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Immunisation Safety

A Priority of the World Health Organization's Department of Vaccines and Biologicals

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Abstract

In 1999, the World Health Organization (WHO) Department of Vaccines and Biologicals launched the Immunisation Safety Priority Project to boost its activities in this area, with the aim of establishing a comprehensive system to ensure the safety of all immunisations given in national immunisation programmes. Countries are the primary focus of this project. The WHO has a role to play not only because of its technical and normative role but also because of its privileged relationship with country authorities and other partners, its global vision and mandate, and because it is perceived as free from conflicts of interest. There are four areas of focus in the project: (i) quality control and assessment tools to ensure vaccine safety from clinical trials up to and including the point of use; (ii) research and development of safer and simpler delivery systems; (iii) access to safer and more efficient systems for vaccine delivery and sharps waste management; and (iv) mechanisms to respond promptly and effectively to vaccine safety concerns. The project emphasises the importance of advocating safety and developing necessary infrastructure and human resource to properly deal with immunisation related safety issues at a national level.

Although immunisation programmes are repeatedly referred to as 'one of the most effective and safest of all health interventions', several challenges must be faced for their implementation. One such challenge is achieving 'immunisation safety' (i.e. ensuring and monitoring the safety of all aspects of immunisation, including vaccine quality, storage and handling, vaccine administration and the disposal of sharps). Those advocating the use of vaccines must find ways to address and to live with this challenge, since it is here to stay.

It has been recognised since the inception of vaccination against smallpox that adverse events may follow the administration of a material given for prevention of an infectious disease. These events have been reported to be local (at the site of injection) or systemic. Although the vast majority of these events are mild (such as low-grade fever and limited local reactions), some have been more serious (such as febrile convulsions following the administration of diphtheria, tetanus and pertussis vaccine). It has also been recognised that although some of these events are indeed a result of the vaccine itself and constitute actual 'vaccine reactions', many other events are coincidental and occur as a result of other medical conditions. The large number of doses administered, together with the fear of injections, make it fertile ground for merely coin-

cidental events to occur and be reported after vaccination (although they share no relationship whatsoever with vaccination) and to lead to undue fears and allegations.

Many years ago, after an adverse event or a series of events was reported, attention was immediately focused on the quality of the vaccine and potential production problems or mishaps. Because of the need to assure and improve vaccine quality, the World Health Organization (WHO) and national regulatory authorities worldwide have devoted much energy and resources towards working with vaccine manufacturers to enhance their compliance with good manufacturing practices. Yet the availability of vaccines of good quality is not sufficient. Simonsen et al.,[1] who carried out a literature review to quantify the prevalence of unsafe injections (defined as the reuse of syringe or needle between patients without sterilisation), reported that at least 50% of injections were unsafe in 14 of 19 countries for which data were available. Although this review pointed to some evidence in a limited number of countries that childhood immunisations were safer than curative injections, it is clear that infectious diseases could actually be transmitted by the very act of immunisation. In addition, there have been reports of unfortunate programme mistakes such as the inadvertent and tragic reconstitution of vaccine vials with insulin or curarimimetic substances (kept in the same refrigerator) instead of the proper vaccine diluent.

Vaccination is expected by both the public and health professionals to be a safe medical intervention that will not lead to harm. Part of this expectation is because vaccines are given most often to well children and childbearing women. This is in contrast to therapeutic drugs, which are taken for the most part to cure or alleviate disease. Any adverse event or vaccine safety issue, be it real or perceived, may lead to rumours in the community and more widespread reports in the various media. Such rumours regarding adverse events following immunisation (AEFIs) that are not rapidly and effectively dealt with can undermine confidence in a vaccine and, ultimately, have dramatic consequences for immunisation coverage and disease incidence. Examples of such dramatic consequences include the impact of antivaccine movements on pertussis control and the more recent impact of allegations of a possible link between administration of measles, mumps and rubella (MMR) vaccines and autism. Gangarosa et al.[2] reported that pertussis incidence was 10 to 100 times lower in countries where high vaccine coverage was maintained than in countries where immunisation programmes were compromised by antivaccine movements. In the UK, MMR coverage rates for 2-year-old children declined from 92% in 1995 to 88% in 1998, and public health authorities and researchers have suggested that negative publicity (coverage of studies proposing a link between the vaccine and bowel disease and autism) may be a factor in the decrease of vaccine coverage.[3-6] Of course there are situations where true safety issues may occur and these should be promptly identified to allow additional research and appropriate action to take place.

Paradoxically, the very success of immunisation programmes in decreasing the incidence of long-dreaded scourges such as poliomyelitis, diphtheria and measles can actually lead to increased public concern about vaccine safety. If there is no obvious risk from the infectious disease concerned, why should one take the risk of being vaccinated against it?

Many accusations have been investigated and shown to be unfounded scares, such as the purported link between MMR and autism,[3] and the one associating an experimental polio vaccine with the origin of HIV.[7] However, we cannot deny that real safety problems arise from time to time with vaccination and a claim of absolute safety would just be foolish and short sighted. The serious adverse events experienced after use of the killed measles virus vaccine in the 1960s are one of the rare but sad memories in immunisation history.[8] A more successful example is that of the relationship between rotavirus vaccination and intussusception that was detected in the prelicensing studies but appeared possibly coincidental at the time. The reaction was promptly detected during the first

months of vaccine distribution, and vaccine use was quickly stopped as a result. Only after use on a wider scale did the reaction become really evident, and it was because of the concerted efforts of the postlicensing surveillance programmes and tools in the US [using the Vaccine Adverse Events Reporting System (VAERS) and the Vaccine Safety Datalink system (VSD)] that the association could be detected and studied so promptly.[9]

1. Immunisation Safety: a Priority of WHO's Department of Vaccines and Biologicals

In 1999, WHO's Department of Vaccines and Biologicals (V&B) launched the Immunization Safety Priority Project (ISPP) to establish a comprehensive system to ensure the safety of all immunisations given in national immunisation programmes by the year 2003.[10] This project is one of three priority projects selected by V&B through broad consultation with partners inside and outside WHO. The other two priority projects are Accelerated Vaccine Introduction and the Polio Eradication Initiative. These projects encompass the expertise and contributions of all five teams in V&B, i.e. Quality Assurance and Safety of Biologicals, Vaccine Development, Vaccine Assessment and Monitoring, Access to Technologies, and the Expanded Program on Immunization.[10] Achievement of the priority project targets involves cross-cutting activities, and specific resources were earmarked for this purpose, thereby allowing for not only continuation but actual strengthening of activities in relation to these projects.

Achievement of the ISPP's target requires an overall awareness of the importance of safety and the need for prevention, early detection, and quick response to AEFIs to lessen their negative impact on health and on immunisation programmes themselves. The project aims at identifying remaining gaps and priorities and establishing the necessary infrastructure to ensure safety. It offers a set of objectives and milestones[10] in each of the four major areas of activity identified by the project: (i) to ensure vaccine safety, from vaccine development all the way through clinical trials and vaccine distribution to the point of use; (ii) to promote and coordinate research and development of safer and simpler delivery systems; (iii) to broaden access to safer and more efficient systems for vaccine delivery and sharps waste management; and (iv) to establish efficient mechanisms to detect serious or potentially serious AEFIs and enable prompt and effective response.

The first three areas aim at prevention and the fourth at early management of risks. The third area is also an area of concerted action within the strategic framework of the Safe Injection Global Network (SIGN).[11] SIGN is a voluntary association of stake-holders made up of individuals, representatives of public and private organisations, and national public health officials aiming to achieve safe and appropriate use of injections throughout the world. The network is supported by a permanent secretariat located within the Blood and Safety and Clinical Technology department of WHO. SIGN was officially launched in October 1999.

First and foremost, the ISPP is about partnership, with a primary focus on supporting countries to ensure immunisation safety. The project entails a close working relationship with UNICEF (which is involved in the delivery of immunisation programmes), vaccine manufacturers, professional organisations and other partners of the recently created Global Alliance for Vaccines and Immunization (GAVI). GAVI is the new umbrella that embraces all major global and national stake-holders (industrialised and developing countries, UNICEF, WHO, the World Bank group, foundations, the vaccine industry, public health institutions, non-governmental organisations and the research and development community). These stake-holders are united around a set of objectives ranging from currently established goals such as polio eradication and measles control, to future achievements such as the development and application of HIV and malaria vaccines. GAVI has placed immunisation safety high on its agenda. The new Global Fund for Children's Vaccine set up by GAVI, has received commitments that are in excess of $US1 billion

and is becoming a major new financing instrument for the poorest countries. The fund will provide support for the purchase of new and under-used vaccines and associated safe injection equipment, and represents a major opportunity to improve the safety of injection practices and sharp waste disposal.

The following sections elaborate on selected ISPP-related activities (whether these activities are conducted by the V&B department itself or not) and issues with respect to advocacy, immunisation-related injection safety, ensuring vaccine quality and safety, and mechanisms to detect AEFIs and enable prompt and effective response.

2. Advocacy: A Necessity

The project emphasises the importance of advocating safety and developing necessary infrastructure and human resource to properly deal with immunisation related safey issues at a national level. A number of key advocacy messages have been developed for professionals, professional organisations and national authorities, based on an acknowledgement of the existing deficiencies and challenges, and consistent with the various WHO technical documents and recommendations from the Steering Committee of the Priority project. These include the need to ensure the safety of vaccines, the need to secure the safety of injections (to minimise the risk to the recipient and the care provider) and the need to control the safety of disposal (to minimise the risk to the community). The latter is apparently a recurrent problem in many developing countries, as indicated by the results of various injection safety assessments conducted recently. This might be partly a result of medical and nursing staff wrongly assuming that their responsibility ends with contact with the patient and the duty of care. Advocacy messages are further detailed in table I. It is crucial that political will and financial resources are available to ensure the safety of immunisations and immunisation programmes.

Table I. Key safety advocacy messages

Ensure the safety of vaccines
Use only vaccines of demonstrated quality, safety and efficacy
Strengthen national regulatory authorities
Optimise immunisation safety by ensuring collaboration among all key players, particularly physicians' and nurses' associations, in the health community
Ensure a commitment to safety in financing of immunisation services
Emphasise immunisation safety as a priority in health system reforms
Secure the safety of injections
Switch to auto-disable syringes by 2003
Rigorously adhere to sterilisation procedures while still using sterilisable equipment
Do not recap syringes to prevent needle stick
Control the safety of disposal
Include immunisation safety and waste disposal management in national immunisation policies
Raise awareness on medical waste disposal
Implement these policies and procedures at all levels
Ensure accountability for safe waste disposal

3. Immunisation-Related Injection Safety

WHO's currently preferred syringe for immunisation is the auto-disable (AD) syringe. AD syringes have plastic or metal ratchets that prevent the plunger from being pulled twice so that it cannot be reused. Overall, the AD syringe contributes to decreased blood-borne pathogen transmission between patients by preventing reuse and resale, practices that exist in developing countries. However, AD syringes lack needle protection and do not eliminate the hazards of needle stick injury for the healthcare provider or of sharp waste in the environment. Furthermore, and although their price is decreasing, they are still more expensive than other types of syringes (nearly 30% more expensive than standard disposable syringes), which represents a serious barrier to their use in a number of the poorest developing countries. However, efforts are being made to reduce cost further through technology transfer. In this regard, WHO is contributing to the process of technology transfer through manufacturers' assessments, liaison between intellectual property owners and manufacturers, market assess-

ment in collaboration with Health Ministries, provision and modification of specifications, and laboratory qualification testing. A joint WHO/UNICEF/United Nations Population Fund (UNFPA) statement on the safety of all injections related to immunisation has been developed and recommends the sole use of AD syringes in national immunisation programmes by the end of 2003.[12]

Promoting the use of AD syringes implies efforts devoted to the availability and access to systems for safe disposal of sharps. WHO has initiated actions to test various solutions and equipment and to develop guidelines on waste management at health centres. Activities relating to waste management are now coordinated by WHO's Department on Protection of the Human Environment (Water, Sanitation and Health), which is also finalising a database on local solutions for waste disposal. More information can be obtained on the following website: *http://www.healthcarewaste.org*.

Various aides-mémoires on injection safety and waste disposal have been developed by WHO to help ensure safety. They include an aide-mémoire for a national strategy for the safe and appropriate use of injections (*www.injectionsafety.org*) and one for a national strategy for healthcare-waste management (*www.healthcarewaste.org*). These have been developed by WHO by the SIGN Secretariat in the Department of Blood Safety and Clinical Technology and by the Department of Protection of the Human Environment, respectively. WHO is further developing other aides-mémoires or brief reference documents, such as practical guidelines for planners and managers with respect to the management of wastes from immunisation campaign activities. A standard and representative specific injection safety assessment tool has been developed to assess the safety of injection practices at the national level and to help drive change where needed.[13]

4. Ensuring Vaccine Quality and Safety

Ensuring the consistent safety and quality of a vaccine is a basic element in any successful immunisation programme. Dellepiane et al.[14] have published a fairly comprehensive review of steps and procedures taken during and after the manufacturing process to ensure that vaccines are safe. These include characterisation of starting materials by suppliers' audits, cell banking, seed lot systems, compliance with the principles of good manufacturing practices, independent release of vaccines on a lot-by-lot basis by national regulatory authorities, and enhanced pre- and postmarketing surveillance for possible adverse events following immunisation. As an example, the management of concerns associated with the acceptability and use of mammalian cells for the production of vaccines is a major issue. The perceived risk associated with continuous cell lines used for vaccine production is the presence in the product of residual host cell DNA and transforming proteins, both associated with the possibility of carcinogenesis, and contamination with viruses or the agents of transmissible spongiform encephalopathies.[15] These risks are managed by developing up-to-date criteria and guidelines for production and quality control, as well as international reference materials intended for vaccine manufacturers and national regulatory authorities and for the production and testing of vaccines. Defining appropriate quality controls is the key and this involves continuous vigilance and regulatory research. New technologies need to be evaluated and standardised and decisions made regarding interpretation and reliability of results.

Two relatively recent events raised awareness of the challenge of dealing with viral contamination of vaccines and its consequences.[15] The first is the detection of low levels of reverse transcriptase in chicken cell-derived vaccines (e.g. measles, mumps, yellow fever), suggesting the possibility of contaminating retroviruses. The second is the detection, using new and highly sensitive molecular-based techniques, of the simian virus (SV) 40 genome in rare human tumours, raising the spectre of a connection with polio vaccine made in primary monkey kidney cells.[16]

Such discoveries require a coordinated international response. Work undertaken by WHO's Collaborating Centres on Biological Standardization

confirmed that measures to exclude SV40 from polio vaccine, introduced into WHO requirements over 30 years ago, have been successful.[17,18] Although this was reassuring, a supplementary level of security has now been added by requiring that all seed viruses be shown to be free of SV40 sequences.[19]

In response to these and similar issues, a WHO Task Force was established to coordinate and evaluate continued collaborative regulatory research relevant to the characterisation, quality control and safety assessment of all cell substrates intended for use in vaccine production.

Regarding combined vaccines, WHO, through the Expert Committee on Biological Standardization, will be supporting regulatory research that addresses specific issues for new combination vaccines: (i) definition of minimum potency levels for each component; (ii) establishment of new reference materials; (iii) impact of preservatives and adjuvants; (iv) research on interference between antigens and data to aid in assignment of adverse events.

Strengthening national regulatory authorities and enabling them to exercise all required functions is an important activity of WHO, of which the Global Training Network (GTN) is core. This WHO initiative aimed at improving the quality of vaccines and their use was developed in 1996 as a means of providing educational resources to vaccine control and production staff throughout the world. The GTN currently consists of 14 training centres that offer instruction in priority areas. As well as national regulatory authorities, the GTN provides training to national control laboratories and vaccine producers in the following areas: good manufacturing practices, laboratory quality systems, quality control testing, licensing, animal husbandry, lot release and laboratory access, and most recently in postmarketing surveillance/AEFI monitoring (described further in section 5). The GTN differs from previous training activities in vaccine quality because it is coordinated (rather than *ad hoc*); trains in a small number of curricula defined by needs; uses standardised curricula and training materials approved by experts; screens applicants carefully, requiring an institutional training plan; prioritises countries that will benefit to maximise impact; and expects a return on the investment by contributions to quality from trainee institutions.

Another important activity of WHO is the development of specific guidelines on clinical trials for vaccines, which will put emphasis on safety as a major endpoint. These guidelines will specifically cover the problem of assessing combined vaccines. Recent articles have highlighted a tendency of clinical research not to give safety all the attention it deserves.[20,21]

5. Mechanisms to Detect Adverse Events Following Immunisation and Safety Issues, and Enable Prompt and Effective Response

Monitoring and proper management of AEFIs is important for the success of the immunisation programme, since such events can influence community acceptance of immunisation. Careful surveillance and investigation of AEFIs are necessary to identify causes of these events that require correction. Staff must understand how to carry out a careful epidemiological investigation in the event of an adverse event. Such an investigation is of critical importance to pinpoint the cause of the incident and to correct immunisation practices. A comprehensive set of resource documents, guidelines on AEFIs and AEFI monitoring have been developed by WHO.[22-24] In addition, WHO has invested in the training of immunisation managers and the staff of national regulatory authorities as part of the GTN described above. The AEFI monitoring curriculum is specifically designed for staff of national regulatory authorities and immunisation and surveillance programmes working together in the area of vaccine safety.[25] In recent years there has been a growing interest in the media with respect to AEFIs, and such events are now reported more frequently. Managers who have to deal with the impact of such reports in health terms are often faced with an entirely new environment that can be perceived as hostile to a large extent. Few, if any, have been trained to cope with this situation. Materials to train managers to handle the media and media

crises have therefore been developed, and a strong component on how to develop partnerships with the media is built into the AEFI training module.

Postmarketing surveillance capabilities are improving; more countries now have AEFI monitoring systems, and more importance is attached to the reporting of suspected links between vaccination and adverse events. However, such surveillance may have some limitations. Case-series reports can identify spurious associations, with false hypotheses being generated. Although most of the purported associations have been properly investigated and health risks ruled out, this has created a huge amount of work, public attention and avoidance of vaccination. Disproving spurious associations (which can be considered as 'spurious' only after hypothesis testing) diverts resources away from real priorities. One has to clearly distinguish hypothesis generating and hypothesis testing. Hypothesis testing must be done quickly and to high-quality scientific standards. Epidemiological and laboratory investigations need to be carefully conducted to avoid introducing bias; data must be carefully validated and scrutinised before results are communicated. Only a few countries have the capacity and tools, e.g. large linked databases, to complete these tasks easily, so international collaboration can be vital to a successful outcome. The process adopted for the recent investigation of a potential link between oral polio vaccination and intussusception is an ideal model; this was prompted by a similar experience with rotavirus as mentioned in the introduction.[9] International collaboration in hypothesis testing, and independent scientific review of studies enabled the hypothesis of a causal relationship to be rejected,[26] thereby avoiding the potential damage to both vaccine acceptance and polio eradication objectives.

To respond promptly, efficiently and with scientific rigour to vaccine safety issues, WHO has established a Global Advisory Committee on Vaccine Safety. This committee provides an independent scientific assessment of vaccine safety issues[27] and makes scientific recommendations which are intended to assist WHO, national governments and international organisations in formulating their policies regarding vaccine safety issues, including problems which particularly affect developing countries. Where necessary, *ad hoc* task forces have been and will be created with a mandate to commission, monitor and evaluate appropriate methodological and empirical research on any purported association of specific vaccines/components and adverse event(s). The committee has published the principles it uses in vaccine adverse event causality assessment.[28]

6. Conclusions

Technological advances have led to improvements in vaccine safety and now give us the capability to prevent, quickly detect and deal with vaccine safety problems on a global basis. WHO's role and responsibility is to provide a global approach that facilitates and empowers each country's ability to ensure immunisation safety. Interested readers who would like to have more information on WHO resources and on the project itself might wish to access the ISPP website (*http://www.who.int/vaccines-surveillance/ispp*).

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