine shortages.

Introduction

The vaccine development pipeline has never been more proliferative. Technological advances are bringing forth a progressive array of vaccine constructs and compounds. Global access to life-saving vaccines is being promoted actively and implementation of novel immunization programs worldwide is becoming increasingly concerted. It can be challenging for clinicians and clinical pharmacologists to follow this highly dynamic and broad field of science and public health development. In this article, we have selected hot topics with practical relevance for clinicians and clinical pharmacologists.

We provide an update on the malaria and dengue that have received a positive opinion/have been licensed for use in endemic regions. The malaria vaccine is of particular interest as it is the first vaccine against human parasitic disease of any kind, for its mechanism conferring immunity to *P. falciparum* and the regulatory process at the European Medicines Agency (EMA) facilitating access to the vaccine in endemic countries outside of Europe. It is also an instructive example of how a vaccine with relatively low efficacy and effectiveness may still be a contributing element or “piece of the puzzle” of a comprehensive disease prevention program. We chose to update on the dengue vaccine as it was long awaited and is an exquisite construct mastering many challenging requirements of a vaccine against this complex infection – a high wire act. While it showed promising efficacy, important safety have emerged and are currently limiting its indication and lowering expectations on is impact on global burden of disease. Novel serogroup B meningococcal vaccines complement the toolbox against the global burden of meningococcal disease. Much can be learned about regional experience and considerations for global vaccines by looking at the European experience and considerations with these vaccines. In spite of the availability of a safe and effective vaccine, universal immunization is still a distant prospect. We are providing an overview of key considerations in the current debate pertinent to many regions. Prevention of RSV is a promising approach to reducing morbidity and mortality in pregnancy and infancy. With a new RSV vaccine approaching licensure, we present the latest developments of vaccine candidates and approaches to confer passive immunity to RSV by anti- and nanobodies representing elements of a multi-pronged approach including treatment options. Immunization in pregnancy is indeed a hot topic beyond RSV vaccine. In addition to the increasing number of vaccines with indication in pregnancy, one of the most challenging aspects is integrated mother-child safety monitoring. We outline current needs and solutions. Finally, we highlight the emergence of global supply issues and practical aspects of coping with increasing vaccine shortages.

Progress in the development of Malaria Vaccines

A piece of the puzzle

Malaria is one of the leading causes of morbidity and mortality in low and medium income countries. In 2015 there were about 215 million cases globally with 88% of them occurring in Africa, 10% in South East Asia and 2% in the East Mediterranean region.[1] In the same year, approximately 438,000 malaria deaths were reported, with children under five years accounting for 306,000 of the deaths. A malaria vaccine can reduce the burden of disease and possibly eliminate malaria, particularly when malaria vaccine programs complement existent interventions.[2]

The development of a prophylactic vaccine against malaria

To identify and understand the type of immune responses associated with protection against malaria remains challenging. Thus, different candidates are being pursued targeting different stages in the parasite lifecycle. [3]

The RTS,S/AS01 vaccine (GlaxoSmithKline, Rixensart, Belgium) targets the pre-erythrocytic form of *Plasmodium falciparum*, the deadliest of the plasmodium species pathogenic to humans. It is the most advanced vaccine against malaria and is the first and only vaccine to be studied in a phase III trial in Africa, the region with the highest malaria disease burden.[4] The vaccine contains sequences of the circumsporozoite protein found on the surface of the sporozoite. The R and T regions of the circumsporozoite protein are bound to Hepatitis B Surface antigen (HBsAg) and this combination is co-expressed with free HBsAg in yeast to form the virus-like particle: RTS,S.[5] This antigen is adjuvanted with AS01, a proprietary liposome-based vaccine adjuvant, containing two immune-stimulants: 3-O-desacyl-4-monophosphoryl lipid A (MPL) and saponin QS-21.[6] This combination enhances and sustains a protective immune response. The vaccine aims to prevent the invasion of sporozoites into the hepatocytes and subsequently reduces the blood stage parasites that are responsible for clinical manifestations of malaria.[5]

Development of the RTS,S vaccine started as early as 1984 when GlaxoSmithKline and the Walter Reed Army Institute of Research, a public-private partnership, pioneered the use of a HBsAg carrier matrix for the circumsporozoite central regions of *Plasmodium falciparum* (Figure 1).[7] Sustaining the development process was possible through continued collaboration between organizations sharing the same goal in the quest to develop a potent novel malaria vaccine.[8]

Results of the pivotal trials

The RTS,S/AS01 phase III trial was conducted in 11 sites in seven countries in sub-Saharan Africa and was primarily designed to evaluate vaccine efficacy, safety, and immunogenicity during an average of 41 months after the first dose of the study vaccine in young infants and an average of 49 months in children.[9] Participating infants and children were randomly assigned to receive three doses of RTS,S/AS01 at months 0, 1, and 2 months, followed by a 4th dose booster or active control at month 20. A second group received active control vaccines. [10]

Local reactions such as pain and swelling together with systemic complications such as fever were common in participants who received the vaccine as compared to those who received the comparator vaccine.[11] The incidence of febrile convulsions was similar in RTS,S vaccine recipients and controls.[9] Meningitis cases were found to be more common among children who received the RTS,S vaccine[9], and further investigations were undertaken .[11]

Over the four years of RTS,S/AS01 Phase III trial follow-up, vaccine efficacy was 36.3% (95% confidence interval [CI], 31.8 to 40.5) in children aged 5 to 17 months who received all four doses and 28.3% (95% CI, 23.3 to 32.9) among those who received three doses. After 38 months of follow-up, vaccine efficacy in infants (6 to 12 weeks of age) who received the fourth dose was 25.9% (95% CI, 19.9 to 31.5) and 18.3% (95% CI, 11.7 to 24.4) among those who did not receive the fourth dose.[12] Importantly, among the children who received 4 doses of the malaria vaccine, 1774 cases of clinical malaria per 1000 children (95% CI 1387-2186) were averted; while in the 3-dose group 1363 per 1000 children (95% CI 995-1797) cases were averted. In young infants (6 to 12 weeks of age), 983 per 1000 cases (95% CI 592-1337) of clinical malaria were averted after four doses and 558 (158-926) after three doses. [10]

HIV positive children in WHO clinical stage 1 or 2 on antiretroviral therapy and co-trimoxazole were found to tolerate the RTS,S/AS01 malaria vaccine well. This renewed confidence in future RTS,S/AS01 vaccine studies and programs involving children with HIV to be pursued.[13]

While the RTS,S/AS01 vaccine was shown to confer limited efficacy in both children and infants and limited duration of immunity [14], it is nevertheless expected to have a significant

impact on the high disease burden of this deadly parasitic disease.[15] A malaria vaccine mathematical model showing the supply and demand forecast and the impact on public health and financial costs projected that 150 million uncomplicated malaria cases and 1.1 million mortalities would be averted through vaccination over a period of 10 years.[15] In July 2015, EMA's Committee for Medicinal Products for Human Use (CHMP) and the World Health Organization (WHO), through the Article 58 procedure, adopted a positive scientific opinion for the use of the RTS,S/AS01 vaccine in markets outside the European Union. [16] This was to protect children 6 weeks to 17 months of age in malaria endemic countries against *Plasmodium falciparum* infections together with other interventions such as insecticide treated nets, residual spraying and use of Artemisinin Combination Therapies (ACTs).[16] Based on this EMA opinion, a WHO policy recommendation was made supporting national regulators in endemic countries to consider licensure.

WHO recommendations

The WHO Strategic Advisory Group of Experts on Immunization and Malaria Policy Advisory Committee made recommendations to guide the further evaluation of the candidate malaria vaccine. The committee suggested that infants aged between 6 and 12 weeks of age should not receive the vaccine due to the low vaccine efficacy observed during the Phase III vaccine trials in that age group. It was recommended that the four dose schedule should be used in pilot implementation studies of children 6 weeks to 17 months in 3 to 5 moderate to high malaria transmission epidemiological settings in sub-Saharan Africa.[17] Ghana, Kenya and Malawi are partnering with the WHO to make the vaccine available in these countries beginning 2018. By 2020, the Malaria Vaccine Implementation Program should provide insights into the feasibility of delivering the vaccine and its safety profile. With support from WHO, pharmacovigilance centers in the different countries will be involved in Phase IV studies and will collect safety data including rare and serious adverse events.[16]

Conclusion

Even a partially protective vaccine may prove to be a valuable asset in preventing malaria parasite transmission, particularly in high risk populations. The RTS,S/AS01 vaccine may provide protection with short-term efficacy due to rapidly waning immunity. Further research should provide a better understanding of the vaccine's immunogenicity and safety profiles. [17] The pursuit of other vaccine approaches remains important in the search for answers to the many remaining questions around effectively preventing malaria by immunization.

Progress in the development of Dengue vaccines - A high wire act

The incidence of dengue has increased dramatically over recent decades with close to 100 million clinical cases out of a total 390 million dengue infections occurring worldwide every year. More than half of the world's population in 128 countries is at risk of Dengue infection.[18,19] The risk of developing severe dengue (Dengue Hemorrhagic Fever; DHF) has historically been greater in children ≤ 15 years with a gradual shift towards those ≥ 15 years of age in the last decades.[20] Travelers returning from endemic areas can import the disease, and local transmission has been observed outside of endemic areas on occasion when conditions allow for the presence of the mosquito vector.[20 21]

In the past, the only options to control or prevent dengue virus transmission were through interventions directed at the vector. However, problems regarding the widespread implementation, sustainability, and cost remain.[22] Thus, immunization remains an important tool to reduce the disease burden, morbidity and mortality of Dengue.

The development of a prophylactic vaccine against Dengue

Among the candidate dengue vaccines currently in development, the most advanced is a recombinant, live-attenuated tetravalent dengue vaccine (CYD-TDV; Dengvaxia®) developed by Sanofi Pasteur. [23] It was first licensed in Mexico 2015 for use in individuals aged 9 - 45 years of age, living in endemic areas.[24] The vaccine contains 5 log 50% cell culture infectious dose (CCID50) of each live attenuated recombinant dengue virus serotype (DENV 1-4) based on the yellow fever vaccine 17D (YFV 17D) backbone. It is provided as a freeze dried powder to be reconstituted in 0.4% sodium chloride. [25]

CYD-TDV was evaluated in 18 clinical trials including two parallel pivotal efficacy trials, known as CYD14 and CYD15. CYD14 was conducted in 5 countries in Asia (Indonesia, Malaysia, Philippines, Thailand, and Vietnam), at various sites with 10,275 participants aged 2-14 years[26]. Taking into account the regional epidemiology, CYD15 was conducted in 5 Latin American countries (Brazil, Colombia, Honduras, Mexico, and Puerto Rico (USA)), with 20,869 participants aged 9-16 years.[27] In each of these trials, participants were randomized at a ratio of 2:1 to receive either vaccine or placebo at 0, 6 and 12 months. Participants were actively followed-up for 25 months after the 1st dose with a long-term follow up (LTFU) of 4 years after the 3rd dose.[26,27] The pooled vaccine efficacy against virologically confirmed dengue in those who were 9 years or older during the active phase of surveillance (25 months) was 65.6% (95% CI, 60.7 to 69.9).[28] Importantly, vaccine efficacy against severe dengue was observed as 93.2% (95% CI, 77.3 to 98).[28] The pooled vaccine efficacy was

higher among those who were seropositive at baseline as compared to those who were seronegative at baseline: 81.9% (95% CI, 67.2 to 90.0) and 52.5% (95% CI: 5.9 to 76.1), respectively.[28] Efficacy levels varied against the individual serotypes (83.2%, 73.6%, 47.1% and 58.4% for serotype 4, 3, 2 and 1 respectively).

An integrated safety analysis performed in the 9-60 years of age (20,667 subjects) who had received at least one dose of vaccine showed no safety concerns related to the nature and frequency of unsolicited adverse events. Headache, myalgia, injection site pain, malaise and fever were the most frequently reported adverse reactions (>10%). Rash was reported in <1% of vaccines.[29] The details are shown in figure 2.

Furthermore, in the phase III trials, the frequency of serious adverse events was observed to be similar in the vaccine and placebo groups with 5% and 6%, respectively, observed in the CYD14 trial, and 4.1% and 4.4%, respectively, in the CYD15 trial.[26,27,30] Although a hypothetical risk of acute viscerotropic or neurotropic disease remains due to the Yellow Fever 17D backbone; no cases have been detected so far. Based on current data, neither vaccine-related deaths nor serious adverse events were reported. Assessment of viremia and immune profiles (cytokines, chemokine and growth factors) among hospitalized dengue cases due to any serotype in these trials showed no difference between the vaccine and placebo groups.[27,31] This indicates that the vaccine did not appear to induce host-immune responses with more pronounced dengue disease after a second dose as described following subsequent wild-type virus infections.[32] However, post hoc analyses of trial data suggested a sustained excess of hospitalized and severe dengue in seronegative patients starting two years after receiving Dengvaxia®.

Implementation

Recently, a dengue school-based immunization program was conducted in the Philippines in 729,110 children aged nine years and older attending public schools (2015-2016 school year).33 The results showed an acceptance rate of 74% and an uptake rate of 91% with the main adverse events being fever, dizziness and headache after the first dose at a rate of 8.13, 5.84 and 5.14, per 10,000 vaccine recipients respectively. The adverse event rates after immunization (AEFI) were decreased to about half or lower after the second dose (4.24, 2.24 and 1.43 per 10,000 vaccinees for fever, dizziness, and headache, respectively) as shown in Table 1. Similar AEFI were reported in the implementation progress in Brazil.34,35 These large-scale, successful vaccine introduction programs can serve as a benchmark for dengue prevention efforts elsewhere. Due to the latest product safety

concerns, however, the manufacturer has recommended to limit use to individuals with prior dengue virus infection and the immunization program in the Philippines was stopped.

WHO recommendations

The WHO recommends that the potential safety issues should be taken into consideration in the assessment of a dengue vaccine and its long-term safety surveillance. Issues include possible vaccine associated dengue-like disease due to vaccine viremia and any enhancement of dengue illness.[36] WHO further recommends vaccination of populations with a seroprevalence between 50% and 70% where epidemiological data indicate a high burden of disease.[24] Data on the baseline seropositivity to dengue obtained from the phase III clinical trials of CYD-TDV in Asia Pacific and Latin America showed rates ranging from 53% to 92% across pediatric age groups (2-16 years and 9-16 years [37]), highlighting the high disease burden in dengue-endemic countries. However, WHO recommends that each country should define the target age group. Routine immunization should be considered between 9 and 45 years of age.

In an updated information, WHO recognizes that preliminary data suggest a significantly increased risk of hospitalized and severe dengue among vaccinated individuals who were seronegative for dengue at the time of first vaccination in all age groups. WHO will conduct a full review of the data through the Global Advisory Committee on Vaccine Safety and SAGE, for revised guidance of the use of Dengvaxia®. Pending the full review of the data, as a precautionary and interim measure, WHO recommends that Dengvaxia® is only administered to individuals that are known to have been infected with dengue prior to vaccination.[38]

Remaining challenges

The post-licensure plan is critical to evaluate the long-term efficacy and safety of the vaccine in the real world.[39] Further information is needed on the duration of protection as well as co-administration of the dengue vaccine with other vaccines used in public health immunization programs in older children (e.g., HPV, Influenza and Td/TT/Tdap).[40,41] It will be challenging to have appropriate pharmacovigilance systems in place in all countries at the time of the dengue vaccine introduction. The availability of seroprevalence data on children and adults above nine years of age before implementing immunization programs is complicated by the

fact that not all countries have access to the latest diagnostic tests and thereby rely mainly on clinical assessments and passive reporting, which may vary. Serological assays are used more widely but can lead to false positive results during post-vaccination surveillance.[42] With most surveillance unable to detect every dengue case, the capacity to monitor program baseline rates and success of disease prevention remains limited.

Conclusion

Based on available data, the licensed CYD-TDV vaccine appears efficacious especially in reducing the severity of dengue disease and reduced hospitalization during active surveillance in the 25 months after the first dose. Adverse events were mostly mild to moderate in nature and no differences in the clinical signs and symptoms nor the virological or immunological profiles among dengue cases in the vaccine or placebo groups were observed. The concern of increased risk of hospitalized and severe dengue among seronegative vaccinees is being evaluated and will influence WHO and national policy recommendations. While access to an effective dengue vaccine is most desirable, many countries remain cautious in the introduction of CYD-TDV.[43] It will be important to see whether any of the candidate vaccines still in development will achieve licensure and widespread adoption in the coming years.

Universal Immunization against serogroup B meningococci in Europe- a distant prospect

Prevention of invasive meningococcal disease becomes a desire of every health care provider who has ever cared for a patient experiencing this devastating condition. In 1999/2000, the the first conjugate vaccine against serogroup C meningococci (MenC-CV) was introduced in the UK. Subsequently, many other countries followed the successful example of the UK campaign.[44] A substantial reduction of the burden of meningococcal disease was feasible by mass vaccination of pre-specified target populations with conjugate vaccines directed against prevalent meningococcal serogroups. The conjugate vaccines showed clinical effectiveness, but limited duration of immunity and efficacy, particularly in the first year of life. Thus, booster vaccinations were introduced in the second year of life and in early adolescence.[45] A key factor for the effectiveness of conjugate vaccines against meningococci group C was their impact on the colonization with this pathogen in vaccinated subjects. Similar to the UK, the vaccination campaign in the Netherlands starting in 2002

demonstrated that a vaccination coverage above 95% in the target population (14 months through 18 years) was associated with herd immunity protecting the entire population including unvaccinated individuals.[46]

However, group C meningococci are not the most frequent serogroup causing invasive meningococcal disease globally. Also, strain distribution differs by region and over time.[47] The next logical step was the development of conjugate vaccines containing additional serotypes. MenA-CV (MenAfriVac) fundamentally changed meningococcal epidemiology in sub-Saharan Africa by reducing the impact of epidemic and hyperendemic meningococcal serogroup A disease in the African "meningitis belt".[48] Combination conjugate vaccines against meningococci of serogroups A, C, W, and Y (MenACWY-CV) allowed for a further broadening of the serogroup coverage and thus an adaptation to the geographic variation of serogroup distribution and epidemiologic changes over time. These combination vaccines demonstrated efficacy comparable to the monovalent group C vaccines. Their global epidemiological importance may increase, as currently several countries experience an increases of group W and Y strains, partially due to the occurrence of hypervirulent clones (e.g., cc-11 after capsular switching).[49a]

The important Serogroup B has not been assailable by a vaccine until recently, as the conjugation of capsular polysaccharide antigen used for all other serogroups is not feasible against serogroup B meningococci. Like group C polysaccharide, the group B capsular antigen is a homopolymer of sialic acid, but the group B polysaccharide shows antigenic similarity to human neural antigens, which leads to immunotolerance. While this may at least partially explain the endemic predominance of group B meningococci, the use group B polysaccharide also bears the risk of inducing autoimmune reactions. Therefore, development of vaccines against serogroup B meningococci (MenB) required new antigenic approaches.

Protein-based vaccines against serogroup B meningococcal disease

In response to two recent outbreaks of meningococcal B disease, two different MenB vaccines using protein surface components as antigens were developed and approved by FDA and EMA: MenB4C (Bexsero®, Novartis/GSK) and MenB-FHbp (Trumenba®, Pfizer). MenB4C contains four different antigens identified as pathogenetically significant by reverse vaccinology, a genetic approach predicting the epitope by analyzing the genome of pathogen. In Europe, it is currently approved by EMA for the prevention of meningococcal group B disease in individuals two months and older - vs 10 years and above in the US.

MenB-FHbp consists of 2 distinct subfamily variants of the meningococcal factor H binding protein, a factor which downregulates human complement activity, the major defense mechanism against invasive capsular pathogens. Its indication granted by EMA is currently limited to individuals 10 years and older – this is in line with the US license. Both MenB vaccines may cover the majority of circulating meningococcal group B strains in various countries around the world, based on multiple and extensive epidemiological analyses using human serum bactericidal activity (hSBA) as a surrogate efficacy endpoint.

Clinical experience with MenB vaccines is limited so far. In September 2015, the UK Joint Committee on Vaccination and Immunisation decided after extensive and repeated evaluation to recommend the systematic use of MenB4C (Bexsero®) in all infants, using a two-dose priming schedule at the age of two and four months, followed by a booster dose at two years. Preliminary results, evaluating the effect of the two priming doses with a high vaccine coverage of ≥85%, showed a vaccine effectiveness of 82.9% against all MenB cases, equivalent to a vaccine effectiveness of 94.2% against the highest predicted MenB strain coverage of 88%. Compared to the pre-vaccine period, there was a 50% reduction of the incidence rate in MenB cases in the vaccine-eligible cohort, irrespective of the vaccination status or the predicted MenB strain coverage. As vaccine effectiveness was only 22.0% after the first priming dose, it appears that MenB4C vaccine shows good short-term effectiveness after a 2-dose priming schedule in infants, given a high vaccination coverage with at least 2 doses. The effect of MenB vaccines on colonization in a post-outbreak prevention setting has shown rather disappointing results so far. Serial evaluations of colonization after a vaccination campaign in university students vaccinated with either MenB4C or MenB-FHbp after a local MenB outbreak have failed to show an impact of vaccination on MenB colonization for both MenB vaccines [49b,49c].

Is a general vaccination against serogroup B meningococci with the current protein-based vaccines justified?

Though total meningococcal prevalence and serogroup distribution differ considerably between the countries, Group B meningococci have remained the most frequent serogroup in most European countries over the last decades. Many countries have seen a decline in their overall meningococcal incidence rates over time. This decrease can only partially be explained by immunization control programs against non-B serogroups, as serogroup B could not be prevented until recently. Other factors, including decreasing family size, less smoking, changed adolescent social behavior may play an important role in this development.

What might currently be the arguments for and against the introduction of national meningococcal group B immunization programs?

- Despite the continuous drop of incidence over the last years, the burden of disease of serogroup B meningococcal disease is currently still at least as high as it was for serogroup C when the MenC vaccination programs were introduced.
- MenB4C has shown clinical effectiveness against MenB in UK infants.
- The two currently available MenB vaccines have shown immunogenicity against the majority of circulating MenB strains in various countries around the globe, including European countries. However, immunity seems to decrease over time.
- So far, there is no evidence for an effect on colonization. This would limit the impact of MenB vaccines to the direct effects in vaccinated individuals, and thus substantially reduce the impact on the entire population (no herd effect) and the cost-benefit rates.
- Both licensed MenB vaccines require multiple doses, according to age and/or individual risk factors. The tempting prospect of a one-shot coverage, as it is possible for anti-capsular vaccines against serogroups A, C, W, and Y in individuals from the age of one year is thus not feasible.
- The non-capsular, protein antigens included in both vaccines are also expressed by other, non-serogroup B meningococci. The impact of these “universal” antigens may therefore well go beyond MenB only (Ref).
- Vaccine manufacturers are currently developing pentavalent combination vaccines (MenABCWY), which may facilitate the administration of a full meningococcal coverage, though for the MenB component, still, at least two doses will be necessary.
- The perception of health care providers and the public of the dreadful clinical picture in individuals affected with invasive meningococcal disease may foster the wish to implement prophylactic vaccination against MenB, despite the high costs for such a program.

Progress in Vaccines and Antibodies against RSV-

A Multi-pronged approach

Respiratory syncytial virus (RSV) is an enveloped, single-stranded RNA pneumovirus from the *Paramyxoviridae* family. Two antigenic subgroups, A, and B infect humans as they co-circulate during seasonal winter epidemics. Among the eleven proteins encoded by the RSV genome, the F – fusion, and G- attachment, surface glycoproteins are the determinants for viral infection, pathogenesis, and immunity through the production of neutralizing antibodies that provide immediate and relatively short-term protection against RSV infection.[50] Recurrent infections occur throughout life.

For decades, RSV has been the most important cause of lower respiratory tract illness (LRTI) in children in the first two years of life, in the US and worldwide.[51-54] Importantly, RSV bronchiolitis and pneumonia are recognized, substantial causes of infant mortality, particularly in low-income and middle-income countries.[52,53] Globally, a recent study estimated that in 2015, approximately 33 million episodes of RSV related acute LRTI resulted in 3.2 million hospital admissions and nearly sixty thousand in-hospital deaths in children younger than five years of age.[53] Among these, deaths associated with RSV in the first six months of life are estimated to range between 20,000 and 36,000. [53] While the presence of co-morbidities such as chronic lung disease, congenital heart disease, prematurity and others are more commonly observed in fatal cases in high-income countries (~70% of deaths associated with co-morbidities), in other settings, particularly in low-income and middle-income countries, the majority of deaths occur in otherwise healthy infants (less than one third have associated co-morbidities).[54] Furthermore, the potential for long-term consequences of RSV infection in early life, e.g. recurrent wheezing and asthma, has been raised.[55] Antiviral agents with activity against RSV are currently in development. Stakeholders, including scientists, academicians, industry, funders and regulators are invested in the development of safe and effective novel antibodies and vaccines for the prevention of RSV infection in high-risk populations, including infants in the first few months of life, as the main intervention strategy to reduce the burden and impact of RSV globally.[56-58]

Treatment options for RSV

Currently, supportive care is the mainstay of the management of infants and young children with RSV bronchiolitis.[59] Administration of oxygen and maintaining an adequate hydration status are recommended in most patients who require medical attention, while some patients

with severe disease may require different levels of mechanical ventilatory support. While approved for the treatment of RSV, Ribavirin, a guanosine analog antiviral agent with broad spectrum of activity against RNA viruses, is not widely used due to its complex requirements for administration through nebulization and limited clinical benefit unless started early in the course of the disease. A number of new antivirals with activity against RSV are under development and evaluation in phase I and II clinical trials in adults and children, as well as in high-risk stem cell and lung transplant populations.[60] The main target for antiviral drug development is the RSV F protein. Prevention of RSV infection and severe disease, and potentially its long-term consequences such as recurrent wheezing and chronic lung disease, is currently the most important focus of research.

Prevention of RSV through passive antibodies

Epidemiologic studies demonstrated the protective effect of maternally derived, transplacentally acquired antibodies in delaying the onset and decreasing the severity of RSV disease in infants.[61] In 1996, the first polyclonal antibody product (RSV-Immunoglobulin intravenous) was licensed in the US for prevention of RSV in high- risk infants, including premature infants with bronchopulmonary dysplasia (now chronic lung disease of prematurity), after clinical studies showed a reduction of RSV hospitalizations by 41% and also a 53% decrease in length of hospital stay (reduced severity) in this population.[62] In 1998, the humanized monoclonal IgG1 antibody to the RSV F-protein, palivizumab, safer and 50-fold more potent than RSV-IG to neutralize RSV, was licensed. Palivizumab is directed to the antigenic site II on the F protein of both RSV A and B, and binds to a conserved central region of the F protein.[50] The American Academy of Pediatrics recommends five monthly doses of palivizumab during the winter months for all premature infants born before 29 weeks of gestation and for other high-risk populations including premature infants with chronic lung disease of prematurity, infants with hemodynamically significant heart disease, the immunocompromised, and other high-risk conditions.[63]

Other polyclonal antibodies with high titers of IgG against RSV have been developed and are under evaluation. (Table 2). However, monoclonal antibodies and nanobodies are the primary focus of current research, and are in various phases of development, from pre-clinical to phase III clinical trials.[50] (Table 2 and Figure 3) Although multiple antibodies and their targets are being evaluated, in general, monoclonal antibodies target viral epitopes in the F-protein of RSV, and more recently, the pre-F protein, a conserved pre-fusion conformation that is the active form of the F-protein on the surface of the RSV virion, resulting in potent neutralization of RSV and other paramyxoviruses. Specific antigenic sites

of interest include antigenic site 0 and site II, and multiple products are in early phases of development, from discovery to pre-clinical. [50,64] Nanobodies are described as small antibody fragments that consist of a single monomeric variable domain of the heavy chain, and which have antigen binding capacity and similar activity as conventional antibodies. However, they are easier to produce and their small size and stability permits the creation of multivalent constructs to bind to specific antigenic sites and the option of mucosal (intranasal/inhaled) instead of systemic administration.

Palivizumab, which has now been found to neutralize both the pre-F and the post-F forms of the F protein, resulting in high potency and effectiveness, remains the only licensed monoclonal antibody for the prevention of RSV in high-risk infants. Safe and potent polyclonal and monoclonal antibodies, with extended half-life to reduce the number of doses needed and improve compliancy while retaining high efficacy, are being sought.[50] Unlike nanobodies, neither polyclonal or monoclonal antibodies, have been shown to have a therapeutic effect in RSV disease.

Prevention of RSV through vaccination

The development of a safe and effective vaccine for the prevention of RSV has been challenging, although achieving this elusive goal is more realistic today.[65-67] Progress has been made in the understanding of the pathogenesis of RSV and the host immune responses to RSV infection, to inform vaccine development, and numerous vaccine candidates are under evaluation and in various phases of development by industry and other investigators worldwide. (Figure 3) The main approaches for RSV candidate vaccines include live attenuated virus vaccines, particle-based, subunit vaccines based on the F and G surface glycoproteins, nucleic acid, gene-based vector vaccines. This variety of vaccine types allows covering the specific needs of target populations. Live-attenuated RSV vaccines have been in development for several decades and continue to be of interest for young pediatric populations, given their potential effect in preventing infection but also in reducing or eliminating transmission of the virus from infected individuals to susceptible individuals who are unable to be immunized.[68] Given that natural RSV infection does not result in permanent immunity and reinfection occurs throughout life, pre-existing immunity in adults precludes the use of live-attenuated vaccines because of its neutralizing effect on vaccine virus and interference with its immunogenicity. Similarly, live vaccines are not an available option for infants in the first few months of life, because a balance between reactogenicity and immunogenicity has been difficult to achieve.

Maternal immunization, vaccination of pregnant women with a safe and immunogenic non-live RSV vaccine is currently considered the most direct and efficient strategy for the prevention of RSV infection in early life when the greatest morbidity and mortality occurs.[67,69] Maternal immunization will boost maternal RSV-neutralizing antibodies that can be efficiently transferred to the newborn transplacentally and provide protection for several weeks, depending on the concentration of antibodies at the time of birth. Vaccines under evaluation for pregnant women are particle-based or subunit vaccines that ideally should be immunogenic enough to be administered only once during pregnancy, likely in the second trimester of gestation to allow for adequate maternal immunity to develop and sufficient time for transplacental antibody transfer to occur. Although no correlate of protection has been identified, infants born with higher concentrations of antibody are likely to benefit from a longer period of protection against severe RSV disease. Candidate vaccines have to be safe and minimally reactogenic to minimize the risk to the mother, the fetus, and the outcomes of pregnancy. One candidate alum-adjuvanted nanoparticle vaccine targeting the RSV F protein has met these criteria in studies of adult populations and women of childbearing age, and has now completed phase II clinical trials and progressed to a phase III global clinical trial in pregnant women, with the primary goal of preventing severe RSV disease in infants.[69]

Conclusions

Reducing the burden of RSV in susceptible populations, particularly young children and infants with high-risk conditions remains challenging. Novel agents for the prevention and treatment of RSV and intervention strategies are under active development and evaluation. Safe and effective antibodies and vaccines directed to conserved antigenic sites of RSV A and B could have a significant impact on the prevention of severe RSV disease, hospitalization, and death in children worldwide.

Safety Monitoring of Immunization in Pregnancy- two for one?

Immunization during pregnancy prevents or minimizes serious morbidity, mortality and adverse pregnancy outcomes in pregnant women, the fetus, and young infants.[70-72] Protective concentrations of vaccine-induced immune globulin G are transferred across the placenta and can protect infants while most vulnerable.[70,71,73,74] IgG transfer from the mother to the fetus can occur from the 13th week of gestation, with the largest amount transferred during the third trimester of pregnancy.[73,75,76]

Maternal tetanus, inactivated influenza (seasonal inactivated influenza vaccine and monovalent pandemic vaccine) and acellular pertussis vaccines are routinely recommended for pregnant women in several countries.[70,71] These programs have demonstrated the feasibility and effectiveness of immunization in pregnancy programs in high, middle and low-income countries. There are numerous published studies supporting the safety of these vaccines in pregnant women.[70,71,77] Promising new vaccines are being developed to prevent infections in pregnant women and young infants. These include vaccines for Group B streptococcus, respiratory syncytial virus, and cytomegalovirus.[71]

Introduction of vaccines for maternal immunization comes with a tremendous potential benefit. They will be particularly important for low and middle-income countries (LMICs), where there is the greatest burden of vaccine-preventable diseases and limited access to basic health services. However, there are many barriers to immunization of pregnant women. These include concerns of providers and pregnant women of adverse pregnancy outcomes, and other adverse events in the mothers and their infants.[71,78]

Challenges of safety monitoring of immunization in pregnancy

No vaccine currently has been approved for a specific indication for use during pregnancy. Currently recommended vaccines (e.g., Tdap and inactivated influenza) by the ACIP (Advisory Committee on Immunization Practice) are not contraindicated for use during pregnancy and can be used in pregnant women.[71] Studies have shown that healthcare provider (HCP) recommendation is the strongest predictor of immunization in pregnancy uptake by pregnant women.[71,73] however, the absence of a specific indication for use during pregnancy on package inserts of licensed vaccines might lead to confusion among HCP.[70,71] This has been addressed by a modification in the product labeling, which allows for the inclusion of any available data on the safety and effectiveness of vaccines given to pregnant women.[79]

The safety of vaccines administered during pregnancy is a key consideration for pregnant women, HCP, vaccine manufacturers, researchers, regulatory agencies, ethics committees, program managers, and civil society.[71] Well-designed, globally harmonized safety monitoring with timely communication of results to HCP and their pregnant patients is important for improving the uptake of immunization in pregnancy.[70,71]

It is important to distinguish between vaccine-related and pregnancy-related outcomes, as pregnancy complications are common (e.g. stillbirth, preterm birth, congenital malformations). Thus, it is critical to know background rates for these events in the population to determine whether the risk of these events is increased following immunization. Both false alarms as well as overlooking real concerns can have significant detrimental effects on the overall health of pregnant women and their children [70,71] Today, background rates are often not known and need to be collected in the target populations particularly in LMIC.[71]

Whenever possible, it is important to utilize accepted and standardized definitions of key bstetric and neonatal outcomes of immunization in pregnancy to evaluate possible adverse events associated with maternal immunization.[70,71] Standardized definitions for key events are required for defining, identifying, capturing, reporting, and analysis of adverse events following immunization (AEFI) and lead to a common understanding of key events, data comparability, pooling of data from clinical and observational studies (including for vaccine labels), and consistent analysis within and across safety studies and surveillance systems worldwide. It is key to ensure applicability and usefulness of definitions for data analysis in both high and low and middle income countries (LMIC).

Another key challenge for safety monitoring of immunization in pregnancy is to determine a practical and implementable follow-up duration in LMICs, where transportation and access to health facilities is often challenging for the women and infant.[71] Moreover, long-term studies of child development and women's health may be needed to detect risks to growth and cognitive development in the fetus and adverse events in the pregnant women. This is not necessary for all research, but the need is to be scientifically determined based on the properties of the vaccine, drug or adjuvant being tested.[71,80]

Finally, the health care data required for active pharmacovigilance of immunization in pregnancy programs are limited, fragmented and not harmonized. As global immunization in pregnancy programs are increasingly being implemented, methodological and capacity

challenges have to be addressed, and a globally harmonized approach would give added value to local or national strategies.

Harmonized safety monitoring

The need for immediate actions to strengthen monitoring of immunization in pregnancy programs and the need to harmonize safety monitoring globally was recognized in a joint WHO – Brighton Collaboration meeting in 2014.[81,82]

The GAIA (Global Alignment of Immunization Safety Assessment in Pregnancy) project (http://gaia-consortium.net/) was established to address this need with a specific focus on LMICs needs and requirements.[83] A series of guidelines, standardized case definition, and tools was developed in the first two years of the project. A map of disease codes across coding terminologies, including MedDRA and ICD, was created to enable pooling of data from various sources. A searchable database of terms, concept definitions and ontology of over 3000 terms related to key events for monitoring immunization in pregnancy was developed. An online tool for automated case classification (single case or batch cases classification) of events according to the standardized case definitions has also been created. GAIA has also developed two guideline documents for the conduct of clinical trials of vaccines in pregnant women, including recommendations on the collection, analysis and presentation of safety data, to provide guidance on the prioritization and classification of the data to be collected in such studies, and to facilitate their applicability in various settings, including LMICs. These guidelines may also assist in the safety surveillance of vaccines already recommended for pregnant women (tetanus, influenza, and pertussis). Guidance on study design and the standardization of data collection will help to promote collection of a minimal set of high priority parameters in various settings, including LMICs.[84,85]

The GAIA outputs are developed based on the standard Brighton Collaboration consensus process including global consultation of professionals from key regulatory organizations, public health institutes, investigators, vaccine manufacturers and academia to ensure their applicability, usefulness, and acceptability especially in LMICs. The WHO Global Advisory Committee on Vaccine Safety (GACVS) provided a highly supportive assessment of the key GAIA guidance document and considered them to be timely and useful. Two special issues of the Vaccine journal was published on GAIA outputs so far.[86,87] The GAIA outputs are being increasingly utilized in the field of Immunization in Pregnancy and Maternal and Child Health by key stakeholders such as clinical trialists, investigators, regulators, and industry.[71]

Conclusion

Immunization in pregnancy is a well-accepted public health intervention to prevent pregnant women and their fetus and infants from potentially lethal, vaccine-preventable infectious diseases. Existing research strongly supports the safety of immunization in pregnancy. The uptake of immunization in pregnancy can be improved considerably. Safety remains a major concern and a globally harmonized approach to safety data collection, reporting, and communication of the results to HCP and pregnant women are likely to improve the acceptability and implementation of immunizations in pregnancy programs. This could substantially help reduce illness and death among pregnant women, neonates and young infants globally.

Vaccine shortages and coping strategies -

Substitutes of Protection

Vaccine shortages are a result of imbalance in demand and supply and are an increasing threat to immunization programs worldwide, affecting low, middle and high-risk countries.[88] Typically, each year one third of World Health Organization (WHO) Member States experience at least temporary vaccine stockouts of at least one vaccine for one month or longer.[89] At their most severe, they represent a major threat to critical public health programs, such as global tuberculosis (TB) prevention. As well as impacting national immunization programs for children and adults, they may also impact the ability to provide licensed vaccines on the private market, for both locally acquired and travel-related vaccine preventable disease.

The long lead-time for manufacturers to be able to respond to unexpected changes in demand or supply underlines the importance of coordinated efforts to predict demand and ensure supply security. Optimal communication and collaboration between manufacturers, regulatory authorities, as well as national, regional and global health agencies will help minimize the risk of shortages. Streamlined regulatory pathways for rapid licensure and WHO pre-qualification for new manufacturers may also play a role.

At the delivery level, understanding what may be safely substituted when a specific vaccine shortage occurs maximizes the ability to achieve protection of individuals and populations.

The emergence of new manufacturers also offers hope following an era where progressive concentration of manufacturing capacity has been the norm for recent decades.

Epidemiology

Vaccine Security has been defined by UNICEF as the sustained, uninterrupted supply of affordable vaccines of assured quality. Although there have been consistent global improvements in vaccine coverage and delivery, vaccine shortages appear to be an increasing threat to preventive health in all settings. In 2015, 77% of countries surveyed by WHO Euro region reported a supply shortage of at least one vaccine since the start of that year.[90] The Global Vaccine Action Plan 2011-2020 has recognised the global threat of vaccine shortages, with 2 directly relevant resolutions being endorsed by the World Health Assembly in 2015.[91] In developing settings recent vaccine shortages have posed a threat to the control of a 2015 meningococcal meningitis epidemic in Niger, and BCG shortfalls of up to 71 million doses have threatened the global control of childhood TB.[90] However, middle-income countries (MICs) have been especially affected, with 60% of 50 countries reporting national level stockouts in 2014 being MICs. High-risk countries are also affected, with a recent US review of vaccine and immune globulin shortages between 2001 and 2015 describing 59 shortages, with viral vaccines accounting for 58% of these. Vaccine deferrals were required for 36% of shortages. Pediatric immunization schedule vaccine shortages accounted for 51%, with a median duration of 21 months.[92] As of October 2017, the US Centre for Disease Control (CDC) reported shortages of Hepatitis A vaccine due to ongoing hepatitis A outbreaks, as well as unavailability of Merck adult and pediatric hepatitis B vaccines.[93]

Etiology

The origins of vaccine shortages can be broadly categorized into supply, demand, and information derived causes summarized in table 3. The long lead time to develop or expand Good Manufacturing Practice approved production facilities, combined with the limited number of manufacturers, limits the ability to respond rapidly to changes in demand or production failures. While much demand is potentially predictable, unexpected changes in national or regional policy, disease outbreaks or major consumer demand changes may put rapid pressure on vaccine availability. Similarly, lack of coordinated information flow about projected supply and demand changes can increase the potential for shortages.

Prevention

To minimize the chance of vaccine shortages, a continuously updated global ascertainment of vaccine supply, and supply pipeline needs to be married with the local, regional and global understanding of demand and their projections. Ideally, this information, which is contributed to by the many stakeholders (including manufacturers, regulators, policy organizations, and immunization technical advisory groups [ITAGs]) should be collated and presented centrally. Currently, much of the required information is available only from each stakeholder, although recent initiatives including with WHO and UNICEF are improving communication and outcomes. Processes to fast-track WHO pre-qualification of BCG vaccines from new manufacturers helped ameliorate the projected shortfall in 2016. Regional efforts to improve vaccine security have included the Pan-American Health Organization (PAHO) setting up a regional fund for vaccine purchasing, enabling more stable supply of quality vaccines at an affordable price. Currently, the Association of Southeast Asian Nations (ASEAN) is developing a similar structure. A recent proposal by the WHO Global Vaccine Safety Initiative to establish a Vaccine Safety Observatory, which would include a centralized 'clearinghouse' of vaccine recalls and safety warnings, offers an example of providing a single source of information accumulated from multiple sources to improve safety and supply communication.[94]

Practical strategies for healthcare providers

Healthcare providers may mitigate the risk of vaccine shortages impacting their services in a number of ways. Large providers may consider having supply from than one manufacturer for each vaccine type. While this may add complexity and cost, it offers some insurance against shortages. Knowledge of commercial and regulatory processes for accessing and using vaccines not already licensed in their region is important. Accurate tracking of stock also enables redistribution from areas with surplus supply.[95] At a more local level, cooperation between nearby pharmacies and other major providers can also mitigate brief shortages.

As part of the management of vaccine shortages, clear communication of what may be used as an acceptable alternative to the original vaccine is required, ideally from advisory bodies such as national or regional ITAGs. For example, pediatric and adult hepatitis B formulations may be used in the case of shortage of the age-approved product. Most, but not all, vaccines sharing similar antigens, may be used to complete a course already commenced with a vaccine subject to a new shortage. Even the currently globally licensed live attenuated rotavirus vaccines, RV5 (a bovine-human reassortant pentavalent mix) and RV1 (an attenuated G1P[8] monovalent vaccine) have been permitted by the Australian Immunization

Technical Advisory Group in a mixed schedule during brand transition.[96] While there is limited trial evidence demonstrating immunogenicity of such “mixed schedules”, there is broad acceptance they offer a high likelihood of protection and are usually a superior alternative to waiting until the original vaccine may become available.

However, care must be taken, especially with combination vaccines, to ensure that the one or more vaccine alternatives chosen provide antigens for all of the diseases prevented by the original vaccine subject to a shortage. Similarly, age-inappropriate formulations, such as plain polysaccharide vaccines, cannot be used as substitution for conjugate vaccines in infants.

Conclusions

Vaccine shortages remain an ongoing threat to the control of vaccine preventable diseases in adults and children. They affect all regions and countries of all from low to high-risk status. While there are factors that have contributed to their increased impact, especially manufacturer concentration and the long lead-time to increase production capacity, there is hope. The emergence of new manufacturers in developing markets, improving coordination of information regarding supply and demand threats, changes and projections, as well as proactive facilitation of WHO prequalification for necessary vaccines, offer real hope. Similarly, practical communication and pragmatic approaches to utilizing appropriate substitute vaccines can enable providers to maintain protection for their patients.

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Figure 1: The RTS, S development timeline through 2015 [8]

Figure 2 Overview of safety from 18 studies: solicited reactions after any CYD dengue vaccine injection by age group (subset of subjects) [29]

Figure 3. RSV vaccine and mAb snapshot, as of September 05, 2017

Table 1 Rates of Top 10 AEFIs following CYD-TDV Dengue vaccine experienced by vaccinated students in implementation program in the Philippines after 1st Dose and 2nd Dose [33]

Symptoms	1st dose AEFI rate	2nd dose AEFI rate
Fever	8.13	4.24
Dizziness	5.84	2.24
Headache	5.14	1.43
Rashes	2.5	0.45
Vomiting	1.95	0.9
Abdominal pain	1.14	0.41
Colds	0.61	0.41
Cough	0.57	0.45
LBM	0.53	0.12
Fainting	0.49	0.16

***** AEFI rate per 10,000 vaccinees

Modified from Lecciones J. From Dengue Vaccine to Dengue Vaccination: Vaccination Program Implementation in the Philippines. Presented at: Asian Dengue Vaccination Advocacy Symposium at the 8th Asian Congress of Paediatric Infectious Diseases 2016, 2016; Queen Sirikit National Convention Center, Bangkok, Thailand.

Table 2. Summary of Antibodies for the Prevention of RSV

Product Description	Name	Status	Indication	Comments
ANTIBODIES				
Polyclonal RSV immunoglobulin antibodies	RSV-IG Respigam	Licensed 1996	Prevention in high-risk infants	IV administration Not available since 2004
	RI-001 (ADMA Biologicals)	Phase II RCT	Prevention of progression of RSV URI to LRTI in 2-65 year-old immunocompromised patients	IVIG from pooled plasma donors with high titers of RSV Investigational only
	RI-002 (ADMA Biologicals_	Phase III open label clinical trial	Prevention of serious bacterial infection in patients with primary immunodeficient-cies	IVIG with high titers of RSV and polyclonal antibodies against *S. pneumoniae* and *H. influenzae* type b Investigational
Humanized monoclonal antibody to RSV F-protein	Palivizumab Synagys (MedImmune)	Licensed 1998	Prevention in high-risk infants	IgG1 mAb IM administration during RSV season AAP updated recommended indications in 2014
	Medi-524 Motavizumab (MedImmune)	Phase III clinical trials	Showed non-inferiority vs. palivizumab at reducing RSV hospitalizations and superiority in reducing RSV LRTI outpatient visits Associated with increased risk of hypersensitivity reactions	Second generation IgG1 mAb based on palivizumab Increased affinity and neutralizing activity increasing potency by 20-fold compared to palivizumab Not FDA approved due to hypersensitivity Development discontinued by manufacturer
	MEDI-557 Motavizumab-YTE (MedImmune)	Phase I RCT	Showed increased half life	Third generation IgG1 mAb derived from motavizumab Longer half life Development also discontinued
	MEDI-8897	Phase I and II RCT	Prevention of RSV in premature infants 32-35 weeks gestation Goal: Prevention of RSV LRTI in high-risk and also other preterm and term infants	Recombinant human IgG1 mAb Extended half-life and Increased potency compared to palivizumab IM administration Continues under development
	REGN-2222 (Regeneron)	Phase I and II RCT	Prevention of serious RSV LRTI in premature infants 29 to $\leq$ 35 weeks of gestation and $\leq$ 6	Fully human IgG1 mAb targeting conserved epitope of the F-protein, different from site 0 or II

			months in whom palivizumab is not recommended	More potent than palivizumab in vitro and animal models Longer half life Failed to meet primary endpoint in
Nanobodies	ALX-0171 (Ablynx)	Preclinical and phase I/IIa RCT	Antiviral treatment in healthy infants and toddlers hospitalized with RSV infection	Trivalent nanobody Binds to antigenic site II in the pre-F and post-F configurations of the F-protein Intranasal (inhalation) administration once daily No dose limiting toxicity to date

Table 3: Factors contributing to vaccine shortages

Supply	**Demand**	**Communication**
Long production set up: 2-3 years	Vaccine hesitancy	Projected demand
Long time to increase production	Disease Outbreaks	Local recalls or warnings not communicated more broadly
Batch failures	National and regional policy changes	Outbreaks not rapidly communicated
Complex manufacturing compared with medicines	Funding changes	Between policy makers, regulators and manufacturers
Manufacturing economics (investment versus return for manufacturers)	Community perception changes re vaccine desirability	Inadequate response to vaccine scares
Industry consolidation (less manufacturers)	Public awareness and advertising campaigns	
Loss of state vaccine manufacturers		

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