

Off-label vaccine use: explanatory note for countries

Licensure and registration procedure for vaccines and recommendations for use

Registration and licensure of vaccines and their recommendations for use are based on separate, but related processes. Before vaccines can be placed on the market, they need to obtain a market authorization by the National Regulatory Authority (NRA). The NRA assesses the vaccine's quality, safety and efficacy based on the dossier provided by the manufacturer. The NRA then evaluates all available data on the desirable (benefits) and undesirable effects (risks) of the vaccine and weights the beneficial effects against the potential undesirable effects. When the NRA decides there is sufficient evidence of consistent quality of vaccine manufacturing, and adequate data on efficacy and safety, the NRA authorizes the use of the vaccine for a given indication outlined in the vaccine product information sheet. The vaccine product information sheet, also called the vaccine label, is owned by the manufacturer but overseen by the NRA. Once the vaccine label is approved by the NRA, a public health advisory body, usually the National Immunization Technical Advisory Group (NITAG), can issue public health recommendations for use of the vaccine.

The NITAG tries to optimize the public health benefit of a vaccine and, therefore, has a different mandate from the NRA. While like the NRA, the NITAG considers data submitted by the vaccine manufacturer on vaccine safety and efficacy, the NITAG also considers a wider range of issues in its country context. These include vaccine effectiveness and impact in the target population, equity, acceptability, programmatic feasibility including vaccine schedules, and the cost-effectiveness of the vaccine.

Recommendations on vaccine use at the global level are formulated by Strategic Advisory Group of Experts on Immunization (SAGE) that advises World Health Organization (WHO) and serve as guidance to countries and their NITAGs. Many NITAGs consider WHO's advice and use the data collected and analyzed by SAGE to formulate their own, country specific recommendations.

What is "off-label" public health use of vaccines¹

The initial vaccine market authorization is normally limited to the populations enrolled in the clinical trials where evidence supports safety and efficacy of vaccine use or where convincing bridging data exists. The clinical trials used for market authorization usually involve healthy, immune-competent populations of age ranges relevant to the disease. For example, immunocompromised persons are rarely enrolled. This is to avoid exposing vulnerable populations to possible harm during the research evaluation and to optimize the probability to demonstrate efficacy. Consequently, clinical trials tend to exclude participants with underlying diseases and pregnant individuals, even though these groups may be at higher risk of severe disease from vaccine-preventable diseases and would benefit from vaccination. For populations for whom there is insufficient or no evidence to support the use of the vaccine, cautionary statements may be added

¹ [Off-label use of vaccines - PubMed \(nih.gov\)](#)

to the vaccine label. Also, initial vaccination schedules are designed for optimal individual protection, and less so for programmatic ease and population-level protection.

After the vaccine has entered the market, the NRA will request the vaccine company to conduct post-marketing studies to collect more evidence to continue the vaccine safety assessment and measure effectiveness when used in an unselected, larger population.

After the vaccine has obtained authorization and is widely used, the NRA can also ask the manufacturer to provide more data, such as in response to any safety signals that might occur. Separate from studies requested by the NRA, post-marketing studies initiated by academic or public health institutions may become available that investigate additional research questions or other use cases. Such studies may investigate different vaccine schedules, routes of administration, or include groups excluded from clinical trials such as pregnant individuals. These studies will not directly lead to a vaccine label change, unless submitted by the manufacturer to the NRA since the label is owned by the manufacturer. Such studies may, however, generate evidence that is sufficiently robust to support use of a vaccine beyond its label use indication.

Such studies results may be used by SAGE or NITAG's to issue recommendations that differ from the label use indications, which then leads to "off-label" public health use of a vaccine. Off-label recommendations must be guided by a clear public health benefit, and risks need careful consideration. Examples include the use of human papillomavirus (HPV) vaccine as a single dose schedule instead of a two-dose schedule in adolescents, SAGE recommendations to include pregnant individuals among the priority target groups for inactivated influenza and COVID-19 vaccines and recommendations to administer yellow fever vaccines at reduced (fractional) dosage in situation of significant supply limitations.

Vaccine label indications may differ between countries. This can be due to differences in the burden of disease or other criteria used in the NRA vaccine assessment. The assessment of the balance between benefits and risks by the NRA will be based on national methods, standards, and laws. The same evidence may lead to a label indicating use in specific groups in one country, while another country's NRA may have a different interpretation of the data and decide that the evidence is not sufficient to approve the same vaccine for use in the same groups in their country. Difference in timing and availability of data when assessing a vaccine may also lead to different labels between countries. Policy recommendations for the same vaccine issued by NITAGs may therefore be "off-label" in certain countries and in line with market authorization in other countries.

[Why does SAGE make recommendations for "off-label" public health use of vaccines?](#)

Reasons for SAGE to issue recommendations for "off-label" use of vaccines may include direct benefit for specific population groups (e.g., pregnant individuals), vaccine shortages, motivating schedule or dosing changes, simplified immunization schedules or a response to a disease outbreak. As for all recommendations, when considering a recommendation for "off-label" use, SAGE will review all available data, including data from post-marketing and other studies to conduct a benefit-risk assessment. A recommendation is only made when data exist to support the "off-label" recommendation.

A SAGE recommendation for “off-label” use can provide global guidance to NITAGs to consider the public health benefit when going beyond the labelled use-indication. If WHO issues an “off-label” recommendation it will be explicitly noted in its guidance.

To minimize the use of “off label” recommendations, WHO encourages vaccine manufacturers, developers, and funders to consider the inclusion of populations who are often excluded but that may particularly benefit from vaccination, such as persons with co-morbidities, into the design of clinical trials that are used for market authorization. For priority vaccines, WHO may develop considerations for data needs important for policy recommendations, to reduce unnecessary obstacles and delays to the programmatic introduction of vaccines. WHO also strongly encourages that clinical trials are being conducted in countries of greatest medical need and encourages manufacturers to update their labels as new information becomes available.

Considerations for countries when using vaccines “off-label “

Liability: Countries may have concerns about who would be liable when a vaccine is used “off-label” and an adverse event following vaccination (AEFI) occurs or if an “off-label” recommendation would result in reduced effectiveness. In some countries, NITAGs are therefore explicitly precluded from making recommendations for “off-label” use of vaccines. Conversely, in other countries, incorporation of “off-label” use of a vaccine into the routine immunization programme ensures healthcare providers are protected by the government. As for all recommendations, protection against liability is dependent on the health care providers following the latest NITAG recommendations.

Collaboration between NITAG and NRA: Collaboration between NITAG and NRA should be encouraged to inform decision-making and ultimately reduce the need for “off-label” recommendations. Interaction can be achieved by, for example, having an NRA representative attend NITAG meetings or being part of the NITAG as a liaison member. The NRA representative could provide scientific information which may help the NITAG in their decision-making process. Collaboration between the NITAG and NRA may also result in the NITAG informing the NRA once “off-label” use of a vaccine is being considered.

Communication: Confidence in public health recommendations may be affected if the differences between the vaccine product information and public health recommendations are not fully explained and communicated to health care providers and vaccinees. Therefore, countries should clearly explain variations from the product information and communicate the underlying reasons leading to the recommendations. Countries should ensure plain language communication materials are made available in a timely way to inform health workers and the public on “off-label” vaccine use.