Safety Testing Vaccines, with reference to Vaccines against Covid-19

Vaccines have made an enormous contribution to control and even eradication of infectious diseases since they were first given to humans more than two centuries ago. However, vaccines, like any medicine, can cause adverse events in some recipients. Some important examples are summarized in the addendum.

All medicines, including vaccines, must have an acceptable balance of benefit and risk before being licenced for human use. Since vaccines are given to healthy individuals, i.e. their use is prophylactic, the benefits of a vaccine need to be very substantially greater than the risks of adverse effects.

Another risk must also be weighed; that of infection and death in the population which would result from the unchecked spread of the virus in the absence of either a vaccine or continuation of social distancing measures. Thus, during an active pandemic caused by a novel, highly contagious virus such as Covid-19, consideration must be given to special measures to expedite the development of a safe and effective vaccine.

A wide variety of approaches to developing vaccines against Covid-19 are being studied. These include conventional antigen vaccines (in some cases administered with an adjuvant) nucleic acid based vaccines, virus like particles or inactivated virus. It is important to recognise that, as for other types of medicine, the majority of vaccines that are studied in clinical trials are not successful, and do not result in a marketed vaccine.

Safety considerations in the development of a vaccine for Covid-19

In this rapidly evolving situation, there is little, if any, specific information currently in the public domain about preclinical safety testing of the vaccines for Covid-19 that are in development. Therefore, we outline the framework of regulatory guidelines and practice which will determine the choices that will be made.

Recently, regulators met to discuss the type of experimental safety tests that are required for a Covid-19 vaccine prior to the first human clinical trials. When experimental safety data already exist for a particular viral vector, or for a very closely related product (e.g. well studied platform technology), regulatory authorities may consider that no additional safety data are needed before clinical trials can start.

What experimental (preclinical) safety tests are needed for vaccine development?

Prior to a human clinical trial with a vaccine (including Covid-19 vaccines) experimental studies are normally performed in a human-relevant animal species, to characterise the immune response. The type of preclinical safety tests which are appropriate depends upon the nature of the vaccine being developed, as detailed below. A vaccine's effectiveness can only be tested *before* a clinical trial if there is an appropriate experimental model. As at present, there is no appropriate experimental model for Covid-19, the ability of a vaccine to protect against infection can only be tested in a clinical trial.

Tests with antigen[1] based vaccines

Toxicity studies normally consist of single or repeated dose toxicity studies in one human-relevant species (rodent, rabbit, or non-rodent) of a vaccine and of any adjuvant[2], assessed separately and in combination, using the clinical route of administration, for a duration that can vary from days to weeks. These studies examine effects at the site of vaccine administration and systemic effects, and include a post treatment recovery period to assess the development of any delayed effects, or the reversibility of effects. An assessment of the potential for hypersensitivity or for autoimmune reactions is included, although because these reactions are rare, experimental studies have limited ability to detect them. For vaccines with a novel mechanism, studies in a second experimental species may be appropriate (WHO Guidance on Preclinical testing Vaccines 2005).

If women of reproductive potential are included in the target population, reproductive toxicity studies in rodent (fertility and peri- and post-natal development) and in both a rodent and the rabbit (embryo-foetal development) may be expected. For Covid-19 vaccines, it may be acceptable for these studies to be conducted in parallel with Phase II/III clinical studies, provided that women of childbearing potential who participate in the clinical trial are adequately counselled and protected against pregnancy.

Adjuvants are normally tested for genetic toxicity and, if warranted, safety pharmacology studies or tests for other more specific types of toxicity are included (WHO Guidance on Safety tests for Adjuvants 2014).

For all vaccines marketed in the EU and USA, a summary of experimental data from preclinical safety tests is published by Regulatory Agencies, for example Cervarix EPAR 2007, Shingrix EPAR 2018.

Tests with attenuated virus vaccines

In addition to the studies above, the potential for an attenuated virus to revert to a virulent form (by mutation) or to recombine (acquire virulence genes from other viruses) should be studied.

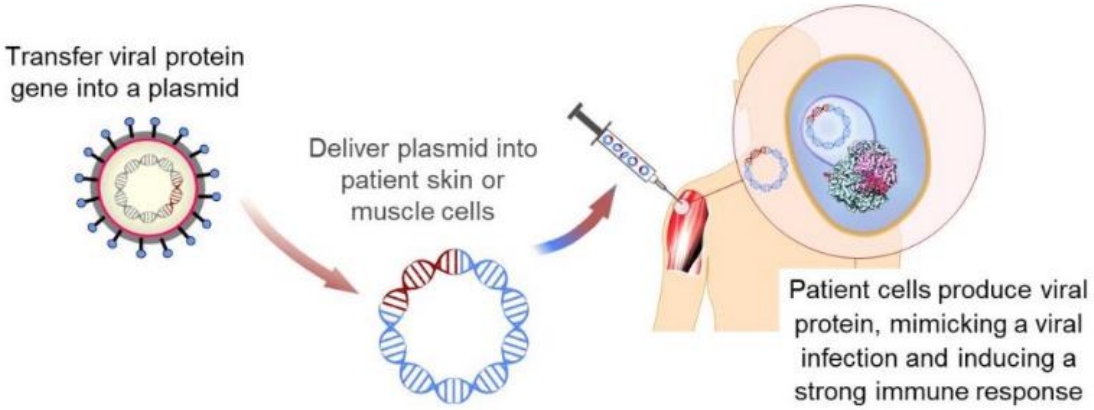
Tests with nucleic acid (DNA or RNA) based vaccines

The type of testing depends on the vaccine construct and the delivery mechanism; vaccine constructs can include plasmids (see illustration), virus-like particles and genetically engineered viral vectors. Studies should include examination of the potential for integration into the human genome, the potential to cause mutation at sites of genomic integration, and the potential for effects on genome stability. Also, experimental data on bio-distribution in a human relevant animal species, persistence of the vaccine construct, and the potential for transmission to germ cells, should be investigated. In cases where a viral vector or vaccine construct has previously been characterised sufficiently to support clinical trials, no additional experimental safety data may be needed (WHO Guidance on Safety tests for DNA Vaccines 2007, EMA Guidance on gene Therapy Medicinal Products 2008).

[1]An antigen is a foreign substance (usually protein or protein fragment) that causes an immune response in the body

[2] An adjuvant is one or more co-formulated ingredients, which can be added to a vaccine to enhance the immune response, thereby creating a stronger and longer lasting immunity against infections than the vaccine alone. The use of an adjuvant is of particular importance in a pandemic situation since it can reduce the amount of antigen required per dose, allowing more vaccine doses to be produced and made available to more people.

DNA Vaccination (courtesy of Biotech Primer 2017)



A plasmid is a short circular piece of DNA commonly used to shuttle DNA into cells in the lab.

It is important to appreciate that as of May 2020, *no* DNA Vaccine has yet been approved as a human medicine - although 3 DNA vaccines are approved and are in use as veterinary medicines. *If* a nucleic acid vaccine is capable of protecting humans against coronavirus infection, this will be a medical breakthrough.

What clinical safety testing or monitoring is needed?

Previous experience of adverse effects in vaccinated humans informs the approach to possible risks for a new vaccine. Risk mitigation strategies for volunteers in initial (Phase I) clinical trials, which are conducted in specialised clinical research centres, include frequent monitoring for a wide range of immunological and physiological responses. In subsequent (Phase II and Phase III) clinical trials, where the number of volunteers is increased, the pattern of safety monitoring can be adjusted according to emerging safety data.

As for all new vaccines, clinical safety monitoring should also examine the potential for vaccine induced disease enhancement. In practice, the long-term safety of all vaccines is only determined during their widespread use in humans.

Conclusion

Marketed vaccines usually have a highly favourable balance of benefit compared to risk. This is a consequence of the extensive experimental and clinical safety studies that are conducted *and* independently reviewed before a vaccine can be approved and marketed. Because of the urgent humanitarian need for an effective vaccine against Covid-19, regulatory reviews are likely to be expedited and the balance of benefit and risk may be viewed more flexibly than for previous vaccines.