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Decision Dilemmas
Worse in Emerging Economies

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One frequently asked question about pharmacovigilance is 'how does one assess causality?' Another is 'how does one do signal detection?' These are weighty questions indeed, to which there is no easy single answer. During a recent WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (WHO-UMC) training workshop these topics were explored in some detail, and during the discussions the real dilemma of how one makes decisions in the face of uncertainty was raised.[1]

Anyone working in pharmacovigilance faces this problem continually. The data one uses is often incomplete and is of variable quality and content. The kind of decisions needed varies from passively waiting for more and better information, through active research of one sort or another, right through to safety warnings and limiting the availability of a medicine. More than this, the context of the decisions varies considerably and there are many 'non-scientific' considerations that must be taken into account, and it is mainly these that I want to pursue in relation to the challenges of the emerging economies.

1. Lack of Resources

Drug regulation is resource demanding if every medicine used is to be evaluated for safety and efficacy, and its use in the community sufficiently controlled to maintain effective clinical use. Two problems exist with this situation: there are too-limited financial and human resources to do the regulatory job fully, and safety aspects in any country depend on controls and good patient information – by prescription and dispensing. This professional service is also resource limited. Open sales of drugs through general retail outlets, with no health professional advice, is common, and are indeed necessary to make medicines available to all. In this situation, any pharmacovigilance decisions and messages therefore need to be disseminated broadly for them to have any effect. This leads to a further consideration that any decision on such communication needs to consider the literacy of the audience even more than in the developed world.

Drug availability is a major equity challenge in emerging economies. There is a more striking variability in between the poorer, larger majority and the smaller, affluent population than in the developed world.[2] The affluent in emerging economies often have ready access to the same range of medicines and healthcare expertise as in the developed world. Pharmacovigilance should try therefore to provide a sophisticated service for those affluent people and their demands for up-to-date information.

More important are the decision challenges over matters that affect the non-affluent majority, who have much more limited healthcare choices and are dependent on governmental and donor decisions about drugs. Public finance for healthcare means that rationing of available drugs is considerably more stringent than in the developed world. The compromises that need to be made pose humane dilemmas which, however much one may wish, lead to the much more frequent use of older, cheaper medicines rather than modern alternatives. For example,when vaccine programmes compete for finance against treatment for HIV and cancer these tough decisions need to be made, and a

limited range of inexpensive drugs may be all that can be managed for the latter diseases when considering the overall public interest. Certainly some limitations to availability also apply in the developed world but the much more restrictive cost consideration leads to quite a different level of effectiveness-risk concerns. Pharmacovigilance has a difficult and crucial role in these decisions. Decisions predicated strongly on affordability may lead to using less effective and perhaps more harmful drugs, and the consequence of this may itself be a burden on the economy.

Two examples are illustrative. One is the treatment of HIV/AIDS. The balance between choosing effective and cheap first-line drugs is difficult enough, but the more difficult decisions relate to the choice of second-line drugs, not only in an individual case but also to decide when a first-line drug has such reduced effectiveness that it must be replaced for the broader public health purpose. The latter decision requires continuous monitoring for population effectiveness and then a decision as to the cheapest, most effective, safest, appropriate drug as a replacement. Due to the lack of monitoring and pharmacovigilance in many countries where the disease is most prevalent, it is difficult to get this information. Lack of monitoring also makes it difficult to manage complications of the disease and its drug treatment; without a level of medical supervision that is not possible in many situations, much useful information will go unknown. More than this, the adverse effects of treatment may well be dissimilar in different genetic groups and with different, coincident disease burdens, so decisions in one country cannot be directly transferred to another. Some of the particular challenges in HIV/AIDS monitoring are reviewed by Bakare et al.[3]

Another contemporary example of the problems faced over decisions is the use of moxifloxacin in drug-resistant tuberculosis in emerging economies. The WHO recommends its use as a third-line drug, yet no licence exists for this use in the developed world. This poses ethical, legal and practical dilemmas regarding any harm that may be caused by the use of this drug. Who is responsible for collecting case reports or other evidence of harm and reporting them within the global pharmacovigilance network? Is the manufacturer responsible? WHO? The national regulator? Who does the healthcare professional report to? Is that healthcare professional responsible for off-label prescribing?

2. The International Context of Pharmacovigilance

The international influences of pharmacovigilance on national centres in emerging economies is very significant both for good and ill. The examples above can also be used to demonstrate this, since most of the drugs are donated or subsidized in some way. Global manufacturers have a responsibility to collect and report instances of harm caused by their products internationally, so they may feel they must interact with pharmacovigilance centres in emerging economies in order to fulfil their obligations.

Both manufacturers and donors require national pharmacovigilance systems to actively contribute information, although often at the same time as helping with the development of national pharmacovigilance programmes. However benign these pressures may be there is a danger of distorting the focus of national centres' work away from overall vigilance and national health priorities in order to fulfil the needs of the major providers, particularly of new drug products on that market. This can clearly include trying to fulfil the strictly enforced reporting timelines of the International Conference on Harmonisation countries. There may also be pressures involved in the donations for large public health programmes to report any harm or risks identified in a certain way, to collect specific case material, and other requirements. From the donors' perspectives these may seem reasonable and even minor requests, but they all take time and resources. A more sinister feature I am aware of is occasions when some donors collect and use data without the national centre being fully involved in decisions that are made. This may happen at a national level or perhaps internationally when collected data to which they have contributed is involved. This should never happen since it completely undermines the authority and development of national pharmacovigilance.

When pharmacovigilance centres in emerging economies do need to make decisions on drugs, perhaps to change product information there may also be resistance to adding warnings that are not in the pharmaceutical company's international core data sheet or indeed in the Summary of Product Characteristics (SPC) used in the developed world. I have always felt that the idea of *standardization* of the SPC and patient information should not be a rigid goal. What is much more useful is that *harmonization* should be the aim where local ethnic issues (that include the whole society and healthcare context) are taken into account when producing guidance and communicating with healthcare professionals and patients. It should be clear that patient information in particular should be very carefully thought out, not only in content but the medium of delivery.

Perhaps more important is the availability of various drugs with some significant risk when those drugs are on open sale. This is a major challenge to pharmacovigilance because of the increased chance that patients will fail to recognize a drug-related problem, or indeed jump to a false causal association. The coinciding absence of ready health professional consultation may mean an increased chance of a significant adverse drug reaction (ADR) being misinterpreted or missed altogether.

When a drug is considered for a warning or indeed taken off the market in the developed world, this nearly always causes problems for pharmacovigilance staff in emerging economies. Often this is because there is no advanced warning, perhaps the pharmacovigilance centre will even be unaware of a problem before the news reaches the general media in emerging economies. Inevitably, questions may be asked about why a particular drug is still on the market in emerging economies when it is not in use in the developed world. This situation can also arise with older drugs that may have fallen out of use in the developed world for a variety of reasons. The problem for pharmacovigilance staff in emerging economies is that they may be ill-equipped with access to the media, including the social media, and in any case they need to find out exactly why decisions have been made in order to judge the necessity to act in their own jurisdictions.

3. Prevalent Safety Issues in Pharmacovigilance in Emerging Economies

That many drugs are on open sale in some countries might clearly lead to a greater chance of medication errors of one kind or another (although this might be difficult to prove!). Patient errors can dominate and those errors might not be reported in full when the patient has an adverse effect. Root-cause analysis is a useful tool in investigating these many cases of medication errors that are seen in emerging economies. Therefore, both recognized and unreported medication error adds to the complexity and nature of pharmacovigilance professional practice.

The too-frequent matter of substandard/spurious/falsely labelled/falsified/counterfeit (SSFFC) drugs is another area that makes pharmacovigilance in emerging economies different from that in the developed world. Whilst SSFFC happen in the developed world, the relative lack of regulatory control and quality monitoring facilities in emerging economies means that reports of drug inefficacy, and indeed outbreaks (clusters) of adverse effects, are often reported to the national pharmacovigilance centre. These cases will require very careful follow-up and analysis, perhaps without readily available laboratory analytical back-up.

New drug products often come into an emerging economy via the private healthcare sector or as drugs for use in public health programmes. In the former situation, with health professionals and patients being on an upward 'learning curve', problems may occur as in any country, but reporting in emerging economies may be infrequent or absent until there is general media coverage and a drug safety crisis occurs: crises are always challenging to handle!

In public health programmes the new drugs might be used for the first time for clinical treatment or prevention and the drugs may be used for illness not seen in the developed world. In most emerging economy countries, case harm reports will not be made at all often enough, in a timely enough fashion, nor in enough detail to prevent major public health consequences should a drug be found to cause harm. The WHO is promoting

cohort event monitoring in such situations, allowing for both safety and efficacy to be assessed. This requires staff in areas where the drug may be used to collect the relevant information.[4] This is special work that requires coding and data management skills. Fortunately, this resource is increasingly provided by the donor organizations. Nevertheless, public information, training and other services (e.g. data analysis and interpretation) must involve pharmacovigilance centres.

There are many other considerations in emerging economies that are general problems to be overcome, affecting everybody and every sector of the community. I will not even attempt to catalogue those.

4. Conclusions

This has been a very limited attempt to draw some picture of the differences between pharmacovigilance work in the developed world and those in emerging economies. Those in the developed world might consider how they may help make the way of those in emerging economies a little easier. Readiness to share information, both in general and over specific matters, is a good starting place. Sharing information must mean as complete openness as is possible, with no reluctance to indicate where decisions might not have been easy. This is important since nuances might be important in making a decision in a different setting. At least there could be prior notice of major drug regulatory decisions made available through the WHO network. This certainly happens now, but perhaps it could be improved in information content and consistency.

Through the WHO Programme for International Drug Monitoring and with the support of the WHO-UMC, the WHO has tried to organize 'twinning' between the developed world and pharmacovigilance centres in emerging economies. This twinning has not happened all that often, but where it has, it has usually been successful. It has certainly aided the use of global tools and processes in pharmacovigilance. The Programme also organizes training programmes and provides many other services and tools via the UMC. The WHO annual meeting for all national pharmacovigilance centre representatives is a valuable forum meeting for exchanging ideas.

This leads me to a final thought. There are many ways that centres in the developed world can help emerging economies. The opposite is also true. Initiatives in exploring medication error, better patient communication and patient reporting, considering ways of finding out about SSFFC drugs, audit of pharmacovigilance centre performance, and even smart phone and social media reporting of ADRs have all been ideas either generated or more keenly pursued in emerging economies than in the developed world.

Emerging economies have a different view of the world, and with resources they will add even more knowledge and wisdom to pharmacovigilance as they face and overcome their dilemmas.

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