BMJ Global Health

Vaccine safety issues at the turn of the 21st century

Laura Conklin,[1] Anders Hviid,[2] Walter A Orenstein,[3] Andrew J Pollard,[4,5] Melinda Wharton,[6] Patrick Zuber [7]

To cite: Conklin L, Hviid A, Orenstein WA, *et al*. Vaccine safety issues at the turn of the 21st century. *BMJ Global Health* 2021;**6**:e004898. doi:10.1136/bmjgh-2020-004898

Handling editor Seye Abimbola

Received 29 December 2020
Revised 2 March 2021
Accepted 4 March 2021

[1]Global Immunizations Division, Centers for Disease Control and Prevention, Atlanta, Georgia, USA
[2]Department of Epidemiology Research, Statens Serum Institut, Kobenhavn, Denmark
[3]Emory Vaccine Center, Emory University, Atlanta, Georgia, USA
[4]Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Oxford, UK
[5]NIHR Oxford Biomedical Research Centre, Oxford, UK
[6]Immunization Services Division, Centers for Disease Control and Prevention, Atlanta, Georgia, USA
[7]Essential Medicines and Health Products, Organisation mondiale de la Sante, Geneve, Switzerland

Correspondence to
Dr Laura Conklin; dvj3@cdc.gov

ABSTRACT

Global gains in vaccination coverage during the early 21st century have been threatened by the emergence of antivaccination groups that have questioned the effectiveness of vaccines to generate public distrust of vaccines and immunisation programmes. This manuscript summarises six key topics that have been at the centre of global discussions on vaccine safety during the early 21st century: thiomersal in multi-dose non-live vaccines, aluminium adjuvants used with several non-live vaccines, autism and auto-immune conditions as possible consequences of vaccination, a risk of immune overload with increasing numbers of vaccinations, and detrimental non-specific effects (NSEs) of vaccination. For each topic, we describe the hypothesis behind the public concern, the evidence reviewed by the WHO's Global Advisory Committee for Vaccine Safety (GACVS) during 1999–2019, and any significant new data that has emerged since GACVS conclusions were made. Although the scientific evidence on these issues overwhelmingly supports the safety of vaccines, communication messages to caregivers and providers need to condense and convey scientific information in an appropriate way to address concerns contributing to vaccine distrust. In addition, there is need for further studies specifically designed to address both positive and negative NSE of vaccination. The role of GACVS will be increasingly important in evaluating the evidence and engaging the global community in promoting and assuring the safety of vaccines in the decades to come as we move into an era in which we use new vaccination platforms, antigens and formulations.

Summary box

- During 1999–2019, the Global Advisory Committee for Vaccine Safety (GACVS) reviewed several key topics that have been at the centre of the discussion on vaccine safety.
- Evidence from multiple sources and epidemiological settings, including both prelicensure and postlicensure data, on six vaccine safety issues, was critically reviewed by GACVS, an independent advisory board of the WHO.
- The Committee found a lack of association between different vaccinations or ingredients and autism, auto-immune conditions, and immune overload.
- Conclusions on the non-specific effects (NSE) of vaccines have consistently been and remain that the evidence is not sufficient to warrant changes in global immunisation policy.
- However, further studies specifically designed to address both positive and negative NSEs are needed.

INTRODUCTION

Due to advances in modern medicine, the global community now benefits from greatly reduced rates of serious infectious diseases that used to be common. Immunisation is the largest clearly documented contributor to this progress, and vaccines may also play an increasingly important role in controlling the spread of antibiotic-resistant and antiviral-resistant organisms.[1] Nevertheless, sustaining the gains in global vaccination programmes requires maintaining public trust in both vaccine efficacy and vaccine safety. Misinformation on vaccinations, their ingredients and their mechanisms of action, is now easily perpetuated through social media and misinformed public figures. Numerous vaccine safety concerns have drawn much public attention over the last several decades and were reviewed in detail during the early years of the Global Advisory Committee for Vaccine Safety (GACVS), an advisory committee established by the WHO in 1999 to provide independent, scientifically rigorous advice on vaccine safety issues of potential global importance. The GACVS terms of reference includes the transparent review of the latest scientific data, in all fields ranging from basic sciences to epidemiology, concerning any aspect of vaccine safety of global or regional interest. Reports from committee meetings are available to the public on the internet on the GACVS website https://www.who.int/vaccine_safety/committee/reports/en/. GACVS may revisit a given safety topic multiple times when new or otherwise relevant information becomes available.

Since 1999, the GACVS has reviewed the evidence on different vaccine components (eg, thiomersal in multi dose non-live

vaccines and aluminium adjuvants used in several non-live vaccines) multiple times, as well as any association between vaccination and broad categories of adverse health outcomes, including autism, overloading the immune system, a possible association between vaccines and auto-immune syndromes, and increased mortality among vaccine recipients as possible non-specific effects (NSEs) of immunisation. Each of these issues has been linked to reduced public trust in vaccines and vaccination programmes. Therefore, a robust body of scientific evidence has been generated in the last several decades to assess the biological and epidemiological plausibility of these safety concerns and assure the safety of vaccinations worldwide.

In this manuscript, we summarise the GACVS review of these topics, the conclusions and recommendations that were made, any recent data for the Committee's consideration, and the implications for future work on these topics.

ALUMINIUM ADJUVANTS

Aluminium is ubiquitous in the environment and is a component of many consumer products, including antacids, astringents and antiperspirants. Since the early 20th century, aluminium has been used as an adjuvant to enhance immune responses to vaccines in a variety of forms including aluminium oxide, hydroxide and soluble salts. The mechanism of action is complex and includes direct stimulation of multiple immune receptors, thereby enhancing the body's natural immune response to the antigen.[2] Concentrations of aluminium vary greatly among different vaccine products, primarily non-live vaccines, ranging from none in measles, mumps, rubella (MMR) vaccine to 1.5 mg of aluminium phosphate per dose in diphtheria-tetanus (DT) vaccine.[3]

While daily aluminium exposure in humans can range from 0.06 mg/day (from inhaling particulates in the air) to 3500–5200 mg/day (from antacid consumption), aluminium has been associated with encephalopathy in high intravenous exposures, such as those received through renal dialysis or intravenous nutritional products.[3] These data have been used by organised groups who are opposed to vaccination to hypothesise a link between the immunisations and developmental delays and other adverse neurological outcomes.[4–6] More recently, aluminium adjuvants have been alleged to cause poorly defined autoimmune syndromes.[7]

Multiple high-quality studies have shown that children who receive vaccines containing aluminium adjuvants do not have aluminium in their blood or hair above the minimum risk levels established by the Agency for Toxic Substances and Disease Registry, and they are not at increased risk of adverse neurodevelopmental outcomes.[8–10] The GACVS reviewed the available safety data on adjuvants, including aluminium compounds for the first time in 1999, specifically addressing a type of histopathological lesion of unknown origin called macrocytic myofasciitis[11 12] (table 1). In 2004, the Committee recognised the need for surveillance of vaccine adjuvant safety, particularly in low-income and middle-income countries, and made recommendations for WHO to consider developing a website for adjuvant contents of vaccines. In addition, the Committee asserted that the role of GACVS and WHO regarding adjuvant safety was to review and consolidate the evidence. After reviewing several studies in 2012 alleging an association between aluminium and autism spectrum disorders, the GACVS emphasised that ecological studies should not be used to assess a causal association because these types of studies are unable to link exposure outcomes to individuals.[1]

Table 1 Global Advisory Committee for Vaccine Safety (GACVS) reports released during 1999–2019 that included review of data on aluminium adjuvants

GACVS report		Exposure	Outcome	Report link
1999	September	Aluminium	MMF	https://www.who.int/vaccine_safety/committee/reports/wer7441.pdf?ua=1
2002	June	Aluminium	MMF	https://www.who.int/vaccine_safety/committee/reports/wer7747.pdf?ua=1
2003	December	Aluminium	MMF	https://www.who.int/vaccine_safety/committee/reports/wer7903.pdf?ua=1
2004	June	Adjuvants (general)	General safety	https://www.who.int/vaccine_safety/committee/reports/wer7929.pdf?ua=1
2004	December	Adjuvants (general)	General safety	https://www.who.int/vaccine_safety/committee/topics/thiomersal/wer8001.pdf?ua=1
2005	December	Adjuvants (general)	General safety	https://www.who.int/vaccine_safety/committee/reports/wer8102.pdf?ua=1
2012	June	Aluminium Aluminium	Autism Pharmaco-kinetics	https://www.who.int/vaccine_safety/committee/topics/thiomersal/wer8730.pdf?ua=1

MMF, macrocytic myofasciitis.

During the same meeting in 2012, the Committee also reviewed a pharmacokinetic model of aluminum-containing vaccines from the US Food and Drug Administration.[13] Results from this quantitative risk assessment showed that the body burden of aluminium following the injections of aluminium-containing vaccines never exceeds the safe US regulatory thresholds based on orally ingested aluminium, even for low birthweight infants.

Although the evidence on the safety of aluminium adjuvants is strongly reassuring, the public concern continues to be fueled by poorly designed studies and inaccurate extrapolation from such studies.[14] As new vaccines and adjuvants are developed, continued safety monitoring is important during both prelicensure and postlicensure to ensure safety of the vaccine, address public concerns and maintain trust.

THIOMERSAL

Thiomersal is best known as a vaccine preservative, primarily used in multidose vials of non-live vaccines for its antiseptic and antifungal properties.[15] Thiomersal is metabolised into ethylmercury, an organic mercury compound, and is used in concentrations corresponding to 12.5–50 µg of ethylmercury per vaccine dose. Concerns about the cumulative exposure of mercury from childhood vaccination schedules and other sources led to the replacement of thiomersal-containing vaccines with thiomersal-free formulations in many high-income countries in the 1990s and early 2000s. For example, the estimated exposure to ethylmercury from vaccines in the US childhood immunisation schedule in 1999 was 237.5 µg (275 µg if three doses of influenza vaccine were also administered) by 2 years of age.[16] While mercury compounds are all neurotoxic at sufficiently large doses, most of the concern about thiomersal-containing vaccines were based on experiences with methylmercury—a different organic mercury compound with known neurotoxic effects. Humans primarily encounter methylmercury through fish consumption, and there is ample evidence that fetal exposure, especially through fish consumption in pregnancy has adverse effects on neurodevelopment.[17] However, ethylmercury has different pharmacokinetic properties than methylmercury. The half-life of ethyl mercury is short (less than 1 week) compared with methyl mercury (1.5 months), making exposure to ethyl mercury in blood comparatively brief. Moreover, it is excreted rapidly via the gastrointestinal tract.[18 19]

Large studies from Denmark, the UK, and the USA during 2003–2010, comprising more than 690 000 children have evaluated the association between thiomersal-containing vaccines and autism; they have all reached the same conclusion: there is no evidence that thiomersal-containing vaccines increase the risk of autism.[20–23] Similarly, studies looking at a wide range of neurodevelopmental outcomes, including both diagnostic outcomes and early life behaviour, cognition and motor skills have been reassuring.[21 22 24 25] The most notable study was conducted in the USA with the prospective enrolment of 1047 children at the ages of 7–10 years, assessing 42 neuropsychological outcomes.[24] Thiomersal exposure was determined retrospectively from medical records and included exposure from immunisations, immunoglobulins and prenatal exposure during pregnancy. Overall, the results did not support an association between thiomersal and increased risk of neuropsychological outcomes. A few associations, both positive and negative, were noted, consistent with what would be expected due to chance when conducting a large number of statistical tests.

GACVS has reviewed the thiomersal issue multiple times from 2002 to 2012 (table 2), including comprehensive

Table 2 Global Advisory Committee for Vaccine Safety (GACVS) reports released during 1999–2019 that included review of data on thiomersal

GACVS report		Exposure	Outcome	Report link
2002	June	DTP HepB	Neurodevelopmental delay Leukaemia	https://www.who.int/vaccine_safety/committee/reports/wer7747.pdf?ua=1
2003	June	HepB, other	General safety	https://www.who.int/vaccine_safety/committee/reports/wer7832.pdf?ua=1
2004	Dec	Thiomersal (animal models)	Autism, neurodevelopmental delay	https://www.who.int/vaccine_safety/committee/topics/thiomersal/wer8001.pdf?ua=1
2005	June	Thiomersal	Mercury levels	https://www.who.int/vaccine_safety/committee/topics/thiomersal/wer8028.pdf?ua=1
2008	June	HepB Thiomersal	Mercury levels Neuropsychological performance	https://www.who.int/vaccine_safety/committee/reports/wer8332.pdf?ua=1
2012	June	Thiomersal	Mercury levels, autism, neurodevelopmental delay, special risk groups	https://www.who.int/vaccine_safety/committee/topics/thiomersal/wer8730.pdf?ua=1

DTP, diphtheria, tetanus and pertussis vaccine; HepB, hepatitis B vaccine.

reviews of both pharmacokinetic studies on ethylmercury and epidemiological studies of neurodevelopmental outcomes. The Committee concluded that thiomersal-containing vaccines do not increase the risk of autism or the risk of many other neurodevelopmental outcomes.[13]

Thiomersal has a proven history of efficacy and safety. While thiomersal has been removed from the routinely used paediatric vaccines in most high-income countries as a precautionary measure, as an effective preservative it continues to play a vital role as a preservative in allowing access to uncontaminated vaccines for millions of people globally. It is also noteworthy, that in countries where thiomersal has been removed from childhood vaccines, the prevalence of neurodevelopmental disorders such as autism has continued to increase.

AUTISM

The hypothesised link between vaccines and autism continues to cause concern and fear among parents despite many large, well-conducted studies showing that administration of vaccines is not associated with increased risk of autism.[26–36] An increasing body of evidence supports that autism is a predominantly genetic disorder with an inheritance of up to 80%.[26] The concept of a vaccine-autism link originally gained mainstream attention in the wake of a later retracted *Lancet* paper from 1998, suggesting an association between the MMR vaccine and autism.[27] At the beginning of the 2000s, the mercury-containing vaccine preservative thiomersal was also linked to autism via claimed neurotoxic effects, as discussed earlier.[26] More recently, aluminium adjuvants and expanding routine immunisation schedules have been postulated to cause autism via neurotoxicity and immune overload, respectively.[5 29] Many anecdotal observations of autistic signs, developing shortly after or even immediately after vaccination, and a supposed autism epidemic coinciding with expanding immunisation schedules have been the two common arguments raised by the proponents of the link between vaccination and autism. First, it must be recognised that the natural onset of autism symptoms coincides with the scheduled vaccinations at certain ages; hence, purely by chance, some parents will observe early autistic signs after vaccinations. Second, the notion of an autism epidemic is disputed. The main reasons contributing to the increased reporting of autism diagnoses in many countries are the increased recognition of the condition—including the less debilitating manifestations on the autistic spectrum—and the fact that a diagnosis is often needed for government help and support.[30]

The Committee reviewed the issue of MMR vaccination and autism in late 2002 and concluded that there was no evidence to support a link.[31] During the period of 2002–2012, the Committee reviewed several times the issue of thiomersal and neurodevelopmental disorders, including autism and reached the same conclusion: there was no support for a link between thiomersal and autism[13] (table 3).

The strongest evidence against the postulated links between vaccination and autism comes from large, well-controlled epidemiological studies, including several key studies originating from Denmark. In 2002, Danish researchers reported a nationwide cohort study of more than 537 303 children with individual-level information on MMR vaccination and autism diagnoses.[32] In this large cohort, there was no significant difference in the rate of autism between the group of children who received the MMR vaccine and those who did not. A similar nationwide study in 2003 compared 467 450 Danish children vaccinated with either a thiomersal-containing pertussis

Table 3 Global Advisory Committee for Vaccine Safety (GACVS) reports released during 1999–2019 that included review of data on autism

GACVS report		Exposure	Outcome	Report link
2002	June	DTP	Neurodevelopmental delay	https://www.who.int/vaccine_safety/committee/reports/wer7747.pdf?ua=1
2002	December	Multiple	Autism	https://www.who.int/vaccine_safety/committee/reports/wer7804.pdf?ua=1
2004	December	Multiple	Autism, neurodevelopmental delay	https://www.who.int/vaccine_safety/committee/topics/thiomersal/wer8001.pdf?ua=1
2012	June	Aluminium	Autism	https://www.who.int/vaccine_safety/committee/topics/thiomersal/wer8730.pdf?ua=1
2012	June	Thiomersal	Mercury levels, autism, neurodevelopmental delay, special high-risk groups (eg, premature infants, immunocompromised infants)	https://www.who.int/vaccine_safety/committee/topics/thiomersal/wer8730.pdf?ua=1

DTP, diphtheria, tetanus and pertussis vaccine.

vaccine or a thiomersal-free formulation of the same pertussis vaccine.[20] There was no association between thiomersal content and autism. The Danish researchers revisited the MMR–autism issue in 2019. In a new cohort of 657 461 children not included in the two previous studies; they found no association between MMR vaccination and autism.[33] Other notable studies include case–control studies from the UK and the USA on MMR vaccination and autism[34 35] and cohort studies on thiomersal and autism, also from the UK and the USA.[21 22] A 2014 meta-analysis confirmed that vaccines do not increase the risk of autism.[36] A common response to the many well-conducted observational studies reporting no association has been the claims of vulnerable subgroups of children or specific vaccine-induced phenotypes of autism. These claims are also not supported by observational research.[33]

AUTO-IMMUNITY

Auto-immune diseases include a wide variety of different pathologies that are often poorly defined. Associations between vaccination and chronic auto-immune conditions (eg, multiple sclerosis, thyroid disease and auto-immune encephalitis) are largely based on the concept of molecular mimicry whereby auto-antibodies are produced after exposure to an infectious agent. This phenomenon has been linked to some natural infections, including Group A Streptococcus (rheumatic fever) and measles virus (acute disseminated encephalomyelitis).[37]

The postulated link between vaccination and auto-immune conditions has been extensively explored via controlled trials, observational studies and epidemiological analyses in multiple countries and in subpopulations.[38–53] For the hepatitis B vaccine, the lack of an association with rheumatoid arthritis, thyroid disease or multiple sclerosis has been clearly proven.[38] In the case of the human papillomavirus vaccine (HPV), there is strong evidence against an elevated risk of Guillain-Barré syndrome (GBS),[40 41] central demyelinating disease and multiple sclerosis.[42 47] Current evidence does suggest a small elevated risk of GBS after influenza vaccination although these data are limited, and the risk is considerably lower than the risk of GBS after natural influenza infection.[43] During the 2009/2010 influenza pandemic, there was also the evidence of a causal relationship between narcolepsy and one adjuvanted H1N1 vaccine among school-aged children who had a genetic predisposition. Nevertheless, investigators concluded that natural viral infection may have played a role in this observation as a vaccine-enhanced viral immunopathology rather than an isolated vaccine-induced autoimmune event.[44–46]

The Committee has reviewed data on the possible relationship between autoimmune conditions and a variety of different vaccines over the years (2002–2017) (table 4); however, the safety profile of HPV remained a major focus from 2009 to 2017 due to ongoing public concerns fuelled by antivaccination groups. In 2009, GACVS concluded that there was no convincing evidence of an association between HPV vaccination and central demyelinating diseases.[47] In 2013, the Committee reviewed evidence from the USA, Australia, Japan, France, and the manufacturers of Cervarix (GlaxoSmithKline) and Gardasil (Merck) in regard to autoimmune diseases with a focus on multiple sclerosis. They concluded that the studies demonstrated no increased risk of autoimmune diseases, including multiple sclerosis, among girls who received the HPV vaccine compared with those who did not.[48–52] The topic of autoimmunity was again revisited in 2015 when GACVS reviewed data from a retrospective cohort study in France, involving over 2 million girls, which showed a similar incidence of autoimmune conditions in the vaccinated and unvaccinated populations for all conditions studied, with the exception of GBS where increased risk was identified, mainly focused within 3 months after vaccination.[53] The risk in the first few months after vaccination was very small (~1 per 100 000 vaccinated children) and had not been seen in other smaller studies. The Committee concluded that additional studies with adequately sized populations would help evaluate this finding. In July 2017, safety data for >3 million women aged 18–44 years from Denmark and Sweden were reviewed, and it showed an apparent increased risk of coeliac disease after HPV vaccination.[54] The Committee and study investigators agreed that this most likely represented an unmasking of an existing condition during the vaccination visit rather than a causal association and that overall, the study did not raise any other autoimmune safety issues of concern. The Committee expressed concern that, despite accumulated safety evidence, including several million persons comparing the risks for a wide range of health outcomes in HPV-vaccinated and unvaccinated subjects, public attention continued to focus on spurious case reports and unsubstantiated allegations. In 2019, the Committee released a communication about the safety of HPV vaccines to address the rumours and misinformation.[55]

The temporal association of the autoimmune disease with vaccination is not sufficient to support a causal relationship, and the global evidence supports that vaccines do not increase the risk of auto-immune diseases. One of the challenges associated with continuous safety monitoring data is that temporal but not causal relationships will be observed, which could pose further challenges for communication when taken in haste, out of context, and in the absence of the overall body of evidence.

IMMUNE OVERLOAD

The number of antigens recommended by WHO's Expanded Programme on Immunisation to be delivered in routine immunisation schedules during infancy has increased over the past few generations from 6 in 1974 to 12 antigens in 2019.[56] The concept of immune system 'overload' from many vaccinations is poorly defined but generally refers to the belief that the body has either a reduced response to multiple antigens given at the same

Table 4 Global Advisory Committee for Vaccine Safety (GACVS) reports released during 1999–2019 that included review of data on auto-immune and related conditions

GACVS report		Exposure	Outcome	Report link
2002	June	HepB	Multiple sclerosis	https://www.who.int/vaccine_safety/committee/reports/wer7747.pdf?ua=1
		Influenza	Bell's palsy	
2003	December	Influenza	GBS, multiple sclerosis, optic neuritis	https://www.who.int/vaccine_safety/committee/reports/wer7903.pdf?ua=1
2005	December	HepB	Chronic fatigue	https://www.who.int/vaccine_safety/committee/reports/wer8102.pdf?ua=1
		Meningococcal	GBS	
2006	November	Meningococcal	GBS	https://www.who.int/vaccine_safety/committee/reports/wer8203.pdf?ua=1
2007	June	Meningococcal	GBS	https://www.who.int/vaccine_safety/committee/reports/wer8228_29.pdf?ua=1
2007	December	Influenza, DTP tetanus, meningococcal	GBS	https://www.who.int/vaccine_safety/committee/reports/wer8304.pdf?ua=1
		HepB	Rheumatic arthritis	
		Meningococcal	Chronic fatigue	
		Rotavirus	Kawasaki's disease	
2008	December	HPV	Central demyelinating disease, other	https://www.who.int/vaccine_safety/committee/reports/wer8405.pdf?ua=1
2013	June	HPV	GBS, allergic reaction	https://www.who.int/vaccine_safety/committee/reports/wer8829.pdf?ua=1
2013	December	HPV	Multiple sclerosis, other	https://www.who.int/vaccine_safety/committee/reports/wer8907.pdf?ua=1
2015	December	HPV	GBS, POTS, CRPS, other	https://www.who.int/vaccine_safety/committee/reports/wer9103.pdf?ua=1
		Influenza (H1N1)	Narcolepsy	
2016	December	Influenza (H1N1)	Narcolepsy	https://apps.who.int/iris/bitstream/handle/10665/253062/WER9202.pdf;jsessionid=76C2DBD97AC473A2997E329FE2EE2C4B?sequence=1
2017	June	HPV	GBS, POTS, CRPS, other	https://www.who.int/vaccine_safety/committee/reports/June_2017/en/

CRPS, complex regional pain syndrome; DTP, diphtheria, tetanus and pertussis vaccine; GBS, Guillain-Barré syndrome; HepB, hepatitis B vaccine; HPV, human papillomavirus vaccine; POTS, postural orthostatic tachycardia syndrome.

time or that an individual is more vulnerable to other infections after vaccination due to an immune system weakened by response to multiple vaccine antigens.

Multiple studies have assessed the immune response to different vaccines and vaccine combinations, whether administered concomitantly or as multi-component vaccines.[57–61] Randomised controlled trials and epidemiological studies of MMR vaccine have shown similar immunological responses, whether given singly or in combination with other vaccines, and no increased risk of invasive bacterial infection up to 90 days after immunisation was found.[57 58] Similarly, MMR has been shown to have no interference with responses to other vaccines given concomitantly.[59 60] Nevertheless, some studies have shown that other combination vaccines reduce immunological responses due to individual components.[60 61] For example, in one randomised trial of coadministration of DT-acellular pertussis (DTaP) and haemophilus influenzae type B vaccine (Hib) conjugate vaccines at 4 and 6 months of age, a difference in Hib antibody concentrations was observed in groups receiving Hib capsular polysaccharide mixed with diphtheria, tetanus and pertussis vaccine (DTP) when compared with groups receiving the vaccines separately.[60]

Still, it is estimated that infants have the theoretical capacity to respond to about 10 000 vaccines at any given time and that only 0.1% of the immune system would be 'used up' if 11 vaccines were administered at one time.[62] Despite this, parental concerns about immune system overload have persisted and resulted in delayed or

Table 5 Global Advisory Committee for Vaccine Safety (GACVS) reports released during 1999–2019 that included review of data on immune overload

GACVS report		Exposure	Outcome	Link
2006	June	Multiple (MMR, DTaP, Hib, other)	antibody concentrations, disease outcomes	https://www.who.int/vaccine_safety/committee/reports/wer8128.pdf?ua=1

DTaP, diphtheria, tetanus-acellular pertussis; Hib, haemophilus influenzae type B vaccine; MMR, measles, mumps and rubella vaccine.

alternative dosing schedules, particularly in high-income countries. A survey of US paediatricians in 2016 revealed that 73% encountered parental requests for delaying of vaccines because of concerns about immune system overload, despite the strong evidence on the immune system's ability to handle multiple vaccinations, either in combination or when administered simultaneously.[63]

GACVS reviewed the evidence on immune overload in June 2006 and discussed the influence of vaccination schedules on the protective responses that may be induced, as well as the effect of factors such as malnutrition or exposure to environmental pathogens that may differ in various country settings (table 5). It concluded that the available evidence did not support the hypothesis that vaccines weaken or harm the immune system but emphasised that additional epidemiological studies, assessing the presence of an association between vaccination and recurrent infant infections or atopic dermatitis would be welcome and would reinforce the confidence of both healthcare providers and the public in infant immunisation programmes. Since that time, a large body of new evidence has accrued on this topic underscoring that the number of vaccines or vaccine antigens does not increase the risk for other infections or other conditions.[64–66]

NON-SPECIFIC EFFECTS

NSEs of vaccines, whereby vaccination induces protection from or susceptibility to infections not targeted by the vaccine, remains a polarising topic. While there is some support for the existence of NSEs, there is little consensus on if and how these translate into clinically meaningful effects and if they should inform public health policies.[67] The best evidence indicates that certain vaccines might have beneficial effects, reducing all-cause mortality.[68] However, the claim that certain inactivated vaccines increase mortality is of the greatest concern. In 2000, it was reported that the DT-whole cell pertussis (DTwP) vaccine increased mortality among children in Guinea-Bissau.[69] Among children followed during infancy, receiving at least one dose of DTwP increased mortality by 72% compared with children without DTwP vaccinations although it was concluded that the DTwP effect was complicated by the concomitant administration of the oral polio vaccine. Since 2000, several observational studies on NSEs from low-income countries have been published, many of them from Guinea-Bissau. An ambitious systematic meta-analysis attempted to summarise all available evidence on NSEs and childhood mortality in 2016.[70] The authors reported a statistically non-significant increase in all-cause mortality of 38% associated with DTwP vaccination (almost always administered together with oral polio) based on 10 studies all classified as being at 'high risk' of bias. Proponents of the hypothesis that DTwP is detrimental claim that common sources of bias does not skew towards an increase in risk, and that the true effect of DTwP on mortality may be even greater than reported.[71] However, as a recent simulation study demonstrates, scenarios where DTwP If has no causal effect on mortality but is observed to be associated with increased mortality, do exist when right-censoring occurs, for example, at the time of measles vaccination, as has been the case for some of the studies on DTwP.[72] Prior DTwP increases the probability of measles vaccination and better health (lower mortality risk) increases the probability of measles vaccination, then conditioning on measles vaccination by right-censoring introduces selection bias in the observed association between DTwP and mortality in the form of increased risk. This suggests that caution is warranted when attempting to predict the influence of bias in these studies. The observations between DTwP and mortality cannot be evaluated in high-income countries. DT-acellular pertussis (aP) vaccine is predominantly used and infant mortality is low. A number of studies have attempted to evaluate the effect of DTaP and other inactivated vaccines on off-target infectious disease hospitalisation (IDH).[73–78] A group of Danish researchers has reported that (1) receiving a third dose of a DTaP vaccine as the last vaccine was associated with increased risk of IDH compared with receiving MMR as the last vaccine in a small cohort of children not vaccinated according to the recommended schedule and (2) receiving MMR together with a third dose of DTaP increased the risk of being hospitalised with lower respiratory infections compared with receiving MMR alone.[73 74] A US study evaluated live vaccines compared with inactivated vaccines as the latest vaccine given and observed a reduced risk of IDH, following a live vaccine compared with an inactivated vaccine.[75] These results are in contrast to another Danish study which did not report any increased risks of IDH after different inactivated vaccines including whole-cell pertussis vaccine, a Dutch study reporting a protective effect on IDH of receiving a fourth DTaP vaccine compared with three, and a self-controlled case series study from England reporting no increased risk of IDH for children receiving MMR

Table 6 Global Advisory Committee for Vaccine Safety (GACVS) reports released during 1999–2019 that included review of data on non-specific effects (NSEs) of vaccines

GACVS report		Exposure	Outcome	Link
2002	June	DTP	NSE, child mortality	https://www.who.int/vaccine_safety/committee/reports/wer7747.pdf?ua=1
2003	December	DTP, BCG	NSE, child mortality	https://www.who.int/vaccine_safety/committee/reports/wer7903.pdf?ua=1
2004	June	DTP	NSE, child mortality	https://www.who.int/vaccine_safety/committee/reports/wer7929.pdf?ua=1
2008	June	DTP	NSE, child mortality	https://www.who.int/vaccine_safety/committee/reports/wer8332.pdf?ua=1

BCG, bacille Calmette-Guérin vaccine; DTP, diphtheria, tetanus and acellular pertussis vaccine.

vaccine together with an inactivated vaccine compared with children receiving MMR alone.[76–78] In a rare study of mortality following vaccination in a high-income country, Danish researchers reported reduced mortality for more doses of the DTaP vaccine received compared with fewer.[79]

The GACVS, the WHO Strategic Advisory Group of Experts on Immunisation and dedicated global Task Forces have reviewed the evidence on NSEs[68 80] (table 6). The conclusions have consistently been and remain that the evidence on NSEs is not sufficient to warrant changes in global immunisation policy.[81 82] Claims of DTwP increasing childhood mortality are not based on biological mechanisms and have not been shown to be scientifically reproducible. Therefore, further studies specifically designed to address both positive and negative NSEs are needed, especially given the well-established beneficial effects of DTwP vaccines.

CONCLUSIONS

During the 20th century, global immunisation efforts have seen unprecedented gains. An estimated 116.5 million children completed a 3-dose series of DTP-containing vaccine in 2016 alone compared with only 24.2 million in 1980.[83] This progress has been accompanied by an abundance of data on the safety of immunisations and their components, although sometimes with conflicting results. As an independent scientific advisory board, the GACVS has played an essential role in critically reviewing the available body of evidence on vaccine safety issues of potential global importance and making recommendations to ensure that public trust in vaccinations is maintained.

The issues that have been central to the discussions on vaccine safety in the 21st century highlight the importance of robust scientific studies from multiple disciplines to make adequate conclusions on the safety of each vaccine at a global level. This includes both prelicensure and postlicensure safety assessments and surveillance data from multiple sources and epidemiological settings. The new Global Vaccine Safety Blueprint V.2.0 emphasises the role of adequate country safety surveillance systems; however, only 64% of the countries met the WHO's minimum criteria for a functional system in 2015.[84] Even when such data are available, their interpretation may be complex and has the potential for ambiguity that may contribute to vaccine distrust. Communication messages regarding vaccine safety need to incorporate subtle science to effectively address public concerns. With new vaccines under development and the potential for additional antigens to be added to the routine schedule in the next decade, explanations about dosing schedules and basic immune system function are particularly important to reduce fears and encourage timely dosing. This includes the translation of GACVS decisions into tools and other resources to help healthcare providers communicate effectively with caregivers when the data clearly support or disprove the safety of immunisation, as well as when the data are less clear regarding a specific outcome of public concern. The WHO has been working with global partners to establish global resources, such as the Vaccine Safety Net (https://www.who.int/vaccine_safety/initiative/communication/network/vaccine_safety_websites/en/), that promote effective communication strategies, bolster community confidence and allay public concerns when they arise.

Although some of the data presented here have come to light since GACVS last convened for a formal review, they further support the committee's conclusions. As we move into an era of new vaccination platforms, antigens and formulations, the role of GACVS will be increasingly important in decoding the evidence and engaging the global community in promoting and assuring the safety of vaccines in the decades to come.

Contributors LC, AH, AJP, WAO, MW and PZ have all contributed to the content, analysis, write up and review of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository.

ORCID iD

Patrick Zuber http://orcid.org/0000-0002-8966-5054

REFERENCES

1 Klugman KP, Black S. Impact of existing vaccines in reducing antibiotic resistance: primary and secondary effects. *Proc Natl Acad Sci U S A* 2018;115:12896–901.

2 Hogenesch H. Mechanism of immunopotentiation and safety of aluminum adjuvants. *Front Immunol* 2012;3:406.
3 Excipients in vaccines per 0.5 mL dose. Available: http://www.vaccinesafety.edu/components-Excipients.htm [Accessed 31 Oct 2019].
4 Willhite CC, Karyakina NA, Yokel RA, *et al*. Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminum, aluminum oxides, aluminum hydroxide and its soluble salts. *Crit Rev Toxicol* 2014;44 Suppl 4:1–80.
5 Tomljenovic L, Shaw CA. Do aluminum vaccine adjuvants contribute to the rising prevalence of autism? *J Inorg Biochem* 2011;105:1489–99.
6 Tomljenovic L, Shaw CA. Aluminum vaccine adjuvants: are they safe? *Curr Med Chem* 2011;18:2630–7.
7 Gherardi RK, Crépeaux G, Authier F-J. Myalgia and chronic fatigue syndrome following immunization: macrophagic myofasciitis and animal studies support linkage to aluminum adjuvant persistency and diffusion in the immune system. *Autoimmun Rev* 2019;18:691–705.
8 ATSDR - Minimal Risk Levels for Hazardous Substances. Available: https://www.atsdr.cdc.gov/mrls/mrllist.asp
9 Mitkus RJ, King DB, Hess MA, *et al*. Updated aluminum pharmacokinetics following infant exposures through diet and vaccination. *Vaccine* 2011;29:9538–43.
10 Karwowski MP, Stamoulis C, Wenren LM, *et al*. Blood and hair aluminum levels, vaccine history, and early infant development: a cross-sectional study. *Acad Pediatr* 2018;18:161–5.
11 Global Advisory Committee on vaccine safety, 10-11 June 2004. *Wkly Epidemiol Rec* 2004;79:269–72.
12 Global Advisory Committee on vaccine safety, 3-4 December 2003. *Wkly Epidemiol Rec* 2004;79:16–20.
13 Global Advisory Committee on vaccine safety, June 2012. *Wkly Epidemiol Rec* 2012;87:281–7.
14 Exley C, Siesjö P, Eriksson H. The immunobiology of aluminium adjuvants: how do they really work? *Trends Immunol* 2010;31:103–9.
15 Clarkson TW, Magos L, Myers GJ. The toxicology of mercury — current exposures and clinical manifestations. *N Engl J Med Overseas Ed* 2003;349:1731–7.
16 Ball LK, Ball R, Pratt RD. An assessment of thimerosal use in childhood vaccines. *Pediatrics* 2001;107:1147–54.
17 Debes F, Budtz-Jørgensen E, Weihe P, *et al*. Impact of prenatal methylmercury exposure on neurobehavioral function at age 14 years. *Neurotoxicol Teratol* 2006;28:536–47.
18 Pichichero ME, Cernichiari E, Lopreiato J, *et al*. Mercury concentrations and metabolism in infants receiving vaccines containing thiomersal: a descriptive study. *Lancet* 2002;360:1737–41.
19 Global Advisory Committee on vaccine safety, June 2006. *Wkly Epidemiol Rec* 2006.
20 Hviid A, Stellfeld M, Wohlfahrt J, *et al*. Association between thimerosal-containing vaccine and autism. *JAMA* 2003;290:1763–6.
21 Andrews N, Miller E, Grant A, *et al*. Thimerosal exposure in infants and developmental disorders: a retrospective cohort study in the United Kingdom does not support a causal association. *Pediatrics* 2004;114:584–91.
22 Verstraeten T, Davis RL, DeStefano F. Safety of thimerosal-containing vaccines: a two-phased study of computerized health maintenance organization databases. *Pediatrics* 2003;112:1039–48.
23 Price CS, Thompson WW, Goodson B, *et al*. Prenatal and infant exposure to thimerosal from vaccines and immunoglobulins and risk of autism. *Pediatrics* 2010;126:656–64.
24 Thompson WW, Price C, Goodson B, *et al*. Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years. *N Engl J Med* 2007;357): :1281–92.
25 Heron J, Golding J, ALSPAC Study Team. Thimerosal exposure in infants and developmental disorders: a prospective cohort study in the United Kingdom does not support a causal association. *Pediatrics* 2004;114:577–83.
26 Bai D, Yip BHK, Windham GC, *et al*. Association of genetic and environmental factors with autism in a 5-Country cohort. *JAMA Psychiatry* 2019;76:1035.
27 Wakefield AJ, Murch SH, Anthony A, *et al*. Retracted: Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998;351:637–41.
28 Clements CJ, McIntyre PB. When science is not enough - a risk/benefit profile of thiomersal-containing vaccines. *Expert Opin Drug Saf* 2006;5:17–29.
29 Gerber JS, Offit PA. Vaccines and autism: a tale of shifting hypotheses. *Clin Infect Dis* 2009;48:456–61.
30 Elsabbagh M, Divan G, Koh Y-J, *et al*. Global prevalence of autism and other pervasive developmental disorders. *Autism Res* 2012;5:160–79.
31 Global Advisory Committee on vaccine safety, 16-17 December 2002. *Wkly Epidemiol Rec* 2003;78:17–20.
32 Madsen KM, Hviid A, Vestergaard M, *et al*. A population-based study of measles, mumps, and rubella vaccination and autism. *N Engl J Med* 2002;347:1477–82.
33 Hviid A, Hansen JV, Frisch M, *et al*. Measles, mumps, rubella vaccination and autism: a nationwide cohort study. *Ann Intern Med* 2019;170:513–20.
34 Smeeth L, Cook C, Fombonne E, *et al*. Mmr vaccination and pervasive developmental disorders: a case-control study. *Lancet* 2004;364:963–9.
35 DeStefano F, Bhasin TK, Thompson WW, *et al*. Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: a population-based study in metropolitan Atlanta. *Pediatrics* 2004;113:259–66.
36 Taylor LE, Swerdfeger AL, Eslick GD. Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies. *Vaccine* 2014;32:3623–9.
37 Cusick MF, Libbey JE, Fujinami RS. Multiple sclerosis: autoimmunity and viruses. *Curr Opin Rheumatol* 2013;25:496–501.
38 Elwood JM, Ameratunga R. Autoimmune diseases after hepatitis B immunization in adults: Literature review and meta-analysis, with reference to 'autoimmune/autoinflammatory syndrome induced by adjuvants' (ASIA). *Vaccine* 2018;36:5796–802.
39 Genovese C, LA Fauci V, Squeri A. Hpv vaccine and autoimmune diseases: systematic review and meta-analysis of the literature. *J Prev Med Hyg* 2018;59:E194–9.
40 Andrews N, Stowe J, Miller E. No increased risk of Guillain-Barré syndrome after human papilloma virus vaccine: a self-controlled case-series study in England. *Vaccine* 2017;35:1729–32.
41 Gee J, Sukumaran L, Weintraub E, *et al*. Risk of Guillain-Barré syndrome following quadrivalent human papillomavirus vaccine in the vaccine safety Datalink. *Vaccine* 2017;35:5756–8.
42 Scheller NM, Svanström H, Pasternak B, *et al*. Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system. *JAMA* 2015;313:54–61.
43 Haber P, DeStefano F, Angulo FJ, *et al*. Guillain-Barré syndrome following influenza vaccination. *JAMA* 2004;292:2478–81.
44 Feltelius N, Persson I, Ahlqvist-Rastad J, *et al*. A coordinated cross-disciplinary research initiative to address an increased incidence of narcolepsy following the 2009-2010 Pandemrix vaccination programme in Sweden. *J Intern Med* 2015;278:335–53.
45 Trogstad L, Bakken IJ, Gunnes N, *et al*. Narcolepsy and hypersomnia in Norwegian children and young adults following the influenza A(H1N1) 2009 pandemic. *Vaccine* 2017;35:1879–85.
46 Van Effelterre T, Dos Santos G, Shinde V. Twin peaks: A/H1N1 pandemic influenza virus infection and vaccination in Norway, 2009-2010. *PLoS One* 2016;11:e0151575.
47 Sutton I, Lahoria R, Tan I, *et al*. Cns demyelination and quadrivalent HPV vaccination. *Mult Scler* 2009;15:116–9.
48 Siegrist C-A, Lewis EM, Eskola J, *et al*. Human papilloma virus immunization in adolescent and young adults: a cohort study to illustrate what events might be mistaken for adverse reactions. *Pediatr Infect Dis J* 2007;26:979–84.
49 Callréus T, Svanström H, Nielsen NM, *et al*. Human papillomavirus immunisation of adolescent girls and anticipated reporting of immune-mediated adverse events. *Vaccine* 2009;27:2954–8.
50 Arnheim-Dahlström L, Pasternak B, Svanström H, *et al*. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. *BMJ* 2013;347:f5906.
51 Chao C, Klein NP, Velicer CM, *et al*. Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. *J Intern Med* 2012;271:193–203.
52 Descamps D, Hardt K, Spiessens B, *et al*. Safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine for cervical cancer prevention: a pooled analysis of 11 clinical trials. *Hum Vaccin* 2009;5:332–40.
53 Agence nationale de sécurité des medicaments et des produits de santé, Vaccination contre les infections HPV et risque de maladies auto-immunes : une étude Cnamts/ANSM rassurante - Point d'information, 2015. Available: https://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Vaccination-contre-les-infections-a-HPV-et-risque-de-maladies-auto-immunes-une-etude-Cnamts-ANSM-rassurante-Point-d-information
54 Meeting of the global Advisory Committee on vaccine safety, 7–8 June 2017. *Wkly Epidemiol Rec* 2017;92:393–402.

55 Global Advisory Committee for Vaccine Safety, Communication about the safety of human papillomavirus vaccines,. Who Weekly epidemiological record, 2019. Available: https://www.who.int/vaccine_safety/committee/topics/hpv/July_2019/en/
56 WHO recommendations for routine immunization - summary tables. Available: https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization-summary-tables
57 Miller E, Andrews N, Waight P, *et al*. Bacterial infections, immune overload, and MMR vaccine. measles, mumps, and rubella. *Arch Dis Child* 2003;88:222–3.
58 Shinefield H, Black S, Thear M, *et al*. Safety and immunogenicity of a measles, mumps, rubella and varicella vaccine given with combined Haemophilus influenzae type B conjugate/hepatitis B vaccines and combined diphtheria-tetanus-acellular pertussis vaccines. *Pediatr Infect Dis J* 2006;25:287–92.
59 Miller E, Andrews N, Waight P, *et al*. Safety and immunogenicity of coadministering a combined meningococcal serogroup C and Haemophilus influenzae type B conjugate vaccine with 7-valent pneumococcal conjugate vaccine and measles, mumps, and rubella vaccine at 12 months of age. *Clin Vaccine Immunol* 2011;18:367–72.
60 Eskola J, Ölander R-M, Hovi T, *et al*. Randomised trial of the effect of co-administration with acellular pertussis DTP vaccine on immunogenicity of Haemophilus influenzae type B conjugate vaccine. *Lancet* 1996;348:1688–92.
61 Lerman SJ, Bollinger M, Brunken JM. Clinical and serologic evaluation of measles, mumps, and rubella (HPV-77:DE-5 and RA 27/3) virus vaccines, singly and in combination. *Pediatrics* 1981;68:18–22.
62 Offit PA, Quarles J, Gerber MA, *et al*. Addressing parents' concerns: do multiple vaccines overwhelm or weaken the infant's immune system? *Pediatrics* 2002;109:124–9.
63 Hough-Telford C, Kimberlin DW, Aban I, *et al*. Vaccine delays, refusals, and patient Dismissals: a survey of pediatricians. *Pediatrics* 2016;138:e20162127.
64 Sherrid AM, Ruck CE, Sutherland D, *et al*. Lack of broad functional differences in immunity in fully vaccinated vs. unvaccinated children. *Pediatr Res* 2017;81:601–8.
65 Iqbal S, Barile JP, Thompson WW, *et al*. Number of antigens in early childhood vaccines and neuropsychological outcomes at age 7-10 years. *Pharmacoepidemiol Drug Saf* 2013;22:1263–70.
66 Glanz JM, Newcomer SR, Daley MF, *et al*. Association between estimated cumulative vaccine antigen exposure through the first 23 months of life and non-vaccine-targeted infections from 24 through 47 months of age. *JAMA* 2018;319:906–13.
67 Kandasamy R, Voysey M, McQuaid F, *et al*. Non-Specific immunological effects of selected routine childhood immunisations: systematic review. *BMJ* 2016;355:i5225.
68 Evidence based recommendations on non-specific effects of BCG, DTP-containing and measles-containing vaccines on mortality in children under 5 years of age. Available: https://www.who.int/immunization/sage/meetings/2014/april/1_NSE_Backgroundpaper_final.pdf?ua=1 [Accessed April 2020].
69 Kristensen I, Aaby P, Jensen H. Routine vaccinations and child survival: follow up study in Guinea-Bissau, West Africa. *BMJ* 2000;321:1435–8.
70 Higgins JPT, Soares-Weiser K, López-López JA, *et al*. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. *BMJ* 2016;355:i5170.
71 Aaby P, Ravn H, Benn CS. The who review of the possible nonspecific effects of diphtheria-tetanus-pertussis vaccine. *Pediatr Infect Dis J* 2016;35:1247–57.
72 López-López JA, Sterne JAC, Higgins JPT. Selection bias introduced by informative censoring in studies examining effects of vaccination in infancy. *Int J Epidemiol* 2019;48:2001–9.
73 Sørup S, Benn CS, Poulsen A, *et al*. Simultaneous vaccination with MMR and DTaP-IPV-Hib and rate of hospital admissions with any infections: a nationwide register based cohort study. *Vaccine* 2016;34:6172–80.
74 Sørup S, Benn CS, Poulsen A, *et al*. Live vaccine against measles, mumps, and rubella and the risk of hospital admissions for nontargeted infections. *JAMA* 2014;311:826.
75 Bardenheier BH, McNeil MM, Wodi AP, *et al*. Risk of nontargeted infectious disease hospitalizations among US children following inactivated and live vaccines, 2005–2014. *Clin Infect Dis* 2017;65:729–37.
76 Tielemans SMAJ, de Melker HE, Hahné SJM, *et al*. Non-Specific effects of measles, mumps, and rubella (MMR) vaccination in high income setting: population based cohort study in the Netherlands. *BMJ* 2017;358:j3862.
77 Hviid A, Wohlfahrt J, Stellfeld M, *et al*. Childhood vaccination and nontargeted infectious disease hospitalization. *JAMA* 2005;294:699–705.
78 Andrews N, Stowe J, Thomas SL, *et al*. The risk of non-specific hospitalised infections following MMR vaccination given with and without inactivated vaccines in the second year of life. Comparative self-controlled case-series study in England. *Vaccine* 2019;37:5211–7.
79 Jensen A, Andersen PK, Stensballe LG. Early childhood vaccination and subsequent mortality or morbidity: are observational studies hampered by residual confounding? A Danish register-based cohort study. *BMJ Open* 2019;9:e029794.
80 Who Task force on routine infant vaccination and child survival. Report of a meeting to review evidence for a deleterious effect of DpT vaccination on child survival. London, 2004. Available: www.who.int/vaccine_safety/topics/dtp/en/taskforce_report.pdf
81 Effect of diphtheria–tetanus–pertussis (DTP) vaccination on child survival. *Wkly Epidemiol Rec* 2004;79:271–2.
82 Non-Specific effects of vaccines on childhood mortality. *Wkly Epidemiol Rec* 2014;89:233–5.
83 Feldstein LR, Mariat S, Gacic-Dobo M, *et al*. Global routine vaccination coverage, 2016. *MMWR Morb Mortal Wkly Rep* 2017;66:1252–5.
84 Lei J, Balakrishnan MR, Gidudu JF, *et al*. Use of a new global indicator for vaccine safety surveillance and trends in adverse events following immunization reporting 2000-2015. *Vaccine* 2018;36:1577–82.