History of Vaccine Information Statements

2016 was the 40th anniversary of the first vaccine patient information sheet produced by the Centers for Disease Control and Prevention (CDC). Since then, these materials have evolved, influenced by a variety of internal and external factors. How have these factors transformed vaccine information materials from the first "Important Information Statement" in 1976 to the 28 "Vaccine Information Statements" in use today?

› Introduction:

Vaccines are among the most important public health interventions in history[1], having led to the eradication of smallpox, and to significant reductions in the incidence of many other viral and bacterial diseases.[1] But like any medical intervention, vaccines also entail risk. Vaccine reactions are generally mild but they can, rarely, be severe. When a disease is common and can have serious consequences, the public generally finds that the benefits of a vaccine that can prevent it outweigh the relatively low risk of a severe side effect. But as the incidence of a disease declines, risks from vaccination, which remain relatively constant, can appear more prominent.[2] Ultimately, risks from the vaccine can seem more threatening than risks from the disease.

Providing patients (and the parents of pediatric patients) with accurate information about the benefits and risks of vaccination is important for both ethical and legal reasons. The Centers for Disease Control and Prevention (CDC) produces information sheets called "Vaccine Information Statements" (VISs), which describe the risks and benefits of vaccines, and are given to patients at the time of vaccination. The genesis of VISs was a 1974 legal case, and their subsequent history has been determined, in part, by a series of events and decisions that have transformed the earliest materials into those used today.

› Evolution of VIS Development:

1976. In the legal case, Reyes v. Wyeth Laboratories, parents of a child who developed vaccine-associated paralytic polio after receiving oral polio vaccine administered by a nurse, sued the vaccine's manufacturer and won. The court ruled that in the absence of a "learned intermediary" (i.e., a physician) the manufacturer is responsible for warning patients about a vaccine's potential risks.[3] Predictably, this caused consternation among manufacturers, as well as increases in vaccine prices to cover the cost of litigation.[4]

A challenge arising from this case was the need to provide patients with accurate and consistent information about vaccine risks and benefits. CDC negotiated with manufacturers and agreed to assume this responsibility by adding a "duty to warn" clause to CDC vaccine purchase contracts. This clause required that vaccines be administered only after an individualized medical judgment by a physician, or after "meaningful warnings related to the risks and benefits of vaccination" were provided in understandable language. On July 15, 1976, CDC issued the first vaccine information document in compliance with the second condition of this clause – an "Important Information Statement" (IIS) for bivalent "Swine and Victoria Influenza" vaccine.[5] Over the next decade, more than 50 IISs were issued for other vaccines, such as DTP (diphtheria, tetanus, and pertussis), MMR (and its single-antigen components: measles, mumps, and rubella), polio, and hepatitis B. IISs were required to be given only to persons receiving publicly purchased vaccines.

1986. IISs addressed the immediate goal of informing patients about vaccine risks. However, the problem of litigation over alleged vaccine injuries remained. The number of lawsuits involving DTP vaccine alone increased from one in 1978 to 73 in 1984, and there was danger of vaccine manufacturers withdrawing from the market.[6]

The new challenge was to not only inform patients about the risks and benefits of vaccines, but to find a no-fault alternative to the tort system for adjudicating vaccine injury claims. Public health agencies, physicians, vaccine manufacturers, and parent groups collaborated to draft mutually acceptable legislation, and in 1986 Congress

passed the National Childhood Vaccine Injury Act (NCVIA).[7] Along with creation of the National Vaccine Injury Compensation Program (VICP) and the Vaccine Adverse Event Reporting System (VAERS), the NCVIA mandated the development and distribution of written information materials for vaccines covered by the VICP (essentially those vaccines routinely recommended for children). The Secretary of the Department of Health and Human Services (HHS) was given authority to develop and disseminate these materials, and delegated that authority to CDC. These materials would be required for both publicly and privately purchased vaccines.

1991. The law established very specific criteria for the content of the vaccine information materials it had mandated (Figure 1), and also a very specific process for developing them. The latter involved multiple reviews, participation by a wide range of interest groups, publication in the Federal Register for 90 days of public comment, an opportunity for a public hearing, and development by "rule" through the notice and comment process of the Administrative Procedure Act. Consequently, initial development of these materials took nearly five years, from passage of the law in 1986 until publication in 1991 of four 12-page "Vaccine Information Pamphlets" (VIPs), for DTP, MMR, oral polio, and tetanus-diphtheria (Td) vaccines.

1994. In spite of the time and effort spent developing the VIPs, and the fact that many patients found them informative and easy to understand, they were criticized by both providers and patients for the overwhelming amount of information they contained, for being too unwieldy to be read and comprehended during a clinic visit, and for the amount of time required to develop and finalize them.[8] It was even suggested that the VIPs' length discouraged careful reading, resulting in patients who were actually less informed than they would have been given simpler materials.[9]

The challenge was to make vaccine information documents easier to produce and easier for patients to use. In response to concerns about the VIPs' length and the difficulty and time required to develop them, Congress amended the NCVIA in 1993, simplifying the requirements for both their content and the process for developing them. Ten specific elements required by the 1991 law were replaced with four more general requirements (See Figure 1). The length of the required public comment period was reduced to 60 days, and requirements for a public hearing and development by rule were eliminated.[10] In compliance with the amended law, CDC developed new, single-sheet (two-sided), information materials and renamed them "Vaccine Information Statements" (VISs).

1996. Throughout the early 1990s, new vaccines were developed, licensed, and recommended. By 1996, there were nine vaccines requiring VISs – more than twice as many as when the law mandating them was passed. In addition, CDC's recommendations were frequently changing as new data became available, requiring updating of the relevant VISs. At the same time, providers who used the documents, patients who received them, and subject-matter experts who reviewed them were requesting that VISs incorporate additional "nice to know" information, beyond that required by law. Given the long production time, even under the amended law, VIS drafts were frequently out of date before they were finalized, requiring the process to be restarted. This, in turn, led to continued use of existing VISs, which might not contain current information, or delay of publication of a new VIS until months after the vaccine became available – leaving patients temporarily without this legally-mandated document.

Now the challenge was to assure that VISs could be made available to patients in a timely manner, by reducing development time. This was achieved by producing "interim" VISs – essentially temporary VISs that could be published after review by only CDC and FDA experts, and used until a final edition could be developed. Over the following years, many VISs became interim editions.

1997. The law requires that VISs be developed for all vaccines that are covered by the VICP, but there are vaccines that are not covered – travel and special-purpose vaccines such as rabies, typhoid, Japanese encephalitis, anthrax, and yellow fever; and vaccines recommended only for adults, such as zoster. There were no VISs for these vaccines.

By 1997, CDC had produced VISs for all vaccines for which they were required, and developers were able to turn their attention to the remaining vaccines. The first VIS for a non-covered vaccine was pneumococcal polysaccharide vaccine. Subsequently, VISs have been developed for other non-required vaccines, and now exist for virtually every vaccine licensed in the United States. (There are two exceptions: BCG, which is not used as a vaccine in the U.S., and smallpox, for which a comprehensive "Medication Guide" was developed to serve the same purpose.) Because these vaccines are not covered by the NCVIA, they are not subject to the same development requirements and can be produced much more quickly, with only CDC and FDA reviews.

2008. A child between 2 months and 6 years of age could (and still can) receive as many as nine vaccines at a single visit.[11] A parent could realistically find him- or herself required by law to read four or five VISs at a time, adding to the stress inherent in childhood clinic visits.

The challenge was to reduce this burden on the parent, while still providing information required by law. In January of 2008 CDC introduced the first "Pediatric Multi-Vaccine" VIS. By consolidating information from five childhood VISs (DTaP, polio, hepatitis B, pneumococcal conjugate, and *Haemophilus influenzae* type b) into a single two-page document, VIS developers were able to reduce parents' reading load considerably. This reduction was accomplished by eliminating some "nice to know" information, such as detailed explanations of indications or catch-up schedules, and consolidating information, such as descriptions of VICP and VAERS, which are common to all VISs.

2013. As noted above, interim VISs have allowed CDC to comply with the spirit of the NCVIA by making vaccine risk and benefit information available to patients in a timely manner. However, the law still requires VISs to be developed according to a lengthy mandated process. Changes in recommendations that required corresponding changes on VISs continued to delay production of final editions. It became evident that to allow VISs to be finalized in a reasonable amount of time they had to be made less vulnerable to these changes. This was easier said than done. Information required by the NCVIA is relatively stable, but other information that was being incorporated into VISs was more susceptible to change. Interestingly, much of this information (e.g., lists of indications, technical details about the composition of the vaccine, or complex catch-up schedules) is of little use to patients, but relevant to providers. Vaccine providers liked having this information on VISs because it was a convenient reminder of information that can be time-consuming to find in CDC recommendations, or because it contained answers to questions patients frequently asked them.

The challenge, therefore, was to remove useful but unnecessary information from VISs but still have it easily accessible by providers. In 2013, CDC produced the first "provider information document" – a VIS supplement accessible from the same webpage as the corresponding VIS, containing a summary of ACIP recommendations and other information designed to give the provider a single, convenient source of relevant information about the vaccine. Provider documents were produced for five VISs, and informal communications between providers and CDC staff suggested that providers found them very helpful. In 2016 it was determined that, rather than creating these new documents, which might require periodic updates, the same end could be served by adding links from CDC's VIS webpage to other CDC webpages containing comparable information.

In addition to these major changes in VISs over the decades, VISs have evolved in response to other factors. Requests from providers serving non-English speakers have resulted in translation of VISs into more than 40 languages;[12] the population's transition from a "paper" to an "electronic" society led to reformatting of VISs to make them accessible through electronic media;[13] and ongoing concerns about readability inspire continuous re-evaluation of VIS language conventions.

› Public Health Implications

It is estimated that vaccines have prevented more than 300 million childhood illnesses and more than 700,000 premature deaths between the years 1994 and 2013.[14] While this time period happens to coincide with the introduction of VISs and their continued use, whether VISs have had an impact on vaccine coverage is unknown. However, a recent study looking at acceptance of human papillomavirus (HPV) vaccine reported that CDC's VIS "significantly increased perceptions of vaccine benefits and decreased perceived risks."[15]

No figures are available on the number of paper copies of VISs distributed prior to their availability on the internet; but since then the annual number of downloads from CDC's VIS website has grown substantially. For example, downloads of influenza VISs increased from 113,004 in 2005, to 316,378 in 2010, to 621,054 in 2015; and the number of providers who have registered to receive VIS e-mail updates has grown from fewer than 70,000 in July 2011 to more than 235,000 by February 2017.

CDC's Vaccine Information Statements have evolved considerably through several decades of growth and change in the US vaccination program. As future needs and challenges arise, they will undoubtedly continue to evolve, and continue to fulfil their mandate to clearly inform patients about the benefits and risks of all vaccines.

NCVIA Requirements for Content of Vaccine Information Materials Under the Original (1986) vs. Amended (1993) Laws

ORIGINAL LAW	AMENDED LAW
1. The frequency, severity, and potential long-term effects of the disease to be prevented by the vaccine	
2. The symptoms or reactions to the vaccine which, if they occur, should be brought to the immediate attention of the health care provider	
3. Precautionary measures legal representatives should take to reduce the risk of any major adverse reactions to the vaccine that may occur	
4. Early warning signs or symptoms to which legal representatives should be alert as possible precursors to such major adverse reactions	
5. A description of the manner in which legal representatives should monitor such major adverse reactions, including a form on which reactions can be recorded to assist legal representatives in reporting information to appropriate authorities	1. A concise description of the benefits of the vaccine
6. A specification of when, how, and to whom legal representatives should report any major adverse reactions	2. A concise description of the risks associated with the vaccine
7. The contraindications to (and bases for delay of) the administration of the vaccine	3. A statement of the availability of the National Vaccine Injury Compensation Program
8. An identification of the groups, categories, or characteristics of potential recipients of the vaccine who may be at significantly higher risk of major adverse reaction to the vaccine than the general population	4. Such other relevant information as may be determined by the Secretary
9. A summary of: a. Relevant federal recommendations concerning a complete schedule of childhood immunizations, and b. The availability of the National Vaccine Injury Compensation Program	
10. Such other relevant information as may be determined by the Secretary [of Health and Human Services]	

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