PP27

Vaccines: Benefits for public health

Statistical programming specificities in clinical trials

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1) Introduction

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]. However, their modes of action, benefits and risks are sometimes not well known, and analyzing data from vaccine clinical trials requires good knowledge of this therapeutic area.

2) How do vaccines work?

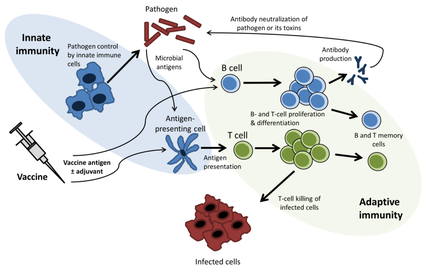


Figure 1: Vaccine' mode of action

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

Like natural infections, vaccines act by initiating an innate immune response, which in turn activates an adaptive immune response [1, 2].

Adaptive immunity 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., killing by T cells)

Most current vaccines work through the induction of specific antibodies [2].

3) What are the benefits of vaccines for public health?

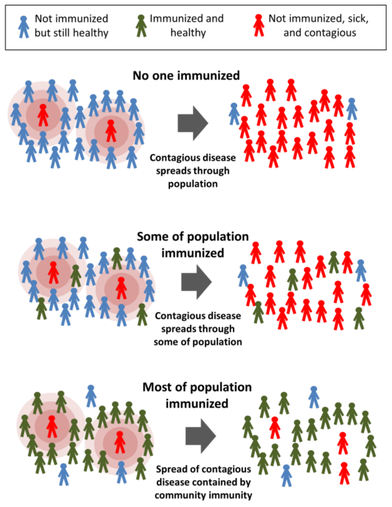




Figure 2: Indirect benefits of vaccination

Reused 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 [1].

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

4) 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 [4].

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

5) What are the statistical programming specificities in vaccine clinical trials?

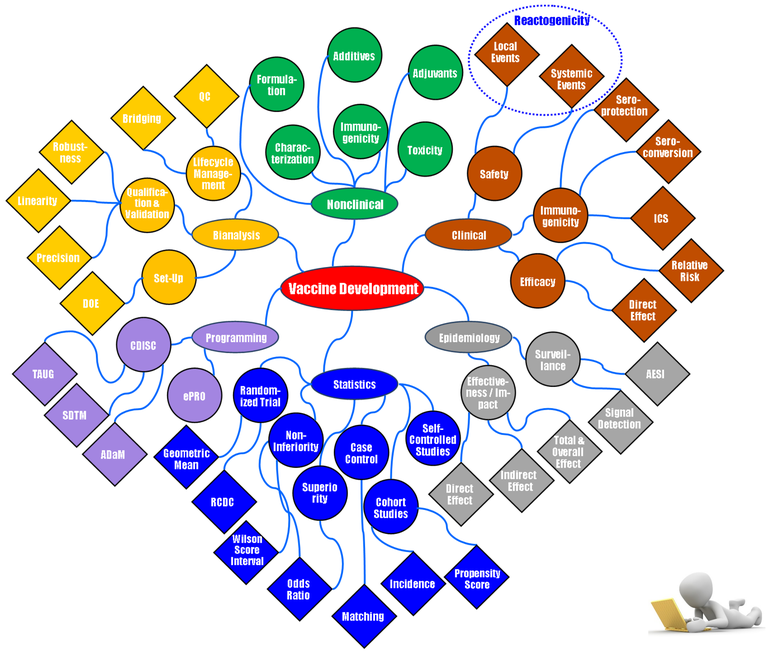


Figure 3: Mental map of statistical and programming keywords in vaccine development

Vaccine development is a complex process that differs from other therapeutic areas. Vaccine specificities may impact study design, statistical methodologies and programming activities from nonclinical studies to post-licensed epidemiological studies in real life. Examples of specificities:

1) Reactogenicity analysis, which describes expected short-term reactions to vaccines.
2) To improve long-term protection, a booster dose of the vaccine is often necessary at a given interval after the primary series. Results from primary and booster vaccinations should be analyzed separately, in distinct analyses or in distinct studies.
3) Maternal antibodies found in newborns can interfere with vaccination. When vaccines are given to newborns, statistical models measuring the decay of maternal antibodies over time may be used to make final decision regarding the vaccination schedule.
4) Estimation of the minimum vaccination rate necessary to achieve herd immunity, which is important for health authorities and governments.
5) Vaccine specificities may impact CDISC deliverables, especially SDTM, as described in the provisional CDISC Therapeutic Area Data Standards User Guide for Vaccines [5].
6) The use of specific study designs such as the "ring vaccination" (i.e., vaccination of the people in contact with a sick person) to deal with outbreaks, as recently done for an Ebola phase III clinical trial [6].

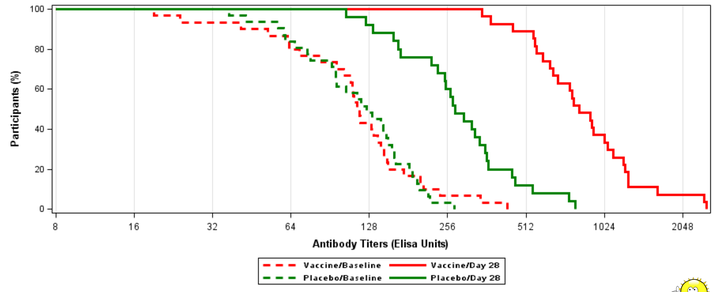


Figure 4: Example of reverse cumulative distribution curves

The reverse cumulative distribution curve is a graphic tool that provide a complete view of the serology data [7]. It allows rapid visualization of the different distributions and simplifies comparisons.

At Day 28, the antibody titer is higher (i.e., shifted to the right) in the Vaccine group than in the Placebo group, whereas the curves are roughly similar between groups at Baseline.

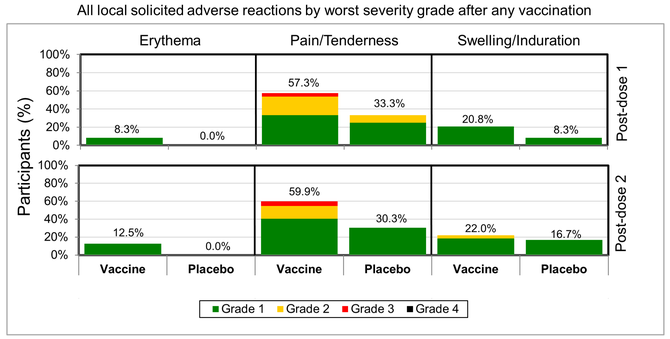


Figure 5: Example of reactogenicity data

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.

Here, local symptoms are more frequent in the Vaccine group than in the Placebo group after both doses, especially grade 2 and 3 events.

Table 1: Solicited adverse events generally analyzed:

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

6) 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.

References

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