Vaccination the Important Public Health Tool

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Throughout the twentieth century, worldwide improvements in sanitation and vaccination have led to impressive declines in the incidence and mortality of many infectious diseases. Perhaps the greatest public health achievement of this era was the global eradication of small pox in 1978. This was only possible because of the judicious use of small pox vaccine. In India the practice of vaccination existed since the beginning of 1900. The common vaccines used were small pox, cholera and later typhoid vaccine. BCG vaccine was introduced under the National Tuberculosis program in the year 1962. Just after launching the ICDS program for child Development by the Social Welfare Department of HRD ministry in 1975 on pilot basis, the health department in 1978 launched Expanded Program of Immunisation. This was aimed to reduce the morbidity and mortality caused by six vaccine preventable diseases (VPD): viz. Diphtheria, Whooping cough, and Tetanus, Poliomyelitis, typhoid and childhood tuberculosis. (1) After gaining some momentum to improve the coverage the program was designated as Universal Immunization Program in 1985. In this format typhoid vaccine was replaced by measles vaccine. The UIP program was implemented in phased manner in different districts with the objective of increasing immunization coverage, improving quality of services by establishing a reliable cold chain system from the manufacturing up to the field level. The program also envisaged to achieve self sufficiency in vaccine production and establish a district based efficient monitoring system for assessing the performance. In 1986 UIP was included as a component of the National Technological mission and became operational in all the districts of the country during 1989-90. The successful implementation of the UIP laid the foundation to launch other programs for mother and child viz. CSSM in 1992 and later RCH in 1997. (1 &2)

Standard Protocol For Introducing a Vaccine in the immunization Schedule:. Most of the countries have their own policy & standard protocol to introduce new vaccine in their immunization schedule and follow the same. Is a standard protocol to introduce a new vaccine essential requirement? Logically it is a sound proposition as we are investing a reasonable amount of available scarce resources for health and are using it for protecting our children and young population from the risk of infections causing high morbidity and mortality. It is also a fact that introduction of a vaccination program in a country may or may not be effective to reduce the incidence of infection in the community unless and until all the scientific facts are known from the epidemiological and other health system context prevailing in the country. On the other hand due to the availability advance methods of case management and people's effective utilization of continuously increasing availability of health services the mortality may also drastically reduced which may be falsely credited to success of vaccination. So before introducing a new vaccine in a community a rigorous scientific process should be followed and basing on the scientific evidence gathered new vaccines are to be introduced. In the following paragraph we shall describe the steps necessary for introducing a vaccine in a community from "laboratory to community". This will give us an insight of the necessity of formulating standard protocol/ policy for introducing a vaccine in the country.

The first step in vaccine development is vaccine innovation which includes identification and characterization of antigen that induces neutralizing antibody, identification of genetic clone that produce these antigens, identification of vaccine's biochemical formulation and conducting numerous animal studies for extensive manufacturing leading to mass production of vaccine. (3)

The second step is to conduct Pre clinical Study: This is the first step of getting a licensure for any candidate vaccine. The purpose of this phase is to determine the dose response relationship and to identify the best route and dose for administration to achieve the maximum beneficial dose. Maximum beneficial dose is defined as the dose which induces the maximum protective immune response with the minimum serious adverse reaction. Appropriate animal models are used to develop assays that assess the humoral and cellular immune response to the candidate vaccine. In this phase different types of vaccine induced toxicities are observed and listed. This may include severe systemic effects, organ system damage, and carcinogenicity and teratogenicity. If at the end of this phase the potential benefit is deemed to outweigh the observed harm and toxicity of the vaccine than one can proceed for subsequent human studies. The next step is the process of filling an Investigational New Drug (IND) application with the licensing authority. In India it is the Drug Controller of India the counterpart of the Food and Drug Administration (FDA) in USA. Detailed information related vaccine formulation, vaccine manufacturing, stability, and sterility testing and results of animal testing is submitted. The Licensure authority approves the human studies only when the candidate vaccine demonstrates potency, safety and effectiveness in the animal studies. (3)

Phase-I Dose finding and safety study: Following the approval of FDA/or other statutory body, in India we require to have clearance from Drug Controller and ICMR. Next the study has to be placed before the Local Institutional Review Board (IRB) and Institutional Ethics committee for approval. The purpose of these studies is to determine the dose response and/or beneficial dose (BD). It is defined as the dose which achieves immunogenic response without severe adverse reaction (SAE). Route of administration and dosing schedule necessary to achieve BD with lowest chances of SAE are evaluated. Evidence of immune response (e.g. Rise in anti-vaccine antibody titre is assessed and surrogate serological markers for vaccine efficacy are defined. It is conducted among consented healthy adult population with no condition that contradicts vaccination. The study design may be "open label study in single or sequential samples". The end points are dose finding, (dosing schedule and route of administration that are required to achieve beneficial immunological response i.e. rise in neutralizing antibody titre) safety (number and proportion of expected or unexpected adverse events including local reaction e.g. pain & swelling and SAE) and biologic effect (proportion of persons achieving protective immune response) and are measured by estimates of single means of proportion. (3)

Phase-II Safety & immunogenicity Study: This study measures the proportion of side effects (general, serious, non-reversible) and assesses evidence of efficacy. Immune response is assessed by determining the proportion of subjects who achieve a predetermined immunogenic response (e.g. two or four fold rise in antibody titre).. In a comparative trial the proportion of side effects and level of immune response can be compared between dose groups or between

vaccine and placebo group. The study is conducted in Health adults, with no condition that contradicts vaccination. The design of the study is open label prospective cohort study or small randomized controlled trials are used to assess fixed dose of vaccine or to comparing differing doses or vaccine schedule. The number of samples needed to estimate proportion of person who achieves a favourable immunological outcome without hindering the study's ability to measure side effect level. Sample ranges from 20-200. The end points of the study are 1. Safety (expected & unaccepted adverse events are enumerated graded for severity and relationship to vaccine adverse events which includes: local reaction e.g. pain, erythema, swelling, indurations; systemic reaction e.g. allergic reaction, fever, arthalgia, myalgia, lymphadenopathy, , hepatic, renal, haematologic, neurologic, irritability, fussiness, gastro intestinal , cardiac reaction and other toxicities). 2. Immunogenicity: The proportion of persons who achieve protective immune response (after 1 or multiple doses of vaccine) is used as an indicator of clinical efficacy. Markers of protective immune response include neutralizing antibody titre, and rise of antibody titre from base line and proliferation of specific cytotoxic T lymphocytes. The measures of effects are calculated by estimates of single proportion (mean) or difference between two proportions (means) for comparative trial. Additional Phase II studies are conducted in Children & Infants (for primary series) to fine tune the dose and define the vaccine schedule and continue monitoring immune response and vaccine safety. (3)

Phase- III Comparative Efficacy study: Only those vaccines that are shown to be safe and immunogenic in phase I and II trials are allowed to go for the Phase III trials. The objective is to find out the true vaccine efficacy. Vaccine efficacy trial determines the impact of vaccination on prevention of infection and also to assess the feasibility of administering vaccination in "at risk population". The trial involves large number of susceptible people in "real world" settings. The study design used for determining vaccine efficacy is the double-blinded, placebo controlled randomised trial. Sample size for conducting such study depends on the incidence of infection in an unvaccinated population or a vaccinated population if a standard vaccine is already available and the reduction in incidence one expects to observe after vaccination. The endpoints to be studied are; 1: Efficacy, (the number of new infection in the vaccinated versus the control group. Vaccine efficacy is also measured in all study participants, then within the strata by number of doses received. Clinical or biological efficacy is estimated by comparing the proportion of vaccinated and controls who achieves a defined threshold of protective immune response (such as fourfold rise in neutralizing antibody. This measure is important when determining whether new vaccine is equivalent to standard vaccine). 2. Safety: (Number and grade of adverse events in both the groups). 3. Feasibility. (Large clinical trials begin to demonstrate the feasibility of adding a new vaccine to an immunization program. Feasibility indicators include follow up rates, i.e. completion & drop outs; tolerability and acceptability of vaccine, as well as barriers to compliance to immunization schedule). The measures of effects are estimated by estimate of difference between two means or proportion & estimate of vaccine efficacy. Vaccine efficacy is calculated as the observed reduction in incidence in the vaccinated versus the unvaccinated population expressed as a percentage.

$$\text{I (control)} - \text{I (vaccinated)}$$

VE: ——————————————

I (controls)

As the demographic character, environmental factor and personal/ lifestyle factors are related to the outcome of the exposure to risk of natural infection, randomization process is used to achieve comparability between vaccinated and unvaccinated groups. It can only minimize but residual confounding may persist even after randomization. To avoid bias one should know the nature and extent of the confounding, which depends on factors relating to host agent and environment. Following are some of the examples of confounding. Besides age the risk factors for most childhood infections include status of other immunization, attendance in day care, crèche, school or any congregation and exposure to infected individuals and also his general health & nutritional status. In vaccine trials like HIV, HBV and Hepatitis C risk factors that require consideration include the number of unprotected sexual acts and sharing of potentially contaminated injection equipment. For infections like malaria that are transmitted by vectors, it is important to take into account the level of endemicity of plasmodium species and the residents use of any measures against vector exposure viz. Use of mosquito net and use of insecticide, repellents etc. In any disease where there is very effective treatment and the health service utilization for that specific disease is high. The above confounders cause differential exposures to the infectious agent across the vaccinated and control groups and can bias the estimate vaccine efficacy. In all these cases appropriate adjustment for these potential confounders is crucial. (4,5,)

Phase IV vaccine effectiveness study: This step is necessary after licensure of vaccine for use it as an immunizing agent for mass vaccination. Here the vaccine is administered in heterogeneous population at risk of disease who will vary in age, infirmity, access in health care and risk of exposure. Observational studies play an important role in assessing vaccine effectiveness. In contrast to randomized clinical trials evaluating vaccine efficacy, community intervention studies (case control or cohort) evaluate the combination of vaccine efficacy and success of a given immunization program. A significant decline in the overall incidence of disease is one of the key indicators that the vaccine itself and the immunization campaign have contributed to the prevention of the disease. This is called the effectiveness of the vaccine. The scope of measurements of the vaccine efficacy and effectiveness is discussed below for better understanding. The effectiveness of a vaccine depends on various factors other than efficacy. Potency of an inactivated vaccine may not be optimal due to strain difference or due to a specific lot of vaccine was less antigenic. The potency of a live attenuated vaccine can be compromised if the cold chain was not maintained. Vaccine effectiveness can also be low due to incomplete vaccine coverage. Vaccine effectiveness is generally determined by comparing risk of disease among vaccinated and vaccinated groups. An ideal study should ensure that the two groups are comparable with respect to exposure, risk of infection, access to vaccine and opportunity for diagnosis. (4,5,6)

Measurements of Vaccine Efficacy & effectiveness: Measurement of vaccine efficacy (VE) is carried out all throughout the process of evaluation from the pre-licensure phase through phase I and Phase II randomized double blind clinical trial and culminates in phase III comparative efficacy trial. In these studies efficacy is linked with the disease outcomes with vaccine failure in fully vaccinated and inadequately vaccinated individuals in Phase I and phase II studies and populations with low vaccine coverage in Phase III comparative efficacy trial. Vaccine trials up to phase III measure vaccine efficacy but it is the **observational epidemiological study that provide us the overall estimate of protective effect of vaccine. This is also defined as Vaccine effectiveness (VEf).** This measurement is based on two presumptive effect of the vaccine. One is direct which refers to its ability to protect an individual who is a recipient of vaccine and the other its ability to reduce the spread of infection in a population.

The dynamics of infection in a population can be explained with the following conceptual model. (Adapted from (4,5,)

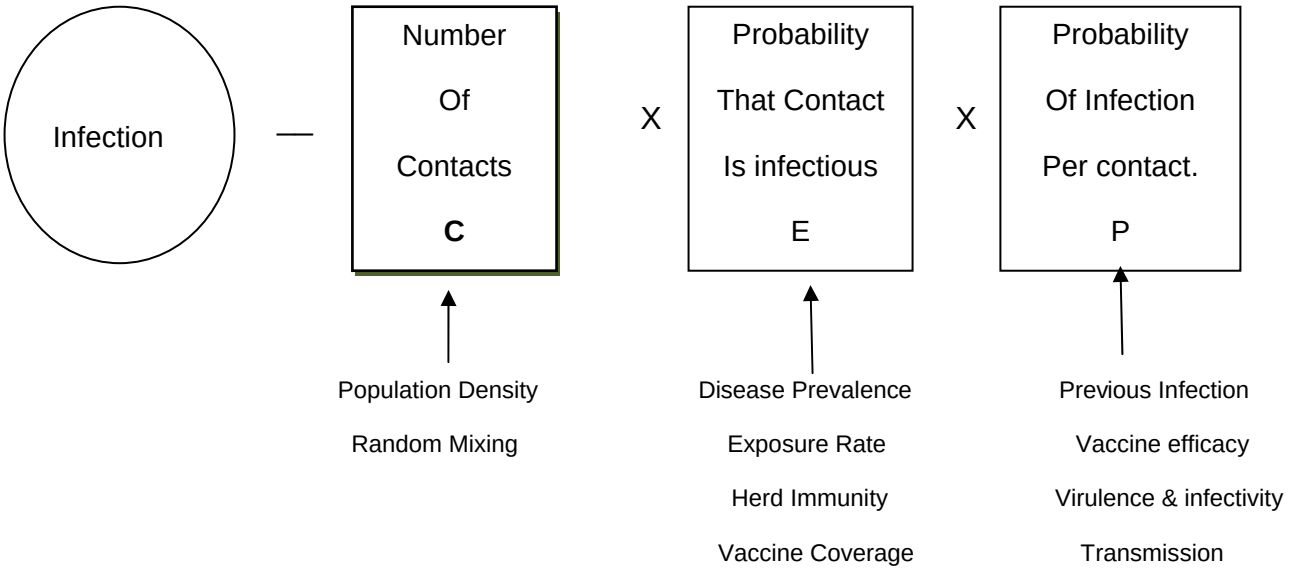

Fig 1 Dynamics of infection in a population (4, 5)

The diagram in figure 1 depicts that in any given population, spread of a disease is a function of the rate of contact (C), the probability of exposure to an infection (E) and the probability that the exposure leads to infection (P). In determination of Vaccine Effectiveness (VE#), it is assumed that infected, immune and susceptible persons are mixed randomly in the population and the population is sufficiently dense so that contact (C) will be common. Probability of contact (exposure) is related to both the prevalence of the disease and the number of immune person. .i.e. community /herd immunity. It refers to the level of immunity in a population and is related to the effect of previous exposures of the population to the same infection during epidemics/ outbreaks and/or vaccination coverage. The probability that a contact with an infected person will result in an infection is a function of an individuals' susceptibility and the virulence of the organism. Individual susceptibility against any specific disease can be reduced if the person suffered from the infection earlier which has conferred him a protective immunity or if the person was inoculated with the specific vaccine effectively. Both of these would confer the person immunity against the disease. In a randomized clinical trial Vaccine efficacy is calculated using

the following equation where VE expresses vaccine efficacy, I (unv) represents incidence in the unvaccinated, and I (vac) represents incidence of infection in vaccinated persons.

$$VE = \frac{I(unv) \quad I(vac)}{1(unv)}$$

The following equation is derived from dividing by the incidence in the unvaccinated.

$$VE = \frac{I(vac)}{1(nvc)} = I - \frac{C(vac) \times E(vac) \times P(vac)}{C(uvc) \times E(uvc) \times P(uvc)} = 1\text{-}RR$$

In the above equation it is observed that the ratio of incidence in the vaccinated to unvaccinated groups is a measure of Relative Risk (RR). The equation VE= 1 RR is useful in epidemiological studies, where vaccine effectiveness can be assessed (VEf). The vaccine efficacy (VE) and Vaccine Effectiveness (VEf) are two different connotations. But Vaccine effectiveness (VEf) approximates Vaccine efficacy (VE) under the following conditions:

- When exposure (E) to infectious agent is not dependent on vaccination status and does not differ across comparison group.
- When the vaccinated and unvaccinated persons are the constituents of the same population where the rate of contact (C) is equivalent.

If the comparison groups are similar vaccine effectiveness (VEf) = 1 P(vac)/P(unv) is a function of the ratio of individual immunity in the vaccinated and un vaccinated groups and can be estimated by VEf = 1 RR (3,4,5). It is evident from the above facts that vaccine efficacy and vaccine effectiveness is not synonymous. A vaccine may have efficacy but may not effective in reducing infection in a community. For deciding immunization in a person the efficacy data can be utilized and probability of protection can be scientifically predicted with inherent limitation. But the efficacy data can not be utilised for predicting the effectiveness of the vaccine in reducing the infection. Only the effectiveness statistics gathered by conducting good epidemiological study in the country can provide us the data of the effectiveness of any vaccination program.

Monitoring Adverse Events: Monitoring the adverse events after vaccination is one of the cost effective method for identifying potential harmful effects of mass vaccination. When a vaccine is found to be efficacious by scientific studies and is approved by the controlling authorities to be introduced in the market. The practitioner after being convinced of its efficacy starts using the vaccine on an individual basis after one to one consultation with the clients. This is the usual practice. It may also be used in groups of consented individuals by NGO's or medical practitioner while discharging their social responsibility. While it is being used for individual or community protection and also immunization program monitoring of the various type of adverse reaction of the vaccine in use through Vaccine Adverse Event Reporting System (VAERS) is a must for public health safety. In USA under the National Childhood injury act of 1986 it is mandated to track vaccine related adverse events under VAERS by the Department of Health and Human Services. (5). VAERS is a passive surveillance system designed to collect case series data to detect rare events and to identify trends in community reported adverse events. Accordingly the data are subject to bias due to under or over reporting of suspected vaccine reaction (5, 6.) It is also difficult to calculate the rate of adverse events as the system does not collect denominator data i.e. number of persons vaccinated or number of dose given. But it may

be included. However VAERS data can be used to identify clusters of adverse reaction and proper clinical, epidemiological and laboratory investigation may be carried out to assess causal association. If the study substantiate that there is severe adverse reaction the vaccine should be withdrawn. A vaccine safety data link is a must in any health service system to continuously monitor the vaccine effectiveness. (6, 7)

Current Practice in the India: Unfortunately at present in India new vaccines are introduced on ad hoc basis. Most commonly whenever a new vaccine becomes available in the market professionals uses it in their practice for protection of individual patients. When the public becomes aware of the usage of the vaccine the next step is to promote the usage of the same among groups of individuals with the help of professionals/NGO by arranging vaccination camps. If we recollect the history of Hepatitis B vaccine in this country we shall observe that in late eighties and early nineties this was the most common public health activities by the drug company and the NGO's. This created an artificial demand and people of all age group used to flock for such vaccination camp. No body has conducted any study on the efficacy or harmful effects of such ad hoc community intervention carried out in the form of vaccination camps. The other usual way of introducing a new vaccine in the community is observed during epidemics. As an interim preventive measure the health authority in the country in collaboration with some selected technical experts which may or may not include public health experts decides to introduce a new vaccine which may be used in some other countries based on evidence of its efficacy in their epidemiological context. The recent example is that of introduction of Japanese encephalitis vaccine. Hence it is evident that due to non existence of any clear cut vaccination policy or scientific protocol based on scientific evidence, to introduce a new vaccine in the national program many extraneous forces may play a decisive role. "National immunization programs must be led by scientifically established public health needs" (8) The public health needs are dependent on the epidemiology of the target disease, its incidence, pathogenic strain causing it, available vaccines its efficacy for personal protection and effectiveness in protecting the community as well as capability of the health system to maintain effective level of vaccination in the community. The other important factor is vaccine security It is reported that shortage of primary vaccine in developing countries including India began to emerge in the late 1990s. This was as a result of due to the introduction of new, more sophisticated, more expensive vaccines in the markets of the industrialized countries leading to phasing out of most commonly used vaccines in developing countries by the manufacturers. It is stated that within a four year period (1998-2001) ten out of fourteen major manufacturers partially or totally stopped production of traditional vaccines, out of these eight were major suppliers to UNICEF. This has resulted in decrease in availability of primary vaccines and the escalation of prices (http://www.unicef.org/publications/index.4442.html). The above situation has compelled many of the critics of our vaccination policy comment in different journals as "With epidemiology taking a backseat, government decisions on vaccination are increasingly determined by price competition and supply "push" (by the companies) rather than "pull" (demand) from proven public health needs.: " (8). Others are pointing out that "Many western countries have included several other new vaccines (such as influenza type B, meningitis, measles-mumps-rubella, and chicken pox) in their regular immunization program. And these trends are used as the

justification to include it in our National Immunization program. (8). The other important issue is the new trend of introducing “One Shot Vaccine” which is combining four or five vaccines in one. Logistically it sounds the best but is it suitable in our context, whether there was a multi-centric community based efficacy or effectiveness study. Once we switch over the other vaccines will be out of the market and if it proves to be ineffective than we can not fall back to the traditional vaccine. Moreover most of our public sector vaccines producing units were systematically closed down for one or the other reason. So at present we are mostly dependent on the Private companies and as such they will be the prime movers of our vaccination policy.

Conclusion and Recommendation:

After much deliberation the Indian Academy of Public health strongly recommends the following to make India’s Vaccine Policy scientifically sound and self sustainable:

1. Government of India should evolve its own Immunization policy based on scientific evidence and should avoid taking ad hoc decision based on selective expert opinion.

2. The criteria for selection of a vaccine in the National Immunization schedule should be *epidemiologically relevant* : based on epidemiological data including incidence etc that qualifies for vaccination as a public health intervention strategy, *immunologically effective*: choices of vaccines based on scientific evidence of not only efficacy but also effectiveness from studies carried out in Indian population and peer reviewed & verified by experts, *Operationally feasible*: cost benefit analysis of the intervention, vaccine availability, safety, vaccine security in context to our current health system and availability of resources.

3. To strengthen the disease surveillance system for effective reporting of occurrence of vaccine preventable diseases, vaccine coverage also reports of periodic “Sero prevalence” studies.

4. Government should introduce Vaccine Adverse Event Reporting System (VAERS). As complication from vaccination is an area which involves human rights the matter should strictly monitored and thus the reporting of such events should be made mandatory and strictly followed with penal provision for defaulters.

5. Decisive intervention of the Government to meet the shortfall of the vaccines included in the National Immunization schedule. This may be done either by public sector or by encouraging the private sector to make safe and effective vaccines available at affordable price. Vaccine security of a country like India should not be left to the vagaries of global market force.

6. Before taking any decision of importing any vaccine the suitability of imported vaccine to deal with the Indian pathogenic strain needs to be conclusively established.

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