Round Table Discussion

Presenting the case for an immunization safety surveillance system

Ahmed A. Darwish[1]

Brian Ward is to be congratulated on stating so clearly the reasons for a monitoring system being necessary for any adverse events that could be related to vaccination (*1*). I believe the reticence of governments about inaugurating surveillance systems has several causes. First, although WHO encourages its Member States to develop and sustain a monitoring system, they still do not see the need for such a system or the value of it very clearly. Second, health departments are concerned that systematic searching for adverse events related to vaccination might have a negative impact on their immunization programmes, by giving the impression to immunization teams that the vaccines are not safe, contrary to what they had learnt during training. In addition, asking questions in the community might prompt people to think that something wrong with the vaccines, concealed from the users, is the reason for data being collected, even though the vaccines have been in use for a long time without the issue being raised.

The importance of surveillance of adverse events following vaccination was not widely recognized in Egypt until April 1998 when a few adverse events occurred in one governorate and were considered to be vaccine-related. The media received information about these cases before the medical authorities did, as at that time there was no surveillance system for such occurrences. Irresponsible handling by the media caused rumours to spread that the vaccine was unsafe. This tarnished the reputation of the immunization programme, led to community panic, and had a negative effect on the coverage for all seven antigens included in Expanded Programme on Immunization (EPI) activities all over the country.

After that, the Ministry of Health decided to establish a comprehensive system for the surveillance of adverse events following vaccination aimed at detecting such events early so that they could be investigated and proper action could be taken. The system was established with a central surveillance officer assigned to work closely with the national regulatory authority. Surveillance officers were assigned within the immunization programme in each governorate to maintain a regular reporting system and ensure that the health department could move immediately and appropriately whenever a report made it necessary. In addition, health staff at various levels were given special training in signs and symptoms to look out for.

Seven serious events and many minor ones were discovered through this surveillance system between July 1998 and September 1999. No problems were encountered, and the situation was controlled and contained without any negative impact. There was a rapid response to the need for investigation and management of cases, and for satisfying the local community and parents that proper care was being taken.

Our experience in Egypt indicates the importance of having a comprehensive system for surveillance of adverse events following immunization, and I should like to encourage other countries to go ahead with similar plans. The reservations I enumerated in my first paragraph have proved unfounded, and even people who were initially sceptical have seen the value of our activities. Nevertheless, I would like to propose a change in the terminology. The term "Immunization Safety Surveillance System" would be more suitable and positive, as "adverse events" has negative connotations especially when translated into some other languages, such as Arabic. ■

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Ref. No. **0556**

A view from the media on vaccine safety

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In general, the contribution of the media to increasing parents' awareness of the dangers Brian Ward mentions (*1*) can be seen in a positive light. Nevertheless, for anyone who lives in the industrialized countries, vaccine safety stories seem to appear in the media as frequently as food scares. In the developing world such stories are rarer but certainly not unknown. Public health officials, aware of real problems such as the recently withdrawn rotavirus vaccine in the USA, must take all doubts about safety seriously. But when they watch immunization rates decline in the aftermath of a scare that is later shown to be unfounded, their exasperation with the media is understandable and hard to conceal. Public health officials, who are clear about their own role as health advocates, sometimes fail to see that the agenda of the news media can differ from theirs.

Though tension exists between media personnel on one hand and public health officials on the

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Ref. No. **0553**

other, as illustrated by Ahmed Darwish's account of his experience in Egypt, the relationship is not a simple one. I asked a number of people for their views, which I give below. They suggest that both parties are subject to potentially awkward internal conflicts that can increase the likelihood of unbalanced coverage.

First, though, it is important to know why stories about problems with vaccines appear: it is because they are news. If a peer-reviewed journal publishes a paper claiming a problem with a vaccine, it is because that information, right or wrong, exists. Many reporters believe it is their job to report news in a balanced way, but not necessarily their responsibility to judge how the public will act on the information. "While it's important to be aware of the impact of the report you do, that is not a reason to stop doing the story," insists Susan Watts, an award-winning reporter with the BBC's flagship TV news-analysis programme, *Newsnight*. The reporter's job is to know whom to ask about the validity of the claims being made, and to set them in context, she says.

Watts reported highly controversial research which claimed a link between the measles–mumps–rubella (MMR) vaccine and autism and inflammatory bowel disease (*2*). Although other researchers have found no evidence of such a link (*3*), significant numbers of British families have been avoiding MMR vaccine (*4*) and interest in the issue is spreading beyond Britain. For example, the same concerns were also aired in late 1999 on CNN. Health officials have warned of possible measles epidemics as a result.

Watts says that she simply wanted to give "a fair picture to the public", and took care in her report to point out other researchers' criticisms of the study. She says, too, that her determination to do the story was fuelled by what she perceived as an "unusually" hostile response from public health officials when she began to make enquiries. "There is no doubt that they were trying to manipulate the way the story was told and to suppress information," she claims. Even before the paper was published, government health officials contacted Watts and, she says, attacked its findings.

But is it too easy for journalists to say that they just want to tell people the facts? That depends on how you tell them, says Steve Connor, another award-winning journalist, on *The Independent* newspaper. He thinks the responsibility is on the science reporter to make sure that any rare adverse events attributed to vaccines are set fully in context against the risks of the disease and the benefits of vaccines to the population as a whole. But, as he points out, it is not always that simple. While researchers and public health officials may see the media as monolithic, there are in fact strong internal conflicts, as Connor's experience illustrates. At the time of the MMR scare in Britain, when he was working for a different newspaper, he was asked for a report. He put the controversial findings in context and reported other scientists' criticisms of the paper — such as the fact that it was based on only 12 children, eight of whom had behavioural problems that had been linked retrospectively by their parents or doctors to the timing of MMR immunization. Connor's report appeared, but was overshadowed by the harrowing testimonies of some of the families. He was not surprised. "Human interest is the lifeblood of journalism," he says, "but it's not science. It's interesting, and it makes great copy, but it is not proof."

Lawrence Altman, a writer on the *New York Times*, observes that there are potential conflicts for public health officials too, in their role both as sources of scientific information and as advocates for immunization. For example, he says, it is difficult to find researchers who are willing to talk about the theory that HIV might originally have entered humans in experimental polio vaccines made in primate kidney tissues and tested in central Africa during the 1950s. Researchers "understand why we might write about it, but they wish that we would not, because they worry that it might do more harm than good." Some fear that the campaign to eradicate polio could be set back by such public debate. But Altman thinks the instinct of officials to avoid discussion of a troubling theory in the interests of protecting public health can be counter-productive. "I feel that the suppression [of information] can do more harm than good, and I think there should be open discussion," he says. For science reporters, the reasonable dialogue that they expect to have with scientists about observations and probabilities can sometimes be replaced with what sounds suspiciously like dogma.

Dr Harry Hull, WHO's senior adviser on poliomyelitis in Geneva and a frequent interviewee of many journalists, recognizes the problem of communication. Hull, who is surprised by the number of journalists who "seem to feel that you are hiding something", believes that the healthy publics of the industrialized countries have forgotten what the vaccine-preventable diseases are like. Insulated from the realities of the diseases, people confuse absolute risk with relative risk. This confusion is not restricted to vaccines. Frequently, interviewers, like politicians, try to get scientists to tell them whether any new technology — vaccine, treatment, or genetically modified organism — is "safe" or not. Scientists, used to dealing in probabilities rather than absolutes, are unlikely to have the simple assurance that politicians and the media want. The question is whether members of the public really have an outlook as simplistic as media people and politicians seem to believe?

The answer, of course, depends on whom you ask. But a report from UK government-funded researchers (*5*) says that the public has a more sophisticated perception of risk in relation to new technologies than it is generally given credit for. If public health and media alike see themselves as serving the public, then perhaps both should listen and adapt. An increasingly informed and sophisticated public is the future, whether in high-income or low-income countries. It will no longer be enough for scientists merely to say "trust me" or for newspapers to present sensational testimonies as the whole story. ■

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Evaluating vaccine safety before and after licensure

John Clemens[1]

The current approach to evaluating new vaccines divides prelicensure evaluations into three phases (*1*). Phase 1 trials are generally undertaken in small numbers of healthy adults and are designed primarily to find out whether a vaccine has frequent side-effects. These trials are usually not well-suited to finding out whether such side-effects can occur in the target population for the vaccine (children, for example) or whether there are important side-effects that occur infrequently.

If a vaccine performs well in Phase 1 trials, Phase 2 trials are carried out to decide whether it is suitably immunogenic and safe for ultimate use in a target population. Usually in Phase 2, randomized double-blind trials are used, with larger numbers of subjects than in Phase 1, though still not large enough to detect rare vaccine side-effects. Moreover, because side-effects may differ in occurrence between different populations, as pointed out by Ward (*2*), a Phase 2 trial conducted in one population may not provide assurance of vaccine safety in all populations in which the vaccine might ultimately be used.

Finally, if a vaccine proves acceptable in Phase 1 and 2 trials, one or more Phase 3 trials may be done to find out whether it is suitably protective against the naturally occurring infections or diseases that the vaccine is intended to prevent. Although Phase 3 trials are generally undertaken on a much larger scale than Phase 1 and 2 trials, the number of subjects for them is usually calculated to evaluate vaccine protection rather than to detect rare potential side-effects. This means that Phase 3 trials will usually not be large enough to detect such side-effects. Moreover, the results of a Phase 3 trial may not pertain to all other populations. Thus, although a vaccine may have had a considerable number of studies done on it and although the results of these studies may warrant licensure, the data thus obtained may still not be sufficient to guarantee that a vaccine will be suitably safe when it is introduced into practice in all populations at risk for the disease targeted.

Is there any evidence that the pre-licensure evaluative sequence currently used is not always adequate to prevent unsafe vaccines from passing into public health practice? Although it is difficult to estimate the frequency with which they occur, there are examples of lapses. In the early 1990s one such instance occurred for high-titre Edmonston-Zagreb measles vaccine, a vaccine that was capable of protecting infants even when administered at 6 months of age. The results of Phase 1–3 trials of this vaccine (*3*, *4*) led to an official recommendation by WHO for its use in selected populations (*5*). Subsequently, however, continued analyses of populations that had participated in the earlier trials revealed an entirely unexpected increase in mortality among vaccinees (*6*), which led to a rescinding of the WHO recommendation (*7*). Another example is provided by a rhesus rotavirus reassortant vaccine that was licensed in the USA in 1998. Pre-licensure trials of this vaccine revealed it to be acceptably protective and safe, but were inadequate in size to rule out rare severe side-effects. One such side-effect, intussusception, was noted in pre-licensure trials but did not have a statistically significantly higher incidence in vaccine recipients than in placebo recipients. Only after the vaccine had been administered in practice to large numbers of infants in the USA was the number of cases of intussusception large enough to enable appreciation of a statistically significant link between this side-effect and receipt of the rotavirus vaccine (*8*). These assessments led to the withdrawal of earlier recommendations for use of the vaccine in the USA.

Examples of this kind do not invalidate the current paradigm for Phase 1–3 trials as a basis for vaccine licensure. Nevertheless, such events inevitably reduce public confidence in the producers, regulators, evaluators, and deliverers of vaccines. They therefore raise several questions. Should prelicensure trials enrol subjects in target groups in sufficient numbers to evaluate rare but serious side-effects? If so, what threshold of "rarity" should be used for calculating the needed numbers of subjects? Moreover, how long after vaccination should subjects be followed up to detect the occurrence of long-latent side-effects? Finally, in view of the possibility of differences from population to population in reactions to vaccines, in how many populations must a vaccine be tested to provide assurance to regulators in a particular country that results of trials done elsewhere are valid for their own setting?

Post-licensure evaluations of vaccine safety are conducted by using case series of voluntarily reported putative side-effects, or, preferably, by conducting controlled studies. In contrast to pre-licensure studies, which usually employ randomized trial designs, controlled post-licensure studies rely on non-randomized observational study designs, such as cohort or

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Ref. No. **0554**

case-control designs (*9–11*). In the past, such studies were generally done on an ad hoc basis by investigators with particular interests in the putative associations. In recent years, allegations that adverse events are caused by vaccines have apparently increased. Because such allegations can undermine public confidence in vaccines and because of the ethical necessity to conduct studies of these potential side-effects both rapidly and credibly, new research strategies have been required. As discussed by Chen in this issue of the *Bulletin* (*12*), a particularly attractive approach for conducting such studies in a rapid yet scientifically rigorous fashion has been the creation of computerized, large linked population databases that record vaccination status, visits for medical care, and information on potentially confounding sociodemographic variables for each person of interest in a target population. The great advantage of such databases is that they enable evaluation of multiple putative associations without the need to mount a specific study for each one. They also allow public health researchers to evaluate such associations rapidly.

The establishment of such large linked databases is well under way in several industrialized countries, but it presents substantial challenges. Among the requirements for these databases are the following:

- a defined and demographically monitored population base of sufficient size;
- complete and accurate recording of immunizations given to the population of interest;
- a reasonable medical care infrastructure to which the population has access;
- complete and accurate recording of salient diagnoses for both inpatient and outpatient encounters at the treatment sites serving the population;
- the capacity to computerize, manage, and analyse large volumes of data on immunizations and outcomes on an ongoing basis.

A major concern for public health professionals is the virtual absence of such databases in developing countries, or even of locations that can meet these requirements. WHO has recently taken the lead in a major effort to create systems of post-licensure surveillance for vaccine safety in developing countries. Working with WHO, the International Vaccine Institute, recently set up by the United Nations Development Programme and hosted by the Republic of Korea, plans to establish several model sites with large linked population databases in developing countries of Asia. Setting up databases that will be adequate to monitor vaccine safety will involve considerable methodological work, but such databases, at least in selected countries, will be essential as new generation vaccines are introduced into these settings. ■

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Vaccination benefits, risks and safety: the need for a complete picture

Robert Pless[1]

Since the first attempt at vaccination more than 200 years ago, debate has been ongoing about the relative benefits and risks. However, debate was overshadowed by the threat of crippling illness and death. Today, past successes of the vaccination programme — exemplified by the eradication of smallpox, the near eradication of polio, and control of other diseases — may threaten the continuation of its success. In the absence of perceptible disease threats, concerns about the risks of vaccines dominate renewed debate. While high immunization coverage and recent surveys (*1*) suggest that the majority of parents today readily accept vaccines, allegations of risk have greater impact than before and are more challenging to address. Certainly, as experience has shown (*2*), the concern among public health professionals is that coverage will decrease and disease may re-emerge. Risks — proven or unproven,

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Ref. No. **0578**

real or perceived — must therefore be not only examined in the light of the best scientific information obtainable but responsibly communicated.

This is particularly important when speculating or generating hypotheses. Thirty years ago Sir Graham Wilson, former Director of the Public Health Laboratory Service in England, wrote a book reviewing *real* vaccine mishaps (*3*) at a time when diseases were not yet well controlled. Even so, he took great pains to acknowledge in his preface that the book may be criticized and actually expressed concern that it would "... merely strengthen the case of the anti-vaccinationists". However, truth was his overriding purpose: "... the need to understand how mishaps have arisen, so that with the exercise of due care they may be avoided in the future". Some of his lessons unfortunately still remain an issue: programme errors leading to contaminated injections continue to be a problem in developing countries (*4*). But other lessons Wilson reviewed are being applied more effectively: modern regulatory standards and techniques have corrected previous production faults, and vaccine safety monitoring systems have improved. Consciously or not, though, Ward is updating Wilson's message by suggesting that we must further improve our vigilance about vaccine safety in the light of ongoing progress in immunology and vaccine design (*5*). While Wilson drew on real untoward experiences of the past to illustrate the need for care in the future, Ward does not present proven concerns. However, by describing some rather "creative" (as he put it) and speculative hypotheses, he makes a case that we must all be even more proactive in our efforts at monitoring safety in order to prevent untoward events that may arise in the future.

But can such speculation, which is not born of real events, unlike those described by Wilson, cause harm? According to recent history, it can. When an allegation arose that measles–mumps–rubella vaccination may lead to autism, however unsubstantiated the evidence (*6*), a small but measurable decrease in immunization coverage resulted (*7*). Does this mean we should not engage in "creative" thinking and discuss our concerns? No, but it does suggest that we must be all the more clear and responsible in our discourse. For example, Ward notes in his paper that some investigators suggest that age at vaccination may have an impact on the development of autoimmune disease, but that the theory is not accompanied by "hard" data. However, he misses this important opportunity to inform the reader that this contentious idea, raised with immunization and diabetes, is being carefully investigated and epidemiological evidence against it does exist (*8*).

Communicating risk information about vaccination is one of the most difficult challenges in all drug safety research. In September 1997, participants from 34 countries including experts from clinical medicine, academia, industry, government, the media and the public, gathered in Erice, Sicily, to discuss the most effective way to communicate drug safety (*9*). They drafted a declaration, which included the following preamble: "Flaws in drug safety communication at all levels of society can lead to mistrust, misinformation and misguided actions resulting in harm and the creation of a climate where drug safety data may be hidden, withheld, or ignored." They went on to describe five principles paraphrased here.

- Drug safety information must serve the health of the public. Such information should be ethically and effectively communicated. Facts, hypotheses and conclusions should be distinguished, uncertainty acknowledged, and information provided in ways that meet both general and individual needs.
- Education in the appropriate use of drugs, including interpretation of safety information, is essential for the public at large. Such education requires special commitment and resources.
- All the evidence needed to assess and understand risks and benefits must be openly available. Constraints on communication, which hinder the ability of those concerned to meet this goal, must be recognized and overcome.
- Every country needs a system with independent expertise to ensure that safety information on all available drugs is adequately collected, impartially evaluated, and made accessible to all.
- A strong basis for drug safety monitoring has been laid over a long period, although sometimes in response to disasters. Innovation in this field now needs to ensure that emergent problems are promptly recognized and efficiently dealt with, and that information and solutions are effectively communicated.

None at the Erice meeting were blind to the fact that it is difficult to implement and live with these ideals in relation to drug safety. It is all the more difficult in the case of vaccines. As vaccine-preventable diseases are brought under control, and the need to maintain high immunization coverage to avoid a return to the past becomes a harder message to convey, it is ever more crucial that we try. In the end, it is only by merging better public education on appreciating benefit and risk issues, with extra care in maintaining an honest and open discourse on benefit and risk, that we can see a future protected against the misinterpretation of information about vaccination and the all too ready acceptance of misinformation. With commitment to safety being an ongoing priority of the highest order, public confidence in vaccines can continue and low disease incidence can be maintained for everyone's benefit. ■

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Vaccine adverse events in the new millennium: is the sky really falling?

Alan R. Hinman[1]

In the children's story, Chicken Little was hit on the head by an acorn falling from an oak tree and subsequently rushed around crying "The sky is falling!" (*1*). Ward's ringing affirmative response to the question in the title of his piece — "Is there reason for concern?" (*2*) — suggests that the sky may be falling. Those with long immunization experience might be inclined to dismiss the paper out of hand as alarmist. However, that would miss some of the important issues regarding vaccine safety it raises.

Before proceeding to the real issues, I feel it is important to detail the main reasons why it would be easy to dismiss the paper as merely alarmist.

– Lack of context or balance. The paper virtually ignores the tremendous impact that vaccines have had, saving millions of lives each year. It also fails to mention that knowledge about adverse events has represented the best science available at the time.
– The paper presents an indiscriminate and unlabelled mixture of conjecture, speculation, hypothesis and fact. A reader who is not fully versed in vaccine issues might see each of the points made as equivalent. For example, the notion that randomness of exposure is good and that reducing randomness may somehow be bad is totally unproven, whether or not the possibility has been raised. Similarly, the "wisdom of targeting co-evolutionary 'partner' pathogens" is highly speculative. These possibilities have not even reached the stage of hypotheses to be tested. Nonetheless, they are granted the same level of consideration (or more) than proven adverse events such as vaccine-associated paralytic poliomyelitis. This presentation seems to increase the possibility that the ideas might be "taken out of context and add to the anti-vaccination rumble."
– An underlying theme of the paper is the plea for essentially unlimited resources to study vaccine safety issues. Although substantially more resources need to be devoted to study both the occurrence and the pathophysiology of vaccine-associated adverse events, the author gives no indication of how much is needed or what is a reasonable sample size for studying such events (a birth cohort of 400 000 clearly being considered inadequate). As it is, the author seems to be asking that the negative be proved (i.e., absolute proof that the vaccine does *not* cause an event), which is impossible in practice.
– The criticism about including societal or indirect costs (perspective) in economic analyses seems both inappropriate and out of date. Communicable diseases do not discriminate between those who willingly accept risk by forgoing vaccination and those who wish to be protected but are not because of some obstacle such as contraindication to vaccination, or vaccine failure. An individual's decision on vaccination not only affects that individual but has significant implications for the community at large. Consequently, a societal perspective is appropriate when developing vaccine policy.

  Although there has been considerable lack of standardization in the past, the field of economic analysis has been evolving. The US Public Health Service Panel on Cost-Effectiveness in Health and Medicine (*3*) states that in Reference Case analyses (which seek to improve comparability for analyses that will be used to inform resource allocation) "the major categories of resource use that should be reflected in the numerator of a cost/effectiveness ratio include costs of health care services; costs of patient time expended for the intervention; costs associated with caregiving (paid or unpaid); other costs associated with illness such as childcare or travel expenses; and costs associated with non-health impacts of the intervention (e.g., on the education system or the environment)."

The significant negative features of Ward's paper should not overshadow what I believe to be the key issues in vaccine safety and vaccine adverse events, many of which are mentioned in the paper.

– All current vaccines are associated with adverse events and it is virtually certain that future vaccines will also be. Novel approaches to vaccine composition or presentation and new combinations of vaccines raise additional possibilities for adverse events. Both laboratory and epidemiological studies are needed to characterize and understand these events. These should include approaches based on molecular epidemiology and population genetics.
– Newer technologies used in vaccine development mean that newer technologies will also be necessary to study the occurrence and pathophysiology of vaccine adverse events. In other words, state-of-the-art technology must continue

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Ref. No. **0579**

to be applied to studies of vaccine safety as the technologies develop. These technologies may also make it possible to design future vaccines with reduced potential for causing adverse events.
- More resources need to be devoted to studies of vaccine safety. Current linked databases need to be enlarged and potentially linked across national boundaries.
- Industrialized countries will have to bear the primary burden of these studies as they are beyond the resources of most developing countries. This may require supporting studies in developing countries to ascertain if there are geographical, cultural or genetic differences in occurrence of vaccine adverse events.
- Communication to the public about risks and benefits of vaccines is both essential and complex. Scientists and health officials need to learn more about risk communication and about how to help the public distinguish between real issues and wild speculation such as may be seen on some sites on the internet.
- Open discussion in the scientific community about vaccine adverse events is essential but needs to be conducted in a way that neither unduly alarms people nor appears to minimize the issues. Scientists from divergent areas (such as population genetics, molecular genetics, immunology, immunization and behavioural science) need to work together to develop an accurate perspective on vaccine safety and differentiate between empty speculation and potential areas of scientific research.

There are serious issues in vaccine safety which warrant serious deliberation, investigation, funding, and implementation but do not warrant an alarmist approach. The sky is not really falling in the area of vaccine safety. Whether Ward's paper ends up advancing the field or merely "stirring the pot" remains to be seen. I hope it is the former and not the latter. ■

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Concern, but not with surveillance

Adrian J. Ivinson[1]

Brian Ward tackles a subject of immense importance (*1*) — vaccines are probably the most efficacious and cost-effective medical interventions ever invented. Given that they are intended to treat whole populations, that the number of vaccines is growing, and that their successful deployment requires the confidence and good faith of whole populations, it is crucial that they are safe and are seen to be safe. One way to develop this confidence is increased surveillance and a better understanding of the risks.

On the other hand, most would agree that current vaccine programmes are woefully inadequate. In developing countries, many of the proven vaccines (including measles and tuberculosis) simply fail to reach those that need them most; newer vaccines (including hepatitis B and influenza) are not being introduced at all or only very slowly; and insufficient research effort is devoted to developing vaccines desperately needed by developing countries (including malaria and rotavirus). And even in the wealthy countries, otherwise successful vaccines may not achieve full population penetration partly because of the ironic link between success and perceived need and partly because of exaggerated media reaction to rare adverse events.

Thus, whereas Ward's basic tenet — that surveillance of vaccine-related adverse events is important and resources should be made available for monitoring vaccine safety at a time of increasing vaccine activity — cannot be disputed, in an environment of limited resources the question is really, what level of resources should be devoted to vaccine surveillance versus vaccine deployment? To answer this question we need to examine the balance of risk versus benefit.

Here the article is disappointing. While arguing that surveillance is patchy, Ward acknowledges that current vaccines are, by and large, quite safe and compare favourably to other medical interventions. So what's the problem? The risk, it is argued, lies ahead.

First, we are faced with an ever-increasing list of essential vaccines, each with the possibility of adverse effects. Secondly, the trend is toward multivalent vaccines that may give rise to altered and more dangerous immune reactions than the sum of reactions to a series of single-component vaccines. Third, whereas the move towards developing simpler, single peptide-based vaccines may result in a more vigorous protective reaction, there may be a concomitant increase in adverse reactions. And then there is the problem that by vaccinating against a plethora of infectious organisms we may diminish the important impact that microbes have had on the evolution of the human immune system and its ability to respond to microbial attack. And so the arguments go on.

The great weakness here is that all these arguments are highly speculative. No evidence exists that these threats are real or that, if they are real, they would pose a significant threat to the health of a vaccinated population. Simply put, there is no tangible evidence to support the claim that the

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Ref. No. **0557**

increased use of new vaccines will be more trouble than it is worth.

The author offers a more worthy argument against the use of vaccines (such as that against influenza) aimed at maintaining productivity rather than securing personal health and well-being. The ethical questions surrounding this and related issues are interesting, but receive scant attention in the article.

Ward concludes, "As the pace of vaccine development accelerates, it is crucial that we find the political will and financial resources to ensure that surveillance systems and support for basic and epidemiological studies of vaccine-associated adverse effects keep pace". Few would argue. However we must also recognize that resources are limited and that in many countries — the poorest countries — they are severely limited. Yet it is these countries that stand to gain most from improved vaccine use. Under these circumstances, surely the question is not whether vaccine surveillance is important but whether it is more important than the effective deployment of existing vaccines and the development of new vaccines.

If the intention of the author was to raise awareness of the importance of good vaccine surveillance and perhaps tilt the scales slightly in favour of more surveillance particularly for less pressing vaccines, then the article has probably achieved a worthwhile purpose. But if the purpose was to convince the powers that be that we are at risk of excessive immunization, and that resources should be shifted from vaccine development to vaccine surveillance, then I hope it falls on ears as deaf as mine.

The history of vaccines is not perfect, but it is pretty good. As such, WHO and others should continue to push for expanded use of new and existing vaccines and accelerated vaccine research. If we are going to have sleepless nights thinking about vaccines, for now it should be under-achievement, not under-surveillance, that keeps us awake and thinking. ■

1. **Ward BJ.** Vaccine adverse events in the new millennium: is there reason for concern? *Bulletin of the World Health Organization*, 2000, **78**: 205–215.