COMMENTS

Protection is not just about preventing disease: vaccine equity and ethics in the developing world

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Vaccines are intended to prevent disease. In 1798, Jenner used the principle of an animal virus that caused a localised lesion but afforded protection against severe disease. This started the practice of "vaccination". The idea of preventing disease and avoiding unnecessary suffering is attractive, but since vaccines are generally given to prevent disease in people who do not already have it, they must not themselves cause disease, or at least no more than acceptable discomfort (1).

It is incredible how quickly it is possible for diseases to disappear and how people are left with only a vague remembrance of them with the passage of time. They find a place only in the tales of our grandparents' generation, and then not even that. Smallpox, which once devastated regions and countries, has been eradicated. Polio and the ubiquitous calipers and braces (and earlier still, the "iron lungs") have been long gone from industrialised countries. India is planning a switch to an injectable vaccine to avoid the damage to one in a million vaccinated children who develop paralysis *because* of the oral vaccine. Neonatal tetanus, a horrible experience in which the helpless child bends and arches in ways that seem impossible, is a rare event now that mothers are immunised during pregnancy. Measles, whooping cough and diphtheria continue to afflict us, but are no longer the large-scale killers that they once were in all regions.

Vaccines have been a remarkable success story, but although there are dozens of vaccines that are available and administered to children and adults, several of them are for diseases which are restricted to certain regions, such as the Japanese encephalitis virus vaccine, and others are restricted for reasons that have nothing to do with the absence of disease. Currently, the Centers for Disease Control and Prevention, a US federal agency responsible for public health, recommends vaccines to confer protection against 16 infectious diseases, including measles, mumps, rubella, varicella, hepatitis B, diphtheria, tetanus, pertussis, *Haemophilus influenzae* type B, polio, influenza, and pneumococcal disease (2). The BCG vaccine is not recommended for everyone in the US because tuberculosis is not a disease of major public health significance there. American children are given 14 of these vaccines in the first two years of life. Of the basic package of 16 vaccines, Indian children in all states receive only BCG and five other vaccines (if they receive immunisation at all), and in some states, this may go up to eight other vaccines. This is despite the fact that all these vaccines are available in India. With the exception of the seasonal influenza vaccine, all of them are given to children who can access private healthcare.

Why is this? Why can a country that has built its own space and atomic energy programmes not deliver a basic intervention to its children? The infrastructure for delivery exists and vaccines are not an expensive intervention for the value they deliver. Their value can be measured not just in terms of the suffering averted but also in real economic terms. Vaccines prevent disease, and the prevention of ill health and suffering is an investment in the country's future (3). It is true that the provision of access to healthcare in India is difficult, that challenges abound and that there are enormous hurdles. However, an advantage of vaccines is that they can be delivered according to a schedule, so that the demand for them and the location where they have to be delivered are predictable. Further, since they are given generally to healthy children, other than monitoring for rare serious adverse events, little more is required than a "well-baby" check-up and vaccination by trained primary healthcare providers who follow a protocol.

Of course it would be ideal to have services available to all across the continuum of care, but if we cannot deliver curative healthcare, can we not at least try to provide services for the prevention of disease as part of primary care on the widest possible scale, with at least as many vaccines as children elsewhere receive? Bangladesh and a host of other poorer countries perform better than India in the delivery of immunisation, both in terms of the number of antigens and the coverage rate (4). It is true that there are challenges to be confronted, particularly in systems in which the same staff and structures are responsible for both preventive and curative services, but approaches to strengthen the routine delivery of preventive and primary care services will go a long way to ensure the protection of all Indian children (and not just the rich) from disease.

Accepting the responsibility for protecting its population from internal and external threats is the remit of the government. Just as protection from aggressive neighbours requires investment, there is at least an equal and considerably more urgent need to invest in protecting the population from the preventable threats of infectious disease. Compared to an annual "formal" defence budget of Rs 2,03,672 crore (12.3% of the central government expenditure or 1.79% of GDP) (5), India spends about Rs. 600–700 crore on its national immunisation programme annually. Of this, we are told that Rs 200 crore is

the cost of vaccines. The inadequacy of this investment defies any kind of logic.

We know that when vaccines are evaluated in situations in which delivery of healthcare is excellent, the incremental advantage shown by the introduction of the new vaccine is less than that of comparable interventions in previous decades, or that of interventions in areas where the access to curative health services is deficient, However, vaccines, and oral rehydration therapy, are still considered among the most cost-effective public health interventions for childhood diseases, according to the CHOICE guidelines of the World Health Organisation (WHO), which compare the relative value of investments (6).

There is clearly an ethical need for equity in the provision of access to vaccines, but it is not against preventable disease alone that protection is needed. There are three kinds of protection required for the ethical, equitable use of vaccines in India. The first is, of course, against disease. The vaccines available are considered and a case is made for or against their use in the public health programme. The second is protection from harm. For this, the immunisation programme must ensure that any possibility of damage, either because of errors in the delivery of the programme or because of the product itself, is minimised. The third is protection from misinformation, which requires that opinions are not presented as facts, and that pseudo-science or any claims that affect the introduction or use of the vaccine are evaluated and presented independently. All three of these kinds of protection require investment from the government, which should emphasise that the activities related to them are necessary and complementary to immunisation.

There are individuals and groups who argue against vaccines, who believe that the decrease in the incidence of several infectious diseases is a result of improvements in sanitation and hygiene, living conditions and nutrition. While such improvements have clearly contributed to the decline of some diseases, such as tuberculosis and cholera in the industrialised countries, the remarkable decrease in the incidence of measles, *Haemophilus influenzae*-associated meningitis and more recently, rotavirus gastroenteritis in these same countries has been too rapid to be attributable to anything other than vaccines (7–9).

Nonetheless, every intervention, whether preventive or curative, requires a cautious approach. Vaccines are administered prophylactically to protect healthy individuals against diseases to which they are likely to be exposed. Clearly, the benefit offered by a vaccine must be greater than any potential risk it poses, and this benefit and risk must be evaluated at the level of the individual and the population separately. At the level of the individual, parents seek information and make decisions on whether their child should be given a vaccine, whether its administration should be deferred or whether it should be avoided, thus taking the responsibility for decisions that affect their child's health.

However, at the population level, how should decisions regarding benefit and risk be made and who should make them? If a disease is common and devastating, and the vaccine is inexpensive, effective and safe with no side-effects, then the decision should be easy enough to take. Again, it is not difficult to take a decision if a disease is rare and non-fatal, or easily curable or treatable, and if there is no safe and effective vaccine. However, if there is no accurate knowledge of the disease burden (and this can be the case for a number of reasons), or the vaccine is expensive or not effective enough, then both issues (disease burden and cost-effectiveness) must be studied carefully before taking a decision on the use of the vaccine. In recent times, there has been tremendous pressure from some vaccine manufacturers for the introduction of new vaccines, sometimes mis-presenting arguments as in the case of the HPV vaccines, and this needs to be guarded against (10). There are several advisory bodies, consisting mostly of independent experts, at the country level as well as internationally, that make recommendations and help governments to consider the evidence. In addition, organisations such as WHO, through its Strategic Advisory Group of Experts on immunisation, make recommendations on the introduction of vaccines into public health programmes (11).

Before licensure, vaccines are expected to undergo phased testing among an increasingly larger population. The safety and efficacy of a vaccine are the determinants of licensure by the regulatory authorities. Once a vaccine is licensed, considerations such as the disease burden it can avert, its societal value in terms of equity, the public demand for it, politics and programmatic considerations determine whether it is finally seen as a public health priority. However, concerns have been expressed regarding the safety of several vaccines which have been introduced into national programmes. Two key elements related to safety need to be recognised.

The first is that no vaccine can claim to be 100% safe. Since most vaccines are developed to mimic infection, they result in some reaction, which is usually mild. For example, there may be some redness and swelling around the site of the injection or fever following the injection. Rarely, however, serious adverse events may occur in the case of some vaccines. Some examples are the occurrence of intussusception in 1 in 20,000–60,000 recipients of the oral rotavirus vaccine, anaphylaxis in 1 in 1000,000 recipients of the hepatitis B vaccine and encephalitis following the mumps vaccine. The WHO has published the expected rate of adverse events for several vaccines (12), and these can be useful when deciding upon whether or not the risk of a vaccine is acceptable, compared to the vaccine's potential benefit, at the population level.

The second concern is that careful and constant monitoring is required for the continual evaluation of safety signals, which may have previously gone undetected or appear because of a change in the composition or administration of the vaccine. For example, it is now recognised that narcolepsy may follow immunisation with a swine flu pandemic vaccine in individuals with a specific HLA type DQB1*06:02 in northern Europe. It was initially difficult to make a causal association with the vaccine, but following thorough studies

in several countries that evaluated large databases, a risk of 1 in 52,000 doses was assigned (13). An example of a change in composition resulting in safety issues is the occurrence of cases of aseptic meningitis when the Urabe strain of mumps virus replaced the Jeryl Lynn strain (14).

There are many instances in which the potential dangers of a vaccine have been identified and appropriate action has been taken. In all these cases, a biologically valid explanation for an event was found and an estimation of the risk made on the basis of comprehensive investigations. Unfortunately, this is not always the case. All too often, events that are related in time to the vaccination events are considered the cause of an adverse event, and no attention is paid to the possibility of whether the supposed association can be explained biologically and from the evidence available. For example, given the infant mortality rate in India, approximately 300 children would be expected to die during any 24-hour period. If the child happened to receive a vaccine on that day, it may be wrong to conclude that the vaccine caused the death, without gathering further information on the circumstances and sequence of events. Did the vaccine really cause the death? How can this causality be determined?

WHO has come up with a tool that can serve as a guide in the assessment of causality. The approach adopted lays emphasis on constructing and testing a biologically plausible hypothesis to support the association (15). However, it must be pointed out that for the assessment of causality to be satisfactory and for it to be able to provide a clear message regarding safety, it is critical that a stable, comprehensive and structured Adverse Event Following Immunisation (AEFI) reporting system is functional, capable of providing detailed data on each event. When clear data pointing to a safety concern are supported by epidemiological and laboratory evidence, a causal association is indicated and the risks and benefits of vaccination must be re-assessed.

One example of the application of this tool has been the recent developments related to the pentavalent vaccine. This vaccine contains five antigens that have been used in different combinations in millions of children around the world. As for the combination used in developing countries, it has been deployed in countries with birth cohorts of several million children, and some countries in Asia have reported safety signals, with children dying shortly after the administration of the vaccine. Sri Lanka, India, Bhutan and Viet Nam have all reported and investigated serious adverse events following immunisation with this vaccine. Each case was investigated by the national programmes in collaboration with WHO, using the criteria on the assessment of causality developed by WHO. These criteria err on the side of abundant caution, in not saying that there is no association unless a clear alternative cause is found. It was determined that there was no causal association. The Global Advisory Committee on Vaccine Safety posted a report of the discussion on its website (16). Fortunately, countries have made a re-assessment and decided to continue with the pentavalent vaccine or re-introduced it into their national programmes.

The pentavalent vaccine will need continued monitoring, but there is currently no peer-reviewed scientific report based on analysis of a complete data set in a quality journal to support a causal association. Unfortunately, not everyone who has to make a decision regarding vaccines reads the scientific literature. The notorious case of Andrew Wakefield is worth mentioning in this context, and it must be noted that it was a flawed peer review process and the media, which thrives on demonisation, that allowed him to get away with a fraudulent research paper. In his paper, Wakefield claimed that the measles, mumps and rubella vaccine could cause autism. The claim and data were flawed and there was clearly no causal association. The findings were disproved over and over again, but the damage done to public health is reflected in an ongoing outbreak of measles in Wales (17). Measles is not usually life-threatening in Wales, but a similar scare regarding vaccines has the potential to endanger lives in a developing country. There were scares following the circulation of stories that the polio vaccine causes sterility, that the measles vaccine virus results in autism and that the thiomersal in vaccines causes cerebral palsy or autism. None of these notions has stood the test of a causality assessment (18–21), but that does not stop individuals and organisations from continuing to make unproven claims. Spreading this sort of panic can deprive children of the opportunity for vaccination. The ill effects of this are bad enough in the developed countries, but in the case of countries where access to healthcare is already limited, they result in a further denial of equity.

In summary, vaccines are valuable for individuals and populations, and public health ethics requires that we ensure access to all the appropriate vaccines for all our children so that they are protected from disease. However, we also have an ethical responsibility to see to it that the use of a vaccine is monitored through a system that carefully assesses safety signals after the vaccine has been licensed and introduced. The importance of an AEFI surveillance system to promote safety, appropriately assess risk and prevent misinformation cannot be over-emphasised. Finally, we have an ethical responsibility to employ the best scientific tools available to evaluate and use whatever evidence has been collected carefully (and not use selected information and cherry-picked data), to direct decision-making so that programmes do not, without clear and compelling evidence, withdraw vaccines. The withdrawal of vaccines without such evaluation would have consequences for people who have few other opportunities to prevent illness among their children.

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The H1N1 influenza pandemic: need for solutions to ethical problems

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Abstract

The rapid spread of the novel influenza virus of H1N1 swine origin led to widespread fear, panic and unrest among the public and healthcare personnel. The pandemic not only tested the world's health preparedness, but also brought up new ethical issues which need to be addressed as soon as possible. This article highlights these issues and suggests ethical answers to the same. The main areas that require attention are the distribution of scarce resources, prioritisation of antiviral drugs and vaccines, obligations of healthcare workers, and adequate dissemination and proper communication of information related to the pandemic. It is of great importance to plan in advance how to confront these issues in an ethical manner. This is possible only if a comprehensive contingency plan is prepared with the involvement of and in consultation with all the stakeholders concerned.

Introduction

A novel influenza virus of swine origin, A H1N1, emerged in Mexico in 2009 and spread rapidly, in a matter of weeks, across multiple countries in the four major continents. The high mortality among young Mexicans, coupled with the rapid spread of the virus worldwide, revived memories of the devastating severe acute respiratory syndrome (SARS) epidemic of 2003. Sensing the initial panic and in view of the case fatality associated with the virus, many countries rushed to control the epidemic. Some of the most drastic steps were taken by China and Hong Kong. The former quarantined Canadian and Mexican nationals, while the latter sealed off an entire hotel when the first case of H1N1 influenza (a Mexican guest) was detected. All other guests and the staff were placed in quarantine [http://news.bbc.co.uk/2/hi/asia-pacific/8032157.stm]. Soon, the World Health Organization (WHO) raised the pandemic alert level to five and declared an orange alert. All healthcare workers were required to wear N95 masks at work and have their temperature monitored twice daily. Each patient could have only one visitor a day, and checkpoints were set up at all hospital entrances. The movement of patients and healthcare workers between hospitals was restricted, and rotations of junior doctors suspended. Medical conferences were cancelled, leave for healthcare workers was curtailed, and elective surgical procedures were postponed. Restrictions were placed on overseas travel by hospital employees, and quarantine or viral screening was made mandatory on their return from countries that had reported local transmission. Additionally, travellers who had returned from Mexico were quarantined for seven days. Schools were required to begin monitoring the temperature of all students. Public health