Novel safety issues and areas that require further research

Situation paper

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Executive summary

Vaccines are held to a very high safety standard as they are given to prevent rather than treat disease, often administered to a large proportion of the population, and supported by governments and health authorities. Separating adverse events following immunization (AEFI) that are coincidental versus true vaccine reactions is critical. Vaccines routinely used are very safe, though adverse reactions do occur albeit serious adverse reactions are very rare. Vaccine safety activities throughout the product life cycle are designed to ensure that vaccines used routinely are very safe, the benefits outweigh the risks in the populations indicated for use and if safety problems arise they are quickly identified, characterized, and prevented when possible.

In this paper, we review five vaccine safety case studies: 1) dengue vaccine and enhanced disease, 2) pandemic influenza vaccine and narcolepsy, 3) rotavirus vaccination and intussusception, 4) Human papillomavirus (HPV) vaccine and Postural orthostatic tachycardia syndrome (POTS) and Complex regional pain syndrome (CRPS), and 5) RTS,S vaccine and meningitis, cerebral malaria, female mortality and rebound severe malaria. For each of these case studies we review why it is a safety issue, potential biological mechanisms, epidemiological data and finally causality conclusions and areas for future research. Bringing these case studies together, we then develop lessons learned that can be useful for addressing safety issues that will inevitably arise.

Vaccine safety science must be proactive and timely, and conducted with rigor, objectivity and transparency. Vaccine safety scares are often for outcomes that seem to be increasing in
incidence, have poorly understood aetiology, and are concerning to the public. Good science takes time whereas anecdotes and misinformation spread quickly. It is advisable for vaccine safety science to inform the public’s views, rather than try to change views that have already been formed. Strong infrastructure, adequate funding and a willingness to address public concerns from the scientific community can improve the timelines of rigorous safety science and its ability to impact public views and vaccination decisions.

Most AEFIs that are causally linked with vaccination occur within a few weeks after vaccination. Such temporal associations increase the plausibility of causal associations, but there are important caveats. AEFIs that occur with no clear temporal relationship to vaccination are the most challenging to assess. Some vaccinations increase the susceptibility to adverse events from other exposures that may occur any time after vaccination. More research is needed on the long-term effects of vaccinations, both beneficial and detrimental, beyond their effects on the target disease. Proving a negative is difficult and consequently upper limits on the possible risk must be defined. Often in vaccine safety science, there is too great a focus on relative risks, rather than vaccine-attributable risks, which may heighten fears about rare events. Interactions between the vaccine, natural disease and the AEFI are particularly challenging.

A systematic review of vaccine safety issues would facilitate development of a vaccine safety research agenda. Consideration should be given to scientific uncertainties, public concerns, how many people are exposed to the vaccine, and the frequency and severity of the AEFI to facilitate prioritization. Communication around vaccine safety must be proactive and timely,
evidence-based, finding commonalities with the public, tailored to individuals, and from credible sources.
Introduction

Vaccines are held to a very high safety standard as they are given to prevent rather than treat disease, often administered to a large proportion of the population, and supported by governments and health authorities. Vaccines routinely used are very safe, though adverse reactions do occur albeit serious adverse reactions are very rare. Despite the remarkable safety record of vaccines and the tremendous benefits afforded through vaccination, vaccine hesitancy has been identified as a global threat by the World Health Organization (WHO).¹ The causes of vaccine hesitancy are complex. Often vaccines are a victim of their own success when public attention shifts from the risks of disease to the risks of vaccines because vaccines have been so effective in reducing disease. Furthermore, the public and clinicians often over-attribute adverse events following immunization (AEFI) as causally linked to the vaccine.

Vaccine safety activities throughout the product life cycle are designed to ensure that vaccines used routinely are very safe, the benefits outweigh the risks in the populations indicated for use and if safety problems arise they are quickly identified, characterized, and prevented when possible. Vaccine safety is often important in deciding the type of vaccine being developed, including the selection of antigens and ingredients. For example, HIV vaccine development has avoided live attenuated strains due to concerns that the vaccine could mutate to be pathogenic. Prior to human testing of vaccines, products are characterized by physical, chemical and biological methods and animal studies are conducted to assess both safety and likely efficacy.
Double blind randomized clinical trials are conducted prior to vaccine licensure to assess both safety and efficacy. These trials are the gold standard as they reduce confounding and bias. Strict inclusion and exclusion criteria also reduce risk to study participants. Despite these strengths of prelicensure clinical trials, such studies also have limitations. Typically, they cannot evaluate adverse events in persons with specific characteristics who are excluded from studies, adverse events with long delayed onset, or adverse events that are not common or occur in sub-populations. As can be seen in Table 1, very large clinical trials are needed to detect an increase in rates of adverse events which have the potential to impact very large numbers of people if the vaccine is universally used. For example, a clinical trial would require 50,000 persons to detect a doubling of risk for an adverse health outcome that occurs at a baseline rate of 1 in 1,000. A doubling of risk for such an event would potentially impact 4,000 persons in the US, 5,100 persons in Europe and 23,000 persons in India annually if the vaccine were administered to each birth cohort.

National regulatory authorities (NRA) review applications from the vaccine developer and license a vaccine based upon consideration of how the vaccine is produced and on the results of clinical trials. The vaccine must be shown to have benefits substantially greater than any adverse effects of the vaccine in the populations indicated for use. WHO may pre-qualify vaccines, which is required for vaccines purchased by GAVI and UN agencies and which may also be of value when NRAs in LMICs consider vaccines for licensure in their countries. National Immunization Technical Advisory Groups (NITAGs) provide recommendations to the NRA and for vaccine usage recommendations.
Passive surveillance systems are widely used once a vaccine is introduced into immunization programmes to detect signals of unanticipated events that may be causally related to vaccination. Passive surveillance systems are widely used, are inexpensive to set up and operate, but there are considerable limitations to passive surveillance systems. Most notable, with few exceptions, reports of adverse events following vaccination to passive surveillance systems cannot determine if the event is caused by the vaccine or if it is coincidental as there is a lack of good denominator data and a comparison (unvaccinated) group, and there are many potential biases in reports including poor case definitions, under-reporting, over-reporting and incomplete reporting. Passive reports are also prone to misinterpretation by the public who can mistakenly assume that the adverse events reported are caused by the vaccine.

Active surveillance systems, sentinel surveillance and ad hoc post-licensure studies can largely overcome the limitations of passive systems. Active surveillance systems typically rely on healthcare administrative datasets from healthcare systems that serve a defined population. Typically, these systems include impatient, outpatient and vaccination data. Unlike passive systems, these datasets include cases of the events of interest occurring among both vaccinated and unvaccinated persons. Matched cohort, vaccinated-only (risk interval) cohort, case-control and self-controlled case-series methods are typically employed.⁴,⁵ Methods have been developed and widely used to optimize these systems and address vaccine specific challenges. For example, Rapid Cycle Analysis monitors pre-specified outcomes and rapidly compares rates occurring to what would be expected.⁶ While active surveillance systems are widely used in many high-income countries, they are costly (at least compared to passive systems) and require substantial health system infrastructure. Low- and middle-income
countries largely do not have such capacity and are thus dependent on ad hoc studies as needed.

Many countries have the capacity to conduct clinical assessment and individual-level causality assessment to ascertain if a vaccine caused an adverse reaction in an individual, or if the adverse health outcome was caused by something else or coincidental. WHO has an algorithm to facilitate such assessments.\textsuperscript{7,8} These causality assessments typically try to answer the question “did” the vaccine cause the adverse event. At the population level, causality assessments are conducted to answer the question “can” the vaccine cause the adverse event.

There are many important uses for the information that comes from the safety components. Safety findings may impact vaccine recommendations, but if serious safety effects are identified in some circumstances a vaccine may be pulled from the market. In some countries, vaccine adverse reactions are compensated.\textsuperscript{9}

Safety signals can frequently require additional studies to provide clarity or further explore unanswered scientific questions. In this paper, we review five vaccine safety case studies: 1) dengue vaccine and enhanced disease, 2) pandemic influenza vaccine and narcolepsy, 3) rotavirus vaccination and intussusception, 4) HPV vaccine and POTS and CRPS, and 5) RTS,S vaccine and meningitis, cerebral malaria, female mortality and rebound severe malaria. For each of these case studies we review why it is a safety issue, potential biological mechanisms, epidemiological data and finally causality conclusions and areas for future research. These case studies were selected because they are timely and varied in the vaccine safety challenges they
elucidate. Bringing these case studies together, we then develop lessons learned that can be useful for addressing safety issues that will inevitably arise.

Dengue vaccine and enhanced disease

Conservative estimates suggest 50 million dengue infections per year\textsuperscript{10} with some estimations as high as 390 million infections annually\textsuperscript{11}. More than 3.6 billion people live in areas at risk for dengue virus (DENV) infection and there are an estimated 390 million infections annually in over 120 tropical and sub-tropical countries\textsuperscript{11}. Development of a dengue vaccine has been hampered by the lack of a good animal model, the need to protect against four serotypes and fear of antibody-dependent enhancement\textsuperscript{12}. After decades of research, the world’s first dengue vaccine, Dengvaxia\textsuperscript{®}, produced by Sanofi Pasteur, was licensed in 2015 in Mexico and now in 20 countries\textsuperscript{13}. Dengvaxia\textsuperscript{®} is a live attenuated recombinant tetravalent vaccine that was evaluated in Phase 3 efficacy trials with a 3-dose 0, 6 and 12 month schedule\textsuperscript{14}. Despite licensure in multiple countries, the vaccine has only been introduced in two public health programmes to date: in the Philippines and Brazil.

Results from a comprehensive Phase 3 clinical trial programme indicated that protective efficacy varied according to serostatus, serotype, at least in the short-term there was protection after only one dose\textsuperscript{15}, vaccine-induced immunogenicity was not predictive of protective clinical efficacy, and no immune correlates (for protection or enhancing disease) were established\textsuperscript{15}. 


In the Philippines, it was planned to administer the vaccine in schools to approximately one million 4th grade children (9- to 10-year olds) in regions of high endemicity, starting April 2016. When Sanofi Pasteur announced a safety signal, post-licensure, in November 2017 (https://mediaroom.sanofi.com/en/press-releases/2017/sanofi-updates-information-on-dengue-vaccine/), indicting that there was an increased risk of severe dengue in vaccinees who had not had a previous dengue infection, the programme was suspended. By then, over 830,000 children had received the vaccine, of whom about 370,000 had received 3-doses and the remainder one or two doses. The public reaction in the Philippines was immediate outrage and political turmoil ensued. The result was broken public trust around the dengue vaccine and heightened anxiety around vaccines in general. The Vaccine Confidence Project™ measured the impact of this crisis, comparing confidence levels in 2015, before the incident, with levels in 2018. The findings reflect a dramatic drop in vaccine confidence from 93% "strongly agreeing" that vaccines are important in 2015 to 32% in 2018, with a subsequent resurgence of measles in the Philippines.

Evidence for serostatus dependent performance of CYD-TDV and WHO`s recommendations on the use of CYD-TDV

The data indicating an increased risk of severe dengue in dengue-naïve vaccinees were based on additional retrospective analyses of the Phase 3 trial data. As pre-vaccination blood samples were only taken from a subset, a novel antibody assay was used on blood samples taken from all trial participants in month 13 of the trial, one month after the 3rd vaccine dose, and the results were used to infer retrospectively dengue serostatus at pre-vaccination. These analyses
showed that in seropositive trial participants aged 9–16 years, in the 66 months after administration of the first vaccine dose, the vaccine was protective, hazard ratios (HRs), comparing vaccinated to placebo recipients, for hospitalized virologically confirmed dengue (VCD) and severe VCD, were 0.21 (95% CI: 0.14–0.31) and 0.16 (95% CI: 0.07–0.37), respectively. However, in seronegative participants aged 9–16 years, vaccinees had an increased risk of hospitalised and severe dengue, with corresponding HRs of 1.41 (95% CI: 0.74–2.68) and 2.44 (95% CI: 0.47–12.56), respectively.\(^\text{17}\)

A plausible hypothesis for these findings is that the vaccine acts as a silent infection, so that the first natural infection in seronegative recipients is then “secondary-like”, with an associated higher chance of severe disease, whereas in seropositive recipients the first natural infection after vaccination is “tertiary-like”, which is not associated with a higher risk of severe disease.\(^\text{18}\)

In December 2017, GACVS recommended that Dengvaxia\(^\text{®}\) should not be administered to individuals who have not been previously infected with wild dengue virus.\(^\text{19}\) Based on SAGE recommendations, WHO’s position published in 2018 is that for countries considering Dengvaxia\(^\text{®}\) vaccination as part of their dengue control programme, a pre-vaccination screening strategy, in which only dengue-seropositive persons are vaccinated, is recommended.\(^\text{18}\)

Implementing a pre-vaccination screening strategy poses major challenges, including the logistics of administering a test prior to vaccination, and the additional costs. Also, because serological tests are likely to be affected by cross-reaction with other flaviviruses, it is likely to be difficult to develop highly specific and sensitive tests for prior dengue infection. In a high seroprevalence area, a test with a very high sensitivity is required, to identify most who would
benefit from the vaccine, whereas in a low seroprevalence area, very high specificity is the most important feature to ensure that those at risk from vaccination are excluded from vaccination.\textsuperscript{20}

Lessons learnt from the first licensed dengue vaccine for second-generation dengue vaccines

A comprehensive risk management strategy and enhanced communication at the introduction of any new vaccine is critical to avoid false expectations and maintain vaccine confidence. This was particularly the case for Dengvaxia®, as there were some indications and theoretical concerns about disease enhancement when SAGE first made recommendations, before the manufacturer had conducted the post-licensure analyses, which consolidated the previous theoretical concerns and led to revised SAGE recommendations. There are also important lessons to be learned for clinical development of second-generation live attenuated dengue vaccines.\textsuperscript{21}

1. Until a surrogate or correlate of protection or risk is established, efficacy trials of dengue vaccines will need to be conducted based on a clinical endpoint.

2. The licensure of the first dengue vaccine and sponsor-requested label revision in response to a safety finding introduces additional complexities to the design and site selection for second-generation vaccine development and will require close consultation with national regulatory authorities.

3. Dengue serostatus at baseline remains a critical variable, and safety and efficacy by serostatus should be presented in stratified analyses.
4. Active surveillance used to assess efficacy against all dengue disease and severe dengue
disease should be in place for at least 3, and preferably 5, years after the last vaccine
dose.
5. Immunogenicity and efficacy results should be interpreted in the context of potential
transient heterotypic immunity that could wane over time.

**Pandemic influenza vaccine and Narcolepsy**

In 2009, the A(H1N1) pandemic influenza virus rapidly spread globally starting from Mexico. As part of a WHO coordinated pandemic mitigation plan, manufacturers developed several monovalent adjuvanted influenza vaccines to increase immunogenicity and spare doses. Pandemrix®, an AS03 adjuvanted vaccine, was available primarily in Europe. Approximately 31 million doses were administered to populations in Finland, France, Germany, Ireland, Norway, Sweden and the United Kingdom. A similar AS03 adjuvanted vaccine, Arepanrix®, was primarily available in Canada. Another pandemic vaccine, Focetria®, an MF59 adjuvanted vaccine, was primarily utilized in Europe, with approximately 6.5 million doses mainly administered to populations in Italy, Netherlands and Spain.

In August 2010, the Swedish Medical Products Agency announced a possible increased risk of narcolepsy, a rare chronic sleep disorder, following Pandemrix vaccination. Soon thereafter, authorities in Finland confirmed a similar signal. Both countries had offered Pandemrix to more than half of their population and coverage up to 80% of school aged children.
After the initial safety signals, the European Medical Agency (EMA) commissioned a signal validation study via the European Center for Disease Control and the VAESCO consortium; a case control approach was used. Several other epidemiological studies including register based linkage studies in Finland and Sweden, and self-controlled case series studies in the UK were conducted to evaluate the association in Europe. Most of these studies indicated significant association with Pandemrix vaccination, although the absolute risk was small, translating into attributable risk of one per 16,000 vaccinated in the susceptible age group at the highest. In Canada, a case control study was carried out, which found a small risk also for the AS03 adjuvanted Arepanrix®, i.e. one per million vaccinated. Also, the US Center for Disease Control commissioned a global case control study, the SOMNIA, in 13 different study sites in 9 countries. It did not find an increased risk for the MF59 adjuvanted vaccine Focetria® or for Arepanrix. Due to limited sample size in the population at risk, the SOMNIA results remain, however, inconclusive for Pandemrix®. A systematic review and meta-analysis of the published studies was conducted by Sarkanen et al, which demonstrated a 5 to 14-fold increased risk in children and adolescents and a 2 to 7-fold increased risk in adults of the Pandemrix® vaccine, and an attributable risk of 1/18,400. The risk has remained elevated for 24 months in the susceptible age groups in those countries where follow up studies were done, i.e. Sweden, Finland and the UK. As a consequence of the European studies, EMA made a precautionary recommendation to avoid using Pandemrix in those under 20 years of age, should there be an alternative vaccine to combat A/H1N1 influenza virus.
While the epidemiological studies were being carried out, animal and immunological studies were initiated to explore the biological plausibility of causation. This was a demanding task as the complete pathophysiology of narcolepsy remains unclear after over 100 years of research.

Understanding the pathogenesis of the vaccination-associated narcolepsy would be of importance for future vaccination strategies in pandemic situations. What causes the damage to hypocretin secreting neurons? Narcolepsy is likely to be immune-mediated in view of the association of the disease with the HLA-DQB1*06:02 haplotype. In the case of vaccination associated narcolepsy, there is still scarce evidence of an autoimmune process. Hypocretin-specific CD4 T cells cross-reacting with some influenza hemagglutinin peptides were detected in patients but at extremely low frequency. They were also seen in about 30% of controls. However the pathogenic role of these CD4-T cells is unclear since neurons do not express MHC class II (including DQ*06:02) and cannot present self-peptides to CD4 T-cells. Classical neuronal autoantibodies were not detectable in these patients.

Besides, there is a growing evidence for a role of the influenza viral infection in the disease, as suggested by the peak of narcolepsy observed in China and Taiwan following the 2009 pH1N1 outbreak in non-vaccinated populations. During the 2009 pandemic with the delay in the availability of vaccines, there was considerable circulation of the pandemic virus in some countries before the vaccine was introduced especially outside North America where the pandemic originated. Thus, it was extremely difficult to sort out whether many of the immunized subjects had previously been infected with the wild type H1N1 pandemic strain, and particularly in those vaccinees that ultimately developed narcolepsy. To address this issue, the Finland National Institute of Health and Welfare assessed whether patients who fell ill with
narcolepsy after vaccination with AS03-adjuvanted Pandemrix had specific antibody responses
to non-structural protein 1 from the H1N1pdm09 virus, which was not a component of
Pandemrix vaccine.\textsuperscript{27} Serum specimens from 45 narcoleptic patients were collected during
2011, unfortunately only 2 years after circulation of the first wave of the pandemic. Paired
serum specimens from 28 adults suffering from a clinical, laboratory-confirmed H1N1pdm09
virus infection were collected acutely and convalescent samples were obtained 14–21 days
later. The study used quantitative Western blot analysis and only 2 of the 45 (4.4%)
Pandemrix\textsuperscript{®}-vaccinated narcoleptic patients showed specific antibody responses against the
non-structural protein 1 from the H1N1pdm09 virus 2 years after the exposure. The paired
serum samples from patients who suffered from a laboratory confirmed H1N1pdm09 infection,
showed high levels of antibody against the non-structural protein 1 in the convalescent samples
obtained soon after the infection. The interpretation of these data was hampered by the very
different timing of sampling in the narcoleptic vs control infected group. In contrast, another
study using published and unpublished H1N1pdm seroepidemiologic data reported that 47% of
children 5-19 years old from 19 different countries were infected with wild-type virus during
the pandemic.\textsuperscript{28} However, it should be noted that in Nordic European countries, the pandemic
peak overlapped or immediately preceded the vaccination.\textsuperscript{29} In Norway, serological studies
indicated that over half of school children were infected just before vaccination.\textsuperscript{28} (\textcolor{blue}{Figure 1}).

Experimental data indicate that most Influenza A viruses can infect olfactory receptor neurons,
that some of these viruses (H1N1, H5N1) can move to the olfactory bulb (OB) within a few
days\textsuperscript{30,31,32} and that exceptionally, some Influenza A viruses can slowly move from olfactory
bulb to other CNS sites (H5N1>H1N1>>H3N2), including lateral hypothalamus and hypocretin-
producing neurons.\textsuperscript{33} In transgenic mice expressing H1N1-HA in hypocretin-producing neurons, anti-H1N1 HA CD8 T-cells were shown to eliminate HA-expressing Hcrt-neurons.\textsuperscript{34} On these experimental bases, it was hypothesized (double hit hypothesis, \textit{Figure 2}) that in some rare patients infected by pH1N12009 influenza, viruses may migrate through the olfactory pathway to the hypothalamus and infect hypocretin producing neurons. By itself this may cause some neuronal damage, likely amplified by natural CD8 responses to viral antigens. The administration of a strongly adjuvanted influenza vaccine at the time or soon after infection could considerably amplify the CD8 response and its pathogenic effects.\textsuperscript{35} Timing of vaccination in relation to the outbreak may be critical.

The role of HLA-DQB1*06:02 in this association is still an open question. It has been shown that HLA-DQB1*06:02 patients are high responders to influenza vaccines. Conversely, HLA-DQB1*06:03 individuals appeared to be associated with poor responsiveness to influenza vaccines and to be protected against narcolepsy.\textsuperscript{36} Thus, immunoregulation of the immune response to influenza peptides may be another critical factor in the development of narcolepsy.

After the initial safety signals in Sweden and Finland, the European Medical Agency (EMA) commissioned a signal validation study via the European Center for Disease Control and the VAESCO consortium; a case control approach was used. Several other epidemiological studies including register-based linkage studies in Finland and Sweden, and self-controlled case series studies in the UK were conducted to evaluate the association in Europe. Most of these studies indicated significant although small absolute risk associated with Pandemrix vaccination, translating into attributable risk of one per 16 000 vaccinated in the susceptible age group at the highest. In Canada, a case control study was carried out, which also found even a smaller
risk for Arepanrix®, i.e. one per million vaccinated. Also, the US Centers for Disease Control and Prevention commissioned a global case control study, SOMNIA, in 13 different study sites in 9 countries. It did not find an increased risk for the MF59 adjuvanted vaccine Focetria®. Due to limited sample size in the population at risk, the SOMNIA results remain, however, inconclusive for Pandemrix®. A systematic review and meta-analysis of the published studies was conducted by Sarkanen et al,37 which demonstrated a 5 to 14-fold increased risk in children and adolescents and a 2 to 7-fold increased risk in adults of the Pandemrix® vaccine, and an attributable risk of 1 per 18400. The risk has remained elevated for 24 months in the susceptible age groups in those countries where follow up studies were done, i.e. Sweden, Finland and the UK. As a consequence of the European studies, EMA made a precautionary recommendation to avoid using Pandemrix in those under 20 years of age, should there be an alternative vaccine to combat A/H1N1 influenza virus.

Causality conclusion and areas for future research

At present, the association between narcolepsy and Pandemrix® vaccination has been well established. The mechanism and degree of causality is still being debated. In the Nordic countries, where approximately 2,000 vaccinated are estimated to have been permanently affected, the interpretation is that Pandemrix contributed to the onset of narcolepsy, but that other factors also played a role. This interpretation has also been accepted by the authorities in charge of vaccine injury compensation in these countries, but not necessarily elsewhere. It also has been agreed that such a rare event would not have been picked up in Phase 3 trials. The
public health implications of this incident, and its handling by scientists, and medical authorities have been manifolds, ranging from significant drop in influenza vaccine coverage among children to distrust in authorities in charge of vaccination programmes. At present, there is no Pandemrix vaccine available. The adjuvant AS03, however, has been stockpiled for future pandemic use. It is likely that there will be future pandemics; in that light it is important that to continue research to understand the biological mechanisms of what happened.

Rotavirus vaccination and Intussusception

Intussusception, a condition in which the intestine folds in on itself, is the leading cause of acute intestinal obstruction among infants. The global incidence of intussusception in infants is 74 per 100,000, with considerable geographic variability from <10 per 100,000 in Bangladesh to 300 per 100,000 in parts of Southeast Asia. Intussusception is rare in the first 2 months of life, with incidence increasing rapidly thereafter, peaking between 4 and 9 months of age. Most intussusception cases are of unknown cause. Some infectious agents, particularly respiratory adenoviruses, have been associated with intussusception. If treatment is sought early, intussusception can be reduced by air or barium enema. In the absence of facilities for enema reduction or for cases that present late, surgical intervention is generally required. Untreated, intussusception is often fatal.

In 1999, the first licensed rotavirus vaccine, RotaShield® (Wyeth), was withdrawn from the US market less than one year following its introduction because it was associated with intussusception at an estimated rate of 1 case per 10,000 vaccinated infants. While pre-
licensure trials of RotaShield® that included a total of ~10,000 subjects would not have identified this level of risk, intussusception was listed as a potential adverse event because of a few reported cases during the trials and careful post-licensure monitoring was conducted.\(^{50,51}\)

Because of the RotaShield® experience, the next generation of live oral rotavirus vaccines – RotaTeq® (Merck, West Point, PA, USA) and Rotarix® (GlaxoSmithKline, Rixensart, Belgium) – each underwent large clinical trials involving 60,000-70,000 infants, specifically powered to rule out an intussusception risk of similar magnitude to RotaShield®.\(^{52,53}\) No elevated risk was found with either vaccine in the trials; they were both subsequently recommended by the World Health Organization (WHO) for global use starting in 2006.\(^{54}\) As millions of infants have been vaccinated in routine programmatic use, a low risk of ~1-5 excess intussusception cases per 100,000 infants after the first dose of vaccine has been identified in post-licensure evaluations with both RotaTeq and Rotarix in several high and middle income countries (Figure 3).\(^{55,56,57,58,59,60,61}\)

However, given that the health benefits of rotavirus vaccination greatly exceed this small risk, policy makers in countries and at the global level continue to recommend routine use of rotavirus vaccines\(^{62}\) (Table 2). Of note, the only data available to date from low income countries did not show any increased risk of intussusception in an evaluation conducted in 7 African countries using Rotarix® vaccine.\(^{63}\) Similarly, in a separate evaluation, no increased risk of intussusception was observed after Rotarix® vaccination in South Africa.\(^{64}\) Given differences in intussusception epidemiology by region, additional data are needed to assess whether intussusception risk varies by geographic and socioeconomic setting.

The biological mechanisms for the association between rotavirus vaccines and intussusception are not fully understood. Studies in mice demonstrated that, despite the induction of intestinal
lymphoid hyperplasia following wild-type rotavirus infection, lymphoid hyperplasia is not required as a lead point for rotavirus-induced intussusception. Mice studies also showed that changes in intestinal motility resulting from intestinal inflammation and cytokine induction may contribute to intussusception, although how well these data apply to humans is unclear. Regardless of the precise mechanism, the finding that intussusception risk appears to be greatest during the period from 3-7 days after administration of the first rotavirus vaccine dose suggest that it is related to intestinal replication of the orally administered live vaccine virus, which also peaks in the same interval after the first vaccine dose. This might also explain the apparent lack of intussusception risk seen in the African evaluations, as both the immune response to vaccination and levels of vaccine virus shedding in stools are substantially lower in infants from low-income compared with high-income countries.

Some evidence suggested a potentially higher risk of intussusception among children administered the first RotaShield® dose at age >3 months, although debate continues whether this represented a greater relative risk or a higher attributable risk given the greater background intussusception rates among older infants. Because of this concern, age restrictions were initially recommended for Rotarix® and RotaTeq® – the first dose was to be administered no later than 15 weeks of age, and the last dose no later than 32 weeks. However, these age restrictions could potentially disqualify a substantial number of children from receiving rotavirus vaccination, particularly in LMICs where delays in timing of vaccination are common. Consequently, after additional post-licensure safety data were available, the risk-benefit of rotavirus vaccination with and without age restrictions was re-examined. This analysis showed that, compared with an age-restricted schedule, rotavirus vaccination without
Age restrictions could prevent an additional 47,200 (range: 18,000-63,700) rotavirus deaths while potentially causing an additional 294 (range: 161-471) intussusception deaths.\textsuperscript{72} Given these benefit-risk considerations, WHO recommended removal of upper age restrictions for rotavirus vaccination in LMICs, although administration of the first dose of rotavirus vaccine as soon as possible after 6 weeks of age is still recommended to maximize the health benefits of vaccination.\textsuperscript{62}

It is not known whether the short-term increased risk of intussusception in the first few days after vaccination translates into an overall population-level increase in intussusception. Some have hypothesized that vaccination may simply “trigger” intussusception earlier in some infants among whom intussusception would have occurred anyway later in infancy, and thus there may be a compensatory decline later in life.\textsuperscript{73} Also, given that intussusception has been associated with three biologically-different live oral rotavirus vaccines based on different rotavirus strains, it has been hypothesized that wild-type rotavirus infection could be a cause of intussusception and vaccination may protect against rotavirus-induced intussusception.\textsuperscript{40,74} In the United States after several years of routine rotavirus vaccination, population-level data do not show an overall increase in intussusception rates among infants <12 months of age despite a small increase in the age group of 8-14 weeks of age when the first rotavirus vaccine dose is administered.\textsuperscript{75,76} Furthermore, a recent study did not show long-term increased risk of intussusception among US infants given rotavirus vaccine compared with those who are not vaccinated; instead, a trend toward decreased long-term risk was seen.\textsuperscript{77} More data are needed to fully understand the overall population-level impact of rotavirus vaccination on intussusception risk in the first few years of life.
In 2018, two new live-oral rotavirus vaccines manufactured in India – Rotavac® (Bharat Biotech, Hyderabad, India) and Rotasiil® (Serum Institute of India, Pune, India) – were pre-qualified by WHO. Pre-licensure trials of these vaccines that included about 5,000 infants each were primarily designed to examine vaccine efficacy and were conducted only in India for Rotavac® and in India and Niger for Rotasiil®. Consequently, as larger numbers of infants are immunized with these vaccines in different geographic locations, generating additional post-licensure intussusception data for these vaccines is a public health priority.

**HPV vaccine and POTS and CRPS**

Human Papillomavirus (HPV) vaccines are a powerful public health tools for preventing cervical cancers and other HPV-related diseases worldwide. There are three HPV vaccines licensed: bivalent (2vHPV, Cervarix®), quadrivalent (4vHPV, Gardasil®) and 9-valent vaccines (9vHPV, Gardasil-9®). Since 2006, HPV vaccines have been licensed in over 90 countries and prequalified by WHO. Substantial vaccine safety data have been accumulated from prelicensure clinical trials as well as post-licensure monitoring and evaluations. The safety data available to date are reassuring. Syncope and anaphylaxis are known adverse events that occur after HPV vaccination. Despite a favourable safety profile, concerns about safety have impacted the acceptability of HPV vaccines in some countries. The safety concerns that have been postulated include complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS). Both syndromes have challenged national immunization programs, especially in
countries such as Japan, Denmark, and Ireland, resulting in decreased public confidence, decreased coverage rates, or withdrawal of HPV vaccination recommendations.82

The biologic mechanisms of POTS and CRPS are not well understood. CRPS is a rare chronic pain disorder that affects one part of the body and is disproportionate to the intensity of any injury or tissue damage.83 It is typically precipitated by some form of trauma, exposure, or illness causing nerve or tissue injury and is commonly associated with autonomic nervous dysfunction.84 POTS is a form of dysautonomia that is characterized by orthostatic intolerance and often accompanied by a range of other symptoms, including headache, other aches and pain, fatigue, and nausea.82 Both POTS and CRPS syndromes are diagnostically challenging, with unclear heterogeneous aetiology and onset. While the two syndromes are clinically distinct, symptoms often overlap and can also overlap with other conditions such as chronic fatigue syndrome, fibromyalgia, and other autonomic disorders. Both CRPS and POTS are known to occur in adolescence and early adulthood.85 Estimated incidence rates for CRPS and POTS are 6.28 per 100,000 person-years and 10.1 per 100,000 person-years, respectively.86

Published case reports of both CRPS and POTS following HPV vaccination among girls have garnered media attention, contributing to public concern about HPV vaccination. Efforts to describe dysautonomia symptoms following HPV vaccination have included studies with small samples and some have included cases that are not representative of the general population, recruited from clinics that evaluate persons with an existing concern of HPV vaccine-induced illness or online sites discussing HPV vaccine injury.87,88,89 The generalizability and validity of these studies are questionable. Data from large population-based studies are limited. Data mining efforts from two large US studies using health plan data did not identify any signals for
CRPS or POTS. Vaccine safety monitoring from the US Vaccine Adverse Event Reporting System did not find any patterns to suggest a casual association of CRPS or POTS following Cervarix®, Gardasil®, or Gardasil-9®. The data from this spontaneous reporting system found very few reports of these conditions following HPV vaccines. An extensive review of GlaxoSmithKline’s safety database for CRPS following Cervarix® did not find an increase in the incidence of CRPS following vaccination. In 2015, the European Medicines Agency conducted a detailed review of CRPS and POTS following HPV vaccines from a variety of data sources and, with input from experts on these syndromes, concluded that the available evidence does not support that CRPS or POTS are caused by HPV vaccine. In 2017, after a review of available data, WHO’s Global Advisory Committee for Vaccine Safety found no new evidence for a causal association between HPV vaccines and CRPS and POTS. More recently, the American Autonomic Society published a position statement on HPV vaccine and autonomic disorders, concluding that there are no data to support a causal relationship between HPV vaccination and CRPS and POTS.

Lessons Learned

Despite the reassuring data available finding no association between HPV vaccines and CRPS and POTS, concerns continue to challenge immunization programs. Background rates in populations aged 9-26 years (the recommended age group for HPV vaccine) should be calculated to determine if CRPS and POTS cases observed following HPV vaccination exceed what is expected. Quality population-based epidemiologic studies with medical record validation can also serve as reliable resources to more convincingly evaluate whether HPV
vaccination affects the risk of CRPS or POTS. Lastly, improved communication about vaccine safety concerns is essential in maintaining the public’s confidence in vaccines.

RTS, S vaccine and meningitis, cerebral malaria, female mortality and rebound malaria

The RTS,S/AS01 malaria vaccine was introduced as part of a pilot programme in Malawi, Ghana and Kenya in 2019, following a positive scientific opinion on the vaccine from the European Medicine Agency in 2015,98 and a recommendation from SAGE and MPAC for pilot implementation to precede potential more widespread use of the vaccine in malaria endemic areas.99 The development of the vaccine started in 1984 and the pivotal Phase 3 trial was conducted between 2009 and 2014.100 RTS,S is a recombinant yeast-expressed subunit vaccine using the hepatitis B surface antigen as a matrix carrier for epitopes derived from the P. falciparum circumsporozoite protein. It is formulated with a proprietary adjuvant system (AS01E) that includes two immunostimulants (MPL and QS21). At the time of the Phase 3 trial, the adjuvant had not been widely used in other vaccines, but subsequently has been included in a now licensed vaccine against herpes zoster101 and an experimental vaccine against tuberculosis.102

The Phase 3 trial of RTS,S/AS01 included about 9,000 children aged 5-17 months and 6,500 infants aged 6-12 weeks, enrolled at 11 centres in seven countries from sub-Saharan Africa. Participants were randomly assigned (1:1:1) at first vaccination to receive three doses of RTS,S/AS01E at months 0, 1, and 2 and a 4th dose at month 20; three doses of RTS,S/AS01E and
a dose of comparator vaccine at month 20; or a comparator vaccine at months 0, 1, 2, and 20. Cases of clinical and severe malaria were captured through passive case detection and any serious adverse events were recorded. For the final trial results, children were followed up for a median of 48 months and infants for 38 months after the 1st vaccine dose.\textsuperscript{103} The vaccine was efficacious against clinical malaria in both age groups but had higher efficacy in the older age group. Protection was relatively high after the first vaccine course but declined with time since vaccination, with little residual protection two or more years after vaccination. It was boosted by the 4th vaccine dose but protection against severe malaria over the whole trial period was demonstrated only in the older age group among children who received 4 vaccine doses. This was the basis for conducting the pilot implementation only in children vaccinated aged 5 months or above.

\textbf{Safety concerns arising from the Phase 3 trial}

There were 4 safety concerns that arose from the results of the Phase 3 trial.

\textit{Meningitis:} Among children in the older age group, there was an excess of cases on meningitis in the two groups who received RTS,S/AS01E (with or without a 4th dose) compared to the control group (10, 11 and 1 case respectively). An excess was not observed in the younger age group (6, 7 and 6 cases respectively). The cases in the older age group showed no temporal association with vaccination and included a mixture of aetiologies. Most cases were reported
from two trial sites. GACVS reviewed these data and determined that meningitis should be regarded as a potential signal which requires further assessment post-licensure.

Cerebral malaria: In the older age group, there was an excess of cerebral malaria in the 4 and 3 dose groups compared to the control group (19, 24 and 10 cases, respectively). Cases showed no clustering with respect to dates of vaccination and no excess was seen in the younger age group (6, 7 and 7 cases, respectively).

Female mortality: Mortality was not a primary endpoint in the Phase 3 trial as it was expected that this would be lower in a carefully monitored trial as many illnesses would be effectively treated that might otherwise have proved fatal. Evidence for this was provided in a study at one of the Phase 3 trial sites in Kenya that showed the overall mortality of children in the trial was 30% of that of children living close by but not in the trial, irrespective of whether they were in the vaccinated or control groups. In the older age group, overall mortality was higher in the 2 vaccinated groups than in the control group (112 deaths vs 46 [2:1 ratio]) but not significantly so, and the same was true in the younger age group (105 deaths vs 42). However, in a post hoc analysis, while boys mortality rates were lower among those vaccinated than in the control group (older age group 1.5% vs 2.0%; younger age group 2.2% vs 2.4%), girls mortality rates were higher among those vaccinated (older age group 2.3% vs 1.1%; younger age group 2.6% vs 1.5%). Analysis of the causes of death, largely ascertained by verbal autopsies, found no obvious pattern to explain the gender-specific imbalances.

Rebound malaria: A post-hoc analysis of hospitalized severe malaria cases revealed a safety signal for cerebral malaria (CM). The analysis used a computer algorithm to identify
cases with parasitemia >5,000/μL and a Blantyre coma score (BCS) ≤2 as a proxy for cerebral malaria (CM), regardless of whether the CM clinical diagnosis was confirmed by the investigators and without excluding children with comorbidities. Based on this algorithm, in the older age group there was a reduced risk of severe malaria between the first vaccine course (3-doses) and the time of the 4th dose, 18 months after the initial course. Following the time of the 4th dose to the end of the trial, the rate of severe malaria in those who received the 4th dose was similar to that in the control group, such that over the whole study period there was significant protection against severe disease. However, in those who received the first 3 doses but were randomised not to receive the 4th dose, the incidence of severe malaria was higher than in the control group in the period from that time to the end of follow-up, such that over the whole trial period the incidence of severe malaria was similar in the 3-dose group as in the control group. This raised two potential longer-term safety concerns. First that the incidence of severe malaria in the 3-dose group would exceed that in the control group in the longer term and, secondly, that there may be a similar “rebound” in the 4-dose group after a longer time interval. These concerns were addressed by a study in which children in the trial from a subset of 3 trial sites were followed up for 7 years post-vaccination in an open-label study. No evidence of a rebound in severe malaria was found and there was overall protection against severe malaria over the 7-year period.

Conclusions

Further investigation of the safety signals is included in the manufacturer’s risk management plan for post-licensure studies and in the evaluation of the pilot implementation. Specifically, the
sentinel hospital and community mortality surveillance of the pilot evaluation as part of the malaria vaccine pilot has been powered to address the safety concerns related to meningitis, cerebral malaria and gender-specific mortality. These studies are incorporated into the investigation of the signals and the impact of the vaccine in the pilot implementation studies. In the Phase 3 trial, nearly all participants received their vaccine doses according to the planned schedule, however, in programmatic conditions, some children may be incompletely vaccinated, and any risks of rebound malaria or other adverse effects will require assessment in the implementation studies.

Except for the possibility of rebound malaria, there are no clear biological mechanisms to potentially explain any of the other safety signals observed. The incidence of meningitis in the control group among the older children, only 1 case, was lower than in the younger age group and chance may explain the finding, though other hypotheses have been proposed.\textsuperscript{109}

Monitoring findings from the pilot evaluation by regulators and investigators in the three implementing countries will be key to the risk-benefit assessment for the eventual expanded use of RTS,S/AS01E in vaccination programmes in sub-Saharan Africa.

Lessons Learned

Vaccine safety science must be proactive, timely, and conducted with rigor, objectivity and transparency. Vaccine safety scares occur when health outcomes seem to be increasing in incidence, have poorly understood aetiology, and are concerning to the public. When new or unexpected AEFI occur, it is helpful to have case definitions already available or quickly developed. Poor understanding of disease aetiology and challenges in disease diagnostics
hamper vaccine safety studies as exemplified with POTS and CRPS. Diseases such as these require rapid consultation from experts not typically engaged in vaccine safety monitoring. It is important to have mechanisms to rapidly engage such expertise. The alleged association between HPV vaccine and POTS or CRPS also exemplifies the importance of rigorous and timely studies. Quality population-based epidemiologic studies with medical record validation would provide far more conclusive evidence than what is currently available. Several countries have already experienced drops in immunization coverage because of these issues. Good science takes time whereas compelling anecdote and misinformation spread quickly. It is advisable for vaccine safety science to inform the public’s views, rather than try to change views that have already been formed, which is far more difficult. Strong infrastructure, adequate funding and a willingness to address public concerns with rigorous safety science can improve timelines for sound communication and our ability to positively impact public views and vaccination decisions.

Most vaccine adverse reactions (the AEFI has been causally related to vaccination) occur within a few weeks or months following vaccination. They are concentrated in a defined time window after vaccination (e.g. narcolepsy following pandemic flu vaccination, intussusception following rotavirus vaccination). Such temporal associations increase the plausibility of causal associations, but there are important caveats. First, in passive surveillance systems, AEFIs purported to be related to vaccination are most likely to be reported if they occur close to the time of vaccination and events more distant from vaccination may not be reported, even if they are truly causally related. Furthermore, many morbid conditions vary in incidence with age and
if an age with high incidence happens to be just after the age at which a vaccine is given, the
temporal association may be falsely interpreted as causal.

AEFIs that occur with no clear temporal relationship to vaccination are the most challenging to
assess. Surveillance systems for AEFIs are not set up to detect such associations, even though it
is not implausible that such causal associations may exist, if, for example, vaccination increases
susceptibility to adverse events from other exposures that may occur any time after
vaccination. This seems the only plausible causal mechanism if an increased risk of meningitis
following RTS,S vaccine was confirmed. More research is needed on the long-term effects of
vaccinations beyond their effects on the target disease. Proving the lack of an effect is
challenging (e.g. the HPV associations, the trials of second-generation rotavirus vaccines) and
consequently upper limits on the possible risk must be defined according to available evidence.

Often in vaccine safety science, there is too great a focus on relative risks, rather than
attributable risks, which may heighten fears about uncommon events (e.g. intussusception
following rotavirus vaccine). Relative risks are important for determining if a vaccine causes an
AEFI. However, the public is far more interested in attributable risks to the vaccine so proper
comparisons can be made to the risks of disease and the benefits of vaccination. Vaccine risk
must be viewed alongside the benefits, and the risk-benefit ratio may vary (e.g. between high
and low-middle income countries) as is the case with intussusception and rotavirus vaccines.

Interactions between the vaccine and natural disease and the AEFI is particularly challenging.
Attention to these interactions between natural disease and the vaccine may be explored
through vaccine development and clinical trials or studied for safety in populations with a low
burden of natural disease.
Communications around vaccine safety must be proactive and timely, evidence-based, finding commonality rather than polarizing the public, tailored to individuals, and from credible sources. As was seen with the dengue vaccine in the Philippines, one vaccine safety issue can affect other vaccines and adversely impact vaccination programs. Communication must address the specific issues at hand, but also consider the broader issues of vaccine benefits and confidence in immunization programs.
Tables and Figures

Table 1: Samples Sizes Needed to Detect an Increase in Rate of AEs

<table>
<thead>
<tr>
<th>Rates (baseline vs increase)</th>
<th>Sample Size(^2)</th>
<th>Number Potentially Affected(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>US</td>
<td>EU</td>
</tr>
<tr>
<td>0.1 v 0.2</td>
<td>50,000</td>
<td>4,000</td>
</tr>
<tr>
<td>0.1 v 0.3</td>
<td>17,500</td>
<td>8,000</td>
</tr>
<tr>
<td>0.05 v 0.1</td>
<td>100,000</td>
<td>2,000</td>
</tr>
<tr>
<td>0.01 v 0.02</td>
<td>500,000</td>
<td>400</td>
</tr>
<tr>
<td>0.01 v 0.03</td>
<td>175,000</td>
<td>800</td>
</tr>
</tbody>
</table>

1 Two-arm trial, power 80%, alpha (2 sided) = 5%


Adapted from Ref 3.
Table 2: Risk-benefit of rotavirus vaccination by country on rotavirus hospitalizations and deaths and associated intussusception risk for one vaccinated birth cohort to age 5 years.

<table>
<thead>
<tr>
<th>Country</th>
<th>Vaccine evaluated</th>
<th>Vaccine dose(s)</th>
<th>Overall attributable risk (excess intussusception cases per 100,000 vaccinated infants)</th>
<th>Rotavirus outcomes averted</th>
<th>Intussusception outcomes caused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mexico</td>
<td>Rotarix</td>
<td>Dose 1 only</td>
<td>2.0–3.7</td>
<td>Hospitalizations: 11,551</td>
<td>Hospitalizations: 41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Deaths: 663</td>
<td>Deaths: 2</td>
</tr>
<tr>
<td>Brazil</td>
<td>Rotarix</td>
<td>Dose 2 only</td>
<td>1.5</td>
<td>Hospitalizations: 69,572</td>
<td>Hospitalizations: 55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Deaths: 640</td>
<td>Deaths: 3</td>
</tr>
<tr>
<td>Australia</td>
<td>Rotarix</td>
<td>Doses 1 and 2</td>
<td>4.3</td>
<td>Hospitalizations: 6528</td>
<td>Hospitalizations: 14</td>
</tr>
<tr>
<td></td>
<td>RotaTeq</td>
<td>Doses 1 and 2</td>
<td>7.0</td>
<td>Deaths: Not reported</td>
<td>Deaths: Not reported</td>
</tr>
<tr>
<td></td>
<td>Rotarix</td>
<td>Doses 1 and 2</td>
<td>5.3</td>
<td>Hospitalizations: 53,444</td>
<td>Hospitalizations: 35–166</td>
</tr>
<tr>
<td>Region</td>
<td>Vaccine</td>
<td>Dose</td>
<td>Incidence</td>
<td>Hospitalizations</td>
<td>Deaths</td>
</tr>
<tr>
<td>-----------</td>
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</tr>
<tr>
<td><strong>United States</strong>&lt;sup&gt;57,60&lt;/sup&gt;</td>
<td>RotaTeq</td>
<td>Dose 2 only</td>
<td>7.3</td>
<td>Not reported</td>
<td>Deaths: 0.1–0.5</td>
</tr>
<tr>
<td>England&lt;sup&gt;61&lt;/sup&gt;</td>
<td>Rotarix</td>
<td>Dose 1 only</td>
<td>1.68</td>
<td>Hospitalizations: 21</td>
<td>Deaths: Not reported</td>
</tr>
</tbody>
</table>

Note: Table adapted from reference 110
Figure 1: Kinetics of 2009 pH1N1 influenza outbreak and vaccination coverage in Norway

Trogstad, Vaccine 2017
Figure 2: The two-hit hypothesis - a possible mechanism for an enhanced risk for narcolepsy following 2009 pH1N1
Figure 3: Relative incidence of intussusception from self-controlled case-series analyses in the 1–7 days following dose 1 and dose 2 of rotavirus vaccine by country

* = Rotarix®; ** = RotaTeq®

Note: Figure adapted from reference 111
References


81 WHO/ Immunization, Vaccines and Biologicals database, as of 9 August 2017.


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