The Science of Vaccine Safety

Vaccines are everywhere hugely successful but are also under attack. The reason for the latter is the perception by some people that vaccines are unsafe. However that may be, vaccine safety, life any other scientific subject, must be constantly studied. It was from this point of view that a meeting was organized at the Wellcome Trust in London in May 2019 to assess some aspects of vaccine safety as subjects for scientific study. The objective of the meeting was to assess what is known beyond reasonable doubt and conversely what areas need additional studies. Although the meeting could not cover all aspects of vaccine safety science, many of the most important issues were addressed by a group of about 30 experts to determine what is already known and what additional studies are merited to assess the safety of the vaccines currently in use. The meeting began with reviews of the current situation in different parts of the world, followed by reviews of specific controversial areas, including the incidence of certain conditions after vaccination and the safety of certain vaccine components. Lastly, information about the human papillomavirus vaccine was considered because its safety has been particularly challenged by vaccine opponents. The following is a summary of the meeting findings. In addition to this summary, the meeting organizers will explore opportunities to perform studies that would enlarge knowledge of vaccine safety.

General Remarks [Offit]

Any medical product that has a positive effect can have a negative effect. Vaccines are no different. Serious adverse events following vaccination have been reported since the first vaccine (smallpox) was developed. Historically, real vaccine safety issues include eczema vaccinatum, progressive vaccinia, congenital vaccinia, myopericarditis, encephalopathy, and encephalitis caused by the smallpox vaccine[1] as well as seizures, paralysis, and coma caused by nervous tissue-based rabies vaccines contaminated with myelin basic protein.[2]

Two historical tragedies were also noted. In 1929, a laboratory error in Lubeck, Germany, resulted in the inadvertent inoculation of 250, 10-day old children with *Mycobacterium tuberculosis* instead of attenuated *Mycobacterium bovis* (BCG). Seventy-two infants died as a result of the mistake.[3] Also, in 1955, Cutter Laboratories failed to fully inactivate a poliovirus vaccine. As a consequence, about 120,000 children were inoculated with live, fully virulent poliovirus. When the dust settled on this man-made polio epidemic, 70,000 people developed abortive, short-lived polio, 164 people were paralyzed, and 10 were killed. This was arguably one of the worst biological disasters in American history.[4]

More recently, the oral polio vaccine was shown to be a rare cause of paralysis, affecting about 1 person per 2.4 million doses.[5] Measles-containing vaccine was found to be a rare cause of transient thrombocytopenia, affected about 1 of every 25,000 recipients.[6] Gelatin, which is used as a stabilizer in the MMR, MMRV, and Zostavax vaccines has been shown to cause a severe, immediate, type 1 hypersensitivity reaction in about 1.3 per million vaccine recipients.[7] Rotavirus vaccines were found to be a rare cause of intussusception, which,

depending on the currently licensed product, affects between 1.5 to 5 children per 100,000 vaccinated.[8] Yellow fever vaccine can itself cause yellow fever, affecting about 1 per million recipients primarily greater than 65 years of age.[9] Influenza vaccine is a rare cause of Guillain-Barré Syndrome, affecting about 1 per million recipients.[10] Pandemrix, an influenza vaccine with a novel adjuvant was used in Europe during the 2009 influenza pandemic, and was found to cause narcolepsy, a permanent disorder of wakefulness, in between 1 in 16,000 to 1 in 55,000 recipients.[11] Finally, dengue vaccine (Dengvaxia) has been shown to enhance hemorrhagic-shock syndrome upon exposure to wild-type virus in seronegative, vaccinated children.[12]

All of these issues have been instructive. It is an uncomfortable truth that science evolves. We learn as we go. And sometimes that learning process comes with a human cost.

The role of vaccine safety monitoring in maintaining vaccine confidence [DeStefano]

The existence of a comprehensive robust vaccine safety monitoring system can bolster public confidence in the safety of vaccines. Pre-licensure activities, from the initial development of a vaccine through the various phases of pre-licensure clinical trials, form the foundation of vaccine safety. Pre-licensure trials, however, may not be large enough to detect rare adverse events following immunization (AEFI), they may not last long enough to detect adverse events with delayed onset, and they may not include certain population groups (e.g., pregnant women). Thus, post-licensure monitoring is crucial to assure the safety of vaccines after they begin to be used on a large scale in the general population.

In the United States, several government agencies, vaccine manufacturers and other entities are involved in evaluating and monitoring the safety of vaccines. The core of the U.S. vaccine safety post-licensure monitoring enterprise consists of four systems operated by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA): 1)the Vaccine Adverse Event Reporting System (VAERS); 2) the Vaccine Safety Datalink (VSD); 3) the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) Program; and 4) the Clinical Immunization Safety Assessment (CISA) project. VAERS is co-managed by CDC and FDA. [13] It is a national surveillance system intended to rapidly detect potential safety problems or signals. It is a voluntary (i.e., passive) reporting system that accepts reports from anyone, including physicians, manufacturers, patients and parents. VAERS is subject to a number of limitations, including incomplete reporting and lack of an unvaccinated comparison group, and generally cannot be used to assess causality. VSD is a large linked database system that is operated by CDC in collaboration with several large integrated health care systems that cover over 10 million people. [14] It can be used for active surveillance and epidemiologic research by linking computerized vaccination records with computerized databases of hospital, emergency department and outpatient clinic encounters, as well as other databases and medical records. PRISM is a post-licensure safety surveillance network run by FDA to actively monitor the safety of vaccines.[15] It comprises a distributed data network that utilizes claims data from 4 national health insurance companies and vaccine data from 8 immunization registries. CISA is operated by CDC and involves the participation of 7 medical research centers. It conducts clinical research and provides expert consultation to U.S. healthcare providers with complex vaccine safety cases.[16]

Outside of the United States, vaccine safety monitoring capabilities tend to be limited. A few efforts are underway to establish multi-country distributed vaccine data networks in Europe and more globally. These could offer several advantages, such as: 1) providing local data that may be more persuasive in fostering confidence in vaccines at the country level; and 2) the possibility of combining data from several countries to quickly detect extremely rare adverse events (e.g., in a pandemic mass vaccination situation).

Vaccine Safety Concerns in Europe [Larson]

In 2016 and 2018, global studies on public confidence in vaccines showed that the lowest levels of confidence were specific to vaccine safety, with the European region being the least confident in vaccine safety globally.[17-19] Similar findings have emerged in other studies with safety consistently being reported as the biggest reason for vaccine reluctance or refusal.[20,21]

Contributing to these safety anxieties are a variety of tactics by vaccine-critical groups, including billboards instilling doubt with headlines such as “Vaccines are not Safe: Know the Risks” and “If an apple contained: Aluminium, Mercury, Formaldehyde, Polysorbate 80, MSG, Animal & Fetal Cells, would you eat it?” While billboards and similar social media sentiments spread ungrounded fears and heighten risk perceptions, these images and messages also reveal key issues and questions that are on the minds of the public and are important clues to inform where safety research is needed, or where already available safety research needs to be made more accessible to the public.

The European Medicines Agency(EMA) conducted a study monitoring online and social media in all European Union (EU) member states, in order to listen for concerns related to the human papillomavirus(HPV) vaccine. In response to a series of adverse events following immunization, particularly in Denmark, the EMA was asked to conduct a review of the safety of the HPV vaccine[22], and the media monitoring preceded the launch of the EMA safety review and helped to prepare the EMA officials to anticipate questions around the launch of the final report, which confirmed the HPV vaccine's safety.[23-25]

Vaccine safety concerns vary across countries, with aluminium a more prominent concern than thimerosal, and France home to an organized movement against aluminium and formaldehyde in vaccines. France also has historic concerns about multiple sclerosis following hepatitis B vaccination, a risk perception which has also transferred to HPV vaccination along with anxieties about auto-immune disease following HPV vaccination. While we have considerable evidence for the safety of HPV vaccine, what is needed is more evidence for the safety of the ingredients in the HPV as well as other vaccines.

Vaccine Hesitancy in Lower Middle-Income Countries [Arora]

In 2013, the pentavalent vaccination program was suspended in Vietnam, Sri-Lanka and Bhutan and was the subject of public controversy in other Lower Middle Income Countries (LMICs) due to unverified reports of serious vaccine side-effects, including deaths.[26] More recently, the Measles Rubella (MR) campaign was disrupted in parts of India in 2018-2019 due to negative social media messaging.[27]. In Karachi, Pakistan entrenched socio-cultural norms

regarding decision making informed pregnant women's intention to reject pertussis vaccination [28].

Common concerns regarding vaccination in LMICs include fear of adverse events, lack of trust in medical community or public health program, health system related issues such as quality of service delivery, cost and access to vaccines and may even be politically motivated.[29]. The above reasons accounted for nearly 80% of the responses for missing vaccinations from care givers of under-vaccinated children during the Mission Indradhanush (MI) campaign in India. Ethnicity and faith based perceptions towards vaccination, reinforced by local social, economic and community connections have also been identified as factors driving hesitancy during the Pulse Polio (2006) and the MI campaigns (2018) in India. [30,31]. In Brazil, nearly one in five parents with children under the age of five surveyed were vaccine hesitant with concerns about vaccine safety and effectiveness being the most commonly cited reasons for hesitancy.[32] A pre-existing environment of mistrust towards local governments and politically motivated resistance to public health interventions have also been identified as factors contributing to lack of vaccine acceptability in a study investigating the Oral Cholera Vaccine in Mozambique.[33]

The past decade has seen a dramatic transformation of the communication and information exchange landscape; the spread and reach of vaccine associated misinformation, exacerbated by nearly universalized access to internet has derailed on-going immunization campaigns against polio and measles rubella in several Asian countries.[27,31] The current

systems for pharmacovigilance are not mature enough to address emerging concerns by rapidly and systematically investigating safety signals.

Diagnosis of vaccine hesitancy requires a multi-dimensional diagnostic approach particularly in traditional societies and emerging economies with aspirations for better health and civic services. It is necessary to take comprehensive approaches to delineate local socio-cultural and economic contexts, historical and anthropological factors, the effect of geo-political events and specific programmatic determinants of vaccine hesitancy to inform strategies for addressing this complex interdisciplinary challenge. Adopting a human centered approach with proactive engagement of the local communities is essential for diagnosing and finding solutions. Findings from proposed studies might be country and context specific but the lessons learnt shall have the potential to support initiatives with similar contexts elsewhere and strengthen global efforts to maintain public trust in immunization program.

Vaccine safety concerns as seen by the World Health Organization [Zuber]

Safety of vaccines utilized in global public health programs is a paramount concern for the World Health Organization (WHO). In the past 20 years, WHO has paid increasing attention to vaccine safety and developed a program dedicated to managing those issues. The Global Advisory Committee on Vaccine Safety (GACVS) was established in 1999 to respond promptly, efficiently and with scientific rigor to vaccine safety issues of potential global importance.[34] GACVS has examined the robustness of vaccine safety concerns to assist risk/benefits-based vaccine safety policies development. On occasions GACVS has proposed contra-indications to

vaccine utilization (BCG in HIV infected persons,[35] Dengvaxia in dengue-naïve individuals).[36] Beyond those examples, the most important role of the committee is in assessing the robustness of scientific evidence and to advise on how to enhance monitoring and hypothesis-testing. This work is documented on a dedicated website and is a proven global scientific reference.[37] Table 1, adapted from Asturias et al [37a] displays the range of issues examined by the committee over 20 years. Those are related to vaccine components, specific vaccine products including all novel products that became available during that period, methods of vaccine pharmacovigilance and systems building.

Spectacular progress with global immunization programs (better coverage, new and geographically-indicated vaccines), warranted additional investments into capacity-building for vaccine safety monitoring. The goal is to ensure that any concern, anywhere in the world, could be detected, reported and documented through a competent network and corrective action promptly taken. The Global Vaccine Safety Initiative (GVSI) was established by WHO in 2012 to implement a vaccine safety strategy that aims to ensure minimal capacity for vaccine safety monitoring everywhere, enhanced capacity (for surveillance of specific safety concerns) where newer products are deployed, and the establishment of a global network with adequate expertise and geographical proximity.[38]

Enhanced capacity to monitor novel vaccines, many of which dedicated to parts of the world where adequate safety systems are not available, requires concerted efforts. A global network, with adequate expertise, cultural and geographical proximity is progressively being established through the GVSI.[39] Beyond broader capacity for general vaccine pharmacovigilance through the GVSI, the GACVS is on the forefront of safety concerns of global

relevance. Occasional acute safety issues are addressed. Those include early post-licensure deviations from quality and safety profiles as well as novel safety signals. The GACVS-ALERT system allows timely reviews of emerging safety concerns as illustrated with the detection of porcine circovirus DNA in rotavirus vaccines.[40]

Methodologies for vaccine safety require agile epidemiological designs, such as the use of case-based studies where time intervals are the preferred measurement unit which allows dissecting rare effects.[41] Novel vaccines are being developed for pregnant women. Monitoring their benefits and risks in resource-poor countries, will require enhanced collaborations with harmonized methodologies (distributed data networks) that take full advantage of current information technologies.[42] Evidence-based policy-making is currently driven by the gold standard of randomized trials. Assessing rare events, so critically important for the monitoring of preventive interventions, cannot meet that standard. Yet, powerful data analytic systems are available that allow testing numerous hypotheses. Novel approaches to qualify available evidence in pharmacovigilance are therefore urgently needed.

Autism [Fombonne]

In the late 1990s, claims that childhood vaccines increased the risk of autism were made and widely publicized despite weak, if any, empirical evidence to support them. The claims entailed two purported separate mechanisms. The first one incriminated the measles component of the triple MMR vaccine, arguing that in children previously developing normally, a regression and loss of skills occurred 5 to 6 days after vaccination, leading to autism

associated with gastrointestinal symptoms and inflammatory pathology. The second implicated the cumulative dose of thimerosal (ethylmercury) received through other childhood vaccines up to age 2 that was deemed to be too high and possibly exceeded safety thresholds.

Several epidemiological investigations tested both claims. Ecological studies showed in various countries that underlying trends in rates of autism (equivalent to PDD: Pervasive Developmental Disorders, and to ASD: Autism Spectrum Disorders) were not correlated to trends in MMR coverage,[41] to the introduction or discontinuation of monovalent measles vaccines and later introduction of MMR,[42] to increased use, and to discontinuation of inclusion of the preservative thimerosal in most vaccine preparations.[41] Controlled observational studies (case-control and cohort studies) equally failed to show that past exposure to MMR vaccination was higher in children with autism compared to controls[43]; similarly, infants and toddlers exposed to MMR or to thimerosal-containing vaccines in various doses, when followed up several years later, were not an increased risk of developing autism, findings that extended to their siblings.[44,45] Remarkably, no well-designed study ever supported a risk association of autism with vaccines, and the convergence of negative findings across investigators, study designs, samples and countries has been impressive. Several metanalyses of these questions confirmed the lack of association between exposure to MMR and thimerosal containing vaccines and autism.[46,47]

Further claims were made that the risk could be confined to a small, vulnerable, subgroup that epidemiological studies would not be capable to detect. Limited evidence was brought forward to describe this group (defined by regression/loss of skills days following the MMR vaccine, association with gastro-intestinal symptoms, and purported persistence of the

measles virus in the gut and other biological specimens). A systematic search for this hypothetical phenotype failed to validate its existence.[48] Regression/loss of skills had been described since the 1940s in up to 30% of children with ASD, and there was evidence that this regressive phenotype had not increased recently or in post-MMR years. Comparative studies showed that children exposed to MMR were not more likely than unexposed children to experience regression, or a combination of regression and GI symptoms; furthermore, parents of vaccinated children compared to those of unvaccinated children were not more likely to express earlier concerns about their child's development, or at a time clustering around the immunization date, or more often seek health care provider advice after the MMR immunization. Moreover, studies of peripheral blood mononuclear cells, measles antibodies titers,[49] and measles RNA in gut specimen[50] all failed to document the presumed persistence of the measles virus in biological compartments of children with autism exposed to MMR. In addition, studies investigating possibly higher exposure to methylmercury in autism showed no increased levels in hair or blood samples, no toxicity levels, and no evidence that well know signs of mercury toxicity were part of the autism phenotype.[51,52] Moreover, new data indicated that ethylmercury used in vaccines had a much shorter half-life than methylmercury[53] ruling out that the cumulative use of thimerosal in vaccines from birth to age 2 could surpass already conservative safety thresholds and lead to toxicity.

Quite separately, research on autism has established through twin and family studies the strong role of genetic factors in autism etiology. Current sequencing techniques can identify up to 25% of inherited or de novo genetic variants in subjects with autism, and the ever-growing list of high-risk genes now contains 141 genes and 19 additional copy number variants

(https://www.sfari.org). Studies examining the early developmental trajectories of children at risk of autism identified, in research experiments, abnormal social development in the first 6 months of life as well as biological markers (increased brain volume, eye-tracking abnormalities, etc.) that point to a prenatal onset of atypical brain development in autism. Research on environmental risk factors has provided new insights on factors that may operate, alone or in conjunction with genes, during prenatal life although most remain to be confirmed (with the exception of advanced paternal age, and the rare prenatal exposure to valproic acid).[53a,53b] Yet, reliable diagnosis assessment cannot be reached before age 15 months, at best. The middle of the second year of life remains the period when parents commonly become first aware of the atypical development in their child while the average age at diagnosis remains around age 4 in the US. This developmental trajectory creates conditions for parental causal attributions in the etiologic role of environmental factors (e.g. MMR immunization) to develop, contemporaneously of first ASD symptoms emergence. This temporal correlation supports the persistence of beliefs that something happening in the second year of life could be the 'cause' of autism in their child despite all scientific findings pointing at genetic, peri-conceptional and prenatal etiologies.

Neurologic Adverse Events Following Immunizations [Sejvar]

Neurologic adverse events following immunizations (NeuroAEFI) are fortunately infrequent, but are among the most devastating of the AEFIs; there are few 'benign' neurologic conditions. As such, there is a very low threshold for tolerance of these adverse events. There are various potential mechanisms for the etiology of NeuroAEFI depending on whether the

vaccine is a live vaccine, an inactivated vaccine, or a toxoid / protein vaccine. NeuroAEFI, which causally related to vaccination or not, can basically be broken down into two large categories – 'Neurotropic' illness, and 'Autoimmune / Post-immunization' illness. Neurotropic illness can happen when vaccine (usually live vaccine) gains access to the nervous system, producing an infection within the nervous system. By nature, neurotropic illnesses involve the Central Nervous System (CNS); autoimmune illnesses may affect either the CNS or the peripheral nervous system (PNS). When we refer to the neurotropic illnesses, we are referring to (aseptic) meningitis, encephalitis, and anterior (polio)myelitis. The autoimmune illnesses are constituted by acute disseminated encephalomyelitis (ADEM), Guillain-Barre syndrome (GBS), and less common ones such as transverse myelitis, brachial neuritis, optic neuritis, and others. Again, they may or may not be caused by vaccination.

NeuroAEFI neurotropic disease may be seen with live vaccines.[54,55] These illnesses are characterized by an incubation period of around 2 – 10 days (roughly) after the immunization. They are associated with evidence of CNS inflammation, including a cerebrospinal fluid (CSF) pleocytosis (elevation of CSF inflammatory white blood cells) and protein elevation, and evidence of brain parenchymal changes / abnormalities on neuroimaging, usually magnetic resonance imaging (MRI). NeuroAEFI may be substantiated by finding evidence of vaccine viral invasion of the intrathecal space.

Autoimmune NeuroAEFI may consist of an immune response to the antigenic stimulus provided by a vaccination; this results in the formation of cross-reactive antibodies and/or autoreactive T-cells that are stimulated by vaccine epitopes to react with self-neural proteins. Alternatively, the antigenic stimulus of the vaccine may lead to perturbation of

immunoregulatory mechanisms by vaccine proteins resulting in a loss of self-tolerance. The association with the vaccine is generally temporal only; this is because vaccine virus or vaccine-specific IgM antibodies may not be present, peripheral serology is not useful since one would expect an antibody response to the vaccine, and often there is a limited search for alternative antecedent events that may lead to the reaction. Thus, 'temporal association' does not equate to 'causality'.

Acute disseminated encephalomyelitis (ADEM) is an autoimmune demyelinating disease of the CNS.[58] Two-thirds of persons with ADEM will report an antecedent infectious-like illness or vaccination in the days and weeks prior to onset of neurologic signs. It is more common in childhood; it is estimated that ADEM may represent up to 10-15% of childhood encephalitides. It is characterized by clinical signs / symptoms of encephalitis approximately 3-20 days following the antecedent event; patients will present with altered mental status, cranial nerve palsies, focal weakness, ataxia, and other neurologic signs. It is by definition a monophasic illness, with progression followed by a plateau of symptoms, or more frequently, recovery. Neuroimaging will demonstrate characteristic scattered or confluent multifocal white matter lesions in the subcortical white matter or deep gray structures. CSF shows pleocytosis and protein elevation. The diagnosis rests upon the clinical features and the characteristic MRI findings, along with report of an antecedent illness or immunization.

Guillain-Barré syndrome (GBS) is a post-infectious / post-immunization autoimmune disease of the peripheral nerves. Autoantibodies or T-cells lead to damage to the peripheral nerves / nerve roots to produce limb weakness and sensory abnormalities.[57] Incidence in North America and Europe is estimated to be 1.2 – 1.6 / 100,000 population / year; this

incidence increases with age, particularly after age 50. Incidence also tends to be higher in Asia and South America, presumably due to increased exposure to infectious agents. This is because, similar to ADEM, 2/3 of persons with GBS will report an antecedent viral – like illness or immunization. There are several subtypes of GBS; the most common one in North America and Europe being the demyelinating form, while the axonal form predominates in Asia and South America. Clinically, GBS is characterized by an acute or subacute onset of weakness that evolves over days to weeks; onset is generally between 1-4 weeks after the antecedent event, and most persons experience maximal weakness ('clinical nadir') within 2 weeks. Weakness tends to be ascending, e.g. beginning in the legs and spreading to the arms and then cranial nerve-innervated muscles. CSF is characterized by 'cytoalbuminologic dissociation' – an elevation in CSF protein levels, but with an absence of pleocytosis. Electrodiagnostics – nerve conduction studies and electromyography – may be very useful in confirming the diagnosis and differentiating the various subtypes of GBS.

Although the 1976 formulation of the H1N1 swine-origin influenza vaccine was associated with a slightly increased risk of developing GBS – to the amount of approximately 1 excess case of GBS per 100,000 vaccinees – subsequent formulations of the seasonal influenza vaccine have demonstrated either no increased risk or a very mild increased risk, to the amount of 1-3 excess GBS cases per million vaccinees, and nothing like the magnitude of that seen with the 1976 formulation. These studies, however, may be underpowered, and the 2009 formulation of the H1N1 pandemic influenza vaccine was associated with a mild increased risk (1 excess case/million vaccinees). Nonetheless, the Centers for Disease Control and Prevention has stated that it is 'prudent' for persons who developed GBS following influenza vaccine to

avoid subsequent influenza immunizations; of course, this would depend on an individual's particular risk profile for developing influenza illness. Current evidence suggests that there is no increased risk of relapse of multiple sclerosis following immunizations, and in fact the infectious illnesses that immunizations prevent may present a more significant antigenic challenge, leading to risk of relapse of multiple sclerosis demyelinating events. It would appear that the risks of immunizations for MS relapse are greatly outweighed by the benefits of prevention of infectious illnesses.

Future investigations into vaccine-associated GBS will benefit from exploration of epitopes in vaccines and how they may lead to cross-reactions with peripheral nerve neural substrates. In addition, host factors are likely to play a role in vaccine-associated GBS, and should be explored.

Vaccination and Autoimmunity [Lambert]

There are an increasing number of allegations suggesting the occurrence of autoimmune manifestations following vaccination, listed in Table 2 The scientific basis of these allegations is usually lacking. This situation is largely the result of coincidental events linked with the increasing administration of vaccines in adolescents and young adults at an age known to be associated with autoimmune diseases. It is also reflecting a trend to call autoimmune a variety of vague clinical manifestations of unknown origin (e.g. the ASIA syndrome)(' Everything is autoimmune until proven otherwise". [58] Serious epidemiological studies did not confirm an association of autoimmune diseases with HBV, HPV nor with seasonal influenza vaccination.

[59,60]

However some older vaccines were occasionally associated with autoimmune manifestations. This was the case for the Semple rabies vaccine [61] and the 1976 swine influenza vaccine.

Present immunological concepts allow the understanding of the relative risk of post-vaccination autoimmunity. Cross-reacting autoantibodies can occasionally be generated by some vaccines. The risk is limited by the basic level of tolerance for self B-cell epitopes. It can be assessed at pre-clinical or early clinical stages of development. A higher risk exists (i) for vaccines against infections known to be associated with autoimmunity, e.g. Group A Streptococci, (ii) when a vaccine antigen has a B cell epitope that cross-reacts with a host antigen. This usually requires extensive sequence homology, e.g. >35% identity in >50-80 aa peptidic sequences (conformation!) and a linkage of the cross-reacting B-cell epitope to a dominant T helper epitope (foreign). It is facilitated by a strong concomitant activation of innate immunity (danger signal!).[62]

Although T-cell epitope mimicry is common, cell-mediated autoimmune manifestations are particularly rare. This reflects the potent regulatory mechanisms which limit the activation of self-reacting T-cells.[63] When exceptionally occurring, it likely reflects a particular host susceptibility related to multiple factors, e.g. genetics, failure of thymic negative selection for relevant self-peptides, or failure of peripheral regulatory mechanisms.[64] These should also be combined with a strong activation of innate immunity and is difficult to predict at pre-clinical or early clinical trial stages. Existing adjuvanted vaccines do not appear to exacerbate autoimmune

diseases.[65,66] Post-licensure studies in autoimmune patients may be useful for novel adjuvants.

An example of the complexity of this issue is the observation of an increased incidence of narcolepsy after vaccination with AS03-pH1N1 influenza in Nordic European countries[67] which was assumed to be due to a vaccine-induced autoimmune response to hypocretin producing neurons. However, there is still scarce evidence for an autoimmune process in this situation whereas there is a growing evidence for a role of the influenza viral infection in the disease. Indeed, a peak of narcolepsy was seen in China [68] and Taiwan following the2009 pH1N1 outbreak. In Nordic European countries, the pandemic peak overlapped or immediately preceded the vaccination.[69] Experimental data also indicate that most Influenza A viruses can infect olfactory receptor neurons, that some of these viruses (H1N1, H5N1) can move to the olfactory bulb (OB) within a few days [70-72] and that exceptionally, some Influenza A viruses can slowly move from olfactory bulb to other CNS sites (H5N1>H1N1>>H3N2), including lateral hypothalamus and hypocretin-producing neurons.[73]. In transgenic mice expressing H1N1-HA in Hypocretin-producing neurons , anti-H1N1 HA CD8 T-cells were shown to eliminate HA-expressing Hcrt-neurons.[74] AS03-pH1N1 vaccine-associated narcolepsy may represent an example of vaccine-enhanced viral immunopathology rather than a vaccine-induced autoimmune event. Timing of vaccination in relation to the outbreak may be critical.

Thiomersal and Mercury [Hviid]

Thiomersal has been used as a vaccine preservative since the 1930s primarily in multidose vials. Thiomersal contains ethylmercury and concerns about expanding childhood

vaccination schedules with increasing cumulative mercury exposure in infants led to the withdrawal of thiomersal-containing vaccines in many high income countries throughout the 1990s. Mercury compounds including ethylmercury are neurotoxic at sufficiently large doses.[75] Accidental poisoning episodes involving ethylmercury at much larger doses than those found in vaccines have been reported to cause neurotoxicity. Ethylmercury has been compared to methylmercury, another organic mercury compound. Adverse effects on neurodevelopment are well-established for methylmercury exposure through primarily maternal fish consumption. However, ethylmercury has a shorter half-life in the body.[76]

The majority of large observational studies of thiomersal exposure have focused on autism. There have been no support for an association in key analytical studies from Denmark, the United Kingdom and the United States comprising more than 690,000 children.[77-80] 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.[79-84] Some of these studies do test a large number of possible statistical associations and as expected purely by chance report a small number of both beneficial and adverse effects which should be carefully interpreted in the context of multiple testing. Tics have been associated with thiomersal exposure in several studies.[79,80,84] The ascertainment of tics differ in all of these studies, and the clinical relevance of this finding is unclear.

The available observational evidence do have some noteworthy limitations. First, a common feature of many of the available observational studies is the lack of a large group of thiomersal-unexposed children. The majority of studies compare children with varying degrees

of thiomersal exposure at pre-defined ages. Second, while some studies do include subgroups such as low birth weight infants and do try to take other mercury sources into account, low statistical power limits the interpretability. Third and final, there is little evidence available on fetal exposure throughout pregnancy primarily from maternal vaccination.

In conclusion, the available evidence is reassuring; thiomersal-containing vaccines do not increase the risk of autism or the risk of many other neurodevelopmental outcomes.

Formaldehyde and Aluminum [Halsey]

Formaldehyde is a natural component of cell metabolism in all mammalian cells, many plants, and some foods.[85] In humans, metabolism is very rapid with a half-life only 1-2 minutes. Normal human blood levels are 2-3 mcg/mL. Most people are exposed to formaldehyde every day from wood products, automobile exhaust, cigarette smoke, paints and varnishes, carpets permanent press fabrics, and some food products. Prolonged exposure via inhalation can rarely cause nasopharyngeal cancer(adenomas) and repeated contact with highly concentrated solutions can cause irritation, cell changes, and squamous cell carcinoma.[86] Advocates for removal of formaldehyde exposures from vaccines want to eliminate exposure to any potentially carcinogenic substance, but this is not feasible or necessary. The very small amounts of residual formaldehyde in vaccines following removal after inactivation of the target organisms are not additive to the amounts produced from the body's natural metabolism, are below the levels deemed acceptable by regulatory authorities, and are not harmful.[87]

Aluminum is used in the manufacture of many household products. People are exposed to aluminum from cookware, water, drinking containers, and foods including breast milk, infant formulas, flour, baking powders, coloring agents, anticaking agents, seafood, and other products. An average adult consumes 7–9 mg of aluminum per day, but only 0.1% - 0.3% is absorbed.[88] The brain normally contains about 1% of the total body aluminum stores. Intravenous exposure through parenteral nutrition and renal dialysis has resulted in encephalopathy. Guidelines for maximum intake from food vary from 1 mg/kg body weight per week (European Food Safety Authority) to 1 mg/kg/day in the United States (Agency for Toxic Substances and Disease Registry).

Aluminum adjuvants do rarely induce delayed type hypersensitivity reactions manifested as injection site urticarial papules, nodules, and sterile abscesses[89]. Completing recommended immunization series for these patients is problematic due to the lack of the recommended vaccines without aluminum adjuvants. The amount of aluminum in vaccines with aluminum adjuvants varies from 0.125 mg per dose for Prevnar 13, to 1.5 mg in DT; most vaccines contain 0.5 mg per dose or less (http.//www.vaccinesafety.edu). After injection, aluminum adjuvants are dissolved by alpha-hydroxycarboxylic acids, absorbed into the blood, distributed to tissues, and slowly excreted in the urine[90]. Some remains in tissues with most storage in bone.[91] Aluminum taken up by macrophages can be detected by injection site biopsy for at least 12 months.[92] Although there have been allegations that aluminum adjuvants cause persistent myalgia, fatigue, autoimmune diseases, encephalopathy and other conditions based on poor science, expert reviews have concluded that the scientific evidence does not support these claims. The detection of aluminum at injection sites many months after

vaccination "… represent(s) a simple marker of vaccination with long-term persistence of aluminum at the injection site and local inflammatory response to it, without other symptoms or consequences."[93] Similarly, the U.S. FDA has concluded "…episodic exposures to vaccines that contain aluminum adjuvant continue to be extremely low risk to infants and that the benefits of using vaccines containing aluminum adjuvant outweigh any theoretical concerns."[94]

New adjuvants in vaccines [Garçon]

For a vaccine to induce protection, it must be able to stimulate the immune system efficiently. Nature has designed a way for humans to mount such an immune response, by designing what is known as pathogen associated molecular patterns that are recognized by the first line of defense, the innate immune response, and initiate the cascade of events leading to the generation of a protective immune response.

Through the continuous evolution of vaccines, from the pathogen itself to fractions of it, pathogen-associated molecules have been lost, decreasing or losing the ability to launch the response. Adjuvants augment the responses to those molecules.[96,97]

Within a vaccine, the antigen brings the specificity of the response against the pathogen while the adjuvant enhances and modulates the immune response to the vaccine antigen. Therefore the quality of the immune response will depend on the potential of the antigen to be protective, and the adjuvant to optimize its potential. Both efficacy and safety are therefore

considered in the context of each adjuvanted vaccines individually following the current guidelines defined by regulatory agencies.

In general, adjuvants can induce some local reactogenicity such as redness, heat, swelling, the 3 markers of a local immune response (as seen during a local infection) as well as some systemic effect (flu-like symptoms, fever in particular). Their intensity can vary depending on the age, status (naïve versus primed) of the individual vaccinated, and all individuals do not respond in the same way.

Over the past 20 years and through the evolution of knowledge and available technologies, it has been possible to assess the mode (what the adjuvant does) and the mechanism of action (how the adjuvant acts). Those studies have shown for current licensed adjuvanted vaccines, that they act locally (effect limited to the site of administration and the draining lymph nodes, with an effect limited in time (days), supporting the safety observed in animal models and humans.[97-99] Knowledge of the mechanism and defining the pathway triggered during the response, have allowed us to establish more finely their safety profile, and to evaluate hypothetical risks of adverse events. For example, the knowledge of cell populations that can be activated or not allows closer study of hypothetical risks associated with vaccination.

As their mode of action is limited in space and time, no adjuvants currently present in vaccines have been shown to induce de novo rare events such as autoimmune diseases.

[100-101]

Residual Cell-Substrate DNA in Vaccines [Peden]

The production of viral vaccines in eukaryotic cell substrates inevitably means that they contain some cell-substrate DNA. When mammalian cell lines were considered for vaccine production, concerns were raised that the residual DNA could induce cancer or contain infectious agents. These concerns were heightened with regard to tumorigenic cells or cells derived from human cancers. The issue of whether cellular DNA could be a risk to vaccine recipients has been debated for more than 50 years without resolution.[102,103]

DNA can have two activities that could be of concern.[102,104] DNA could have an infectivity activity, *i.e*., the mammalian genome contains the genome of a DNA virus or of a retroviral provirus, or it could have an oncogenic activity, either through the introduction of a dominant activated oncogene or by inducing an oncogenic event through insertion into the host genome. To address whether DNA can induce an infectious event and with what efficiency, we have established a transfection/co-culture system to quantify HIV DNA infectivity. In dose-response studies, we showed that 1 pg of HIV DNA and 2 µg of the cellular DNA isolated from HIV-infected cells can be infectious. We have used this system to quantify the reduction in infectivity afforded by various treatments used in vaccine manufacture, such as nuclease digestion, beta-propiolactone treatment and binary ethylenimine treatment. We have shown that these treatments can reduce infectivity by $\geq 10^5$-fold and combined with reducing the amount of DNA to 10 ng (the WHO recommended amount of residual DNA per vaccine dose), safety margins of $\geq 10^7$ can be achieved.[105]

With respect to DNA oncogenicity, we generated expression plasmids for activated human H-*ras* and murine c-*myc*; these genes are driven by a long-terminal repeat [106]. When inoculated into mice, we found that tumors were induced but with low efficiency. To increase

the efficiency, we combined the two oncogenes on the same plasmid, and used it to evaluate the efficiency of various rodents to tumor induction.[107] With certain newborn rodents, DNA amounts of ≤ 1 ng induced tumors. However, even with such sensitive animal models, no cellular DNA from tumorigenic cells or from tumors induced by the ras/myc plasmid has ever scored positive. Also, not all dominant oncogenes are active in these *in vivo* systems. As a consequence, regulators have considered the best approach to dealing with DNA is to reduce both the amount of DNA and its size. Such considerations have recently permitted the introduction of vaccines produced in tumorigenic cell substrates.

Non-specific effects of vaccines [Pollard]

Non-specific or off target effects of vaccines refer to the responses induced by an immune stimulus to a vaccine (or infection) which alter the immune response to a subsequent heterologous infection.[108]. That such effects occur is without doubt as it is embedded in current and long-standing understanding of the innate and adaptive immune system, that the initiation of immune responses are non-specific, and can result in alterations in resistance to infection through production of mediators. For example, production of interferon-alpha during viral infection reduces susceptibility of cells to subsequent heterologous viral challenge. More recent evidence indicates that there is a profound activation of the transcriptome during infection or vaccination with the vast majority of the genes that are being expressed being non-specific innate responses.[109] Indeed, adjuvants are utilized to capture these nonspecific components of the immune response and enhance the focused adaptive response to the vaccine with which it is formulated. The extent to which alterations in innate immune

responses occur following vaccination in human infants has been little studied, and the effects of these responses on resistance or susceptibility to subsequent infection is unknown. We attempted to systematically analyze the literature in 2016 with a focus on EPI vaccines and concluded that there was “some evidence that in some study designs, with some vaccines, administered in some settings, where samples are taken at some time-points, and some in vitro assays are undertaken that non-specific immunological effects may be detected in response to some in vitro stimuli but it is difficult to identify consistent findings”.[110] We noted that measles and BCG vaccines were associated with increased interferon-gamma responsiveness during later in vitro stimulation. A recent study by Blok et al in 75 adults indicated that there were changes in responsiveness to various in vitro stimuli measurable at one and 4 days after vaccination with either BCG or BCG+DTaP, and they have proposed that such changes that are observed are likely to be driven by changes in the epigenome following an immune trigger[111].

While the immunological phenomenology is fascinating and further exploration of the characteristics, magnitude and persistence of these effects is warranted in understanding of the immune system, the clinical significance of the measurable changes is unknown, and there is currently no rationale for attempting to deliberately enhance or reduce any of these effects for clinical benefit.

However, a large number of animal studies have provided compelling evidence that infection with one organism or exposure to an antigen can confer some resistance to another heterologous infection. For example, live candida administration in mice can provide up to 70% protection against lethal infection with *Staphylococcus aureus*[112]; BCG vaccination protects

mice against malaria infection[113]; and rabies vaccine protects young dogs against fatal sepsis[114].

While there is great interest in the phenomenon, the scientific community has become very polarised in views about the importance of non-specific clinical effects in humans. A systematic review[115] concluded that BCG and measles-containing vaccines reduced all cause mortality, though the relative risks, when restricted to the highest quality RCTs showed that these findings were non-significant. Recent studies have found that there was a non-significant reduction in morality with early vs late BCG in premature infants in Guinea Bissau, which was significant in a sub-population censored for oral polio vaccine. By contrast there was no difference in hospitalisation rates for infants randomised to receive BCG in Denmark up to 15 months of age.[116] A high quality study in low birthweight infants (<200g) in India found that there was no difference in mortality with early BCG-Russia.[117] While the data are inconclusive for the magnitude or clinical importance of these effects with BCG and measles, some investigators now claim that all live vaccines have substantial beneficial effects, which is supported by the current WHO position paper, despite the uncertainty that is presented by evaluating the data.

The systematic review also evaluated studies of non-specific effects of DTP containing vaccines but found no high-quality studies. However, observational studies resulted in a positive relative risk, indicating increased mortality following vaccination, especially in girls, but without statistical significance. Despite the high risk of bias in these low-quality studies, which did not provide statistically robust relative risks, some investigators have seized on these data and claim that all non-live vaccines might be harmful.

Recent studies have investigated how bias could influence the observations described above, and further increase the uncertainty about the clinical importance of the claims.[118,119]

While it seems that immunological non-specific effects occur, we don't know enough about them to predict when or for how long they might last and have no understanding of their clinical relevance. The animal studies show that there are intriguing effects, whether underpinned by the above immunological observations or not, which can be induced in these controlled settings and can have a profound impact on survival. The animal studies, provide a strong case for improved understanding of the biology that might one day be translated into benefits for humans. The human data, with clinical endpoints, indicate that there are intriguing signals which warrant investigation, but trials to provide a definitive answer will be challenging to realize as global childhood mortality continues to fall. Today we do not have definitive evidence of non-specific effects of vaccines that should lead to a change in immunization policy.

HPV vaccines [Markowitz]

Available human papillomavirus (HPV) vaccines are virus-like particle (VLP) vaccines, made from the L1 major capsid viral protein. Three HPV vaccines have been licensed: bivalent (2vHPV), quadrivalent (4vHPV) and 9-valent vaccines (9vHPV). The adjuvant in 2vHPV is ASO4, which contains aluminum hydroxide and monophosphoryl lipid A, while the adjuvant in 4vHPV and 9vHPV is alum. The first vaccine was licensed in 2006; by the end of 2018, vaccination

programs had been introduced in over 80 countries. Despite reassuring safety data from HPV vaccine clinical trials and post-licensure monitoring studies, listed in Table 3, safety concerns continue to be raised. Several countries have had challenges with their programs due to safety concerns, including Japan (chronic regional pain syndrome [CRPS]), Denmark (postural orthostatic tachycardia syndrome [POTS]), and Ireland and Colombia (a variety of different concerns).

The World Health Organization's (WHO) Global Advisory Committee on Vaccine Safety (GACVS) reviewed safety of HPV vaccines seven times since 2007; in 2017 GACVS conducted a comprehensive assessment and systematic review focusing on serious events after 2vHPV and 4vHPV.[120] In this systematic review, 26 randomized controlled trials and six good quality post-licensure cohort studies were included.[120-122] Among the cohort studies: four looked at autoimmune diseases, two venous thromboembolic disease and one multiple sclerosis and other demyelinating conditions. Results from both clinical trial evidence and cohort studies were consistent in finding no relationship between serious adverse events and HPV vaccination. POTS and CRPS were not considered in the systematic review, as WHO used a report by the European Medicines Agency (EMA) to inform about these events.[123] While EMA did not find a relationship between HPV vaccination and POTS or CRPS, they felt that further monitoring should be conducted given public concern.

Since the GACVS systematic review, numerous additional large post-licensure safety studies have been published for 4vHPV and 2vHPV from several countries.[124-130] At least ten evaluated autoimmune disease, including six that evaluated multiple autoimmune diseases,

three Guillain Barré Syndrome only [128-130] and one type 1 diabetes only.[127] In addition, since the 2017 review, there have been systematic reviews examining autoimmune disease.[131,132] Aside from these outcomes, studies specifically investigated primary ovarian insufficiency[133] and chronic fatigue[134] finding no consistent evidence of safety concerns. A study using a new methodology, the self-controlled tree-temporal scan statistical method, scanned hundreds of diagnoses among 1.9 million 4vHPV recipients and found no new associations.[135] At least five post-licensure studies of inadvertent HPV vaccination in pregnancy, such as one examining data from Denmark's nationwide registers [136], have been published since 2017, showing no association with adverse outcomes of pregnancy.

To date, the only post-licensure safety data for 9vHPV are from the United States. During a period of time when 29 million doses were distributed, VAERS identified no concerning signals.[137] A rapid cycle analysis in the Vaccine Safety Datalink raised no safety concerns.[138]

Too Many Vaccines? (Glanz)

Many parents have concerns that children are receiving too many vaccines in too short of a time, with specific concerns that vaccines are overloading the child's immune system and vaccine ingredients are toxic. To minimize vaccine exposure, an estimated 10-15% of parents are choosing alternative vaccination schedules for their children.[139] The Institute of Medicine (IOM) responded by publishing a report in 2013 that recommended additional research on the safety of the recommended childhood immunization schedule.[46] The report emphasized that the studies should be observational, focused on the schedule as a whole rather than individual

vaccines, and be designed to evaluate chronic and long-term outcomes occurring months to years after vaccination. The report also concluded that the Vaccine Safety Datalink (VSD) represents an ideal research environment to conduct such studies.

The Centers for Disease Control and Prevention has made the safety of the recommended schedule a research priority and commissioned a white paper on how the VSD could be used to address the safety gaps presented in the IOM report.[140] Through subject matter expert engagement, the white paper identified important methodological challenges to studying the schedule and generated a list of 20 outcomes prioritized by public health significance and public concern. The methodological challenges with studying the safety of the recommended schedule included unmeasured confounding, inadequate statistical power, and misclassification of exposures and outcomes. The prioritized outcomes included both acute and chronic conditions, such as asthma, anaphylaxis, type 1 diabetes mellitus, epilepsy, juvenile rheumatoid arthritis, seizures, all-cause mortality, all-cause morbidity (non-targeted infection), and chronic urticarial

Guided by the white paper, the VSD has developed analytic metrics for measuring adherence to the recommended schedule, including cumulative vaccine antigen exposure, cumulative vaccine aluminum exposure, and a summary measure called the average days under-vaccinated. Thus far, these metrics have been used to study all-cause mortality and non-targeted infection, both of which produced null results.[141,142] Studies examining asthma and type 1 diabetes mellitus are currently underway.

While progress is being made, there remain substantial challenges to studying the safety of the schedule, including the potential for uncontrolled bias and inadequate sample sizes to study the rarer outcomes on the white paper priority list. This points to a need for independent data sources in which both positive and negative safety signals can be replicated and validated, and for continued research to develop methodological approaches to minimize biases that may affect safety studies of the recommended childhood immunization schedule.

Summary

As stated in the introduction, this review of major safety issues related to vaccination has identified gaps in the scientific evidence and the need for new studies so as to add new knowledge to a controversial field. Although vaccination remains a highly positive procedure to maintain the health of populations, science requires that careful study continues to add to our knowledge and to maintain public confidence in the vaccine enterprise.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

The findings and conclusions in this report are those of the authors and have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination of policy.

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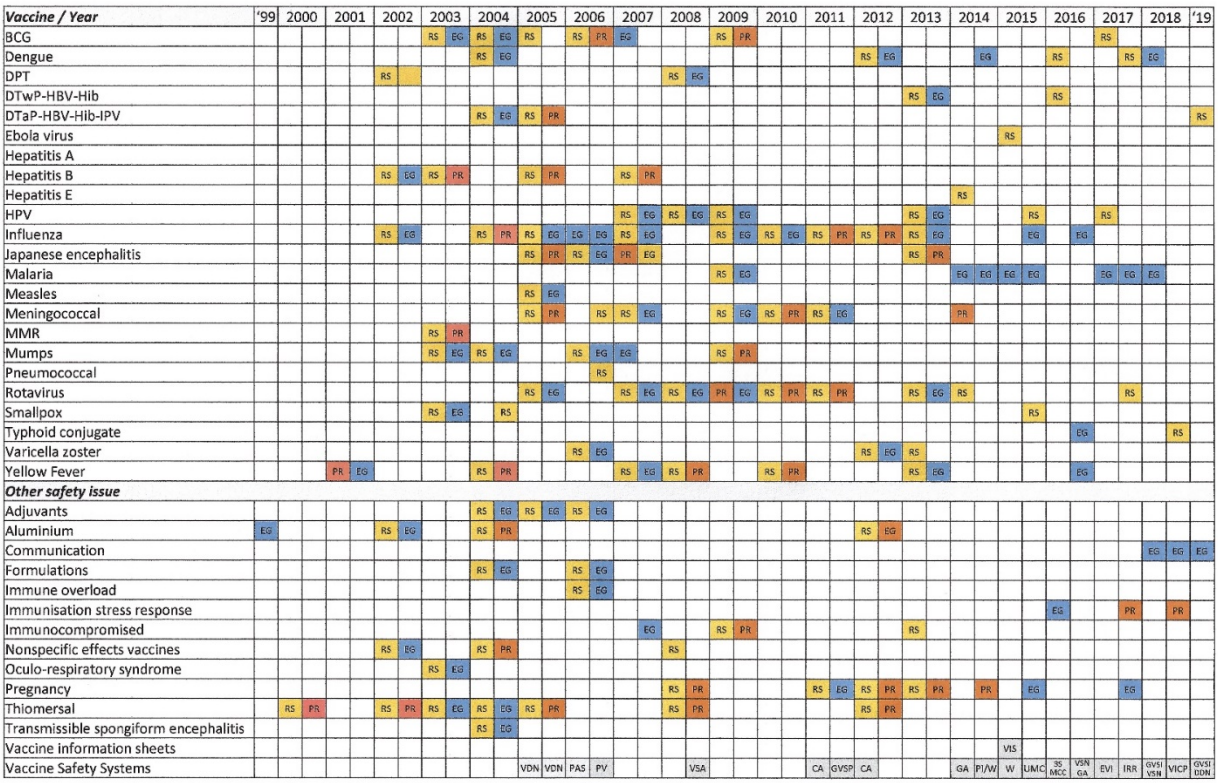
Table 1

Table Vaccine safety issues addressed by the Global Advisory Committee for Vaccine Safety by year, type of review and decision 1999 –2019 (Adapted with permission from Asturias et al. Vaccine 2016)



GA: GACVS evaluation; PI: Performance indicators; W: Websites assessment; UMC: Uppsala Monitoring Centre; 3S: Project 3S; MCC: Multi-country collaborations; VSN: Vaccine Safety Net; EVI: Essential Vaccine Information; IRR: Inter-rater reliability; GVSI: Global Vaccine Safety Initiative; VICP: Vaccine injury compensation programmes; DDN: Distributed data networks; VS: Vaccine safety; VDN: Vaccine safety detection networks; PV: Pharmacovigilance; VSM: Vaccine safety monitoring; CA: Causality assessment; GVSP: Global vaccine safety plan

Table 2. Autoimmune or Immune-mediated diseases reported following vaccination		
Autoimmune/ immune-mediated disease	**Type of vaccine**	**Confirmed association**
ncephalitis	Rabies	YES
Multiple sclerosis	HBV	NO
Rheumatoid arthritis	HBV, tetanus, typhoid, MMR	NO
Systemic lupus erythematosus	HBV, tetanus, anthrax	NO
Reactive arthritis	BCG, typhoid, MMR, influenza, Ebola	YES
Guillain-Barrè syndrome	Swine Influenza,	YES
Idiopathic thrombocytopenia	MMR	POSSIBLE
Diabetes mellitus-type I	HIB	NO
Hashimoto thyroiditis	HBV	NO
Polymyositis/ dermatomyositis	BCG, smallpox, diphtheria, DPT	POSSIBLE
Polyarteritis nodosa	Influenza, pertussis, HBV	NO
Narcolepsy	Pandemic influenza (p2009)	YES
Myocarditis	Smallpox	POSSIBLE
ASIA syndrome	Adjuvanted vaccines	NO

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Table 3*

Outcomes studied in post-licensure human papillomavirus vaccine safety evaluations and selected references[a]

Outcome	Selected References	Vaccine
Autoimmune and neurologic diseases[b]	Chao C. J Intern Med 2012	4vHPV
	Arnheim-Dahlstrom L. BMJ 2013	4vHPV
	Grimaldi-Bensouda L. J Intern Med 2014	4vHPV
	Langer-Gould A. JAMA Neurol 2014	4vHPV
	Baxter R. Clin Infect Dis 2016	4vHPV
	Grimaldi-Bensouda L. J Autoimmun 2017	4vHPV
	Sridhar G. Hum Vaccin Immunother 2017	4vHPV
	Miranda S. Vaccine 2017	4vHPV
	Hviid A. J Intern Med 2018	4vHPV
	Frisch M. Int J Epidemiol 2018	4vHPV
	Liu EY. CMAJ 2018	4vHPV
Guillain-Barré syndrome only	Andrews NJ. Vaccine 2017	2vHPV and 4vHPV
	Gee J. Vaccine 2017	4vHPV
	Deceuninck G. Expert Rev Vaccines 2018	4vHPV
Type-1 diabetes only	Klein NP. Vaccine 2019	4vHPV
Thromboembolism[C]	Arnheim-Dahlstrom L. BMJ 2013	4vHPV
	Scheller NM. JAMA 2014	4vHPV
	Naleway AL. Vaccine 2016	4vHPV
	Yih WK. Vaccine 2016	4vHPV
	Frisch M. Int J Epidemiol 2018	4vHPV
Multiple outcomes[d]	Gee J. Vaccine 2011	4vHPV
	Klein NP. Arch Pediatr Adolesc Med. 2012	4vHPV
	Yih WK. AJE 2018	4vHPV
	Skufca J. Vaccine 2018	2vHPV
	Donahue JG. Pediatrics (in press)	9vHPV

Primary ovarian insufficiency	Naleway AL. Pediatrics 2018	4vHPV
Chronic fatigue	Feiring B. Vaccine 2017	4vHPV
	Schurink-Van't Klooster TM. Vaccine 2018	2HPV
Death	McCarthy NL. Pediatrics 2016	4vHPV

2vHPV, bivalent HPV vaccine; 4vHPV, quadriavlent HPV vaccine; 9vHPV, 9-valent HPV vaccine

[a]case series, case reports and reports from passive reporting systems not included

[b]Studies focused on autoimmune outcomes, demyelinating or other neurologic conditions (most included many different outcomes including Guillain-Barré syndrome)

[c]Naleway and Scheller studied only thromboembolism; other studies included many outcomes [d]Studies not limited to autoimmune or neurologic outcomes

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