**INTRODUCTION**

Immunizations are among the most successful and cost-effective disease prevention interventions available (1). In the United States, the introduction of routine immunizations has greatly reduced the incidence of several vaccine-preventable diseases (table 1). Similar success in disease reduction has been demonstrated by immunization programs in many other countries (2, 3). The World Health Organization’s Expanded Programme on Immunizations (EPI), with assistance from the United Nation’s Children’s Fund (UNICEF) and other donors, has made great strides in extending these benefits to developing countries (4). Immunizations permitted the global eradication of smallpox (5) and may do the same for poliomyelitis (6) and some other diseases. Interest in immunization programs continues to grow as countries attempt to improve the rational allocation of their scarce health resources. Developments in biotechnology and immunology offer the promise of new vaccines against many diseases old and new, ranging from malaria to acquired immunodeficiency syndrome (AIDS) (7), including some noninfectious diseases like cancer (8). In sum, immunization programs represent an impressive attempt by the human species, via science and social organization, to purposefully alter the ecology of certain infectious diseases in its favor. While some individuals may view this as hubris against nature (9), most persons willingly accept that less disease is better.

Epidemiologic studies and principles, experimental and observational, play a critical role in guiding almost all steps of a successful immunization program (10). Prior to licensure, a vaccine must demonstrate its safety and efficacy in phased clinical trials. Post-licensure, continued close monitoring of the vaccine’s safety and effectiveness is needed, especially early on. But equally important to a vaccine’s ultimate success is the close monitoring of the immunization program itself.

Surveillance for vaccine coverage, disease incidence, and adequacy of the cold chain provide the benchmarks for an immunization program to judge its progress. Rigor in design, conduct, and analyses of epidemiologic studies to understand the risk factors for nonvaccination, vaccine failure, and cold chain failure permits development of accurate and timely adjustments to immunization programs and policies to ensure their ultimate success. This review will discuss the epidemiologic methods used in the various phases of an immunization program drawing largely, though not exclusively, on the experience in the United States.

**PRE-LICENSE**

**Clinical trials**

The goals of the pre-licensure studies are to 1) identify a candidate vaccine, 2) show that the vaccine is safely tolerated in terms of local and systemic reactions (“safety”), and 3) demonstrate that the vaccine confers protection against the target disease (“efficacy”), either directly in terms of disease reduction, or indirectly in terms of elicitation of protective antibodies. Pre-licensure studies are carefully phased in design and conduct. Impressive progress in biotechnology during recent decades has revolutionized not only the capability to rapidly identify the causative organisms for new illnesses (11), but also to engineer and produce vaccines that are potentially safer, more effective, easier to produce, and less costly (12). This biotechnology revolution poses a tremendous challenge to the traditional “vaccine development system” to provide adequate and timely assessments so that maximum benefits might be reaped from these advances (7).

After isolation and characterization of the causative organism for a disease, inactivation or attenuation permit the development of candidate vaccines (13).
TABLE 1. Comparison of maximum and current reported morbidity: vaccine-preventable diseases and vaccine adverse events, United States, 1995

<table>
<thead>
<tr>
<th>Disease</th>
<th>Maximum cases (year)</th>
<th>1995*</th>
<th>Percentage change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diptheria</td>
<td>206,939 (1921)</td>
<td>0</td>
<td>-99.99</td>
</tr>
<tr>
<td>Measles</td>
<td>894,134 (1941)</td>
<td>301</td>
<td>-99.97</td>
</tr>
<tr>
<td>Mumps</td>
<td>152,209 (1968)</td>
<td>840</td>
<td>-99.45</td>
</tr>
<tr>
<td>Pertussis</td>
<td>265,269 (1934)</td>
<td>4,315</td>
<td>-98.37</td>
</tr>
<tr>
<td>Polio (wild)</td>
<td>21,269 (1952)</td>
<td>0</td>
<td>-100.00</td>
</tr>
<tr>
<td>Rubella</td>
<td>57,866 (1969)</td>
<td>128</td>
<td>-99.78</td>
</tr>
<tr>
<td>Congenital rubella syndrome</td>
<td>20,000† (1964-1965)</td>
<td>7</td>
<td>-99.96</td>
</tr>
<tr>
<td>Tetanus</td>
<td>601 (1948)</td>
<td>34</td>
<td>-97.82</td>
</tr>
<tr>
<td>Invasive Haemophilis influenzae type b disease</td>
<td>20,000† (1994)</td>
<td>1,164</td>
<td>-94.18</td>
</tr>
</tbody>
</table>

Vaccine adverse events

0† 10,594

* Final totals of reported cases to the Centers for Disease Control and Prevention.
† Estimated because no national reporting existed in the prevaccine era.

Such candidate vaccines are tested in animals (14) before advancing to phased human clinical trials. Phase I trials usually enroll 10–100 adult volunteers to assess initial safety tolerance and acceptable vaccine dosage in humans. Phase II trials seek to expand knowledge about the safety, optimal dose, route of administration, and schedule (primary series and if needed, boosters) of the candidate vaccine. Sample sizes usually range from 25 to 1,000 persons.

Phase III clinical trials aim to show that the candidate vaccine is efficacious in conferring protection on a targeted, at-risk population under controlled conditions. Safety issues are also examined to the extent the sample size and study duration permit. As with any clinical trial, issues such as case definition, case finding, trial design, and sample size must be considered carefully (15). Classically, a prospective, double-blind, randomized, controlled design is used. Occasionally, studies with open (16), historic control (17), or household secondary attack rate (18) designs are used.

Based on a comparison of the disease incidence rate of vaccinated to unvaccinated individuals, the percentage reduction in disease as a result of the vaccination, or vaccine efficacy, is calculated (see the section on Vaccine efficacy and vaccine effectiveness studies below) (19). Comparison of adverse event rates between the two groups is also made. The accurate ascertainment of cases and, therefore, the accuracy of the vaccine efficacy calculation, depends greatly on which endpoint is selected for the trial.

The endpoint “case definition” may be a laboratory result, a clinical finding, or combination of both. The goal of the immunization may be to prevent infection (e.g., by human immunodeficiency virus (HIV)), to prevent the final disease (e.g., AIDS), or prevent severe disease (e.g., pertussis). Whatever the endpoint chosen, the specificity of the diagnosis is more critical to the accuracy of the vaccine efficacy estimate than the sensitivity of diagnosis (20). Another key goal of Phase III trials is to establish a laboratory correlate of human protection if possible. This permits a potency test to be developed and standardized for use in prerelease testing as well as a surrogate endpoint in future trials.

Program goals and strategies

After a vaccine completes the clinical trials and licensure is imminent, several decisions must be made prior to its introduction into a vaccine program. The goals of the program and the appropriate strategies to reach them need to be defined. This in turn determines how widely the vaccine can be used, which target populations should receive it, and how rapidly use of the vaccine must be implemented. The disease control strategy is dictated to a large degree by 1) the epidemiologic features of the disease (21), 2) the adequacy of the health infrastructure, and 3) the resources available (22). Vaccination strategies in developing countries may confront difficult choices (23), especially in terms of the balance between a "vertical" (immunization is directed from the national level as a separate program) versus an “integrated” (where it is part of a comprehensive primary care effort) immunization program (24).

After considerable experience in disease prevention through vaccination has been gained, elimination or eradication of the vaccine-preventable disease (the absence of disease with, and without, a continuing threat of reintroduction, respectively) is usually considered. Special strategies like “ring immunization” for smallpox (25) or “national immunization days” for poliomyelitis (26) are usually required to move from simple disease control to eradication.
Disease surveillance data on age groups, special populations at risk, and illness complications are important in evaluating the cost and benefits of vaccination strategies. For example, surveillance data were useful in designing strategies for vaccination against measles and rubella. Measles was a disease that affected many young children prior to school entry while rubella was uncommon before school age (27, 28). Thus, measles immunization programs needed to target both children at 1 year of age and those in elementary school. In contrast, vaccination efforts against rubella could either be narrowly targeted at prepubertal females (29) or be used universally among all children of both sexes (30). The latter strategy has been shown to be more successful as vaccine coverage is higher and provides greater herd immunity by reducing rubella transmission but at a higher cost (31). When adequate surveillance data are available, different options for control strategies can be modeled mathematically to obtain quantitative insights in lieu of mere intuition (32).

Once a vaccine has shown good results in an efficacy study, an effectiveness study may be needed to determine if the use of the vaccine in routine public health practice is indicated. The initial evaluation of the Ty21a oral typhoid vaccine was done with a liquid formulation that was efficacious but was not suitable for mass production. Subsequent trials compared more convenient capsule and enteric-coated tablets against the liquid formulation (33). New health programs today frequently also need to demonstrate cost effectiveness, as was done prior to licensure of the *Haemophilus influenzae* type b polysaccharide (34) and varicella (35) vaccines.

Phase III trials by necessity must evaluate the efficacy of the candidate vaccine when used alone. With the increasing number of antigens routinely recommended in infants and children, simultaneous or combined administration of multiple antigens becomes increasingly attractive to minimize the costs and the number of health care visits and injections needed to complete the immunization series (36). The safety and immunogenicity of simultaneous or combined vaccinations require careful evaluation to ensure there is no interference in immunogenicity or enhancement of adverse reactions (37). Such “Phase IIIb” trials are practical only if a serologic correlate of efficacy is established during the “Phase IIIa” trials, as was done for the licensure of combined diphtheria-tetanus-pertussis- *H. influenzae* type b vaccines (38).

**POST-LICENSEE**

Once a vaccine has been shown to be efficacious, it would be unethical to deliberately withhold it from certain populations in further studies to provide a comparison group. Therefore, in contrast to pre-licensure studies which have the relative “simplicity” of experimental designs, most post-licensure studies are observational and epidemiologic in nature. Issues of confounding and bias, which were minimized by random allocation of vaccinated and unvaccinated persons in pre-licensure studies, must now be either rigorously controlled for in-study design and analyses, or taken into account during the interpretation of surveillance data.

Because of the limits in size, duration, and population heterogeneity of preclinical trials, usually much remains to be learned about the characteristics of a vaccine and its optimal use after licensure. Rarer adverse events, such as vaccine-associated paralytic poliomyelitis (39) or mumps vaccine-associated aseptic meningitis (40), may not have been detected earlier. Certain batches of vaccine may turn out to be unsafe or ineffectual, leading to improvements in manufacturing and quality control (41). Some issues, such as duration of vaccine-induced immunity, may require decades to assess (42).

Surveillance on several aspects of an immunization program are needed to assure its optimal performance. This may include collection of data on vaccine distribution, adequacy of the cold chain, adequacy of sterilization, the cost of the vaccine, public attitudes toward the importance of immunizations, characteristics of populations who have not been vaccinated, characteristics of remaining cases of disease, characteristics of persons experiencing adverse reactions (43), and even the number of lawsuits filed against vaccine manufacturers (44). Special studies, epidemiologic, laboratory, combination, or others, may be needed to better understand and solve potential problems identified by these immunization program surveillance/information systems.

As immunizations change the epidemiology of vaccine-preventable diseases, the immunization schedule may require fine tuning based on risk data from outbreak investigations. This was the basis for changing the age for measles vaccination in the United States from 9 months upon initial licensure to 12 months and then to 15 months (45). Modeling studies may also be used to better analyze strategy options (46). Additional cost-effectiveness studies may be needed to garner continued program support (47). Serum surveys may be used to assess any major gaps in immunity that could result in future outbreaks (48).

A sophisticated surveillance system is also needed because of the dynamic nature of the relation between 1) disease incidence, 2) vaccine coverage, and 3) vaccine adverse events as an immunization program progresses from preimplementation to final disease
elimination/eradication (figure 1). Information about at least these three variables is needed by health authorities with responsibilities for weighing the costs, risks, and benefits of an immunization program and recommendations for the use or discontinuation of a vaccine. When the risk of complications from smallpox vaccine exceeded that from smallpox itself in the United States, the Advisory Committee on Immunization Practices (ACIP) recommended that smallpox vaccination be discontinued (49). To assure the correct decisions are made, the information system needed will have to be tailored to each phase. At all times, both surveillance and special studies are needed. However, the level of sophistication required of both types of information generally increases with each phase.

Surveillance of vaccine-preventable diseases

General issues. Surveillance systems differ from special studies in that they are usually designed to monitor trends, detect and describe problems, and to establish hypotheses to be tested in more refined research designs (50). Surveillance systems are ongoing, limited data are collected on each case, and data analysis is traditionally straightforward. In contrast, special studies are usually designed to test specific hypotheses, are usually time-limited, data collection can be complex, and analyses are often sophisticated.

All passive surveillance systems tend to generate incomplete data. Cases of disease reported to surveillance systems are not random and may reflect a number of biases. For example, reports of pertussis cases tend to include persons with the most severe disease. About 40 percent of the pertussis cases reported to the Centers for Disease Control and Prevention (CDC) were hospitalized (51), compared with <10 percent in community-based studies (52). Despite underreporting and other potential biases, surveillance data have been remarkably useful in serving the needs of public health programs (53).

Analysis of age-group specific measles surveillance data during the 1989–1990 measles outbreak pointed to the importance of unimmunized preschool children as the main risk group (54). A gradual increase in pertussis incidence after a long historic decline may reflect waning immunity in adolescents and adults due to decreased circulation of pertussis mostly from a successful vaccination program (55). Analysis of surveillance data may point out areas for special vaccination campaigns. Examination of the US measles surveillance data from 1980 through 1989 showed that measles was endemic in only 0.5 percent of the nation’s 3,137 counties (56). Measles cases from these counties were probably responsible for much of the measles transmission during these years. These data added impetus to programs targeted at age-appropriate immunization of children by age 2 years in the United States (57).

Innovative analysis of surveillance data may provide insight into the pathogenesis of vaccine preventable diseases. The lack of expected increase in the interepidemic period with increasing pertussis vaccination levels led Fine and Clarkson (58) to hypothesize that pertussis vaccine was more effective in protecting against disease than against infection. This hypothesis has since been supported by other studies (59). The rapid disappearance of diphtheria (60) and H. influenzae type b (61) relative to population vaccination levels suggests that, in addition to individual protection, immunization may play a role in reducing carriage of pathogenic organisms. Comparison of measles immunization rates, obtained via retrospective school surveys with measles attack rates among census tracts in Milwaukee, Wisconsin, provided insight on the level of herd immunity necessary to halt transmission (62).

Sources of data. Most surveillance systems generally rely upon case reports by physicians, other health care workers, or laboratories. This is particularly true for diseases like measles and mumps with characteristic clinical symptoms and signs and for which few cases are hospitalized and few attempts are made to confirm cases through the laboratory. School-based surveillance, usually based with the school nurse, needs to identify reasons for absenteeism. Frequently such reports are delayed because ill students may otherwise escape detection until their return to school. This can impede control efforts if vaccinations need to be started at the time of the first case.

For surveillance of diseases like invasive H. influenzae type b, laboratories and hospitals can be more useful because most cases of invasive illness are both hospitalized and confirmed via the laboratory. Laboratory surveillance is also important for pertussis, rubella, and hepatitis B because of the difficulties in
making the clinical diagnosis. Mortality records are used for evaluating health impact and the characteristics of persons who die with a given disease. A special surveillance system including deaths registered in 121 US cities each week is used to determine the existence of an epidemic of influenza by comparing the reported proportion of total deaths due to pneumonia and influenza with expected proportions based on nonepidemic years (63).

In the United States, the Council of State and Territorial Epidemiologists, in collaboration with the CDC, develops the list of diseases recommended to be reported by states to the CDC. Canada and most other countries have a similar process (64). Among the vaccine-preventable diseases, cases of diphtheria, tetanus, pertussis, polio, H. influenzae type b (invasive disease), measles, mumps, rubella, congenital rubella syndrome, hepatitis A, and hepatitis B are currently officially reportable via health departments of the States and the District of Columbia on a weekly basis to the CDC. For selected diseases like measles, pertussis, tetanus, and polio, additional details on each case are gathered via a supplementary surveillance form by county and state health staff. In addition, there are special surveillance systems for H. influenzae type b and hepatitis B disease. Varicella is a notifiable disease in some states, and those data are shared on an annual basis with the CDC.

Case definitions. Case definitions vary with the goals of the surveillance system. For example, prior to beginning a vaccination program or during its early phases, all physician reports are usually accepted (i.e., the case definition is a physician diagnosis). However, as disease incidence decreases and a greater degree of disease control is achieved, individual cases are investigated by health department personnel, and case definitions tend to become more precise. For example, the case definition for measles can also require laboratory confirmation or epidemiologic linkage to another case meeting the same clinical criteria. Clinical information from reported suspected cases of poliomyelitis is now reviewed by a panel of three experts before being accepted as a case (65). These stricter definitions increase the predictive value positive of reported cases. The predictive value positive would normally fall as disease incidence decreases unless stricter definitions are used.

The current case definitions used by the CDC for notifiable vaccine-preventable diseases have been published (66). Similar definitions have been elaborated by Canada (64). Most of these definitions are based on clinical and epidemiologic experience; some have been evaluated for sensitivity and specificity during special investigations. For example, outbreak investigations in Wisconsin, Delaware, and Missouri revealed that a case definition for pertussis of cough for 14 or more days duration was 81–92 percent sensitive and 58–90 percent specific in the outbreak setting (67, 68). The ideal sensitivity and specificity of case definitions depends upon the outcomes desired from surveillance. For controlling outbreaks, particularly during disease elimination and eradication, high sensitivity with rapid reporting becomes important for early action. For studies, such as vaccine efficacy evaluation, specificity assumes greater importance (20).

Disease registries, sentinel surveillance, and universal surveillance. Because of the expense and other difficulties of conducting large-scale active surveillance on an entire population, some programs target sentinel sites for special emphasis. For example, since 1982, the CDC has conducted intensive surveillance and investigations of hepatitis in four sentinel counties (69). This surveillance suggested that hepatitis B disease was underreported by 50 percent. In addition, the comprehensive nature of the surveillance allowed greater confidence to be placed in the data which showed decreasing prominence of persons citing homosexual behavior as a risk factor and increasing prominence of intravenous drug abusers and persons engaging in heterosexual activity (70).

Well developed sentinel surveillance systems are used by some European governments to provide information on disease occurrence (71). The World Health Organization’s EPI has encouraged many developing countries to adopt sentinel systems in which reports are accepted from selected providers within a community, generally the large hospitals (72). Such sentinel systems, while generally inexpensive, may give biased information depending upon how representative the sites are of the general community. For example, hospital-based systems are more likely to report sicker children who tend to be younger and unvaccinated than cases occurring in the community at large. Nevertheless, even these surveillance data are useful for evaluating trends and estimating the initial impact of the vaccination program (73). Such systems may become less useful as wide vaccine use reduces disease incidence.

Special registries may be maintained for rare diseases of special interest. The CDC maintained a registry which compiled data on women vaccinated with rubella vaccines within 3 months of conception (74). The women were followed prospectively to determine whether vaccination was associated with adverse pregnancy outcomes. In 1989, the registry was discontinued when adequate data had been accumulated to indicate that the risk of congenital rubella syndrome.
following vaccination, if any, was less than 1.2 percent. A similar registry has been started to follow pregnancy outcomes after varicella vaccination. A subacute sclerosing panencephalitis registry was created to determine both whether vaccination against measles prevented this disease or whether it could be caused by vaccination (75). Data thus far show that subacute sclerosing panencephalitis has virtually disappeared from the United States (76).

**Evaluation.** Guidelines for evaluation of public health surveillance systems have been developed (77). Such evaluations consist of determining usefulness, simplicity, flexibility, acceptability, sensitivity in detecting the true number of cases or epidemics, predictive value positive of reported cases (i.e., the proportion of cases reported that are true cases), representativeness of reported cases, timeliness of reporting, and cost-effectiveness. With regard to immunization, major questions have revolved around sensitivity and predictive value positive.

Estimates of underreporting are possible for diseases like measles which are essentially universal childhood infections. Prior to the licensure of measles vaccines in 1963, approximately 400,000–500,000 cases were reported annually at a time when roughly 4,000,000 children were born each year (27). Thus, the 400,000–500,000 cases reported represented approximately 10 percent of the total cases occurring in the United States. Surveillance data were supplemented by special population-based studies which corroborated the validity of the surveillance information (28).

Once the disease burden decreases due to vaccination, however, the total remaining burden is difficult to estimate. Particular use has been made of the Chandrasekar and Deming method of estimating the reporting efficiency for various vaccine-preventable diseases in the United States (78–81). This method requires two independent surveillance systems detecting the same illness and measures the degree of overlap to estimate the total burden. It is similar to capture-recapture systems used to estimate animal populations. The efficiency of measles notification in England and Wales has been estimated to be 40–60 percent, while that of pertussis is 5–25 percent (82). Efficiency of vaccine adverse events reporting can be evaluated if population-based estimates based on prior studies are available (83). Predictive values positive studies use gold standards such as laboratory confirmation to evaluate the proportion of cases, given a particular case definition, that are laboratory confirmed (67).

**Serologic surveillance**

Immunization programs aim to substitute vaccine-induced immunity for that from disease. Neither history of disease nor vaccination may be an accurate marker of true immunity. Therefore, if a serologic correlate of protective immunity against a vaccine-preventable disease exists, periodic serologic surveys are useful in 1) evaluating the success of an immunization program and 2) identifying groups with low immunity that might require changes in vaccination strategy (48).

The United Kingdom switched from a selective to a universal rubella immunization policy after results of routine antenatal testing showed an unacceptably high rate of susceptibility (84). Hungary selected the age groups for a special measles vaccination campaign based on serosurveys (85). Serosurveys in recruits have been used to refine immunization policy in the military (86). Serosurveys in all countries with long-standing childhood vaccination programs against diphtheria have shown a high proportion of adults to be susceptible (60). Not surprisingly, adolescents and adults constitute a high proportion of diphtheria cases in the current resurgence in Russia and Ukraine (87).

As with all surveys, representativeness of the sample and participation rate are critical to interpreting the results. More importantly, requires for obtaining, shipping, and laboratory assay of serologic specimens make serosurveys relatively expensive. These factors plus the relative slow change in population immunity profiles suggest that the frequency of serosurveys should be periodic (e.g., decennial National Health and Nutrition Examination Survey (NHANES) in the United States (88)) versus annual.

**Vaccination coverage**

Because no vaccine is perfectly efficacious, vaccination levels are not the same as immunity levels. Once rates of primary and secondary vaccine failure are known from special studies, an estimate of immunity levels is possible in conjunction with knowledge of the vaccination levels. In practice, because primary and secondary vaccine failure rates are fairly low for most routinely recommended vaccines, vaccination levels provide a reasonable measure of the progress of a vaccination program. Vaccination coverage can be monitored via direct measurement of vaccination levels, or estimated indirectly by several ways including 1) surveys, 2) reports of doses of vaccine administered, and 3) reports of doses of vaccine distributed. As vaccine coverage reaches high levels, indirect measurements may not provide the accuracy and precision needed to improve the marginal coverage. Accurate ascertainment of vaccination history is also critical to any epidemiologic study of vaccines as this represents the "exposure".

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Direct measurement (vaccination registry, school entry census). Since 1978, national immunization levels in the United States have been assessed at school entry. Each state health department reports the results of their assessment to the CDC where a national estimate is calculated. School enterer levels are not measured by sample survey but represent a census of the immunization status of all en enters. Each school must review the immunization status of each new enterer because of laws requiring specified immunizations prior to admission to school. Data from each school are usually compiled by school nurses or other school officials from immunization records on file for each student. State immunization program personnel perform sample validation surveys to confirm the school reports (89).

The major advantage of this approach is that coverage levels are based on records rather than parental recall. Since many parents do not have immunization records of their children at home, persons doing telephone surveys, or even home visits, would have to list persons without records as unknown or rely on parental recall. Another advantage of the school enterer assessment is that because it is a census, there is no potential bias from sampling.

The major disadvantage is that immunization levels are measured several years after vaccination should have been administered. A second problem relates to validity of the records. Most states require physician confirmation of immunization status. However, if physicians rely on parental recall rather than records to certify immunization, falsely high immunization levels may be reported. Finally, assessment of newly recommended infant vaccinations like *H. influenzae* type b and hepatitis B on a timely basis are not possible from examining school enterer vaccination data.

In the United States, requirements for recording of vaccination administration by providers has recently been legislated (90). These requirements plus the increasing automation of health care practice has led several health maintenance organizations to fully computerize their vaccination records (91). This permits easy, timely assessment of vaccination levels by physicians, by clinic, as well as for the health maintenance organization (92). Planning for expanded use of such vaccination registries in the United States is underway (93). In England and Wales, computerized preschool child registers combined with vaccination histories have permitted more rapid, frequent, and accurate assessment of vaccine coverage in almost all districts (94).

Indirect measurement—EPI 30 cluster survey. Surveys are commonly used to provide a more efficient estimate of vaccination levels. Perhaps the best known is the 30 cluster two-stage stratified random survey initially developed for use during the smallpox eradication program (95). This method has since been used widely in the World Health Organization’s EPI as a “gold standard” (with validity generally ±10 percent of actual levels) to validate administrative estimates of vaccine coverage (96). It has also been adapted to examine rates of neonatal tetanus deaths and polio lameness (97). Coverage Survey Analysis System (COSAS), a software to rapidly analyze the results of EPI 30 cluster surveys has been developed (98).

The EPI survey has been criticized because the sampling frame is not based on households but a convenience sample of the target population living in close proximity to the selected starting point (99). Evaluation of the 30 cluster method, however, has shown it to be generally accurate within the desired 10 percent of the true levels, though it is particularly insensitive to pockets of unvaccinated persons (100). This can be ameliorated by expanding the number of clusters to what resources permit (101). The advantage of the 30 cluster method includes its relative ease of use with moderate training. Its standard methodology permits aggregation of results from smaller geographic areas.

The main disadvantage of the EPI survey is that the method requires a sampling frame for the population of interest. Any census data available may be woefully out-of-date, especially in rapidly growing urban areas in developing countries (102). Home vaccination records may be limited. Substantial logistical resources may also be needed for the survey team to travel to remote locations selected for study. The EPI survey can be particularly difficult to interpret if a substantial proportion of respondents lack accurate vaccination records. This problem is likely to worsen as EPI adds more vaccines, requiring greater recall by parents. Techniques for improving the accuracy and precision of the cluster survey method have been proposed (99, 101).

Indirect measurement—other surveys. The United States has tried a variety of approaches to estimating vaccination levels among preschool children, none of which are entirely satisfactory. From 1959 to 1985, an annual survey of households to determine immunization levels for all key age groups (United States Immunization Survey (USIS)) was performed (published and unpublished data, US Immunization Survey Reports, Division of Immunization, CDC, Atlanta, Georgia, 1959–1985). Beginning in 1972, the data were collected principally by telephone interview. Most of the answers were based on parental recall, and the results were generally substantially lower than the results of the school enterer assessments. In 1979, a
question on whether parents were reading from records was added. Vaccination levels based on the approximately one-third of respondents with records more closely approximated results from the school enterer assessments (103). Due to concerns with the accuracy and cost of the United States Immunization Survey, it was abandoned after 1985.

The continuing need for timely data on national vaccination levels by 2 years of life, however, led to resumption of such surveys in 1991 via the National Health Interview Survey (NHIS) using household interview of parents (104). The most difficult problem for the National Health Interview Survey was the lack of validity of parental history. In general, parents tended to underestimate the number of doses of multidose vaccine their child received, and overestimate single dose vaccines (e.g., measles). When asked whether their child was up-to-date, however, parents tend to overestimate coverage (105). To compensate for these problems, beginning in 1992, a spontaneous response of "my child is up-to-date" was accepted and children with unknown history were excluded. These changes caused estimates to correlate better with other survey results. Beginning in 1994, parental responses are verified with providers. Preliminary data for the first two quarters of 1994 suggest such verification will generally raise coverage by about 5 percent (106).

In 1994, the National Immunization Survey was also initiated in the United States. Using random digit dialing technology to locate eligible children, this survey collects data quarterly to estimate immunization coverage in 19- to 35-month-old children in all 50 states and 28 large urban areas (107). Consent is obtained from the interviewee to validate the vaccination history with the provider. Data are adjusted for children from households without telephones based on National Health Interview Survey data (108). Resources permitting, this survey will become the standard means for measuring coverage in the future in the United States.

Other approaches to measuring preschool levels have included statewide follow-up of a sample of children at 2 years of age who were selected from state birth certificates (109). This technique also was abandoned in most states because response rates were frequently low, often less than 50 percent, casting concerns on the validity of the results. Recently, most states began measuring immunization levels retrospectively using data obtained at school entry. Using date-specific information, immunization personnel calculate immunization levels for these enterers as of the date of their second birthday (110).

Guidelines and software for assessing vaccination levels of the 2-year-old population in clinic settings have also recently been developed (111). Standards for definition of a 2-year-old, active versus inactive files, age markers for assessing vaccination levels, definition of "up-to-date" and complete vaccination levels, and sampling of clinic charts, may permit comparisons of clinics within and between states. Such routine assessment and feedback of vaccination rates (112), combined with reducing "missed opportunities" for vaccinations (113), have been shown to be highly effective in raising and sustaining high vaccination rates. Because the increasingly complicated childhood vaccination schedule (114) will increase the difficulty of accurately ascertaining vaccination history via interview, computerized immunization registries are increasingly looked to as the answer for timely and accurate assessment of vaccine coverage (93).

### Indirect measurement—administrative estimate, biologics surveillance, and other approaches

If the number of doses of vaccine administered and the number of children in the target age group (e.g., number of surviving infants) are known, an inexpensive "administrative" estimate of vaccine coverage can be calculated. Again, if the same method is used everywhere, then aggregation of data is possible. This is the method used routinely by the World Health Organization's EPI to estimate vaccine coverage (115). This method is most useful when the great majority of vaccinations are performed in government-financed clinics (e.g., most developing countries) and accurate denominator data on the population at risk is known. Commonly, however, these results are higher than actual coverages as the census data used to estimate denominators tend to be low.

Since 1962, the CDC has received data from vaccine manufacturers concerning the number of doses of vaccines they distributed minus the number of doses returned (published and unpublished data, US Biologics Surveillance, National Immunization Program, CDC, Atlanta, Georgia, 1962–1996). Data on the "net doses" of vaccines distributed have been helpful in tracking use of various types of measles vaccines. Biologics data have also been useful in tracking the use of diphtheria-tetanus-pertussis and diphtheria-tetanus vaccines following adverse publicity about diphtheria-tetanus-pertussis vaccine which began in 1982 and triggered concerns that vaccine coverage against pertussis would drop (116). The advantage of the biologics surveillance system is that data become available relatively rapidly. If school entry data were required, it would have taken about 5 years to obtain any information on infants born and immunized following the onset of the adverse publicity.

In the United States, at least half of the childhood vaccines are purchased by the government via annual

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negotiated contracts with the vaccine manufacturers (117). A database recording purchases from this contract also provides an alternative source of denominators. The major uses of these data have been in monitoring the proportion of the population served by the public sector and in calculating rates of adverse events reported following vaccination in the public sector.

Disease surveillance

The ultimate purpose of immunization is to prevent disease and complications of disease. Surveillance data on reported cases are critical to determine whether the program is having an impact, to assess why disease is still occurring, to evaluate whether new strategies are necessary, and to detect problem areas and populations that require more intensive program input.

Disease surveillance systems initially need to be simple. Physician diagnosis is usually the case definition, and reported information may include date of onset or report, age, and place of residence. Such limited data have been useful to demonstrate the marked impact of vaccination on disease incidence and for analyzing how best to reduce remaining morbidity. For example, surveillance data were used to develop policies to enhance rubella vaccination of postpubertal populations in the United States (81).

Surveillance data were instrumental in the spread of regulations to require vaccination for schoolchildren in the United States. Beginning in the mid 1970s, surveillance data clearly showed that states without laws requiring vaccination at school entry had 1.7- to 2.0-fold higher incidence rates of reported measles than states with laws (118). This information was extremely useful in the universal adoption of school enterer requirements by showing legislators that laws could lead to significant impact. By the late 1970s, the epidemiology of measles had changed. Cases were more prominent in junior high and high school students (119). These students were not covered by the recently enacted school enterer laws since they had already been enrolled when such regulations went into effect. This led to the adoption of comprehensive laws covering all students, kindergarten through 12th grade. Surveillance data showed such states had lower incidence rates for measles than other states and lead to adoption of comprehensive laws by most states (120).

More recently, an analysis of reported mumps cases by age and by state demonstrated that the marked increases in incidence were due to failure to vaccinate large numbers of older children and adolescents rather than to vaccine failure (121). The highest incidence rates were in states without comprehensive school laws requiring mumps immunization. If vaccine failure was the predominant concern, increased incidence should have occurred in all states. Thus, evaluation of the role of vaccine failure was possible without any data on vaccination status of cases.

Case investigations

As programs mature and cases become more uncommon, surveillance tends to move from simply the passive collection of limited data on cases to more sophisticated individual case investigations by health department personnel. During these investigations, staff generally collect relevant clinical and laboratory data as well as information on disease complications, hospitalizations, vaccination status, and other desired information such as potential sources and contacts of the case. Health department personnel may assist in collecting critical laboratory specimens such as acute and convalescent phase sera or providing transport media for bacterial and/or viral cultures. In the United States, special case investigation forms were used historically for congenital rubella syndrome, diphtheria, tetanus, pertussis, and hepatitis B. Detailed information is collected on individual measles and polio cases. More recently, electronic systems to compile this information directly have been developed. These data are used to analyze cases in greater depth, particularly with regard to health impact and problems with vaccination.

A major question in control of vaccine-preventable diseases is whether a given case represents a failure of implementation of the vaccine strategy (a preventable case) or failure of the strategy (a nonpreventable case). For example, a preventable case of measles is disease in someone who was eligible for vaccine but was unvaccinated.

In the past, such persons must have been born after 1956, be at least 16 months of age, be a US citizen, have no medical contraindications against measles vaccination, have no religious or philosophical exemptions to vaccination under state law, and have no evidence of measles immunity (122). Measles immunity was defined as documented evidence of prior physician-diagnosed disease, receipt of live vaccine on or after the first birthday, or laboratory evidence of immunity. Analyses of cases by preventability status played a major role in new policy recommendations for more aggressive revaccination efforts. In the mid to late 1980s, only a minority of cases were preventable and, especially among school-age children, vaccine failure was the predominant reason for nonpreventability (123). Analyses of large school-age outbreaks in 1985 and 1986 (≥100 cases) reported through the measles surveillance system demonstrated as many as 69 percent of cases in such outbreaks were
appropriately vaccinated with one dose of measles-containing vaccine. Of the school-age cases in these outbreaks, a median of 71 percent were vaccinated, ranging up to 90 percent. Case reports, many of them initiated by physicians, played a crucial role in recommendations for a routine two dose schedule for measles and for more aggressive outbreak revaccination efforts (124).

**Outbreak investigation**

Disease outbreaks in a vaccinated population can raise doubts as to the efficacy of the vaccine and the vaccination program (73). Such outbreaks may result from accumulation of susceptible persons from 1) lack of vaccination, 2) primary vaccine failures (persons vaccinated but not immunized), and/or 3) secondary vaccine failures (persons successfully immunized initially but whose immunity subsequently wanes) (125). Special studies to determine which of these factor(s) caused the outbreak are needed to prevent recurrence and maintain public confidence in the vaccination program.

Special studies may be laboratory and/or epidemiologic in design. Testing of residual vaccine used in outbreak areas may indicate poor potency, suggesting problems in production (126), formulation (127), or refrigeration during shipping (128). Careful analysis of descriptive epidemiologic data from surveillance or outbreak investigations may offer insights and hypotheses on possible causes worth testing via a controlled epidemiologic study. Case-control studies were used in two measles outbreaks to show that lack of provider verification of a school record of measles vaccination and vaccination at <12 months of age were independent risk factors for measles disease (129, 130). When the outbreak persisted despite a mass immunization campaign, a case-control study showed that cases occurring after the campaign had all received vaccine from one jet injector team, possibly due to poor administration technique (129). The same studies showed that children who had been vaccinated in earlier years were no more likely to be at risk for measles than recent vaccinees, suggesting waning immunity did not play a role.

Unusual circumstances during outbreaks may permit the design of studies to answer long-standing questions. A blood drive serendipitously scheduled before a measles outbreak on a college campus permitted correlation of preexposure antibody titers with protection against classic and nonclassic measles (131). An explosive measles outbreak in a high school where a single index case apparently exhausted all susceptibles in the school during 2 days provided insight on the role of a superspreader and airborne modes in measles transmission (130).

Whenever studying outbreaks, however, it is important to place them in the proper context. Most of the factors associated with vaccination failure are not uniformly or randomly distributed in a population. Outbreaks, therefore, usually represent exceptions rather than the rule. Modeling shows that investigation of outbreaks will tend to underestimate the true vaccine efficacy in the population. The extent of underestimation is dependent on epidemic size, vaccination coverage, clustering of vaccination failures, community size, and contact rate (132). The high visibility of outbreaks may detract from the larger overall accomplishment of the immunization program in decreasing disease incidence. A large measles outbreak in Burundi in 1988 (73) raised doubts about the effectiveness of the measles vaccination program begun in 1982. Further analysis suggests that this was most likely a "post-honeymoon period" outbreak predicted by mathematical models of a partially immunized population (133). Such periods are caused by the rapid impact of early vaccination substantially decreasing susceptibility and limiting disease transmission (the "honeymoon"). In the absence of disease, susceptibles accumulate because of both failure to vaccinate and vaccine failure. Over time, these susceptibles may be sufficient to fuel a megaoutbreak. However, even though this outbreak may be large, it is more than compensated for by the long period of low disease incidence. In Burundi, measles immunization had, in fact, successfully reduced measles morbidity and mortality by 50 percent and increased the interepidemic period (73). An understanding of the dynamic interactions between susceptible and immune persons in a population and the oscillations introduced by immunization programs are critical to immunization program managers and policy makers (32).

**Vaccine efficacy and vaccine effectiveness studies**

No current vaccine is perfectly effective. The "intrinsic", non-preventable, primary vaccine failure rates generally range from 2 to 50 percent for licensed vaccines even under the ideal circumstances of clinical trials. Paradoxically, as the vaccine coverage in a population increases, an increasing proportion of susceptibles and, hence, cases will have a history of prior vaccination due to the intrinsic vaccine failure rate (table 2). While the size of outbreaks should decrease with increasing vaccine coverage, the proportion of cases with a vaccine history will increase. In the practical world of immunization programs, vaccine failures may also occur due to preventable causes such
TABLE 2. Relation between vaccine coverage and proportion of cases vaccinated for a vaccine with <100% vaccine efficacy

<table>
<thead>
<tr>
<th>Vaccine efficacy (%)</th>
<th>Total population</th>
</tr>
</thead>
<tbody>
<tr>
<td>% population vaccinated</td>
<td>100</td>
</tr>
<tr>
<td>No. vaccinated (total population x % population vaccinated)</td>
<td>90</td>
</tr>
<tr>
<td>No. unvaccinated, i.e., susceptible (total population - no. vaccinated)</td>
<td>20</td>
</tr>
<tr>
<td>No. protected by vaccine (no. vaccinated x vaccine efficacy)</td>
<td>20</td>
</tr>
<tr>
<td>No. vaccinated but still susceptible (no. vaccinated - no. protected by vaccine)</td>
<td>80</td>
</tr>
<tr>
<td>Total no. susceptible (no. unvaccinated + no. vaccinated but still susceptible)</td>
<td>82</td>
</tr>
<tr>
<td>% susceptibles vaccinated (no. vaccinated but still susceptible/total no. susceptible)</td>
<td>2.4</td>
</tr>
</tbody>
</table>

as problems in manufacturing (126), refrigeration (128), or administration techniques (129).

An epidemic in a highly vaccinated population along with the presence of cases in many persons who had been vaccinated previously inevitably leads to public concerns about vaccine efficacy. Post-licensure epidemiologic studies to assess vaccine effectiveness may be needed to distinguish preventable from non-preventable causes of vaccine failure and allay such concerns (20). As discussed earlier, such studies may also be needed because routine use of the vaccine after licensure may be in populations or schedules that differ from pre-licensure trials. The range of efficacy with the *H. influenzae* type b polysaccharide vaccine, depending on the population (134) and of influenza vaccine depending on the age group (135), are some of the best examples.

Once a vaccine has been licensed, however, it would be unethical to deliberately withhold an efficacious vaccine from a needy population. Therefore, observational or epidemiologic studies (with their greater attendant design challenges) are used, instead of experimental study designs, to assess vaccine efficacy post-licensure. Such studies are generally preferred to serologic surveys for logistical reasons, and also that for some vaccines there is no accurate serologic correlate of protection.

**Definitions.** Immunization usually has the direct effect of inducing protective immunity in the individual vaccinee. Occasionally, a vaccinated person may not develop immunity due to primary failure. For most vaccine-preventable diseases, immunization also has indirect effects of producing herd immunity for the population (21). Generally, the term vaccine efficacy has been applied to estimates of efficacy derived from clinical trials where 1) vaccination occurs under optimal conditions and 2) the limited sample size usually means that only direct protection is measurable. The term vaccine effectiveness has been applied to observational epidemiologic studies of efficacy, reflecting measurement of both direct and indirect effects of immunization in a population under possibly suboptimal field conditions of vaccine storage, handling, and administration (136). In practice, this distinction between vaccine efficacy and vaccine effectiveness is frequently ignored; the term “vaccine efficacy” tends to be used universally with some resultant confusion (137).

Both vaccine efficacy and effectiveness (VE) can be calculated using the classic formula of Greenwood and Yule (19): $1 - \text{Relative risk}$ (equation 1), where the relative risk is of developing disease. By convention, VE results are multiplied by 100 and expressed as a percent. Two different measures of the relative success of a vaccine in protecting the recipient against disease are used in calculating VE. Classically, when the data collected are in the form of total number of cases, the vaccine efficacy calculation has been based on a comparison of the attack rates (or more accurately, cumulative incidence or risk) among vaccinated and unvaccinated persons (equation 2) (19, 138). Alternatively, when the data available are in the form of number of cases during a certain period of observation, person-time measures like incidence rates, hazard, or force of infection are more appropriate (equation 3) (139, 140). Other measures used for VE calculation include relative transmission probabilities (141) and hazard ratio (142).

Smith et al. (140) have noted that how vaccines confer effective protection may differ depending on a
vaccine’s mode of action. For example, a vaccine with 95 percent VE may 1) reduce the probability of infection by 95 percent, given equal exposure to infection in all vaccinees, or 2) completely prevent infection in 95 percent of vaccinees and confer no protection in the other 5 percent. Halloran et al. (143) have further elaborated the theoretical implications of the various models of vaccine action on both vaccine efficacy and failure. Most clinical models assume that most vaccines either offer full protection or no protection. The biologic basis for that assumption is clear. The biologic basis for reducing the probability of infection is not clear. Dose-response phenomena, in which the dose of pathogen a vaccinee is exposed to, might be a partial explanation for the latter.

**Screening for vaccine effectiveness.** Before a formal epidemiologic study of vaccine effectiveness is undertaken, it is useful to review whether the surveillance data permit a rapid “screening” analysis. If the surveillance system routinely collects information on the proportion of population vaccinated and the proportion of cases vaccinated in the same population, and there is good confidence in the accuracy of these data, then VE can be calculated by using equation 4 derived algebraically (by Orenstein et al. (144)) from the classic VE equation of Greenwood and Yule (19).

\[
VE = 1 - \text{Relative risk} \\
= 1 - \frac{\text{Attack rate}_{\text{vaccinated}}}{\text{Attack rate}_{\text{unvaccinated}}} \\
= 1 - \frac{\text{Incidence rate}_{\text{vaccinated}}}{\text{Incidence rate}_{\text{unvaccinated}}} \\
= 1 - \left( \frac{\text{Proportion of cases vaccinated}}{1 - \text{proportion of cases vaccinated}} \times \frac{1 - \text{proportion of population vaccinated}}{\text{proportion of population vaccinated}} \right)
\]

Equation 4

Figure 2 depicts the relation between the two variables in equation 4 for VEs ranging from 40 to 100 percent. This VE “nomogram” permits field health workers to rapidly “screen” to see if the VE is within the expected range given the data on the proportion of population vaccinated and the proportion of cases vaccinated, which would suggest that the vaccine failures are nonpreventable. A special epidemiologic study for validation and identification of risk factors would be indicated only if the screening suggests the VE is low. In the United Kingdom, linkage of cases, their vaccination histories, and district vaccination coverages have permitted routine use of this screening method for VE (145).

In using the screening method, several cautions should be noted. First, the method requires a dichotomous population of unvaccinated and fully vaccinated. Hence, partially vaccinated persons need to be excluded from the calculations of both proportion of cases vaccinated and proportion of population vaccinated. Second, the method is most vulnerable to error under conditions of very low or very high proportion of population vaccinated and proportion of cases vaccinated. In these conditions, the VE curves tend to converge and small changes in proportion of cases vaccinated or proportion of population vaccinated can lead to major differences in VE.

**Study design considerations.** Several epidemiologic study designs to evaluate VE are possible (20). Cohort design is most appropriate when a discrete population at risk can be defined, usually retrospectively (e.g., outbreaks in institutions and schools). If, however, the outbreak is of longer duration or if vaccination status changes substantially during the outbreak due to control efforts, then person-time or life-table analysis is needed (139, 140). Case-control (137) studies may be more efficient and perhaps the only practical design for VE studies of diseases with lower case-to-infection ratio such as diphtheria (146), polio (147), and tuberculosis (148). When the case attack rate is high, the “rare” disease assumption for a cumulative incidence case-control study is no longer valid. The case-cohort design (149), essentially an
incidence density case-control study (150), can be used instead. A sample of the population giving rise to cases is taken irrespective of whether the sample includes some cases (151).

The household secondary attack rate method aims to minimize bias introduced by potential differences in risk of exposure among vaccinees and nonvaccinees. Data on attack rates among vaccinated and unvaccinated secondary contacts in many households are aggregated into a cohort. VE for measles vaccine using this method is similar to that from clinical trials (152). On the other hand, household secondary attack rate studies may underestimate pertussis vaccine efficacy (18, 153) due to intense exposure, selection of households with high likelihood of vaccine failure, and retrospective case finding (154).

Irrespective of the study design selected, an accurate VE calculation requires 1) the accurate ascertainment of susceptibility, vaccination, and disease status among the study population and 2) similarity in other characteristics of the vaccinees and nonvaccinees. While these criteria are relatively easily met in a prospective clinical trial, they are not in an observational nonexperimental study (figure 3), especially in regards to comparability of vaccinees and nonvaccinees. The direction and the magnitude of distortion from the true VE introduced due to errors in each of these variables in study design have been extensively reviewed (20, 144, 155). Among the major errors to avoid are:

1. Assuming persons without a vaccination record are unvaccinated. Such persons may have been vaccinated and lost their records or be truly unvaccinated. If the former, this would falsely decrease the attack rate_{unvaccinated} and lead to falsely low VE. Table 3 shows the calculated VE in a study in Burundi was only 51 percent using this assumption (73). Some studies attempt to ascertain history of vaccination among persons without records by interview. Such recall tends to be unreliable, however, given the large number of injections and vaccinations administered. The best strategy generally is to exclude the unknowns and restrict the analysis to persons with record-documented vaccination and nonvaccination status (20). The VE in Burundi increased to 59 percent when this was done (table 4).

2. Using a nonspecific case definition is an example of the “bias towards the null” in epidemiologic studies (156). As one would not expect a vaccine to protect against a disease other than its target disease, specificity of diagnosis is more critical to the accuracy of the vaccine efficacy estimate than sensitivity (20). The endpoint “case definition” may be a laboratory result, a clinical finding, or combination of both (59). For diseases with classic symptoms like measles, clinical diagnosis by parent and/or doctor may be adequate in some studies (157), but not all (73). In Burundi, the VE further increased to 67 percent when a more specific case definition was used (table 5). Assuming 100 percent sensitivity, the magnitude of the error introduced by different levels of false-positive case definitions is estimated by:

$$VE_{observed} \sim VE_{true} \left(\frac{x}{x + y}\right)$$

TABLE 3. Measles vaccine efficacy, Muyinga sector, Burundi, 1988: all children in census (measles cases as reported by mother; children without vaccination card counted as unvaccinated)

<table>
<thead>
<tr>
<th></th>
<th>Measles</th>
<th>No measles</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated</td>
<td>115</td>
<td>893</td>
<td>1,008</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>207</td>
<td>685</td>
<td>892</td>
</tr>
<tr>
<td>Total</td>
<td>322</td>
<td>1,578</td>
<td>1,900</td>
</tr>
</tbody>
</table>

Attack rate_{unvaccinated} = 207/892 = 23%
Attack rate_{vaccinated} = 115/1,008 = 11%
Vaccine efficacy = (23% - 11%)/23% = 1 - (11%/23%) = 51%

FIGURE 3. Flow diagram of vaccine efficacy study. Prospective clinical trial flows from left to right, while observational nonexperimental study during an outbreak generally seeks to reconstruct the flow retrospectively going from right to left.

TABLE 4. Measles vaccine efficacy, Muyinga sector, Burundi, 1988: unvaccinated children restricted to those with vaccination cards (on which there is no record of measles vaccination)

<table>
<thead>
<tr>
<th></th>
<th>Measles</th>
<th>No measles</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated</td>
<td>115</td>
<td>893</td>
<td>1,008</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>122</td>
<td>316</td>
<td>438</td>
</tr>
<tr>
<td>Total</td>
<td>237</td>
<td>1,209</td>
<td>1,446</td>
</tr>
</tbody>
</table>

Attack rate_{unvaccinated} = 122/438 = 28%
Attack rate_{vaccinated} = 115/1,008 = 11%
Vaccine efficacy = (28% - 11%)/28% = 1 - (11%/28%) = 59%
where \( x \) is the true incidence rate of the vaccine-preventable disease in the population and \( y \) is the incidence of the condition misdiagnosed as the vaccine-preventable disease (155).

3. Assuming vaccinees and nonvaccinees are otherwise similar, especially in terms of susceptibility and risk of exposure to disease. In nonexperimental settings, nonvaccinates generally differ from vaccinates in many ways, ranging from having contraindications to vaccination, to personal choice, to others unknown to the investigator. If the differences are related to both the exposure and outcome of interest, the VE estimate may be biased by confounding. Potential confounding factors include, but are not limited to, age, sex, race, socioeconomic status, attendance at school or institution, and place of residence. Studies should collect data on, or match on, suspected confounding variables to maximize comparability of vaccinees and nonvaccinees (20). Attempting to adjust for age further increases the VE estimate in Burundi to 73 percent (table 6).

### Surveillance of vaccine safety

Vaccines are widely recommended, or mandated, generally to otherwise healthy persons. Because no vaccine is perfectly safe, immunization programs have an obligation for careful monitoring of the safety of vaccines as well as their efficacy (158). As the incidence of vaccine-preventable diseases is reduced by increasing coverage with an efficacious vaccine, vaccine adverse events, both causal and coincidental, become increasingly prominent (figure 1) (159). The annual reports of such events now outnumber the total reported childhood vaccine-preventable diseases in the United States (table 1). Close monitoring and timely assessment of suspected vaccine adverse events are critical to prevent loss of confidence, decreased vaccine coverage, and return of epidemic disease. Epidemics of pertussis occurred in several countries during the 1970s when concerns with the safety of pertussis vaccine were widely publicized (160–162).

Recommendations for use of vaccines represent a dynamic balancing of benefits and risks. Vaccine safety monitoring is necessary to accurately weigh this balance. When diseases are close to eradication, data on complications due to vaccine relative to that of disease may lead to discontinuation of routine use of the vaccine, as was done with smallpox vaccine (49). Few vaccine-preventable diseases are likely to be eradicated in the near future, however. Most vaccines are, therefore, likely to be needed indefinitely, with their attendant adverse events and potential for loss of public confidence.

Common adverse reactions caused by vaccines can usually be detected in precensure randomized, double-blind, placebo controlled trials. However, limits in sample size, duration, and heterogeneity of precensure trials also mean that rare, delayed, or group-specific vaccine reactions are detectable only with wider use post-licensure. The term "adverse events" temporally related to vaccine is generally used post-licensure rather than "adverse reactions", since the word reaction implies causation by the vaccine and causality is difficult to demonstrate in the post-licensure setting.

Most commonly, post-marketing surveillance is done via passive reports. Examples include the Vaccine Adverse Event Reporting System (VAERS) (159) in the United States and similar systems in other countries (163). Such passive adverse events monitoring systems are most useful for identifying hypotheses for more detailed investigation in special studies. Such hypotheses may consist of either previously unreported vaccine adverse events (e.g., Guillain-Barré syndrome after "swine flu" vaccine) (164) or unusual increases in known events (e.g., cluster of sterile abscesses associated with one manufacturer's product) (165). Passive systems are also used to monitor trends in reporting and can be used to evaluate some hypotheses. For example, the predecessor system to the VAERS requested information on personal and family histories of seizures. Analysis showed that persons

### Table 5. Measles vaccine efficacy, Muyinga sector, Burundi, 1988: criteria in table 4 plus measles patients restricted to those with symptoms meeting the case definition of fever, rash, and cough, or runny nose, or red eyes

<table>
<thead>
<tr>
<th></th>
<th>Measles</th>
<th>No measles</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated</td>
<td>50</td>
<td>893</td>
<td>943</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>60</td>
<td>316</td>
<td>376</td>
</tr>
<tr>
<td>Total</td>
<td>110</td>
<td>1,209</td>
<td>1,319</td>
</tr>
</tbody>
</table>

\[
\text{Attack rate}_{\text{unvaccinated}} = \frac{60}{376} = 16\
\text{Attack rate}_{\text{vaccinated}} = \frac{50}{943} = 5\
\text{Vaccine efficacy} = \frac{16\% - 5\%}{16\%} = 1 - \frac{5\%}{16\%} = 67\%\
\]

### Table 6. Measles vaccine efficacy, Muyinga sector, Burundi, 1988: criteria in table 4 plus table 5 plus analysis restricted to children ≥9 months of age

<table>
<thead>
<tr>
<th></th>
<th>Measles</th>
<th>No measles</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated</td>
<td>41</td>
<td>701</td>
<td>742</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>31</td>
<td>118</td>
<td>149</td>
</tr>
<tr>
<td>Total</td>
<td>72</td>
<td>819</td>
<td>891</td>
</tr>
</tbody>
</table>

\[
\text{Attack rate}_{\text{unvaccinated}} = \frac{31}{149} = 21\
\text{Attack rate}_{\text{vaccinated}} = \frac{41}{742} = 6\
\text{Vaccine efficacy} = \frac{21\% - 6\%}{21\%} = 1 - \frac{6\%}{21\%} = 73\%\
\]
with such histories were significantly more likely to have seizures following diphtheria-tetanus-pertussis vaccine than persons without such histories, leading to development of precautions for vaccinating such individuals (43).

Interpretation of passive systems is difficult due to 1) underreporting of events and 2) biased reporting in favor of events occurring in closer temporal proximity to vaccination. The greatest deficiency of passive surveillance, however, relates to their general inability to determine whether a given reported event was actually caused by the vaccination or simply coincidental to it. This is because most adverse events reported do not have specific clinical (e.g., vaccine-associated polio) or laboratory (e.g., mumps vaccine meningitis) characteristics to differentiate them from events that occur in the absence of vaccination. In such settings, epidemiologic studies are necessary.

Passive reports like VAERS, however, generally contain only a biased fourth of the information in a \(2 \times 2\) table of vaccination exposure and adverse event outcome needed for an epidemiologic assessment (i.e., they represent cell "a" only: those vaccinated with adverse event). They lack built-in control groups to allow measurement of the incidence of the event in the absence of vaccination. Therefore, true determination of causation usually requires special studies to gather information for all four cells of a \(2 \times 2\) table. The special studies can either be ad hoc (158) or increasingly, preorganized large-linked databases. Such databases take advantage of the increasing automation of vaccination and medical records within medical care settings like Health Maintenance Organizations (91) and national health services (167) to provide more scientifically rigorous estimates of vaccine risks.

To determine vaccine causation epidemiologically requires the demonstration that either vaccinees are more likely to suffer the event than nonvaccinees (cohort design) or persons with the event are more likely to have a history of recent vaccination than persons without the event (case-control design). In highly vaccinated populations, those persons remaining unvaccinated may confound studies of vaccine adverse events (168). Person-time "risk interval" analysis is then preferred (158). A risk interval for the adverse event is defined a priori based on biologic plausibility, the incidence rates of the adverse event within and without the risk interval are then compared. Adverse events with delayed or insidious onset cannot be assessed via this method, however.

Recent reviews have identified major "gaps and limitations" in both knowledge and research capacity on vaccine safety (169, 170), suggesting this as one area requiring additional attention in maturing immunization programs.

FUTURE ISSUES

Recent explosive advances in biotechnology and biomedical knowledge offer promises of development of candidate vaccines against many other infectious diseases. Epidemiology will continue to play a critical role in their evaluation. Many other difficult economic, ethical, and social issues need to be solved, however, before trials for vaccines against HIV/AIDS can begin, let alone used routinely (171). Similarly, vaccines with a target population that is either limited in size or poor may never be developed (7).

The addition of new vaccines to the routine immunization schedule suggests that combined vaccines requiring fewer injections and fewer visits are needed to maintain continued high population immunity with minimal discomfort and highest compliance. Special challenges, logistically and scientifically, exist in evaluating the safety and efficacy of such combined vaccines (172). On the other hand, changes in health care organization, especially its increasing centralization and automation (173), offer promising opportunities for epidemiologists to organize the studies necessary to continue the miraculous conquering of diseases by immunizations.

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