Reduction of deaths after drug labelling for risk of Reye's syndrome

SIR,—The debate about the effectiveness of drug labelling should consider one recent public health success—labelling of aspirin for the risk of Reye's syndrome.[1] First proposed in 1981 by the Centers for Disease Control (CDC), such labelling eventually took place in 1986. Recent data on the prevalence of this disease reveal that over ten times more deaths occurred before aspirin was labelled for this risk than afterwards and incidence dropped more than ten-fold.

By the early 1980s, clinicians had reached a consensus that use of aspirin for fever during acute viral infections such as chickenpox caused the fairly rare Reye's syndrome, which was fatal in 33–40% of all cases.[2,3] The CDC forwarded its recommendations that aspirin be labelled about this risk to the Commissioner of the Food and Drug Administration (FDA) in November, 1981.

After a lawsuit filed by the American Public Health Association and Public Citizen in the USA in September, 1982, the Secretary of Health and Human Services Richard Schweiker signed proposed regulations for the FDA requiring that aspirin should be labelled with a warning that use during influenza or chickenpox infections conveyed a risk of Reye's syndrome. Final regulations on this labelling were not issued until June, 1986, after a US Court of Appeals review that the record "strongly suggests that the pace of agency decision-making is unreasonably dilatory", and the Congress threatened mandatory legislation.

PREDOMINANT INFLUENZA STRAINS, REPORTED CASES OF REYE'S SYNDROME (RS) AND VARICELLA-ASSOCIATED RS, RS INCIDENCE, AND RS FATALITY RATE, USA, 1974 and 1977–1989*

Year†	Predominant influenza strains Jan-May	RS			
		Total	Varicella associated	Incidence‡	Case fatality rate (%)
1974	B	379	—	0·6	41
1977	B	454	73	0·7	42
1978	A(H3N2)	236	69	0·4	29
1979	A(H1N1)	389	113	0·6	32
1980	B	555	103	0·9	23
1981	A(H3N2)	297	77	0·5	30
1982	B	213	45	0·3	35
1983	A(H3N2)	198	28	0·3	31
1984	A(H1N1)+B	204	26	0·3	26
1985	A(H3N2)	93	15	0·2	31
1986	B	101	5	0·2	27
1987	A(H1N1)	36	7	0·1	29
1988	A(H3N2)	25	4	0·0	45
1989	A(H1N1)+B	25	3	0·0	42

*Continuous RS surveillance began in December, 1976
†RS reporting year begins Dec 1 of previous year
‡Per 100 000 US population <18 years of age (US Bureau of the Census data)
Source, ref 4.

The warning label in the US now reads: "Children or teenagers should not use this medicine for chickenpox or flu symptoms before a doctor is consulted about Reye's syndrome, a rare but serious illness reported to be associated with aspirin". Recently released data from the CDC record the positive impact of this labelling. The table shows that the number of cases and the incidence began to fall shortly after medical journals first reported the association between aspirin use and Reye's syndrome.[4] But the lowest rates were achieved only after labelling began, in 1986.

The CDC estimates that about 20% of all cases are recorded under its surveillance system and that between 33% and 40% of these are fatal (Dr Ali Khan, personal communication, Division of Viral and Infectious Diseases, CDC, 1992). On the basis of these assumptions, between 1981 and 1986 about 5025 cases would have occurred, with 1005 reported. After labelling was in place, the number of cases fell by more than ten times to 28 a year (140 projected), which would mean about 46 deaths. This small number is thought to indicate inborn genetic metabolic errors and not to be associated chiefly with aspirin use.[5]

Thus, delays in labelling aspirin have had a measureable effect on public health. During the 5 years that labelling was under consideration, about 1700 deaths due to Reye's syndrome occurred, whereas only about 230 would have been expected if labelling had been in place during this same period. These 1470 excess deaths are especially tragic, because they were, typically, healthy children who never recovered from viral infection or chickenpox. For rare preventable diseases such as Reye's syndrome, opportunities for labelling should be pursued with all vigour internationally, because this policy can save lives.

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Recall of therapeutic devices in Australia

SIR,—Peter Harrigan's report in your Aug 29 (p 543) issue is misleading in some respects. Regulatory controls on therapeutic devices in Australia have developed since 1984 and are now quite comprehensive by world standards. However, as for most countries, we do not have the resources to, as Harrigan says, strictly evaluate all devices before registration.

Only eight classes of therapeutic device are subject to pre-market evaluation with respect to quality, safety, and efficacy. These are: powered drug infusion systems, intraocular lenses, intrauterine contraceptive devices, pacemakers, heart valves, visco-elastic intraocular fluids, materials of animal and human origin, and, most recently, breast implants. Although the manufacture of sterile devices, contraceptive devices, and some others is subject to compliance with good manufacturing practice and mandatory standards, most devices, including electromedical devices, have only to meet minimum requirements, and labelling is one of these.

An examination of Australian recalls for 1991/92 shows that only 8 of the 144 were in relation to devices of a type that are subject to pre-market evaluation:

Device	*No*
Implantable cardiac pacemakers and their implantable accessories	6
Intraocular lenses	1
Powered drug infusion systems	1

Whether or not these recalled devices were actually evaluated depended on whether their entry into the market predated the evaluation programme. The occurrence of several recalls for evaluable devices is, however, not surprising since it is known that some 50% of in-service failures cannot reasonably be prevented by pre-market evaluation.

Harrigan also refers to the need for export certificates. These are required for export only products but are more usually supplied on request for locally manufactured devices that have been properly entered on the Australian Register of Therapeutic Goods. Certificates of free sale are also provided for the exportation of imported products and goods that are not in legislative terms regarded as therapeutic goods. These mechanisms assure importing countries that the goods they receive are of a standard equivalent to those supplied in Australia.

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Maasai diet

SIR,—The international aid and donor community is becoming increasingly aware of the central role of research in the planning and preparation of health initiatives. This is particularly relevant in populations who are subjected to cyclical drought and famine.

Without such research, important variations and changes might not be detected, and longstanding assumptions could blind us to actual behavioural trends and patterns. One such assumption is the belief that traditional pastoralists maintain a diet essentially of meat, blood, and milk, which may not necessarily be so. During a recent evaluation of certain community-based health programmes among the pastoral Maasai, we noted a high prevalence of trachoma blindness. This finding prompted the thought that vitamin A deficiency might be contributing to this tragic state of affairs.

We decided to undertake a dietary survey based on a sample of 514 mothers (286 pastoral Maasai in southern Kenya, 112 pastoral Maasai in northern Tanzania, and in northern Kenya 68 pastoral Samburu and 48 Randille), between March and May, 1992. The data derive from tape-recorded interviews that sought to discover what a family had eaten in the previous 24 h. Translation was undertaken by Maasai speakers who were not part of the interviewing team.

The main items of diet were white maize (434 mothers), tea (365), milk (362), rice (174), and beans (121). Traditional items were rarely eaten, although they were more common among the Samburu and Rendille than the Maasai—ie, meat (29), blood (42), wild animals (24). Yellow maize, a potentially important source of vitamin A, was only mentioned by 34 mothers. Milk, another important source, although retinoid content varies with season, was not mentioned by 30% of mothers.

These data are preliminary and are at best an indicator for further investigation. Careful study of nomadic and semi-desert populations would provide important information on dietary patterns and changes in eating habits. It may be that pastoral populations in areas of successive droughts are modifying their eating habits. Should this be the case, important questions concerning strategic planning, aid, and development priorities would arise.

If there is a major shift among populations at risk towards cereals away from blood, milk, and meat, this may indicate not only the effects of persistent drought but also changing culture and ecosystem transition. Yellow maize may be generally regarded as animal feed and not suited to man, yet it is a much richer source of retinoids. Any absence of milk from the traditional diet might also be important. We plan, despite the difficulties, a survey of serum vitamin A concentrations that will provide a more definitive answer to the possibility that deficiency exists in such population.

This study was part of a community-based health programme funded by Comic Relief (UK).

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Reporting side-effects

SIR,—Your report (Oct 3, p 845) summarised many of the individual points we made at the London seminar about the challenges of adverse drug reaction (ADR) monitoring across Europe but did not give our main conclusions. Differences in the way in which drugs are used in different countries, for different indications, by different routes, and in different populations may all add to the chance of finding a signal of concern about a drug's safety. Every situation carries the potential for something new to be found. The data we presented showed that there were clear differences between reporting of ADRs between countries and that we have only limited information about why such differences exist. Those mentioned are only a few of those possible.

Interpretation of signals is always a matter of debate because the first intuitions reflected in a few spontaneous reports are usually suspicions only and need validation by other methods. Your report mentions our concern that expeditious methods of signal follow-up are less than ideal in Europe. We strongly urged the development and support of systems such as prescription event monitoring. Together with information about drug use these should be able to shed light on international differences in ADR reporting.

We also concluded that where a gold standard for methodology is discernible, harmonisation may allow us to reduce unnecessary variables that cause inefficiencies. Differences in definitions and ADR terminology and requirements for data storage and exchange, for example, are currently receiving attention. We were, however, against forced harmonisation where there are defensible differences in approach; in these circumstances "vive la différence" and let us strive to find out objectively which method gives what result and then try to decide which is best and in what circumstances.

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Availability of information about AIDS

SIR,—Dr Najera and Dr De Andres (Sept 12, p 677) report their initiative in providing information on AIDS in Spanish. We should, however, point out that in 1988, before the Spanish AIDS Society's publication, this Bureau was contracted by the Global Programme on AIDS of the World Health Organisation to produce the *WHO AIDS Technical Bulletin*, including 3–4 extended précis similar to those in *Morbidity and Mortality Weekly Report*, 12 or so critical abstracts, 40–50 annotated bibliographic entries each month, and covering reports on many and varied topics. This information was published in English, French, and Spanish. WHO distributed the editions widely, with 12 000 copies in English, 5000 in French, and 3000 in Spanish. For budgetary reasons WHO phased out the Spanish edition in 1990 and this year transferred its support, but at a reduced level, to the Bureau's *Current AIDS Literature*, which it is distributing mainly to the researchers it supports in developing countries.

The Bureau's AIDS database is an effort to overcome the shortcomings that Najera and De Andres identify in MEDLINE. We scan many non-English sources, from all parts of Europe, the former USSR, Africa, Latin America, and Asia, to identify information on HIV/AIDS, giving special emphasis to public health aspects. Large areas of the world that will have to bear the greatest burden of AIDS are still not served well by information services about this subject (often because of lack of foreign currency to buy Western services), and we note that the Spanish information is being distributed predominantly in Spain, with only 200 copies being distributed in Latin America. Francophone and Anglophone, Africa and central and eastern European countries and Asia also need information. We are unable to satisfy the demand, and have to charge for the information provided. The Bureau is engaged in talks with public health authorities in Poland and Czechoslovakia about making its AIDS information services available in those countries, and we are seeking funding.

We regret that, especially in times of economic recession, the information component of research and research proposals is the first to be pruned. The collection, analysis, and dissemination of information is labour-intensive and costly (and paradoxically MEDLINE, produced in the home of the market economy, is heavily subsidised). We urge funding bodies to give urgent consideration to greater support of information services in HIV/AIDS, in both preventive and research programmes.

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Transmission of HIV-associated tuberculosis to health-care workers

SIR,—Dr Di Perri and colleagues (Sept 12, p 682) report that the rate of clinical tuberculosis in health-care workers (HCW) caring for HIV-infected patients with tuberculosis was significantly higher than the rate in HCW caring for HIV-negative tuberculosis cases. However, they provide no information on the prevalence of HIV in HCWs who cared for HIV-infected patients, the rate of recent tuberculosis infection in HCWs, or the environmental and other infection control practices in the three divisions of infectious diseases wards and the division of pneumology wards.

In the USA, HIV-infected HCWs commonly volunteer to provide care for HIV-infected patients. Thus, a high proportion of