STATISTICS IN MEDICINE
Statist. Med. 2002; **21**:2027–2044 (DOI: 10.1002/sim.1157)

On the assessment of adverse drug reactions from spontaneous reporting systems: the influence of under-reporting on odds ratios

Peter G. M. van der Heijden[1,2,*,†], Eugène P. van Puijenbroek[3], Stef van Buuren[1] and Jacques W. van der Hofstede[1]

[1]*TNO Prevention and Health, Leiden, The Netherlands*
[2]*Department of Methodology and Statistics, Utrecht University, Postbus 80140, 3508 TC Utrecht, The Netherlands*
[3]*Netherlands Pharmacovigilance Foundation Lareb, Goudsbloemvaki 7, 5237 MH Den Bosch, The Netherlands*

SUMMARY

A well-known problem in spontaneous reporting systems (SRSs) for adverse drug reactions (ADRs) is under-reporting, that is, the problem that not all occurrences of ADRs are reported to the SRS. We look at the question of how to draw statistical conclusions from analyses of SRS data using reporting odds ratios. We will show that certain under-reporting problems play no role in assessing ADRs from SRSs: the results from the analyses turn out to be biased by some specific under-reporting problems, but not by others. SRS data can be particularly useful for the assessment of drug–drug interactions. If the assumption holds that there is an under-reporting problem for a first drug, and an under-reporting problem for a second drug, but that these two under-reporting problems do not influence each other, then reporting odds ratios estimated from SRSs are useful for signalling drug–drug interactions in the ADR-experiencing population. Similar results hold for covariate–drug interactions. We illustrate our results using two examples. Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS: spontaneous reporting system; under-reporting; adverse drug reactions; pharmacovigilance

1. INTRODUCTION

Before marketing a new drug, many adverse drug reactions (ADRs) may either be suspected from chemical similarity to known drugs or detected in clinical trials. In these trials, drugs are used in a selected, rather small, population [1]. Detection of ADRs in clinical trials is hampered by the fact that rare ADRs and ADRs with a long time to onset are difficult to detect. Since trials are carried out under controlled circumstances, the detection of ADRs in specific

*Correspondence to: Peter G. M. van der Heijden, TNO Prevention and Health, P.O. Box 2215, 2301 CE Leiden, The Netherlands
†E-mail: pgm.vanderheijden@tno.pg.nl

Contract/grant sponsor: Dutch Fund for Prevention; contract/grant number: 28.2632

populations, like the elderly, patients with chronic diseases or patients with multiple drug use, are even more difficult to detect. Spontaneous reporting systems (SRSs) are commonly used to detect new or unexpected ADRs after the marketing of drugs. Because of methodological reasons, such as selective under-reporting, SRSs can only be used to signal the possible existence of new or unexpected ADRs. Further (pharmacoepidemiological) studies are needed to evaluate these ADRs in more detail [2–4].

A special case is the detection of drug–drug interactions. Since in clinical trials drugs are used in a specific population, and multiple drug use is often a criterion for exclusion, the detection of drug–drug interactions is more difficult. Until now, a drug–drug interaction is usually detected when it is suspected by a physician or pharmacist, and subsequently reported to an SRS. In daily practice, an interaction between two different drugs is often detected by the occurrence of an ADR. When a patient who already uses one or more drugs is administered another drug, however, it is not always clear if the ADR is caused by the new drug, the drug–drug interaction, or by some other cause. Based on the idea that in the event of drug–drug interactions the chance for an ADR to occur is increased, SRSs can be used to detect such drug–drug interactions [5–7]. It is essential in this respect to compare four different situations: reports of patients who, among all other medication, use both drugs suspected of causing a possible drug–drug interaction; the two situations where only one of the suspected drugs is used, and finally the control situation where neither drug is used.

The amount of absolute under-reporting can be quite large. By comparing the 'true' ADR rate and the reported ADR rate, sometimes only 1 in 70 ADRs were reported [8–10]. Much recent statistical work on the analysis of SRS data [11–13] acknowledges the additional complexities created by under-reporting, but at the same time tends to ignore these complexities in the quantitative analysis. The present paper gives conditions under which this strategy is appropriate.

In this paper we discuss aspects of the statistical study of SRS data, with special attention to the under-reporting problem. We will show that there are different types of under-reporting problems, and that not all under-reporting problems are bothersome in the analysis of SRS data. For the under-reporting problems that can be problematic, we discuss what can be concluded under what type of assumptions. In Section 2 we further motivate the problem by giving three typical examples and do a typical analysis of the SRS data. The question that remains to be answered is what can be concluded from the analysis in the light of under-reporting problems. For each of the typical examples the answer will then be given in a separate section, namely Sections 3 to 5. We summarize and discuss our results in Section 6.

2. MOTIVATING EXAMPLES

Suppose we are interested in the question of whether some specific drug leads to a specific adverse drug reaction (ADR). In the population that takes the drug there is a group of patients who experience this ADR, and there is a group of patients who do not experience this ADR. We are interested in whether the drug is associated with the specific ADR. How can spontaneous reporting systems (SRS) help us to answer this question?

It is clear that usually only some of the patients who take the specific drug and experience the specific ADR report to the SRS. This is called the under-reporting problem. This under-reporting problem can be more or less severe according to the seriousness of the ADR in

relation to the indication for use, the clarity of the causal relation between the drug and the ADR, or due to other possible reasons [8, 10, 14, 15].

SRSs are known for their signalling function. Because of various confounders and under-reporting, a causal relationship cannot be determined. Further studies under controlled circumstances are necessary to demonstrate any possible association. Apart from qualitative aspects of the reports, the number of reports concerning a possible association between a drug and an ADR may also indicate the presence of a true relationship. The number of reports necessary to generate a signal, however, depends on the total number of reports in the database, the total number of ADRs in the database and the number of reports concerning the association.

In SRSs this problem is often tackled by comparing the different profiles of ADRs reported. Usually a cross-classification of all registrations available from the SRS is constructed, that is, not only registrations involving both the specific ADR and the specific drug, but also registrations involving other ADRs and other drugs. Based on this cross-classification, for instance, a reporting odds ratio can be calculated [16, 17]. Another option would be applying a 'proportional reporting ratio', based on the same 2×2 contingency table. This proportional reporting ratio can be considered as a representation of the safety profile of a drug [18]. In other words, other reports in the database provide a proxy of the 'background incidence' of the ADRs. Indeed the under-reporting factors cannot account properly for the size of the exposed population, but regarding the population of patients who actually experience an ADR, the use of the reporting odds ratio may provide a valid estimate. The reporting odds ratio offers advantages in the sense that in a logistic model adjustments for various confounders can be made and statistical interactions between various covariances can be analysed in more detail [15–17, 19].

The Netherlands Pharmacovigilance Foundation Lareb collects and analyses reports of suspected adverse drug reactions from health professionals in the Netherlands. Every report is assessed on a regular basis. However, due to the increasing number of reports, analysis by the human mind alone becomes more difficult and statistical analysis of the data may be helpful. Moreover, a statistical approach enables the identification of more complex relationships like drug–drug interactions and the analysis of syndromes [6, 7]. These reports have a 'spontaneous' character, which implies that reporting of the suspected ADR by a physician or pharmacist is not compulsory. For this reason, under-reporting is inherent in this approach and signals of possible ADRs from SRSs should be considered in this perspective [14, 20]. For every possible association present in the database, the influence of under-reporting on various factors should be carefully weighted. We discuss three examples using data provided by Lareb.

2.1. Diuretics and possible ADRs

Assume that we would like to investigate whether there is an association between the presence of diuretic drugs on the report forms and ADRs possibly representing the presence of congestive heart failure (see Table I).

The suspected ADRs of reports to Lareb are coded by means of the WHO adverse drug reaction terminology [21], drugs are coded according the ATC terminology. A report may be used to report one or more suspected drugs and one or more suspected adverse drug reactions. Between 1 January 1990 and 1 January 1999, a total number of 9822 reports concerning patients older than 50 years were received by Lareb, of which sex of the patient involved and

Table I. C03 presence of a diuretic drug, and congestive heart failure as ADR. Observed frequencies.

Diuretic	Congestive heart failure	
	Absent	Present
Absent	7820	227
Present	1697	78

the type of reporting health professional (physician or pharmacist) were known [7]. A selection was made of WHO preferred terms that might indicate the presence of congestive heart failure. Cases were defined as reports in which one of the following WHO preferred terms were present: oedema; oedema dependent; oedema generalized; oedema peripheral; cardiac failure; cardiac failure left; cardiac failure right; or oedema legs. Non-cases were defined as all other reports. Exposure categories were the presence of diuretics among the medication used (ATC code beginning with C03) versus no diuretics.

A typical way to analyse the data is to fit a model in which the probability of congestive heart failure in the reports where diuretic drugs are present is identical to this probability in the reports where diuretics are absent. This is equivalent to fitting the independence model. This model is rejected (likelihood ratio chi-square is 10.9, d.f. is 1, $p < 0.001$). The observed odds ratio is 1.58 (95 per cent confidence interval is 1.21–2.05), showing that the use of diuretics and signs of possible congestive heart failure are related in the SRS data, which is not surprising, given the fact that diuretics are commonly used in the treatment of congestive heart failure. The reports concerned therefore might either represent the background incidence of oedema or congestive heart failure, or a lack of efficacy of the drugs concerned. Since we are interested in the population of patients that actually uses the drugs in question, we subsequently want to evaluate whether this relation in the SRS data is a close representation of the relation in the ADR-experiencing population? For this we need a better understanding of the under-reporting problem, and we will elaborate this problem in Section 3.

2.2. Drug–drug interaction of diuretics and NSAIDs

Besides generating signals concerning ADRs, databases of SRSs may also be used to generate signals of possible drug–drug interactions or identifying risk factors in patients. Consider the following example. Several case-reports and studies suggest that concomitant use of diuretics and non-steroidal anti-inflammatory drugs (NSAID, ATC code beginning with M01A) can lead to an increased risk of developing signs of congestive heart failure [22, 23], due to a decreased efficacy of the diuretics involved. For the data in Table I we now would like to investigate whether there is an indication of a drug–drug interaction of diuretics and NSAIDs with signs associated with the presence of congestive heart failure [7]. Exposure categories were the use of NSAIDs or diuretics versus the use of neither of these drugs (see Table II).

A typical analysis would again involve odds ratios. The odds ratio for diuretics and congestive heart failure without NSAID prescription is 1.29, whereas this odds ratio with NSAID prescription is 3.04. In a log-linear model with no three-factor interaction these two odds ratios would be restricted to be equal, but such a model fits poorly (LR chi-square is 7.53,

Table II. Two drugs: C03 presence of a diuretic and presence of an NSAID. Congestive heart failure as ADR. Observed frequencies.

NSAID	Diuretic	Congestive heart failure	
		Absent	Present
Absent	Absent	6527	185
	Present	1444	53
Present	Absent	1293	42
	Present	253	25

Table III. Diclofenac as drug, anaphylactic reactions as ADR, and sex as covariate. Observed frequencies.

Sex	Diclofenac	Anaphylactic reactions	
		Absent	Present
Male	Absent	6108	30
	Present	181	11
Female	Absent	10658	61
	Present	331	19

d.f. is 1, $p<0.01$), showing that these two observed odds ratios differ significantly. We conclude that, in the SRS data, taking NSAIDs besides diuretics leads to an increase in signs of congestive heart failure, but what can be said about the ADR-experiencing population? This problem will be addressed in Section 4.

2.3. Sex differences for ADRs of diclofenac

Controlling for covariates is illustrated by a last example. Acute allergic reactions are associated with various NSAIDs including diclofenac [24]. Although these ADRs are mentioned in the Dutch Summary of Product Characteristics, Lareb received a substantial number of reports on anaphylactoid reactions or anaphylactic shock associated with diclofenac. We analysed this association using a case-control design, controlling for sex. All 17 399 reports received by Lareb between 1990 and 1999 of patients older than 10 years were included. All reports were coded using the WHO adverse drug terminology [21]. Cases were defined as all reports coded with 'anaphylactic shock' or 'anaphylactoid reaction'. All other reports were considered as non-cases, see Table III.

The observed odds ratio for males is 12.4 (95 per cent CI is 8.7–17.8) and for females 10.0 (7.6–13.1). These results show that, for males as well as females, anaphylactic reactions are disproportionally reported on diclofenac as compared to other NSAIDs, which would suggest an increased risk of these reactions during the use of diclofenac.

By fitting the log-linear model without interaction term for sex by drug by ADR, we investigate whether the two observed odds ratios differ significantly. The likelihood ratio chi-square is 0.22 (d.f. is 1, n.s.) showing that the data do not provide evidence for a difference.

Table IV. The under-reporting problem in data from a spontaneous reporting system.

Specific drug	Specific ADR	
	Absent	Present
Absent	n_{11}	n_{12}
Present	n_{21}	n_{22}

The estimated odds ratio estimated in this way is 10.8, but in what way might under-reporting influence these results? This will be discussed in Section 5.

3. THE UNDER-REPORTING PROBLEM FOR ONE DRUG

3.1. Theory

We will now discuss the question raised at the end of Section 2.1: in what way does under-reporting distort the relation between estimates from the SRS data and the ADR-experiencing population? Table IV will help to answer this problem.

Assume a variable 'specific ADR' (for example, congestive heart failure) having levels 'present' (in report) and 'absent'; assume further a variable 'specific drug' (for example, diuretics) having levels 'present' (in report) and 'absent'. Table IV shows the observed counts in the SRS population, denoted by n_{ik}, where $i = 1, 2$ indexes the levels of the specific drug, and $k = 1, 2$ indexes the levels of the specific ADR. Naturally, the number n_{11} is in most cases much greater than the other three numbers, since this embraces all the reports where neither the specific drug nor the specific ADR play a role (compare Table I). If the specific ADR is more common with the specific drug than with other drugs, one would expect $n_{22}/(n_{21} + n_{22})$ to be larger than $n_{12}/(n_{11} + n_{12})$.

When looking for ADRs in the SRS population, a relative high count of an ADR reported for a certain drug is used as a signal for a more detailed study. However, different forms of under-reporting have effects on these numbers. Therefore we want to know in what way the elements in Table IV, showing the information in the SRS population, provide us with information of the ADRs in the ADR-experiencing population.

It is clear that, since we have four frequencies in Table IV, each of the frequencies is plagued by under-reporting. Thus we could say that there are four under-reporting problems, one for each frequency. However, it is more insightful to approach these four under-reporting problems differently, namely by distinguishing between four separate processes that cause these four frequencies to be under-reported. We distinguish four types of problems of under-reporting:

(i) There is an overall under-reporting problem, which pertains to all cells of Table IV.
(ii) There is an under-reporting problem for the specific drug compared to the other drugs, in the sense that the overall factor in (i) does not show that for some drugs the under-reporting problem is more severe than for others. For instance, recently introduced drugs are more likely to be reported. Media attention might also increase the reporting rate of a specific drug.

(iii) There is an under-reporting problem for the specific ADR compared to the other ADRs, in the sense that the overall factor in (i) does not show that some ADRs are more often reported than others. For instance, death due to a serious allergic reaction is more likely to be reported than mild gastro-intestinal side-effects.

(iv) There is an under-reporting problem for each combination of levels of the specific ADR and the specific drug that describes a deviation from the overall effect (i), the specific drug effect (ii) and the specific ADR effect (iii). For instance, hair loss caused by chemotherapeutic drugs is a commonly occurring ADR, that is rarely reported. The ADR is more easily accepted by physicians and patients because of the necessity for the use of these drugs. Hair loss is a relatively rare ADR of terbinafine [18]. Since this antifungal drug is used frequently for onychomycosis, which is usually a cosmetic indication, the occurrence of hair loss is reported relatively frequently to Lareb. Under (iv) therefore it is the severity of the ADR compared to the severity of the indication that seems to play a role.

We will now explore this further using appropriate notation. We distinguish the ADR-experiencing population, for which we will denote the true frequencies by t_{ik}, from the SRS population, for which we will denote the expected frequencies by m_{ik}. Thus the observed frequencies n_{ik} are realizations of the expected frequencies m_{ik} from the SRS population, but not from the ADR-experiencing population. The problem that we study in this paper is that we would like to make statements about the ADR-experiencing population on the basis of the SRS population. The question is: under what assumptions are we allowed to do this?

We assume that the true frequencies t_{ik} from the ADR-experiencing population are related to the expected frequencies m_{ik} from the SRS population by the four under-reporting problems (i) to (iv). There are different ways to work out this relation in mathematical terms. We use deviation coding, which leads to the following notation:

(a) the general effect (i) will be denoted by an overall under-reporting factor c that is identical for each of the four frequencies. That is, when we go from the ADR-experiencing population t_{ik} to the SRS population with elements m_{ik}, each element t_{ik} has to be multiplied with c;
(b) the drug effect (ii) will be denoted by c_{d} if the specific drug is present and $1/c_{\mathrm{d}}$ if not (note that the product of c_{d} and $1/c_{\mathrm{d}}$ equals one);
(c) the ADR effect (iii) will be denoted by c_{a} if the specific ADR is present and $1/c_{\mathrm{a}}$ if not;
(d) the effect for the combination (iv) will be denoted by c_{da} if both the specific drug and ADR are present. In order to let the product of combination effects over the rows and over the columns equal one, the effect for ADR present and drug absent, and ADR absent and drug present, will both be $1/c_{\mathrm{da}}$, and the effect for both ADR and drug absent by c_{da}.

In Table V the expected frequencies m_{ik} of the SRS population are expressed in terms of the true frequencies t_{ik} of the ADR-experiencing population taking the four under-reporting problems into account. Table V shows that the expected frequency m_{22} in the SRS population is related to the expected frequency t_{22} by $m_{22} = cc_{\mathrm{d}}c_{\mathrm{a}}c_{\mathrm{da}}t_{22}$.

Using the data from an SRS we are unable to estimate the constants $c, c_{\mathrm{d}}, c_{\mathrm{a}}$ and c_{da} to derive the true frequencies of the ADR-experiencing population. We will now look at the way

Table V. One drug. Expected frequencies m_{ik} for the SRS population, expressed in terms of true frequencies t_{ik} used for the ADR-experiencing population.

Specific drug	Specific ADR	
	Absent	Present
Absent	$\frac{cc_{da}}{c_d c_a} t_{11}$	$\frac{cc_a}{c_d c_{da}} t_{12}$
Present	$\frac{cc_d}{c_a c_{da}} t_{21}$	$cc_d c_a c_{da} t_{22}$

these unknown constants bother us when we want to determine from SRS data whether the specific drug causes the specific ADR in the ADR-experiencing population.

Let us assume that we want to study a possible relation between the specific drug and the specific ADR by estimating the odds ratio from observed counts derived from a SRS. In what way would this estimate provide a biased account of the odds ratio in the ADR-experiencing population? The odds ratio θ^t for the ADR-experiencing population is

$$\theta^t = \frac{t_{11} t_{22}}{t_{12} t_{21}} \tag{1}$$

and when we derive the odds ratio θ for the SRS population by using the relations provided in Table V, many of the constants vanish:

$$\theta = \frac{m_{11} m_{22}}{m_{12} m_{21}} = (c_{da})^4 \frac{t_{11} t_{22}}{t_{12} t_{21}} = (c_{da})^4 \theta^t \tag{2}$$

This shows that estimate θ for the SRS population gives a biased account of the odds ratio of interest θ^t due to c_{da}, that is, combined effect (iv). The under-reporting problems (i), (ii) and (iii) are not important if odds ratios are used. This is not surprising given the well-known property of the odds ratio that it is insensitive to marginal changes in a two-way contingency [25]. In the context of under-reporting in SRSs, some others have already noticed this [16, 26].

Without detailed knowledge of the subject matter, it is difficult to say for particular applications whether $c_{da} = 1$, $c_{da} > 1$ or $0 < c_{da} < 1$. It should be borne in mind that the factor c_{da} should be interpreted as a factor which corrects the more general correction effects c, c_d and c_a. Basically, therefore, when a particular contingency table like Table IV is studied, the conclusion as to whether the estimate of θ is an overestimate or an underestimate of θ^t can be drawn only from substantive knowledge of the processes that play a role in reporting. However, equation (2) shows that, in deciding this, we do not need to bother about the overall under-reporting discussed in (i), about general under-reporting of the drug discussed in (ii), and general under-reporting of the ADR discussed in (iii). We only need concern ourselves with the specific combination under-reporting (iv).

We now make a remark on the estimation of the odds ratio by the log-linear model and by logistic regression as this is helpful in understanding the generalization of our findings to drug–drug interactions, and it enables us later in this paper to control for possible covariates such as gender and age. The log-linear model for the 2×2 table with elements m_{ik} is

$$\log m_{ik} = u + u_i^A + u_k^D + u_{ik}^{AD} \tag{3}$$

where, u refers to the overall mean effect, u_i^{A} refers to the ADR effect, u_k^{D} refers to the drug effect, and u_{ik}^{AD} refers to their interaction effect. These parameters add up to zero over each index in order to identify the model. Filling in (3) into (2) gives us the relation between the parameters u_{ij} and the odds ratio θ

$$\theta = \frac{m_{11}m_{22}}{m_{12}m_{21}} = \exp(4u_{11}^{\mathrm{AD}}) \tag{4}$$

It follows that, if there is no interaction term u_{ik}^{AD} needed in the log-linear model for Table IV (that is, in the SRS data the specific drug and ADR are unrelated), the estimated odds ratio will be equal to one.

We can also rewrite the log-linear model into a logistic regression model:

$$\log \frac{m_{i1}}{m_{i2}} = u_1^{\mathrm{D}} + u_{i1}^{\mathrm{AD}} - u_2^{\mathrm{D}} - u_{i2}^{\mathrm{AD}} = 2u_1^{\mathrm{D}} + 2u_{i1}^{\mathrm{AD}} = b + b_i^{\mathrm{A}} \tag{5}$$

This shows that $\theta = \exp(2b_1^{\mathrm{A}})$, and it follows that both the log-linear model as well as the logistic regression model can be used to test whether the odds ratio in the SRS departs significantly from 1.

3.2. Diuretics and possible ADRs revisited

In Section 2.1 we studied Table I. The odds ratio estimated in the SRS data was 1.58, and the question is in what way this odds ratio is biased by under-reporting.

Section 3.1 shows that three under-reporting effects do not concern us here, namely the general effect (i) that holds for all four frequencies in Table I, the drug effect (ii) that the under-reporting of ADRs the group for which diuretics are prescribed differs from ADRs in those for which they are not prescribed, and the ADR effect (iii) that the under-reporting of congestive heart failure may be different from the under-reporting of other ADRs. Only the combination effect (iv) should concern us here, that is, the possible effect that physicians and pharmacists submit more or fewer reports specifically for the occurrence of signs indicating congestive heart failure when diuretics are prescribed. Such a possible effect will bias the observed odds ratio of 1.58 positively or negatively. If the bias is negative, the odds ratio in the ADR-experiencing population will be larger. Since the aim of an SRS is to generate signals for an existing drug–ADR relation, negative bias should not worry us in this example. However, in general the bias may be such that it reduces the odds ratio to a small value that then is not a large enough signal to stand out from the noise. If the bias is positive, the odds ratio in the ADR-experiencing population will be smaller, and the SRS is possibly generating a 'false' signal. In this particular case we may be looking at a situation in which a lack of efficacy of the diuretics was perceived, possibly due to a confounding by indication. Nevertheless, since this situation is not to be expected, the odds ratio may be overestimated in the SRS population.

4. THE UNDER-REPORTING PROBLEM FOR TWO DRUGS

First we will work out the general case of two drugs (Section 4.1), then proceed to make some further assumptions and study the consequences of these (Section 4.2). In Section 4.3 we

reconsider the example of drug–drug–ADR interaction of diuretics and NSAID, and discuss the consequences of Sections 4.1 and 4.2 for the interpretation.

4.1. Theory: the general case

In this section we will study the under-reporting problem in the case of two drugs. This pertains to a table of $2 \times 2 \times 2$ with elements m_{ijk}, where i $(i = 1, 2)$ refers to the presence or absence of the first specific drug in a report, j $(j = 1, 2)$ refers to the presence or absence of the second specific drug, and k $(k = 1, 2)$ refers to the presence or absence of the specific ADR. There are thus eight cells. We adopt the same approach as in Section 2, that is, for these eight cells we distinguish eight types of under-reporting problems. First we write the expected frequencies of the SRS in terms of the true frequencies for the ADR-experiencing population using constants c to c_{dea} for these eight types of under-reporting problems. Then we will show in what way the odds ratios calculated on the SRS data are biased as a result of these under-reporting problems.

We distinguish the following eight types of under-reporting problems:

(i) The general under-reporting effect that pertains to each of the eight cells, denoted by c;
(ii) The general under-reporting effect for the first drug, denoted by c_{d};
(iii) The general under-reporting effect for the second drug, denoted by c_{e};
(iv) The general under-reporting effect for ADR, denoted by c_{a};
(v) The paired under-reporting effect between both drugs denoted by c_{de}; this statistical interaction is unrelated to the column variable ADR, but only shows whether the first drug is found relatively more or less often together with the second drug;
(vi) The paired under-reporting effect for the first drug and the specific ADR, denoted by c_{da} (this effect is comparable to combination effect (iv) in Section 2);
(vii) The paired under-reporting effect for the second drug and the specific ADR, denoted by c_{ea};
(viii) The joint under-reporting effect for both drugs with the specific ADR, denoted by c_{dea}. This under-reporting effect shows the effect that a combination of two drugs has on reporting an ADR, above the general and paired under-reporting effects. For example, c_{dea} can be smaller than 1 when a drug–drug–ADR interaction is well known so that health professionals do not take the trouble to file a report; it can be larger than 1 when a drug–drug–ADR interaction is suspected but not proven yet – for example, in the situation that a new drug is marketed with properties similar to existing drugs for which a drug–drug–ADR interaction is proven. See Section 4.2 for a thorough discussion of the joint under-reporting effect.

In Table VI we relate the expected frequencies m_{ijk} in the SRS population to the true frequencies t_{ijk} in the ADR-experiencing population using the constants c to c_{dea}. Thus we can answer the question of how the SRS estimates provide a biased account of the odds ratios in the ADR-experiencing population.

In three-way tables, the possible relations between the variables can be summarized by so-called conditional odds ratios, that is, two odds ratios between i and j for $k = 1, 2$, two odds ratios between i and k for $j = 1, 2$, and two odds ratios between j and k for $i = 1, 2$. We will denote the odds ratios derived from the SRS between i and j for $k = 1, 2$ as $\theta_{ij|k=1}$

Table VI. Two drugs. Expected frequencies m_{ijk} for the SRS population, expressed in terms of true frequencies t_{ijk} used for the ADR-experiencing population.

Specific drug 1	Specific drug 2	Specific ADR	
		Absent	Present
Absent	Absent	$\frac{cc_{de}c_{da}c_{ea}}{c_d c_e c_a c_{dea}} t_{111}$	$\frac{cc_a c_{de} c_{dea}}{c_d c_e c_{da} c_{ea}} t_{112}$
	Present	$\frac{cc_e c_{da} c_{dea}}{c_d c_a c_{de} c_{ea}} t_{121}$	$\frac{cc_e c_a c_{ea}}{c_d c_{de} c_{da} c_{dea}} t_{122}$
Present	Absent	$\frac{cc_d c_{ea} c_{dea}}{c_e c_a c_{de} c_{da}} t_{211}$	$\frac{cc_d c_a c_{da}}{c_e c_{de} c_{ea} c_{dea}} t_{212}$
	Present	$\frac{cc_d c_e c_{de}}{c_a c_{da} c_{ea} c_{dea}} t_{221}$	$cc_d c_e c_a c_{de} c_{da} c_{ea} c_{dea} t_{222}$

and $\theta_{ij|k=2}$, and the corresponding odds ratios derived from the ADR-experiencing population by $\theta^t_{ij|k=1}$ and $\theta^t_{ij|k=2}$. The odds ratios for the other variables are denoted in similar ways. If we want to relate the odds ratios derived from the SRS population to the odds ratios derived from the ADR-experiencing population we get the following results (compare equations (1) and (2)):

$$\theta_{ij|k=1} = \frac{m_{111}m_{221}}{m_{121}m_{211}} = \frac{(c_{de})^4}{(c_{dea})^4}\frac{t_{111}t_{221}}{t_{121}t_{211}} = \frac{(c_{de})^4}{(c_{dea})^4}\theta^t_{ij|k=1} \tag{6}$$

$$\theta_{ij|k=2} = (c_{de})^4(c_{dea})^4\,\theta^t_{ij|k=2} \tag{7}$$

$$\theta_{ik|j=1} = \frac{(c_{da})^4}{(c_{dea})^4}\theta^t_{ik|j=1} \tag{8}$$

$$\theta_{ik|j=2} = (c_{da})^4(c_{dea})^4\theta^t_{ik|j=2} \tag{9}$$

$$\theta_{jk|i=1} = \frac{(c_{ea})^4}{(c_{dea})^4}\theta^t_{jk|i=1} \tag{10}$$

$$\theta_{jk|i=2} = (c_{ea})^4(c_{dea})^4\theta^t_{jk|i=2} \tag{11}$$

We conclude from these equations that:

1. General under-reporting effects (i), (ii) (for the first drug), (iii) (for the second drug) and (iv) (for the specific ADR) do not lead to bias in the odds ratios derived from the SRS population. This follows from the fact that the constants c, c_d, c_e and c_a do not appear in (6) to (11).
2. The odds ratios estimated from SRS data are biased by paired under-reporting effects, denoted by the constants c_{de}, c_{da} and c_{ea}.
3. The odds ratios estimated from SRS data are biased by the joint under-reporting effect for both drugs, and the specific ADR, by the constant c_{dea}.

We will indicate shortly how these odds ratios can be obtained by means of parameters of a log-linear model. Similar to equation (3), the log-linear model for the $2 \times 2 \times 2$ table with

elements m_{ijk} is

$$\log m_{ijk} = u + u_i^{\mathrm{D}} + u_j^{\mathrm{E}} + u_k^{\mathrm{A}} + u_{ij}^{\mathrm{DE}} + u_{ik}^{\mathrm{DA}} + u_{jk}^{\mathrm{EA}} + u_{ijk}^{\mathrm{DEA}} \tag{12}$$

where the parameters add up to zero over each index. Therefore the relation between the log-linear parameters and, for example, the conditional odds ratio $\theta_{ik|j=1}$ is

$$\theta_{ik|j=1} = \frac{m_{111}m_{212}}{m_{112}m_{211}} = \exp(4u_{11}^{\mathrm{DA}} + 4u_{111}^{\mathrm{DEA}}) \tag{13}$$

In a similar way, the odds ratios $\theta_{ij|k}$ and $\theta_{jk|i}$ can be obtained from the parameters of a logistic regression model where the logit of the specific ADR is predicted by the first and the second drug, and their interaction.

4.2. Theory: further assumptions

Regarding c_{dea} three different situations can be distinguished. First, in the event that the drug–drug interaction is well known in the literature and is common knowledge to physicians and pharmacists, the chance that this drug–drug interaction is reported to an SRS is probably less likely, so in this situation we might expect that $c_{\mathrm{dea}} < 1$. Secondly, a drug–drug interaction may not yet be associated with a specific drug but may be expected, for example in the event that a related drug is known to cause a similar drug–drug interaction. In this situation, the interaction is probably more easily reported, so we might expect $c_{\mathrm{dea}} > 1$. Finally, in the event that an interaction is not known in the literature and is not to be suspected, one may assume that $c_{\mathrm{dea}} = 1$. After all, generally there is no reason why in the event the specific combination of both drugs is used, an ADR should be more or less frequently reported. Regarding the main purpose of SRSs, however, that is, generating signals of previously unknown ADRs or drug–drug interactions, this situation need not necessarily be unfavourable.

Assume now that the joint under-reporting effect for both specific drugs with the specific ADR can be ignored, that is, in equations (6) to (11) $c_{\mathrm{dea}} = 1$. These equations then simplify considerably. Under this assumption we can make the following observations:

1. The odds ratios are only biased because of the paired under-reporting effects, that is, due to c_{de}, c_{da} and c_{ea}.
2. The bias problem is simple in the sense that the pairs of odds ratios in (6) and (7), in (8) and (9), and in (10) and (11), are biased by the same factor. For example, for $\theta_{ik|j=1}$ and $\theta_{ik|j=2}$ this factor is c_{da}^4.
3. Because of observation 2, it holds for each pair of odds ratios that the ratio of the elements of the pair in the SRS population is unbiased for the corresponding ratio of odds ratios in the ADR-experiencing population. For example, the ratio of odds ratios $\theta_{ik|j=1}/\theta_{ik|j=2} = \theta^t_{ik|j=1}/\theta^t_{ik|j=2}$. This is a useful result. For example, if we find that $\hat{\theta}_{ik|j=1} = 1.0$ and $\hat{\theta}_{ik|j=2} = 4.0$, this implies that, in the SRS population, the odds ratio between the first drug and the specific ADR is estimated as 1 if the second drug is absent (so then there is no relation) but as 4 when the second drug is present. This shows that the combination of both drugs coincides with an ADR in the SRS population. The estimates of both odds ratios are biased by an unknown factor c_{da}, and therefore we do not know the estimate of these odds ratios in the ADR-experiencing population. However, since $\theta_{ik|j=1}/\theta_{ik|j=2} = \theta^t_{ik|j=1}/\theta^t_{ik|j=2}$ both in the SRS population as well as in the

ADR-experiencing population the odds ratio between the first drug and the ADR is four times greater when the second drug is present than when it is absent.

4. Assume now, in addition to the assumption $c_{\text{dea}} = 1$, that in the SRS population there is no drug–drug–ADR interaction, that is, $u_{ijk}^{\text{DEA}} = 0$. For clarity of exposition, we focus our discussion now on $\theta_{ik|j=1}$ and $\theta_{ik|j=2}$ (compare (8), (9) and (13)), but these results also hold for the other odds ratios. By working out (13) for both $\theta_{ik|j=1}$ and $\theta_{ik|j=2}$, we find $\theta_{ik|j=1} = \theta_{ik|j=2} = \exp 4u_{11}^{\text{DA}}$. Second, by substituting this in equations (8) and (9), we find $\theta_{ik|j=1} = \theta_{ik|j=2} = c_{\text{da}}^4 \theta_{ik|j=1}^t = c_{\text{da}}^4 \theta_{ik|j=2}^t$. Since $\theta_{ik|j=1}^t = \theta_{ik|j=2}^t$, this implies the next result: if $c_{\text{dea}} = 1$ and there is no drug–drug–ADR interaction in the SRS population, then there will be no drug–drug–ADR interaction in the SRS population. We now show that the reverse also holds. If in the ADR-experiencing population the interaction $(u_{ijk}^{\text{DEA}})^t = 0$, then $\theta_{ik|j=1}^t = \theta_{ik|j=2}^t = \exp 4(u_{11}^{\text{DA}})^t$. Under-reporting leads to multiplication with a factor c_{da}^{-4} (the reverse of what happens in (8) and (9)), and therefore $\theta_{ik|j=1}^t = \theta_{ik|j=2}^t = c_{\text{da}}^{-4}\ \theta_{ik|j=1} = c_{\text{da}}^{-4}\ \theta_{ik|j=2} = c_{\text{da}}^{-4} \exp 4(u_{11}^{\text{DA}})^t$. This shows that $\theta_{ik|j=1} = \theta_{ik|j=2}$, and therefore, if the drug–drug–ADR interaction is zero in the ADR-experiencing population, it will also be zero in the SRS population.

   Therefore we can carry out a log-linear analysis in the SRS population (or, equivalently, a logistic regression) to assess whether there is a drug–drug–ADR interaction in the ADR-experiencing population. Under the assumption that $c_{\text{dea}} = 1$, if there is *no* drug–drug–ADR interaction in the ADR-experiencing population, we can use data from an SRS to assess this. If there *is* such an interaction, then the ratio of the odds ratios estimated from data in the SRS is equal to the ratio of the odds ratios in the ADR-experiencing population (see result (iii) and the Appendix).

4.3. Drug–drug interaction of diuretics and NSAIDs revisited

In the notation of Section 4.2, the odds ratios estimated for the SRS population in Section 2.2, having values 1.29 and 3.04, are $\theta_{ik|j=1}$ and $\theta_{ik|j=2}$. Equations (8) and (9) show us that these give biased accounts of the odds ratios $\theta_{ik|j=1}^t$ and $\theta_{ik|j=2}^t$ in the ADR-experiencing population by the under-reporting factors c_{da} and c_{dea}. Other under-reporting effects play no role. The factor c_{da} reflects a possible paired under-reporting of the diuretics–congestive heart failure combination. The factor c_{dea} reflects joint under-reporting of diuretics and NSAIDs on congestive heart failure. These two factors may cause the estimates 1.29 and 3.04 to be biased, but without further information it is unclear in what direction and in what magnitude.

Let us now assume that we can ignore c_{dea}, that is, $c_{\text{dea}} = 1$, as is discussed in Section 3.2. This assumption generally is true when under-reporting of congestive heart failure due to a diuretic is not influenced by the presence or absence of NSAIDs. Then $\theta_{ik|j=1}$ and $\theta_{ik|j=2}$ are only biased by the same factor c_{da}. It follows that we can say that, whatever size of the bias factor c_{da}, in the ADR-experiencing population the odds ratio $\theta_{ik|j=2}^t$ is $3.04/1.29 = 2.35$ times as large as the odds ratio $\theta_{ik|j=1}^t$. In other words, the relation between diuretics and congestive heart failure is 2.35 times as strong when an NSAID is used compared with that when an NSAID is not used. Some manipulation of equations from Section 3.2 shows that this value $2.35 = \exp 4\hat{u}_{ijk}^{\text{DEA}}$, and the Appendix shows that if $c_{\text{dea}} = 1$ this $\hat{u}_{ijk}^{\text{DEA}}$ estimated in the SRS population is unbiased for the ADR-experiencing population.

5. COVARIATES

5.1. Theory

Here we discuss the assessment of interaction between a specific drug and a specific ADR in the presence of covariates one would like to control for. We do this for a simple case only, namely, for the case of one drug and one categorical covariate. To make the exposition simple, we take as covariate sex, indexed by s, with levels male and female. The approach of this simple case can also be used for more complicated cases, such as when there are more drugs and more covariates.

The situation is equivalent to the approach for Section 4, with the second drug replaced by the covariate. Therefore we keep this section brief.

Just as in Section 4 there are eight under-reporting problems, leading to the eight constants c, c_s, c_d, c_a, c_{sd}, c_{sa}, c_{da} and c_{sda}. The odds ratios estimated in the SRS population are biased with respect to the ADR-experiencing population using these constants, and it is possible to find equations similar to equations (6) to (11). As in Section 4, in the general case this gives odds ratios that are difficult to interpret due to biases which cannot be estimated from the SRS. However, it is clear that the odds ratios are only biased because of paired and joint under-reporting effects c_{sd}, c_{sa}, c_{da} and c_{sda}, and not because of general under-reporting effects c, c_s, c_d, c_a.

If we make the assumption that there is no joint under-reporting effect, then $c_{sda} = 1$, and all equations simplify considerably (compare Section 4.2). Examples of $c_{sda} \neq 1$ are difficult to imagine. We give a few examples to see this. Consider the appearance of facial hair or the disappearance of scalp hair. Both are more likely to be reported if they occur in women than in men. However, if this reporting is irrespective of the drug, then $c_{sa} \neq 1$ but $c_{sda} = 1$. As a second example, there is wide recognition that women consult their doctors more frequently than men, thus leading to increased opportunities for ADRs to be reported in women. However, if this under-reporting for males is irrespective of drugs and ADRs, then this would lead to $c_s \neq 1$, but $c_{sa} = c_{da} = c_{sda} = 1$. As a last example, ADRs affecting someone's ability to work may be more likely to be reported if they occur in men (assuming men make up a larger proportion of the work-force). Again, if this under-reporting for men is irrespective of drug and ADR, then $c_s \neq 1$, but $c_{sa} = c_{da} = c_{sda} = 1$. Thus we conclude that, although the specific combination of both drug, sex and ADR may give rise to a different level of reporting, generally however it is unlikely that the specific under-reporting factor concerning the combination of both drug, gender and ADR is not equal to one.

As in Section 4.2, if the assumption that $c_{sda} = 1$ is realistic, it is useful to fit a log-linear or logistic regression model to assess whether there is an interaction between drug, sex and ADR in SRS data. If this drug–sex–ADR interaction can be deleted from the model fitted on the SRS data, this means that there is no evidence for this drug–sex–ADR interaction in the ADR-experiencing population either. If the drug–sex–ADR interaction is included in the model, however, the conditional odds ratios are biased, but ratios of these conditional odds ratios are not (see Section 4.2 for details).

5.2. Sex differences for ADRS of diclofenac revisited

We now revisit the analysis of sex differences for ADRs of diclofenac discussed in Section 2.3. We found an odds ratio of 12.4 for males and 10.0 for females. The drug–sex–ADR interaction

in the log-linear model was not significant, and the estimated odds ratio in this model is 10.8. We now discuss the possible effects of under-reporting on these results.

These odds ratios estimated from the SRS data give possibly biased accounts of the corresponding odds ratios in the ADR-experiencing population because of the paired under-reporting c_{da} of drug by ADR and the joint under-reporting effect c_{sda} for sex, drug and ADR. Notice that general under-reporting effects c_s for sex, c_d and c_a, as well as the paired under-reporting effect for sex and drug c_{sd} and for sex and ADR c_{sa}, do not bias these odds ratios.

If we assume that the joint under-reporting effect c_{sda} can be neglected (that is, $c_{sda} = 1$), since there is no reason for anaphylactic reactions due to diclofenac to be reported more frequently in either men or women, then the log-linear model without interaction term for sex by drug by ADR also holds in the ADR-experiencing population. The only problem to worry about is the under-reporting effect c_{da}, but in this example it is unlikely that this under-reporting effect is so large that it will bring down the estimated odds ratio of 10.8 in the SRS population to 1 in the ADR-experiencing population.

6. CONCLUSION

Spontaneous reporting systems (SRS) are plagued by under-reporting problems of ADRs. The aim of this paper was to clarify the different ways in which under-reporting can play a role. In particular, we have focused on the question of which types of under-reporting problems plague SRS data and which types are harmless when we want to make statements about the ADR-experiencing population using data from the SRS population.

It turns out that general under-reporting effects for specific drugs and for specific ADRs are harmless, but paired under-reporting effects result in biases in the odds ratios estimated from the SRS. If there is no so-called joint under-reporting effect of two drugs on the ADR, then SRS data can be very useful for assessing the presence of drug interactions, and their relative size.

We approach the analysis of SRS data by first conducting log-linear analyses of data, secondly by discussing the existence of possible under-reporting effects, and thirdly by discussing whether the odds ratios found in the SRS data are likely to be affected by these under-reporting effects to such an extent that conclusions about the existence (that is, not the size) drug–ADR relations would have to be modified.

We think this paper provides a better understanding of the possible pitfalls, but also of the validity of drawing conclusions from the analysis of SRS data.

APPENDIX: INTEGRATING UNDER-REPORTING INTO LOG-LINEAR MODELS

In this Appendix we present our results in a more general way, set out for the situation of two variables and an ADR. These two variables can be either two specific drugs, as in Section 4, or one covariate and one drug, as in Section 5, or possibly two covariates.

We denote the variables as follows: for the specific ADR we use A, with levels a ($a = 1, 2$), and the other two variables are X with levels x ($x = 1, 2$) and Y with levels y ($y = 1, 2$). As usual, we denote the true frequencies in the ADR-suspected population by t_{xya}, and the expected frequencies in the SRS population by m_{xya}.

We begin by defining a general log-linear model for the true frequencies m^t_{xya} in the ADR-experiencing population as

$$\log t_{xya} = u + u^X_x + u^Y_y + u^A_a + u^{XY}_{xy} + u^{XA}_{xa} + u^{YA}_{ya} + u^{XYA}_{xya} \tag{A1}$$

where the parameters add up to zero over each index. By taking exponents this equation can be reparameterized as

$$t_{xya} = \beta\beta^X_x\beta^Y_y\beta^A_a\beta^{XY}_{xy}\beta^{XA}_{xa}\beta^{YA}_{ya}\beta^{XYA}_{xya} \tag{A2}$$

where, for example, $\exp u = \beta$, $\exp u^X_x = \beta^X_x$, and so on. The identifying restrictions in (A2) are $\Pi_x\beta^X_x = \Pi_y\beta^Y_y = \Pi_a\beta^A_a = \Pi_x\beta^{XY}_{xy} = \Pi_y\beta^{XY}_{xy} = \Pi_x\beta^{XA}_{xa} = \Pi_a\beta^{XA}_{xa} = \Pi_y\beta^{YA}_{ya} = \Pi_a\beta^{YA}_{ya} = \Pi_x\beta^{XYA}_{xya} = \Pi_y\beta^{XYA}_{xya} = \Pi_a\beta^{XYA}_{xya} = 1$.

We now write a general equation for the overall under-reporting of the ADR-experiencing population by the term k_{xya}. We use, for example, the notation c^X_x for the under-reporting of levels $x = 1$ and $x = 2$ of variable X. This leads to

$$k_{xya} = cc^X_x c^Y_y c^A_a c^{XY}_{xy} c^{XA}_{xa} c^{YA}_{ya} c^{XYA}_{xya} \tag{A3}$$

with restrictions similar to those for the β-parameters: $\Pi_x c^X_x = \Pi_y c^Y_y = \Pi_a c^A_a = \Pi_x c^{XY}_{xy} = \Pi_y c^{XY}_{xy} = \Pi_x c^{XA}_{xa} = \Pi_a c^{XA}_{xa} = \Pi_y c^{YA}_{ya} = \Pi_a c^{YA}_{ya} = \Pi_x c^{XYA}_{xya} = \Pi_y c^{XYA}_{xya} = \Pi_a c^{XYA}_{xya} = 1$. In Sections 3,4 and 5, these restrictions are satisfied for the under-reporting constants because, for example, in Tables V and VI, $c_a \times c_a^{-1} = 1$.

The expected frequencies m_{xya} for the SRS are related to the true frequencies t_{xya} in the ADR-experiencing population by

$$\begin{aligned} m_{xya} &= k_{xya}t_{xya} \\ &= (c\beta)(c^X_x\beta^X_x)(c^Y_y\beta^Y_y)(c^A_a\beta^A_a)(c^{XY}_{xy}\beta^{XY}_{xy})(c^{XA}_{xa}\beta^{XA}_{xa})(c^{YA}_{ya}\beta^{YA}_{ya})(c^{XYA}_{xya}\beta^{XYA}_{xya}) \\ &= \gamma\gamma^X_x\gamma^Y_y\gamma^A_a\gamma^{XY}_{xy}\gamma^{XA}_{xa}\gamma^{YA}_{ya}\gamma^{XYA}_{xya} \end{aligned} \tag{A4}$$

where the γ-parameters are restricted by $\Pi_x\gamma^X_x = \Pi_y\gamma^Y_y = \Pi_a\gamma^A_a = \Pi_x\gamma^{XY}_{xy} = \Pi_y\gamma^{XY}_{xy} = \Pi_x\gamma^{XA}_{xa} = \Pi_a\gamma^{XA}_{xa} = \Pi_y\gamma^{YA}_{ya} = \Pi_a\gamma^{YA}_{ya} = \Pi_x\gamma^{XYA}_{xya} = \Pi_y\gamma^{XYA}_{xya} = \Pi_a\gamma^{XYA}_{xya} = 1$. Note that the γ-parameters specify a multiplicative (that is, log-linear) model for the expected values in the SRS population. Analysis of the observed frequencies of the SRS will yield estimates of the γ-parameters, but equation (A4) illustrates the fact that, in principle, every γ-parameter is biased with respect to its corresponding β-parameter by its corresponding under-reporting constant c. For example, γ^{XYA}_{xya} is biased with respect to β^{XYA}_{xya} with a factor c^{XYA}_{xya}. In Section 4.1 we showed how this biases the odds ratios in equations (6) to (11).

Equation (A4) also makes clear what happens when certain under-reporting constants or certain log-linear β-parameters vanish by being equal to one. First we distinguish three situations. In passing we indicate how these situations relate to the special cases that we discussed in Section 4. In our discussion we only deal with so-called hierarchical models, that is, if a higher-order term is included, all the lower-order terms with indices that are a subset of the set of indices of the higher-order term are included.

In the first situation, some of the higher-order under-reporting constants vanish where the corresponding β-parameters do not. The result is that in the expected frequencies in the SRS the higher-order γ-parameters are equal to the β-parameters in the ADR-suspected population. In this situation, in estimating a log-linear model on the observed frequencies from the SRS, the higher-order γ-parameters are unbiased with respect to the corresponding β-parameters of interest. This is discussed in detail in Section 4.2, where interest centred on the situation where $c_{xya}^{XYA} = 1$ (there denoted by c_{dea}), but $\beta_{xya}^{XYA} \neq 1$ (there denoted by u_{dea}. This situation is worked out in observations 1 to 3 of Section 4.2).

In the second situation the corresponding β-parameters and under-reporting constants vanish. Thus the corresponding γ-parameters vanish. In Section 3.2, observation 4, this was discussed in detail for the vanishing of β_{xya}^{XYA} and c_{xya}^{XYA} (there denoted as u_{dea} and c_{dea} (they vanish by assumption), and this leads to the vanishing of γ_{xya}^{XYA} (they vanish by analysis). We refer to Section 4.2 for a further discussion of this point, and the possible interpretation of odds ratios estimated from SRS data.

In the third situation, some of the β-parameters are equal to one, but none of the under-reporting constants vanish. The result is that, if a log-linear analysis is conducted on the observed frequencies in the SRS, the estimates of γ-parameters are in fact estimates of the corresponding under-reporting constants. For example, if in the ADR-experiencing population in the true frequencies $\beta_{xa}^{XA} = \beta_{xya}^{XYA} = 1$, then $\gamma_{xa}^{XA} = c_{xa}^{XA}$ and $\gamma_{xya}^{XYA} = c_{xya}^{XYA} = 1$. This situation is not discussed in Section 4. If the higher-order under-reporting constants dominate the corresponding higher-order β-parameters, SRS data are not useful for the assessment of causal links between drugs and ADRs.

ACKNOWLEDGEMENTS

We gratefully acknowledge the comments of the editor and a referee that improved the paper substantially, and the support from the Dutch Fund for Prevention (number 28.2632).

REFERENCES

1. Finney DJ. The detection of adverse reactions to therapeutic drugs. *Statistics in Medicine* 1982; **1**:153–161.
2. Finney DJ. Statistical logic in the monitoring of reactions to therapeutic drugs. *Statistical Logic in Drug Monitoring* 1971; **10**:237–245.
3. Finney DJ. Systemic signalling of adverse reactions to drugs. *Methods of Information in Medicine* 1974; **13**: 1–10.
4. Waller PC, Lee EN. Responding to drug safety issues. *Pharmacoepidemiology and Drug Safety* 1999; **8**:535–552.
5. Amery W. Analysis of the information in a central ADE database. *International Journal of Risk and Safety in Medicine* 1993; **5**:123.
6. Van Puijenbroek EP, Egberts ACG, Meyboom RHB, Leufkens HGM. Signaling possible drug–drug interactions in a spontaneous reporting system: Delay of withdrawal bleeding during concomitant use of oral contraceptives and itraconazole. *British Journal of Clinical Pharmacology* 1999; **47**:689–693.
7. Van Puijenbroek EP, Egberts ACG, Heerdink ER, Leufkens HGM. Detecting drug–drug interactions using a database for spontaneous adverse drug reactions: an example with diuretics and non-steroidal anti-inflammatory drugs. *European Journal of Clinical Pharmacology* 2000; **56**(9–10):733–738.
8. de Koning GHP. A regionalized spontaneous surveillance program for adverse drug reactions as a tool to improve pharmacotherapy. Thesis, Utrecht University, 1994, pp. 76–96.
9. Stephens MDB. *Detection of New Adverse Drug Reactions*. MacMillan Publishers Ltd: London 1992.
10. Haramburu F. Estimation of underreporting. *Post Marketing Surveillance* 1993; **7**:39–49.
11. DuMouchel W. Bayesian data mining in large frequency tables, with an application to the FDA Spontaneous Reporting System (with discussion). *American Statistician* 1999; **53**:177–202.

12. Praus M, Schindel F, Fescharek R, Schwarz S. Alert systems for post-marketing surveillance of adverse drug reactions. *Statistics in Medicine* 1993; **12**:2383–2393.
13. Tsong Y. Comparing reporting rates of adverse events between drugs with adjustment for year of marketing and secular trend in total reporting. *Journal of Biopharmaceutical Statistics* 1995; **5**:95–114.
14. Martin RM, Kapoor KV, Wilton LV, Mann RD. Underreporting of suspected adverse drug reactions to newly marketed ('black triangle') drugs in general practice: observational study. *British Medical Journal* 1998; **317**(7151):119–120.
15. Eland IA, Belton KJ, van Grootheest AC, Meiners AP, Rawlins MD, Stricker BH. Attitudinal survey of voluntary reporting of adverse drug reactions. *British Journal of Clinical Pharmacology* 1999; **48**(4):623–627.
16. Stricker BHC, Tijssen JGP. Serum sickness-like reactions to Cefaclor. *Journal of Clinical Epidemiology* 1992; **10**:1177–1184.
17. Egberts AC, Meyboom RH, De Koning FH, Bakker A, Leufkens HG. Non-puerperal lactation associated with antidepressant drug use. *British Journal of Clinical Pharmacology* 1997; **44**:277–281.
18. Evans SJW. Pharmacovigilance: a science or fielding emergencies. *Statistics in Medicine* 2000; **19**:3199–3209.
19. Egberts ACG, Van der Hofstede JW, Meyboom RHB, de Koning GHP, Bakker A, Leufkens HGM. Transformation of a database of spontaneously reported suspected adverse drug reactions and its use as a tool in signal detection. Pharmacoepidemiological approached to the evaluation of antidepressant drugs. Thesis, Utrecht University 1997, pp. 111–124.
20. Pierfitte C, Begaud B, Lagnaoui R, Moore ND. Is reporting rate a good predictor of risks associated with drugs? *British Journal of Clinical Pharmacology* 1999; **47**(3):329–331.
21. WHO. *WHO Adverse Drug Reaction Dictionary*. WHO Centre for International Drug Monitoring, Uppsala, Sweden, 1995.
22. Feenstra J, Grobbee DE, Mosterd A, Stricker BH. Adverse cardiovascular effects of NSAIDs in patients with congestive heart failure. *Drug Safety* 1997; **17**:166–180.
23. Heerdink ER, Leufkens HG, Herings RM, Ottervanger JP, Stricker BH, Bakker A. NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. *Archives of Internal Medicine* 1998; **158**:1108–1112.
24. O'Brien WM. Adverse reactions to nonsteroidal anti-inflammatory drugs. Diclofenac compared with other nonsteroidal anti-inflammatory drugs. *American Journal of Medicine* 1986; **80**:70–80.
25. Agresti A. *Categorical Data Analysis*. Wiley: New York 1990.
26. Baudraz-Rosselet F, Rakosi T, Wili PB, Kenzelmann R. Treatment of onychomycosis with terbinafine. *British Journal of Dermatology* 1992; **126**(39):40–46.

