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Statistical Issues in Vaccine Safety Evaluation

By *C. Paddy Farrington,*[1] *Heather J. Whitaker,*[1] *and Mounia N. Hocine*[1,2]

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Abstract: This article describes some of the main statistical methods used to evaluate the safety of vaccines. The methods are illustrated using examples of public health concerns that arose following claims of associations, both real and unproven, between vaccination and adverse events. Prelicensure evaluation, surveillance methods, and observational study designs including case-control, cohort, and case-only methods are discussed.

1 Introduction

Mass vaccination programmes have greatly reduced the **incidence** of many common infections of childhood. However, since vaccines are often administered to healthy children, there is heightened public interest in their safety. Because vaccines are used on a large scale, rare reactions can result in substantial numbers of adverse events, with potentially disastrous consequences for public confidence in vaccination programmes. Evidence of **safety**, and rapid identification of potential problems, are thus essential to the success of vaccination programmes. In this article, some of the statistical methods used for monitoring vaccine safety are described.

2 Prelicensure Evaluation of Vaccine Safety

Vaccines are evaluated rigorously for safety and efficacy prior to being licensed. At the developmental stage, an experimental vaccine is evaluated extensively in the laboratory. Once sufficient data have been accumulated in the laboratory, the new vaccine is evaluated in humans. Since the 1940s, such evaluations have been based on the methodology of **clinical trials** [1].

[1]Open University, Milton Keynes, UK
[2]INSERM, Villejuif, France

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2.1 Phase I and Phase II Studies

Phase I studies are the first trials in which the experimental vaccine is used in humans. They are usually conducted in small numbers of adult volunteers. In view of their small size, the safety data available from phase I trials is limited to documenting common reactions and identifying serious or unusual side effects.

The next stage is to evaluate the vaccine in **phase II studies**, which are conducted in those individuals for whose benefit the vaccine was developed. Phase II studies are usually comparative, involving one or several vaccine groups and a control group, and are undertaken using the methodology of double-blind (*See* **Single and Double-Blind Procedures**), randomized controlled trials (*See* **Clinical trials, overview**) [2]. Phase II trials are of appreciable size, typically including 50–500 participants. However, sample sizes of this order are sufficient only to compare rates of common adverse reactions.

2.2 Phase III Trials

The primary purpose of a **phase III** vaccine trial is to assess the protective efficacy of the vaccine, and to provide further evidence of safety. Phase III trials typically involve 1000–50 000 participants. They are usually double blind and randomized. A phase III trial provides a unique opportunity to assess the safety of the vaccine in a large study under experimental conditions. However, even the largest phase III vaccine trials are too small, and follow-up periods are too short, to provide robust evidence of safety in respect of rare adverse events, or delayed events. This must be achieved by surveillance after the vaccine is licensed (*See* **Phase IV Trials**; **Postmarketing surveillance of new drugs and assessment of risk**).

3 Postlicensure Surveillance of Vaccine Safety

Once a vaccine has been shown to be effective, is licensed and is recommended for routine use in mass vaccination programmes, it is necessary to monitor its safety using epidemiological **surveillance**.

3.1 Two Examples

Surveillance is necessary both to identify rare or delayed adverse events that cannot be picked up in clinical trials, and to monitor safety more generally.

3.1.1 Example 1 The Cutter Incident

The 1954 field trial of the **Salk inactivated polio vaccine** remains to date one of the largest vaccine trials ever undertaken. The trial involved 1.8 million children in the United States, of whom 400 000 were randomly assigned to vaccine or **placebo**, and the remainder enrolled in an open study. On April 12, 1955 the Salk vaccine was declared to be safe and effective. The vaccine was licensed and mass immunization began a few days later. On April 26, reports were received of children who had become paralyzed after receiving polio vaccine from batches made by Cutter Laboratories. It was found that a production fault had caused live virus to enter these vaccines, causing 163 cases of paralysis and 10 deaths, and undermining public confidence in an otherwise safe and effective vaccine [3, 4].

3.1.2 Example 2 Swine Flu Vaccine and Guillain-Barré Syndrome

In 1976 concern grew in the United States that an epidemic of influenza A virus of a type commonly known as *swine flu* was about to occur. Accordingly the authorities organized a mass vaccination campaign using swine flu vaccines. Between October 1 and mid-December, some 45 million doses of vaccine were administered. However, on December 16 the immunization programme was suspended following reports of Guillain-Barré syndrome (GBS), an uncommon disorder resulting in paralysis of the limbs, occurring in close temporal relation with swine flu vaccination [5].

Note that in both the Cutter incident and the swine flu episode, the association between vaccination and the adverse event became apparent from spontaneously reported instances of adverse events (*See* **Toxicity (Adverse Events)**) by medical personnel, owing to the close temporal relationship between vaccination and the adverse event.

3.2 Temporal Association and Spontaneous Reporting Systems

Spontaneous reporting systems rely on individuals reporting adverse events which they believe may be causally associated with particular vaccines. Such systems have been formalized in several countries, for example through the "Yellow Card" system in the United Kingdom and the Vaccine Adverse Event Reporting System (VAERS) in the United States [6].

Spontaneous reporting systems, however, suffer from two main shortcomings. First, it is seldom possible to attribute **causality** or estimate effect parameters such as **relative risk**s, since the data are not controlled. It is sometimes possible, however, to identify changes in reporting patterns, using measures such as proportional reporting ratios [7]. A second shortcoming is that reporting may be incomplete or inaccurate. This may mean that some adverse events are missed, or that their importance is underestimated. The experience of Urabe mumps vaccines and aseptic meningitis is a case in point.

3.2.1 Example 3 Urabe Mumps Vaccine and Aseptic Meningitis

Measles, mumps, and rubella (MMR) vaccines were introduced in the United Kingdom in 1987. Spontaneous surveillance methods had suggested that there was a small risk (between 0.4 and 10 per million doses) of aseptic meningitis after mumps vaccine. A subsequent study found that the true risk of aseptic meningitis in the period 15–35 days after receipt of an MMR vaccine containing the Urabe mumps strain was much higher, about 1 in 11 000 doses [8]. As a result of this finding, Urabe-containing vaccines were replaced by other types of vaccines for which there was no evidence of an association with aseptic meningitis.

Following this experience, active surveillance methods based on record linkage between hospital and vaccination databases were put in place, to provide more reliable estimates of postvaccination risks than those available from spontaneous reporting systems [9].

In most instances, adverse events may occur for reasons unconnected with vaccination. Thus, observing a temporal association provides no evidence of causal association. To demonstrate a causal association, it is necessary to estimate the rate at which events occur in temporal association with vaccination, relative to the rate at which they would have occurred in the absence of vaccination, and provide convincing statistical evidence that this relative rate is greater than 1. The following controversies exemplify the risks of placing too much reliance on close temporal association as an indicator of causality.

3.2.2 Example 4 DTP Vaccine and Brain Damage

The diphtheria-pertussis-tetanus (DTP) vaccine was introduced in the United Kingdom in the 1950s, leading to a large reduction in whooping cough. By 1974, 81% of children in the United Kingdom were vaccinated with the DTP vaccine. However, in 1974, public confidence in the vaccine was undermined following intense media coverage of a report describing 36 cases of neurological complications occurring in close temporal association with DTP vaccination [10]. The idea took hold that DTP vaccine caused brain damage, and as a result the coverage of the vaccine dropped sharply to 31%, resulting in the reemergence of whooping cough epidemics. However, subsequent epidemiological investigations and close scrutiny of the evidence led to the conclusion that severe side effects of the DTP vaccine, including brain damage, are so rare that they defy measurement [11].

3.2.3 Example 5 MMR Vaccine and Autism

In 1998, a report was published suggesting that MMR vaccine might cause autism. This report was based on 11 children who were reported to have suddenly experienced serious behavioral problems within 2 months of receiving the MMR vaccine [12]. The report received wide publicity in the media, and generated a controversy that threatened to undermine the MMR vaccination campaign. MMR vaccine coverage dropped from 92 to 60% in some areas, measles outbreaks occurred resulting in the first death from measles in a decade. Several large epidemiological studies were undertaken, none of which confirmed the association between MMR vaccination and autism [13–15].

In both examples, much publicity was given to **serious adverse events** occurring shortly after vaccination. However, subsequent epidemiological investigations did not confirm a causal link. It is reasonable to conclude that the observed temporal associations were chance events, the incidence of the events coincidentally peaking at the recommended ages for vaccination.

4 Postlicensure Study Designs for Evaluating Vaccine Safety

Surveillance systems based on spontaneous reporting play an important role in monitoring vaccination programmes and generating hypotheses. However, they can seldom be used for testing hypotheses and providing reliable estimates of vaccine-associated risks, owing to reporting biases and the difficulty in establishing appropriate baseline rates. Instead, epidemiological studies are required.

4.1 Cohort Studies

In **vaccine safety** evaluation, **cohort studies** are usually retrospective, based on preexisting databases such as the Vaccine Safety Datalink (VSD) database in the United States [16] and the General Practitioner Research Database (GPRD) in the United Kingdom [17], or using several databases combined by **record linkage** techniques. Two basic types of cohort studies are used: parallel group and risk-interval cohort studies.

4.1.1 Example 6 Organic Mercury in Vaccines and Developmental Disorders

Some vaccines contain thiomersal, a preservative made from ethyl mercury. Concern has been expressed that the administration of vaccines containing thiomersal might cause developmental disorders in later life. A retrospective parallel group cohort study was undertaken [18]. Exposure groups were defined according to the cumulative dose of ethyl mercury received through the administration of thiomersal-containing vaccines by age 6 months. The subsequent occurrences of developmental disorders in the different exposure groups were then analyzed using **survival analysis** techniques, including **Cox regression** [19]. Little evidence was found that exposure to thiomersal-containing vaccines cause neurodevelopmental disorders.

In many cases, the biological mechanism through which a vaccine may cause adverse events is short lived. Thus it is appropriate to represent the putative vaccine effect by a **step function** taking a value β within a predefined risk period after vaccination, and 0 outside this risk period. The value β is the logarithm of the **hazard ratio** (or incidence ratio) over the risk period. In some cases, it is appropriate to use several risk periods, to represent different effects, or to obtain a more accurate impression of how the vaccine-associated risk varies with time since vaccination. Exposure is thus a time-varying **covariate**.

4.1.2 Example 7 Sudden Infant Deaths and DTP Vaccine

The possible association of DTP vaccine and sudden infant death syndrome (SIDS) was investigated in a risk-interval cohort study [20]. Four postvaccination risk periods were used: 0–3, 4–7, 8–14, and 15–30 days postvaccination. Other times were allocated to the baseline or control period. There was no evidence of a positive association between DTP vaccination and SIDS: for the 0–3 day risk period, for example, the **hazard ratio** was 0.18, with 95% confidence interval (CI) (0.04, 0.8).

The apparent protective effect in this study may be due to a **selection bias**, immunizations being postponed if the child is in poor health. Such biases potentially affect all risk-interval methods [21].

4.2 Case–Control Studies

For rare adverse events, cohort studies require access to very large databases. **Case–control studies** thus represent an attractive alternative, and are commonly used for the evaluation of vaccine safety [22]. In view of the importance of age effects, especially for the evaluation of pediatric vaccines, case–control studies are usually individually matched on date of birth, and analyzed by **conditional logistic regression** [23]. Exposures within each case–control set are determined according to vaccination history prior to the index date, namely the date of onset for the case. Case–control studies for vaccine safety evaluation, like cohort studies, can be broadly classified into two categories according to whether or not the putative vaccine-associated risk is believed to be time limited after vaccination.

4.2.1 Example 8 MMR Vaccination and Autism

A large case–control study was undertaken within the GPRD to investigate the association, if any, between MMR vaccination and autism [15]. One thousand two hundred and ninety-four cases were included, individually matched to up to five controls per case on year of birth, sex, and general practice. The primary

exposure variable was ever having received MMR vaccine: thus, in this analysis, the postvaccination risk period is assumed to be unlimited. The adjusted **odds ratio** was 0.86, 95% CI (0.68, 1.09).

4.2.2 Example 9 Hepatitis B Vaccination and Multiple Sclerosis

Mass vaccination against hepatitis B was introduced in France in 1994, targeted at infants and older children, with a catch-up vaccination programme in adults. By July 1996, 200 cases of multiple sclerosis occurring within 2 months of a hepatitis B vaccination had been reported. Several studies were subsequently undertaken to assess the risk of multiple sclerosis following hepatitis B vaccination.

One case–control study involved 236 new cases of multiple sclerosis and two or three controls per case individually matched on age, gender, date, and center of referral [24]. Two exposures were used: hepatitis B vaccination 0–2 months or 2–12 months prior to the index date. These choices reflect the belief that the postvaccination risk is time limited, and is highest in the 0–2-month risk period after vaccination. A raised but nonsignificant odds ratio was found for the 0–2-month period: 1.8, 95% CI (0.7, 4.6), though when the analysis was restricted to individuals with vaccination certificates the odds ratio dropped to 1.4, 95% CI (0.4, 4.5).

As shown in this example, it is important in all vaccine safety studies, but particularly in risk-interval studies, to use documented (rather than self-reported) data on vaccination histories.

4.3 Studies Using Only Cases

A variety of statistical methods based only on cases have been used for evaluating vaccine safety, often exploiting the natural experiments resulting from changes in vaccination schedules [25]. Two generic methods are particularly attractive because they automatically control fixed **confounders**. These are the self-controlled case series method (*See* **Self-Controlled Case Series Analysis**) [26, 27] and the case-crossover method [28]. The self-controlled case series method is derived from a Poisson risk-interval cohort model (*See* **Poisson Processes**) by conditioning on the total number of events experienced by each individual in the cohort, from which only the cases are informative. The method allows for adjustments for age. In contrast, the case-crossover method is a version of a matched case–control study in which control periods are sampled from the life history of the case prior to the event. In this method it is assumed that there is no time trend in the probability of vaccination.

4.3.1 Example 10 Rotavirus Vaccine and Intussusception

In 1998 a new vaccine against rotavirus infection was introduced in the United States. After receiving reports of intussusception soon after vaccination, the vaccination programme was suspended and an epidemiological study was undertaken [29]. A case series analysis of 432 cases was conducted, with observation period 1–12 months of age. The risk periods 3–7, 8–14, and 15–21 days after each dose of vaccine were used. The analysis found a relative incidence of 58.9, 95% CI (31.7, 110), for the 3–7-day risk period after the first dose, thus confirming a significant association between rotavirus vaccination and intussusception in infants.

Self-controlled cases series work best when the risk period or periods used are short compared to the observation period, namely the period over which cases are ascertained. However, in some circumstances, the method may be used with indefinite risk periods [25, 30].

The self-controlled case series method controls for age effects. In the parametric version of the model these effects are represented by a step function. In the semiparametric model (*See* **Semi-Parametric Models**), they are unspecified [31]. Allowing for age effects is essential when dealing with adverse events relating to pediatric vaccines, since the incidence of such events is usually highly age dependent. Since pediatric vaccines are usually administered according to a schedule, vaccination rates are also highly age dependent, precluding the use of case-crossover methods. However, in adult populations, age effects may be less important, and the case-crossover method may be used.

4.3.2 Example 11 Hepatitis B Vaccine and Relapses in Multiple Sclerosis

A case-crossover study was set up to investigate the possible association between a range of vaccinations, including hepatitis B vaccination, and relapses in multiple sclerosis [32]. Vaccination histories were obtained from 643 individuals with multiple sclerosis who suffered a relapse in 1992–1997. The case period was defined as the 2 months preceding the relapse. The 8 months prior to the case period were split into four 2-month control periods. Hepatitis B vaccination in the case and control periods were documented, and analyzed as in a case–control study under the assumption that vaccination rates did not vary appreciably over the 10-month age range spanned by the control and case periods. The odds ratio for the association between hepatitis B vaccination and relapse was 0.67, 95% CI (0.20, 2.17).

5 Wider Statistical Issues

Vaccines are to some extent the victims of their own success. After an effective vaccine is introduced, the perceived balance of risks and benefits shifts as memories of the disease fade, to be replaced by more immediate concerns about potential risks. This raises some wider issues. First, evidence of safety or lack of it is often required quickly. Thus, timeliness is an important consideration, as well as statistical **power**. Second, evidence of safety can never be absolute, since it is not possible scientifically to prove that administration of a vaccine carries zero risk. Thus statisticians working on vaccine safety issues must be prepared to engage in a public evidence-based discussion about risks and benefits.

6 Related Articles

Vaccine Studies, Statistics in
- **Vaccine studies**
- **Vaccine**
- **Salk vaccine**
- **Safety**
- **Overview of Safety Pharmacology**
- **Surveillance**
- **Public Health Surveillance**
- **Disease Surveillance**
- **Postmarketing surveillance of new drugs and assessment of risk**

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