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The clinical development process for a novel preventive vaccine: An overview

K Singh and S Mehta

Malaria Vaccine Development Program (MVDP), International Centre for Genetic Engineering and Biotechnology (ICGEB) Campus, New Delhi, India

Address for correspondence: Dr. Kavita Singh, E-mail: kavita.singh@mvdp.org.in

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Abstract

Each novel vaccine candidate needs to be evaluated for safety, immunogenicity, and protective efficacy in humans before it is licensed for use. After initial safety evaluation in healthy adults, each vaccine candidate follows a unique development path. This article on clinical development gives an overview on the development path based on the expectations of various guidelines issued by the World Health Organization (WHO), the European Medicines Agency (EMA), and the United States Food and Drug Administration (USFDA). The manuscript describes the objectives, study populations, study designs, study site, and outcome(s) of each phase (Phase I-III) of a clinical trial. Examples from the clinical development of a malaria vaccine candidate, a rotavirus vaccine, and two vaccines approved for human papillomavirus (HPV) have also been discussed. The article also tabulates relevant guidelines, which can be referred to while drafting the development path of a novel vaccine candidate.

KEY WORDS: Clinical development, objective, study design, study population, vaccine

Introduction

A novel vaccine candidate (defined either as the first of its kind based on the mechanism of protection or as the first vaccine for a disease) undergoes an elaborate development process after discovery. Regulatory agencies worldwide divide this development process into preclinical (*in vitro* and *in vivo* testing in animals) and clinical (clinical trials in human subjects) stages. To plan the clinical development path of a novel vaccine candidate, guidelines have been issued by the European Medicines Agency (EMA), the World Health Organization (WHO), and the United States Food and Drug Administration (USFDA) [Table 1].

This review article is primarily based on the recommendations made in the guidelines mentioned above and the literature on the development of RTS, S [*Plasmodium falciparum* malaria vaccine of GlaxoSmithKline (GSK)], Rotarix™ (RIX4414, rotavirus vaccine of GSK), and Cervarix and Gardasil™ [human papillomavirus (HPV) vaccines of GSK and Merck & Co., respectively].

Common principles guide the development of any vaccine candidate, but each vaccine follows a unique developmental path depending on characteristics such as the type of vaccine, (live/killed/subunit/DNA/peptide), disease epidemiology, target population, and the availability of a pre-

existing vaccine. In addition, decisions to continue or stop development (go/no-go criteria) are based on attributes predefined in the target product profile (TPP).[1]

Guidance documents are summarized in Table 1 for reference, including important definitions/terms regularly used in vaccine development.

An Overview on Clinical Development

Few vaccine candidates make the transition from the laboratory to clinical trials. Some of the criteria considered to advance development are animal immunogenicity, toxicity data, immunogenicity response in adults, possible impact on public health, chances of acceptance by community, cost-effectiveness, and preexistence of a vaccine with a satisfactory risk-benefit profile.

The following differences from drug development mandates special precautions while conducting vaccine clinical trials in a pediatric population:[2,3]

- Unlike drugs, which are given to patients, vaccines are received by healthy individuals, thus the safety margin should be very high.
- As vaccines have to be stored under refrigeration, there are always logistical challenges during clinical trials considering that Phase II and Phase III are field studies.
- As healthy children also receive immunization under the national program, the trial design gets complicated due to the possibility of interference during coimmunization.
- The clinical development for vaccines for infants involves a step-down approach where safety is first tested in adults, followed by adolescents, children, and lastly infants.
- Adjuvants are incorporated into vaccine formulations to modulate and improve the immune response. The compatibility of the adjuvant with the vaccine antigen and the quality and stability evaluation of antigen/adjuvant formulation are important aspects of clinical development.
- The immune response primarily measured during early stages of vaccine development (Phase I/II) should evaluate: Amount, class, subclass, and function of each specific antibody.
- Relationship between functional and nonfunctional antibody assays.
- Kinetics of immune response such as lag time for onset, antibody persistence, seroconversion rate, and induction of immune memory.
- Components of the immune response according to mode of delivery [whether immunoglobulin A (IgA) or immunoglobulin G (IgG)].
- Quality of the antibody response: Specificity and/or epitope recognition and avidity.
- Potential for formation of cross-reactive antibodies or immune complexes.
- Immunological factors that might affect the humoral immune response as preexisting antibodies (including maternal antibodies).
- Cell-mediated immune (CMI) response and the possibility of immune interference and/or cross-reacting immune responses when vaccines containing more than one antigen or two or more vaccines are coadministered, especially to children and young infants with immature immune systems.[3]

Prior to regulatory approval, a vaccine candidate usually undergoes three phases of development in humans, which, for the most part, progress sequentially: Phase I, Phase II, and Phase III. After successful completion of Phase III trials and following licensure of the product, Phase IV studies, also referred to as postmarketing surveillance studies (PMS) are used to continue to monitor the vaccine for safety and effectiveness in the population.[2,4,5,6]

Phase I Studies

Objective

Phase I, first-in-man studies refer to the first administration of a vaccine candidate to humans. The primary objective is to evaluate the safety and reactogenicity, while the secondary objective is collection of immune response. Often times, the dose, immunization schedule and mode of vaccine administration are also assessed.[2,3,4]

Study population

First-in-man Phase I studies are usually small trials in healthy, immunocompetent naïve adults who are at low risk of acquiring a vaccine-relevant infection (determined by serology, exposure, and travel history).

Based on results of adult studies (referred to as Phase Ia trials), subsequent Phase I studies may be conducted in different age or population groups closer to the target population to assess possible differences in dose, safety, vaccine schedule, or route of administration. Such subsequent studies in different geographies and populations are referred to as Phase Ib.

For example, RTS, S underwent Phase I testing first in malaria-naïve (USA) adults and then in malaria-exposed adults (Mozambique, Kenya, Tanzania Africa), followed by trials in 1-11-year-olds and finally in infants residing in malaria-endemic regions.[7,8] During the development of Rotarix™, the parent vaccine strain was tested for safety and immunogenicity in North American adults, seropositive children and infants. Further, the safety and immunogenicity of the lyophilized vaccine RIX4414 were evaluated in Belgian adults, followed by German seropositive (previously infected) and Finnish uninfected children. It also included dose-ranging evaluation and comparison of responses using antacid versus a buffer solution containing calcium carbonate.[9,10] Buffering of gastric acid is necessary to prevent inactivation of rotavirus during passage through the stomach. Cervarix was tested in 18-30-year-olds in USA who were seronegative for HPV DNA to assess the monovalent and bivalent formulations, while another Phase I/II study was conducted in 18-30-year-old women positive for HPV 16 or HPV 18 DNA.[11,12,13,14]

Study design, study site, and outcomes

Phase I trials are usually open-label and nonrandomized, but it is possible to conduct randomized controlled trials (RCTs) in which a placebo or a vaccine against a different disease is used as a comparator.[2,4] To control for bias, such a study can be single-blinded or double-blinded. The practice of using bedside formulations wherein the vaccine antigen and adjuvant are mixed just prior to immunization is frequently followed in Phase I trials.[15] This can allow the vaccine developer to test more than one adjuvant with the same vaccine antigen without having too many vaccine formulations. The formulations are prepared under laminar flow by a trained pharmacist. However, any change in formulation will require it to be tested again in a new Phase I trial.

It is recommended that the Phase I study site be located within or in the vicinity of a tertiary care hospital.[16] After immunization, the need for day-care observation is guided by the need for monitoring adverse events.[2] Tolerability and reactogenicity due to the vaccine or the process of vaccination[17,18,19,20] is the major safety outcome evaluated in a Phase I trial. To ensure comparability of safety data within and across clinical trials, it is recommended to follow a standardized approach of data collection, analysis, and reporting. For healthy volunteer vaccine studies, the toxicity grading scales provided by the USFDA[21] and the case definitions developed by the Brighton Collaboration[22] for specific solicited events are recommended as standard references.

Clinical safety laboratory testing (e.g., hematology, biochemistry, urinalysis) also forms a part of the safety data that are collected at baseline, at defined intervals, and at the end of the trial.

The immunogenicity assays should preferably be validated and performed under Good Clinical Laboratory Practice (GCLP). The immunological data can be presented as recommended in EMA guidelines:[3]

- The percentage of “responders” or individuals who “seroconvert” [with 95% confidence interval (CI)]. Responders are either individuals developing an immune response above a certain threshold level or those who reach a certain minimum increment in antibody concentration/titer after

vaccination. These increments may or may not indicate protection. These criteria should be defined in the protocol prior to study initiation.

- Geometric mean concentration/geometric mean titers (with 95% CI) and pre-/postvaccination ratios (geometric mean ratios) provide absolute values and increase in antibody titers at defined time points after each vaccination.
- Reverse cumulative distribution (RCD) curves display percentage of vaccinees versus antibody levels, which allows a direct comparison of the responses achieved in different study groups.
- Data must be provided on antigen-specific T cell responses including cluster of differentiation (CD)4+ and CD8+cytotoxic T lymphocytes (CTLs) and relevant cytokines, if applicable.

Special features

Live attenuated/killed vaccines pose concerns about possible shedding of infectious agents, transmission to contacts, and a possible reversion to a more virulent state. Therefore, volunteers of such Phase I trials require intensive investigations in closely monitored clinical settings, including evaluation for any clinical signs of infection. The extent, route, and duration of shedding vary with the type of vaccine and route of administration. Immunocompromised persons should avoid contact with such vaccinees for a certain time period to avoid contracting an indirect infection.[2]

Phase II Studies

A candidate vaccine should proceed to Phase II clinical evaluation after achieving a satisfactory outcome in Phase I studies in terms of both safety and immunogenicity.[2] The transition from a controlled clinical setting to field evaluation incurs much greater monetary investment, hence stringent go/no-go criteria are observed by the developers.

Objective

The objective is to identify the vaccine preparation, optimal dose, and schedule to be taken up for confirmatory Phase III trials. These studies have the desired statistical power and a defined sample size, and hence are expected to provide a clinically meaningful outcome on the safety, immunogenicity, and efficacy end points.[2,4,5]

Phase II studies assess the impact of multiple variables on immune response, such as age, ethnicity, gender, and presence of maternal or pre-existing antibodies (in infants),[2,4,5] and evaluate the following: [2,4,5,9,10,11,12,13,14]

- Age of first administration of vaccine [e.g., during the development of Rotarix™, the age of first administration varied between countries depending on factors such as nutrition status, influence of maternal antibodies, and Expanded Program on Immunization (EPI) schedule].
- Number of vaccine doses (For Rotarix™, two and three doses were studied in Phase II studies, while for Gardasil™ the dosing schedule remained standard throughout clinical development).
- Sequence or interval between vaccine doses, route of administration, duration of immunity, potential need for booster immunizations, and qualitative aspects of the immune response.

In a Phase II trial of Gardasil™, incidence of persistent infection associated with HPV 6, HPV 11, HPV 16, or HPV 18 decreased by 90% in women allocated active vaccine compared with those allocated placebo over 36 months follow-up.[23] In the Phase I/IIb clinical trial of RTS, S, in addition to safety and immunogenicity, efficacy was evaluated by comparing the time to the first clinical episode of symptomatic *P. falciparum* malaria in children who had received RTS, S/AS02D malaria vaccine.[24]

During Phase II trials, if an immune correlate of protection is identified, it facilitates the interpretation of results in future clinical studies with immune response as end points.[2,3,4]

Study population

Phase II studies recruit hundreds to thousands of subjects from the target population at multicentric sites.[2,4,5] A large population allows researchers to conclude with confidence that the vaccine candidate is safe, sufficiently immunogenic, and maybe protective.

The study population can comprise adults, adolescents, children, infants, or even pregnant women, depending on the study objective. However, for a vaccine being developed for infants a step-down approach is usually followed wherein trials are conducted sequentially in adults, adolescents, children, and infants.[5] In one dengue vaccine test, adults, adolescents, and children were studied in a single trial.[25] Additionally, different populations can be enrolled in different countries to reduce costs, save time, and still collect meaningful data to be able to proceed to the next phase of development (e.g., Rotarix™ studies were conducted in parallel in Brazil, Mexico, Venezuela and Singapore).[9,26,27] Vaccines are also being developed for diseases prevalent in adults and adolescents. The most recent example is of the vaccine developed for cervical cancer (Gardasil™), in which case Phase II studies were conducted in both female and male populations aged 9-25 years.[28,29]

Study design, study site, and outcomes

In randomized controlled designs, the investigational vaccine is tested against either a placebo or another vaccine. These studies are usually conducted in community-based study sites where controlled trials are feasible, i.e., in places where information about the population (demography, migration, sex ratio, disease patterns, etc.) and the pathogen/disease of interest (different strains of pathogen, disease severity and pattern, seasonality) is available.

However, depending on the type of vaccine being studied, the study area can differ, e.g., for Gardasil™ the target population was young adults and adolescents, therefore the sources of the study population were colleges, universities, and their surrounding communities,[28,29] while rotavirus vaccine studies enrolled children and infants from communities, hospitals, and polyclinics.[26,27]

Phase II studies designed to report partial efficacy of a vaccine candidate are conducted in settings of high incidence of the infectious disease so as to be able to provide a good readout of the end point.[5] For example: Two similar Phase IIb studies were conducted with Rotarix™ in Latin America and Singapore to evaluate the safety, immunogenicity, and efficacy of different dose concentrations. Both studies were placebo-controlled, proceeded in parallel with almost similar sample sizes, and achieved good seroconversion rates, but the Latin America trial also demonstrated protective efficacy against two serotypes of rotavirus.[26,27]

It is clear from the clinical pathways of different vaccines that multiple Phase II studies need to be conducted to address the impact of variables such as dose, schedule, age group, and duration of follow-up before proceeding to Phase III studies.[2,5] To illustrate this, a list of published studies conducted during the clinical development of RIX4414 is provided in Table 2.[9]

During the development of Rotarix™, the effects of nourishment status of infants and interference with oral polio vaccine (live oral vaccine) were evaluated.[30,31] The vaccine formulation may also undergo changes as and when clinical development proceeds. For this reason, when a liquid formulation of Rotarix™ that does not require reconstitution was developed, it was tested against the lyophilized product in a Phase II study.[32,33]

As described for Phase I studies, the humoral and CMI response to the immunogen(s) in the vaccine candidates should be evaluated.[2,3,4] The mode of protection of the vaccine guides the measurement of immune response. With Rotarix™ (oral), serum IgA antibody concentration was monitored,[10] while in the case of Gardasil™ (parenteral), serum IgG was measured to determine the seroconversion rates.[34] Rarely, Phase II studies can be the definitive study for licensure with immune markers as outcomes. For example, the meningococcal C conjugate (MCC) vaccine was licensed on the basis of serological correlates of protection without efficacy data in United Kingdom.[35]

The type of adverse events (solicited, unsolicited, laboratory) collected during Phase II trials and the mode of collection (through visits to clinics and subject diary cards/questionnaires) are similar to Phase I trials. However, as Phase II studies are statistically powered and better designed, they are able to provide

meaningful differentiation in terms of distribution and differences in adverse events between groups. In some cases, Phase II data may also provide information regarding specific adverse events that should be evaluated more carefully in larger Phase III trials.[4]

Special features

Phase II trials can also provide preliminary information on protective efficacy through human challenge studies, wherein healthy participants are deliberately infected with the pathogen. Such studies are commonly referred to as Phase IIa studies and are appropriate only for selected diseases wherever it is scientifically and ethically justified, where the pathogen does not cause lethal infection and is not resistant to available treatment, and a complete and successful cure can be obtained. Human challenge studies have been conducted to test the preliminary efficacy of vaccine candidates against malaria, typhoid, and cholera.[36]

In case of RTS, S, investigators conducted multiple combined Phase I/IIa studies to assess preliminary efficacy.[7,8]

Such studies offer rapid assessment of the usefulness of a vaccine candidate in a limited number of subjects, thereby preventing the unnecessary exposure of thousands of individuals, mostly children and infants, in large Phase II/III trials to a potentially ineffective vaccine. It thus allows quicker vaccine development and serves as a go/no-go step for advancing development.

Phase III Studies

Objective

Pivotal Phase III trials, essential for registration and approval to market of a vaccine, assess the effect of the final formulation. These trials are typically designed to evaluate efficacy and safety. Vaccine Efficacy (VE) is defined as the percent reduction in incidence (of disease or infection) among the vaccinated. If incidence of disease in unvaccinated subjects is Iu and in vaccinated subjects is Iv, then the VE is calculated as:[2]

$(Iu-Iv/Iu) \times 100\% = (1- Iv/Iu) \times 100\% = (1-RR) \times 100\%$

where Iu = incidence in unvaccinated population; Iv = incidence in vaccinated population; RR = relative risk.

Occurrence of disease is the most common end point; however, the trial may be based on other clinical end points, such as incidence of infection or immunological correlates of protection.[2,4]

Study population

Phase III trials are large-scale clinical trials enrolling thousands of subjects from the target population. They are conducted in “field” conditions that are similar to future routine use.

Incidence of disease in the study population impacts the sample size: A low incidence means that large numbers of subjects are required to estimate vaccine efficacy in comparison to the numbers needed if disease incidence is greater. In diseases where an immunological end point correlates with clinical protection, it can be used as a primary efficacy end point, and smaller sample sizes often suffice.[2]

Study design, study site, and outcomes

RCTs are considered the “gold standard,” where participants are randomly allocated to receive either the investigational or the control vaccine (placebo, different vaccine, or nothing). A prospective RCT controls variables, prevents bias, and maximizes the chances of detecting a difference between the investigational vaccine and control.[2,3,4] Superiority trial designs are employed if there is currently no effective vaccine for the disease. They estimate the percentage reduction in the incidence rates of disease due to vaccine against the placebo comparator. For comparisons against existing vaccines, a noninferiority trial is planned to demonstrate that the relative risk of disease or infection with the new vaccine is not greater than the available vaccine.[2,3]

RCTs also provide early indication of likely long-term protection and the need for booster vaccination by following a subset of subjects for a longer duration.[2,3] A single study may not be able to address all questions; therefore it is often necessary to test the vaccine under different conditions, disease patterns, and populations.

To obtain vaccine efficacy, intervention studies (where a vaccine is allocated as an intervention to the study participants) or observational studies (where the individuals who have either received or not received the vaccine are observed/followed up) can be planned. Though observational studies are usually part of postlicensure assessment, they can be considered part of prelicensure evaluation in special situations. In such studies, participants are not allocated randomly and the individuals are not blinded to the vaccination. [2]

Vaccine efficacy can also be studied through group randomized trials. Such group/cluster randomized trials study the indirect protection offered by the vaccine in a community. However, for licensure studies, individual randomization studies are preferred because if the product is not giving any direct protection, it is unlikely to have any indirect effect. Further, safety evaluations are difficult to conduct in cluster randomized trials.[2,37]

Possible alternative approaches to RCTs include:[2,3]

- Secondary attack rate study or household contact study (can be randomized): These are preexposure cohort trials for infections with a high secondary attack rate. The unit of intervention may be an individual, family, or community. The indirect effect is the difference in the outcome in an unvaccinated individual when living in a vaccinated community or living in a comparable unvaccinated community. Such clinical trials are not done for vaccine licensure as yet but may become common in the near future.
- Observational cohort studies: May be considered where a RCT is not ethically justified or where the clinical end point requires long-term follow-up (e.g., hepatitis B vaccination in neonates) or where the number of individuals is too large to follow up.

To select a clinical trial site, it is critical to have studied the baseline epidemiology. This implies the need of data on regular census, migration, occupation, birth rate, age-specific death rates, age-specific incidence and prevalence of target disease, risk of transmission, and clinical manifestations including incidence and prevalence of comorbidities. An understanding of the full clinical spectrum of illness and seasonality of exposure is essential.[2] For example, before initiating an RTS, S trial at a field site in infants, the following parameters were evaluated:[38]

- Site-specific incidence rate of clinical malaria in children aged 1-5 years.
- Surveillance system to be used in the trial.
- Prevalence of malariometric indicators: Plasmodic index, splenomegaly, anemia, and parasite densities in children aged 1-5 years.

It is also recommended to define laboratory values for the population to avoid unnecessary exclusions.[2] In addition, comprehensive dialogue should be established with the local community representatives, explaining the critical aspects of the proposed study and assuring them that the best and ethical practices will be followed during the study. A dummy run of the informed consent procedure can be performed. The fact that the product being tested is investigational and may or may not provide any benefit to the participants, and that some participants will receive a placebo must also be conveyed.

In Phase III studies of vaccines against infectious diseases, the end point chosen should be of importance to public health and should also be clinically important. Often the evaluation of protective efficacy focuses on the ability of the vaccine to prevent clinical disease. However, if an organism causes a range of infections (e.g., from mild infection to clinical disease to severe disease), then the primary end point can be carefully selected in accordance with the proposed indication.[2,3] The various vaccine effects of interest that can be evaluated are:[39]

- Vaccine efficacy for susceptibility, colonization, progression, and pathogenicity and infectiousness.

- Total vaccine efficacy.
- Indirect effects of vaccination in those not vaccinated.
- Total effects of vaccination in those vaccinated.
- Overall population-level effects.

Vaccine efficacy is normally assessed on the basis of a single end point (e.g., severe gastroenteritis in Phase III study of Rotarix™[40]); however, a composite efficacy end point can also be studied [e.g., incidence of genital warts, vulvar or vaginal cervical intraepithelial neoplasia (CIN), or cancer, and incidence of CIN, androgen insensitivity syndrome (AIS) or cancer associated with HPV type 6, 11, 16, or 18 were composite end points for evaluating Gardasil™[41,42,43].

While in the Phase III trial of RTS, S, the primary end point was to assess efficacy against clinical malaria disease, there were multiple secondary end points including efficacy against severe malaria, incident severe anemia, and malaria hospitalization.[44] While selecting an end point, it is important to note that the more serious the end point, the lower is its incidence, which in turn lowers the probability of studying the impact of a vaccine. The primary end point should be carefully chosen because that will generally determine the size of the trial. The remaining outcomes can be studied as secondary end points.

To accurately identify the end points in clinical protection studies, confirmation of cases through laboratory methods, antigenic detection, and the clinical picture is necessary to support a clinical case definition.[2,3,5] Case definitions for the trial end points should be clearly defined in the protocol - e.g., during Phase III study of Gardasil™, investigators were given standard protocols for anogenital examination, conducting colposcopy, and classifying cervical samples on a standard scale.[41,42] Similarly, for the Rotarix™ trial, standard case definitions were used for defining an episode of severe gastroenteritis.[40] The validity of the diagnosis is most important for evaluation of efficacy or safety. If no well-validated methods for establishing infection and/or progression of infection exist during the period of prelicensure clinical development, then experimental laboratory methods can be used. The sensitivity, specificity, and reproducibility of the methods used to ascertain a case are included in the study reports. In clinical trials where prevention of disease is used as an end point, considerable efforts should be made to establish the immunological correlate of protection.[2,3,4,5] To determine immunogenicity, serological data are usually collected from a subset of the immunized population at predefined intervals and from persons classifiable as vaccine failures.[2,3,4]

In the prelicensure studies, it is recommended to enroll approximately 3000 subjects.[3] However, where Phase III studies are designed with safety as the primary end point, huge sample sizes are seen, e.g., >37000 subjects were enrolled in a 7-valent pneumococcal conjugate vaccine study,[45] while for Rotarix™[46] and RotaTeq™[47] ~63,000 and ~70,000 infant subjects, respectively, were assessed to detect the risk of intussusception.

If the phase III results demonstrate efficacy and safety, the manufacturer of the vaccine can submit an application to the national regulatory authority to license and market the product.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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Figures and Tables

Table 1

Guidelines relevant to clinical evaluation of vaccines

Name of guideline	Remarks
ICH: E6: Guideline on Good Clinical Practice	An international ethical and safety quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects
Good Clinical Practice Guidelines for Clinical Research in India	To ensure uniform quality of clinical research throughout the country and to generate data for registration for new drugs before use in the Indian population
ICH: E8: General Consideration for Clinical Trials	Describes internationally accepted principles and practices in the performance of both individual clinical trials and overall development strategy for new medicinal products
Schedule Y: Requirements and Guidelines for Permission to Import and/or Manufacture of New Drugs for Sale or to Undertake New Trials	Schedule Y is the CDSCO-enforced law in India established under the Drugs and Cosmetics Act, 1945. This regulation is followed when conducting clinical trials in India
Annex 1: WHO Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations	Guidelines for national regulatory authorities, vaccine manufacturers, clinical researchers, and investigators
Guidelines on Clinical Evaluation of New Vaccines (EMEA/CHMP/VWP/164653/2005)	Provides guidance on the design of clinical development programs for new vaccines that are intended for pre- and postexposure prophylaxis
Guidelines on Adjuvants in Vaccines for Human Use (EMEA/CHMP/VEG/134716/2004)	Addresses the quality, nonclinical, and clinical issues arising from the use of new or established adjuvants in vaccines
Brighton Collaboration	Provides case definition documents that are intended to standardize collection, analysis, and presentation of vaccine safety data following immunization
Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (FDA/CBER/ 2007)	Provides sponsors, monitors, and investigators of vaccine trials, with recommendations on assessing the severity of clinical and laboratory abnormalities in healthy adult and adolescent volunteers enrolled in clinical trials
ICH: E9: Statistical Principles for Clinical Trials	Intended to give direction to sponsors in the design, conduct, analysis, and evaluation of clinical trials of an investigational product in the context of its overall clinical development
ICH: E3: Structure and Content of Clinical Study Report	Compilation of clinical study report in a format acceptable to all regulatory authorities of ICH region

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CDSCO = Central drug standard control organization

Table 2

Published Phase I-III studies on the human-attenuated rotavirus vaccine RIX4414

Product	Phase	Principal aim	No. of subjects/RV serotypes	Most relevant results
89-12 10^5 pfu	I	Safety and immunogenicity in adults, and in rotavirus-seropositive children and infants. Placebo-controlled	34 adults; 40 positive 2-12-year-old children; 9 and 42 infants 6-26 weeks receiving 1 and 2 doses, respectively.	Proof of concept: Acceptable tolerance and safety; high vaccine shedding; high IgA seroconversion
89-12 10^5 pfu	II	Safety, immunogenicity, and efficacy of two doses in infants. Placebo-controlled	215 healthy infants 10-16 weeks of age/G1 rotavirus season	Fever >38.1°C only significant side effect; 95% seroresponse; 89/78% efficacy against all/severe RVGE
89-12 10^5 pfu	II	Second year follow-up of previous study	184 infants available for follow-up/G1 rotavirus season	59-90% efficacy against all/severe RVGE for year 2
RIX4414 $10^{4.7}$-$10^{6.4}$ ffu	I	Similar to Phase I study. Includes evaluation of doses and of a buffer for vaccine dilution. Finnish children; placebo-controlled	33 adults, 26 positive 1-3-year-old toddlers; 192 infants divided into 4 groups	No significant side effect; 73-96% seroconversion and 38-60% shedding by ELISA both increasing with increasing doses; catch-up, but no booster effect with second dose
RIX4414 $10^{5.2}$ and $10^{6.4}$ ffu	II	Safety, immunogenicity, vaccine shedding, and effect of breastfeeding and other coadministered vaccines. Placebo-controlled	529 infants divided into 3 groups received either the lower or the higher concentration or placebo in a 2:2:1 randomization	No significant side effects; 81-88% vaccine take in lower/higher concentration and 54-58% vaccine shedding by ELISA. 10-12% reduced take with breastfeeding

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*Similar to 10^6 ffu, RVGE = Rotavirus gastroenteritis, DTP-HepB-Hib = Diphtheria-tetanus-pertussis, hepatitis B and *Haemophilus influenzae* type B vaccine, DTP-Hib-IPV = Diphtheria-tetanus-pertussis, *Haemophilus influenzae* type B and inactivated polio vaccine, ELISA = Enzyme-linked immunosorbent assay, ffu = focus-forming unit, GE = Gastroenteritis, Ig = Immunoglobulin, IS = Intussusception, pfu = plaque-forming unit, RVGE = Rotavirus gastroenteritis