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Novel vaccine safety issues and areas that would benefit from further research

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ABSTRACT

Vaccine licensure requires a very high safety standard and vaccines routinely used are very safe. Vaccine safety monitoring prelicensure and postlicensure enables continual assessment to ensure the benefits outweigh the risks and, when safety problems arise, they are quickly identified, characterised and further problems prevented when possible. We review five vaccine safety case studies: (1) dengue vaccine and enhanced dengue disease, (2) pandemic influenza vaccine and narcolepsy, (3) rotavirus vaccine and intussusception, (4) human papillomavirus vaccine and postural orthostatic tachycardia syndrome and complex regional pain syndrome, and (5) RTS,S/adjuvant system 01 malaria vaccine and meningitis, cerebral malaria, female mortality and rebound severe malaria. These case studies were selected because they are recent and varied in the vaccine safety challenges they elucidate. Bringing these case studies together, we develop lessons learned that can be useful for addressing some of the potential safety issues that will inevitably arise with new vaccines.

Summary box

- Adverse events following immunization that are rare, happen in subpopulations, and have delayed onset are monitored post-licensure.
- Vaccine adverse reactions can be related to genomics.
- There are opportunities for additional research to fully define the safety profile of vaccines.
- Unanswered safety questions and real safety problems can undermine public confidence in vaccines.
- Transparent and timely communication about adverse events following immunization is crucial to maintaining public trust.

INTRODUCTION

Vaccines are held to a very high safety standard as they are given to healthy individuals to prevent rather than to treat disease, often administered to a large proportion of the population, and their use is supported by governments and health authorities. Vaccines routinely used are very safe and, while adverse reactions do occur, serious adverse reactions are very rare. Vaccine safety is monitored throughout the product life cycle—from research and development through postlicensure surveillance. This ensures that routinely used vaccines are very safe, the benefits outweigh the risks in the populations for which they are indicated and safety problems if they arise are quickly identified, characterised and further problems prevented when possible.

In this paper, we review five vaccine safety case studies (box 1):

1. Dengue vaccine and enhanced disease.
2. Pandemic influenza vaccine and narcolepsy.
3. Rotavirus vaccine and intussusception.
4. Human papillomavirus (HPV) vaccine and postural orthostatic tachycardia syndrome (POTS) and complex regional pain syndrome (CRPS).
5. RTS,S/AS01 malaria vaccine and meningitis, cerebral malaria, female mortality and rebound severe malaria.

For each of these case studies, we review the safety issues that have been identified, potential biological mechanisms, epidemiological data, and finally, conclusions about causality and areas for future research. These case studies were selected because they are recent and varied in the vaccine safety challenges they elucidate. Bringing these case studies together, we develop lessons learnt that can be useful for addressing some of the potential safety issues that will inevitably arise with new vaccines.

DENGUE VACCINE AND ENHANCED DENGUE DISEASE

Dengue poses a significant public health problem in the tropics and subtropics with as many as 390 million infections annually.[1] After decades of research, the world's first

Box 1 Summary of case study elements and key lessons

Dengue vaccine and enhanced dengue disease
Dengvaxia was protective for seropositive vaccinees; seronegative vaccinees had an increased risk of hospitalisation and severe dengue. Recommendations for vaccination only for dengue-seropositive people.
Key lessons: Need more understanding of impact of natural disease on vaccines.

Pandemic influenza vaccine and narcolepsy
Small but significant increase in narcolepsy following one adjuvanted pandemic influenza vaccine. Pandemrix in Sweden, Finland, and UK (various rates, highest 1:16 000); the Sleep Apnoea Monitoring with Non-Invasive Applications study (1:18 400).
Key lessons: Postlicensure studies in large populations with different genetic backgrounds is important. Timing of vaccination during an outbreak may be important.

Rotavirus vaccine and intussusception
RotaShield was the first rotavirus vaccine on the market with intussusception rates of 1:10 000 (postlicensure). Concerns of higher risk if given before 3 months led to age restriction; risk–benefit analysis led to discarding restriction. RotaShield was eventually pulled from market.
RotaTeq and Rotarix, next on the market, underwent large clinical trials with intussusception rates 1-5:100 000 in high-income and middle-income countries; Rotarix showed no elevated risks in low-income and middle-income country (no data from RotaTeq).
Key lessons: Postlicensure studies in large populations are essential.

Human papillomavirus vaccine and postural orthostatic tachycardia syndrome and complex regional pain syndrome
Concerns over complex regional pain syndrome and postural orthostatic tachycardia syndrome following the human papillomavirus vaccines on the market, Cervarix, Gardasil and Gardasil-9, led to lower coverage, confidence and some loss of country recommendations. Vaccine adverse event reporting system, European Medical Agency, Global Advisory Committee on Vaccine Safety and AAS and large-scale studies found no signals or patterns.
Key lessons: Postlicensure studies in large populations are essential and effective communication about safety is vital

RTS,S/adjuvant system 1 malaria vaccine and serious adverse events
- Exploratory analyses in phase 3 trial showed.
- Meningitis: increase risk of meningitis in two trial sites in one age group; regarded as potential signal.
- Cerebral malaria: increased in vaccinees versus controls.
- Mortality: increased mortality in vaccinated girls.
- Malaria: group receiving only three doses, higher severe malaria rate after 18 months versus controls, but effect ameliorated by booster dose at 18 months.

Key lessons: Postlicensure studies in large populations are essential to address potential safety signals from Phase 3 trials. Need for continuation of vaccine trials beyond initial demonstration of efficacy. If booster doses may be necessary, these should be built into the design of phase 3 trials.

dengue vaccine, chimeric yellow fever-dengue tetravalent dengue vaccine (CYD-TDV) (Dengvaxia), developed by Sanofi Pasteur, was licensed in 2015.[2] CYD-TDV is a live attenuated recombinant tetravalent vaccine that was evaluated in phase 3 efficacy trials with a 3-dose 0, 6 and 12 months schedule.[3] Results from a comprehensive phase 3 clinical trial programme indicated that protective efficacy varied according to serostatus prior to vaccination and serotype.[4] Vaccine-induced immunogenicity was not predictive of protective clinical efficacy, and no immune correlates (for protection or enhancing disease) were established.[4]

In the phase 3 trial, excess hospitalisations for dengue were observed among vaccine recipients 2–5 years of age. Precise risk estimates according to dengue serostatus prior to vaccination could not be ascertained because of the limited numbers of samples collected at baseline. A post hoc analysis of safety and efficacy used a novel dengue anti-non-structural protein 1 (NS1) IgG ELISA on samples from month 13 to retrospectively infer baseline serostatus. 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. HRs, comparing vaccinated to placebo recipients, for hospitalised virologically confirmed dengue (VCD) and severe VCD, were 0.21 (95% CI 0.14 to 0.31) and 0.16 (95% CI 0.07 to 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 to 2.68) and 2.44 (95% CI 0.47 to 12.56), respectively.[5] 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 increased risk 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.[6] In December 2017, Global Advisory Committee on Vaccine Safety (GACVS) recommended that Dengvaxia should only be administered to individuals who had been previously infected with wild dengue virus.[7] Based on WHO's Strategic Advisory Group of Experts (SAGE) recommendations, WHO's position published in 2018 is that for countries considering Dengvaxia vaccination as part of their dengue control programme, a prevaccination screening strategy, in which only dengue-seropositive persons are vaccinated, is recommended. [8]

Implementing a prevaccination 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.[8]

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

Causality conclusions and areas for future research

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 (antibody dependent enhancement can occur with dengue disease) when SAGE first made recommendations, before the manufacturer had conducted the postlicensure analyses, which consolidated the previous theoretical concerns and led to revised SAGE recommendations. There are also important lessons to be learnt for clinical development of second-generation live attenuated dengue vaccines (now in phase 3 trials).[9] 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. The licensure of the first dengue vaccine in several countries, though not necessarily approved for use by national public health agencies, 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. Dengue serostatus at baseline remains a critical variable, and safety and efficacy by serostatus should be presented in stratified analyses. 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. Immunogenicity and efficacy results should be interpreted in the context of potential transient immunity against the other serotypes that could wane over time and be associated with enhanced disease.

PANDEMIC INFLUENZA VACCINE AND NARCOLEPSY

In 2009, the A(H1N1) pandemic influenza virus (A/H1N1pdm09) rapidly spread globally starting from Mexico.[10] As part of a WHO coordinated pandemic mitigation plan, manufacturers developed several monovalent adjuvanted influenza vaccines to increase immunogenicity and spare doses.[11] Pandemrix, an Adjuvant System 03 (AS03) adjuvanted vaccine, was available primarily in Europe. Approximately 31 million doses were administered to populations in Finland, France, Germany, Ireland, Norway, Sweden and UK. A similar AS03 adjuvanted vaccine, Arepanrix, was primarily available in Canada. Another pandemic vaccine, Focetria, an MF59 adjuvanted vaccine, was used in Europe, with approximately 6.5 million doses globally, 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.[12] Both countries had offered Pandemrix to more than half of their population and coverage was up to 80% among school-aged children.

After the initial safety signals in Sweden and Finland, the European Medical Agency (EMA) commissioned a signal validation study via the European Centre for Disease Prevention and Control and the Vaccine Adverse Events Monitoring and Communication consortium; a case–control approach was used.[13] Several other epidemiological studies, including registry-based linkage studies in Finland[14] and Sweden[15] and self-controlled case series studies in the UK,[16] were conducted to evaluate the association in Europe. Most of these studies indicated significant although small absolute risk associated with Pandemrix vaccination, translating at the highest to an attributable risk of one per 16 000 vaccinated in the susceptible age group. In Canada, a case–control study was carried out, which found a smaller risk for Arepanrix, that is, one per million vaccinated.[17] Also, the US CDC commissioned a global case control study, the Sleep Apnoea Monitoring with Non-Invasive Applications (SOMNIA), in 13 different study sites in 9 countries.[18] It did not find an increased risk for the MF59 adjuvanted vaccine Focetria or the AS03 adjuvanted Arepanrix vaccine. Due to limited sample size in the population at risk, the SOMNIA results remain inconclusive for Pandemrix. A systematic review and meta-analysis of the published studies was conducted by Sarkanen *et al*, which demonstrated a 5-fold to 14-fold increased risk in children and adolescents and a 2-fold to 7-fold increased risk in adults of narcolepsy following receipt of the Pandemrix vaccine, and an attributable risk of 1 per 18 400 vaccinated. The risk has remained elevated for 24 months in the susceptible age groups in those countries where follow-up studies were done, that is, Sweden, Finland and the UK.[19]

Understanding the pathogenesis of the vaccination-associated narcolepsy would be of particular importance for future pandemic vaccination strategies. Narcolepsy is likely to be immune-mediated in view of the association of the disease with the HLA-DQB1*06: 02 haplotype.[20] In the case of vaccination associated narcolepsy; however, there is still scarce evidence of an autoimmune process.

In addition, there is growing evidence for an aetiological role of natural influenza viral infection, as suggested by the peak of narcolepsy observed in China[21] and Taiwan following the A/H1N109 outbreak in non-vaccinated populations.[22] During the 2009 pandemic, with the delay in the availability vaccines, there was considerable circulation of the pandemic virus in some countries before the vaccine was introduced. Thus, it was extremely difficult to sort out whether many of the immunised subjects had previously been infected with the wild-type H1N1 pandemic strain, and particularly in those vaccinees that ultimately developed narcolepsy. It should be noted that in Nordic European countries, the pandemic peak overlapped or immediately preceded vaccine implementation.[23] In Norway, serological studies indicated that

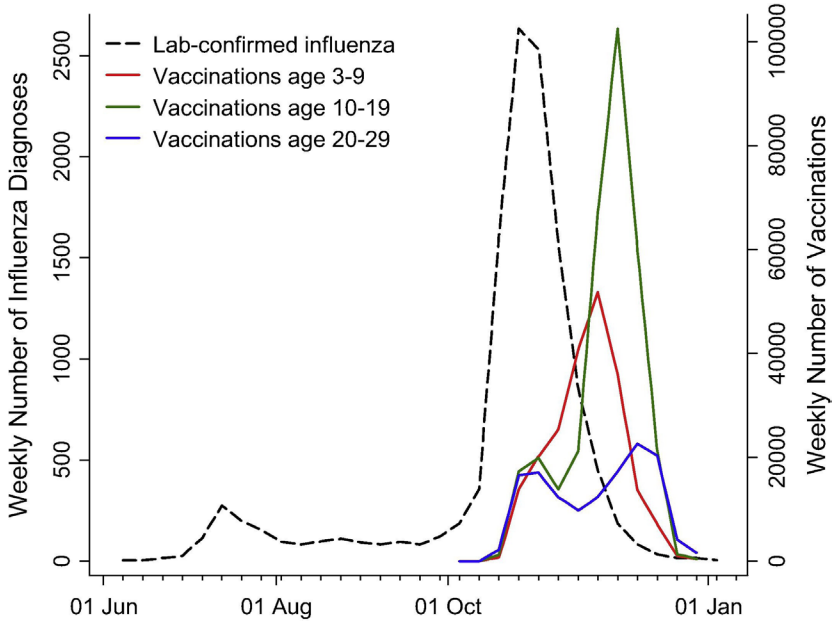

Figure 1 Kinetics of 2009 pH1N1 influenza outbreak and vaccination coverage in Norway.

vaccination of school-aged children peaked shortly after the peak of disease[24] (figure 1).

It was hypothesised that in some rare patients infected by H1N1/09 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 (cluster of differentiation 8) 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 pathogenicity (figure 2).[25] Timing of vaccination in relation to the outbreak may be critical.

Causality conclusion and areas for future research

At present, the association between narcolepsy and Pandemrix vaccination has been well established.[19] The exact mechanism of causality, that is, what actually causes the damage to hypocretin neurons, is not well understood. In the Nordic countries, where approximately 2000 vaccinated persons are estimated to have been permanently affected, the interpretation is that Pandemrix contributed

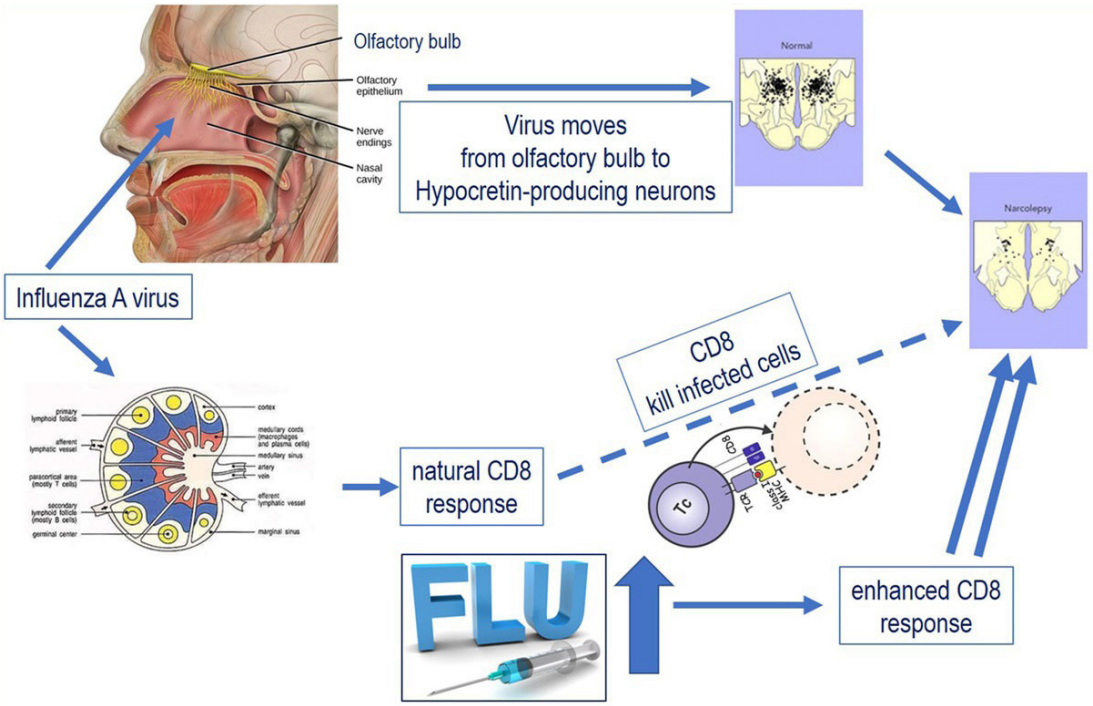

Figure 2 The two-hit hypothesis—a possible mechanism for an enhanced risk for narcolepsy following 2009 pH1N1.

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 programmes in these countries, but not necessarily elsewhere.[26] It also has been agreed that such a rare event would not have been detected a priori in phase 3 human clinical trials. The handling of this incident by scientists, medical authorities, and media have resulted in a significant drop in influenza vaccination coverage among children and distrust in authorities in charge of routine vaccination programmes in the most affected countries. As of 2020, there is no Pandemrix vaccine in use. The adjuvant AS03, however, has been stockpiled for future pandemic use, and now forms part of the scientific development of at least one vaccine candidate against COVID-19. It is evident that there will be future influenza and other pandemics; in that light it is important that research be continued to better understand the possible biological mechanisms of what happened.[27]

ROTAVIRUS VACCINATION AND INTUSSUSCEPTION

In 1999, the first licensed rotavirus vaccine, RotaShield (Wyeth), was withdrawn from the US market (about 14 months after it was licensed) shortly after its introduction because it was associated with intussusception at an estimated rate of 1 case per 10 000 vaccinated infants.,[28 29],[30] While the prelicensure trials with ~10 000 total subjects were unlikely to have identified this risk because of power limitations for this sample size, intussusception was listed as a potential adverse event because of a few reported cases during the prelicensure clinical trials and careful postlicensure monitoring was conducted.[31 32] Because of the RotaShield experience, the next generation of live-oral rotavirus vaccines—RotaTeq (Merck, West Point, Pennsylvania, USA) and Rotarix (GlaxoSmithKline, Rixensart, Belgium)—each underwent large clinical trials involving 60 000–70 000 infants to detect a low risk of intussusception. No elevated risk was found with either vaccine in the trials; both were subsequently recommended by WHO for global use starting in 2006.[33]

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 postlicensure evaluations with both RotaTeq and Rotarix in several high-income and middle-income countries (figure 3).,[34 35],[36],[37],[38],[39],[40] However, given that the health benefits of rotavirus vaccination greatly exceed this small risk, country and global policymakers continue to recommend routine use of rotavirus vaccines (table 1).[41] Of note, an evaluation in seven African countries using Rotarix, the only data available to date from low-income countries, did not show any increased risk of intussusception.[42] Similarly, in a separate evaluation in South Africa, no increased risk of intussusception was observed after Rotarix vaccination.[43] 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.[44] 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.[45] Regardless of mechanism, the finding that intussusception risk appears greatest in the 3–7 days after administration of the first rotavirus vaccine dose suggest that it is related to intestinal replication of the orally

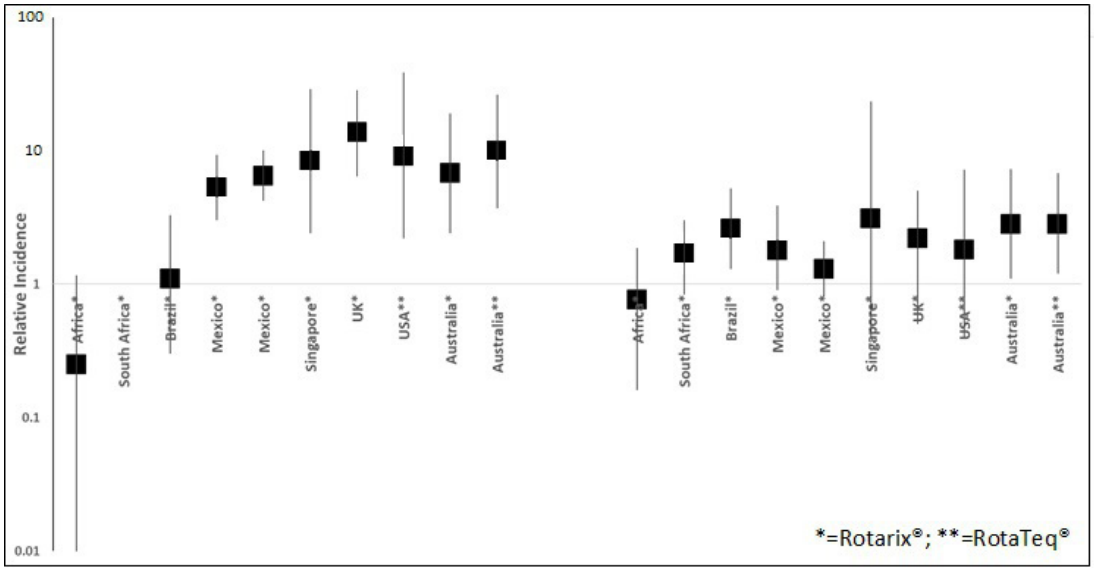

Figure 3 Relative incidence of intussusception from self-controlled case-series analyses in the 1–7 days following dose 1 and dose 2 of rotavirus vaccine by country.

Table 1 Risk–benefit of rotavirus vaccination by country on rotavirus hospitalisations and deaths and associated intussusception risk for one vaccinated birth cohort to age 5 years

Country	Vaccine evaluated	Vaccine dose(s)	Overall attributable risk*	Rotavirus outcomes averted	Intussusception outcomes caused
Mexico[34]	Rotarix	Dose 1 only	2.0–3.7	Hospitalisations: 11 551 Deaths: 663	Hospitalisations: 41 Deaths: 2
Brazil[34]	Rotarix	Dose 2 only	1.5	Hospitalisations: 69 572 Deaths: 640	Hospitalisations: 55 Deaths: 3
Australia[35]	Rotarix	Doses 1 and 2	4.3	Hospitalisations: 6528 Deaths: not reported	Hospitalisations: 14 Deaths: not reported
	RotaTeq	Doses 1 and 2	7.0		
USA[36 39]	Rotarix	Doses 1 and 2	5.3	Hospitalisations: 53 444 Deaths: 14	Hospitalisations: 35–166 Deaths: 0.1–0.5
		Dose 2 only	7.3		
	RotaTeq	Dose 1 only	0.7–1.5	Not reported	Not reported
England[40]	Rotarix	Dose 1 only	1.68	Hospitalisations: 25 000 Deaths: not reported	Hospitalisations: 21 Deaths: not reported

Note: Table adapted from Reference.[87]
*Excess intussusception cases per 100 000 vaccinated infants.

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 and middle-income countries (LMICs) versus high-income countries.[46]

Although debated, some evidence suggested a potentially higher risk of intussusception among children administered the first RotaShield dose at age >3 months.[4748 49] Because of this concern, age restrictions were initially recommended for rotavirus vaccines—the first dose to be administered no later than 15 weeks of age and the last dose no later than 32 weeks.[50] However, these age restrictions could potentially disqualify a substantial number of children from receiving rotavirus vaccination, particularly in LMICs where delays in vaccine administration are common. Consequently, 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 rotavirus deaths while potentially causing an additional 294 intussusception deaths in LMICs.[51] Given these risk–benefit considerations, WHO recommended removal of 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 maximise the net benefits of vaccination.[29]

Causality conclusion and areas for future research

Whether the short-term increased risk of intussusception immediately after vaccination translates into an overall population-level increase in intussusception is unknown. Some have hypothesised 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.[52] Also, given that intussusception has been associated with three biologically different live-oral rotavirus vaccines, it has been hypothesised that wild-type rotavirus infection could be a cause of intussusception and vaccination may protect against rotavirus-induced intussusception.[53] In the USA, population-level data post-vaccine introduction do not show an overall increase in intussusception rates among infants despite a small increase in the 8–14 weeks age group when the first dose is administered.,[5354] Furthermore, no long-term increased risk of intussusception in the year after vaccination was observed among rotavirus vaccinated vs unvaccinated infants; instead, a trend towards decreased long-term risk was seen.[55] More data are needed to fully understand the overall population-level impact of rotavirus vaccination on intussusception risk.

In 2018, two new live-oral rotavirus vaccines—Rotavac (Bharat Biotech, Hyderabad, India) and Rotasiil (Serum Institute of India, Pune, India)—were prequalified by WHO. Prelicensure trials of these vaccines that included ~5000 infants each were primarily designed to examine vaccine efficacy.[565758] Consequently, as larger numbers of infants are immunised with these vaccine in different geographical locations, generating post-licensure intussusception data for these vaccines is a priority.

HPV VACCINE AND POTS AND CRPS

HPV vaccines are powerful tools for preventing cervical cancers and other HPV-related diseases worldwide. Three HPV vaccines are 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.[59] Substantial reassuring vaccine safety data have been accumulated from pre-licensure trials as well as postlicensure monitoring and evaluations.[60] Syncope and anaphylaxis are known,

rare adverse events following HPV vaccination. Despite a favourable safety profile, concerns about safety have impacted the acceptability of HPV vaccines in some countries. A variety of safety concerns have been raised and investigated for HPV vaccine; two safety concerns include CRPS and POTS. Both syndromes have created challenges for national immunisation programmes, especially in Japan, Denmark and Ireland, resulting in decreased public confidence, decreased coverage rates and/or withdrawal of national HPV vaccination recommendations.[61]

The biological mechanisms of CRPS and POTS 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.[61] It is typically precipitated by trauma, exposure or illness causing nerve or tissue injury and is commonly associated with autonomic nervous dysfunction.[62] POTS is a form of dysautonomia that is characterised by orthostatic intolerance and often accompanied by a range of other symptoms, including headache, other aches and pain, fatigue and nausea.[62] Both CRPS and POTS are diagnostically challenging syndromes with unclear heterogeneous aetiology and onset. While the two syndromes are clinically distinct, symptoms often overlap with each other and with other conditions, such as chronic fatigue syndrome and fibromyalgia. Both are known to occur in adolescence and early adulthood.[63] Estimated incidence rates for CRPS and POTS are 6.28 per 100 000 person-years and 10.1 per 100 000 person-years, respectively.[64]

Published case reports of these syndromes following HPV vaccination 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 recruited from clinics that evaluate persons with an existing concern of HPV vaccine-induced illness or online sites discussing HPV vaccine injury.[656667] The generalisability and validity of these studies are unknown. Few data are available from large population-based studies. Two large US data mining studies did not identify any signals for CRPS or POTS.,[6869] Monitoring from the US Vaccine Adverse Event Reporting System found few reports of CRPS or POTS and no patterns to suggest a causal association with either Cervarix, Gardasil, or Gardasil-9.[707172] An extensive review of GlaxoSmithKline's safety database for CRPS following Cervarix also did not find an increase in the incidence of CRPS following vaccination.[73] In 2015, the EMA conducted a detailed expert review of CRPS and POTS following HPV vaccines from a variety of data sources and concluded that the available evidence does not support that CRPS or POTS are caused by HPV vaccine.[74] In 2017, after a review of available data, WHO's GACVS found no new evidence for a causal association between HPV vaccines and CRPS and POTS.[75] More recently, the American Autonomic Society published a position statement concluding that there are no data to support a causal relationship between HPV vaccination and CRPS and POTS.[54]

Causality conclusion and areas for future research

Despite the reassuring data available finding no association between HPV vaccines and CRPS and POTS concerns continue to challenge immunisation programmes. Background rates in populations aged 9–26 years (the recommended age group for HPV vaccine) would be helpful to determine if CRPS and POTS cases observed following HPV vaccination exceed what is expected. Quality population-based epidemiological 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 is essential in maintaining the public's confidence in vaccines.

RTS,S/AS01 MALARIA VACCINE AND MENINGITIS, CEREBRAL MALARIA, FEMALE MORTALITY AND REBOUND SEVERE MALARIA

RTS,S/AS01E is a recombinant yeast-expressed subunit malaria vaccine using the hepatitis B surface antigen as a matrix carrier for epitopes derived from the *Plasmodium falciparum* circumsporozoite protein formulated with a proprietary AS01E. The phase 3 trial of the vaccine included ~9000 children aged 5–17 months and 6500 infants aged 6–12 weeks, enrolled at 11 centres in seven countries in 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, 2 and 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 surveillance and any serious adverse events were also recorded. Children were followed up for at least 3 years after the first vaccine dose.[76] 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. Protection was boosted by the fourth vaccine dose but protection against severe malaria over the whole trial period was demonstrated only in the older age group among children who received four vaccine doses.

Following the trial, the EMA gave the vaccine a positive scientific opinion[77] and the two WHO policy committees on vaccination and malaria (SAGE and Malaria Policy Advisory Committee, MPAC, respectively) recommended pilot implementation studies in children from the age of 5 months. These were started in Malawi, Ghana and Kenya in 2019.[78]

Safety concerns arising from the phase 3 trial

Meningitis: Among children in the older age group, there was an excess of cases of meningitis in those who received

RTS,S/AS01E (with or without a fourth dose) compared with 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 showed no temporal association with vaccination and included a mixture of aetiologies. Most cases were reported from two trial sites.[79] GACVS concluded that meningitis should be regarded as a potential signal which requires further assessment postlicensure.[80]

Cerebral malaria: In the older age group, there was an excess of cerebral malaria in the 4 and 3 dose groups compared with 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 (and observed)[81] that this would be low in a carefully monitored trial. In the older age group, overall mortality was higher in the two 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 (2:1 ratio)). 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%).[82] There was no explanatory pattern for the gender imbalances among causes of death ascertained by verbal autopsies.[67]

Rebound malaria: In the older age group there was a reduced risk of severe malaria between the first vaccine course (three doses) and the time of the fourth dose. After the fourth dose, the rate of severe malaria was similar to that in the control group. However, in those who received only three doses, after 18 months the incidence of severe malaria was higher than in the control group, and over the whole trial period the incidence of severe malaria was similar in the three-dose group as in the control group. This raised two potential longer-term safety concerns. First that the incidence of severe malaria in the three-dose group would exceed that in the control group in the longer term and, second, that there may be a similar 'rebound' in the four-dose group after a longer time interval. However, no evidence of these potential effects was seen in a study in which children in the trial from a subset of 3 trial sites were followed up for 7 years postvaccination.[83]

Causality conclusion and areas for future research

RTS,S/AS01 was reviewed comprehensively by the EMA, and although they are not empowered to licence a vaccine that is not intended for use in the European Union, the 'positive scientific opinion' they gave indicated that the vaccine satisfied the criteria for licensure.[84] Generally, when a vaccine has been licensed, potential safety concerns would be addressed through the manufacturers postmarketing risk management. The recommendation from SAGE and MPAC for pilot implementation studies before more widespread use was a novel approach.[85] As well as assessing impact and delivery feasibility in programmatic conditions, the pilot studies have been powered to address the safety concerns related to meningitis, cerebral malaria and gender-specific mortality.[86]

Except for the possibility of rebound malaria, there are no clear biological mechanisms to explain any of the other safety signals observed and the possibility that they were chance findings cannot be excluded.

Evaluation by regulators and investigators of data gathered in the pilot studies 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.

CONCLUSIONS

Lessons learnt for vaccine safety in genreal and opportunities for future reserarech

Vaccine safety science must be proactive and timely, and conducted with rigour, objectivity and transparency. Vaccine safety concerns are often for outcomes that seem to be increasing in incidence, have poorly understood aetiology and are concerning to the public. When new or unexpected adverse events following immunisation (AEFI) occur, it is helpful to have case definitions already available or quickly developed. Poor understanding of disease aetiology and limitations in disease diagnostics hamper vaccine safety studies as exemplified by POTS and CRPS. Such diseases often end up with rapid consultations from experts not typically engaged in vaccine safety monitoring. It is important to have mechanisms in place to rapidly engage expertise in the AEFI of interest. The HPV/POTS-CRPS situation also exemplifies the importance of rigorous and timely studies. Quality population-based epidemiological studies with medical record outcome validation would provide far more conclusive evidence than we currently have, yet several countries have already experienced drops in immunisation coverage because of these issues. 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 (eg, narcolepsy following pandemic influenza vaccination, intussusception following rotavirus vaccination). Such temporal associations tend to suggest 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. Events occurring more distant

from vaccination may not be reported, even if they are truly causally related. Temporal association may be falsely interpreted as causal, particularly for health outcomes that vary in incidence with age if an age group with a high incidence happens to be around the age at which a vaccine is introduced.

AEFIs that occur with no clear temporal relationship to vaccination are difficult to assess, because most surveillance systems for AEFIs are not set up to detect such associations. For example, the increased risk of severe dengue in seronegative vaccinees only became apparent in the third year after vaccination. Some vaccinations increase the susceptibility to adverse events from other exposures that may occur any time after vaccination. This seems to be the only plausible mechanism for the possible increased risk of meningitis following RTSS/AS01E. 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 (eg, the HPV vaccine associations, the trials of second-generation rotavirus vaccines) and consequently upper limits on the possible risk must be defined. Vaccine safety research is often difficult, and requires substantial resources. Without regulatory requirements, manufacturers may not be incentivised to do so. Who pays for such research and how it gets done remains an outstanding question. This is particularly challenging in LMICs which lack the infrastructure for vaccine safety studies.

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 (eg, intussusception following rotavirus vaccine). Relative risks are important for determining the causal association of an AEFI. However, from a public health perspective attributable risks to the vaccine are of primary interest, so proper comparisons can be made to the risks of a vaccine preventable disease and the benefits of vaccination. Vaccine risk must be viewed alongside the benefits, and the risk-benefit ratio may vary (eg, between high and LMICs) as is the case with intussusception and rotavirus vaccines.

Interactions between the vaccine, natural disease and the AEFI are particularly difficult to identify and separate the effect of disease vs the vaccine. In-depth understanding of natural disease facilitates understanding the interaction between the vaccine and natural disease. 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.

The case studies presented herein elucidate opportunities for future research. These case studies were selected because they are recent and varied in the vaccine safety issues they elucidate. However, a systematic review of vaccine safety would facilitate development of a global vaccine safety research agenda, which would be incredibly useful. 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 prioritisation. The research agenda should then be used to rapidly and rigorously investigate high priority research.

Communication around vaccine safety must be proactive and timely, evidence-based, finding commonalities with the public through shared values, tailored to individuals and from credible sources. One vaccine safety issue can spill over to other vaccines and adversely impact routine vaccination programmes. Communication must address the specific issues at hand, but also consider the broader issues of vaccine benefits and confidence in immunisation programmes.

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