Some Issues Related to the Practice of Immunization

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ABSTRACT

This article reviews the basic principles of immunization, identifies the components of the practice of immunization, and points to some of the issues specific to that practice that will need to be taken into account as the vaccines of the future are coming close to availability. The purpose of immunization is to protect an individual from a specified infectious disease, from the earliest appropriate age, for as long as possible, using the fewest number of doses to achieve that immunity, and with the least possible risk from the procedure. For certain diseases, for example tetanus, the benefit of immunization is only to the vaccine recipient. In the case of vaccines such as polio vaccine, there is a wider purpose. As well as protecting immunized individuals, there can be community benefit to individuals not immunized. When sufficiently high coverage is reached, transmission is interrupted and individuals not immunized are further protected. For routine immunization against any vaccine-preventable disease, there needs to be the provision of routinely available processes that seek to promote the highest possible coverage in the target population; allow for the measurement of that achievement in an accurate and timely way; detect any possible adverse effects of the immunization; and sensitively and rapidly provide information on the target diseases. As the availability of existing resources for health programs comes under increasing scrutiny, countries in all stages in development will need to consider the most cost-effective use of resources, especially as countries are encouraged to become self-sufficient for financing their immunization programs. Finding the necessary resources for present vaccines, let alone the vaccines of the future, may be a considerable challenge.

Key Words: *immunization, infectious diseases, practices, resources, vaccines*

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It is clear that Jenner foresaw that smallpox vaccination could lead to the disappearance of smallpox from the world: "the annihilation of the Small Pox, the most dreadful scourge of the human species, must be the final result of this practice."[1] Within his lifetime vaccination had spread to all continents, and hundreds of thousands of people had been vaccinated. It is difficult to identify any other process that so completely affects the human race, where the objective is to provide a product for every newborn child, and which comes close to that ambition. Immunization is one of the safest medical interventions and is probably the most cost effective of all health care initiatives.[2] This article reviews the basic principles of immunization, identifies the components of the practice of immunization, and points to some of the issues specific to that practice that will need to be taken into account as the vaccines of the future are coming close to availability.

THEORY OF IMMUNIZATION

The purpose of immunization is to protect an individual from a specified infectious disease, from the earliest appropriate age, for as long as possible, using the fewest number of doses to achieve that immunity, and with the least possible risk from the procedure. For many infectious diseases, immunity is passed from mother to baby, providing protection that may last a variable length of time. The duration of that protection may relate to the mother's own exposure to the infectious agent: the infants of mothers who have had natural measles have higher antibodies at birth than infants born to mothers whose immunity is vaccine derived.[3] Thereafter, the infant's antibodies wane, and the child becomes susceptible to infection. Immunization offered at this time moves the recipient to the protected portion of the population where, ideally, it remains for the rest of its life. In some cases, there may be waning immunity; in some cases there will be primary vaccine failure. This transition from one immunity status to another is used in the mathematical modeling of immunization.[4]

For certain diseases, for example tetanus, the benefit of immunization is only to the vaccine recipient. Because of the ubiquitous nature of tetanus spores, any individual not immunized remains at risk, and could contract tetanus on any occasion after being exposed appropriately to that risk. Despite cases of tetanus falling progressively since the vaccine was introduced into the United Kingdom, a small number of cases still occur each year (Figure 1). It is notable that the disease affects mostly the elderly, and particularly women, as they were not subjected to immunization, being older than the targeted

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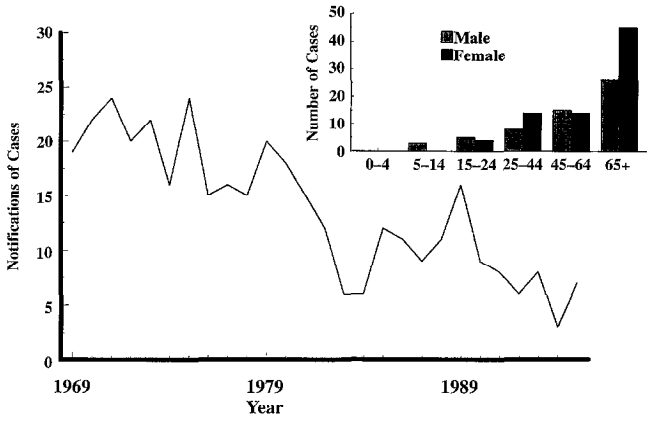

Figure 1. Tetanus notifications for Office of National Statistics (England and Wales) 1969–1995. Inset: Number of cases of tetanus by age and sex, 1984–1993.

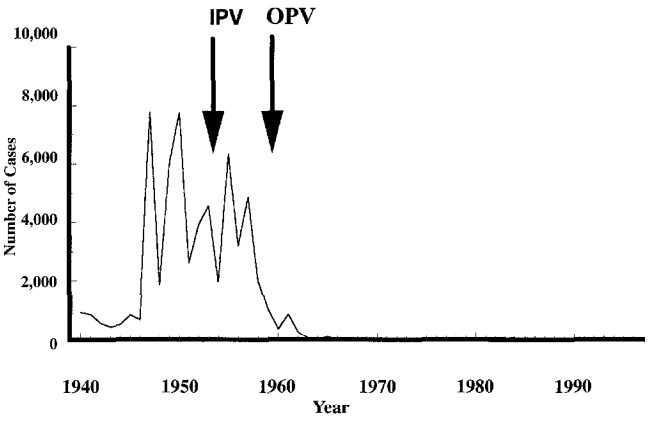

Figure 2. Notifications of paralytic poliomyelitis to Office of National Statistics, England and Wales 1940–1996.

age when the program was introduced, nor were they immunized as part of military service.

In the case of vaccines such as polio vaccine, there is a wider purpose. As well as protecting immunized individuals, there can be community benefit to individuals not immunized. When sufficiently high coverage is reached, transmission is interrupted and individuals not immunized are further protected. This effect benefits those with valid contraindications who should not be immunized. Ultimately, when all countries interrupt transmission of the causative agent, then global eradication can be contemplated. Figure 2 shows the impact of polio immunization in England and Wales. Although coverage for infants only rose above 90% in the 1980s, the risk of wild virus polio had been eliminated considerably earlier.

THE PRACTICE OF IMMUNIZATION

For routine immunization against any vaccine-preventable disease, there needs to be the provision of routinely available processes that seek to promote the highest possible coverage in the target population, allow for the measurement of that achievement in an accurate and timely way, detect any possible adverse effects of the immunization, and sensitively and rapidly provide information on the target diseases. The latter may include estimations of the population's protection against the diseases by age-specific seroepidemiology.[5]

Coverage and Resources

The achievement of the desired levels of coverage can only be ensured if adequate resources are available for implementation of the program, adequate supplies of vaccine are in place when needed, the program to deliver vaccine to the target population is operating efficiently, and the program is promoted effectively to health professionals and the public, creating demand. By 1990, 80% of the world's children had received six essential vaccines, diphtheria, tetanus, pertussis, polio, measles, and BCG, by their first birthday, an outstanding achievement.[6] However, in a number of countries, immunization coverage is falling. Examination of those countries reporting the largest declines in coverage between 1993 and 1994,[7] shows that many have particular economic hardship, civil unrest, or both. Nevertheless, there are other countries where in spite of these factors, high levels of coverage are maintained. UNICEF data for 1993 reveal a number of countries where the annual gross national product (GNP) per capita is less than US $1000 and measles immunization coverage is over 90%; in contrast, three Western European countries with annual GNP per capita in excess of US $20,000, had measles immunization coverage from 50 to 70%.[7]

Vaccine Supply and Vaccine Quality

Industrialized countries are either self-sufficient for supplies of high quality vaccines, or are able to purchase them from multinational manufacturers. Vaccines are required to meet rigorous specifications for purity and potency, demonstrated by the manufacturer, and independently tested before use. Countries in development may import vaccines, requiring hard currency for their purchase, or may manufacture them locally. Where resources are severely restricted, some countries have depended until now on donated vaccines. It is now appreciated that countries should incorporate the provision of vaccines into core national budgets, since the economic gains from the prevention of infectious disease far outweigh the costs.[2] UNICEF and the World Health Organization (WHO) are promoting a vaccine independence initiative to help countries take on the resourcing of vaccines. Countries in the Region of the Americas share in a revolving fund arrangement that allows them to benefit from economies of scale in vaccine pricing, and reduces the need for hard currency. As well as requir-

ing resources to purchase vaccines, countries need to be able to ensure that the vaccines used are of high quality. This may be difficult for some countries, especially those where there has been little investment in quality assurance and quality control. These issues will become even more significant as new vaccines become available. Although the greatest benefit may accrue to developing countries, the ability to afford new vaccines is likely to be particularly challenging, if, as seems likely, new vaccines cost more than existing products. The World Health Organization and UNICEF have developed a model that groups countries according to their GNP per capita and population size. It is evident that for some countries, the relation between GNP and population indicates a continuing need for direct financial support for vaccines, served by the international market, with UNICEF procuring on their behalf. For the most part, these are smaller countries that do not manufacture vaccines. With progressive increases in GNP and population, there should be sustainable financing of vaccines, with the national governments meeting targeted self-financing levels.[8]

Implementation of Immunization

Services to implement immunization exist, in some form or another, in every country in the world. These services range from contractual financial arrangements between parents and health providers in private sector health care systems, to state-provided services, free to all, in public sector programs. In many countries, this latter situation has been formalized as the Expanded Program on Immunization (EPI), a WHO-initiated program that grew out of the smallpox eradication program in the early 1980s. The purpose of the EPI has been to guide countries to develop services to implement immunization, undertake surveillance, train immunization workers, and ensure that vaccines are provided in the best state possible. Ideally, EPI is integrated into primary health care and maternal child health services as a seamless web. Through its provision of training materials and technical services, mobilization of international resources, and focus on particular objectives (such as polio eradication), EPI has become an institutionalized part of the health program of many countries.

Building on an infrastructure of the immunization program, a number of strategies have been developed to implement immunization more effectively. The World Health Organization has identified the importance of missed opportunities and recommends a number of means of minimizing these.[9] Some countries have relied on legal compulsion to achieve high coverage. However, examination of coverage by country reveals that exceptionally high levels are also reached in some of those countries where there is no legal compulsion. In the United States, all states have laws that require demonstration of immunization as a condition for school entry. Consequently, coverage at school entry is close to 100%. But such requirements can act against the epidemiologic best interests of disease prevention. For measles, the primary objective is to achieve the highest possible immunization coverage shortly after young children become susceptible to measles. Despite the high coverage by school entry, coverage in 1992–1993 of 2-year-old American children was only 81%.[10] In the measles resurgence between 1989–1991, cases occurred predominantly in preschool children who had not been immunized.[11]

In 1990, the United Kingdom adopted a novel strategy to promote the implementation of immunization through primary care. In place of the preexisting system of state payments per immunization, family doctors only receive payment for immunization when they attain quarterly targets for cohorts of 2-year-old children for completion of the primary immunizations, and a further target payment for the preschool boosters. If 70% coverage is reached, doctors receive payments that match the average income from immunization on the previous item of service basis. Three times the payment is awarded for the achievement of 90% coverage, or higher. No exclusions from the denominator population are allowed. This scheme has led to progressively higher proportions of family doctors reaching target payments, so that now, more than 90% of doctors are regularly exceeding their higher targets.[12] Figure 3 shows the progressive increase in the proportion of doctors reaching the 90% target payment; fewer doctors reach only the 70% target, and accordingly, few fail to get any target payments.

Promotion of Immunization

In addition to providing services to deliver immunization, it is essential that there should be public acceptance or even demand for immunization. To undertake this effectively, a coordinated and appropriately resourced promotion program is required. In the United Kingdom, this

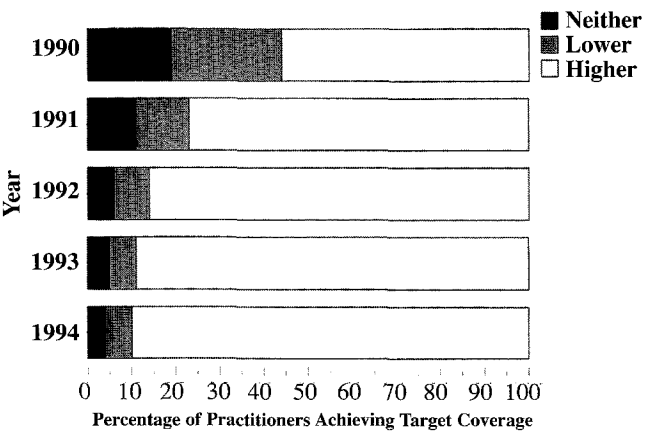

Figure 3. The proportion of general practitioners in the United Kingdom reaching targets. Primary immunization series, April 1990 to April 1994.

process starts with market research on parents and health professionals, to identify the key information needs for the target audience. This is followed by the development of a coordinated communication strategy that involves the provision of written materials for parents and health professionals, advertisements in appropriate newspapers and magazines, television and radio advertising, and the availability of materials appropriate for ethnic community groups. All materials developed in this process are market tested before publication or transmission. Through the use of media buying services, the highest possible exposure of the materials to the relevant target audience is ensured, giving the best return on investment. After each wave of immunization promotion, tracking studies are undertaken to identify the impact of the material. This information is fed back into the development process for the design of future campaigns.

Surveillance of Target Diseases

The measurement of immunization coverage provides an invaluable process indicator for the implementation of immunization programs.[13] However, it is the measurement of the outcome indicator that attests to the program's achievements, or that identifies the program's potential or real weaknesses. Susceptibility identifies its potential and preventable weakness, the occurrence of vaccine-preventable disease demonstrates real weakness. As immunization programs mature, the requirements for surveillance become more sophisticated. When disease is endemic, sentinel surveillance will suffice. As the objectives of an immunization program advance from control to elimination, or even eradication, surveillance must become sufficiently sensitive to be able to detect any cases, or even a potential for cases to occur. After many years of dependence on passive and often insensitive surveillance techniques, new surveillance initiatives are being developed. The foremost such development has been the application throughout Central and South America and the Caribbean of acute flaccid paralysis (AFP) surveillance for the polio elimination initiative in the Region of the Americas. Based largely on the results of 3 years of AFP surveillance that demonstrated the ability to detect sensitively acute flaccid paralysis in children and show that none of them were caused by wild polio virus, the International Certification Commission of Poliomyelitis Eradication was able to conclude that wild virus poliomyelitis has been eliminated in the Americas.[14] As a result of the development of this surveillance system, other vaccine-preventable diseases, such as measles, are now under far better control.

In the United Kingdom, surveillance of measles and rubella has been transformed from the reporting of suspected cases to the ability to confirm cases accurately and non-invasively through the nationwide availability of diagnosis through detection of salivary IgM on a single sample.[15] Less than 1% of tested cases are confirmed as measles; close to 60% of suspected cases are investigated with a saliva sample.[16]

Surveillance of Adverse Events

Just as surveillance systems become more sensitive with program maturity, surveillance of adverse events assumes progressively greater importance: as disease prevalence declines, parents are less concerned with the potential seriousness of the diseases and become more preoccupied with vaccine safety.[17] Since serious adverse reactions occur very rarely, surveillance needs to be sensitive; moreover, many of the events reported as vaccine adverse reactions occur independently of immunization. Thus, data are needed on events temporarily associated with immunization, and background rates of such events independent of immunization are also needed. Many countries have passive reporting systems for vaccine adverse events, but these are prone to considerable under-reporting and reporting bias and do not detect similar rare events occurring without a temporal association with immunization.[18] An active reporting system has been developed in Canada, where there is surveillance in sentinel pediatric hospitals.[19] Information is collected daily by dedicated nurses on all pediatric admissions with diagnoses that may have an association with immunization, and the immunization history is obtained. In the United Kingdom, sophisticated data linkage studies have been pioneered.[20] Hospital discharge diagnosis codes on children in particular age groups are matched with community-held databases of immunization records, so that associations between hospital admissions and immunizations can be examined, comparing risk periods after immunizations with control periods outside of the risk periods. Such studies have demonstrated the risk of idiopathic thrombocytopenic purpura after measles-mumps-rubella (MMR) immunization (1:24,000 immunizations) and have shown that giving the third dose of diphtheria, tetanus toxoids, pertussis (DTP) vaccine before 6 months of age is associated with a fourfold lower frequency of postimmunization febrile seizures than if the third dose is given after 6 months of age. When DTP immunization is completed before 6 months, there is no increased risk of febrile seizures following immunization, compared with time periods outside of the 72 hours after the procedure.

IMMUNIZATION ISSUES FOR THE FUTURE

Resources to Maintain Programs and Resources for Vaccines of the Future

As the availability of existing resources for health programs comes under increasing scrutiny, it is becoming routine to have to show cost-effectiveness predictions for

new health interventions. Such studies have hitherto been more often undertaken in industrialized countries, but it is probable that countries in all stages in development will need to consider the most cost-effective use of resources, especially as countries are encouraged to become self-sufficient for financing their immunization programs. The World Development Report shows clearly that investing in vaccines is to be commended.[2] However, tension often exists in the resource justification in public sector health systems. Preventative programs are low-profile; they achieve undoubted long-term health gains and returns on investment, but the successes are often intangible, as absence of disease may not be easily perceived. In contrast, curative services offer immediacy and high-profile public concern about the possibility of their lack of availability. The results of curative services are highly visible. Nevertheless, preventative services, such as immunization, reach levels of cost-effectiveness that curative services cannot match. In public sector immunization programs, investment in vaccines requires the provision of "hard resources" from the budgets of Health Departments: vaccines must be purchased, there are real costs in the delivery of vaccines to the recipient (payments to health providers, infrastructure costs, consumables), and there may be costs associated with adverse reactions. On the other hand, the gains are often "soft": reductions in disease incidence, handicap, or death. Prevention of illness requiring hospital admission rarely leads to reductions in the facilities provided; rather they are used to treat other patients. The prevention of work days lost through illness may contribute to overall economic success, but the gains do not accrue to the Health Departments that provided the initial resources for the prevention program. Thus, for the most part, in a cost-effectiveness model, program costs are real, and the effectiveness is mostly opportunity gain.

Manufacturers of vaccines also have to demonstrate cost-effectiveness. Here the model is different and depends on the recycling of profit. Shareholders and investors expect a return on their investment. This comes from the manufacturers' profits. But new initiatives must be resourced and the research and development costs are carried with the manufacturing cost and reflected in the vaccine price. This in turn produces profits. The whole of this process is dependent on time for return on investment, the effect of competition on market prices, and the risks of failed products in development. For the vaccine industry to remain healthy and competitive, and for national programs to continue to be able to provide high-quality and up-to-date products, there will have to be mutual understanding of the needs of each party to fulfill its obligations for its relevant cost-effectiveness requirements. The present differential pricing of vaccines for industrialized and developing countries will probably continue as the only way for new vaccines to be available to developing countries. Where a new vaccine is used in both circumstances, the industrialized countries may be carrying the development costs, whereas the developing countries pay just the manufacturing cost. The situation becomes much less clear if there is little application for the product in industrialized countries.

New Surveillance Techniques

Non-invasive confirmation of measles, mumps, and rubella using a single saliva sample is already routinely available in the United Kingdom. But the laboratory technique (antibody capture enzyme-linked immunosorbent assay [ELISA]) requires sophisticated services, and the result is not immediately available as would be ideal for outbreak control purposes. Rapid diagnostic tests for field use will contribute significantly to elimination or eradication programs; identification of viral antigens would allow action before chains of transmission were set up, as distinct from the time lag for tests that depend on detection of antibodies. Molecular genealogy is already allowing polio viruses to be linked to their probable places of origin; similar techniques are being applied to measles viruses to identify imported strains, and mumps vaccine viruses can be distinguished from wild strains. These techniques are likely to revolutionize the surveillance initiatives of the future. With better surveillance, mathematical models will be used increasingly to predict the impact of immunization programs, so that different strategies can be tested and the most effective selected for implementation. In all immunization programs, it is likely that there will be continuing demands for demonstration of vaccine safety. These demands will not be satisfied with the presently available adverse event surveillance systems, along with the lack of diagnostic tests that distinguish temporal events from reactions that are causal. Because of the rarity of serious adverse reactions, it will be difficult to be confident before vaccines are introduced that rare reactions will not occur. Postmarketing surveillance may offer some comfort, until problems are identified, when the consequences of such detection can jeopardize the public's confidence in the whole immunization program.

CONCLUSION

Two hundred years after Jenner's discovery, immunization programs exist in every country in the world and immunization is acknowledged as the most cost-effective medical intervention. Smallpox has been eradicated, polio eradication is on course, and measles could follow. But there is still room for considerable improvement in the delivery of vaccines and in surveillance of their effects, both on disease and on the vaccine recipient. The appli-

cation of presently available scientific advances will transform the vaccines of the future, but finding the necessary resources may be a considerable challenge. The vaccines of the future need to be safe, effective, affordable, and available. National authorities will need to ensure that they are provided for all who will benefit.

REFERENCES

1. Jenner E. The origin of the vaccine inoculation, London: Shury, 1801.
2. The World Bank. Investing in health. World Development Report. London: Oxford University Press, 1993.
3. Pabst HF, Spady DW, Marusyk RG, et al. Reduced measles immunity in infants in a well-vaccinated population. Pediatr Infect Dis J 1992; 11: 525-529.
4. Babad HR, Nokes DJ, Gay NJ, Miller E, Morgan-Capner P, Anderson RM. Predicting the impact of measles vaccination in England and Wales: model validation and analysis of policy options. Epidemiol Infect 1995; 14:319-341.
5. Gay NJ, Hesketh LM, Morgan-Capner P, Miller E. Interpretation of serological surveillance data for measles using mathematical models: implications for vaccine strategy. Epidemiol Infect 1995; 115:139-156.
6. Grant JP. Hope for the future. Editorial. World Health 1993; 2:3.
7. The progress of nations. ISBN: 92-806-3170-5. New York: UNICEF, 1995.
8. Report of the Scientific Advisory Group of Experts. Global program for vaccines and immunization. World Health Organization WHO/GPV/95.05, 1995.
9. Hutchins SS, Jansen HA, Robertson SE, et al. Studies of missed opportunities for immunization in developing and industrialized countries. Bull World Health Organization 1993; 71:549-560.
10. Vaccination coverage of 2-year-old children: United States, 1992-1993. MMWR CDC Surveill Sum 1994; 43:282-283.
11. Measles: United States, first 26 weeks. MMWR CDC Surveill Sum 1994; 43:673-676.
12. Department of Health Statistics. London, UK: Department of Health, 1995.
13. Immunization programmes and their outcomes. In: On the state of the public health for the year 1988. The annual report of the Chief Medical Officer of the Department of Health. London: Her Majesty's Stationery Office, 1989:97-103.
14. Pan American Health Organization. Final report of the Third Meeting of the International Commission for the Certification of Poliomyelitis Eradication in the Americas, Washington DC, August 1994.
15. Measles and rubella immunization campaign. PL CMO(94)12 PL CNO(94)15, London, UK: Department of Health, 1994.
16. One Year On. London, UK: Department of Health, 1995
17. Chen RT. Oral polio vaccines. Lancet 1996; 347:1496.
18. Fine PE, Chen RT. Confounding in studies of adverse reactions to vaccines. Am J Epidemiol 1992; 136:121-135.
19. Morris R, Halperin S, Déry P, et al. IMPACT monitoring network: a better mousetrap. Can J Infect Dis 1993; 4:194-195.
20. Farrington P, Pugh S, Colville A, et al. A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines. Lancet 1995; 345:567-569.