Safety Monitoring in Vaccine Development and Immunization

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The development of vaccines has been one of the most important achievement in preventive medicine. As the incidence of vaccine-preventable diseases is reduced by immunization, general public becomes increasingly concerned about the safety associated with vaccine. Vaccine safety is extensively evaluated through animal safety studies, clinical trials, during manufacturing processes, and postlicensure surveillance. Safety monitoring in postlicensure surveillance has relied on passive reporting system and epidemiological studies, including Vaccine Adverse Event Reporting System (VARES), Vaccine Safety Datalink (VSD) Project and others. Approximately 10,000 reports per year are submitted to VAERS. About 15% of these describe serious events and 85% of reports are classified as not-serious events. The system analyzed frequently reported adverse reactions, rare events, intussusception after rotavirus vaccine, cases of sudden infant death syndrome (SIDS), and safety of various vaccines. The evidence for a causal relationship with vaccines can be classified into five categories: no evidence, evidence was inadequate to accept or reject, evidence favors rejection, evidence favors a causal relationship, and evidence established. Future challenges involve improving survey and monitoring system of adverse events after immunization, enhancing vaccine safety research and vaccine risk communication, and possibility of increased reactogenicity in new and combined vaccines. (Acta Paediatr Tw 2006; 47:7-13)

Key words: safety monitoring, vaccine safety, immunization, vaccine development

INTRODUCTION

The development of vaccines has been one of the most important achievement in preventive medicine. Immunization represents the cost-effective means to achieve the prevention of infectious diseases. No vaccine is, however, perfectly safe or effective. As the incidence of vaccine-preventable diseases is reduced by effective immunization, people have become increasingly concerned about the safety associated with vaccines. The number of reports to the Vaccine Adverse Event Reporting System (VAERS) in the United States, approximately 13,000 per year, has exceeded the reported incidence of most vaccine preventable childhood diseases combined.1,2

In developing countries, the safety concerns involve the inadequate quality control of vaccine production, such as inadequate sterilization of injection equipment causing transmission of pathogens. As developed nations attain high vaccine coverage and lower vaccine-preventable disease incidences, immunization adverse events may threaten the stability of vaccination programs. When diseases are close to eradication, the safety issues to vaccine relative to that disease may lead to discontinuation or decreased use of the vaccine. A dramatic example of the need to balance adverse events of vaccination against protection from disease is illustrated in the case of polio. In 1996, no child born in the U.S. will contract wild-virus polio, yet 8-10 persons each year will develop paralytic polio as a result of vaccination with oral polio vaccine.3 This situation has led to recommendations for replacing the oral polio vaccination with inactivated vaccine to reduce the risk of vaccine-induced paralytic polio.

During late 1970s and early 1980s, public attention in many countries was exerted to the safety of whole-cell pertussis vaccines. Many parents whose children had been seriously injured as a result of vaccination...
SAFETY ASSESSMENT IN VACCINE DEVELOPMENT

Like drugs and many biological products, vaccines must go through extensive animal safety studies and clinical trials before they are licensed. However, unlike other pharmaceutical products, vaccines are primarily applied to healthy people, especially children. Almost all children will receive some vaccinations. Because healthy people are less willing to accept risk than patients who need treatment for illness, vaccine development should be particularly sensitive to the safety risks.

Evaluation of safety is a critical concern in all stages of vaccine development, from clinical trials phase I through phase IV. Safety monitoring is important through the process of experimental vaccine evaluation. Phase I trials usually include fewer than 20 participants and can detect only common adverse events. They are designed as dose-finding studies, assessing toxicity and adverse events, measuring antibody titers, injection site reactions, e.g. erythema, induration, pain and tenderness, and allergic reactions.

Phase II trials generally enroll 50 to several hundred people. These trials are designed to further establish safety to examine the occurrence and magnitude of fever, irritability, injection side redness, swelling, and pain. Safety events are scrutinized as isolated events and as consolidated events. Population size for Phase III vaccine trials are based principally on efficacy consideration, ranging from several hundreds to ten thousands. Phase II controlled trials, often double blind, are designed to estimate vaccine efficacy with health outcomes such as infection, hospitalization, or absenteeism from school or work, rather than exclusively immunologic end points.

Prelicensure studies provide adequate safety data on common adverse events, but usually can not provide estimates of the risk of more serious but rare adverse events. Manufacturing processes are also reviewed carefully by regulators to ensure conformance with good manufacturing practice designed to assure consistency, prevent errors, and avoid contaminations.

SAFETY MONITORING IN POSTLICENSURE SURVEILLANCE

Because rare reactions, adverse events with delayed onset, or reactions in subpopulations may not be detected before vaccines are licensed, postlicensure evaluation of vaccine safety is important. This evaluation has relied on passive surveillance and epidemiological studies. More recently, Phase IV trials and pre-established large linked databases (LLDBs) have improved the methodologic capabilities to study rare risks of specific immunizations.

(A) Vaccine Adverse Event Reporting System (VAERS)

VAERS is a passive surveillance system for voluntarily submitting reports. In addition to health care professionals, patients and their parents are permitted to report to the VAERS, and there is no restriction on the interval between vaccination and symptoms that can be reported. Approximately 10,000 reports per year are submitted to VAERS. About 15% of these describe a serious event including an event resulting in death, life-threatening illness, hospitalization, prolongation of existing hospitalization, or permanent disability. Most of the approximately 85% of reports are classified as not serious events such as local reactions and fever occurring within a day or two of vaccination (Table 1). Many of these events are caused by the vaccination. The serious events, however, are much more difficult to evaluate with regard to their causal relationship with vaccines. Most of these tend to be of a type known to occur in the absence of vaccination as well.

VAERS has many weaknesses. One major problem is that since non-vaccinated people experiencing adverse reactions are not reported to VAERS, there is no control group. Thus, there is no way to evaluate whether the number of reported events is different from the number of population in the absence of vaccination. Because reports are sent in by a wide variety of people in general public, the quality of the data is also less than optimal. Many reports omit important data and contain obvious errors. Nevertheless, this type of national reporting system can rapidly document possible effects, producing early warning signals that can be more rigorously investigated. VAERS data are valuable in evaluating the safety of newly marketed vaccines. Review of reports...
coming in during the initial period of availability can provide additional reassurance on the safety of the vaccine, or rapidly identify potential problems not observed during the prelicensure studies.

The case of sudden infant death syndrome (SIDS) causes the problem with interpreting VAERS data. Approximately 200 deaths a year are reported to VAERS. Most cases are of infants under one year of age and diagnosed as SIDS. The reported time from immunization until death varies from a few hours to many weeks or even months. Most cases involve multiple vaccination. Because SIDS is a documented case that occurs both in the absence and presence of vaccination, one can not presume a causal association when SIDS follows shortly after vaccination; in fact, such events can occur even in the absence of a causal connection. In 1980s the National Institute of Child Health and Human Development, NIH conducted a large case-control study directed at the question of association between SIDS and DTP vaccination. This study did not provide evidence that DTP vaccine caused SIDS; in fact, it demonstrated a lowered risk for SIDS in children receiving DTP vaccine. Several risk factors for SIDS have been identified including prone sleep position, the thermal environment, using heavy and confining bedclothes, and maternal smoking. SIDS rates have decreased in several countries in connection with “back to sleep” approaches. These observations suggest a mechanism for SIDS that may be more related to the physical environment than to systemic factors in the child that might be affected by vaccination.

In March 2003, Immunization Safety Review (ISR) committee under Institute of Medicine (IOM) released a report on vaccinations and sudden unexpected death in infancy. A death that occurs suddenly and unexpectedly in the first year of life has been referred to the term “sudden unexpected death in infancy” (SUDI). SUDI includes death that can be attributed to identifiable causes and deaths for which the causes remain uncertain. SIDS is the diagnosis most commonly given to the deaths of uncertain cause.

Table 1. Main Frequently Reported Vaccines and Adverse Events in VAERS (1991-2001)

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>No.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B, recomb.</td>
<td>12,519</td>
<td>24.2</td>
</tr>
<tr>
<td>DTP + Hib conj. + OPV</td>
<td>5,344</td>
<td>10.3</td>
</tr>
<tr>
<td>Influenzae virus</td>
<td>4,696</td>
<td>9.1</td>
</tr>
<tr>
<td>MMR</td>
<td>3,386</td>
<td>6.5</td>
</tr>
<tr>
<td>TD</td>
<td>2,510</td>
<td>4.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>54.9%</strong></td>
<td></td>
</tr>
</tbody>
</table>

(1-B) Frequently reported adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>33,172</td>
<td>25.8</td>
</tr>
<tr>
<td>Injection-site hypersensitivity</td>
<td>20,359</td>
<td>15.8</td>
</tr>
<tr>
<td>Rash</td>
<td>14,112</td>
<td>11.0</td>
</tr>
<tr>
<td>Injection-site edema</td>
<td>13,960</td>
<td>10.8</td>
</tr>
<tr>
<td>Vasodilatation</td>
<td>13,929</td>
<td>10.8</td>
</tr>
<tr>
<td>Injection-site pain</td>
<td>10,382</td>
<td>8.1</td>
</tr>
<tr>
<td>Infection</td>
<td>9,741</td>
<td>7.6</td>
</tr>
<tr>
<td>Agitation</td>
<td>9,443</td>
<td>7.3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8,908</td>
<td>6.9</td>
</tr>
<tr>
<td>Pain</td>
<td>8,755</td>
<td>6.8</td>
</tr>
</tbody>
</table>

(1-C) Rare adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guillain-Barre syndrome</td>
<td>820</td>
<td>0.6</td>
</tr>
<tr>
<td>Sudden infant death</td>
<td>808</td>
<td>0.6</td>
</tr>
<tr>
<td>Autism</td>
<td>530</td>
<td>0.4</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>480</td>
<td>0.4</td>
</tr>
<tr>
<td>Anaphylactoid reaction</td>
<td>452</td>
<td>0.4</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>449</td>
<td>0.3</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>218</td>
<td>0.2</td>
</tr>
<tr>
<td>Intussusception</td>
<td>143</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Abbreviations: DTP, Diphtheria and tetanus toxoids and pertussis vaccine adsorbed; Hib, *Haemophilus influenzae* type b; OPV, oral poliovirus vaccine live trivalent (sabin strains types 1, 2 and 3); MMR, Measles, mumps, and rubella virus vaccine live; TD, Tetanus and diphtheria toxoid adsorbed for adult use.
for use in the U.S. in 1998, and was recommended for routine use in infants as a 3-doses at ages 2, 4, and 6 months. During clinical trials in vaccine-development, 5 cases of intussusceptions were observed among 10,054 vaccinees, compared with 1 case among 4,633 controls. In July 1999, after RRV-TV had been licensed and given to about 1 million children, 15 cases of intussusception following administration of the vaccine were reported to VAERS. In October 1999, the manufacturer followed the recommendation and withdrew RRV-TV for its use from the market.

Possible etiologies of intussusception following administration of RRV-TV vaccine have been proposed:

1. A strain or strains of rotavirus contained in RRV-TV vaccine may be pathogenic in a manner different from that caused by natural infection.
2. RRV-TV vaccine is probably given in a dose larger than that normally encountered after natural infection.
3. RRV-TV vaccine involves heterologous host viruses.

The exact etiology of intussusception following immunization of RRV-TV vaccine remains unclear. In addition to intussusception, a higher proportion of RRV-TV reports compared to non-RRV-TV reports included fever and various gastrointestinal symptoms, most notably bloody stool and other adverse reactions.

Two vaccines, including bovine (strain WC3)-human rotavirus reassortants and an attenuated G1P human rotavirus (HRV), have been studied intensively. Studies on safety, efficacy, and immunogenicity of live quadrivalent rotavirus vaccine (QRV) containing human-bovine (WC3) reassortant rotavirus serotypes G1, G2, G3, G4 and P were conducted using 2 to 6 months of infants to receive 3 doses of oral QRV or placebo at 4- to 10-week intervals. The vaccine reduced hospitalizations and emergency department visits related to G1-G4 rotavirus gastroenteritis occurring 14 or more days by 94.5%. Efficacy against any G1-G4 rotavirus gastroenteritis was 74.0%; efficacy against severe gastroenteritis was 98.0%. The vaccine reduced clinic visits for G1-G4 rotavirus gastroenteritis by 86.0%. Similar studies were also performed in an attenuated G1P human rotavirus (HRV) vaccine. The efficacy of the vaccine against severe rotavirus gastroenteritis and hospitalization was 85% and reached 100% against more severe rotavirus gastroenteritis. Hospitalization for diarrhea of any cause was reduced by 42%. During the 31-day after each dose, six vaccine recipients and seven placebo recipients had intussusception. The studies indicated that these two rotavirus vaccines were safe and immunogenic and provided a high degree of protection against rotavirus disease. The vaccines were not associated with an increased risk of intussusception.

Recently, the Food and Drug Administration (FDA) in the United States announced the approval of vaccine including bovine (strain WC3)-human rotavirus reassortants (RotaTeq®) which is manufactured by Merck & Co., Inc., a live, oral, vaccine for use in preventing rotavirus gastroenteritis in infants. Overall, approximately 72,000 healthy infants were studied in the United States and other countries in randomized placebo-controlled studies to look at the safety of RotaTeq®. Of these infants, almost 7,000 from the United States and Finland were also studied for efficacy. In these studies, RotaTeq® prevented 74 percent of all rotavirus gastroenteritis cases and 98 percent of the severe cases. In addition, RotaTeq® prevented approximately 96 percent of hospitalizations due to rotavirus gastroenteritis. The risk of intussusception for RotaTeq® was evaluated in a large-scale trial of over 70,000 children, of whom half received vaccine and the remaining half received placebo. In this study, RotaTeq® was not associated with an increased risk of intussusception when compared to placebo. In addition, RotaTeq® was not associated with an increased risk of other serious adverse events when compared to placebo. Extensive postmarketing studies and surveillance plans are being implemented to monitor for any increased risk of intussusception or other adverse events that may not have been detected in the precensure studies.

(B) Newer approaches to vaccine safety monitoring and causality

While VAERS is the initial safety screen providing the earliest signal of new vaccine reactions, it has major limitations, including underreporting, lack of specificity, accuracy, and a natural control group. To improve these limitations, new approaches to vaccine safety monitoring have been established. Since 1990, the CDC has worked with four health maintenance organizations (HMOs) to organize a Large Linked Data Base (LLDB) for vaccine safety studies as part of the Vaccine Safety Datalink (VSD) Project. In this project, automated vaccination records on half a million children under six years of age are linked to their medical records. This system is being used to examine the particular associations identified as requiring further investigation by the IOM safety surveillance. It is also utilized to further evaluate potential associations identified through VAERS, e.g. an association between seizures and DTP and MMR vaccinations by comparing vaccine exposures within specified time periods (one day for DTP, one week for MMR).

The VSD project focused its initial efforts on examining potential associations between vaccinations and a series of serious neurologic, allergic, hematologic, infectious, inflammatory, and metabolic conditions. However, the VSD project also is being used to assess
new vaccine safety concerns that may arise from the medical literature,\textsuperscript{27} VAERS,\textsuperscript{28} changes in immunization schedules,\textsuperscript{29} or from introduction of new vaccines.\textsuperscript{30} Over 30 studies are underway within the VSD project, including studies of the safety of inactivated flu vaccines among children, and thimerosal-containing vaccines. Disease- or syndromic-specific studies are also underway, including autism, multiple sclerosis, thyroid disease, acute ataxia, alopecia, rheumatoid arthritis, asthma, diabetes, and idiopathic thrombocytopenic purpura following vaccination.\textsuperscript{26,31}

Because the VSD project relies on comparison of incidence rates of adverse events between specified time periods following vaccination, these studies are, therefore, limited in their ability to investigate the association between vaccination and events with delayed or insidious onset such as autism and learning disability. Adverse events that do not involve a health care visit are also not easily studied. The project also can not easily assess mild adverse events, e.g. fever, and is not large enough to examine the risk of extremely rare events, e.g. Guillain-Barre syndrome (GBS), after each season’s influenza vaccine. In addition, because vaccines are not delivered in randomized, controlled trials, the VSD project may not be able to control for confounding and bias in each analysis and inference on causality may be limited.\textsuperscript{32,33}

Despite these shortcomings, the VSD project provides an essential, powerful, and cost-effective complement to ongoing evaluations of vaccine safety in the U.S.\textsuperscript{31,34}

The scientific information on the risks associated with pediatric vaccines was extensively reviewed by the IOM in 1990s.\textsuperscript{35,36} The IOM classified the evidence for a causal relationship between vaccine and a specific adverse event into one of five categories:

1. No evidence was available bearing on causality;
2. Evidence was inadequate to accept or reject a causal relationship;
3. Evidence favors rejection of a causal relationship;
4. Evidence favors a causal relationship; and
5. Evidence established a causal relationship.

The IOM’s review indicated that two thirds of the adverse events evaluated had either no (category 1) or inadequate (category 2) evidence for causality assessment. Relatively few associations were in either categories 4 or 5, in which the evidence favored or established a causal relationship (Table 2).\textsuperscript{36} Further revisions will be made as new evidence become available on these and newer vaccines, such as the association between oral polio vaccine (OPV) and GBS.\textsuperscript{37}

### Table 2. Evidence on Causality Between Adverse Events and Vaccine

<table>
<thead>
<tr>
<th>Causality category</th>
<th>DTP vaccine</th>
<th>Measles vaccine</th>
<th>Hib vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No evidence</td>
<td>Autism</td>
<td>Autism</td>
<td>(None)</td>
</tr>
<tr>
<td>2. Inadequate evidence to accept or reject</td>
<td>Asceptic meningitis</td>
<td>Seizure disorder</td>
<td>GBS</td>
</tr>
<tr>
<td>3. Evidence favored rejection</td>
<td>Infantile spasm</td>
<td>SIDS</td>
<td>Early-onset Hib disease (conjugate vaccine).</td>
</tr>
<tr>
<td>5. Evidence established</td>
<td>Anaphylaxis</td>
<td>Thrombocytopenia (MMR)</td>
<td>(None)</td>
</tr>
<tr>
<td></td>
<td>Anaphylaxis</td>
<td>Thrombocytopenia (MMR)</td>
<td>Anaphylaxis (MMR)</td>
</tr>
</tbody>
</table>

Abbreviations: GBS, Guillain-Barre syndrome; SIDS, Sudden infant death syndrome; Hib, \textit{Haemophilus influenzae} type b; MMR, Measles, mumps, and rubella virus vaccine live.
are being explored to permit more antigens to be combined, reducing the number of injections. These changes in vaccine development and delivery system, however, will continue to provide challenges in providing their safety to the general public. Combined with technological difficulties associated with investigating rare, delayed, safety allegations will exert vaccine safety concerns in immunization programs. Adding new vaccines to currently available combinations may induce the increased reactogenicity.

The risks of vaccine adverse events, both the common mild reactions and the rare, more serious reactions, are much outweighed by the public health benefit conferred by current vaccination practices. Epidemiologists, pediatricians, statisticians, and other health-care professionals should be involved in vaccine safety surveillance to investigate new and improved methods to monitor vaccine safety. Understanding of what factors may cause or aggravate certain vaccine adverse reactions, and which individuals are at high risk to experience such events will remain important issues for the public health community.

CONCLUSION

As vaccine-preventable infectious diseases continued to decline, general public became concerned about the adverse events associated with vaccines. Evaluation of vaccine safety is conducted on stages of research and development, clinical trials, and post licensure. Most safety monitoring of licensed vaccines in the U.S. involves passive reporting systems, including Vaccine Adverse Event Reporting System (VAERS), Large Linked Data Base (LLDB) as part of the Vaccine Safety Datalink (VSD) Project and others.

VAERS reports of vaccines during 1991 to 2001 indicate 15% of serious events including death, life-threatening illness, hospitalization, or permanent disability, and 85% of not-serious events, such as local reactions, fever within 1-2 days. The serious events are much difficult to evaluate with regard to their causal relationship with vaccines. The IOM classified the evidence for a causal relationship between vaccine and a specific adverse event into five categories. Two thirds of the adverse events evaluated had either no or inadequate evidence for causality assessment. Relatively few associations were in either the evidence favored or established a causal relationship.

REFERENCES


緒說

疫苗研發與接種時之安全監測

李啟仁¹ LUCIA H. LEE¹ 盧政雄² 黃儀君³ 朱夢麟⁴,⁵

疫苗的發展是現代預防醫學中最重要的成果之一，近年來，由於新疫苗的有效性很高，促使多種可預防的疾病發生率迅速降低，因而導致一般民眾逐漸開始關心疫苗安全的相關問題。疫苗的安全性可廣泛地藉由臨床前動物安全性試驗、臨床試驗、廠商的生產製造過程、與上市後的安全性監測來評估。

上市後的安全監測依賴被動報告系統和流行病學研究，在美國其系統包括：疫苗不良反應報告系統(Vaccine Adverse Event Reporting System, VAERS)、疫苗安全資料連網計畫(Vaccine Safety Datalink, VSD)及其他研究。VAERS每年大概會收到10,000件報告，其中有15%是嚴重的副作用，85%被分類為非嚴重副作用。此系統主要目的是分析各種不良反應的報告頻率、罕見副作用、輪狀病毒疫苗後的腸套疊、嬰兒猝死症候的案例及疫苗的各種安全性問題。這些疫苗副作用研究結果將疫苗與副作用之因果關係歸類為以下五類：(1)無證據(2)無足夠之證據來判定相關或不相關(3)證據支持不相關(4)證據支持有因果關係(5)證據確立。

未來的挑戰包括改善接種後不良反應的調查與監測系統、加強疫苗安全性研究與對疫苗風險之溝通討論、增加新疫苗免疫反應之可能性。

關鍵字：安全性監測，疫苗安全，疫苗接種，疫苗研發

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