Vaccine safety issues at the turn of the 21st century

Situation paper

**Contributors:**

Laura Conklin (CDC)

Anders Hviid (SSI DK)

Walt Orenstein (Emory University)

Andrew Pollard (University of Oxford)

Melinda Wharton (CDC)

Patrick Zuber (WHO)

Disclaimer: This draft situation paper will be finalized after the GACVS anniversary symposium.

The authors alone are responsible for the views expressed in this draft situation paper and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.
Introduction

Due to advances in modern medicine, the global community now benefits from greatly reduced rates of deadly infectious diseases that once were common. Immunization is the largest clearly documented contributor to this progress and vaccines are playing an increasingly important role with the spread of antibiotic and antiviral resistant organisms. Still, sustaining the gains in global vaccination programs requires maintaining public trust in both vaccine efficacy and vaccine safety. Deceptive and distorted information on vaccinations, their contents, and mechanisms of action, is now easily perpetuated through social media and misinformed public figures.

Several vaccine safety issues have drawn much public attention over the last several decades and were reviewed in details during the early years of GACVS. Those include the use of thiomersal in multi-dose non-live vaccines, aluminium adjuvants used with several non-live vaccines, autism and auto-immunity as a possible consequence of vaccination, a risk of immune overload with increasing numbers of vaccinations, and non-specific detrimental effects of vaccination. Each of these issues has been linked to reduced public trust in vaccination programs [citation]. It is in this context that a robust body of scientific evidence has been generated in the 21st century to assess the biological and epidemiological plausibility of these safety concerns and assure the safety of vaccinations world-wide.

Since 1999, the Global Advisory Committee for Vaccine Safety (GACVS) has periodically reviewed the evidence on vaccine components (e.g. thiomersal and aluminium adjuvants) as well as any association between vaccination and broad categories of adverse health outcomes, including overloading the immune system, possible association between vaccines and auto-immune syndromes, and disproportions in death rates among vaccine recipients as possible non-specific effects of immunization. Here, we summarize the committee’s review of these topics, the conclusions and recommendations that were made, any newly available data for GACVS consideration, and the implications for future work on these topics.

Summary of the Evidence

Thiomersal

Thiomersal is best known as a vaccine preservative primarily used in multidose vials of non-live vaccines for its antiseptic and antifungal properties17. Thiomersal is metabolized 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. As an example, the estimated exposure to ethylmercury in the US childhood immunization schedule in 1999 was 237.5 μg (275 μg if three doses of influenza vaccine were also administered) by 2 years of age\textsuperscript{18}. While mercury compounds are all neurotoxic at sufficiently large doses, most of the concern about thiomersal-containing vaccines were based on experiences with methylmercury, another 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\textsuperscript{19}. However, ethylmercury has different pharmacokinetic properties than methylmercury. The half-life of ethyl mercury is short (less than one week) compared to methyl mercury (1.5 months) making exposure to ethyl mercury in blood comparatively brief, and it is excreted rapidly via the gastrointestinal tract, preventing accumulation of ethylmercury above any levels that would raise concern\textsuperscript{20}. (GACVS June 2006)

Large studies from Denmark, the United Kingdom and the United States comprising more than 690,000 children have evaluated the association between thiomersal-containing vaccines and autism and have all reached the same conclusion, there is no evidence that thiomersal-containing vaccines increase the risk of autism\textsuperscript{10,14,15,21}. Similarly, studies looking at a wide range of neurodevelopmental outcomes including both diagnostic outcomes and questionnaire information on early life behavior, cognition and motor skills have been reassuring\textsuperscript{14,15,22,23}. Most notable of these studies is a US study with prospective enrolment of 1047 children 7 to 10 years of age assessing 42 neuropsychological outcomes\textsuperscript{22}. Thiomersal exposure was determined retrospectively from medical records and included exposure from immunizations, immunoglobulins and prenatal exposure during pregnancy. Results showed no association between thiomersal and increased risk of neuropsychological outcomes.

GACVS has reviewed the thiomersal issue multiple times between 2002 and 2012. This has included comprehensive reviews of both pharmacokinetic studies on ethylmercury and epidemiological studies of neurodevelopmental outcomes. It has been concluded that the cumulative exposure from childhood vaccinations do not result in toxic levels of ethylmercury in blood or brain tissue, and that thiomersal-containing vaccines do not increase the risk of autism or the risk of many other neurodevelopmental outcomes\textsuperscript{8}.

Thiomersal has a proven history of efficacy and safety. While thiomersal has been removed from immunization schedules in most high-income countries as a precautionary measure, globally, thiomersal continues to play a vital role in allowing the access to uncontaminated vaccines for millions of people.
Autism

The hypothesized link between vaccines and autism continues to cause concern and fear among parents despite many large well-conducted studies showing that vaccines use is not associated with increased risk of autism. From a scientific standpoint, autism is not the most plausible candidate for a vaccine adverse event. Autism appears to be a predominantly genetic disorder with an inheritance of up to 80%\(^1\). The idea originally gained mainstream attention in the wake of the later retracted Lancet paper from 1998 suggesting a link between the measles, mumps, rubella (MMR) vaccine and autism\(^2\). From a case series of 12 autistic children with reported gastrointestinal abnormalities, 8 were reported having symptom onset in the immediate period following vaccination. It was hypothesized that the MMR vaccine caused intestinal inflammation resulting in the dislocation of encephalopathic peptides from the gut to the brain. In the beginning of the 2000s, the mercury-containing vaccine preservative thiomersal was also linked to autism, through claimed neurotoxic effects, as discussed above\(^3\). More recently, aluminum adjuvants and expanding schedules have been postulated to cause autism through neurotoxicity and immune overload, respectively\(^4,5\). Two common arguments raised by proponents of the link between vaccination and autism have been the many anecdotal observations of autism signs developing shortly after, or even immediately after, vaccination, and a supposed autism epidemic coinciding with vaccine introduction. First, it is important to recognize that onset of autism symptoms coincides with the scheduled age of vaccination and that purely by chance some parents will observe early autistic signs after vaccination. Second, the notion of an autism epidemic is disputed and increased recognition of the condition, including the less debilitating manifestations on the autistic spectrum, together with the fact that a diagnosis is often needed for government help and support, are major contributing explanations for any increases in autism diagnoses reported in many countries\(^6\).

The Committee reviewed the issue of MMR vaccination and autism in late 2002 and concluded that there was no evidence to support a link\(^7\). During the period 2002-2012, the Committee reviewed the thiomersal and neurodevelopmental disorders (including autism) issue several times with the same conclusion, there was no support for a link between thiomersal and autism\(^8\).

The strongest evidence against the postulated links between vaccination and autism comes from large well-controlled epidemiologic studies. Several key studies on the issue have originated from Denmark. In 2002, Danish researchers reported on a nationwide cohort study of more than 537 303 children with individual-level information on MMR vaccination and autism diagnoses\(^9\). In this large cohort, there was no significant difference in the rate of autism between children who received the MMR vaccine and those who did not. A similar nationwide study from 2003, compared 467 450 Danish children vaccinated with either a thiomersal-containing pertussis vaccine or a thiomersal-free formulation of the same pertussis vaccine\(^10\). 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, there was no association between MMR vaccination and autism\textsuperscript{11}. Other notable studies include case-control studies from the UK and US on MMR vaccination and autism\textsuperscript{12,13}, and cohort studies on thiomersal and autism, also from the UK and US\textsuperscript{14,15}. A 2014 meta-analysis confirmed that vaccines do not increase the risk of autism\textsuperscript{16}. A common response to the many well-conducted observational studies reporting no association, have been the claims of vulnerable subgroups of children or specific vaccine-induced phenotypes of autism. These claims are also not supported by observational research\textsuperscript{11}. The science is convincingly settled; available vaccines do not increase the risk of autism.

**Aluminium adjuvants**

Aluminum is ubiquitous in the environment and is a component of many consumer products, including antacids, astringents, and anti-perspirants. Since the early 20\textsuperscript{th} century, aluminum has been used as an adjuvant to immunization in a variety of forms including aluminum 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 [HogenEsch 2013]. Concentrations of aluminum vary greatly between different vaccine products, ranging from 125 mcg/0.5mL dose in Prevnar13 to 1.5mg/0.5 mL dose in DT vaccine [vaccinesafety.edu].

In the 1980’s, public concerns about adverse health effects of aluminum exposure were focused on cancer, Alzheimer’s disease, and occupational exposures [cite]. Due to aluminum’s association with encephalopathy in high intravenous doses, such as renal dialysis or intravenous nutrition products, these data were later utilized by anti-vaccination groups to hypothesize a link between immunizations and developmental delays and other adverse neurological outcomes [Willhite et all 2014; Tomljenovic 2011]. More recently, aluminum adjuvants have been alleged to cause poorly defined syndromes of autoimmune inflammatory syndrome induced by adjuvants (ASIA) and myalgic encephalomyelitis also known as fatigue syndrome [Gherardi et al 2019].

Multiple high-quality studies have shown that children who receive vaccines containing aluminum adjuvants neither have levels of aluminum in the blood or hair above minimum risk levels established by the Agency for Toxic Substances and Disease Registry, nor are they at increased risk of adverse neurodevelopmental outcomes [Mitkus 2011; Karwowski 2018]. GACVS first reviewed available safety data on adjuvants, including aluminum compounds, in 2004 (December and June citations). The committee recognized the need for surveillance of vaccine adjuvant safety in developing countries and made recommendations for WHO to consider a website for adjuvant contents. In addition, the committee asserted that the GACVS and WHO roles regarding adjuvants was
to review and consolidate the evidence. The topic was revisited in 2012 when the committee reviewed the evidence from 2 papers alleging an association between aluminum and autism spectrum disorders [Tomljenovic 2011; Tomljenovic 2011]. GACVS found the studies to be seriously flawed and asserted that ecological studies should not be used to assess a causal association because they are unable to link exposure outcomes to individuals [WER 27 July 2012]. In addition, the studies had several important limitations including incorrect assumptions about known associations of aluminum with neurological disease, uncertain accuracy of the autism spectrum disorder prevalence rates in different countries, and uncertain accuracy of vaccination schedules and resulting calculations of aluminum doses in different countries.

The committee also reviewed a model from US FDA during the same meeting which showed that episodic exposures to aluminum adjuvants have extremely low risk of adverse health effects [WER 27 July 2012]. The FDA calculations were determined to be more accurate than previous models because they incorporated adjustments for gastrointestinal absorption and uptake of aluminum from the site of injection. Results showed that the body burden of aluminum following injections of aluminum-containing vaccines never exceeds safe US regulatory thresholds based on orally ingested aluminum even for low birth weight infants. The committee concluded that the model further supported other clinical trials and epidemiological studies asserting the safety of aluminum in vaccines and encouraged continued research on pharmacokinetics of aluminum in vaccines as a means of further validating and improving on the model.

Although the evidence on the safety of aluminum adjuvants is overwhelmingly reassuring, public concern continues to be fueled by poorly designed studies and unwarranted extrapolation from such studies [Exley citation]. As new vaccines and adjuvants are developed, continued safety monitoring is important both pre- and post-licensure to address public concerns and maintain trust.

**Auto-immunity**

Auto-immune diseases include a wide variety of different pathologies which are often poorly defined [Hayden 2012]. Associations between vaccination and chronic auto-immune conditions, such as multiple sclerosis, thyroid disease, and autoimmune 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 disseminating encephalomyelitis) [Cusick 2013].

The postulated link between vaccination and auto-immune conditions has been extensively explored through controlled trials, observational studies, and epidemiological analyses in multiple countries and sub-populations.
For hepatitis B vaccine, the lack of an association with rheumatoid arthritis, thyroid disease, or multiple sclerosis has been clearly proven [Elwood 2018; Genovese, 2018]. In the case of HPV vaccine, there is strong evidence against an elevated risk of Guillain-Barre syndrome (GBS) [Andrews 2017, Gee 2017], central demyelinating disease [Sutton 2008], and multiple sclerosis [Scheller 2015]. Current evidence does suggest a small elevated risk of GBS after influenza vaccination although these data are limited, and the risk is nevertheless considerably lower than after natural influenza infection [Haber 2004]. There is also some evidence of a causal relationship between narcolepsy and one adjuvanted H1N1 vaccine among school aged children who had a genetic predisposition, in the 2009/2010 influenza pandemic, although natural viral infection is postulated to have played a role in this observation as a vaccine-enhanced viral immunopathology rather than a vaccine-induced autoimmune event [Feltelius 2015; Trogstad 2017; Van Effelterre 2016].

GACVs has reviewed data on the possible relationship between auto-immune conditions and a variety of different vaccines over the years, however the safety profile of HPV remained a major focus from 2009-2017 due to ongoing public concern fuelled by anti-vaccination groups. In 2009 the committee concluded there was no convincing evidence of an association between HPV vaccination and central demyelinating diseases [Sutton 2008]. In 2013, the committee reviewed evidence from USA, Australia, Japan, France, and the manufacturers of Cervarix (GlaxoSmithKline) and Gardasil (Merck) related to auto-immune disease with a focus on multiple sclerosis. They concluded that the studies demonstrated no increase in risk of autoimmune diseases, including MS, among girls who received HPV vaccine compared with those who did not [Siegrist 2007; Siegrist 2007; Callreus 2009; Arnheim-Dahlstrom 2013; Chao 2012; Descamps 2009]. The topic of auto-immunity 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 Guillain-Barre syndrome where an increased risk was identified, mainly focused within 3 months after vaccination [need citation from Agence nationale de sécurité des medicaments et des produits de santé]. 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 in adequately sized populations would help evaluate this finding. Finally, in July 2017, safety data were reviewed from Denmark and Sweden for >3 million women aged 18–44 years which showed an apparent increased risk of celiac disease after HPV vaccination [Hviid 2018]. 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 has 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 issue of rumors and misinformation citation.

Temporal association of autoimmune disease with vaccination is not sufficient to support a causal relationship and global evidence supports the fact that vaccines do not increase the risk of auto-immune diseases. One of the challenges associated with the continued generation of 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 delivered during infancy has increased over the past few generations. WHO’s Expanded Programme (EPI) on Immunization initially recommended vaccination against 6 diseases routinely in 1974 when EPI first began, to a total of 12 globally recommended routine antigens in 2019 [https://www.who.int/immunization/policy/immunization_tables/en/ citation]. 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 time, or that an individual is more vulnerable to other infections after vaccination due to a weaker immune system.

Multiple studies have assessed the immune response to different vaccines and vaccine combinations, whether administered concomitantly or as multi-component vaccines. Randomized controlled trials and epidemiological studies of MMR vaccine have shown similar immunological responses, whether given singly or in combination, and no increased risk of invasive bacterial infection up to 90 days after immunization [Miller 2003; Offit 2002 insert additional citation]. Similarly, MMR has been shown to have no interference with responses to other vaccines given concomitantly [citation]. Still, other combination vaccines have been shown in some studies to reduce immunological responses due to individual components. In one randomized trial of co-administration of DTaP and Hib conjugate vaccines and 4 and 6 months of age, a difference in Hib antibody concentrations was observed in groups receiving Hib capsular polysaccharide mixed with DTP when compared with groups receiving the vaccines separately [Eskola 1996]. Subsequent work suggests that these findings may be due to physical degrading of vaccine components or skewing of the immune response to those components that are present in high dosage [citation].

Still, researchers estimate that infants have the theoretical capacity to respond to about 10,000 vaccines at any one time, and that only 0.1% of the immune system would be ‘used up’ if 11 vaccines were given at one time [Offit 2002]. Despite this, parental concerns about immune system overload have persisted and resulted in
delayed or alternative dosing schedules particularly in high income countries. In one survey of US pediatricians in 2016, 72.5% reported that parents delay vaccines because of concerns about immune system overload [Hough-Telford 2016].

GACVS reviewed the evidence on immune overload in June 2006 and discussed the influence of vaccine 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. It concluded that the available evidence did not support the hypothesis that vaccines, as currently used, weaken or harm the immune system. The committee emphasized 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 health-care providers and the public in infant immunization programme.

There is strong evidence on the ability of the immune system to handle multiple vaccinations, either in combination or when administered simultaneously. Still, with new vaccines under development and the potential for additional antigens to be added to the routine schedule in the next decade, more effective ways of communicating with parents about vaccines is needed. Communication strategies should include explanation about dosing schedules and basic immune system function to reduce fears and encourage timely dosing.

Non-specific effects

Non-specific effects (NSEs) of vaccines, whereby vaccination induces protection or susceptibility to infections not targeted by the vaccine, remains a polarizing 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. The best evidence indicates that certain vaccines might have beneficial effects, reducing all-cause mortality [insert SAGE review citation]. Among the many and varied hypotheses encompassed by the concept of NSEs, the claim that certain inactivated vaccines increase mortality is of the greatest concern. In 2000, it was reported that the diphtheria-tetanus-whole cell pertussis (DTP) vaccine increased mortality in children from Guinea-Bissau. Among children followed in infancy, receipt of at least one dose of DTP increased mortality by 72% compared with children without DTP vaccinations; it should be noted that since oral polio vaccine was often administered concurrently with DTP, it was difficult to fully separate the effect of the two vaccines. Since 2000, a number of observational studies on NSEs from low-income countries have been published, many of them from Guinea-Bissau. An ambitious systematic meta-analysis attempted to summarize all available evidence on NSEs and childhood mortality in 2016. The authors reported a statistically non-significant increase in all-cause mortality of 38% associated with DTP receipt (almost always administered together with oral polio) based on 10 studies all classified as being at “high risk” of bias. The study inclusion
criteria and bias evaluations have been criticized. In particular, the extent to which it is possible to predict the direction of bias in observational studies of NSEs has been debated. Proponents of the hypothesis that DTP is detrimental, claim that all sources of bias, such as healthy vaccinee bias, will bias towards no effect, and thus, the true effect of DTP on mortality is even greater than reported. However, as a recent simulation study demonstrates, scenarios where DTP has no true effect on mortality, but is observed to be associated with increased mortality, do exist. This suggests that caution is warranted when attempting to predict the influence of bias in these studies.

The hypothesis of a detrimental effect of DTP on mortality, is of course difficult to test in high-income countries with low childhood mortality. A number of studies have evaluated the effect of DTP on off-target infectious disease hospitalization (IDH), often as secondary analyses in studies of beneficial NSEs of MMR vaccination. One Danish research group, has reported 1) that receiving a third dose of a DT-acellular pertussis (aP) 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 hospitalized with lower respiratory infections compared with receiving MMR alone. 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. 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 to three, and a self-controlled case series study from England reporting no increased risk of IDH for children receiving MMR vaccine together with an inactivated vaccine compared to children receiving MMR alone. In a rare study of mortality following vaccination in a high-income country, Danish researchers reported reduced mortality for more doses of DTaP vaccine received compared with fewer.

The question of vaccines and NSEs has been a topic of great interest to the WHO. The GACVS, the Strategic Advisory Group of Experts and dedicated Task Forces have reviewed the evidence on NSEs. The conclusions have consistently been and remain that the evidence on NSEs are not sufficient to warrant changes in global immunization policy. Claims of DTP increasing childhood mortality are not based on biological mechanisms and have not been shown to be scientifically reproducible. As such, further studies specifically designed to address both positive and negative NSEs are needed, especially given the well-established beneficial effects of DTP vaccines.

Discussion
During the 20th century, global immunization efforts have seen unprecedented gains. An estimated 116.5 million children received a third dose of DTP-containing vaccine in 2016 alone compared to only 24.2 million in 1980 [Feldstein 2017]. This progress has been accompanied by an abundance of data on the safety of immunizations and their components, albeit sometimes with conflicting results. As an independent scientific advisory board, the GACVS committee has played an essential role in critically reviewing the available 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 pre- and post-licensure safety assessments and surveillance data from multiple sources and epidemiological settings. The new Global Vaccine Safety Blueprint 2.0 emphasizes the role of adequate country safety surveillance systems, however currently only a fraction of countries meeting WHO minimum criteria for a functional system [citation]. Even when such data are available their interpretation may be complex, and communication messages regarding vaccine safety needs to incorporate subtle science to address public concerns contributing to vaccine distrust. This includes the translation of GACVS decisions into tools and other resources for healthcare providers to communicate with caregivers when the data clearly support or disprove the safety of immunization, as well as when the data are less clear regarding a specific outcome of public concern.

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.

References
[to be expanded in excel spreadsheet]


13. DeStefano F, Bhasin TK, Thompson WW, Yeargin-Allsopp M, Boyle C. Age at First Measles-Mumps-Rubella


