Adjuvants: The unsung heroes of vaccines

March 25 2021, by Anita Milicic

Gaston Ramon, a French vet, discovered vaccine adjuvants. Credit: Wellcome Collection/Wikimedia Commons, CC BY-SA

Emerging from vague familiarity into the spotlight as the only route out of the pandemic, vaccines have become an everyday topic of conversation. Most of us now understand the principle of vaccination: our immune system is presented with a part of a pathogen and instructed to create a lasting immune response to it, safeguarding us against future infection. But few people know about vaccine ingredients that can be essential for inducing a potent immune response: adjuvants.

Named from the Latin "adiuvare" meaning "to help," adjuvants have been lending a helping hand to vaccinologists for many decades. Yet a lack of a clear understanding of how they work has tainted their reputation, leading to epithets such as "alchemy" and "the immunologist's dirty secret".

The concept emerged in 1925 when Gaston Ramon, a French vet, discovered that horses vaccinated against diphtheria had a stronger immune response if inflammation developed at the site of injection. Ramon then set out to test a range of common materials and foodstuffs for their ability to cause irritation and inflammation as vaccine additives.

Believed to be safe to inject if they are safe to eat, various substances from breadcrumbs and oil to agar and soap were shown to improve antibody responses in vaccinated animals. Perhaps surprisingly, some of today's adjuvants are still based on related substances, only manufactured using more controlled and regulated methods.

A similarly serendipitous discovery followed a year later when Alexander Glenny, a British immunologist, used aluminum salts to purify the diphtheria protein. This preparation also resulted in superior antibody responses compared with previous diphtheria vaccines and paved the way for aluminum salts to become the most widely used adjuvant to date.

Over the next 60 years, aluminum salts were added to many licensed protein-based vaccines, including those against diphtheria, tetanus, pertussis, hepatitis, pneumococcal and meningococcal diseases.

Notoriety

However, with prominence came notoriety. In the 1970s, false claims emerged that aluminum salts in pediatric vaccines can cause aluminum metal to accumulate in the brain, causing harm. Several large studies followed, but no such effects were found. Although we still don't fully understand how they work, and reports of side-effects still occasionally crop up, aluminum salts remain a trusted and widely used adjuvant. Indeed, the Chinese Sinopharm vaccine against COVID contains dead coronavirus combined with an aluminum salt.

Partly because of the controversies, but mostly because aluminum salts don't effectively stimulate the cellular arm of the immune system—the T cells—scientists continued to work on new types of adjuvants, aiming for high potency with minimal side-effects. During the past few decades, many new formulations have been in development, based on old and new substances: oils and fats, saponins (plant-derived compounds), polymers, but also combinations of active components, guided by our increasing understanding of the immune system.

A new class of adjuvants has emerged, based on common molecules found in viruses and bacteria that stimulate our innate immune system—the immune system's first line of defense. Just a handful of receptors on our immune cells can detect generic features across a vast range of pathogens, from surface molecules to RNA or DNA. This recognition leads to the second half of our defense system, known as adaptive immunity, being activated to recognize and neutralize a specific invading pathogen. Adjuvants that mimic molecules common to many pathogens can be used to kickstart our immune response to the vaccine.

Over the past couple of decades, the regulators have approved only a few adjuvants, other than aluminum salts. Novartis's MF59—an emulsion containing naturally occurring squalene oil and water—has been licensed as part of the seasonal flu vaccine. And three adjuvant systems by GlaxoSmithKline (GSK) are approved as part of vaccines against shingles, pandemic flu and HPV.

Another potent and safe adjuvant is a compound called immunostimulating complex (Iscom). Iscoms are cage-like nanospheres that form when saponin is mixed with two types of fats. An example is Matrix M, included in the COVID vaccine, made by the US biotech company Novavax.

The authorized mRNA vaccines against COVID—made by Pfizer and Moderna – also contain an adjuvant. Messenger RNA (mRNA) is a set of genetic instructions for our cells to make the spike protein, which is found on the surface of the coronavirus. The adjuvants in mRNA vaccines are lipid or polymer-based nanoparticles that protect and stabilize the fragile mRNA and improve its uptake by our immune cells.

Not a one-trick pony

Adjuvants are versatile. They can make vaccines more effective in certain age groups, such as babies or older adults, where it is harder to induce a strong immune response. A notable example is GSK's Shingrix vaccine, which contains an adjuvant cocktail, AS01. Shingrix has shown remarkably good efficacy against shingles, which generally strike the elderly—a notoriously difficult population to protect because immunity fades in old age.

Adjuvants can also modify and broaden the immune response. This can be important for pathogens that need many arms of the immune system to defeat them, as is the case with COVID-19 and complex diseases such as malaria—or for pathogens that mutate a lot, such as flu and HIV. Adjuvants can even enable using a half vaccine dose—an important consideration in a pandemic where huge numbers of doses need to be made and administered in a short timeframe.

In the face of existing and emerging pathogens, and the demand for highly protective and safe vaccines, vaccinologists will need all the help they can get. We might finally be able to dispel any remaining doubts about adjuvants, which are now becoming a mainstream tool in vaccine development.

Provided by The Conversation