Vaccine safety

Stewart Reid

ABSTRACT

The purpose of this article is to offer evidence that vaccine safety is taken very seriously and various examples to support this premise are described. The article covers adverse event reporting following vaccination, the difference between events which occur after vaccination and events which are caused by vaccination, the comprehensive safety monitoring required when vaccines are first introduced, international vaccine withdrawals because of safety concerns and some vaccine changes in New Zealand where safety was an important consideration. Finally, recent developments in vaccine safety monitoring are outlined. It is hoped that this will be a useful resource for those involved in the complex issue of counteracting vaccine hesitancy.

WHO has listed vaccine hesitancy as one of the 10 threats to global health in 2019,[1] and it is of considerable significance in this country. According to the New Zealand Immunisation Handbook, if parents are concerned about vaccinating their children, their concerns are most often about vaccine safety.[2] I submit that there are two key issues relating to vaccine safety which require significant public airing. Firstly, while adverse event reporting following vaccination is of great importance, the difference between adverse events following vaccination and adverse events caused by vaccination requires considerable emphasis. Secondly, the importance with which vaccine safety is regarded by authorities must be prominently publicised. Evidence to support these premises is presented.

Adverse event reporting

Adverse event reporting following vaccination is essential and, for example, an important instance occurred in the MeNZB vaccination programme. The safety monitoring system was set up to detect specific adverse events following immunisation with a catch-all category allowing unanticipated events to be detected.[3] A cluster of cases of Henoch-Schönlein Purpura, an unanticipated event, occurred early in the programme and this cluster led to a detailed investigation which demonstrated that this was simply a random occurrence not related to the vaccine.[3] This illustrates the importance of adverse event reporting as it allows the detection of 'signals', which may indicate that there is a significant vaccine risk. The signal can only be confirmed or refuted as a vaccine reaction by detailed epidemiologic investigation.

Events caused by vaccination

The relationship between adverse events following vaccination and events caused by vaccination was elegantly demonstrated by Peltola and Heinonen in a large, carefully controlled study of adverse events following MMR vaccination.[4] It is generally reported that a fever of 39.4°C or more occurs in 5–15% of children 6–12 days after immunisation and generally lasts one to two days.[5] Rash occurs in approximately 5% of children at the same interval post-vaccination.[5] However, the majority of these events are not caused by MMR immunisation.

In their double-blind, placebo-controlled crossover study on 581 pairs of twins, twin A received MMR and twin B placebo on day one. On day 21 twin B received MMR while twin A received placebo. Both twins were followed up for 42 days with a symptom diary. The study demonstrated that MMR does cause fever >39.5^{0}C, but only in 1.4% recipients 7–12 days following vaccination. Irritability and rash were also more common after MMR but respiratory and gastro-intestinal (GI) symptoms less frequent. They demonstrated that the majority of adverse events following immunisation are not caused by the vaccination but occur coincidentally. This has been called the healthy vaccinee effect.

Children frequently get infections[6] and are usually vaccinated when they are well. A proportion of children will coincidentally suffer infections after vaccination. Parents either intentionally or more likely subconsciously tend to observe their children more closely than usual after vaccination and report minor symptoms which they attribute to the vaccination. Wakefield et al publicised an apparent link between GI symptoms and autism and, in eight of their total of twelve patients, to MMR vaccination in a now withdrawn Lancet article.[7] Interestingly, the article did not refer to the Peltola and Heinonen study which demonstrated a reduction in GI symptoms following MMR vaccination and for the record MMR vaccine has subsequently been shown not to cause autism.[8]

Adverse event reporting following vaccination is of great importance but it cannot be used as evidence of events caused by vaccination without careful further scientific study.

Importance of vaccine safety

Vaccine safety is taken very seriously by health authorities and there have been numerous examples of this. Most recently in New Zealand, the introduction of the MeNZB vaccination was only possible with a comprehensive safety monitoring programme which was described by the Independent Safety Monitoring Board (ISMB), who independently assessed all safety data, as an "outstanding programme of sensitive and objective safety monitoring".[9] The MeNZB vaccine, which was unique to New Zealand, was to be offered to over a million individuals aged 0–19 years in a three-dose regimen with safety and efficacy data available from only 1,068 subjects.[10] That amount of data may be acceptable to provide evidence of efficacy, but it is a very small dataset with regard to evidence of safety. To enable provisional licensure, a comprehensive safety monitoring programme was instituted. This involved establishing a national immunisation register, which used each individual's unique national health index number so that receipt and timing of vaccine doses could be ascertained. Four methods of data collection in addition to the standard passive reporting system were established; hospital-based rare event reporting, hospital-based reporting of all events within seven days of receipt of vaccination, reporting of all deaths within three months of receipt of any vaccine dose and an intensive vaccine monitoring system run by the Centre for Adverse Reaction Monitoring (CARM).[3] The rollout of the vaccine was staggered and progress from one area to the next occurred only after the assessment and approval of an agreed quantity of safety data by the ISMB.

Vaccine withdrawals

In the last 30 years there have been a number of vaccine withdrawals internationally and I offer three examples of these withdrawals. In New Zealand in the last 20 years there have been two changes of vaccine administered in the Childhood Immunisation Schedule, which were made predominately because of safety considerations.

The Nasalflu vaccine developed by Berna Biotech in Switzerland containing *Escherichia coli* heat-labile toxin as an adjuvant was available and administered during the 2000–2001 influenza season. During the pre-licensure studies on 1,218 volunteers no serious adverse events were reported. During the seven months of its use the Swiss passive reporting system received 46 reports of Bell's Palsy. Berna Biotech ceased distribution and invited the University of Zurich to investigate whether the vaccine had caused an increase in the incidence of Bell's palsy. Using matched case-control and case series analysis methodologies, the study concluded that a significantly increased risk of Bell's Palsy was present for vaccine recipients when compared to controls. The adjusted odds ratio was 84 (95% CI 20.1–351.9) with the most likely onset 31–60 days after vaccination. The vaccine is no longer in clinical use, but the signal was detected by standard passive case reporting and studied by careful scientific assessment.[11]

The first rotavirus vaccine to be licensed was RotaShield®, which was licensed for distribution in the US in 1998. Intussusception had been noted in prelicensure trials as a possible adverse effect but there was no statistically significant difference in the incidence between the vaccine and placebo groups.[12] Intussusception occurs in approximately one young child in every 10,000 regardless of vaccination history.[13] After introduction of the vaccine, intensive

surveillance for intussusception occurred and was reported at a rate of approximately 1/10,000 children vaccinated with the majority of these cases occurring in the week after receipt of the first dose of rotavirus vaccine.[13] As a result, the manufacturer voluntarily withdrew RotaShield® from the market.[13] Subsequent rotavirus vaccines were studied in large safety studies involving 60,000–70,000 subjects to exclude the possibility of a similar rate of intussusception. After marketing, the rate of vaccine-associated intussusception has been very carefully studied and shown to occur at a rate of 1–2/100,000 vaccinees,[14] usually after the first dose.

MMR vaccine containing the Urabe Mumps strain was withdrawn in the UK in 1992 following an observation of an increased risk of aseptic meningitis 15–35 days after receipt of the vaccine. It had been previously thought that the rate of aseptic meningitis following receipt of the Urabe strain vaccine was 1/100,000 doses. However, following careful surveillance including hospital- and laboratory-identified cases in the Nottingham region it was ascertained that the rate of aseptic meningitis was 1/10,000–1/15,000 doses. Further, there was a risk of admission to hospital for febrile convulsion, relating to the Urabe strain, 15–35 days after administration of the vaccine at the rate of 1/1,500 doses. This risk led to the withdrawal of the Urabe strain from the vaccine produced by Glaxo-Smith-Kline and its replacement by the alternative Jeryl Lynn strain, which does not cause aseptic meningitis.[15]

New Zealand vaccine safety decisions

In New Zealand in August 2000 the pertussis vaccine administered changed from whole cell pertussis vaccine to the acellular pertussis vaccine. The main reason for the change was that the acellular vaccine is much less reactogenic than the whole cell vaccine, and data available at the time suggested the efficacy was similar. It also resulted in a huge reduction of antigens administered; whole cell vaccines contain approximately 3,000 antigens while the acellular vaccines in use in New Zealand contain only three antigens.[16]

In 2002 the preferred polio vaccine changed from oral (live) polio vaccine (OPV) to inactivated polio vaccine (IPV). This was because in countries with high OPV coverage, cases of polio related to the vaccine strain occurred at the approximate rate of 1/750,000 first doses administered. These cases occurred because the live attenuated vaccine strain present in OPV establishes infection in the vaccinated person and can rarely revert to the original neurovirulent form and cause clinical polio. In contrast, this reversion to neurovirulence cannot occur with the inactivated injected vaccine.[16] In these two examples of changes to the New Zealand Childhood Immunisation Schedule, an increase in vaccine safety was the key deciding factor.

Developments in vaccine safety monitoring

Currently in New Zealand there is only the standard passive monitoring system but, as all vaccines used in New Zealand are widely used internationally, we benefit from the vast amount of safety data that is generated in systems such as VAERS (Vaccine Adverse Event Reporting System) in the US and Eudra Vigilance in the EU. However, there is a move towards more active monitoring such as that used in Australia where vaccinees or their parents/caregivers can directly report adverse events.[17] During the MeNZB campaign an active system was in use in which the clinical records for a six-week period following receipt of any vaccine, from a representative sample of GPs, were sent to CARM.[18] Should this system be resurrected either continuously or at least for several months before and after any change to the childhood vaccination schedule? The Uppsala Monitoring centre has recently reported that it is looking at modernising vaccine surveillance to better detect rare adverse events.[19] It is suggested that new data analysis approaches may allow improved monitoring of vaccine safety, particularly for hard to diagnose illnesses such as postural orthostatic tachycardia syndrome. It is also proposed that it may be possible to identify biomarkers which may indicate individuals at higher risk of suffering adverse events.

Conclusion

Vaccines are not perfect, but their imperfections are taken very seriously. As can be seen from the above examples, vaccine safety is considered extremely carefully, and all vaccines are subject to safety surveillance starting with the prelicensure trials. After marketing the reporting of adverse events after vaccination is essential to detect signals of events which may be related to vaccination, but the causal relationship with a vaccine can only be determined by further study. As shown by Peltola and Heinonen,[4] many events occurring after vaccination are coincidental. However, when events are related to vaccination, even at a relatively low frequency, vaccines are withdrawn from use. The monitoring systems are subject to review and improvement. Vaccine safety is taken very seriously.

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Author information:
Stewart Reid, Retired.
Corresponding author:
Dr Stewart Reid, General Practice, Retired.
stewart_christine@mac.com

URL:
www.nzma.org.nz/journal-articles/vaccine-safety

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