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Review Article

REVIEW ARTICLE ON EPIDEMIOLOGIC METHODS IN IMMUNIZATION PROGRAMS

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ABSTRACT

Immunization programs are essential for controlling and eliminating vaccine-preventable diseases, thereby improving public health outcomes globally. Epidemiologic methods play a fundamental role in the design, implementation, and evaluation of these programs. This review article provides an in-depth examination of the epidemiologic techniques used in immunization programs, including surveillance, cohort studies, case-control studies, and randomized controlled trials. We discuss how these methods contribute to understanding vaccination coverage, vaccine efficacy, and the identification of factors influencing vaccine uptake. Furthermore, the review highlights the importance of monitoring and evaluation systems in detecting and responding to disease outbreaks, assessing vaccine impact, and guiding policy decisions. By enhancing the precision and effectiveness of immunization strategies, epidemiologic methods ensure the successful reduction of disease burden and support the goal of achieving widespread immunization coverage. This article underscores the need for continued application and innovation in epidemiologic approaches to strengthen global immunization efforts.

Key words: Epidemiologic Methods**,** Immunization Programs**,** Vaccine Coverage**,** Disease Surveillance**,** Public Health

INTRODUCTION

Immunizations are among the most successful and cost-effective disease prevention interventions available (World Bank, 1993). In the United States, the introduction of routine immunizations has greatly reduced the incidence of several vaccine-preventable diseases. Similar success in disease reduction has been demonstrated by immunization programs in many other countries. 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. Immunizations permitted the global eradication of smallpox and may do the same for poliomyelitis 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), including some noninfectious diseases like cancer (Linehan *et al.,* 1996).

In summary, 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, 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 (Begg and Miller, 1990). Prior to licensure, a vaccine must demonstrate its safety and efficacy in phased clinical trials. Postlicensure, 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.

Immunization system

The national immunization programme provides a birth dose for hepatitis B, BCG and polio at four weeks; DPT, hepatitis and polio at 8, 12 and 16 weeks; and, measles at nine months. Additional vaccination includes measles, DT and TT for school children, and TT for women of child-bearing age.

Some clear milestones have been set by the programme and include UCI in all villages by 2010, disease-specific targets and milestones for use of auto disable syringes (ADS) and waste management. Norms and standards are also available and include both technical and managerial standards. The immunization programme is one of the five sub-directorates (surveillance for communicable diseases, immunization, Hajj, quarantine, and matra health) under the Directorate of Epidemiology, Surveillance, Immunization and Matra Health (World Health Organization, 2009).

Pre-Licensure:

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 (Rey *et al.,* 1983).But also to engineer and produce vaccines that are potentially safer, more effective, easier to produce, and less costly. 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.After isolation and characterization of the causative organism for a disease, inactivation or attenuation permit the development of candidate vaccines (Levine, 1990).

Such candidate vaccines are tested in animals 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 (Herrington, 1990). Classically, a prospective, doubleblind, randomized, controlled design is used. Occasionally, studies with open, historic control , or household secondary attack rate 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). 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 (Orenstein *et al.,* 1988). 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 (Fine, 1993), 2) the adequacy of the health infrastructure, and 3) the resources available.Vaccination strategies in developing countries may confront difficult choices , 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. 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 or "national immunization days" for poliomyelitis (Hull *et al.,* 1994) 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. 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 (Dudgeon, 1985) or be used universally among all children of both sexes. 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. When adequate surveillance data are available, different options for control strategies can be modeled mathematically to obtain quantitative insights in lieu of mere intuition. 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. New health programs today frequently also need to demonstrate cost effectiveness, as was done prior to licensure of the Haemophilus influenzae type b polysaccharide and varicella (Lieu *et al.,* 1994) 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. 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. Such "Phase Illb" trials are practical only if a serologic correlate of efficacy is established during the "Phase Ilia" trials, as was done for the licensure of combined diphtheria-tetanuspertussis-//. Influenzae type b vaccines.

Post-Licensure:

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 or mumps vaccine-associated aseptic meningitis , may not have been detected earlier. Certain batches of vaccine may turn out to be unsafe or inefficacious, leading to improvements in manufacturing and quality control. Some issues, such as duration of vaccine-induced immunity, may require decades to assess (Christenson and Bottiger, 1994). 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 , and even the number of lawsuits filed against vaccine manufacturers. 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. Modeling studies may also be used to better analyze strategy options (Massad *et al.,* 1994). Additional cost-effectiveness studies may be needed to garner continued program support. Serosurveys may be used to assess any major gaps in immunity that could result in future outbreaks (Evans, 1980). 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. 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.

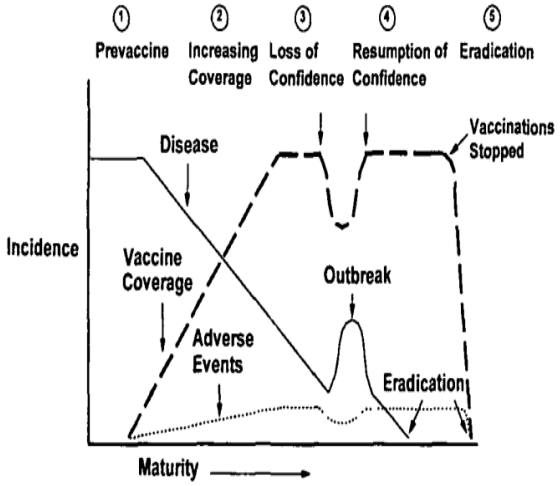

Figure 1: Evolution of immunization programs

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 (Thacker and Berkelman, 1988). 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 , compared with <10 percent in community-based studies. Despite underreporting and other potential biases, surveillance data have been remarkably useful in serving the needs of public health programs. 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 (Gindler *et al.,* 1992). 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. 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. 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.

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 to hypothesize that pertussis vaccine was more effective in protecting against disease than against infection. This hypothesis has since been supported by other studies. The rapid disappearance of diphtheria and H. influenzae type b (Adams *et al.,* 1993) 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.

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. 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. 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 (Strebel *et al.,* 1992). 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. Similar definitions have been elaborated by Canada. 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 (Strebel *et al.,* 1993). 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. 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. 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. Well developed sentinel surveillance systems are used by some European governments to provide information on disease occurrence. 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 (WHO, 1986). 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. 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. 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. Data thus far show that subacute sclerosing panencephalitis has virtually disappeared from the United States. Evaluation. Guidelines for evaluation of public health surveillance systems have been developed (Thacker *et al.,* 1988). 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. 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. 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. 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 capturerecapture 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. Efficiency of vaccine adverse events reporting can be evaluated if population-based estimates based on prior studies are available (Rosenthal and Chen, 1995). 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 (Patriarca *et al.,* 1988).

Serologic surveillance

Immunization programs aim to substitute vaccineinduced immunity for that from disease. Neither his ory of disease nor vaccination may be an accurate marker of true immunity. Therefore, if a serologic correlate of protective immunity against a vaccinepreventable 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 (Evans, 1980).

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".

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 enterers. 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 (Eddins, 1993).

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 (Cochi *et al.,* 1989). 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 (Orenstein *et al.,* 1978). 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. 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.

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.

Outbreak investigation

Disease outbreaks in a vaccinated population can raise doubts as to the efficacy of the vaccine and the vaccination program. 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) (Hinman *et al.,* 1992). 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.

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. 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 as problems in manufacturing (Hlady *et al.,* 1992), refrigeration, or administration techniques.

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 (Chen, 1994). 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. 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 (Kimura and Kuno-Sakai, 1990).

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. Similarly, vaccines with a target population that is either limited in size or poor may never be developed. 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 (Williams *et al.,* 1995). On the other hand, changes in health care organization, especially its increasing centralization and automation, offer promising opportunities for epidemiologists to organize the studies necessary to continue the miraculous conquering of diseases by immunizations.

Conclusion

Epidemiologic methods are fundamental to the success of immunization programs. These methods enable the systematic collection, analysis, and interpretation of data, facilitating the monitoring of vaccination coverage, the assessment of vaccine efficacy, and the identification of disease outbreaks. By employing epidemiologic techniques such as surveillance, cohort studies, and case-control studies, public health officials can make informed decisions to optimize immunization strategies, address gaps in vaccine coverage, and improve overall public health outcomes. Enhanced epidemiologic approaches contribute to the prevention and control of vaccine-preventable diseases, ensuring the effectiveness and sustainability of immunization programs worldwide.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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