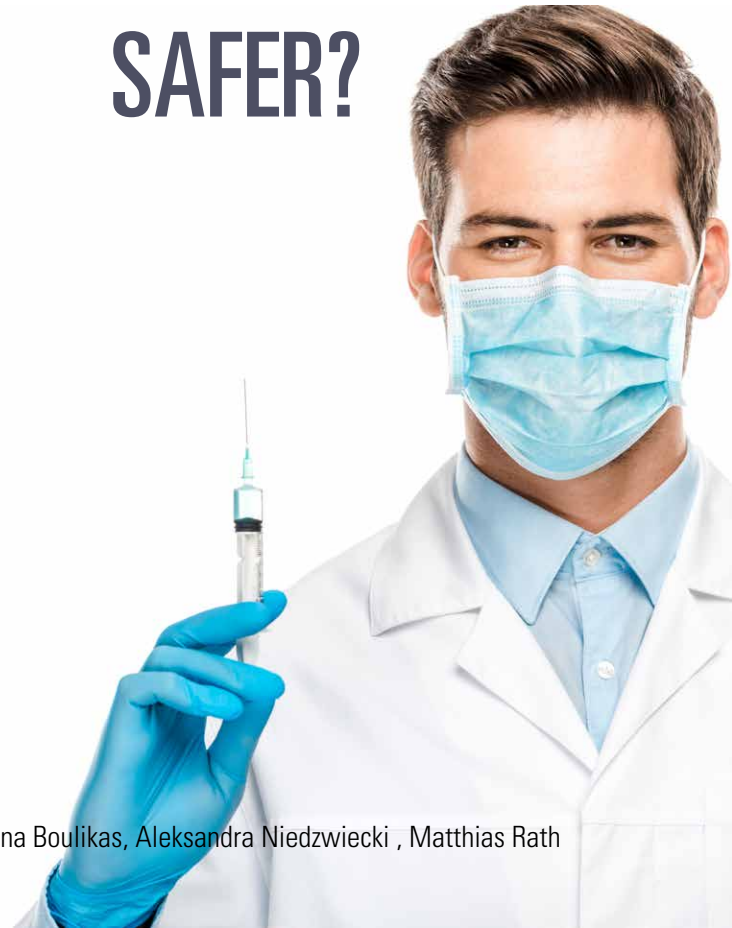
CAN WE MAKE OUR VACCINES SAFER?



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Both vaccines and potential health risks of vaccination—particularly in infants and children—have been surrounded by controversy and the subject of heated debates among parents, doctors, public health officials, politicians and the media. With many new vaccines on the market and new vaccination schedules requiring newborns to receive numerous vaccinations in a short period of time there have been many reports of associated health consequences. Some have legitimate concerns, while others are based on fear of the unknown. Opponents of vaccination are often portrayed in the media as fanatics and religious zealots; however serious and substantiated concerns of vaccine-related side effects have also come from doctors, researchers and many parents. The discussions often turn from questioning a particular type of vaccine to attacking the vaccination on principle. However, vaccines are an effective and economical measure in controlling many diseases, and as a public health measure have contributed to the eradication of many infectious diseases globally.

In order to take an informed position on this issue it is important to understand what vaccines do, how they are produced and what can constitute a health hazard in a vaccine. All this entails undertaking proper measures that can make vaccines safer and more effective. Here we present a short evaluation of this important and still controversial topic.

What is a vaccine?

A vaccine is a biological preparation that activates the immune system to fight a foreign agent that causes disease. This approach was initiated in the late 18th century with a smallpox vaccination. Edward Jenner was the first to demonstrate that vaccination with clinically mild cowpox infection could in the longer term protect humans from developing smallpox. At that time this new and rather mysterious approach to the prevention of infectious diseases by activating the body's immune system with a weakened infectious agent was controversial and not well understood. It inevitably generated a widespread fear among the public that vaccination itself would trigger a disease and even give people cow-like features.

With time however, vaccination has been shown to be an effective method to prevent many infectious diseases in large human populations and in the last two decades various vaccines have been developed to provide immunity against disease.

Vaccines work by mimicking infectious agents (pathogens), and by doing so, train our immune system to respond more rapidly and effectively against them. When the body is exposed to a harmless amount of protein from a disease (antigen) the immune system reacts by producing specialized immune cells (T cells) and antibodies. The T cells (a class of white blood cells) remember the antigen so that if the body encounters it later, another type of immune cells, called B cells, start producing antibodies that bind to and break down this specific agent. That way antibodies create a memory of a specific pathogen ("acquired immunity") and thereafter are able to mount a more rapid and efficient response to a real infection with an active pathogen.

Vaccinating humans and animals is a very effective way to fight infections, and together with improved public health measures it has contributed to a significant reduction and even elimination of many infectious diseases, thereby preventing the need for antibiotics and medical drugs. Today, the application of vaccines extends beyond infectious diseases.

What goes into a vaccine?

The first generation of vaccines was based on weakened pathogens (i.e. bacteria) and their ability as antigens to stimulate a sufficient immune response in a host without causing an outbreak of a disease. Since the 1920s, other chemical compounds called adjuvants were added to the antigen to further enhance the immune system response; this enabled a lower quantity of antigens to be used and so lowered the vaccine production cost. 'Adjuvant' means 'to help/aid' the immunogenic potential of highly purified antigens.

The composition of vaccines can differ and today—in addition to the antigen and adjuvants—they contain many chemicals used in the production process. These include suspending fluid (sterile water, saline, or fluids containing protein), antibiotics to prevent contaminations during the manufacturing process and various preservatives and stabilizers (for example, albumin, phenols, and glycine). Some vaccines contain small amounts of the culture material used to grow the virus or bacteria used in the vaccine, such as chicken egg protein.

Since many of these additional ingredients are potentially toxic, their use generates concern about possible compromises to the safety of the vaccine, especially because these toxins directly enter

the bloodstream, and the ability to detoxify these compounds varies depending on age (infants and elderly), accompanying diseases, or genetic individuality. Below is a short evaluation of the most common ingredients found in many vaccines, along with some information about their purpose and safety.

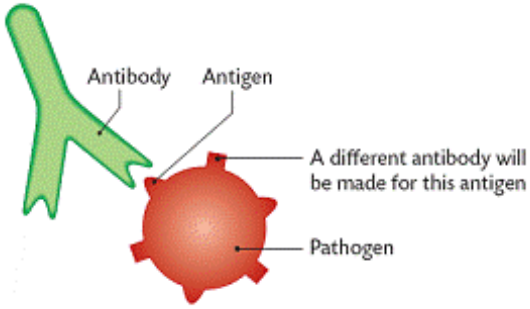
Antigens – essential component of a vaccine

Most vaccines target infectious diseases and contain an agent (antigen) that resembles a disease-causing microorganism such as weakened or killed forms of the infectious microbe, toxins the microbe produces, or a specific surface protein of the microbe—all of which are used to stimulate the immune system to recognize, eliminate and remember this specific agent. Modern vaccines incorporate different synthetic or highly purified compounds as antigens, such as short or long amino acid sequences (peptides), whole protein, or protein subunits.

Some antigens can't provoke a strong response from the immune system and as such a vaccine using this weak antigen would not be effective to protect the person later in life. In this case conjugate vaccines have been developed in which the weak antigen is covalently bound to a strong antigen, thereby eliciting a stronger immunological response to the weak antigen. Most commonly, the weak antigen is a poly-

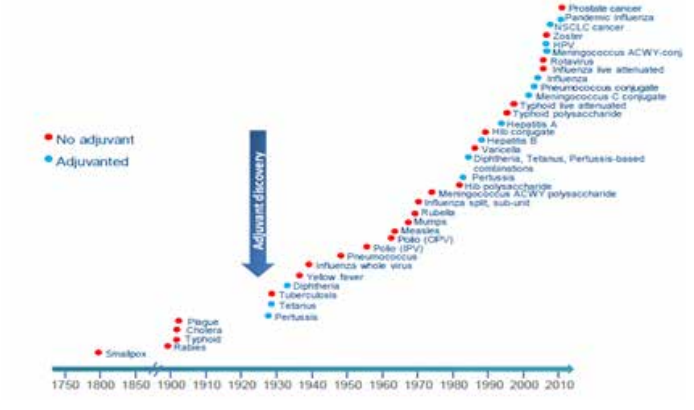
saccharide (a molecule combining a number of sugar molecules bonded together) that is attached to strong protein antigen. Such conjugated (sugar-protein) antigens can increase the efficiency of the vaccine, whereas it has been shown that a non-conjugated, polysaccharide-based vaccine is not effective in young children. Peptide-protein and protein-protein conjugates have also been used in vaccines.

In addition, there are also DNA-based vaccines which use a cell nucleus material—DNA—that codes for specific proteins from a pathogen. The DNA is injected into the body and taken up by cells, which can then use their normal metabolic processes to synthesize a specific protein based on the genetic code provided in this new DNA. Another type of nucleic acid—RNA—which translates the genes of an infectious agent into a protein, is used in vaccines to trigger protective immunity against the infectious agent.



Introduction to vaccine adjuvants

In recent years, adjuvants—the compounds added to vaccines in the manufacturing process —have received much attention. This is because of the development of purified and synthetic antigens which are poor immunogens and as such require an extra 'boost' by accessory agents (adjuvants) to evoke the immune response. Adjuvants are chemicals that stimulate/aggravate the immune system to respond more vigorously, which allows the manufacturer to use less antigen and as a result lowers a vaccine's production costs. The use of adjuvants in vaccines has been growing exponentially and about 57% of vaccines produced since the 1980s contain adjuvants (Figure 1).



Vaccines. 2015;3:320-343

Figure 1: Trends in the use of adjuvants: Between 1930 (first introduction of adjuvants in vaccine production) and 1980 only 20% of vaccines contained adjuvants. After 1980 more than half of the manufactured vaccines (57%) included adjuvants. This

period also marks the appearance of and increase in vaccine safety concerns, both short and long term.

The biggest issue with the use of adjuvants for human vaccines, particularly routine childhood vaccines, is the toxicity and adverse side effects of most of the adjuvant formulations. At present the choice of adjuvants for human vaccination reflects a compromise between a requirement for efficacy and an acceptable level of toxicity/side effects. The most common adjuvants for human use are still aluminum hydroxide and aluminum phosphate, followed by calcium phosphate and oil emulsions. During the last 15 years some progress has been made in the development and chemical synthesis of alternative adjuvants (e.g. liposomes, monophosphoryl lipid A) or using the controlled release of vaccine antigens using biodegradable polymer microspheres and other compounds.

Most common vaccine adjuvants: their role and safety concerns

Thimerosal (ethylmercury)

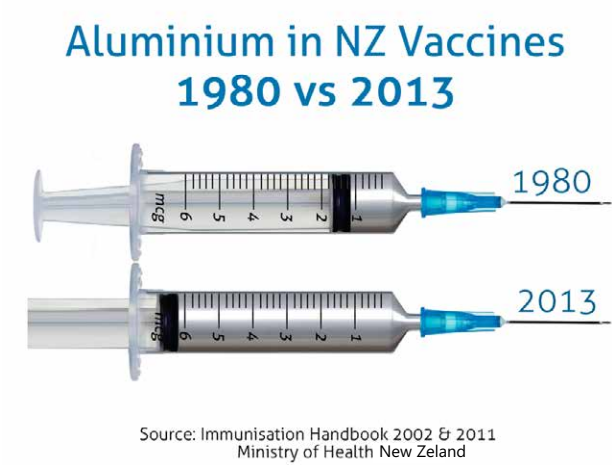
Why it is used: This mercury-containing ingredient has been used in vaccines as a preservative to prevent bacterial or fungal contamination.

Health concerns: Mercury contained in thimerosal is a metal which is poisonous in any form, affecting the neurologic, gastrointestinal (GI) and renal organ systems. Poisoning can result from mercury vapor inhalation, mercury ingestion, mercury injection, and absorption of mercury through the skin. Exposure to mercury is harmful, especially for children. Back in 1997, children were receiving three vaccines that together contained more mercury than the United States Environmental Protection Agency (EPA)

recommended limit, although still within the Food and Drug Administration (FDA) established limits. This triggered concerns that thimerosal in vaccines could be linked to increased incidence of autism or other conditions in children.

Safety: According to the manufacturer the type of mercury found in thimerosal, ethylmercury, differs from methylmercury—the type commonly found in fish and known to be harmful in large amounts. Although some studies have shown that ethylmercury can be broken down and excreted from the body much quicker than methylmercury, in 1999 several public health agencies and vaccine manufacturers agreed as a precautionary measure to cease using thimerosal. Today, most vaccines do not contain thimerosal except the influenza vaccine, and some multi-dose vaccines. Thimerosal-free alternatives are available.

Comments: Although the US and Europe offer the option of mercury-free vaccines, newborns and infants in less developed countries have a concentrated schedule of thimerosal-containing vaccines, and vaccines containing this form of mercury are still given to pregnant mothers. Metabolic changes during early development are demonstrably an important risk factor for the effects of ethylmercury on the developing brain and nervous system, while exposure to thimerosal sensitizes susceptible individuals to life-long contact dermatitis. It has been more than 20 years since rich countries started using thimerosal-free vaccines and there has been a decrease in contact dermatitis during this period. At the same time thimerosal-containing vaccines showed a significant association with increased risk of tic disorders (in studies that explored vaccines and risk of tics, thimerosal was a predisposing factor). In some circumstances, ethylmercury in combination with other neurotoxic candidates had poorer outcomes in neurobehavioral tests, however some test results were inconsistent with these findings.



Aluminum

Why it is used: Aluminum is used to stimulate the immune system response, allowing the manufacturer to use less antigen in a vaccine or to use lower doses of the vaccine to build sufficient immunity.

Health concerns: Aluminum is the third most common naturally occurring element, after oxygen and silicon. It is found in plants, soil, air, and water. However, aluminum inhibits more than 200 important biological functions of the body, is a pro-oxidant, and is a neurotoxin even at very low levels. Long-term exposure to high amounts of aluminum can contribute to brain and bone diseases (e.g. Alzheimer's and anxiety, insomnia, cognitive deficits, as well as interfering with bone calcification and competing with fluoride). Aluminum is associated with kidney and liver dysfunction due to fatty degeneration.

Safety: Aluminum in adjuvant form has been used for over six decades in vaccines. It has been implicated in increased risk for autoimmunity, long-term brain inflammation and neurological complications, and thus may have profound and widespread adverse health consequences. The possibility that vaccine benefits may have been overrated, and the risk of potential adverse effects underestimated, has not been rigorously evaluated in the medical and scientific community. Proponents of using aluminum in vaccines say that breast-fed infants will naturally ingest around 7 milligrams of aluminum in a diet throughout the first six months of life. Food intake in adults can provide 7-9 mg of aluminum per day. However, not all aluminum in food is absorbed in the gut and bioavailable—only about 0.1% reaches the bloodstream. In contrast, in the first six months of life an infant receives about 4.4 milligrams of aluminum in vaccines, all of it going directly into the bloodstream. The argument—to try to show that vaccine aluminum is safe—that we swallow aluminum every day is purposely misleading the public. There's no comparison between swallowed aluminum and injected aluminum. To our knowledge there is no human study that shows that the amount of aluminum in our entire vaccine schedule, when injected, is safe. Again, the ability to detoxify this neurotoxin is very limited in infants and children.

Amount in vaccines: Infant vaccines containing live viruses (i.e. measles, rubella, mumps) do not contain aluminum, however, this neurotoxin is widely used in other vaccines such as hepatitis A and B (up to 250 mcg in pediatric vaccine and 500 mcg adult); diphtheria-tetanus-acellular pertussis (DTaP) contains between 330-625 mcg; polio/DTaP/hepatitis B vaccines can contain up to 850 mcg of aluminum that goes directly into the bloodstream.

Table 1: Amount of Aluminum in vaccines (used in UK)

Vaccine type	Commercial name	Amount of aluminum in vaccine
6-in-1 vaccine (protects against pneumococcal diphtheria, hepatitis B, influenza type b (Hib), pertussis (whooping cough), polio and tetanus)	Infanrix Hexa	0.82 mg
PCV vaccine (conjugated vaccine against Streptococcus pneumoniae infections)	Prevenar 13	0.125 mg
MenB vaccine (new vaccines against meningitis serogroup B)	Bexsero	0.5 mg
Pre-school booster vaccines (also called 4-in-1 vaccine against tetanus, diphtheria, whooping cough and polio)	Repevax Infanrix IPV	0.33 mg 0.5 mg
HPV vaccine (against human papilloma virus implicated in sexually transmitted diseases and cervical cancers)	Gardasil 0	.225 mg
Teenage Booster vaccine (also called 3-in-1 vaccine against tetanus, diphtheria and polio)	Revaxis 0	.35 mg
HepB vaccine (vaccine against hepatitis B)	HBVaxPro 0	.25 to 0.5 mg, depending on vaccine version

The aluminum load from a vaccine can further add to an already significant intake from infant formula (bottle) feeding which can cause health problems in vulnerable infants. Studies reveal that aluminum levels in infant formulas can be about 9.6 times higher than that of human milk, depending on the brand. One soy-based formula has been shown in a study to contain 20 times more aluminum than human milk, which is far higher than “safe” levels set by the World Health Organization. Due to the manufacturing process, aluminum compounds find their way into the formula and this can cause various health problems.

Formaldehyde

Why it is used: Formaldehyde has been used in vaccines to inactivate viruses and neutralize bacterial toxins, ensuring they don't cause sickness when injected.

Health concerns: Formaldehyde is an organic compound; as a gas it is an irritant. Its saturated water solution—formalin—is used to preserve animal tissues and organs. It also has wide industrial applications. The US Environmental Protection Agency classifies formaldehyde as a carcinogen, as does the International Agency for Cancer Research and the US National Toxicology Program. Additionally, several studies have since linked long-term exposure to strong formaldehyde with certain types of cancer.
Safety: The potential for harm depends on the amount. Small amounts of formaldehyde are continually present in the human body as part of our natural metabolic process, but long-term exposure to high amounts can overwhelm our system and be harmful.

Amount in vaccines: The amount of formaldehyde found in vaccines is a residue from the manufacturing process and relatively small. The highest amount of formaldehyde present in any vaccine is 0.02 mg per dose. Proponents of using formaldehyde quote that an average two-month-old baby would have around 1.1 mg of formaldehyde circulating in its body, with even higher naturally occurring amounts in older children. However, this amount is distributed among all organs. Assuming the two-month-old baby has about 400 ml of blood, this would mean that it has 0.003 mg of formaldehyde per ml of blood. Compared to this, in a single vaccine injection a baby receives seven times more formaldehyde than is already present in the blood. This amount may not be easy to process since a baby's organs are not fully developed to effectively neutralize toxins.

Other ingredients present in vaccines

• Antibiotics

Why they are used. Antibiotics are added during the production of some vaccines to counteract the risk of dangerous bacterial infections.

Health concerns: Antibiotics in vaccines increase the risk of allergic reactions in some children and adults.

Safety: Vaccine manufacturers use antibiotics that are less likely to provoke allergic reactions, such as neomycin, streptomycin, polymyxin b, gentamicin and kanamycin. No vaccine produced in the United States contains penicillin, which a significant minority of the population is allergic to. No allergic reaction to a vaccine has been traced back to antibiotics. The industry data shows that the overall odds of child sustaining a severe allergic reaction from an MMR or hepatitis B vaccine, from any of its ingredients, is one in 1,000,000.

Amount in vaccines: During the purification steps of the production process, antibiotics are removed, resulting in trace amounts in the final vaccine.

• Gelatin

Why it is used. Gelatin is used as a preservative and stabilizer, keeping vaccines effective under heat or cold and for the duration of their shelf life.

Health concerns: In sensitive people gelatin can cause an allergic reaction.

Safety: While gelatin is the single largest identifiable source of severe allergic reactions from vaccines, the incidence rate is considered small. Children with a history of gelatin allergies can seek alternatives or exemptions.

Amount in vaccines: The amount of gelatin varies by vaccine, with the MMR and shingles vaccines on the high end, containing 14-20 mg per dose, and the DTaP on the low end, with only 0.0015 mg.

Table 2: Amount of porcine gelatin in vaccines licensed in the US and UK

Type of vaccine	Commercial name	Amount of gelatin/dose	Comments
Nasal flu vaccine	Fluenz	2 mg	
Live, attenuated influenza vaccine	Flumist®	2 mg	
Measles, mumps, rubella	MMRII MMRVaxPro (Merck) MMRV (ProQuad)	14.5 mg 11 mg 11 mg	Priorix (GSK) used in the UK does not contain gelatin.
Shingles vaccine	Zostavax Sanofi Pasteur MSD	15.6 to 20.5 mg	Vaccines available globally
Chickenpox vaccines	Varivax	8.9 to 12.5 mg	Varilrix, used in the UK, does not contain gelatin
Rabies	RabAvert®	less than 12 mg	
Typhoid oral	Vivotif®		Gelatin is present in a capsule

• Monosodium Glutamate (MSG)

Why it is used: MSG is used as a preservative and stabilizer in some vaccines, keeping them effective through heat, cold, and shelf life.

Health concerns: MSG is a food additive which gained a bad reputation starting in the 1960s after reports of nausea, headaches, flushing, or sweating as a result of consuming food with MSG. It is an excitotoxin which can overstimulate certain neurons in the brain causing them to continue firing until they tire themselves and die. Such overexcitement of neurons has been demonstrated to cause brain damage of varying degrees and can potentially trigger degenerative diseases such as Amyotrophic Lateral Sclerosis (ALS, also known as Lou Gehrig's disease), Parkinson's disease or Alzheimer's, all of which develop gradually. As a result, concern has spread about its use in vaccines.

Safety: While the scientific community acknowledges that a very small minority of people may suffer from short-term reactions to MSG, research has not supported that it is harmful in general. The US Food and Drug Administration, the World Health Organization, and the United Nations have all declared MSG to be safe. The US Centers for Disease Control and Prevention (CDC) states that the following vaccines contain MSG: adenovirus, influenza (FluMist Quadrivalent), MMRV (ProQuad), Varicella (Varivax), Zoster (Shingles–Zostavax).
Amount in vaccines: MSG is only present in two scheduled vaccines: adenovirus and influenza.

• Other compounds used as stabilizers in vaccines

Other ingredients present in vaccines as stabilizers include: sugar (sucrose), lactose (milk sugar), mannitol and sorbitol (simple sugars); Medium 199—a solution which contains amino acids (the building blocks of proteins); mineral salts and vitamins; arginine hydrochloride (common amino acid); and urea (organic compound found in the human body).

• Acidity Regulators

Like all other living things, viruses and bacteria need the right pH (acid/alkaline level). A variety of products are used in small quantities to help retain the desired pH of the vaccines during the manufacturing steps. These products include:

Table 3: Acidity regulators used in vaccines

Compound in vaccine	What it is/Purpose in a vaccine
Salts based on potassium phosphate and sodium phosphate	These are common and basically harmless salts. They are added to keep the pH balance and to keep the fragments of active ingredient suspended in water, so that they do not settle out. A product called Hanks' Salts, which contains these salts and others, is sometimes used.
Disodium adipate	Commonly used as a food additive.
Succinic acid	Organic acid involved in several chemical processes in the body.
Sodium hydroxide and hydrochloric acid	These compounds react together to form water and salt (NaCl); therefore, they do not appear in the final vaccine in their original forms.
Histidine	An amino acid found in almost every protein in the human body.
Sodium borate (borax)	A few micrograms (millionths of a gram) may remain in the hepatitis B vaccine (HBVaxPro) and the HPV vaccine (Gardasil). This amount is considered too small to cause harm.
Trometamol	Organic compound used in biological buffers as an alkalizer in the treatment of acidosis, and in other medicines.

• Genetically Modified Organisms (GMOs)

The only vaccine in the UK schedule which contains GMOs—a custom-made virus resulting from combining individual genes to produce the right features—is the nasal flu vaccine (Fluenz). There are several projects at pre- and clinical stages with recombinant and GMO ingredients to be used in vaccines.

Adverse reactions triggered by vaccines

Assessment of vaccine risks and benefits is complex, since while vaccination can be perceived to benefit the population, any adverse reactions are suffered by individuals, potentially raising complex ethical issues. Hence, policy makers and vaccine recipients might have very different perceptions of the immunization risks and benefits.

Adverse reactions to vaccines are not as rare as we are led to believe. In the US the information about vaccine-related health issues comes from the Centers for Disease Control and Prevention, who get their statistics from the Vaccine Adverse Event Reporting System (VAERS). While such reporting is required by law, it is widely known that individual doctors are not diligent in reporting adverse reactions observed in their patients. Some doctors will not even consider the vaccine as a cause and do not report them as such. Also, it is difficult to evaluate a direct link between childhood or even adult vaccination and its consequences appearing years or even decades later.

Local, adjuvant-associated adverse reactions. Most frequent are mild pain at the injection site, tenderness, redness, or swelling which subsides with time. In some people sterile abscesses, enlarged lymph glands and chronic skin ulceration may occur, among other symptoms. These side effects have been often observed with adjuvants such as saponins (e.g. Quil A, QS21, ISCOMS, ISCOMATRIX) and oil emulsions (e.g. complete and incomplete Freund's adjuvant, Montanide, MF59, AS03).

Systemic adverse reactions. Systemic reactions to vaccination typically include symptoms such as fever, headache, malaise, nausea, diarrhea, arthralgia, myalgia, and lethargy, all of which largely reflect adjuvant-associated natural, non-specific immune response and consequent inflammation. Adjuvants that strongly activate innate immune receptors include monophosphoryl lipid A (MPL), flagellin, lipoarabinomannan, peptidoglycan, or acylated lipoprotein. Typically, such inflammation-associated adjuvant reactions would be expected to settle once the immune response subsides but could potentially last up to several weeks post-immunization.

At the more serious end of the adjuvant systemic toxicity spectrum is the potential for rare immunological toxicities resulting from abnormal immune activation driven by the adjuvant. This also includes chronic immune activation and inflammation that does not resolve after immunization. An example would be the syndrome of a rare muscle disease called macrophagic myofasciitis (MMF) linked to aluminum adjuvants. Finally, there is a risk that an adjuvant may either trigger or increase the likelihood of autoimmune diseases. An example is the ability of inflammatory oil emulsion adjuvants to induce adjuvant arthritis in genetically susceptible animal models.

There is also a risk of chronic organ toxicity from the compounds themselves. For example, aluminum or oil emulsions can form long-term tissue deposits and this has been postulated to cause chronic toxic effects. However, the detection of chronic toxicity and determination of any causal relationship can be extremely difficult, if not impossible, due to the long delays between immunization and disease onset which may have occurred decades later.
Many healthcare professionals dismissively assert that it is only a small statistical percentage of the population that suffers from adverse reactions to vaccinations. However, due to an explosion in vaccine administration, from 12 in 1985 to 38 given today, there is now a higher risk of experiencing side effects.

Vaccine potential side effects under scrutiny

When vaccines are first developed, they undergo thorough safety testing to determine whether they are safe for general use. Usually their effects are tested in about 30,000 babies, which are monitored for about a month to look for any severe reactions.
There are a couple of drawbacks with this system. One is impartiality, since safety testing is paid for and administered by the manufacturer of the vaccine. That often causes distrust over the validity of results, since they come from the companies making the product and responsible for funding the research. As a safe-

guard measure the CDC and other parts of the US government oversee that research to make sure it is trustworthy. However, since the basic funding for doing this often comes from the pharmaceutical companies themselves, it is common sense that the oversight of results can be subject to bias. Another shortcoming is a lack of long-term safety research. There is a lack of data on how vaccinated individuals are doing one, two or five years later to see if they experience higher rates of chronic problems or long-term complications. And that is a big gap in the safety research.

There are many scientific studies conducted on vaccines at universities and other public and private research institutions which are published in different types of journals. Of those, the most respected are studies published in what are called 'peer-reviewed' journals. There is also research published in non-peer-reviewed journals. These journals often publish good research as well, but the conclusions reached by the scientists or the study results may go against the grain or call into question some of the mainstream viewpoints about science. Often those kinds of studies won't or are less likely to get published in peer-reviewed journals. That kind of research finds its place in a more alternatively minded journal or one that is not peer-reviewed by university medical researchers. However, if the study methods and evaluation are done correctly these publications may provide very valuable information or observations. The funding of studies and conflict of interest of the authors is also a reason why many people do not always trust the scientific results. Doctors know that virtually all vaccine safety research is performed by the pharmaceutical companies themselves. What would increase that trust is a completely objective and unbiased advisory panel of physicians and researchers that have absolutely no ties to the pharmaceutical industry as well as no ties to vaccine policy or the outcome of the decisions they're making. Unfortunately, it is very difficult to find physicians without any connections to the pharmaceutical industry.

Do safer vaccines exist?

Design and synthesis of potent and safe vaccine adjuvants

Vaccine safety mostly relates to the use of adjuvants and other additional chemical components in the vaccine production process. Vaccine safety can be assessed better in situations where both adjuvant-containing and adjuvant-free vaccines are available for the same indication. For example, an approved seasonal influenza vaccine in Europe contains MF59 squalene emulsion adjuvant, while the vast majority of flu vaccines used in Europe do not contain any adjuvant. This opens up a useful area of study of this adjuvant safety. Interestingly, during the 2009 influenza pandemic both adjuvanted and adjuvant-free pandemic vaccines were utilized in Europe, but consumers were not always given a choice regarding which vaccine was used. By contrast, only adjuvant-free pandemic vaccines were used in the US.

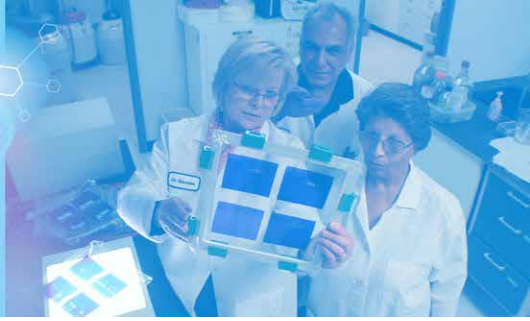
The use of squalene as a vaccine adjuvant presents another controversy. It stems from a problem experienced by Gulf War participants who might have received a vaccine or vaccines with squalene as an adjuvant. This well documented study showed that individuals with antibody levels to squalene had a high incidence of an autoimmune disease. The pharmaceutical industry's objection to this study was widely publicized, with claims that this substance used in an oil-based form would be harmless. However, the problem with any fat-soluble environmental toxin is that small amounts administered in repeated doses can accumulate in fatty tissues from where they can be released later when the body is under stress. Also, they act as inflammatory agents while

residing in fatty tissue. This discussion on using squalene is not complete yet, particularly because it was subsequently revealed that a squalene-adjuvanted vaccine (AS03 squalene oil emulsion) used during the pandemic was associated with an increased risk of childhood narcolepsy.

Only a handful of adjuvants have both enough potency and acceptable toxicity for clinical investigation. One promising adjuvant is QS-21, a natural saponin product that has been found to be a good stimulator of the immune system in many cancer and infectious disease vaccine clinical trials. However, the therapeutic promise of QS-21 adjuvant is curtailed by several factors, including its scarcity, difficulty in purification, dose-limiting toxicity, and chemical instability.

Table 4: Natural adjuvants at experimental stages

Adjuvant W	here it is used now	References
Astragalus saponins combined with cholesterol and liposomes	Cancer vaccines	https://www.liebertpub.com/doi/10.1089/cbr.2017.2369
Plant-delivered saponins, tomatine, inulin, beta-glucans from fungi, a-galactosylceramide from marine sponge mollusk hemocyanins	Treatment of superficial bladder cancer, as adjuvant to dendritic cell-based immunotherapy	DOI: 10.1016/B978-0-12-804019-5.00011-6
TMC (trimethyl chitosan) and sodium alginate combination	Hep B Vaccine in mouse model	https://dx.doi.org/10.1155%2F2016%2F7659684
Xanthan gum (extracellular polysaccharide) with OVA (ovalbumin)	Mouse model and in vitro study	https://doi.org/10.1155/2017/3925024



Can micronutrients help to increase vaccination safety?

Vaccination mimics a real infection by using a weakened infectious agent or active part thereof that is recognizable by the immune system but not strong enough to cause disease. However, since vaccine preparations include additional chemical stimulants with different levels of toxicity, they can easily overwhelm the body's immune system, especially when it is weakened by nutritional deficiency, age or struggling with other pathologies.

It is well known that adequate nutrition is crucial to ensure a good supply of the energy sources, macronutrients, and micronutrients required for development, maintenance and optimum immune response. Micronutrients are essential elements for sustaining life, although they are required in smaller amounts than macronutrients (proteins, carbohydrates and fats) which are consumed in gram quantities. Micronutrients include vitamins, minerals, trace elements, but also certain amino acids and essential lipids as well as some active plant components—all of which must be included in our diet throughout life to maintain health. Nutrition, infection

and immunity are intertwined, since not only does poor nutrition weaken the immune system making a person prone to infections, but nutritional deficiencies are exacerbated by the immune response to infection.

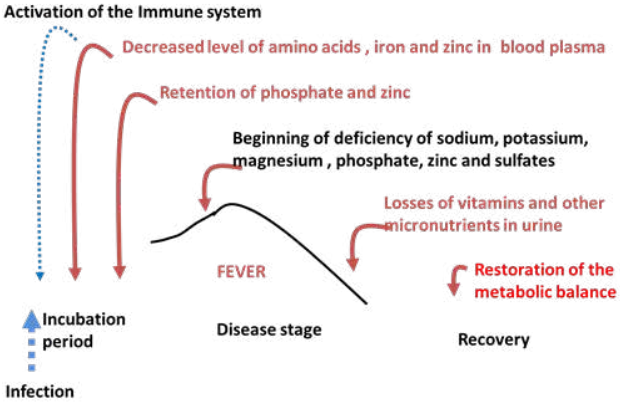


Figure 2: Infection, immunity and nutrition are interconnected

It has been shown that among micronutrients and active plant components, vitamin A (and beta carotene), vitamins C, D, B6 and B12 as well as folic acid, iron, zinc and selenium have immunomodulatory properties and antioxidant efficacy through which they can support the immune response of a host and also affect the course and outcome of infection. Inadequate intake of micronutrients at any stage of life can manifest in lower resistance to infections and a higher severity of adverse symptoms when exposed to foreign agents.

Mechanisms by which vitamins affect the immune response are complex and include among others, cytokine production, innate

immune cell activation, cell integrity, antigen presentation, and lymphocyte activation. Recently it has been discovered that in the specific regions of human immunoglobulin genes there are hot spots for vitamin receptors, which suggests that vitamins may exert both direct and indirect effects on the antibody expression pattern and other phenomena.

Unfortunately no systematic studies on vitamin supplementation in relation to vaccination have been conducted. One study conducted in Africa (Ghana Vitamin A Supplementation Trial) found that vitamin A supplements in infants and children 6-59 months of age decreased mortality, hospital admission and clinic visits compared to placebo. Secondary analysis of this study published in 2009 suggested that the reduced mortality benefits were confined to boys and non-vaccinated children.

Interestingly, vitamins and mineral complexes are listed as excipients in some vaccine formulations. As such, hepatitis B (Heplisav-B) and human HPV (Gardasil 9) contain vitamins and mineral salts, while rotavirus (Rotarix) vaccine includes magnesium and iron salts as well as concentrated vitamin solution, cysteine, tyrosine and amino acid solution. Also anthrax (bioThrax) vaccine contains vitamins, amino acids and mineral salts among other ingredients. Usually these components are a part of growth media used to cultivate the infectious agent.

There are no studies readily available to show whether micronutrient administration can affect the safety and efficacy of vaccination. However, studies in mice immunized with an attenuated influenza virus vaccine showed that double deficiencies for vitamins A and D reduced antibody responses in the respiratory tract, which could be restored by supplementation with vitamins A and D. This implies that vitamin supplementation programs may be beneficial in a clinical setting to promote healthy immune

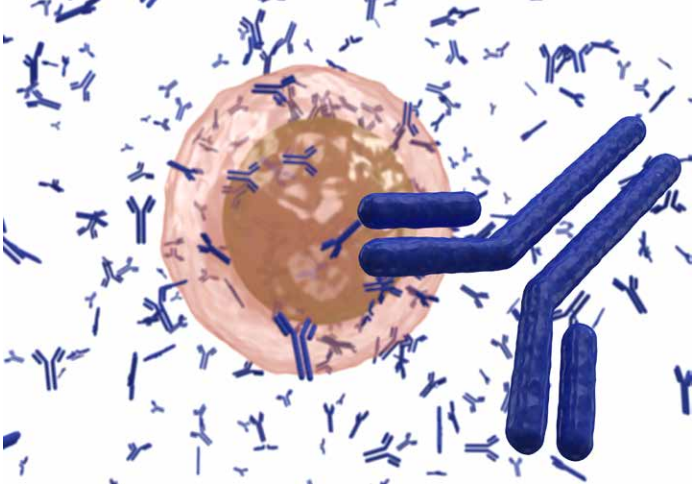
responses to respiratory virus vaccines in vitamin-deficient individuals.

It has been recognized that vitamin and other micronutrient deficiencies and their suboptimal intakes are common worldwide, as it is not always possible to provide adequate amounts from the diet. Even in industrialized nations, various social, economic, or cultural backgrounds influence diet, which can impair the micronutrient supply. Therefore, tailored micronutrient supplementation is the most effective way to address increased demands for micronutrients at different life stages, including during exposure to vaccination.

For instance, the toxic burden of aluminum and mercury in vaccines may be lowered with adequate intake of vitamin C, which has a chelating effect: vitamin C can bind these metals and cause them to be excreted. Vitamin C can also modulate the immune response in various ways and reduce the oxidative burden of vaccination. Vitamin C, B vitamins, N-acetyl cysteine and other nutrients also assist the body in neutralizing and metabolizing toxins present in vaccine preparations.

However, healthy immunity is not based only on a few individual nutrients. Research conducted at the Dr Rath Institute has identified that micronutrients are most effective when they are properly selected and combined based on their synergistic interactions. This research has documented that specific combinations of vitamins and other micronutrients supplied in moderate doses can support immune system functions and decrease associated inflammatory reactions. Not all multivitamins you buy at the store or a pharmacy are equally effective. Ask for proof of efficacy.

Also, probiotics that make for a healthy microbiome can strength-



en immunity and ease some adverse effects of vaccination. While not all probiotic preparations are effective and some may cause a degree of intestinal upset in sensitive people, increasing the consumption of fermented food such as kombucha, buttermilk and yogurt never fails.

It is also important to make sure that the person or a child being vaccinated receives adequate sleep and avoids stress and environmental toxins; even excessive physical exhaustion is an important factor as all these can compromise the immune system. It is important to share with your doctor any medication you or your child take and any health concerns you may have.

There are many ways nutrient combinations can support the immune system. Our research has shown that specific combinations of vitamins with some essential oils such as clove oil, and components such as undecylenic acid, kelp and lichen could have a direct killing effect on various bacteria and fungi, and can even help eliminate infectious microbes from their biological 'hiding places' in biofilm. All this can lessen the burden of fighting infection.

The table below presents some documented benefits of specific micronutrients in supporting better immune response, including in relation to vaccines.

Table: Benefits of micronutrient supplementation for the immune system in response to vaccination and risk of infections

Micronutrient	Effect of Supplementation
Vitamin A	Reduces all-cause mortality in children, also lowers incidence of measles, decreases mortality and morbidity from infectious diseases. No documented benefits in pneumonia.
Vitamin C	Reduction in incidence and duration of pneumonia in elderly. In children and adults decreases severity and duration of cold symptoms, also lowers incidence of common cold. Improves outcome in pneumonia, malaria and diarrhea symptoms.
Vitamin D	Decreases acute respiratory tract infections, influenza.
Vitamin E	Better production of antibodies in response to hepatitis B and tetanus vaccines in elderly. Also, lowers risk of respiratory tract infections and common cold.
Zinc	In children reduces the duration and severity of common cold symptoms; less infections, improvements in pneumonia, malaria and diarrhea symptoms.
Iron	Protection against infections by bacteria, viruses, fungi and other microbes.
Copper	Chronic high doses in young men vaccinated with influenza vaccine may result in lower antibody production.
Selenium	Improves immune response to viral infections.
Vitamin C + D + Zinc	Minimizes risk of infections.
Vitamins C + E + A (beta carotene)	Enhances activity of immune system, better response to influenza vaccine, shortens infection symptoms in elderly.
Multinutrients	Decreases acute respiratory tract infections, lessens cough, nasal congestion, throat inflammation, headache, other symptoms that are often aggravated by pollutants. In elderly, lowers susceptibility to infections, also better responses to immunization and reduced use of antibiotics.

What we can do

This overview of the safety of vaccines centers on health aspects associated with specific ingredients used in vaccine manufacturing and their potential adverse effects. Unfortunately in the current state of regulation some are difficult to assess, especially when combined with poor knowledge of the mechanisms underlying the potential toxicity of these compounds. Any vaccine-related side effects may depend on the type of adjuvant, antigen and other ingredients with which they are combined, but also could be potentiated by the genetic predisposition, underlying health problems as well as the age of individuals being immunized.

Looking at the practicability of a solution it appears that for economic and efficacy reasons, adjuvants will continue to be used

in vaccines. Therefore, consumer pressure should be directed towards developing new adjuvants that will improve vaccine potency without compromising tolerability or safety. The concept of a non-inflammatory adjuvant able to enhance vaccine potency while avoiding serious adverse side effects or safety issues is particularly worthy of exploration. Intensifying research in natural compounds with both immune-modulating properties and a high margin of safety will lead not only to developing safer and more effective vaccines but allow us to better understand both the basis of vaccination and the role of adjuvants. In addition, the role of micronutrients in protecting but also potentiating the effects of vaccines cannot be ignored and should be further explored. The vaccine administration protocol should also include dietary and supplementation measures to ensure safety and optimize the results of vaccination.

In response to sustained public pressure and demands for action, the vaccine manufacturers should eliminate toxic ingredients from vaccines and intensify their efforts to develop new approaches. In the meantime, think twice before you allow the injection of any questionable substance into your body or that of your child. Together with other parents, patients, your doctor and your government, you can work to shake up the entrenched healthcare system, directing it towards prioritizing safety, not protecting exorbitant profits.

Further reading

1. di Pasquale A, et al. Vaccine adjuvants: From 1920 to 2015 and beyond. Vaccines. 2015; 3:320-343.

2. Cao Y, et al. Augmentation of vaccine-induced humoral and cellular immunity by a physical radiofrequency adjuvant. Nature Communications. 2018;9:3695.

3. Nourhan H. et al. Chitosan and sodium alginate combinations are alternative, efficient, and safe natural adjuvant systems for hepatitis B vaccine in mouse model. Evidence-Based Complementary and Alternative Medicine. 2016; 59684- 92.

4. Petrovsky N, Aguilar JC. Vaccine adjuvants: current state and future trends. Immunol. Cell Biol. 2004;82(5):488–496.

5. Vaccine Ingredients: Gelatin. Children's Hospital of Philadelphia. https://www.chop.edu/centers-programs/vaccine-education-center/vaccine-ingredients/gelatin Accessed 8/15/2019

6. Dorea, JG. Abating mercury exposure in young children should include thimerosal-free vaccines. Neurochem Res. 2017;42(10):2673-2685.

7. Ragupathi, et al. Natural and synthetic saponin adjuvant QS-21 for vaccines against cancer. Expert Rev Vaccines. 2011;10(4):463-70.

8. Giuseppe Del Giudice, et al. Correlates of adjuvanticity: A review on adjuvants in licensed vaccines. Seminars in Immunology. 2018;39:14-21.

9. Cibulski SP, et al. Quillaja brasiliensis saponin-based nanoparticulate adjuvants are capable of triggering early immune responses. Scientific Reports. 2018;8:13582.

10. Sjölander A, Cox JC, Barr IG. ISCOMs: an adjuvant with multiple functions. J Leukoc Biol. 1998;64(6):713-23.

11. Hwang SM, et al. Comparison of the adverse events associated with MF59-adjuvanted and non-adjuvanted H1N1 vaccines in healthy young male Korean soldiers. Japan J Infect Dis. 2012;65(3):193-197.

12. Benn CS et al. Does vitamin A supplementation interact with routine vaccinations? An analysis of the Ghana Vitamin A Supplementation Trial. Am J Clin Nutr. 2009;90:629-639.

13. Ghana VAST study Team. Vitamin A supplementation in northern Ghana: effects on clinic attendance, hospital admission, and child mortality. Lancet. 1993;342:250.

14. Maggini S, et al. Immune function and micronutrient requirements change over life course. Nutrients. 2018;10:1531. doi: 10.3390/nu10101531.

15. Egli A, et al. Vaccine adjuvants - Understanding molecular mechanisms to improve vaccines. Swiss Medical Weekly. 2014;144:13940. doi: 10.4414/smw.2014.13940.

16. Lee S, et al. Recent advances of vaccine adjuvants for infectious diseases. Immune Netw. 2015;15(2);51-57. doi: 10.4110/in.2015.15.2.51

17. Schuch RA, et al. The use of xanthan gum as vaccine adjuvant: An evaluation of immunostimulatory potential in BALB/c mice and cytotoxicity in vitro. BioMed Research International. Hindavi Publisher, 2017, Volume (2017), Article ID. 3925024 https://doi.org/10.1155/2017/3925024

18. Zhang X-P, et al. Astralagus saponins and liposomes constitute an efficacious adjuvant formulation for cancer vaccines. Cancer Biotherapy & Radiopharmaceuticals. 2018; 33(1). https://doi.org/10.1089/cbr.2017.2369

19. N.Woods et al. Natural vaccine adjuvants and immunopotentiators delivered from plants, fungi, marine organisms, and insects. In: Immunopotentiators in Modern Vaccines.(2nded), Academic Press; 2017:211-229.

20. AbdelAllah NHet al. Chitosan and sodium alginate combinations are alternative, efficient, and safe natural adjuvant systems for hepatitis B vaccine in mouse model. Evidence-Based Complementary and Alternative Medicine. 2016; Article ID 7659684. doi: 10.1155/2016/7659684

21. Niedzwiecki A, Rath M. Malnutrition: the leading cause of immune deficiency diseases, Dr Rath Research Institute. (ed), 2005.

22. Goc A. Rath M. The anti-borreliae efficacy of phytochemicals and micronutrients: an update. Therapeutic Advances in Infectious Diseases. 2016;3:75-82.

23. Jariwalla JR, et al. Micronutrients in the global fight against influenza. In: Mitrasinovic P, ed. Global View of the Fight Against Influenza. Nova Publishers; Hauppague NY, USA, 2009:Chpt. 17

24. Jariwalla RJ, et al. Micronutrient Synergy in the Control of HIV Infection and Aids, Recent Translational Research in HIV/AIDs. In: Tang YW ed. Recent Translational Research in HIV/AIDs, InTech; London, UK , 2011:513-526.

25. Barbour EK, et al. Holistic efficacy of specific nutrient synergy against avian flu virus: pathology and immunomodulation. Veterinaria Italiana. 2007;43(1):43-54.

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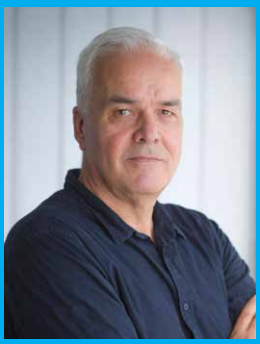

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Dr. Rath is a world-renowned physician and scientist, who is known for his pioneering research in natural and cellular health. He is the founder of the scientific concept of Cellular Medicine - the systematic introduction into clinical medicine of the biochemical knowledge of the role of micronutrients as biocatalysts in a multitude of metabolic reactions at the cellular level.

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