Review Article

Vaccine epidemiology: A review

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Abstract

This review article outlines the key concepts in vaccine epidemiology, such as basic reproductive numbers, force of infection, vaccine efficacy and effectiveness, vaccine failure, herd immunity, herd effect, epidemiological shift, disease modeling, and describes the application of this knowledge both at program levels and in the practice by family physicians, epidemiologists, and pediatricians. A case has been made for increased knowledge and understanding of vaccine epidemiology among key stakeholders including policy makers, immunization program managers, public health experts, pediatricians, family physicians, and other experts/individuals involved in immunization service delivery. It has been argued that knowledge of vaccine epidemiology which is likely to benefit the society through contributions to the informed decision-making and improving vaccination coverage in the low and middle income countries (LMICs). The article ends with suggestions for the provision of systematic training and learning platforms in vaccine epidemiology to save millions of preventable deaths and improve health outcomes through life-course.

Keywords: Child health, epidemiology, vaccines, life course

Introduction

The benefits of vaccination, one of the most cost-effective public health interventions, have not fully reached target beneficiaries in many low- and middle-income countries (LMICs).[1] Though the field of vaccine research and vaccinology has received a lot of attention since the discovery of the smallpox vaccine by Edward Jenner (1749-1823) in 1798, more than two centuries later, an estimated 20% of deaths among children aged less than 5 years occur due to diseases preventable by currently licensed vaccines.[2,3] Since the discovery of smallpox vaccine, a number of vaccines have become available. "Vaccine research and vaccinology" had witnessed a sort of 'renaissances in vaccine research and uses' in the early 1970s and 1980s, and now in the 21st century there are licensed vaccines against nearly 27 agents and ongoing research on candidate vaccines against nearly 130 agents.[1]

There is increasing recognition of the role of vaccines as proven lifesaving interventions and that of the epidemiological principles in maximizing the benefits of vaccines and vaccination. While vaccinology delves into understanding how vaccines work, epidemiology helps to ascertain whether a particular vaccine is needed in targeted population (or age group) or not? For physicians and vaccine users alike, epidemiology and immunology are two important fields in medical science and public health, which helps in the better appreciation of the promise and potential of vaccines. While immunology is essential for understanding vaccine-host interactions, epidemiology is essential for understanding the implications of a vaccination program on the community and individuals. "Vaccine epidemiology" could be described as an interface between public health, basic medical sciences, and clinical medicine aimed at maximizing the benefit of existing knowledge in these areas.

The learning and study of vaccine epidemiology could help in the following: To make decisions on how to choose vaccines for inclusion in a public health program; to assess the disease burden; to identify target pathogens for vaccine research; to identify sources and transmission pathways of disease-causing agents; to determine vaccination strategies; to design disease-specific control, elimination, and eradication strategies; to monitor performance indicators; to take steps to improve surveillance; and to measure the progress and impact of vaccination strategies.

This review article aims to outline the basic concepts and key principles of vaccine epidemiology, and to briefly describe how vaccination program managers and vaccinologists could use this knowledge and understanding in their respective fields of work.

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Historical Background

The terms "vaccine" and "vaccinology" came into use soon after Edward Jenner discovered the smallpox vaccine. Jenner called the smallpox vaccine "variola vaccinae." For his contribution, Jenner is often referred to as the "Father of Vaccinology" (though this epithet is sometimes also used for Louis Pasteur). The word "vaccine" originated from *vacca*, a Latin term for the cow.[4] The credit for the first use of the term "vaccine" goes to Swiss physician Louis Odier (1748-1817), and the terms "vaccination" and "to vaccinate" were first used by Richard Dunning (1710- 1797).[5]

Epidemiology, which literally means "the study of what is upon the people," is derived from the Greek *epi* meaning "upon, among," *demos* meaning "people," and *logos* meaning "study or discourse." Physicians from the times of Hippocrates (460-370 BC) tried to understand the pattern of diseases in the community, though the term "epidemiology" was first used to describe the study of epidemics in 1802 by the Spanish physician Villalba in the *Epidemiología Española*.[6] In modern times, John Snow (1813-1858) and William Farr (1807-1883) pioneered the work on epidemiology and are often referred as one of the "fathers of modern epidemiology."[7,8] Epidemiology, though practiced from earlier times than vaccinology, gained attention and prominence in the 19th century. Now, the practice of vaccinology has become closely linked with that of epidemiology.

Key Concepts in Vaccinology

A vaccine is "an inactivated or attenuated pathogen or a component of a pathogen (nucleic acid, protein) that when administered to the host, stimulates a protective response of the cells in the immune system," or it is "an immune-biological substance designed to produce specific protection against a given disease."[9] The process of administering the vaccine is called vaccination. In other words, vaccination is the process of protecting susceptible individuals from diseases by the administration of a living or modified agent (e.g., oral polio vaccine), a suspension of killed organisms (as in pertussis), or an inactivated toxin (as in tetanus). Immunization is "the artificial induction of active immunity by introducing into a susceptible host the specific antigen of a pathogenic organism."[9] However, immunization and vaccination are often used interchangeably. Vaccinology combines the principles of microbiology, immunology, epidemiology, public health, and pharmacy, amongst other.

The aim of vaccination is to protect individuals who are at risk of a disease. The children, the elderly, immune-compromised individuals, people living with chronic diseases, and people living in disease-endemic areas are those most commonly at risk. Vaccination is a common strategy to control, eliminate, eradicate, or contain disease (i.e., mass immunization strategy). If one wishes to learn about and understand vaccines, vaccination, and immunization programs, one needs to start with the understanding of key terms such as "antigen," "antibody," "immunoglobulins," and "antisera," among others. These are often described in the textbooks on this topic and therefore not covered in this article.

A vaccine is different from immunoglobulin in that the vaccines help in developing protective antibodies in the body of the individual to whom these are administered, and protection is available after a lag period of a few weeks to several months. However, immunoglobulin provides immediate protection. The vaccine administration is followed by two types of immune responses: Primary and secondary [Figure 1].[9,10]

There are different types of vaccines: Live, killed, conjugate, component, and recombinant vaccines. While live vaccines provide protection after the administration of a single dose (though not always), the nonlive (or killed) vaccines usually require multiple doses for a satisfactory primary response. A minimum of 4 weeks' interval is required between successive doses, though a longer interval (often, 8 weeks is considered optimal) results in higher antibody levels. The booster doses are generally given 6 or more months after the completion of the primary series. The booster doses have rapid and higher antibody response, a higher affinity for antibody production, and provide longer duration of protection (this is linked to secondary immune response).[11]

The antibody responses to vaccines are usually identified by "the correlates of protection," an immune response that is responsible for and statistically interrelated with protection and usually linked to B-cell dependent response. Though, for a number of new vaccines, it is assumed that T-cells also play a role in correlates of protection. The correlates of protection are identified by animal challenge models and efficacy trials.[12]

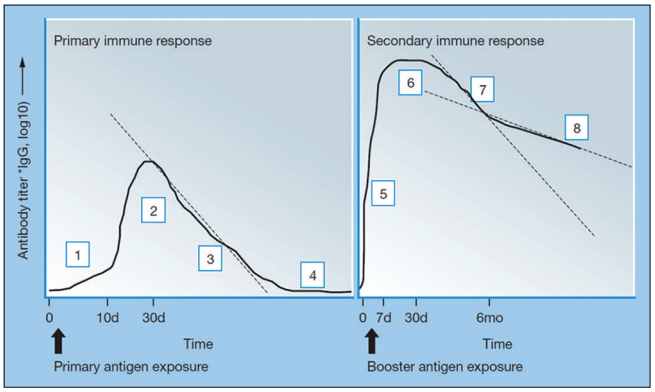

Figure 1: Primary and secondary response
Note: The primary series is the vaccine dose required for a primary response. There is a slow development of antibody in the body after the first dose of the vaccine is administered, and it usually takes 3-4 weeks to reach the peak antibody response. When a subsequent dose is administered (booster dose), a higher and quicker immune response is received (secondary immune response)

Key Concepts in Epidemiology

Epidemiology pinpoints the weak links in the chains, sources, and transmission pathways of the pathogen so that the interventions can be directed. The understanding of epidemiology is required from the very early stage of priority-setting for disease burden, understanding the basis of correlates of protection, development of vaccines, evaluating different vaccination strategies including epidemiological and economic modeling, deciding national vaccination strategies, developing surveillance mechanisms, impact assessment, and designing vaccine introduction strategies.

The term "disease burden" or burden of disease (BoD) occupies a key place in epidemiology. The BoD could be measured by incidence or prevalence of a disease (prevaccine and postvaccine); severity/mortality (measured as case fatality ratio, hospitalization, and disease sequelae); disability [measured by disability-adjusted life years (DALYs)] and quality-adjusted life years (QALYs)]; economics (measured by cost-effectiveness, cost benefit, and cost utility); and social aspects (measured by societal disruption, economic disruption, and household impact).[13] The key concepts and study designs (i.e., cross-sectional, case-control, nested case-control, cohort studies) to understand epidemiology (disease occurrence and trends) are well, documented and thus not described in this article.[14-16]

However, vaccine probe studies requires special mention here, a vaccine probe study is a randomized cluster trial of a vaccine in which, usually, vaccine effectiveness (in other trials, usually efficacy is assessed) endpoints are used. The difference in the incidence of disease between vaccinated and unvaccinated children represents the vaccine-preventable disease burden. These are technically vaccine-effectiveness trials and have been used to measure the vaccine-preventable proportion/incidence of clinically (not microbiologically) defined outcomes. This approach has been used successfully in several countries for studies on *Haemophilus influenzae* type b (Hib) conjugate and pneumococcal conjugate vaccines.[17,18]

Vaccine Epidemiology

Vaccine epidemiology is the study of the interactions and effects of vaccines (and vaccination programs) on epidemiology of vaccine preventable diseases. Understanding the pattern of disease by geographical, rural-urban, and gender variations, linkage between disease burden and immunization coverage is based on principles of epidemiology. Which time of the year the polio mass immunization campaign should be conducted? For conducting mass campaigns, which age group should be targeted? Where should immunization efforts be concerted? Why do outbreaks occur? Why is it that some children do not suffer disease even though they have not received any vaccination? These are some of the questions answered through the application.

Basic reproductive number (R_o)

Basic reproductive number or R_o, measures "the average number of secondary cases generated by one primary case in a susceptible population."[19] A number of factors determine its magnitude, including the course of infection in the patient and the factors that determine transmission between people. The magnitude of R_o varies according to location and population. It is strongly influenced by birth rate, population density, and behavioral factors.[19] The magnitude of R_o can be ascertained by cross-sectional and longitudinal serological surveys.

For organisms to survive:

$R_o = 1$ (A primary case must attempt to generate at least one new case)
$R_o > 1$ (Expansion of infected individuals)
$R_o < 1$ (Shrinking pool of infected individuals).

To calculate the magnitude of R_o, a few key epidemiological, demographic, and vaccination program-related parameters should be known.[19] Parameters such as average age at infection prior to mass vaccination, life expectancy of the study population, and the average duration of protection by maternal antibodies should be considered. While the life expectancy and average age of protection by maternal antibody are known, the average age of infection prior to mass vaccination has been studied in select populations and is provided in Table 1.[20-27] A number of studies have been conducted in different parts of the world to assess the average age of infections and to derive the basic reproductive number.

This information could be used to estimate the fraction of each birth cohort that must be immunized to block transmission of a given disease. R_o provides assessment of the critical fraction of each population immunized if eradication is targeted.

Force of infection

The "force or rate of infection" is "the risk of being infected." The force of infection depends on the prevalence of infectious individuals, rate of contact between individuals, infectiousness of individuals, etc. As transmission is a dynamic process, force of transmission can change over a period of time.[28]

Vaccine efficacy and effectiveness

Vaccines have effect at both individual and population levels. The "biological or individual level effect" of vaccines includes effects on susceptibility (VE*s*), on infectiousness (VE*i*), and on disease progression (VE*p*). The "population level effects" of vaccination depend on the coverage and distribution of the vaccines, as well as on how well different groups mix with each other.[29-31] These effects could result from the biologic as well as behavioral effects of the vaccination. Overall, the public health effect of vaccination programs depends on the effect in both vaccination and the unvaccinated population. This gives at least three types of population level effects of vaccination:

Table 1: Average age of infection and basic reproductive number of select diseases[20-27]

Infection	Average age at infection, A (years)	Location/time period	
Measles virus	5-6	USA 1955-58	
	2-3	Bangkok, Thailand 1967	
Rubella virus	9-10	Sweden 1965	
Varicella virus	6-8	USA 1921-28	
Polio virus	12-17	USA 1920-60	
Mumps virus	7-8	England and Wales 1975	
Smallpox virus	10-15	Bangladesh 1940	
Infection	**Location**	**Time period**	**R_o**
Measles	England	1947-50	13-15
	Canada	1912-13	11-13
Varicella	USA	1943	7-8
Mumps	Netherlands	1970-80	11-14
Rubella	West Germany	1970-79	6-7
Polio	USA	1955	5-6
Influenza A (subtype H1N1)	England	2010	1-1.5

- *Indirect effect*: The population level effect of widespread vaccination on people not receiving vaccine
- *Total effect*: Combination of population level effect and effect of vaccination on individuals receiving vaccine
- *Overall public health effect*: The effect of vaccination program based upon weighted average of indirect effect on the individual not receiving vaccine and total effect on individual receiving vaccination.

In this context, the terms "vaccine efficacy," "vaccine effectiveness," and "program effectiveness" are commonly used. Vaccine efficacy is the percentage reduction in disease incidence attributable to vaccination (usually) calculated by means of the following equation:

$$VE\ (\%) = (RU - RV)/RU \times 100$$

where RU = the incidence risk or attack rate in unvaccinated people and RV = the incidence or attack rate in vaccinated people.[29,30]

The equation for vaccine efficacy can be reformulated as:

$$VE = 1 - RV/RU \times 100$$

where RV/RU is the relative risk or rate ratio in vaccinated and unvaccinated people.

The vaccine efficacy is measured by observational studies under field conditions within a vaccination program or measured by trials conducted under normal program conditions. The vaccine efficacy for a number of vaccines is known, such as Measles 90-95%; mumps: 72-88%; and rubella 95-98%.[32,33] In vaccine trials, the vaccine's efficacy (among other things, including safety) is assessed. This is an important criterion for licensing of the vaccines and for making decisions on programmatic use.

Vaccine efficacy is dependent on internal or individual factors, for example the efficacy of the measles vaccine depends on the presence of inhibitory maternal antibodies, the immunologic maturity of the vaccine recipient, and the dose and strain of the vaccine virus.[34]

Vaccine effectiveness is the sum of the reduction in the clinical events that might be expected to be associated with the disease.[28,29] Under program-based conditions, the effectiveness of the measles vaccine depends on the coverage, cold chain maintenance, correct injection techniques and safety, inaccurate recordkeeping/recall resulting in misclassification errors, and population-specific factors [human immunodeficiency virus (HIV) infection, malnutrition, etc.]. The most commonly used study design to assess a vaccine's effectiveness is a retrospective case-control analysis, and the odds ratio thus obtained can be used to calculate vaccine effectiveness, as follows:

$$Effectiveness = (1\text{-}OR) \times 100$$

Vaccine effectiveness could be assessed by observational studies: Cohort studies, household contact study, case-control study and screening. How the information from screening could be used for estimating of vaccine efficacy is shown in Figure 2.[35,36]

Vaccine efficacy and effectiveness have often been used interchangeably in scientific literature. Vaccine effectiveness is often referred to as vaccine efficacy in field conditions. In other words, vaccine effectiveness is a combination of vaccine efficacy and field conditions such as coverage, immune status of population, and conditions under which the vaccine was administered (cold chain). In general, efficacy is higher than effectiveness. However, vaccines that show herd effect could have higher effectiveness than vaccine efficacy. For example, under program conditions, vaccine effectiveness is lower than vaccine efficacy, while herd effect improves effectiveness and can take it above efficacy. If analyzed from an outbreak, the formula for estimation of vaccine effectiveness is: Attack rate among vaccinated (ARV) vs attack rate among unvaccinated (URU). The formula used for assessing vaccine efficacy with this information is: Vaccine Efficacy (VE) = (ARU-ARV)/ARU*100.[35,36]

The "program effectiveness" refers to "the effectiveness of all antigens in an immunization program at implementation level at district, state and national levels." The program effectiveness is also assessed by analyzing the trends in the occurrence of vaccine-preventable diseases (or VPDs) in identified settings and situation, before and after vaccine introductions. Overall mortality reduction is often considered as an indicator of vaccine program effectiveness/impact. Program effectiveness is the combination of more than one vaccine's effectiveness. Impact is the population level effect of a vaccination program, which depends on many factors, including vaccine efficacy, herd immunity, and effectiveness.

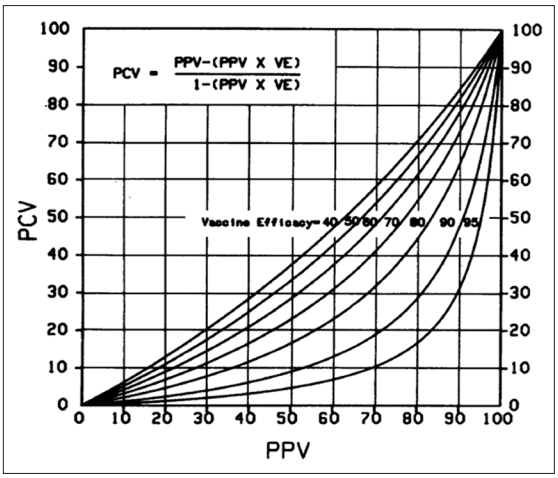

Figure 2: Relationship between percentage of cases vaccinated and vaccine efficacy
Note: With this figure, vaccine efficacy could be assessed by the following formula: PCV = [PPV- (PPV*VE)]/[1-(PPV*VE)]. Here, PCV = Proportion of cases occurring among vaccinated individuals, PPV = Proportion of population vaccinated, and VE = Vaccine efficacy. If any of the two values in this formula is known, the third value can be derived

Study Designs to Assess Vaccine Efficacy and Program Effectiveness

Serological and epidemiological studies can be used to determine vaccine efficacy and program effectiveness with minor methodological adoptions.[9,15,16,18,33-36] Among serological studies, two sub types of studies are utilized for vaccine efficacy: Seroconversion studies and seroprevalence studies. Seroconversion studies are useful in measuring the induction of an immune response in the host. In the absence of disease, it indicates the persistence of antibodies and immunity. These studies are particularly useful in choosing the appropriate age for vaccination. Seroprevalence studies monitor the prevalence of antibodies due to disease in the population and indicate the pattern of occurrence of diseases.

The epidemiological approaches measure the ARV and ARU in various settings. Thereafter, the formula suggested above could be used for estimating vaccine efficacy. The epidemiological study designs[9,15,16,18,33-36] include:

- Double-blind, randomized, placebo-control trials: The ideal vaccine efficacy study is a clinical trial starting with persons susceptible to disease. However, such studies are not possible after the vaccine is licensed, as it becomes unethical to use placebo when the vaccine is of proven benefit
- Observational cohort studies: These are conducted when the randomized-controlled trials or secondary attack rate trials are not ethically justified, or are not feasible due to low incidence of the disease, or there is a requirement for long-term follow-up for the calculation of efficacy (e.g., hepatitis B vaccination in neonates, or where the number of individuals is too large to follow up)
- Case-control studies: These studies are most useful when personal immunization records are not generally available but some other sources such as records from clinics can be obtained. Case-control studies may be useful when prospective controlled trials are not feasible due to low incidence of disease
- Stepped wedge design studies: These are used when previous studies have indicated that the intervention is likely to be beneficial and the public health needs to introduce the intervention precludes withholding it from a population. The intervention is introduced in phases, group by group, until the entire target population is covered. The groups form the unit of randomization
- Outbreak investigations (Community-wide, total population, or population clusters): Such studies are best done when the outbreak is in a defined population, such as a village, town, city, or school
- Secondary attack rates in families and/or clusters: The assessment of secondary attack rate in family members of the "index case" provides a good opportunity to assess vaccine efficacy
- Screening of population: This method provides an estimate of vaccine efficacy if some other information is available. The formula used for assessing vaccine efficacy is given below and is used for assessing vaccine efficacy:
  PCV = [PPV- (PPV*VE)]/[1-(PPV*VE)]
  where PCV = proportion of cases occurring among vaccinated individuals; PPV = proportion of population vaccinated; and VE = vaccine efficacy. If any of the two values in this formula is known, the third value can be derived [Figure 2].
- Cluster Survey Method: In some of the endemic areas, vaccine efficacy can be assessed, even in the absence of an outbreak, by using coverage survey methods.

Other Important Concepts in Epidemiology

Vaccine failure

When a person who has been fully vaccinated develops the disease against which she/he has been vaccinated, it is referred to as vaccine failure. This could be of two types-

- Primary vaccine failure occurs when the recipient does not produce enough antibodies when first vaccinated. Infection can therefore occur at any time post vaccination. For example, this occurs in about 10% of those who receive the measles, mumps, and rubella (MMR) vaccine[37]
- Secondary vaccine failure occurs when adequate protective levels of antibodies are produced immediately after the vaccination, but the levels fall over time. The incidence of secondary vaccine failure therefore increases with time after the initial vaccination and hence booster doses are required. This is a characteristic of a number of the inactivated vaccines.[37]

Herd immunity and herd effect

Herd immunity may be defined as the resistance of a group or a community in total, against the invasion and spread of an infectious agent as a result of a large proportion of individuals in the group being immunized. Herd immunity or contact immunity develops in the case of certain live vaccines (e.g., OPV), wherein the nonvaccinated individuals also develop immunity to the pathogen just by coming in contact with the vaccinated individual.[38]

The level of herd immunity can be assessed through cross-sectional and longitudinal serological surveys. The serological surveys are usually based on serum or saliva in viral infections and activated T-cells for bacterial and protozoal infections. There are a number of quantitative assays, too.[39]

Additionally, immunological and disease surveillance methods provide the empirical base for the analysis and interpretation of herd immunity. Mathematical and statistical methods play an important role in the analysis of infectious disease transmission and control. They help to define both what needs to be measured, and how best to measure and define epidemiological quantities. The level of herd immunity can be measured by reference to the magnitude of reduction in the value of R_o.[22]

Herd immunity threshold (H) is defined as the minimum proportion to be immunized in a population for elimination of infection.

$$H = 1 - 1/R_o = (R_o - 1)/R_o$$

As the immunization coverage increases, the incidence and prevalence rates may decrease not only due to the direct effect of immunization *per se* but also because of indirect effects, such as the development of herd immunity and herd effect.[38,40]

"Herd effect" or "herd protection" is "the reduction of infection or disease in the unimmunised segment as a result of immunising a proportion of the population" or is "the change induced in epidemiology (incidence reduction) among unvaccinated members when a good proportion is vaccinated." Herd effect is seen only for infections where humans are the source, and it extends beyond the age the vaccine is given, i.e., Haemophilus *influenzae* type B (Hib) vaccine is given to infants and protected other under-5 children, flu vaccine to children and beneficial effect among other family members.

Epidemiologic shift or transition

Epidemiological shift or transition denotes the change in the pattern of disease in a specified population. The impact on the person characteristics of a disease is the shift in the age of occurrence and severity of the diseases as observed consistently in communities with partial immunization coverage or immunization coverage for specific age groups only. A number of factors including the age at the time of vaccination, target population for vaccination, serotypes covered by the vaccines (where the disease in question is caused by multiple serotypes), and overall vaccination coverage may affect the epidemiological shift or transition.[41,42]

The phenomenon has importance in diseases such as hepatitis A, rubella, and varicella, wherein the severity of disease worsens with advancing age. It also has significance in diseases where multiple serotypes are associated with the diseases such as pneumococcal diseases and when targeting specific serotype by vaccine may lead to the emergence of other types of serotypes. The epidemiological shift or transition sometimes may offshoots the benefits accrued by the vaccination program. This showcases the need for tracking the epidemiological changes in the vaccination programs and initiating appropriate corrective measures.

One of the well-documented example of epidemiological shifts has been documented from Greece, following the introduction of MMR vaccine in public health program of the country. When the MMR vaccine was introduced in 1975 in Greece, the coverage with the vaccine was around 50-60% of the cohort, which reduced the incidence of diseases in the targeted population; however, shifted the average age of infection to older population. However, the susceptible cohort of un-vaccinated continued to increase over period of time with epidemiological shift to older age groups. By the early 1990s, specially those unvaccinated girls reached in the reproductive age group, still susceptible to rubella virus disease. In such cases, if the infections happened during the time of pregnancy, it led to development of congenital rubella syndrome (CRS) in fetus/infants. In 1993, it was noted that Greece had the highest incidence of congenital rubella syndrome (CRS).[42] This example highlights the need and importance for high coverage at the time of vaccine introduction and sustenance of the coverage in the subsequent cohorts. This situation is sometimes referred to as "perverse outcome," where disease severity increases with age at infection: Vaccination can increase the burden of severe diseases, by raising the average age of infections. The total number of infections falls but the total number of severe disease increases, e.g., CRS, measles, encephalitis, and orchitis due to mumps.

Vaccine-preventable Disease Surveillance

Disease surveillance is another public health and epidemiology tool. A functioning disease surveillance system helps in understanding disease epidemiology before vaccines are introduced. Thereafter, it guides how well the vaccination program is doing in reducing the BoD. It helps in decisionmaking on the introduction of vaccines and also in assessing the impact of interventions. Unfortunately, the disease surveillance system in the majority of the LMICs requires a major boost.

Disease Modeling

The models are often referred to as "tools for thinking and simplification of systems," suitable for analysis.[43]

Epidemiology aims to measure the disease burden; however, where measurement is not practical, estimates must be developed. The modern epidemiological methods and disease modeling have reached the level where accurate projection can be made based on existing knowledge and information. The estimates derived from various sources are often used in vaccination programs. The estimates

are used for decisionmaking at local levels (i.e., state and national levels), for deriving estimates for neighboring countries (with similar settings) and for global (or international) levels. The estimates, if done with similar methods can provide useful information for interstate, intercountry, and interdisease comparisons, to observe the disease trend over a period of time, and for comparison of choices between intervention versus none versus others

In vaccination programs, a number of models are used:

- A static or decision analysis model is used on the assumption of a constant force of infection (or fixed risk). These models are more commonly used for noninfectious diseases. The static models are usually applied to a single cohort[45]
- Markov models[46]
- Dynamic model used for infectious diseases. Suspected, infected, and recovered (SIR) approach is an example of a dynamic model. These models are applied to multiple cohorts.[47]

Economic evaluation

Economic evaluation in healthcare addresses the question whether an intervention or procedure is worth doing when compared with other possible uses of the same resources.[44] This is based on the premise that resources are finite and there are opportunity costs. In such analysis, both costs (resources used) and outcomes (benefits) are considered. There are number of analyses including cost-effective analysis, cost-benefit analysis, cost analysis, and cost utility analysis.

Immunization Program Assessments and Evaluations

It is imperative to ensure the quality of immunization services is evaluated and assessed on a regular basis. The epidemiological methods provide useful tools for such evaluations.

- Thirty cluster survey: This is standard World Health Organization (WHO) methodology to determine immunization coverage based on a survey of small number of individuals (for example, 210 in 30 clusters of seven children each). The home visits are made and a immunization record or history is taken for children aged 12-23 months. The survey provides fairly correct information about immunization coverage in the area. However, it is important that these clusters are selected based on standardized methodology and statistical tools[48]
- Seventy-five-household survey: In this approach, 75 households near the health facility are surveyed. This methodology follows the notion that the households closest to the facilities can provide the best estimates of immunization coverage[49]

Missed-opportunity survey, Lot quality assurance survey (LQAS), the multiple indicator cluster survey (MICS), and coverage evaluation surveys (CES) are the other methods.[49]

Application of Vaccine Epidemiology in Vaccination Programs

Vaccine epidemiology, as described in the earlier sections, is a multidisciplinary science. It has a role to play from vaccine research (proof-of-concept stage and then in clinical trials), in decisionmaking on new vaccine introduction, and once vaccines are introduced in the post-marketing surveillance and other aspects. The practice of vaccinology is gathering momentum since the first immunization schedule was published by the WHO in 1961.[50] Now in the 21st century, there are more licensed vaccines, more in the pipeline, more number of people than ever receive vaccines. There is an increasing amount of research in laboratories, deliberations in academic institutions, and policy discourses in ministries of health about vaccines and vaccination schedules. There is an increasing awareness within the general public about vaccines and vaccination schedules.

One of the important development in the last 2 decades has been that the electronic media and the Internet have empowered people with information. The information received from various sources on the Internet is mostly useful for parents and the general public but is not always correct. At times, it reflects one sided view, and people with vested interests may misuse the information and media. The risk of such incomplete information has been reflected in some of the recent outbreaks of measles in European countries where the Internet has been a major source of information, and people used this source for decisionmaking. Such misinformation has affected the adoption of human papillomavirus (HPV) vaccination in a few countries.[51,52] These examples reflect the two sides of technology, which can help in increasing coverage of vaccines but could also spread misinformation which can lead to disease outbreaks.

The incidences of "vaccine refusal" or "vaccine hesitancy" are increasing.[53] This is an area in which the knowledge and understanding of vaccine epidemiology could help in improving immunization coverage (or at least prevent undesired fall in immunization coverage). The vaccine epidemiology can help in responding to the misinformation and addressing the challenge. Vaccine epidemiology can provide guidance in understanding which diseases are common in which parts of the world and therefore help in decisionmaking about which vaccine should be received by the people traveling to particular endemic countries. It guides in the selection of vaccines for special target groups, i.e., pregnant women, the elderly, and in the changing context.

The disease surveillance system is often used to measure the impact of vaccination programs on disease burden. The vaccine preventable diseases surveillances system could provide useful insight on the benefits of vaccination and is an important tool for programmatic modifications and advocacy. The National Immunization Technical Advisory Groups (NITAGs) use vaccine epidemiology for decision making. The national vaccination

policies and immunization guidelines need to be informed by the vaccine epidemiology.

There are important roles of vaccine epidemiology in reducing morbidity and mortality from vaccine-preventable diseases. This knowledge could be best utilized by policy makers for immunization program decisionmaking and by family physicians and public health specialists for advising individuals on the benefits of vaccination.

In LMICs there is limited capacity for training in vaccinology and epidemiology. There are very few training opportunities and courses that teach vaccine epidemiology. It is a paradox that countries requiring maximum capacity have very limited opportunity. This affects both vaccine research and decisionmaking.

In the absence of sufficient capacity, the country program managers in LMICs often have to rely on international experts for decisionmaking. This adversely affects the reputation and credibility of the country's program managers and raises questions regarding the decisionmaking process, contributing to the delay in the benefits of proven interventions reaching those who are most susceptible to vaccine-preventable diseases.

Conclusion

The understanding of vaccine epidemiology has potential to save additional lives from vaccine preventable diseases and improve health outcomes through life course. The vaccine epidemiology has definitive role in extending the benefits of vaccines to additional populations and in the selection of target groups for vaccination, amongst other. However, systematic efforts would be needed to translate this knowledge into actions. The mechanisms and institutional capacity has to be built into low and middle income countries (LMICs) on vaccine epidemiology. The national governments and international development partners need to support and promote courses and training programs for vaccine epidemiology, and the academic communities need to work together. Vaccine epidemiology should be part of key modules in the teaching of undergraduate and postgraduate medical students. Public-health program managers and policy makers should be trained in vaccine epidemiology through continued medical education and on-the-job training programs.

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The opinions expressed in this article are solely those of the author and should not be attributed to any institution/organization he has been affiliated to in the past or at present.

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