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How vaccines are tested, licensed and monitored

How vaccines are tested

Understandably, people are often concerned to know how rigorously and extensively vaccines have been tested. This is especially true for new vaccines. This page aims to outline the process involved in developing and licensing a vaccine for use in the UK. The standard for testing and monitoring of vaccines is higher than it is for most other medicines, because they are one of the few medical treatments given to healthy people (mainly healthy children). This means that the level of acceptable risk is much lower than it might be for a cancer treatment, for example. It can take many years for a vaccine to pass through all the stages described below. In the case of the MenB vaccine, for example, it took 15 years from the first idea to the vaccine being licensed for use.

These are some of the stages a vaccine will have gone through before use:

- Reviewing what has been done before.
- Theoretical development or innovation: coming up with a new idea, or a variation on an existing idea.
- Laboratory testing and development. This involves 'in vitro' testing using individual cells and 'in vivo' testing, often using mice. The vaccine has to pass rigorous safety tests at this stage, and demonstrate that it works in animals.
- Phase I study – an initial trial involving a small group of adult participants (up to 100 people). This is carried out to make sure that the vaccine does not have major safety concerns in humans, and also to work out the most effective dose.

- Phase II study – a trial in a larger group of participants (several hundred people). Phase II trials check that the vaccine works consistently, and look at whether it generates an immune response. Researchers also start looking for potential side effects.
- Phase III study – a trial in a much larger group of people (usually several thousand). Phase III trials gather statistically significant data on the vaccine's safety and efficacy (how well it works). This means looking at whether the vaccine generates a level of immunity that would prevent disease, and provides evidence that the vaccine can actually reduce the number of cases. It also gives a better chance of identifying rarer side effects not seen in the phase II study.
- Licensing – expert review of all trial data by the UK government (through the Medicines and Healthcare products Regulatory Agency (https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency)- MHRA) At this stage the regulators check that the trials show that the product meets the necessary efficacy and safety levels. They also make sure that, for most people, the product's advantages far outweigh the disadvantages.
- Phase IV studies – post-marketing surveillance to monitor the effects of the vaccine after it has been used in the population. These may be requested by a regulatory body, or carried out by the pharmaceutical industry.

The vaccine and the trials used to test it must meet the regulations laid down by the following authorities:

- ICH-GCP (http://www.ich.org/)(International Conference on Harmonisation of Good Clinical Practice) - international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects
- Declaration of Helsinki (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/) (1964; 2008) - Ethical principles for medical research involving human subjects
- EU Clinical Trials Directive (http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf)- enshrined in UK law by the Medicines for Human Use (Clinical Trials) Regulations (2004) (http://www.legislation.gov.uk/uksi/2004/1031/contents/made)
- RCPCH Guidelines (http://adc.bmj.com/content/82/2/177.full.pdf+html)for the ethical conduct of medical research involving children (2000)

In addition, for trials in the UK, the vaccine and the trial must receive individual approval from the Medicines and Healthcare products Regulatory Agency (MHRA), while the trial itself must be approved from the following authorities:

- An NHS Research Ethics Committee (see more information on the NHS Health Research Authority website (https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/))
- The local NHS Research and Development office, who support and advise researchers in meeting the requirements of the UK regulatory framework (see more information on the framework (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/))
- The Health and Safety Executive (HSE) (http://www.hse.gov.uk/), for certain types of trials

Elsewhere

In the European Union, the European Medicines Agency (EMA) supervises the regulation of vaccines, along with other drugs. See European Medicines Agency - EMA (http://www.ema.europa.eu/ema/).

At an international level, the World Health Organization (WHO) makes recommendations via a committee for biological products (see WHO Expert committee on Biological Standardization (https://www.who.int/biologicals/expert_committee/en/)). Many countries adopt such standards set out by the WHO.

Licensing

Expert scientists and clinicians review data from the laboratory pre-clinical studies, clinical trials, manufacturing and quality controls, and also consider the conditions for its safe supply and distribution before licensing. The MHRA is responsible for regulating all medicines and medical devices in the UK by ensuring they work and are acceptably safe. They undertake robust and fact-based judgements to ensure that the benefits justify any risks.

What is a rolling review?

A 'rolling review' is a regulatory process used to assess a promising medicine or vaccine during a public health emergency. As packages of data become available from ongoing studies, they are reviewed on a staggered basis.

What is the National Institute for Biological Standards and Control?

The National Institute for Biological Standards and Control (NIBSC) (http://www.nibsc.org/) is part of the MRHA that conducts independent laboratory testing so that each batch of the vaccine meets the expected standards of safety and quality.

What is the Commission on Human Medicines?

The Commission on Human Medicines (CHM) (https://www.gov.uk/government/organisations/commission-on-human-medicines) provides adviceon the safety, efficacy and quality of vaccines.CHM is the government's independent expert scientific advisory body established in October 2005.

What is an Emergency Use Approval?

Regulation 174 of the Human Medicine Regulations 2012 enables rapid temporary regulatory approvals to address significant public health issues such as a pandemic. This regulation is an EU provision introduced in national law that allows for the authorisation of a medicine in response to a public health need. Instead of going through the centralised licensing route of the EMA (which is the normal route until the end of the Brexit transition period), the MHRA authorised the supply of the vaccine based on public health need, provided the batches of vaccine meet specific standards.

Monitoring

After a vaccine is licenced it continues to be monitored as part of a post-licensure monitoring of vaccines. The manufacturer of the vaccine may continue to test for safety, efficacy, and other potential uses (called Phase IV Trials). Also, the UK regulator, the Medicines and Healthcare products Regulatory Agency (MHRA)monitors vaccines to detect any possible signals of adverse events.

Who is responsible for monitoring vaccine safety?

Although vaccines undergo rigorous testing before they are licensed for use, it is important that the safety of vaccines is monitored on an ongoing basis, as with all licensed drugs. In the UK this is undertaken by the MHRA through the Yellow Card Scheme. Reports of suspected side effects are sent to the MHRA by drug companies (who are obliged to pass on any reports of suspected side effects that are defined as serious), health professionals, and, since 2005, patients themselves.

What does the MHRA do with these data?

The data are evaluated each week, and the reported side effects are compared against the expected side effects as detailed in the information sheet for the vaccine. If a previously unidentified reaction emerges, or the frequency of reactions is not in line with what is expected, then the MHRA will investigate carefully.

What happens next?

This will depend on the kind of side effect identified, but options include insisting that details of the new side effect are given in the product information leaflet or issuing warnings identifying groups of patients who should not be given the vaccine. In rare circumstances, the vaccine may be withdrawn from use.

Where can I find more information about the Yellow Card Scheme?

You can find detailed information on the scheme here (https://www.gov.uk/report-problem-medicine-medical-device), and data on Yellow Card reports for individual products here (https://yellowcard.mhra.gov.uk/idap).

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Medical content reviewed by **Professor Andrew Pollard** (https://www.paediatrics.ox.ac.uk/team/andrew-pollard). **Please click here to contact us** (http://vk.ovg.ox.ac.uk/contact) if you have comments about the Vaccine Knowledge website. We can't answer all the individual queries we get, but we will use your suggestions and questions to improve the website. You should consult your doctor or other healthcare provider if you need specific advice on vaccines for you or your child.

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