

repeated challenges of allergen could result in an enhanced mediator release from an influx of inflammatory cells and a symptomatic response to further allergen exposure.⁴ Fourth, it is known that hypersensitivity reactions—eg, those after Hymenoptera sting,⁵ are not always reproducible. Therefore, it may be possible that in rare circumstances, allergic patients do not react to the offending foods. Subsequently, false-negative food challenges may also be the expression of one end of the range of reactions which occurs during “natural” exposure to foods.

We noted that after false-negative food challenges, the first administration of the food at home provoked mild immediate-onset symptoms. Since the use of oral food challenges to diagnose food allergy is growing, an increased frequency of such reactions may be anticipated. Our findings suggest that children should be fed openly under observation the day after a negative food challenge, to identify those with an immediate reaction. If this is not possible, parents should receive adequate instructions about the recognition and treatment of immediate-onset reactions.

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Prescription-event monitoring and reporting of adverse drug reactions

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Newly marketed drugs in the UK are marked with a black triangle, indicating that doctors should report all adverse drug reactions associated with them to the Committee on Safety of Medicines (CSM). However, under-reporting of adverse reactions is frequent. Our aim was to establish what types of adverse reactions are under-reported to the CSM by family doctors who work in England. We used prescription-event monitoring data obtained for 15 newly marketed drugs. Only 9% (376) of 4211 events found on prescription-event monitoring were reported to the CSM. However, 53% (27) of 51 events classified as serious adverse drug reactions were reported. Overall, serious events were five times more likely to be reported to the CSM than non-serious events. Our results should not be extrapolated to calculate incidence rates of adverse drug reactions in the community from spontaneous reports.

Lancet 2001; **358**: 1872–73

Schemes for spontaneous reporting of suspected adverse drug reactions have an important role in identifying such

Definition of serious adverse event by International Conference on Harmonisation⁵

A serious report is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires hospital admission or prolongation of stay in hospital
- Results in persistent or great disability, incapacity, or both
- Is a congenital anomaly, birth defect, or both*

*Not included in the British National Formulary definition used in the previous study, however, no reports of congenital anomalies were coded as adverse drug reactions.

effects not seen in premarketing trials. In many instances, regulatory and public-health decisions have to be made on the basis of data from spontaneous reports.¹ Although such schemes are useful to safeguard public health, they have several weaknesses, including under-reporting.² Data from prescription-event monitoring have been assessed by the Drug Safety Research Unit (DSRU), which has reported that there is under-reporting of suspected adverse drug reactions for newly marketed (black triangle) drugs prescribed in general practice in England.³ In the UK, new products are identified by an inverted black triangle on product information usually for the first 2 years of marketing. The Committee on Safety of Medicines (CSM) requests that doctors, dentists, coroners, and pharmacists report all suspected reactions that could conceivably be attributed to these black-triangle drugs. For established products, the CSM asks only to be informed of serious or unusual suspected reactions.

The DSRU monitors the safety of selected newly marketed medicines in general practice by prescription-event monitoring. Since the first study on under-reporting in 1997, 15 such studies have been done on drugs that have not subsequently been withdrawn from the market. During this period, the Medicines Control Agency (MCA) encouraged doctors to report adverse drug reactions, for example, through reminders printed in their publication *Current Problems in Pharmacovigilance*. The aim of our study was to investigate whether under-reporting of suspected adverse drug reactions by family doctors to the CSM also took place for these 15 drugs.

Prescription-event monitoring is a well-established, non-interventional, observational cohort technique of postmarketing surveillance, the methods of which are described elsewhere.⁴ Patients were identified from National Health Service prescriptions dispensed in

Type of adverse reaction	Adverse drug reactions stated on green form	Adverse drug reactions also reported to CSM	Risk ratio (95% CI)
Not serious	3110 (74%)	326 (11%)	..
Labelled	1432 (34%)	125 (9%)	Reference
Unlabelled	1678 (40%)	201 (12%)	1.4 (1.1–1.7)
Serious	51 (1%)	27 (53%)	6.1 (4.5–8.3)
Labelled	12 (0.3%)	7 (58%)	6.7 (4.0–11.1)
Unlabelled	39 (1%)	20 (51%)	5.9 (4.1–8.3)
Total not serious and serious	3161 (75%)	353 (11%)	..
Not categorised	1050 (25%)	23 (2%)	..
Total	4211 (100%)	376 (9%)	..

Data are number (%) unless otherwise stated.

Suspected adverse drug reactions reported by family doctors during prescription-event monitoring studies 1997–2000

England. We then sent questionnaires (green forms) to the prescribing doctor, requesting information on any events that had taken place since the patient had been taking the drug, and also whether the events had been reported to the CSM. We used the data to ascertain what types of adverse drug reactions are under-reported to the CSM.

The prescription-event monitoring studies were completed between 1997 and 1999. The 15 drugs examined were mirtazapine, donepezil, montelukast, tolterodine, valsartan, eformoterol, olanzapine, tamsulosin, pantoprazole, alendronate, fexofenadine, meloxicam, nefazodone, valaciclovir, and nicorandil. Median exposure was 69 642 (IQR 44 637–83 632) patient-months. We assessed questionnaires with events coded as suspected adverse drug reactions. Events were classified as serious or non-serious, by the International Conference on Harmonisation definition (panel).⁵ Because of lack of information, we did not categorise reports on which doctors had written only “unspecified side-effects” or “intolerance”, nor did we include in our analysis questionnaires that were not returned or were miscoded. Two independent research fellows at the unit (EH, JR) classified the results, and a third member of the research staff assessed any discrepancies. We classified every adverse reaction as labelled, if it was listed in the summary of product characteristics at the time that the drug was launched, or unlabelled.

4211 events were coded as suspected adverse drug reactions. The 3161 events classified as serious or non-serious arose in 2039 patients (1371 women, 661 men, and seven unknown). Doctors had reported 376 of the 4211 events (9% [95% CI 8.0–9.8]) to the CSM. This reporting rate is similar to the 9% previously published by the DSRU,³ suggesting that there has been no change in the overall reporting of adverse drug reactions to the CSM (χ^2 test $p=0.89$). However, a higher proportion of serious reactions were reported to the CSM in this study (53% [39–67]) than in a previous study³ (23% [16–30]; χ^2 test $p=0.01$).

The highest proportion reported was for serious labelled reactions and the lowest for non-serious labelled reactions. Reporting rates of serious labelled and serious unlabelled reactions did not differ (Fisher exact test $p=0.51$). By calculating a risk ratio, using non-serious labelled events as the reference group, we identified the likelihood of each category of adverse reactions being reported to the CSM. Serious labelled and unlabelled reactions were at least five times more likely to be reported to the CSM than non-serious labelled reactions (table).

Data from prescription-event monitoring studies suggests that there is both selective reporting and under-reporting to the CSM. Family doctors who returned questionnaires reported a greater proportion of suspected serious reactions, and the proportion of suspected serious adverse effects reported to the CSM seems to have doubled, although numbers are small. Our estimates are still subject to potential biases, including coding conventions at the DSRU, response rate, selective reporting, recall, and misunderstanding of the difference between the CSM yellow-card spontaneous-reporting scheme and the prescription-event monitoring green forms. A further bias is the random variation of the drugs investigated, since there is an association between reporting rate to the CSM and drug for both this and the previous study (χ^2 test $p<0.001$). The average reporting rate between the two studies did not differ (χ^2 test $p=0.965$).

Our results suggest that family doctors are five times more likely to report serious events on black-triangle drugs than non-serious labelled events, irrespective of whether

the serious event is labelled or not. This finding raises the question of whether doctors are fully aware of the meaning of the black triangle, whereby all suspected adverse drug reactions should be reported to the CSM. What is apparent is that the yellow-card scheme run by the CSM has been improved in its effectiveness to detect serious reactions. Prescription-event monitoring continues to show its effectiveness to detect all kinds of adverse reactions (serious and non-serious), especially adverse events that the doctor does not necessarily attribute to the drug. Furthermore, prescription-event monitoring studies do not take into account reactions reported by doctors and pharmacists based in hospitals.

We thank the family doctors who voluntarily took part in prescription-event monitoring studies, Cheryl Key and Andrew Boshier for resolving discrepancies on classifications of events, and Gillian Pearce for retrieval of data. EH was funded by a research grant from AstraZeneca Foundation. The Drug Safety Research Unit is a registered medical charity, which receives unconditional donations from several pharmaceutical companies. These companies have no say in the conduct of studies and have no statistical or editorial control over the analysis or reporting of results.

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Severe reactions to filarial chemotherapy and release of *Wolbachia* endosymbionts into blood

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***Wolbachia* bacteria seem to have evolved as essential endosymbionts of their filarial nematode hosts. Studies in mice have suggested that these bacteria are associated with systemic inflammatory reactions to filarial chemotherapy. We took blood samples from 15 Indonesian patients before and after treatment with diethylcarbamazine for *Brugia malayi* infection, and recorded the severity of any post-treatment inflammatory reactions. Blood from all three patients with severe adverse reactions and from one of six with moderate reactions was positive for *Wolbachia* DNA 4–48 h after diethylcarbamazine treatment. We suggest that these severe inflammatory reactions are associated with the release of endosymbionts into the blood after treatment for filariasis.**

Lancet 2001; **358**: 1873–75

Lymphatic filariasis affects more than 120 million people throughout the tropics. The disease is caused by two