Paper 27

Vaccines: Benefits for public health

Statistical programming specificities in clinical trials

Olfa Guaddoudi, 4Clinics, Waterloo, Belgium
Emeline Burhin, 4Clinics, Waterloo, Belgium
Julie Harriague, 4Clinics, Paris, France
Mohamed Oujaa, 4Clinics, Waterloo, Belgium
Mohamed Amakrane, 4Clinics, Waterloo, Belgium
Mickaël Borne, 4Clinics, Paris, France

ABSTRACT

Vaccines play a major role in preventing infectious diseases, and vaccination is probably one of the biggest achievements in the history of medicine. Vaccination programs save lives each years, have contributed to the eradication of smallpox and translate into savings of billions of dollars each year, demonstrating the importance of vaccines and their benefits to public health, both at the level of the individual and the population.

Vaccines are generally administered to healthy individuals as preventive measures to help the body develop immune responses by imitating an infection, which almost never causes illness but can generates minor symptoms, such as fever. After vaccination, the body is left with an immune memory that will remember how to fight this infection or disease in the future.

Vaccines are developed, tested, and regulated in a very similar manner to other drugs. Vaccines, like drugs, are medical products, can cause adverse events, contain multiple ingredients and have the potential to interact with pathogens, drugs and other vaccines. However, vaccines present some specificities that have an impact on their development. Vaccines are almost always biological products that must be kept refrigerated from production to use. Vaccines are given in global vaccination programs to which the whole population must adhere, and may require repeated dosing to sustain protective efficacy. Vaccine specificities impact development from study design to safety monitoring and require adjustment of statistical and programming activities.

INTRODUCTION

The main theme of the 2019 PhUSE conference is "*the ever-changing landscape, and the implications for the industry*". Vaccine development appeared to us as an interesting example of the need for adaptability and the requirement for always greater transparency for the pharmaceutical industry.

Vaccines are a major public health tool for the prevention and control of infectious diseases. They are estimated to save 2–3 million lives each year [1]. They led to the global eradication of smallpox, which was officially declared in 1980 [2], and have greatly reduced the incidence of several infectious diseases such as poliomyelitis, tetanus and measles [3]. Licensed vaccines are now available to prevent more than 30 different infectious diseases [3], and new vaccines are continuously being developed. Furthermore, vaccines are also being developed to target autoimmune diseases and cancer.

However, vaccination has rapidly become highly controversial, notably because of an erroneous link between vaccines and autism [2]. Lack of vaccine acceptance is a reason why vaccines are underused [2]. It is therefore crucial to provide high-quality evidence that vaccines are immunogenic, effective and have an adequate safety profile to educate people about the benefits of vaccination, both for themselves and for the general population.

WHAT IS A VACCINE?

A vaccine is a biological preparation aiming to induce a protective immune response to a specific pathogen, without the risk of acquiring the disease or its potential complications [3]. They can be used to prevent (prophylactic vaccines) or treat disease (therapeutic vaccines) [4].

Vaccines contain weakened or killed forms of the pathogen, or only parts of the pathogen (Table 1). They may also contain adjuvants to stimulate or modulate the immune responses induced to the vaccine's antigens [1, 3].

Table 1: Types of vaccines

Type of vaccine	Explanation	Examples
Inactivated vaccines	Infectious agent "killed" by chemicals or heat	Whole-cell pertussis Rabies Injected polio vaccines
Live attenuated vaccines	Weakened version of the infectious agent, usually a virus	Mumps-measles-rubella (MMR) Varicella Oral polio vaccines Yellow fever
Subunit vaccines	Only antigenic parts of the infectious agent (proteins, sugars)	Influenza Tetanus toxoid Acellular pertussis Pneumococcal vaccines

Adapted from Pitt and Harriague, *Medical Writing* 2018 [1]

HOW DO VACCINES WORK?

Like natural infections, vaccines act by initiating an innate immune response, which in turn activates a specific adaptive immune response [1]. Innate immunity represents the first line of host defense against pathogens but it is not specific. Adaptive immunity provides the second line of defense. It is highly antigen-specific and can provide the immune memory that protects against re-infection by the same pathogen. Depending on the pathogen and the disease to be prevented, a vaccine may require the induction of different mechanisms to be effective:

- Humoral immunity (i.e., antibodies produced by B cells)
- Cell-mediated immunity (i.e., T cells)

Most current vaccines work through the induction of specific antibodies [5].

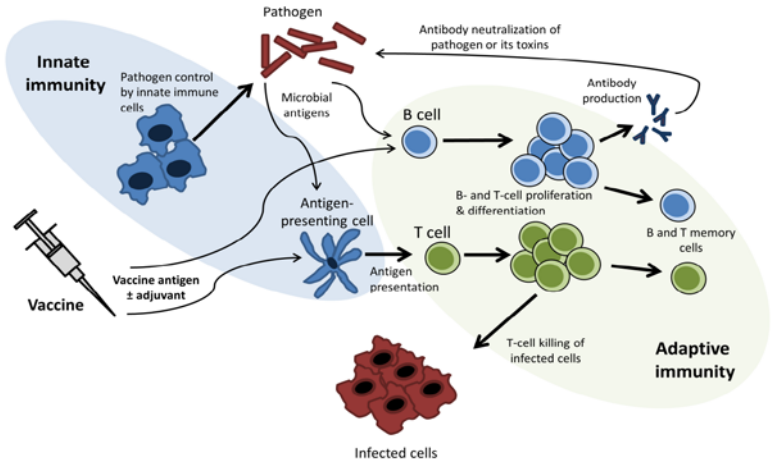

Figure 1: Vaccines' mode of action

Adapted from Pitt and Harriague, Medical Writing 2018 [1].

In addition to protect vaccinated individuals, vaccines can also protect unvaccinated people by reducing person-to-person transmission. This indirect protection is termed "community" or "herd" immunity (Figure 2) [1].

Vaccination of pregnant women can also protect infants in their first months of life due to transfer of maternal antibodies through the placenta.

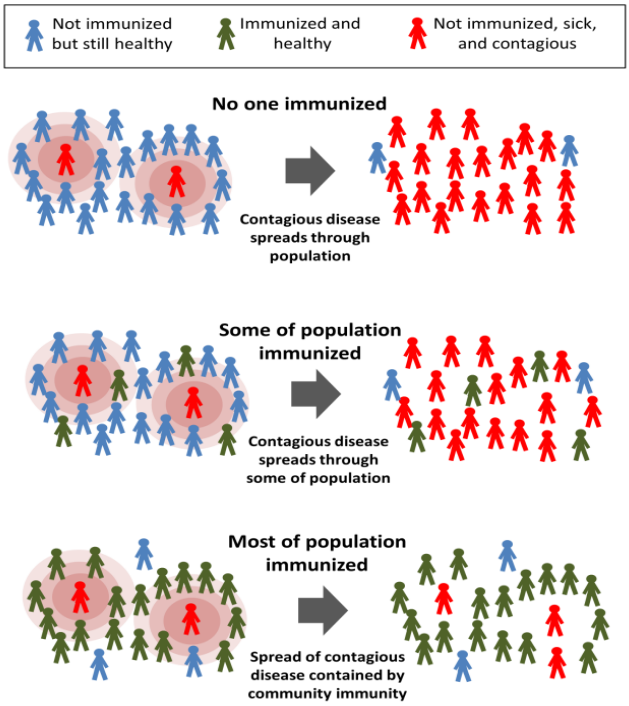

Figure 2: Indirect benefits of vaccination
Reused with permission from Pitt and Harriague, Medical Writing 2018 [1]

ARE VACCINES SAFE?

Like all medicines, vaccines can have adverse events. However, because vaccines are mostly given as preventive measures to healthy people, a highly positive benefit–risk ratio is essential [3]. Vaccine safety is rigorously evaluated in the preclinical and clinical phases of development but is also continuously monitored once the vaccine is on the market [6].

Most reactions to vaccines are mild and transient and are typically centered at the injection site (e.g., pain, redness and swelling). Systemic reactions can also occur (e.g., fever).

VACCINE DEVELOPMENT

MENTAL MAP OF STATISTICAL AND PROGRAMMING KEYWORDS

Many different statistical and programming concepts are used in vaccine development, some of which are specific to vaccines.

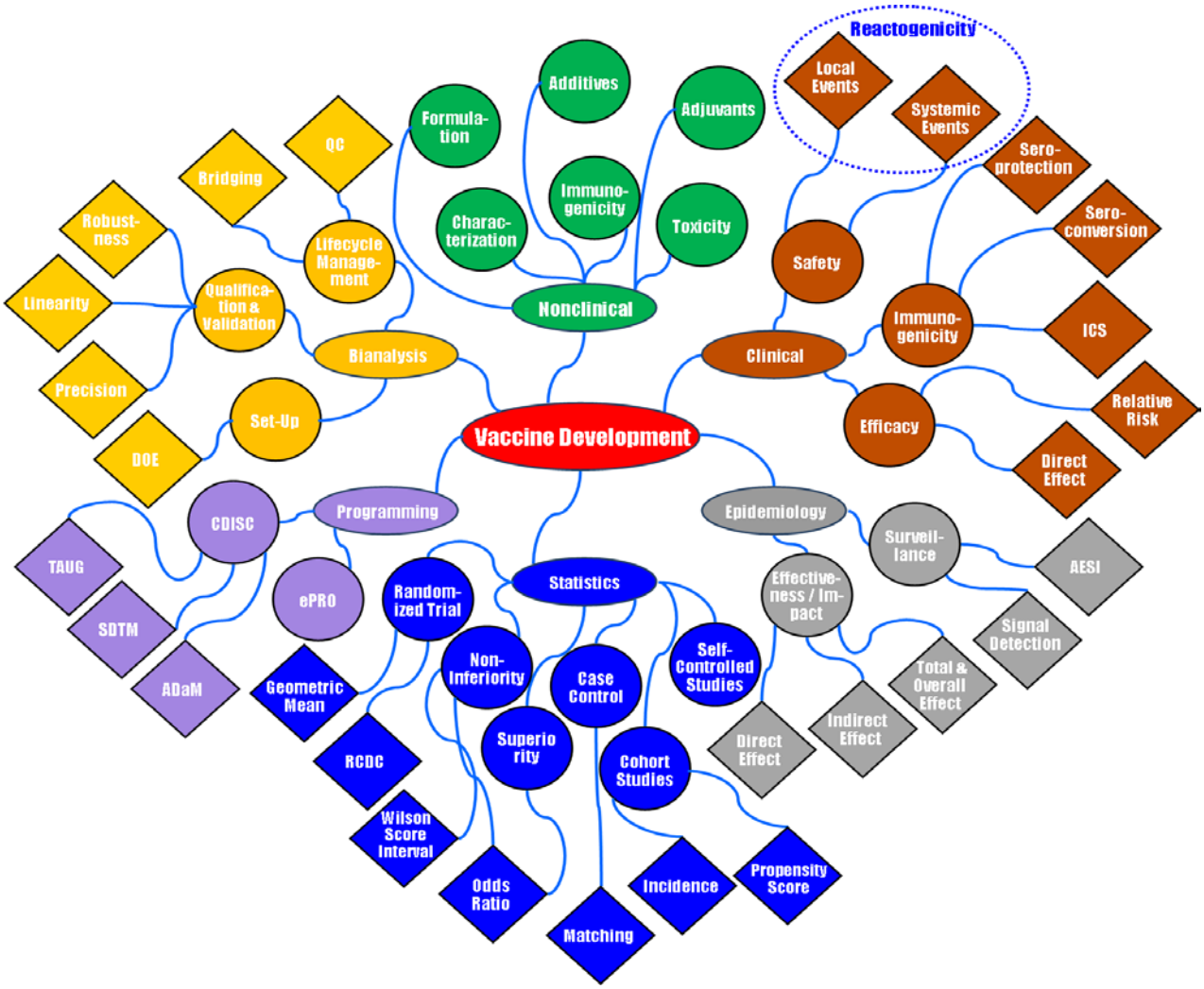

Figure 3: Mental map of statistical and programming keywords in vaccine development

NONCLINICAL EVALUATIONS

The aim of nonclinical studies is to define in vitro and in vivo characteristics of candidate vaccines.

Multiple statistical analyses can be performed to check the vaccine production, the biological activity of the vaccine (i.e., potency), the stability of the batch released [7]. Other independent laboratory evaluations, often using complex algorithms, are required to analyze the variability of production methods. Toxicity will be evaluated to detect potential toxic effects of a vaccine and its local tolerance. Then, immunogenicity studies can be conducted to assess the immune responses to the antigens or pharmacodynamic studies to analyze the pharmacological properties of an adjuvant.

The Biostatistician should take into account the following considerations when performing nonclinical evaluations of vaccines:

- If an adjuvant is used, the effect of the adjuvant as well as its toxicity should be analyzed. *"Adjuvants are any substances that are intended to enhance relevant immune response and subsequent clinical efficacy of the vaccine."* [7].
- If additives are used, toxicity studies of the additives alone should be performed first
- The type of vaccine (inactivated, live attenuated, subunit or combined vaccines) should be taken into account when analyzing immunogenicity

BIOANALYSIS

To assess the immunogenicity of the vaccine, specific assays (e.g., ELISA, neutralization assay) are required. Therefore, Biostatisticians and SAS programmers are needed *"to support laboratory scientists in the Set-Up of the assay, providing Design-Of-Experiment (DOE) tool and allowing for first evaluation of method performances.*

During crucial Qualification and Validation steps, statistical analyses are required by the authorities to ensure accuracy, precision, linearity, and robustness of the assay. Statistical support is also required to determine analytical range (from Lower Limit of Quantitation - LLOQ - to Upper Limit of Quantitation - ULOQ), Limit of Blank (LoB), Limit of Detection (LoD), and to set Quality Controls (QC) acceptance criteria.

Once assay is validated, critical equipment and reagents bridging as well as QC panels and QC charts need statistic input to ensure assay stability over time." [8].

SPECIFICITIES IN STATISTICAL PROGRAMMING FOR VACCINE TRIALS

CLINICAL TRIALS

The conduction of clinical trials (from Phase I to Phase III) is crucial for decisions about vaccine development. Safety, immunogenicity and efficacy are tested in human subjects before licensure.

Here are some statistical specificities in vaccine trials:

- Reactogenicity analysis: refers to predefined immediate short-term reactions to vaccines.
- Management of overlapping adverse events, using the maximum value of the measure for statistical analyses (e.g., maximum number of daily vomiting episodes).
- Safety analysis: refers to safety endpoints such as unsolicited adverse events (serious or non-serious), laboratory data and deaths.
- Immunogenicity assessment: refers to antibody concentrations, seroprotection (i.e., antibody response able to prevent infection), seroconversion (i.e., change from a seronegative to a seropositive status) or cell-mediated immunity. If a booster dose of the vaccine is necessary, primary and booster vaccinations should be analyzed in distinct analyses or in distinct studies
- Efficacy analysis: refers to the protection provided by the vaccine against the infection or the disease to be prevented
- If several vaccines are administered at the same time, it is important to be able to distinguish between the different administration sites when an assessment is performed. This impacts CDISC SDTM deliverables as described in the provisional Therapeutic Area Data Standards User Guide for Vaccines [8].

Maternal antibodies found in the newborn at early stage of life could interfere with the vaccination and its effect. When vaccines are given to newborns, statistical models measuring the decay of these maternal antibodies can be used to make final decision regarding the vaccination schedule.

The vaccine large-scale implementation could lead to additional considerations at the population level. The measure of the minimum vaccination rate to achieve herd immunity is an important indicator for Health Authorities and governments. Public health policies should be then implemented to reach the most effective protection for the whole population.

Real-life settings can be a challenge to measure efficacy. Specific study designs such as the "ring vaccination" can be implemented to deal with outbreaks, as it was done recently for Ebola phase III clinical trial. In this type of study, only people in contact with a sick person are vaccinated, and specific statistical methods are used to support this specific design [9].

Another particularity is that vaccine statistical evaluation is often linked to multiple global factors such as patients' immune and genetic status or previous adverse events, which may have an impact on the statistical model used to conclude.

The reverse cumulative distribution curve is a graphic tool that provides a complete view of the serology data [10]. It allows rapid visualization of the different distributions and simplifies comparisons. As shown in Figure 3, the antibody titer is higher (i.e., shifted to the right) in the Vaccine group than in the Placebo group at Day 28, whereas the curves are roughly similar between groups at Baseline.

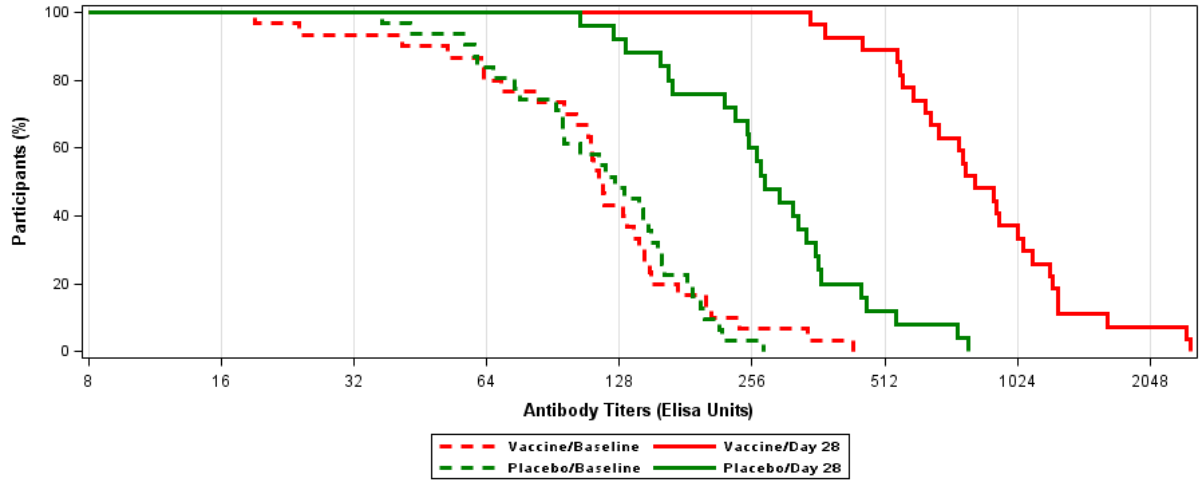

Figure 3: Example of reverse cumulative distribution curves

When a vaccine is given, expected reactions (both local and systemic) are analyzed for a fixed period of time, generally 7 days after each dose.

Table 2: Solicited adverse events generally analyzed

Local adverse events	General adverse events
Pain	Fatigue
Tenderness	Headache
Erythema/Redness	Fever
Swelling	Shivering
Induration	Gastrointestinal symptoms
	Myalgia
	Arthralgia

In the example below (Figure 4), local symptoms are more frequent in the Vaccine group than in the Placebo group after both doses, especially grade 2 and 3 events.

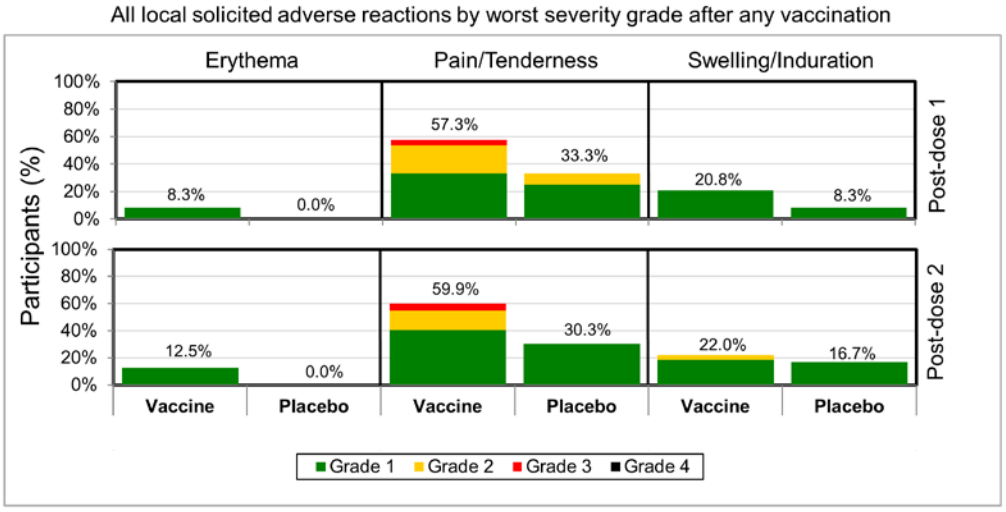

Figure 4: Example of reactogenicity data

EPIDEMIOLOGY – POST-LICENSURE STUDIES

After the licensure of a vaccine, observational studies are frequently conducted to continue evaluating the vaccine safety and effectiveness in the general population. Post-licensure safety surveillance studies can be active or passive and usually monitor adverse events of special interest (AESI).

Each country has a strategy for vaccine surveillance (monitoring and reporting adverse events during immunization programs). For example in the United States, there is a Vaccine Adverse Event Reporting System (VAERS) [11]. When a doctor, nurse or consumer believes that a vaccine recipient had a significant adverse effectthey can file a report in this system, which is continuously monitored for trends in the data. Once alerted, scientists and public health officials will turn to other systems, like the Vaccine Safety DataLink, to analyze whether the issue is causally or coincidentally related to the vaccine.

In contrast to clinical trials that measure direct effects of vaccines (i.e., efficacy), post-licensure studies measure both direct and indirect effects (i.e, effectiveness). Biostatisticians have thus an important role to ensure that the appropriate study design is used (e.g., cohort studies, case control studies, cluster studies).

CONCLUSION

Vaccines play a major role in preventing infectious diseases, through individual or community immunity. They have been recently extended to the prevention and treatment of cancer or autoimmune diseases.

Vaccine development is continuously evolving to optimize efficacy and minimize reactogenicity and safety issues.

The complexity and differences between drug and vaccine development require adjustment of statistical and programming activities, and thus need trained team with combined biology/vaccine and statistics knowledge.

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CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the co-authors at:

Olfa Guaddoudi
4Clinics Belgium
Drève Richelle 161, Bat C
B-140 Waterloo, Belgium
Work phone: +32 2 609 47 25
Email: oguaddoudi@4clinics.com

Mickaël Borne
4Clinics France
18-26 rue Goubet
75019 Paris, France
Work phone: +33 1 84 19 35 59
Email: mborne@4clinics.com