

Communicating Vaccine Safety During the Development and Introduction of Vaccines

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Abstract: Vaccines are the best defense available against infectious diseases. Vaccine safety is of major focus for regulatory bodies, vaccine manufacturers, public health authorities, health care providers and the public as vaccines are often given to healthy children and adults as well as to pregnant woman. Safety assessment is critical at all stages of vaccine development. Effective, clear and consistent communication of the risks and benefits of vaccines and advocacy during all stages of clinical research (including the preparation, approvals, conduct of clinical trials through the post marketing phase) is critically important. This needs to be done for all major stakeholders (e.g. community members, Study Team, Health Care Providers, Ministry of Health, Regulators, Ethics Committee members, Public Health Authorities and Policy Makers). Improved stakeholder alignment would help to address some of the concerns that may affect the clinical research, licensing of vaccines and their wide-spread use in immunization programs around the world.

Keywords: Adverse events, clinical research, communicating, pharmacovigilance, safety, vaccine introduction.

INTRODUCTION

Vaccines are one of the most cost-effective and successful public health measures for preventing morbidity and mortality associated with infectious diseases [1]. Vaccinated individuals are protected from developing a number of potentially serious infectious diseases. The community is also protected as the spread of infectious organisms is reduced. Vaccine development and introduction began at the end of the 18th century but the actual potential of vaccines was recognized only in 1977 when Smallpox was eradicated. Vaccines have also resulted in the elimination of wildtype poliomyelitis virus from the western hemisphere and have controlled rubella, measles, diphtheria, haemophilus influenza type B, Tetanus and other infectious diseases. Most vaccines are cost effective even if only the direct medical costs of treating the disease (and not the associated mortality and morbidity) are considered.

No vaccine and no medical intervention can be considered one hundred percent safe or effective. A high standard of safety is required from vaccines as these are given to expectant mothers, healthy children and adults [2]. Vaccine safety is of major importance to regulatory bodies, ethics committees, vaccine manufacturers, public health authorities, health care providers and the general public [3, 4].

ADVERSE EVENTS FOLLOWING IMMUNIZATION

Vaccination is considered a significant event in the general public's mind and any illness following immunization can be thought to be related to the vaccine. While some adverse events may actually be caused by the

vaccine, the vast majority will be unrelated and occur by coincidence. Safety concerns have led to the withdrawal of vaccines in the past (e.g. RotaShield, a vaccine intended to prevent severe rotavirus diarrhea, was withdrawn in 1999 following an increased incidence of intussusception (a rare bowel obstruction that occurs when the bowel folds in on itself) in vaccinated infants. The decision to withdraw RotaShield arose from the desire of health officials in the United States to preserve public confidence in the country's vaccination efforts. The decision in the US resulted in the vaccine being withdrawn internationally, including in low and middle income countries (LMIC), where the vaccine's benefit and risk profile were significantly different from the US [3, 4].

Scientific researchers and stakeholders need to clearly distinguish between vaccine related adverse events and unrelated, chance events to maintain public confidence in immunization programs. This would ensure adequate vaccination coverage and maintain herd immunity.

The following factors make it difficult to distinguish whether or not adverse events are associated with vaccination [5]:

- Need to study multiple vaccine exposures and multiple outcomes post vaccination to detect rare adverse events
- Absence of unique vaccine-associated symptoms making it difficult to establish causality to the vaccine
- Need to study large sample sizes
- Lack of large, computerized, searchable immunization databases in developing countries including vaccine lot numbers and individual level data
- Incomplete and inconsistent information from individual adverse event reports
- High childhood vaccine coverage often found in

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<p>developing countries rendering unbiased comparison to unvaccinated individuals highly</p> <ul style="list-style-type: none"> • Limited understanding of biological processes underlying adverse events • Inadequate design of clinical trials (not enough participants enrolled for an adequate period of time to detect rare adverse events) • Inadequate systems to track adverse events following immunization (AEFI) • Limited number of randomized clinical trials published in the medical literature
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Before licensure, thorough evaluation and communication of safety are critical as post-licensure, individuals often receive several vaccines simultaneously. This makes it difficult to assess which vaccine caused the adverse event. Several possible adverse events can occur following a vaccination. In the absence of unique symptoms it may be difficult to assess whether these are adverse reactions to the vaccine or a coincidental event.

Unlike drugs (which are given several times a day for a period of weeks), only a few doses of a vaccine are usually given to an individual. If the adverse event is dose-related, the probability that it will occur after vaccine administration is much lower than after the administration of drugs. Large populations are needed to conduct studies to detect rare adverse events. This can be difficult and expensive to do.

Large numbers of children in developed countries receive childhood vaccinations, making it difficult to find a control population that has not received the vaccine to assess how often adverse events occur in the absence of vaccination and determine potential causality of the adverse event. Individuals who do not receive vaccines may be different in other respects from those who are vaccinated and may not be a suitable control population [5].

MONITORING AND COMMUNICATING VACCINE SAFETY DURING CLINICAL VACCINE DEVELOPMENT AND INTRODUCTION

Developing and licensing a vaccine is a lengthy process. It may take ten years or longer. The research, development and manufacturing organizations undertake safety activities at all stages of vaccine development (including the selection and formulation of vaccine candidates, clinical research and post-licensure studies) [4].

Safety is a key consideration from the early phases of vaccine development. The type of vaccine candidate selected onward, technologies for vaccine development and the use and choice of adjuvant are all influenced by safety considerations [4].

Before vaccines are licensed, they are tested extensively in preclinical and clinical trials to ensure their safety. There are specific criteria defined by international regulatory authorities such as the US Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMA) for preclinical and clinical trials for vaccines which should be followed.

Before the initiation of clinical trials, the investigational vaccine dossier and trial protocols are reviewed and approved by an independent investigational review board or ethical committee and the respective regulatory agency.

Clinical trials are conducted according to ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use)-GCP (Good Clinical Practice) guidelines. These are international scientific and ethical standards for designing, conducting, recording and reporting clinical trials. They provide assurance that the clinical trial data are credible and the rights, safety and well-being of trial subjects are protected. This provides a unified standard for the United States, European Union (EU) and Japan and facilitates the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions [6].

Before they can be licensed for use in the general public, vaccines (like drugs) must successfully pass through three phases of clinical trials. Clinical trials are conducted in incremental phases to minimize risk and to optimize the information obtained: initial safety (phase I); dose-ranging (phase II); efficacy (phase III); and post-licensure trials (phase IV). The early phase trials have a small sample size. This reduces the number of persons who might be exposed to unknown risks through an experimental vaccine. The large sample sizes in Phase III and IV trials help to gather additional safety information about the vaccine when it is administered to a larger population [4].

Phase I trials, involve a small numbers of closely monitored volunteers and last for 1-2 years. The trials help to evaluate safety (by identification of commonly occurring side effects) and immunogenicity of the vaccine. Phase II trials are larger and involve one to several hundred volunteers. They last for two to four years and collect additional information on the safety and immunogenicity of the vaccine. The trial results can be used to determine the composition of the vaccine, the number of doses and dosage schedule and side effects that may occur. In case of a good safety and immunogenicity profile of the vaccine, Phase III trials are conducted. These involve several hundred to several thousand volunteers and last several years. They help to determine the efficacy and safety data required for the licensing of the vaccine [7, 8].

Adequate communication about safety and efficacy of the vaccines is critical at all stages of the preclinical or clinical research. If there are concerns about either the safety or the efficacy of a vaccine, regulatory authorities may request additional information or halt the trials. An independent Data Safety Monitoring Board (DSMB) is often established for the trial prior to its initiation ensuring the timely investigation of any serious adverse events that may occur during the trial and to establish causality, if applicable. The DSMB can stop the trial if its members believe that it is warranted. Arbitration Boards are often set up to ensure that the complaints of volunteers are addressed promptly.

If the vaccine is found to be safe and effective during clinical trials, the manufacturer may apply for product licensure. During the application process, the regulatory agency reviews all clinical trial data and the proposed vaccine label, inspects the vaccine manufacturing plant and

reviews the manufacturing protocols. This is to ensure that the vaccine is produced under manufacturing conditions that meet international standards. Only after the regulatory agency is satisfied a vaccine may be licensed for use in the general public.

Vaccine approval also requires product labeling for health care providers to understand the vaccine's target population, proper administration, storage, possible adverse events and its risks-benefit profile to be communicated with patients and parents. This ensures the safe delivery of the vaccine to the public.

Post-licensure, if UNICEF or other UN agencies would like to purchase the vaccine for use in immunization programs, WHO provides prequalification for the vaccine. This ensures the acceptability of vaccines from different manufacturers for supply to UN agencies. This ensures that the vaccines used in immunization programs are safe and effective, vaccine studies are relevant to the target population in the countries and the vaccines meet the needs of the program including temperature stability, presentation, potency, and product labeling.

Vaccine safety needs to be monitored continuously post-licensure. Though critical information on vaccine safety is provided through clinical trials, the data is limited as there are only a relatively small number of trial participants (hundreds to thousands). Even the largest trials with up to 70,000 participants cannot detect with statistical significance vaccine adverse events that occur in less than 1 in 10,000 vaccine recipients [9, 10]. Rare side effects and delayed reactions may only become evident once the vaccine is administered to millions of people post-marketing.

Clinical trials, regardless of their size, may in addition exclude certain populations e.g. people with underlying medical conditions or premature infants [11]. Since vaccination, especially for children, is often given universally, the regulators and public health community have to ensure the safety of new vaccines under the actual conditions of use among varied patient populations. Therefore, the regulatory agencies recommend that adverse events monitoring following vaccination continue through the use of surveillance systems such as the US Vaccine Adverse Event Reporting System (VAERS). Recently, large linked databases containing information on millions of vaccine recipients have been created to study rare vaccine adverse events [5].

It is challenging but critical to improve vaccine safety research, the monitoring of AEFI and vaccine risk communication during clinical research, especially in developing countries where there might not be robust preexisting systems in place.

VACCINE SAFETY DATA COLLECTION

It is critical to ensure that data on vaccine safety are collected at each stage of the clinical research process is accurate and complete. It will then be reviewed by the regulatory body. In addition, vaccine manufacturers are now required to provide risk evaluation and mitigation strategies for new vaccines to the regulatory agency [4].

Prior to the conduct of each phase of vaccine clinical trials, it is important to ensure that all available information is compiled on the safety of the vaccine. This could be from completed or ongoing preclinical or clinical studies with the vaccine candidate used for a specific disease indication, for alternative disease indications or similar vaccine candidates. This requires a comprehensive literature review and discussion with stakeholder organizations and investigators working on similar vaccine candidates to obtain published and unpublished data, if feasible.

This information must be systematically compiled to ensure clarity and timeliness in informing regulatory bodies, ethics committees, reviewing bodies and investigators. This will enable them to make an informed decisions on the continuation of the trial.

If regulatory approval for the trial conduct is obtained, the available information on the vaccine's safety and reactogenicity, risks and benefits along with a brief description of the vaccine preventable disease must be presented in an accurate, simple and easily understandable format in informed consent documents, vaccine information statements and volunteer information leaflets to ensure that the clinical trial participants understand the information before providing informed consent. Informed consent is obtained from any potential trial participants before they become involved in research. This is to ensure that they are able to make an informed decision regarding their participation in the trial. Trial participants need to voluntarily agree to receive the vaccine and undergo any medical tests required to assess the vaccines safety, immunogenicity and efficacy. As new information becomes available regarding the vaccine, it must be provided to the trial participants to ensure that they are fully informed about the risks and benefits of participating in the trial. The volunteers are free to discontinue their participation in the trial at any time.

EFFECTIVE RISK COMMUNICATION

Health professionals must be able to handle vaccine safety concerns appropriately. This ensures that the volunteers understand the trial objective and its possible benefits and risks [5].

The objective of risk communication is to improve collective and individual informed decision making. The process includes reaching the intended audience, making the risk comprehensive and relatable to other risks while paying appropriate respect to their values and perceptions. Thus risk communication is a necessary skill for any healthcare professional conducting clinical trials.

In 1996, there was a workshop on risk communication and vaccination held by the US Institute of Medicine's Vaccine Safety Forum. Three key concepts emerged from the workshop-

1. Effective risk communication depends on the providers' and recipients' understanding of more than only risks and benefits. Background experiences and values also influence the process. Good risk communication recognizes a diversity of form and needs in the general population.

2. Informed decision making should be the goal of risk communication.
3. There is often uncertainty about the risk associated with vaccination. Risk communication is more effective when the uncertainty is stated and the risks are quantified as much as feasible [12].

REPORTING AND COMMUNICATING ADVERSE EVENTS

To ensure that the data on vaccine safety collected in a trial are comparable across different trials conducted by the same or different organizations, it is important to use standardized definitions of adverse events (AEs), methods for assessing severity of AEs, the relationship to the vaccine, defining serious AEs and collection, reporting and clinical management guidelines. AEs would have an impact on the potential discontinuation of vaccinations in the trial, on the withdrawal of the volunteers, on the reporting done to the regulatory authorities, as well as on licensure and use of the vaccine in different populations. Those AEs would remain associated with the vaccine for the duration of its use and impact on the selection of similar vaccine candidates for that or other disease conditions.

The package inserts of licensed vaccines would contain indications for the vaccines use, dosage, contraindications, warnings, precautions, interaction and adverse reactions based on data collected during the clinical studies and in the post licensure period [4].

It is thus critical to explain the importance of accurate and timely adverse event reporting to all the trial team members, field staff, volunteers or parents of children who participate in trials. The information typically collected on vaccine AEs includes information about the recipient (age, gender), the type of vaccine received, the date and time of vaccination, the onset of the adverse event, symptoms, duration, laboratory results, treatment provided, current illnesses, medication, history of AEFI, etc. It is useful if the information is collected on easily accessible, usable, searchable, and linkable database systems. Reporting guidelines are prescribed by the regulatory authorities and are very particular about the timelines, information to be reported, and ensuring confidentiality of the information. This must be explained to the investigators to ensure complete and timely reporting. Training also needs to be provided to the trial team and investigator on AEFI reporting and causality assessment.

IMPROVED VACCINE RISK COMMUNICATION

Training and education programs, along with regular safety updates (SUSARs) keep investigators and trial team members up to date about current vaccination policies and recommendations. They should be aware of vaccine safety issues, including those that have drawn attention from the media. Investigators should understand current scientific findings and be able to explain these simply and clearly to volunteers and parents of children participating in clinical trials [13]. In order to prevent vaccine administration errors

and AEFI, the investigators should follow the recommendations for vaccine storage, handling, administration and follow-up [14].

Well-designed trials with a large population of volunteers conducted before and after a vaccine's licensure help to improve the detection of rare adverse events. Vaccine clinical trials should also address the question whether vaccine combinations lead to more AEFI than vaccines given separately. Vaccine recall procedures could also be improved for removal or correction of marketed vaccines, labels and/or promotional literature that violate existing regulations.

There is a literature that need for long-term studies to determine late onset AEFI and the potential of vaccines to induce or worsen immune disorders. Research could also help determine if age is a factor in the AEFI and consider if some groups of individuals are more prone to adverse events.

During all stages of clinical research including the preparation, approvals, recruitment for clinical trials as well as the post marketing phase, effective, clear and consistent communication of both the benefits and risks of vaccines and advocacy are critically important.

CONCLUSION

Safety is of critical importance in the research and development, manufacture, clinical trials and post-licensure surveillance of vaccines. The common goal during vaccine development is to increase the benefits of vaccines and minimize risk to vaccine recipients [4]. Effective, clear and consistent risk communication of vaccine safety during the preparation and recruitment for clinical trials is an important tool in addressing any concerns that may later affect the licensing of vaccines and the implementation of immunization programs around the world. Vaccine safety communication should be an area for partnership among vaccine stakeholders, professional bodies, manufacturers and nonprofit advocacy groups. This will help to provide clear, consistent and easily understandable information on both the risk and the benefit of vaccines [4,14-26].

Best practice advice for vaccine risk communication in clinical research

- Provide accurate information
- Maintain trust in the source of information
- Keep open lines of communication with volunteers and parents of children participating in the clinical trials
- Refer patients to authoritative resources such as websites and published articles
- Timely communication of vaccine safety issues during clinical trials to regulatory authorities
- Prompt publication of vaccine trial data
- Strengthen research capabilities, surveillance and vaccine safety programs in clinical trials
- Critically examine the factors influencing public perceptions of vaccine-associated risk

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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