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Vaccines are not always perfect: adverse effects and their clinical impact

“Unexplained weight gain, shortness of breath or difficulty breathing, swelling of the abdomen, feet, ankles, or lower legs, fever, blisters, rash, itching, hives, swelling of the eyes, face, throat, arms, or hands, difficulty breathing or swallowing, hoarseness, excessive tiredness, pain in the upper right part of the stomach, nausea, loss of appetite, yellowing of the skin or eyes, flu-like symptoms, pale skin, fast heartbeat, cloudy, discolored, or bloody urine, back pain, difficult or painful urination, blurred vision, changes in color vision, or other vision problems, red or painful eyes, stiff neck, headache, confusion, aggression.”

A side effect profile for a known vaccine? No, the profile for the rather well-used nonsteroidal anti-inflammatory drug (NSAID) ibuprofen, obtainable either over the counter, or on prescription for more serious conditions such as osteo- or rheumatoid arthritis. In 2013, an analysis using data from epidemiological studies in the US estimated the mortality due to ibuprofen to be 64 cases per million.¹ To put this figure in context, a recent commentary on the rare thrombotic events that have been associated with certain of the COVID19 vaccines (ITP, or immune-induced thrombocytopenia) noted:

“Estimates to date suggest that post-COVID vaccine ITP is rare (1 in 100,000 to 1 in 1,000,000) and may be related to vaccination or represent a coincidental event.”²

To calculate the risk of serious side effects for any medicine when in the incidence range of 1–100 per million, a clinical trial would have to involve a large number of participants across all relevant age ranges to detect a sufficient number of serious reaction cases for a statistically valid risk factor to be calculated. But even then, it is not that simple, because any adverse reaction has to be shown to be “caused” by the vaccine rather than being a coincidental reaction, either from a rare preexisting pathology or undetected health issue predisposing the vaccinee to the reaction.

Reluctance to accept vaccination on the basis of unproven risks of health impairment is not a 21st century phenomenon. In the early 1800s, the increasingly accepted use of cowpox secretions as a “vaccine” against smallpox was not without its opponents, some of whom were from the very top of the medical profession. We saw examples of such irrational responses in Chapter 3 (see Fig. 3.2), where William Rowley, a renowned London clinician, publicly proclaimed the dangers of the vaccine citing cases where the recipients had developed bovine physical characteristics (e.g., “cowpox face”), a notion lacking all medical logic. In an extension of his conspiracy theories, Rowley noted that some vaccinated children became idiots, and that adults might become insane.³

By 1853, the dangers of infection with smallpox led to the Vaccination Act in Britain which required compulsory vaccination, a government step not entirely popular since it was seen to be suspending individual liberty. The more pragmatic view is that it only suspended the liberty of the individual to spread infection to others, a not entirely oppressive or unreasonable demand, but only of

course if the danger of vaccination was no less than the danger of the infection itself. Notwithstanding its apparent attack on individual freedom of choice, the present UK government might have found it helpful to have reread the principles behind that Act and wonder if a similar piece of legislation might have been put in place early in 2020. Despite belief in the principle that each person should be vaccinated to protect the population—a C19th version of what Jeremy Farrar, head of the Wellcome Trust says of COVID19 vaccination “*no-one is safe until we are all safe*”—it was reasonable that if society were to acquiesce it should demand the highest quality of whatever was being pumped into their muscles.

Four years after the Vaccination Act, Sir John Simon, sitting on the UK General Board of Health, undertook a major enquiry into the pros and cons of Jenner’s cowpox vaccine. Although the conclusions, examined in nearly 400 pages of analysis and opinion, were seriously in favor of what he later referred to as “... *Jenner’s incomparable benefaction to mankind*,” an important part of the analysis was examination of the anti-vaccination arguments, among which were numerous claims of extraordinary anthropomorphic transformations, such as:

“A child at Peckham had its former natural disposition absolutely changed to the brutal, so that it ran upon all fours like a beast, bellowing like a cow, and butting with head like a bull.”⁴

In the end, the report made absolutely clear that the weight of evidence in favor of cowpox vaccination was overwhelming and that many of the ridiculous claims of side effects were just that, ridiculous. As a note of reassurance, somewhat in jest, Simon observed:

“Those who feared bodily changes...were assured that in Berkeley [Jenner’s birthplace] neither horns had grown nor Minotaurs had been begotten.”⁵

The conclusion of the Medical Council responsible for the report was unequivocal:

“...in their opinion, founded on their own individual experience, and the information which they have been able to collect from others, mankind has already derived great and incalculable benefit from the discovery of vaccination.”⁶

The incalculable benefit was in reality calculable. In 1800, out of every 1000 babies born in the US, more than 450 would die before their fifth birthday. By 1900, it would only have dropped to 239/1000 but by 2020 infant mortality had reduced to 7/1000. This reduction was not all due to vaccines of course since other medical advances and disease management methods improved over time, but the introduction of vaccines for diphtheria, pertussis, tetanus, measles, rubella, and other infections, during and since WWII, contributed immeasurably to lowered infant adverse effects and the mortality rate. But this does not mean vaccines were exempt from blame for some of the observed adverse effects, occasionally mimicking the effects of the pathogens themselves but in other cases generating unexpected reactions that were not always easy to explain. Recognizing the existence of such reactions, and mindful of the disastrous consequences of the Cutter poliovirus incident, the US was particularly cautious and in 1986 introduced the National Childhood Vaccine Injury Act. One of the key aspects of the legislation was to establish causation where possible. While a clinical symptom may appear after a vaccination, the direct causal relationship between the vaccine administered and the effect observed is not established just because the events may be close in time. The removal of a coincidence factor, however, is not trivial. The observed effect may in fact be a pure coincidence in timing, or it may be

triggered by the vaccine in individuals that have certain preexisting health challenges but not experienced by healthy vaccinees, or it may be a direct consequence of the vaccine regardless of health status.

Following the 1986 US Act, a follow-up review was carried out in 1994, and in 2012 a new Committee was formed by the Institute of Medicine of the US National Academies whose remit was to assess the adverse effects of eight different vaccines, based on published clinical trial data, involving 158 vaccine adverse effect (AE) pairings, the largest investigation ever carried out for a vaccine review. The vaccines examined were MMR, Varicella (chicken pox), Influenza, Hepatitis A, HPV (Human Papilloma Virus), Meningococcal, and the Diphtheria, Tetanus, and Pertussis toxin-based vaccines. For some vaccine-adverse effects reported in the published clinical studies, a proportion were excluded from the analyses, because of the absence, or incorrect comparison with, unvaccinated controls, or because of sample sizes too small to draw statistically valid conclusions, and in some cases because of methodological limitations. For example, of the 19 MMR studies reporting febrile seizures in response to the MMR vaccine, only eight were considered to have been adequately performed to allow firm epidemiological conclusions to be drawn. It is also important to note that the remit of the Committee was not to answer the question “Are the Vaccines Safe?,” which was the responsibility of relevant government and medical agencies, but to establish whether or not a causal relationship between administration of particular vaccines and any adverse effects reported was sufficiently clear as to merit flagging to the authorities concerned. The conclusions of the Committee for the various vaccines considered, based on more than 800 pages of analysis and opinion, were expressed on only five pages at the end of the Report, signifying a low number of serious adverse effects for which establishing a formal causal relationship had been possible. In saying that the Committee rightly pointed out that while many of the adverse effects reported in the clinical trial reports were exceeding rare in the vaccinated population, where it was not possible to establish a causal relationship did not mean that the vaccine was not associated with that effect, but that on the evidence available, a cause and effect conclusion could not be reliably drawn. This is an important distinction that is often glossed over, or misinterpreted, occasionally by those promoting vaccination but particularly by anti-vaccination groups, and even by the media.

The evidence for linked adverse effects with the eight vaccines considered was in the end remarkably thin. For the MMR vaccine, the only firmly established link was to febrile seizures at the incidence of one to four per 1000 depending on the clinical trials involved. The committee noted that such seizures can occur from the virus infections themselves, and in vaccinees were rare and usually mild with no permanent sequelae. No other cerebral consequences of the vaccine were proven. Of considerable importance here was the analysis of any evidence linking the MMR vaccine to autism. The committee reviewed 22 studies of which only five passed the test of proper controls and methodological probity. The conclusions of the committee were twofold and worth quoting. On the epidemiological evidence:

“The committee has a high degree of confidence in the epidemiologic evidence based on four studies with validity and precision to assess an association between MMR vaccine and autism; these studies consistently report a null association.”⁷

On the mechanistic evidence:

“The committee assesses the mechanistic evidence regarding an association between MMR vaccine and autism as lacking.”⁸

A second vaccine against Varicella (chicken pox, caused by the herpes varicella zoster virus, VZV) threw up a number of adverse effects for which a link to the attenuated live vaccine was established. The vaccine is given either as single monovalent vaccine (e.g., Varivax from Merck & Co.) or as a combination vaccine with MMR generating the quadrivalent MMRV vaccine (e.g., ProQuad, Merck & Co.). A potential AE can arise if the attenuated vaccine is “reactivated” to an infectious form leading to disseminated disease, known as Oka VZV (Oka refers to the human source of the original virus in Japan from which the attenuated vaccine form was derived). This is most likely to occur, if at all, in immunocompromised persons who are unable to mount a strong immune response, and as a result allow an extended residence time for the attenuated virus theoretically to mutate back to an infectious form. Of course, mutations are typically random and then positively selected for if they give the virus an advantage, but mutations can also be deleterious to the virus. In healthy individuals, the epidemiological assessment was insufficient to establish a link despite the mechanistic assessment being strong. However, in immunocompromised individuals, the causality link was “convincingly supported,” leading to cautionary advice when contemplating Varicella vaccines for such individuals. Reemergence of the Varicella virus after chicken pox can give rise to the extremely painful shingles in older persons, arising from the virus remaining dormant within the sensory nerve ganglia and then breaking out again within the sensory nerve roots. Although the potential for shingles to be described as a possible vaccine adverse effect, the difficulty of distinguishing between a reappearance of the native virus or reactivation of the vaccine attenuated form, led the committee to conclude that any causal connection of such cases was “inadequate.” However, the committee did recommend that this vaccine should not be given to persons with severe cases of immunodeficiency.⁹

The question of anaphylaxis after vaccination is a more complex issue and while rare it can be life-threatening. The world today is acutely aware of the care taken at COVID19 vaccination stations to retain individuals for at least 15 min at such centers after receiving the vaccine, during which time any anaphylactic reaction would normally become evident. The 2012 committee indicated that while it was difficult to determine the rates of such reactions to the various vaccines, the evidence convincingly showed a causal relationship in those instances reported for a number of the vaccines. One difficulty in interpreting the exact origin of the reaction is when multiple vaccines are administered at the same time. For example, a study in 2003 on MMR vaccines reported three anaphylaxis cases out of almost 850,000 vaccinations, but on analysis two of the three children had received other vaccines at the same time confounding accurate attribution of the causative vaccine.⁹ Anaphylactic reactions are mediated by the “allergic” arm of the immune system where certain “allergens” are recognized as foreign, triggering in severe reactions a massive release of inflammatory and vasoactive mediators throughout the body. If left untreated, the reaction may cause death through respiratory obstruction and/or cardiovascular collapse. Many vaccines contain adjuvants and additional stabilizing substances such as gelatin, but also substances carried through from the manufacturing methods, for example, egg proteins in influenza vaccines to which some individuals are allergic. The committee noted that when the level of such components is reduced, the rate of anaphylactic reactions decreases. In the concluding statement, the committee was extremely cautious and aware of misinterpretation of some of the

unproven links. It is worth noting that, as ever in the science of complex biological systems, it is much more difficult to prove a negative than to establish or prove a firm connection between one event and another.

Six years after the 2012 US Committee report, Frank Destafano and Allison Fisher from the US CDC, and Paul Offit of the Children's Hospital of Philadelphia revisited the question of vaccine safety, drawing attention to the fact that while most serious adverse effects are rare, with the increasing application of vaccination in the prevention of a burgeoning assault on the human population by new infectious diseases, the question of even rare adverse reactions to vaccines is an issue to resolve rather than simply accept as a calculated risk. This question has become even more prominent during the SARS-CoV-2 pandemic where life-threatening but rare coronary side effects, albeit often in individuals with known or sometimes undetected preexisting health conditions, has moved the vaccine safety question into sharp focus. This relationship between disease, vaccine efficacy, and adverse effects and the associated behavioral changes, illustrated by Destafano et al.,¹⁰ is shown in Fig. 15.1.

We have already discussed (Chapter 12) an example of “loss of confidence” events during the 1970 and 1980s where a possible link between the pertussis vaccine and brain damage observed in the UK caused a hiatus in vaccine take-up. Eventually the public were convinced that allowing exposure to three of the diseases dangerous for children, measles, mumps, and pertussis (whooping cough), and especially the severe consequences of rubella infection for pregnant mothers, was more of a risk than being vaccinated, leading to a resurgence in MMR vaccination. While adverse reactions may be rare, because the majority of vaccinees are healthy individuals (generally), the standards of safety need to be

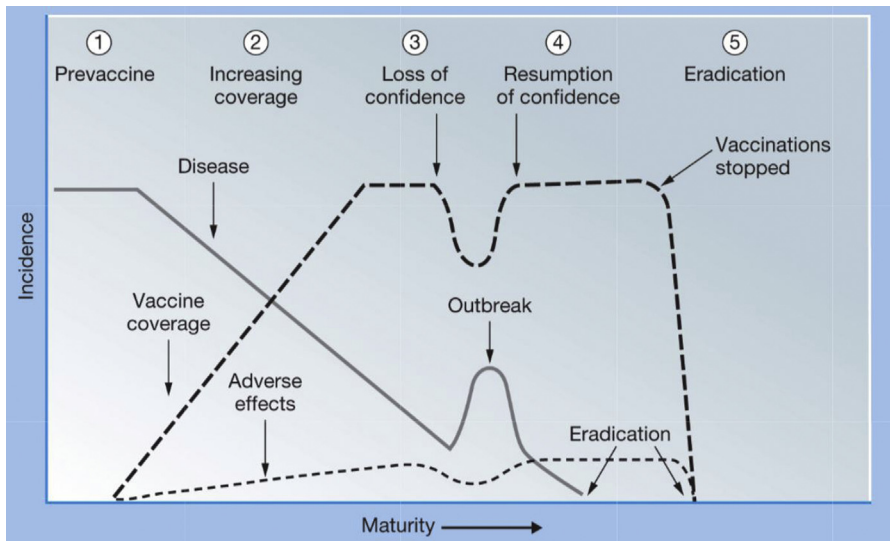


FIGURE 15.1

The evolution of a typical vaccination program and the effect of vaccine safety concerns on the progress of vaccination in the population, and the disappearance of, or stabilization at low-level endemicity, infectious pathogens.

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much higher than for administration of drugs to persons with life-threatening diseases, such as cancer or coronary disease where significant medication-induced adverse reactions are an acceptable risk when compared to their often life-saving effects.

Vaccine safety evaluation

It is in the nature of clinical trial phases that rare adverse events to any new medicine are often difficult to identify. During Phase I of a vaccine trial, a small number (typically 10s to a <100) of volunteer subjects are tested to assess basic safety with different doses of the vaccine and because it is reasonably straightforward to do, their antibody and sometimes cellular immune responses to the vaccine are measured. While it is good to know that the vaccine induces an immune response, the presence of such responses is not a direct measure of efficacy. For example, antibodies may be produced to the vaccine, but they may fail to neutralize the pathogenic effects of the native virus. During a Phase II trial with larger numbers (often 100s) of participants, the effect of the vaccine in single or multiple dosing regimens on the immune responses of the participants may be measured, the vaccine compositions (virus strains used, vaccine combinations, formulation substances, concentration of vaccine component per injection, etc.) may be varied and the route of injection and of course safety will be assessed. For an important infectious disease, the study will normally include vaccinated and control (injected with a placebo substance, or a different vaccine unlikely to interfere and whose properties are known) cohorts in order to compare both safety and immune responses. The results of the Phase II trial will then feed into the Phase III protocol where the vaccine dose, adjuvant selection, and other parameters will form the basis of the much larger trial (typically 1000s with vaccinated and placebo cohorts), involving susceptible persons in or close to an infected region. In such trials, the prime output measures will be efficacy, or protection from the disease outbreak, and safety. While formal procedures are in place for reporting of vaccine adverse events or serious adverse events (AEs or SAEs; in the US the Vaccine Adverse Event Reporting System (VAERS) is used; in the UK a Yellow Card system is used while the EU reports AEs through the EudraVigilance system), as with any other pharmaceutical drug, the statistics of rare events observed during a trial are nontrivial. For example, the Rule of Three, developed to assess risks of AEs during surgical operations,¹¹ when applied to a vaccine trial would state that if none of N vaccinees showed an AE during the trial we can be 95% confident (i.e., with a 5% error) that the incidence of this event is at most one in $3/N$. Thus if 1000 subjects (N) are enrolled in a Phase III vaccine trial and no serious AE has been recorded, we can only be certain at the 95% confidence interval that the real incidence of a serious event is no greater than one in 333. ($3/1000$). Most Phase III clinical trials for COVID19 vaccines involved only a few thousands of subjects. No cases of the serious ITP AE were reported for any of the vaccines (to the author's knowledge) during those Phase III clinical trials. Cases that have been reported after the roll out of different vaccines have been estimated to be in the range 1–10 cases per million vaccinations. Such rare AEs would not have been picked up during the trials which, for example, would have required participant numbers of several hundred 1000 vaccinees to reach the 95% confidence interval of an upper limit for AEs of 1–10 per million by the $3/N$ criterion (e.g., $3/300,000 = 1$ per 100,000 = 10 per million). Those numbers were far exceeded of course during post-approval vaccination of entire populations leading to identification of this extremely low-level AE. So how can rare but serious adverse effects be evaluated, and in particular conclusions drawn on cause and effect, in small clinical trial cohort numbers? They

cannot. The rapid execution of Phase III trials carries regulatory plusses and minuses. The only practical approach for rapid development of vaccines during a pandemic is by continuous monitoring during postregulatory approval roll-out, sometimes captured by regulated Phase IV clinical trials, where vaccination with exponentially rising vaccinee numbers occurs. That is precisely when the ITP cases after COVID19 vaccination began to be picked up. This raises an impossible dilemma for vaccine developers and regulatory authorities. Telescoping the development and release of a new vaccine into shorter and shorter time frames when an epidemic or pandemic has already started is the only way to prevent much larger morbidities and mortalities (cf Ebola Chapter 13). Essentially this means the population at large is required to buy into the notion that they must be guinea pigs in a sort of vast unregulated “vaccine challenge” trial where the appearance of rare adverse events not predicted by results from the normal regulated clinical trials will, unfortunately, become visible. Such then is the “chance and necessity” route to pathogen protection by immunization.

The other “substances” in vaccines!

In 2018, Garcon and Fried made the following important statement in their review of some of the immunological enhancers added to vaccines, known as adjuvants:

“The safety evaluation of a vaccine encompasses all constituents of the product. It cannot be assumed that an adjuvant that is safe in one vaccine with a given antigen will be safe when added to another vaccine....”¹²

The use of added material to vaccines in order to potentiate an immune response to the vaccine itself originates from observations made in the early part of the 20th century. In 1925, Ramon showed that addition of substances such as starch, fish oils, and complex plant extracts to diphtheria toxin potentiated the immune response to the toxin,¹³ while in later work by Glenny, the effect of adding aluminum potassium sulfate (alum) was seen to be highly effective for the same diphtheria toxin.¹⁴ Over time, the active ingredients of the Ramon substances were revealed although the exact mechanism by which such additives enhance immunity is still somewhat fuzzy. The discovery of the “pattern receptors” in the fruit fly *drosophila melanogaster* in 1996 that recognize molecular patterns in pathogens (in the case of the fruit fly, fungi) that enter the body, by a sort of molecular “face recognition” process, was a major breakthrough that led to an understanding of how the innate immune system can kick start an immune response. In 1997, Janaway showed that a close homolog of this fruit fly receptor (named TLR or Toll-like Receptor) was present in humans and was directly connected to the triggering of an adaptive immune response.¹⁵ This was rapidly followed by studies showing that TLRs recognized certain lipopolysaccharides,¹⁶ known components of bacteria, and providing an explanation of how killed bacteria could have an adjuvant or enhancing effect on immune responses, first observed at the close of the 19th century.

Some of the active substances that were present in Ramon’s preparations have subsequently been identified and used as purified adjuvant additives. For example, inulin, a group of storage polysaccharides (sugars), was the likely enhancer in Ramon’s plant extracts, while in fish oils the key component, squalene, has been used as an additive in vaccines although not with an entirely smooth ride in regulatory circles. In the case of Glenny’s alum salts, the reason for this inorganic additive’s effect has had various explanations. For example, the fact that certain aluminum salt compositions

have high surface areas that adsorb the vaccines and then release them slowly from the site of injection, the so-called depot effect, has its supporters but for this to be the mechanism it would need to explain why when the injection site is excised (in animal models) shortly after injection there is no effect on the immunity generated.¹⁷ Other mechanisms suggested include the conversion of the soluble vaccine component to a particulate form whereby it is taken up by immune cells involved in presenting the antigen (known as APCs, Antigen Presenting Cells) more readily, a mechanism that appears to have some weight of evidence behind it.¹⁸ A third possibility is that alum itself stimulates immune cells directly thereby acting as an enhancer to the already foreign antigen(s) in the vaccine. Whatever the mechanism by which alum-based adjuvants act to improve immunity it is to be expected that questions would be asked about the toxicity of any substance containing aluminum and its possible role in reported postvaccination AEs such as myalgia, fatigue, autoimmune diseases, and so on. No epidemiological causation has been found for these effects, however, and the US FDA has concluded that intermittent exposure of infants to these adjuvants is “extremely low” risk.¹⁹ Having said that there are cases of hypersensitivity to this type of adjuvant and manufacturers are continuously looking for alternatives that cause even fewer of these already rare AEs.

The question of squalene as an adjuvant, a metabolizable fish oil component, has a more chequered history although it is only used in three out of fewer than 10 US FDA approved adjuvants. As an example, three different influenza vaccines use adjuvants that contain squalene (Table 15.1).²⁰ The use of such additives is driven by observations that vaccines derived from inactivated viruses, or subunit components produced by laboratory recombinant processes, are often lacking in good antibody and T-cell responses, while the same vaccine with adjuvants such as squalene present can typically elicit robust and protective antibody responses. Squalene is a naturally occurring molecule that is used by the body in the synthesis of cholesterol and vitamin D. Because it is hydrophobic (water hating), it is prepared as an oil-in-water emulsion where it ‘hides’ in the oil droplets. Its reputation as a potential concern may have arisen following reports that soldiers returning from the Gulf War in 2002 showed evidence of antibodies to squalene that was supposedly an adjuvant in anthrax vaccines administered in the region.²¹ Since then, this connection appears to have been debunked by several subsequent studies and analyses. In fact, it seems the anthrax vaccines administered did not actually contain squalene. Individuals who had not been vaccinated also showed evidence of having antibodies, and in other studies participants in an influenza vaccine trial where the vaccine contained the MF59 adjuvant that includes squalene as an additive (see Table 15.1), failed to generate antisqualene antibodies. In the event, a link between the presence of antisqualene antibodies and the physical and psychological traumas experienced by the returning military may have been incorrectly made or at least overstated.²² Added to that, immunology theory would suggest that the squalene molecule is likely to score poorly on chemical and immunological criteria as an “antigen” capable of eliciting a meaningful antibody response. Nonetheless, Lippi and colleagues in their “fact or myth” analysis take a somewhat cautious line in their conclusion, suggesting the scientific jury is not yet prepared to declare “myth” with 100% certainty:

“Taken together, the current scientific evidences (sic) point out that denying vaccination because of the risk of developing antibodies to squalene is probably unjustified.”²³

Immunity enhancers are of course only part of the story that cautious parents and antivaccination groups are concerned about. The use of and then carry-through of formaldehyde in the inactivation of

Table 15.1 Approved influenza vaccines containing squalene as part of the vaccine adjuvant.

Adjuvants	Component	Vaccines	Trade name	Use (age group)	Manufacturer
MF59	Squalene; polysorbate 80; sorbitan trioleate	Seasonal influenza vaccine	FLUAD FLUAD quadrivalent	65 years and older	Novartis
		A/H1N1 pandemic influenza vaccine	Forcetria Celtura	6 months and older	Novartis
AS03	Squalene; α -tocopherol; polysorbate 80	A/H1N1 pandemic influenza vaccine	Pandemrix Prepandrix	6 months and older 18 years and older	GlaxoSmithKline (GSK)
AF03	Squalene; polyoxyethylene cetostearyl ether; mannitol; sorbitan oleate	A/H1N1 pandemic influenza vaccine	Humenza	6 months and older	Sanofi

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some vaccines has long been flagged as a potential safety issue. However, the efficient removal procedures for this reactive molecule during vaccine manufacture means that the level of formaldehyde present in vaccines is typically about 250x lower than the amounts of formaldehyde produced in the body and circulating in the blood as a result of natural metabolic processes. A vaccine component that has received more attention is the preservative and antifungal agent thiomersal, also known as thimerosal, a chemical compound that contains mercury. It was discovered in the 1920s by the US pharmaceutical company Eli Lilly and was given the trade name Merthiolate. When thiomersal enters the body, it is metabolized to a molecule called ethylmercury. The half-life (time to excrete 50% of the starting amount) in the body is around 1 week since it is excreted rapidly by the GI tract. This means that after 3 weeks (3 half-lives), only 12.5% of the original substance is still in the body (50% => 25% => 12.5%). The dangers of mercury poisoning were well known and engrained in the consciousness of many after the events of 1956 in Minamata, Japan where almost 50% of the people exposed to an industrial discharge of methylmercury by eating contaminated fish and shellfish died. In 1971–72, Iraqi farmers and their families became ill with mercury poisoning by consuming flour that had been made from seed wheat treated with a methylmercury-containing fungicide. But this was methylmercury which is not the same as ethylmercury. To the nonscientists, however, the only part of the chemical name that sits in the cautious mind is “mercury” and that is enough, understandably, for antivaccine lobbies and even concerned parents to hang their hats on. During analysis of the Iraqi patients, it was found that the half-life of methylmercury ranged from 1 month to 3 months with a mean half time to clearance of 65 days, around 10 times more slowly excreted than ethylmercury.²⁴ While excessive caution is always advised when considering the potential toxicity of any additive in vaccines, in particular with children, the evidence must take precedence over prejudice. For

thiomersal, an alleged connection between its inclusion in vaccines and autism was disproved by Danish and American retrospective studies of almost 700,000 children between 2003 and 2010,²⁵ while a US prospective study of more than 1000 children aged 7–10 years, reported in the *New England Journal of Medicine* in 2007, found no evidence of neuropsychological effects from vaccinations with thiomersal containing vaccines.²⁶ Perhaps the most convincing, though indirect, evidence is that in the US and other countries where thiomersal has been eliminated as an additive from many vaccines that were licensed after 1999–2000, neurodevelopmental disorders have continued to increase despite its absence.

The question of whether vaccines can induce auto-immune reactions in the way that some viruses can do is important but also complicated. One suggested mechanism is where segments of viral protein antigens resemble parts of normal human proteins by “molecular mimicry.” When and if molecular mimicry occurs, the immune system first sees the viral antigen and makes antibodies to it. Those antibodies can then recognize the human protein if it resembles the viral antigen sufficiently closely, and in so doing bind to the tissues or organs carrying that antigen. Once bound other components of the immune system can then home in on the antibody-antigen complex and cause cellular damage. While there are other mechanisms by which viruses are thought to play a role in autoimmune reactions, “evidence” for mimicry has been reported for herpes virus, cytomegalovirus, measles virus, enteroviruses, rubella, Japanese encephalitis virus, and parvoviruses (see [Table 15.2](#)).²⁷

The testing question that faces epidemiologists and clinicians when attempting to establish a causal relationship between a vaccination and a serious AE is how to dismiss the possibility that the relationship is simply temporal and not causal. Just because an auto-immune effect is seen after a viral infection does not prove a direct link between the two. Considerable efforts were put into analysis of a possible connection between HPV (human papilloma virus—a small DNA virus, some serotypes of which cause cervical cancer) vaccines and central demyelinating disease and multiple sclerosis. While HPV is not an infectious agent in the usual pathogen sense, it serves as an illustration of several advances in safe vaccine design. The most commonly used HPV vaccines are Gardasil & Gardasil 9 (Merck Sharp & Dohme, US), and Cervarix (IGlaxo Smith Kline, UK). Gardasil contains recombinant capsid proteins (on the outer surface of the virus) from four different HPV types including the two most oncogenic HPV16 and 18 types. Gardasil 9 has nine different types representing the serotypes responsible for up to 90% of cervical cancers worldwide. Cervarix is a quadrivalent vaccine that in addition to HPV 16 and 18 includes two other serotypes that cause non-oncogenic genital warts. In 2015, a retrospective cohort analysis in France of 2.2 million girls aged between 13 and 16 years showed no link between HPV vaccination (Gardasil or Cervarix) and 14 different potential autoimmune conditions. The conclusions of the expert committee evaluating the data were

“...l'exposition à la vaccination contre les infections à HPV n'est pas associée à la survenue des 14 pathologies d'intérêt prises dans leur ensemble, ni à celle de 12 de ces maladies auto-immunes étudiées séparément.”²⁸

[... exposure to vaccination against infection by HPV is not associated with the occurrence of the 14 pathologies of interest taken together, nor with 12 of these illnesses studied separately.]

On the question of the observed incidence of the neurological Gullain-Barré syndrome, seen as a rare AE with many viruses and vaccines previously, the committee also noted its occurrence as a rare event with an incidence of 1–2 cases per 100,000 vaccinees. Similar results were obtained during a

Table 15.2 Summary of viruses with associated autoimmune diseases and possible underlying mechanisms.

Family	Virus	Associated diseases	Suggested mechanisms
<i>Herpesviridae</i>	Epstein–Barr virus	MS, SLE, RA, SS	BA (Serafini et al. 2007), MM (Lang et al. 2002), “Mistaken self” (van Noort et al. 2000), ES (Pender 2003)
	Human Herpesvirus-6	MS, SLE, HT	MM (Tejada-Simon et al. 2003), BA (Kubo et al. 2006; Rizzo et al. 2016)
	Human Cytomegalovirus	SSc, SLE, T1D	MM (Lunardi et al. 2000; Hiemstra et al. 2001; Namboodiri et al. 2004; Lunardi et al. 2006), ES (Palafox Sánchez et al. 2009), BA (Bennett Jenson et al. 1980; Pak et al. 1988)
<i>Retroviridae</i>	Human T-Lymphotropic virus 1	HAM/TSP, SS, Uveitis, RA, SLE	BA (Vernant et al. 1988; Eguchi et al. 1992; Araújo et al. 2009; Best et al. 2009; Castro-Costa et al. 2009; Yamano et al. 2009; Romanelli et al. 2010; Nakamura et al. 2015)
<i>Paramyxoviridae</i>	Measles virus	MS	MM (Triger et al. 1974)
<i>Picornaviridae</i>	Enterovirus serotype CV	T1D, Chronic myocarditis	MM (Maisch 1986; Kaufman et al. 1992; Schwimbeck et al. 1993; Root-Bernstein et al. 2009), BA (Blay et al. 1989; Horwitz et al. 2002; 2004; Li et al. 2018)
<i>Togaviridae</i>	Rubella virus	Thyroid diseases, T1D	MM (Ou et al. 2000), BA (Rabinowe et al. 1986; Ou et al. 2000; Banatvala and Brown 2004; Burgess and Forrest 2009)
<i>Flaviviridae</i>	Hepatitis C virus	HT, SS, RA	BA (Akeno et al. 2008), ES (Aktas et al. 2017)
	West-Nile virus, Yellow fever virus, Dengue virus, Murray Valley encephalitis virus, Kunjin virus	Encephalo-myelitis, polymyositis	BA (Bao et al. 1992)
	Japanese encephalitis virus	Encephalo-myelitis, polymyositis	MM (Tseng et al. 2011), BA (Bao et al. 1992; Kalita and Misra 2002; Tsunoda et al. 2003; Swarup et al. 2007; Ghosh and Basu 2009)
<i>Parvoviridae</i>	Human parvovirus B19	RA, SLE, SS, SSc, SD, Gln, SV, KD, HSP, DM, SJIA, GCA, PN	MM (Lunardi et al. 2008)

BA, Bystander activation; DM, Dermatomyositis; ES, Epitope spreading; GCA, Giant Cell Arteritis; Gln, Granulomatosis; HAM/TSP, HTLV-1 Associated Myelopathy/Tropical Spastic Paraparesis; HSP, Henoch Schönlein Purpura; HT, Hashimoto’s Thyroiditis; KD, Kawasaki Disease; MM, Molecular mimicry; PN, Polyarteritis Nodosa; RA, Rheumatoid Arthritis; SD, Still’s Diseases; SJIA, Systemic Juvenile Idiopathic Arthritis; SLE, Systemic Lupus Erythematosus; SS, Sjögren’s Syndrome; Ssc, Systemic Sclerosis; SV, Systemic Vasculitis; T1D, Type 1 Diabetes.

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2017 study of more than three million females aged 18–44 years in Denmark and Sweden, the only flag being an apparent increase in celiac disease thought to have been a temporal unmasking of a preexisting condition rather than caused by the vaccinations.²⁹ This HPV story is useful for several reasons. Both types of vaccine use an alum adjuvant (Cervarix: AS04 adjuvant with aluminum hydroxide; Gardasil: aluminum hydroxyphosphate sulfate). Neither vaccine preparation contains any preservative (e.g., Thiomersal). In addition, the proprietary Cervarix adjuvant contains a modified lipopolysaccharide, known to be an activator of the Toll-like receptor TLR4, and in theory able to activate an innate immune response leading to an improved adaptive response. These details highlight two important points. First, the safety of aluminum based adjuvants in vaccines is heavily supported by these large cohort studies. Second, the emergence of creative developments where vaccine additives are included that target specific elements of the innate immune system to enhance the adaptive immune response (as in Cervarix) is a welcome advance on vaccine design that will surely improve both efficacy and safety.

COVID19 vaccines and safety

While adjuvant content has been a bone of contention among antivaccination groups, curiously none of the four main COVID19 vaccines (Oxford-Astra Zeneca (Vaxzevria and Covishield); Pfizer-BioNTech (Comirnaty), Moderna (COVID19 vaccine Moderna), and Johnson & Johnson (COVID19 vaccine Janssen) contain any of the normally used adjuvants, although the mRNA vaccines (Pfizer and Moderna) are formulated as lipid nanoparticles and therefore contain added lipid (fat) molecules. In any AEs observed with these vaccines, the origin, if proven to be caused by the vaccine itself, is unlikely to have arisen by any adjuvant effect.

But the adjuvant discovery path still needs to be trodden. There are currently no adjuvants that are able to stimulate that part of the T-cell armory that generates cytotoxic T cells (known as CD8⁺ T cells) and which, when deployed, generate memory cells with a greater lifetime than antibody memory B cells. CD8⁺ T cells can destroy virally infected cells without the involvement of antibodies.³⁰ Since virus infection of cells is required for this arm of the immune system to be deployed, vaccines that use “live attenuated” vaccines rather than “pieces” of the virus will be most effective until additives are identified that can trigger this important arm of the immune response.³¹

With the arrival of new vaccines for COVID19, by what under normal development timelines would be seen as an extreme telescoping of regulatory processes, equivalent to that seen with Ebola vaccine trials, and the introduction of an entirely new form of vaccine, the mRNA vaccines of Pfizer/BioNTech and Moderna, safety concerns have surfaced again, with assertions that in some cases are scientifically flawed and in others plausible but not yet proven. The notion that mRNA vaccines may alter the human genome makes little scientific sense for several reasons. First, mRNA had a very short lifetime. A touch of finger sweat on a sample of mRNA would destroy it within minutes due to the ubiquity of low levels of highly active RNA-degrading enzymes. Inside the cells receiving the vaccine, the injected mRNA would be degraded under normal processes within days. Second, mRNA does not enter the nucleus, unlike DNA, where any genomic modifications would need to occur. In comparison, the DNA-based vaccines, Vaxzevria and Janssen COVID19, contain not just the gene for the spike

protein of SARS-CoV-2 but also some of the genes coding for proteins that are important components of the adenovirus vector.

In the main, the AEs of all four vaccines have been similar with mostly mild effects resolving with a day or so. However, a particularly serious AE began to be seen in recipients of both the Astra Zeneca and the Janssen adenovirus-based vaccines. The observed effects were cases of thrombotic thrombocytopenia (sometimes referred to as TTP), a number of which presented with thromboses affecting cerebral venous sinuses. The formation of clots in the brain sinuses prevents blood from draining out of the brain resulting in pressure increases in the blood vessels and if unchecked, hemorrhaging. However, similar effects have been seen in those infected with the virus. The culprit is believed to be a chemokine, platelet factor 4 (PF4), whose release from platelets and subsequent association with other molecules, known as polyanions and which can escape from virus-damaged endothelial cells (cells lining the blood vessels), causes the production of autoantibodies that then promote abnormal blood clotting. In the very rare instances in which this event occurs with the adenovirus vaccines, several hypotheses have been proposed. In a recent “Perspective,” Goldman and Hermans described the possible biological events that could lead to the abnormal clotting effect observed (Fig. 15.2).³² In their hypothesis, the infection of endothelial cells leads to production of the COVID19 spike protein, production of which occurs with both the virus and the vaccine. As the spike protein is secreted from the cells, it binds to a matrix present on the endothelial cell surface composed of “proteoglycans,” hybrid molecules containing proteins and highly anionic heparan sulfate sugar molecules linked to each other. Since endothelial cells also have ACE2 receptors platelets could be activated via direct binding of the spike protein and by the spike—proteoglycan complexes. On activation platelets would release PF4 which would then bind to the heparan sulfate causing an antibody response to the heparan-PF4 complex. Complicated, unless you are a card carrying biochemist!

For such a mechanism to be causally linked, two (at least) requirements would have to be met. First, simply making the COVID19 spike protein inside a cell (e.g., from the mRNA vaccines) is insufficient to trigger the autoantibody response. No equivalent thromboembolic events have been reported for the mRNA vaccines. Second, in the few individuals suffering this serious adverse event an immune process must be triggered by which immune cells capable of generating antiself antibodies are somehow activated by the PF4 complexes formed. Such evidence has not yet been provided and for now this mechanism, however plausible, is just hypothesis. Other suggestions that some part of the spike protein has a region similar to part of the PF4 protein so that antibodies to the spike protein in the vaccine are then able to also bind PF4 (the mimicry mechanism) and induce the thrombotic events have been dismissed, since none of the PF4 antibodies found in patients appear to bind the COVID spike protein.³³ This example illustrates the uncertain world of rapidly developed vaccines. While not all are proven associations, the possibility that a viral antigen is involved in the triggering of serious AEs could explain why the same antigens when offered to the immune system in the context of a vaccine might react in a similar manner in some individuals where the normal barriers to reaction against self-antigens are breached. Recall the example discussed in Chapter 10 where a particular influenza vaccine (Pandemrix) was associated with narcolepsy in a small number of individuals with a genetic predisposition and suggested to have been caused by protein mimicry. Despite significant efforts to identify the origin of this particular influenza AE, the question of whether this was caused by the vaccine or by natural virus infection is still not resolved.

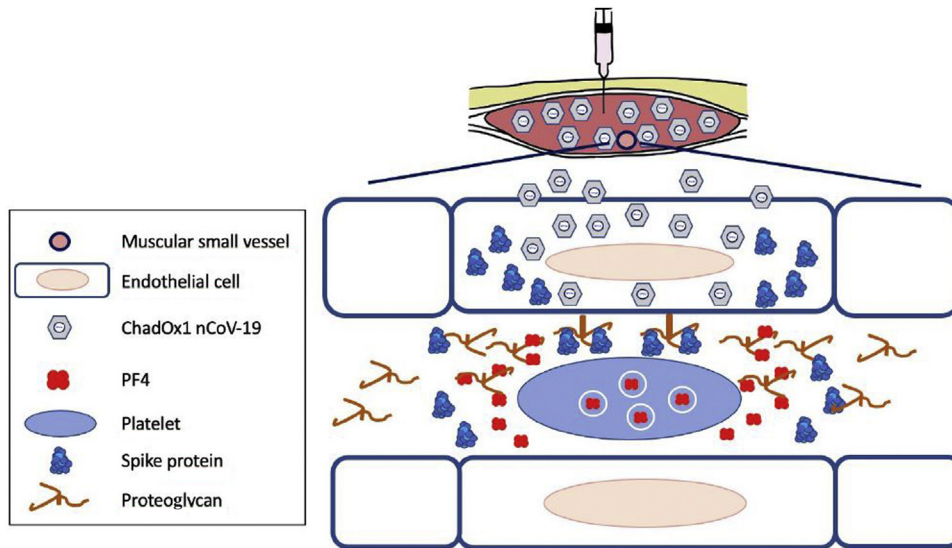


FIGURE 15.2

A possible mechanism by which COVID-19 adenovirus vaccines trigger thromboembolic events.

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Adverse events have always occurred and will continue to occur with vaccines, and in fact occur with many drugs and sometimes even naturally occurring food substances. The vast majority of these events are mild and short lived. The more serious reactions to either the vaccine, its adjuvants or other additives, or as a result of a temporal coincidence, or through a triggering of nonspecific “bystander effects” where cells of the immune system are activated with no direct involvement of the particular viral or vaccine antigen, will be rare but important to understand.³⁴ Current estimates are that the COVID 19 vaccines have saved hundreds of thousands of US lives and prevented more than a million hospitalizations.³⁵ In the face of these numbers, it is hard to understand how antivaccine arguments can be accepted by a public that is informed by balanced scientific explanations.

Efforts to improve the safety of vaccines have been expended continuously since the mid-1950s. Between 1980 and 2016, the annual vaccinations of pertussis vaccine increased almost fivefold to more than 116 million. As of October 25th, 2021 the current COVID-19 vaccine roll out has vaccinated with at least one dose around 87% of the world with ~6.8 billion vaccine doses. But there is also a sad side to this. Only a little over 2% of low-income country eligible persons have received at least one dose. The rarity of serious side effects set against this massive campaign of vaccinating the world is a palpable measure of the safety of today’s vaccines. Those who refuse to accept vaccines on the grounds of scientifically implausible and often fraudulent messages from antivaccination groups should contemplate the words of Martin Luther King when arguing their case:

“An individual has not started living until he can rise above the narrow confines of his individualistic concerns to the broader concerns of all humanity.”

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