LEADING ARTICLE

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Monitoring the Safety of Vaccines
Assessing the Risks

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Abstract

The safety of vaccines, particularly the most widely used vaccines to which most children are exposed as infants and toddlers, has always been an extremely high priority for vaccine manufacturers and government agencies. Products intended for healthy people must be held to a high standard of safety assurance. In addition to the intense safety assessments conducted prior to licensure, post-marketing surveillance programmes are essential to identify and study possible risks that occur too rarely to have been identified in pre-licensure studies or that occur in populations not studied in pre-licensure studies. Studying rare risks of vaccines is more complex than for therapeutic products because the exposure is virtually universal for many vaccines, ensuring occurrence simply by chance of many adverse outcomes in temporal association with vaccination. In the US the Vaccine Safety Datalink (VSD), a consortium of managed care organisations, has been established to study more rigourously possible vaccine-associated risks. These risks may be identified through reports to the Vaccine Adverse Event Reporting System (VAERS), the nationwide passive surveillance programme, as well as other sources. The combination of passive surveillance and more structured case-control or cohort studies possible in the VSD has helped to both identify new vaccine risks and to provide reassuring evidence of lack of risk in other situations where concerns have been raised.

Monitoring the safety of marketed pharmaceutical products is an activity of increasing interest and visibility. Public concerns about the safety of particular products have been raised in many countries; in the US, in addition, the Institute of Medicine (IOM) and the Government Accounting Office (GAO) have performed studies of the safety of marketed products[1-4] and the effectiveness of the surveillance systems established to monitor safety.[5] Monitoring vaccine safety raises special concerns because vaccines are administered to healthy populations and because immunisations are mandated or strongly encouraged for virtually all children in many countries. Loss of public confidence in the safety of vaccines has led to decreased vaccination coverage and a consequent resurgence of vaccine-preventable diseases.[6] Public confidence in vaccine safety cannot be adequately maintained without the perception that serious adverse effects of vaccines will be identified and communicated to the public. Thus, effective post-licensure safety monitoring systems, following

rigourous pre-licensure testing, are critical to immunisation programmes.

1. Passive Surveillance Systems for Safety Monitoring

The 'front line' of post-marketing safety monitoring is the passive surveillance system (sometimes called a spontaneous reporting system), a collection of reports of adverse events following administration of medical products. These systems, maintained by pharmaceutical companies and regulatory agencies, consist of databases of such reports that can be reviewed for trends in reporting, scrutiny of individual reports of interest and occasionally for analytic epidemiological studies. Passive surveillance systems are in place to monitor the safety of medical products in most industrialised countries. These systems rely on individual healthcare practitioners, consumers, and others to report adverse outcomes that may possibly have been caused by a particular product. Approaches to implementing such systems vary by country. For example, in the US, reports may be made by healthcare providers or consumers directly to the Food and Drug Administration (FDA), or to the product manufacturer, who is then required to submit all such reports to the FDA. In other countries, reports are accepted only from healthcare professionals.

Passive surveillance systems are relatively inexpensive to operate because there is no expenditure of resources for staff to actively pursue the collection of data. However, such systems may publicise their existence through general mailings or other publicity such as notices in relevant journals so that reporting forms are more likely to be available to healthcare professionals should an event occur that merits reporting. The vast majority of the cost of such systems is for data entry, adverse event coding and information technology personnel who focus on data management for large computerised databases. Adverse event coding involves classifying each adverse event according to a standardised classification scheme, such as MedDRA (Medical Dictionary for Regulatory Activities)[7] or COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms).[8] There are many limitations to passive surveillance systems, however, that often make the data difficult to interpret.[9]

The increased interest in product safety notwithstanding, monitoring the safety of marketed products is an extremely challenging enterprise. Adverse effects of drugs can be hard to distinguish from the signs, symptoms and sequelae of the disease being treated; exposures other than to the suspect drug could be the causal agent; the reports themselves are often incomplete with diagnoses unverified and; a usually unquantifiable amount of under-reporting precludes estimations of incidence. Most importantly, reports document temporal associations only; causation can usually not be inferred from such reports.

2. Monitoring Vaccine Safety

Monitoring the safety of vaccines is in many ways even more challenging than monitoring drug safety.[10] The target populations for many vaccines are extremely large and diverse. For example, seven childhood vaccines (two of which are combinations of three vaccines each) are recommended for universal use in the US; most of the annual US birth cohort of 4 million infants receive all of these vaccines during their first 2 years of life. While these vaccines protect against a variety of infectious diseases, they clearly do not protect against other adverse outcomes that affect children. Thus, vaccinated children remain susceptible to sudden infant death syndrome (SIDS), childhood cancers, diabetes mellitus, mental retardation, developmental disorders, and other serious conditions that are diagnosed in childhood. Although the incidence of such disorders is rare, the numbers of children newly diagnosed with these conditions range from several hundred to thousands each year. Nearly all of these incident cases will have been preceded by one or more vaccinations, and in some cases, by only a day or two. The fact of such diagnoses cannot therefore be viewed as conclusive evidence of an adverse vaccine effect; but neither can the fact that we expect such events to follow vaccination be considered proof

of non-vaccine causality in any individual case. When the time from vaccination to the adverse outcome is short, many who are not experienced in the review of such data will find it difficult to accept that the temporal association is not sufficient to establish causality.

There are other factors that complicate the reporting and interpretation of adverse events following vaccination as well as the communication of such interpretations to others. Vaccines are given to healthy individuals and convey no immediately recognisable health benefit, making the risk of serious adverse reactions much less tolerable than for a product that treats an evident disease or condition. Further, because vaccinations are frequently mandated for attendance at day care centres, schools and universities, or for certain occupational groups, any major adverse consequence, however rare, is more likely to be viewed as unacceptable. Vaccines are frequently given simultaneously, especially to children; the current recommended immunisation schedule calls for administration of multiple vaccines at 2, 4, 6 and 12 to 15 months of age. Any adverse event following a multiple vaccination could therefore be due to any of the vaccines, some interaction among them, or none of the vaccines (a coincidental event). Also, because vaccines are known to be among the safest of medical interventions, many healthcare providers may not even entertain the idea that vaccination may be a potential cause of a post-vaccination event, thereby leading to substantial underreporting.

Despite the extensive pre-licensing safety evaluations of all new vaccine products, including *in vitro* and animal studies, clinical trials and meticulous monitoring of the manufacturing process,[11] determination of all possible risks prior to licensure is not possible. Although it may be reasonable to question whether pre-licensure trials ought to be large enough to detect (or rule out) risks of a given size in addition to detecting a given level of efficacy,[12] there will always be a threshold beyond which risks are too small to be discovered until a vaccine is in widespread use. Thus, the implementation of programmes to monitor the safety of vaccines in use is a critical public health responsibility.

3. Strengths and Limitations of Current Approaches

3.1 The Vaccine Adverse Event Reporting System

The Vaccine Adverse Event Reporting System (VAERS), a passive surveillance system for monitoring the safety of vaccines in the US, was created in 1990 and is jointly managed by US Centers for Disease Control and Prevention (CDC) and FDA.[13] VAERS is in a sense the nation's early warning system for vaccine safety issues. For example, it provided an important early signal of the problem of intussusception following rotavirus vaccination that ultimately led to the withdrawal from the market of that product.[14,15] VAERS accepts all reports of adverse events from healthcare providers, patients, parents and others, and includes reports transmitted from vaccine manufacturers or state immunisation coordinators as well as those reported directly to VAERS. The VAERS form is a simple one-page form that is printed in the Physician's Desk Reference, available on the Internet[16] and mailed annually to physicians in specialties most likely to administer vaccinations. Once received by the VAERS contractor, forms are rapidly processed and their information entered into a computerised database available for analysis. Reports describing serious events (defined as fatal, life-threatening, resulting in hospitalisation or permanent disability, or requiring intervention to prevent any of these outcomes) or other events of interest are reviewed on an individual basis and followed up to retrieve additional information that could be helpful in assessing causality.

A major strength of VAERS is the wide geographic coverage (the entire US) and the rapid availability of data for analysis. Because the entire US population is potentially covered by VAERS, VAERS may permit the study of extremely rare events such as anaphylaxis following measles mumps and rubella (MMR) vaccine or poliomyelitis following live oral poliovirus vaccine. Such

rare events, which may occur in fewer than 1 per 100 000 individuals, would be impractical to study even in large prospectively followed cohorts.

The limitations of VAERS, however, are substantial. Reports to VAERS represent temporal, but not necessarily causal, relationships between vaccination and adverse events, and it is only rarely the case that a determination of causality can actually be made. Indeed, the term vaccine 'adverse event' is used, rather than vaccine 'reaction' to denote the general uncertainty with regard to causality. This important distinction tends to be overlooked occasionally by members of the press, advocacy groups, healthcare providers, members of the general public and others, but it is especially important for vaccine adverse events because exposure to vaccines is essentially universal. Any adverse outcome experienced by a child, and by most adults, will have been preceded by one or more vaccinations, and, as discussed earlier, it follows that some small proportion of such events will have a close temporal association with vaccination.

Another major limitation, as noted earlier, is under-reporting. All adverse events occurring in close proximity to vaccination are not reported; probably only a small fraction of such events are reported. Although there are data to suggest that the more serious adverse the adverse event, the more likely it is to be reported,[17] it is difficult to predict the extent of underreporting for any given product-adverse event combination. Furthermore, reporting is affected by the proximity of the event to vaccination. Events occurring weeks following vaccination are less likely to be reported than those occurring shortly after vaccination. In general, this reporting tendency acts as a helpful filter, since the most proximal reports may be more plausibly associated with vaccination, but it limits information on non-acute events whose onset after a causal exposure may be delayed. Many of the conditions for which there is public concern about possible connections with vaccination are of this type, for example, type 1 diabetes mellitus, autism, multiple sclerosis.

There are many other limitations of VAERS. VAERS forms are often not completely or accurately filled out, and resources and priorities have not permitted routine editing and follow-up to correct errors and retrieve missing data for all reports. Furthermore, information that would be essential for determining background incidence of adverse events is not readily available. The number of vaccine doses distributed over some period of time can generally be obtained from the manufacturer, but more detailed information – for example, the number of vaccinated persons by age – is not readily available or is unavailable altogether. Such information would be required for the calculation of age-specific adverse event rates, which are usually of primary interest since background rates of events and conditions of greatest concern are almost always highly age dependent.

3.2 The Vaccine Safety Datalink

Most adverse event 'signals' arising from VAERS (or from other sources such as case reports published in medical journals or described in lay media) require further study before conclusions about vaccine causality are possible. The CDC established the Vaccine Safety Datalink (VSD) project in the early 1990s to permit more definitive evaluation of potential adverse effects of vaccination.[18] The VSD is a consortium of managed care organisation databases. For its first decade, this project was composed of four large health maintenance organisations (HMOs) located on the west coast of the US. Recently, three additional sites have been added in the Rocky Mountain, Midwest and east coast regions of the US. The strength of the VSD is that it uses routinely computerised healthcare data, including vaccinations and illnesses, so that ascertainment for many types of vaccinations and illnesses of interest in a defined population may be nearly complete without additional manual data gathering and data entry. (Some adult vaccinations, such as influenza or hepatitis B vaccinations, may occur at the workplace or in other public settings and may be incompletely reflected in the HMO database.) Thus, with both reliable numerators and denominators, estimates of adverse event incidence can be obtained from the VSD.

The VSD has strengths and its own limitations, some of which are complementary to those of VAERS. A limitation of the VSD is that, although the population is defined, it is limited to those in the HMOs. Even this relatively large population cannot provide data to rule out extremely small risks that still, if they did exist, would be of concern. Further, until recently the VSD included only individuals who were subscribers at four west coast HMOs, a population not as representative of vaccine recipients as one might like (in contrast to VAERS, which can include information from any vaccinee in the US). In addition, there usually is a time lag of months between the time a question is identified for a new product and the time data pertaining to that question are retrieved and ready for analysis. This lag is due to the time and effort required to prepare the massive administrative datasets used for analysis. Nevertheless, the combination of VAERS and the VSD provides a powerful capability for identifying and studying possible vaccine reactions.

VSD data permit several types of rigourous controlled epidemiological studies, such as retrospective cohort studies and case-control studies. In addition, the 'case-crossover' methodology has been used.[19] In the 'case-crossover' study design, adverse event incidence during an individual's time periods defined as exposed to vaccination (e.g. just following vaccination) is compared to incidence in the same individual during time periods considered unexposed to vaccination (e.g. before vaccination or long after vaccination). This methodology is best suited to adverse events that occur acutely within a timeframe following vaccination that can be pre-specified. The self-control methodology is particularly useful when vaccine coverage is high and unvaccinated persons similar to the vaccinees are rare, so that other approaches are less feasible. The VSD project has fruitfully investigated a number of events suggested to be associated with vaccination using these study designs, such as inflammatory bowel disease,[20] arthropathy following rubella vaccine,[21] and asthma exacerbation.[22]

3.3 Other Settings for Vaccine Safety Research

In addition to systems specifically designed to investigate or monitor vaccine safety questions, such as VAERS or the VSD, other settings have been useful in investigations of vaccine safety questions. A disease registry and a multipurpose cohort study were recently used effectively to address concerns about whether hepatitis B vaccine increased the risk or relapse of multiple sclerosis. The Nurses Health Study, a multipurpose prospective cohort study of more than 100 000 women, was used to evaluate whether hepatitis B vaccine causes multiple sclerosis. A nested case-control study designed within this cohort employed a questionnaire to gather information about hepatitis B vaccination. The study found no association between hepatitis B vaccination and the development of multiple sclerosis.[23] A disease registry, the European Database for Multiple Sclerosis, was employed to study whether relapse could be triggered by hepatitis B vaccination. A case-crossover study design was employed using vaccination information obtained by telephone interview and confirmed with medical records. The investigators concluded that vaccination does not appear to increase the short-term risk of relapse in multiple sclerosis.[24]

4. Causality Assessment

Ultimately, everyone wants to know whether a particular type of adverse event is caused by the suspect product. In practice, this is often enormously difficult to determine, particularly for vaccines. Criteria to aid in this determination have recently been suggested for vaccines and are also applicable generally.[25] These criteria include: (i) biological plausibility; (ii) strength of association; (iii) specificity; (iv) temporal relation; and (v) consistency among multiple independent studies. Biological plausibility is usually suggested when a credible and coherent biochemical, pathophysiological chain of events can be forwarded to explain the drug-adverse event association. Biological plausibility is strengthened when the event is

known to be associated with natural infection, such as for aseptic meningitis and the Urabe mumps vaccine.[26] Strength of association, such as a large relative risk or a strong dose response effect, supports a causal association between a drug and an adverse event. Although it remains possible that weak associations may also be causal associations, the weaker the association in a study, the more likely it may be explained by confounding, bias and the play of chance. Specificity, the unique (or nearly unique) linkage between an adverse event and a drug, is strongly supportive of a causal association. Swelling and pain at the injection site would represent such a linkage, for example, as would vaccine-strain paralytic polio following exposure to oral polio vaccine. The specificity criterion can support a causal association, but need not necessarily be met even when a causal association clearly exists. For example, Guillain-Barre syndrome, believed to be causally associated with swine influenza vaccine, also occurs in many other settings. A characteristic temporal relationship between a drug and adverse event, a pattern of clustering in time, is supportive of a causal association; for example, the clustering of intussusception cases 3 to 7 days following rotavirus vaccination.[27] Consistency among multiple well-designed studies finding a drug-adverse event association also supports a causal association. Observational epidemiological studies that explore multiple possible associations frequently identify isolated observations of an association that ultimately are not confirmed in subsequent studies, and thus it is important to view such findings cautiously until some consistent pattern across several studies is established.

The five criteria noted above are intended to aid in assessing causality, and judgement is invariably involved in such assessments. All five criteria need not be met for a vaccine-adverse event association to be considered causal.

5. Identification and Interpretation of Potential Vaccine-Associated Risks

Despite its limitations, VAERS has produced valuable findings. Probably the most dramatic example was use of VAERS data to monitor the safety of the first rotavirus vaccine. Several cases of intussusception, a type of bowel obstruction, had occurred in the pre-licensure clinical trials, but the numbers were small and there was at least one occurrence in a placebo recipient.[28] There had been no well established connection of intussusception with naturally occurring rotaviral infection, and the consensus of FDA's expert advisors was that these cases were most likely coincidental. Nevertheless, in order to further assess the possible connection of this event with vaccination, a new VAERS code was established for intussusception so that any reports of this problem would be rapidly retrievable. Intussusception reports were closely monitored following the vaccine's licensure. Less than a year following licensure, the number of reports, though small, was about half of the number that might have been expected based on background rates estimated from other sources and the amount of vaccine estimated to have been administered by that time. Given the underreporting problem, this finding raised substantial concern that the vaccine-intussusception connection might be truly causal, and the CDC initiated further follow-up studies.[14] Ultimately, large numbers of additional vaccine-associated cases were discovered, mostly occurring during a narrow time window within the first week after vaccination, and the manufacturer withdrew the vaccine.

Applying the five causality criteria noted above shows that the strength of association and the temporal relation probably provide the best evidence for causality in this case. The strength of association and its temporal connection to vaccine are quite strong; epidemiological studies have suggested a 20- to 30-fold elevation in risk of intussusception 3 to 7 days following the first dose of rotavirus vaccine in infants. The biological plausibility of the association was not sufficient to discourage licensure, but cannot be completely dismissed as the live attenuated viral vaccine comes into contact with the small intestine and colon, the sites that are affected by intussusception. The specific biological mechanism involved has not been elucidated, however. The published data on the

rotavirus vaccine-intussusception association have been relatively consistent.[27,29] Finally, the specificity criterion does not apply in this case, as intussusception is not an event specific to rotavirus vaccine.

Another example of an adverse event identified through VAERS was hair loss following vaccination.[30] Prompted by a report from a concerned parent, FDA staff searched the VAERS database for similar cases and were somewhat surprised to find about 40 cases of alopecia that had been reported to VAERS over a period of years. The lag in detection may have been due at least in part to the fact that few, if any of these reports met the FDA definition of a serious adverse event (defined as death, hospitalisation, prolongation of hospitalisation, life-threatening illness or permanent disability) so they had not been a priority for review and follow-up. Although follow-up identified other possible causes in many cases (e.g. use of chemical hair treatments), there were several cases of 'positive rechallenge': hair loss after vaccination, followed by regrowth and then hair loss again after the next vaccine dose. These cases provided a strong suggestion of a real, but clearly very rare, effect. Cases were reported in both children and adults; several different vaccines were involved but most cases included receipt of hepatitis B vaccine.

Positive rechallenge represents a type of temporal relation that is particularly persuasive.[31] Despite the absence of strong data supporting the other causality criteria, the high value usually placed on positive rechallenge data lends credibility to the potentially causal association between alopecia and vaccination.

New computer-intensive methods have been developed that may help identify potential signals in the VAERS database by searching for unusually common vaccine-event combinations.[32] These methods, now in use at the FDA for drugs as well as vaccines, show promise for rapid identification of signals of potential events of concern.[33,34]

An example of the way the VSD can be used to follow-up on a VAERS finding is the question of whether one brand of hepatitis B vaccine was more reactogenic than another. This question arose during preparation of an overview of VAERS data on hepatitis B vaccine given to infants,[35] when a substantial excess of reports from one manufacturer compared with the other manufacturer (accounting for the different number of doses distributed) was noted. Although no obvious explanation for this imbalance could be found, the FDA was reluctant to draw any conclusion about increased safety concerns with one of the vaccines; the prior clinical trials safety data for these vaccines gave no suggestion of any difference in safety, and the excess was nonspecific, i.e. not confined to a group of medically-related adverse events. Yet, the possibility that one brand produced more adverse events than the other clearly needed further investigation. Within the VSD there was experience with both vaccines; an analysis of the VSD data found no difference in adverse events following the two vaccines,[36] providing reassurance that the VAERS data were likely the result of some unquantifiable reporting biases.

6. Conclusion

Assuring the safety of the vaccines that protect populations from illness, disability and death due to infectious agents is extremely important. Because of the large numbers of individuals receiving vaccines, even extremely small risks could affect substantial numbers of people. Safety surveillance systems are in place and new approaches have been developed and continue to be enhanced. Monitoring vaccine safety will become even more complicated as new vaccines are developed and administered together with those currently in wide use. Continued attention to improvements in current systems, development of new analytical approaches and access to additional sources of information on vaccine safety will be needed for the foreseeable future.

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