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ORIGINAL REPORT

The effect of exposure misclassification in spontaneous ADR reports on the time to detection of product-specific risks for biologicals: a simulation study†

Niels S. Vermeer[1,2], Hans C. Ebbers[1], Sabine M. J. M. Straus[2,3], Hubert G. M. Leufkens[1,2], Toine C. G. Egberts[1,4] and Marie L. De Bruin[1,2]*

[1] *Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands*
[2] *Medicines Evaluation Board, Utrecht, The Netherlands*
[3] *Medical Informatics, Erasmus Medical Center, Rotterdam, The Netherlands*
[4] *Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands*

ABSTRACT

Background and Objective The availability of accurate product-specific exposure information is essential in the pharmacovigilance of biologicals, because differences in the safety profile may emerge between products containing the same active substance. In spontaneous adverse drug reaction (ADR) reports, drug exposure may, however, be misclassified, that is, attributed to the incorrect product. The aim of this study was to explore the effect of exposure misclassification on the time to detection of product-specific risks in spontaneous reporting systems.

Methods We used data simulations to explore the effect of exposure misclassification. We simulated an active substance-specific subset of a spontaneous reporting system and used the proportional reporting ratio for signal detection. The effect of exposure misclassification was evaluated in three test cases representing product-specific ADRs that may occur for biologicals and studied in relative terms by varying the model parameters (market share and relative risk).

Results We found that exposure misclassification results in the largest delay in identification of risks that have a weak association (relative risk < 2 or 3) with the product of interest and in situations where the product associated with the unique risk has a large ($>50\%$) market share. The absolute public health impact of exposure misclassification, in terms of cases/time to detection, varied considerably across the test cases.

Conclusion Exposure misclassification in ADR reports may result in a delayed detection of product-specific risks, particularly in the detection of weak drug–event associations. Our findings can help inform the future implementation and refinement of product-specific and batch-specific signal detection procedures. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—spontaneous reports; exposure misclassification; signal detection; disproportionality; biological; biosimilars; pharmacoepidemiology

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INTRODUCTION

The availability of accurate exposure information is essential in pharmacovigilance. Incorrect information regarding an individual's exposure status, including underascertainment and misclassification of exposure, may bias measures of association in drug safety research.[1–3] There are multiple facets to the characterization of exposure (product, dosage, treatment compliance, etc.), and the required level of detail depends on the drug–event combination under study. Adverse drug reactions (ADRs) can be evaluated at different levels (Figure 1), most typically on the level of the active substance (e.g., progressive multifocal leukoencephalopathy associated with rituximab,[4]) or therapeutic group ('class effects', e.g., infections with tumor necrosis factor alpha inhibitors).[5] Evaluations for manufacturing source-specific risk are uncommon for small-molecule drugs, notwithstanding exceptions like bowel perforation with Indosmos,[6] but are

*Correspondence to: Dr. Marie L De Bruin, Utrecht University, Utrecht Institute for Pharmaceutical Sciences (UIPS), Universiteitsweg 99, 3584CG Utrecht, The Netherlands. E-mail: m.l.debruin@uu.nl

† Prior postings and presentations: An abstract of this study has been submitted for the upcoming ISOP 2015 Annual Meeting. There have been no prior postings or presentations of this research.

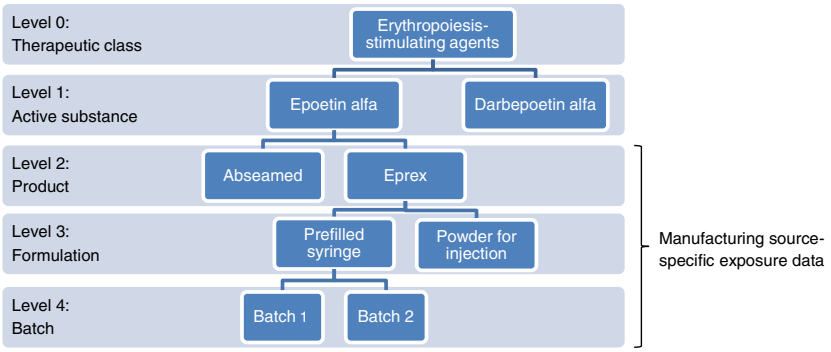

Figure 1. Different levels of exposure information.

routinely required for biologicals. The safety profile of biologicals is highly dependent on the manufacturing conditions and formulation process, and variability in these conditions within or across products, could potentially result in product-specific or batch-specific risks. An example hereof is the risk of epoetin-associated pure red cell aplasia, which was linked to a single manufacturing source of epoetin for which formulation changes had been issued (Eprex).[7]

Because subtle differences in manufacturing conditions for biologicals may give rise to previously unobserved adverse reactions, product-specific and batch-specific information is required for adequate safety evaluations of biologicals.[8] Previous studies have shown that batch-specific data is infrequently available in spontaneous ADR reports,[9–12] although product-specific exposure information is commonly provided for biologicals.[10–12] The validity of the product and batch information is, however, unknown. Reporters may, for example, habitually provide a brand name, without verifying the actual product dispensed or used. The recently reported discrepancy between the high market share, but low number of ADR reports for generics,[13,14] suggests that ADR reports could sometimes be incorrectly attributed to branded innovator drugs in clinical practice. This misattribution of generic-associated ADRs to innovator products in spontaneous ADR reports could result in a delayed detection of potential product-specific safety signals, although no examples hereof have been reported in literature, to our knowledge.

Because the number of biosimilars is expected to expand over the coming years,[15–17] product-specific safety evaluations of biologicals will become increasingly important. Spontaneous ADR reports are essential in product-specific pharmacovigilance. Many recent product-specific signals for biologicals that emerged after approval have been detected through case reports.[7,18,19] Regular screening of spontaneous reporting system databases for undiscovered product-specific safety signals may contribute to a timelier identification of product-specific risks, allowing for a timely implementation of risk mitigation strategies. Such screening involves the use of quantitative signal detection methods, in which the relative reporting of a given drug–event combination is compared to the relative reporting of that event for all similar biological products.[20,21] For example, data for Eprex should be assessed in relation to the aggregated data on all other products containing the active substance epoetin alfa. Drug exposure misclassification (i.e., between similar products) may however distort such product-specific signal detection procedures, though the actual impact hereof is unknown. In this study, we therefore aimed to explore the effect of exposure misclassification on the time to detection of product-specific risks in spontaneous reporting systems.

METHODS

We used data simulations to explore the effect of exposure misclassification. We simulated an active substance-specific subset of a spontaneous reporting system, in which the proportional reporting ratio (PRR) was used for signal detection. The effect of exposure misclassification was evaluated in absolute terms (cases/time to detection) in three test cases representing product-specific ADRs that may occur for biologicals. Furthermore, the overall impact of exposure misclassification was studied by varying the model parameters and assessing the effect of misclassification in relative terms.

DATA SIMULATION PROCEDURE

Number of adverse drug reaction reports

The expected number of spontaneous ADR reports that is collected in a spontaneous reporting system

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database for a given drug–event combination ($N_{i,j}$) can be approximated by the following equation:[22–24]

$$N_{i,j} = I_i \cdot E_j \cdot RR_{i,j} \cdot p_{i,j}$$

In this equation, I_i describes the background incidence of *event i* in the treatment population, E_j describes the patient exposure to *drug j*; $RR_{i,j}$ describes the relative risk of *event i* for patients exposed to *drug j*, and $p_{i,j}$ describes the reporting probability for the drug–event combination. The reporting probability is determined by many factors, including, but not limited to, the seriousness and expectedness of the event, and the time since initial marketing of the drug.

Spontaneous reporting system database

As schematically represented in Figure 2, signal detection from a spontaneous reporting system database is based on a cross-tabulation of all drug–event combinations ($N_{i,j}$) that have been reported at least once. In this study, we only simulated a substance-specific subset for similar biological products of the database.

Signal detection method

Several measures of disproportionality are available to screen spontaneous reporting systems for unidentified associations between drug exposures and events.[20,21] Most measures are—in essence—based on a two-by-two cross-tabulation of the database (Figure 2), comparing the relative reporting for a given drug–event combination to the relative reporting of that event for other drugs. For this study, we used the PRR for signal detection, which method is also used by the European Medicines Agency.[25] Drug–event combinations for which at least three reports have been received, and for which the lower bound of the 95% confidence interval (95%CI) for the PRR is at least 1, are considered to represent signals of disproportionate reporting (i.e., safety signals):

$$\mathrm{PRR} = \frac{A/(A+B)}{C/(C+D)}$$

$$95\%\,\mathrm{CI} = e^{\ln(\mathrm{PRR}) \pm 1.96\sqrt{\frac{1}{A}+\frac{1}{C}-\frac{1}{A+B}-\frac{1}{C+D}}}$$

TEST CASES FOR DATA SIMULATION

Three test cases with product-specific ADRs were selected for this study, for which the characteristics of the drug–event combination were estimated from literature sources (Box 1). Each of the test cases contained one unique ADR (event) that has a true association ($RR_{i,j} > 1$) with one product, but no association ($RR_{i,j} = 1$) with any of the similar products. In two cases, the background incidence of this unique event was low (≤25/100,000 patient-years) and the relative risk high (RR ≥ 5), whereas, in the third case, the background incidence was high (5,000/100,000 patient-years) and the relative risk low (RR = 1.5). The combined incidence of all other ADRs was equal for all products. The reporting probability was assumed non-differential and 0.1 for any drug–event combination. The full list of model parameters assumptions for the test cases is provided in Table 1.

Box 1. Background information on test cases.

Case 1: Hypersensitivity reactions to infliximab

Hypersensitivity reactions (HSR), including infusion-related reactions, are a common ADR of infliximab. In recent studies, between 3% and 10% of the patients experienced HSR during infliximab treatment.[26] The risk was higher among patients who had developed antibodies to infliximab, and numerically (albeit not statistically significant) differed between similar infliximab-containing products, with a factor of 1.25-fold to 3-fold across studies. Although the differences in incidence of HSR may have been a chance finding, potential differences in immunogenicity between products, which is known to be associated with an increased

Spontaneous reporting system database

	Drug_1	Drug_2	…	Drug_j
Event_1	$N_{1,1}$	$N_{1,2}$	…	$N_{1,j}$
Event_2	$N_{2,1}$	$N_{2,2}$	…	$N_{2,j}$
…	…	…	…	…
Event_i	$N_{i,1}$	$N_{i,2}$	…	$N_{i,j}$

Two-by-two cross-tabulation for signal detection

	Drug_1		*Not* drug_1	
Event_1	$N_{1,1}$	A	$\Sigma(N_{1,2}; \ldots; N_{1,j})$	C
Not event_1	$\Sigma(N_{2,1}; \ldots; N_{i,1})$	B	$\Sigma(N_{2,2}; \ldots; N_{i,j})$	D

Figure 2. Schematic representation of spontaneous reporting system database (left) and two-by-two cross-tabulation of spontaneous reporting system (right).

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Table 1. Parameter values for data simulations

Parameter	Test cases			Overall impact assessment
	HSR—infliximab	TMA—interferon beta	PRCA—epoetin alfa	
Background incidence unique event (per 100,000 patient-years)	5000	10	25	1:100*
Relative risk for unique event	1.5	5	17	[1.5; 3; 5; 10; 15]
Incidence all other events (per 100,000 patient-years)	10,000	10,000	10,000	100:1*
Reporting probability	0.1	0.1	0.1	n/a
Total market (patients per year)	50,000	50,000	100,000	n/a
Market share product with unique risk	50%	50%	50%	[5%; 50%; 95%]

PRCA, pure red cell aplasia, TMA: thrombotic microangiopathy; HSR, hypersensitivity reactions.
*The incidence rate ratio between the unique event and all other events is 1:100.

risk of infusion-related reactions,[27] may have contributed to the observed differences.

Case 2: Interferon beta-induced thrombotic microangiopathy

Thrombotic microangiopathies (TMA) comprise a diverse group of severe microvascular occlusive disorders associated with haemolytic anaemia, thrombocytopenia, and organ injury.[28] A recent case series described the unexpected occurrence of TMA among multiple sclerosis patients treated with Rebif™ (interferon beta-1a).[19] Because the increase in TMA cases (no data on relative risk available) coincided with the introduction of a new formulation of Rebif™, the risk has been suspected to relate to changes in manufacturing conditions. The cases of Rebif™-associated TMA predominantly comprised thrombotic thrombocytopenia purpura and hemolytic-uremic syndrome. Both disorders are extremely rare, and the combined population incidence has been estimated to be between 2.2 and 11.3 per 1,000,000 person-years,[29,30] although the background incidence in multiple sclerosis patients is unknown.

Case 3: Epoetin alfa-induced pure red cell aplasia

Pure red cell aplasia (PRCA) is a rare condition of profound anaemia, which may occur as a result of anti-erythropoietin antibodies, secondary to treatment with recombinant human erythropoietin (epoetin). As exemplified by previous incidents, the risk is highly dependent on the manufacturing and formulation process and may accordingly vary between different formulations of epoetin.[7,31] Recent data from prospective registries showed that the background incidence of PRCA among patients exposed to epoetin alfa is between 14.0 and 35.8 per 100,000 patient-years.[32] The incidence may however increase up to 17-fold, as estimated for the post-manufacturing change formulation for Eprex.[33]

EVALUATION OF THE IMPACT OF EXPOSURE MISCLASSIFICATION

Direction of exposure misclassification

In this study, we assumed misclassification of drug exposure to be non-differential of the outcome (i.e., irrespective of the type of ADR) and to occur in one direction only. That is, a varying proportion of all events for the product associated with the unique risks was misattributed to any of the similar products. We thereby specifically aimed to study the impact of the previously reported finding that reporters may tend to misattribute generic-associated ADRs to innovator products (i.e., in one direction). Also, considering that the reporters are unaware of the specific product used by the patient, the misclassification was considered to be non-differential of the type of ADR reported.

Effect of exposure misclassification in test cases

For the three test cases, we calculated the number of cases and years to detection of the unique risk, along various levels (0–50%) of exposure misclassification. For this, we calculated the required patient exposure to generate a safety signal in the spontaneous reporting system for each test case in the situation of no misclassification and compared this with the situation in which exposure information was misattributed. As described above, two conditions should be met to generate a safety signal: [I] the lower-bound of the 95% CI of the PRR should be at least one, and [II] at least three reports should be available for the drug–event combination. The required patient exposure to generate a safety signal was calculated by combining the two conditions with the equation for the expected number of spontaneous ADR reports for a given drug–event combination ($N_{i,j}$), as further explained in the Supporting Information.

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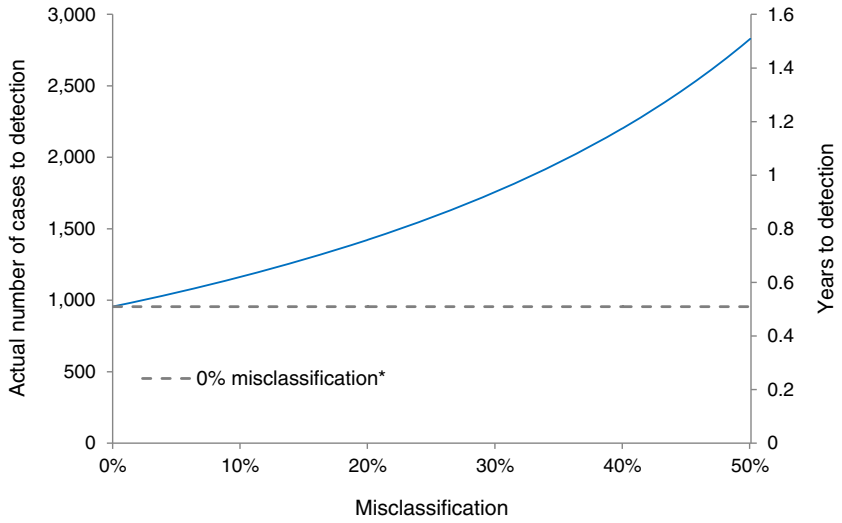

Figure 3. Effect of exposure misclassification on the ability to detect a product-specific risk for hypersensitivity reactions to infliximab.‡

All simulations were performed in Microsoft Excel 2013 (Microsoft, WA, USA). The tool we developed can be used to test additional scenarios and can be freely downloaded from escher.tipharma.com/tool.

Overall impact assessment of exposure misclassification

The overall impact of exposure misclassification was studied in general terms by varying the model parameters (relative risk and product market share) as described in Table 1 and assessing the effect of misclassification (0–99%) in relative terms. A number of model parameters (total patient exposure and background incidence unique event) were not included in this evaluation, because these parameters do not impact on the relative effect.

RESULTS

The analyses on the three test cases gave insight in the range of absolute effects of misclassification that can be expected in real-life signal detection, whereas the overall impact assessment shows which parameters are most affected by exposure misclassification.

For the case of hypersensitivity reactions to infliximab, which assumes a high background incidence but weak association with the product of interest (RR = 1.5; Table 1), we observed a large impact of exposure misclassification. As shown in Figure 3, the product-specific increased incidence is detectable through signal detection after the occurrence of 956 cases (of which 10% is assumed to be reported), which takes 0.5 years, in the situation where all ADR reports are attributed to the correct product (no misclassification scenario). In a scenario of 20% exposure misclassification, an additional 478 cases are required to detect the product-specific risk, taking an additional 0.25 years. This corresponds to a 49% increase in time and cases as compared with situation with no misclassification. A doubling in cases and time to detection of the product-specific risk was observed in the scenario of 34% misclassification.

As shown in Figure 4, a smaller impact of exposure misclassification was observed for the case of thrombotic microangiopathy with interferon beta, which assumed a low background incidence but relatively strong association (RR = 5) with the product of interest. In the scenario of 20% misclassification, an additional 30 cases are required, taking an additional 2.4 years to detect the product-specific risk. This corresponds to a 34% increase in cases and time as compared with situation with no misclassification. A doubling in cases and time to detect the product-specific risk was observed in the situation of 40% misclassification.

For the case of epoetin alfa-induced PRCA, which assumes a low background incidence and very strong association (RR = 17) with the product of interest, we observed only a modest impact of exposure misclassification. As shown in Figure 5, up to 22% misclassification will not result in a delayed identification of the safety signal, but, in contrast, in an earlier identification. This finding may be explained by the fact that low levels of exposure misclassification ensure that sufficient data is available in the reference category (i.e., PRCA cases for other products) for the disproportionality measure to reach statistical significance. It should, however, be

‡See Table 1 for model parameter assumptions. *In absence of exposure misclassification, it takes 956 cases/ 0.5 years (assuming 90% underreporting) to detect the product-specific risk.

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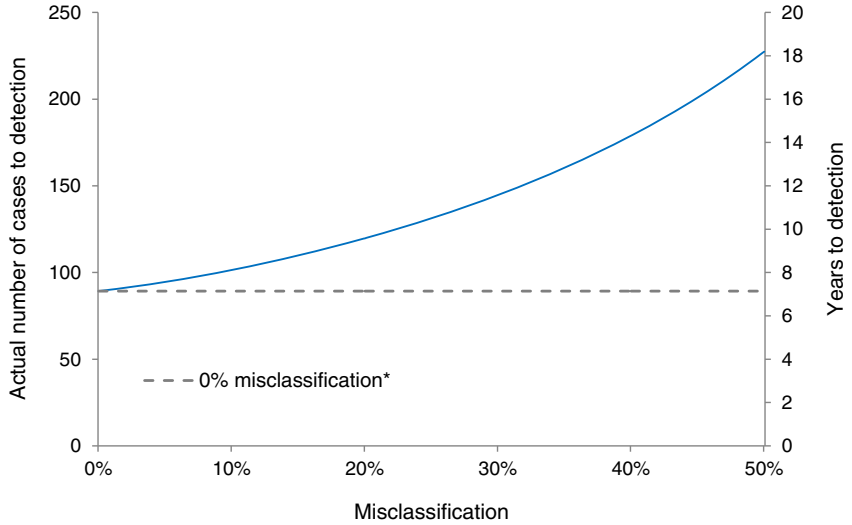

Figure 4. Effect of exposure misclassification on the ability to detect a product-specific risk for interferon beta-induced thrombotic microangiopathy.[§]

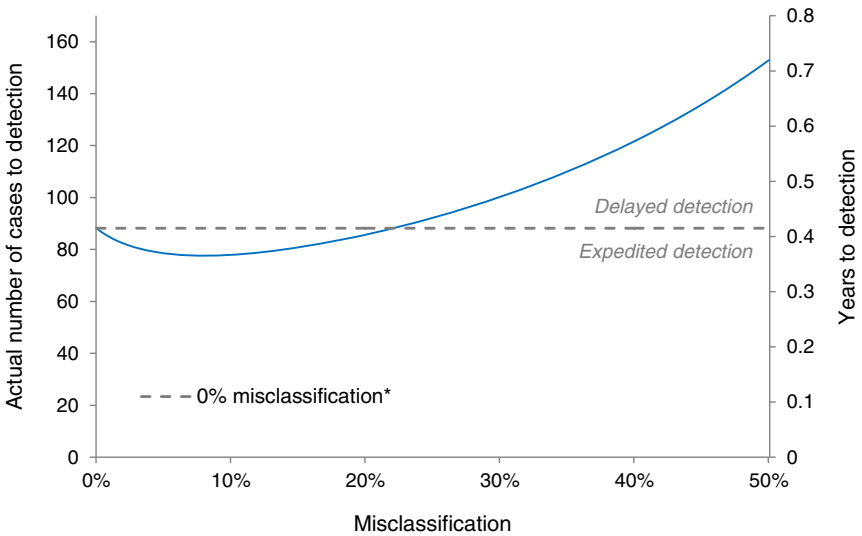

Figure 5. Effect of exposure misclassification on the ability to detect a product-specific risk for epoetin alfa-induced pure red cell aplasia.[¶]

noted that the detection of product-specific risks is in similar scenarios, in which an event with a low background incidence has a (very) strong association with one product, is mainly determined by the required time to have at least one case in the reference category. This was, however, not a condition in our model in which continuous variables (i.e., also values smaller than one) were allowed, and the actual impact of exposure misclassification may therefore even be smaller within similar scenarios.

In relative terms, the effect of exposure misclassification was found to be mostly dependent on the market share of the product, and to a lesser extent of the relative risk of the unique risk. As shown in Figure 6, for products with a low market share, 50% misclassification will result in an approximate 100% delay (i.e., doubling in cases and time) to recognition of new safety signals, largely irrespective of the relative risk of the event (Figure 6(A)). By contrast, for products with a high market share, 5% misclassification will already result in a doubling in cases and time to detect new safety signals with a low relative risk (Figure 6(C)). As shown in the situation for products with a 50% market share (Figure 6(B)), the relative delay increases with lower relative risks.

[§]See Table 1 for model parameter assumptions. *In absence of exposure misclassification, it takes 89 cases/ 7.1 years (assuming 90% underreporting) to detect the product-specific risk.

[¶]See Table 1 for model parameter assumptions. *In absence of exposure misclassification, it takes 88 cases/ 0.4 years (assuming 90% underreporting) to detect the product-specific risk.

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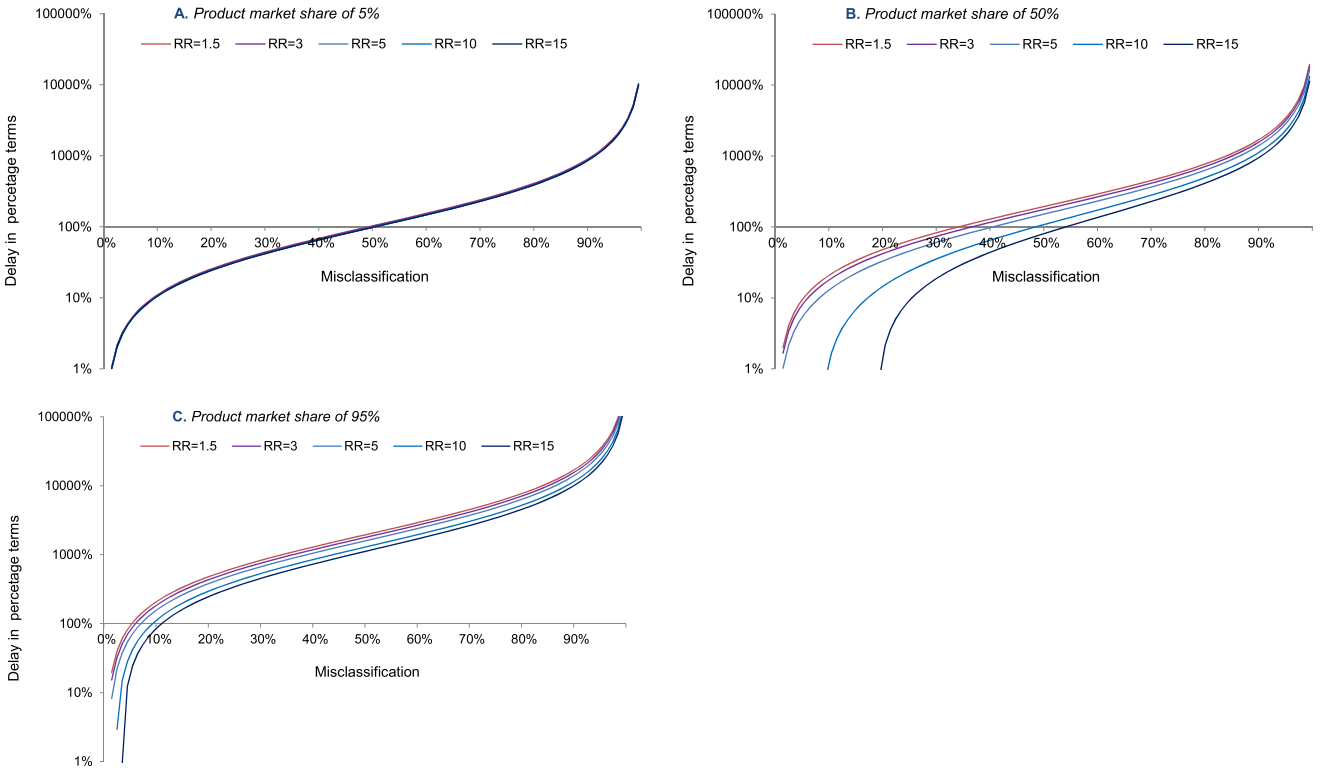

Figure 6. Delay in identification of product-specific safety signals (in percentage terms) through exposure misclassification, stratified by market share and relative risk.

DISCUSSION

This study shows the effect of exposure misclassification (i.e., incorrect exposure attribution) in spontaneous ADR reports on the time to detection of product-specific risks in spontaneous reporting systems. More specifically, we focussed on situations where product-specific signal detection is performed, and an ADR associated with one particular product (e.g., a biosimilar) is incorrectly attributed to another product containing the same active substance (e.g., the innovator) or vice versa. We found that exposure misclassification results in the largest delay in the identification of risks that have a relative weak association with the product of interest and in situations in which the product associated with the unique ADR has a large market share. By contrast, the detection of strong drug–event associations was found to be relatively robust to low levels of exposure misclassification. The absolute public health impact of exposure misclassification, in additional time and cases to detection of the product-specific risk, is highly dependent on the characteristics of the drug–event combination (patient exposure, background incidence event, etc.) and should therefore be assessed on a case-by-case basis.

The finding that the identification of strong drug–event associations is particularly robust to the effects of exposure misclassification is important. Spontaneous reports are highly effective in detecting events that are strongly associated with a certain exposure, but have a low background incidence in the treatment population. Well-known examples hereof include the risk of progressive multifocal leukoencephalopathy with natalizumab,[34] rhabdomyolysis with cerivastatin,[35] and the occurrence of congenital anomalies with thali domide.[36] Events that are, by contrast, only weakly associated with a certain exposure but occur with a relative high background rate are particularly difficult to detect. From the reporter's perspective, it may be difficult to recognize commonly occurring events (e.g., cardiovascular disease) as drug-induced, particularly when the drug only imparts a small risk.[37] Moreover, as previously demonstrated,[23] only strong associations may sufficiently 'compensate' for the variability in reporting to generate a signal in a spontaneous reporting system. For the detection of weak drug–event associations, which nevertheless may have a significant public health impact (e.g., cardiovascular events with rofecoxib[38]), one should therefore resort to other methods, and the observed effect of exposure misclassification in spontaneous reporting may be less relevant.

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A second finding from our study was that the product market share largely determines the relative impact of exposure misclassification. While a doubling in time and cases to detection was observed when 50% of the ADR for products with a low (5%) market share were misattributed, a similar effect was already observed when 5–10% of the ADR reports for products with a high (95%) market share were misattributed. The finding that products with a low market share are more robust to exposure misclassification is important, as it may be expected that the potential for misclassification will be higher for these products. For example, when a new product is gradually taken up in clinical practice, healthcare professionals and patients may initially not be familiar with the new product and, therefore, more likely to incorrectly attribute the ADR to the innovator product.

In this study, we focused on the occurrence of product-specific ADRs among biological, and explored the effect of exposure misclassification in product-specific signal detection procedures. Our findings may, however, also apply to evaluations for other manufacturing source-specific risks. Previous studies have, for example, shown that quantitative signal detection methods could also be used to study potential formu lation-specific (e.g., haemolytic events with liquid and lyophilized formulations of immunoglobulin[39]) and batch-specific ADRs (e.g., local reactions and fever with different batches of pandemic influenza vaccines[40]). Within batch-specific signal detection methods, the ADRs reported for a single batch are compared with the ADRs reported for all other batches of the same product. Although misclassification on the batch level may resemble the effects observed in this study, it is considered unlikely that reporters may misattribute ADRs to a specific batch, as was assumed for generic-associated ADRs to innovator products in this study. The main challenge for batch-specific safety evaluation is the general poor availability of batch-specific exposure information, as shown by previous studies,[9–11] which may hamper the timely identification of batch-specific safety signals. It is important to note that quantitative signal detection methods are not the only strategy through which product-specific safety signals may be identified in spontaneous reporting systems. Historically, the detection of safety signals has been based on the manual review of every ADR report sent to a spontaneous reporting system. Such case-by-case evaluations are still routinely carried out and play an important role in the identification of new ADRs.[41] These case-by-case evaluations may have a particular important role in the identification of strong drug–event associations. In this study, we found that for very high relative risks, the time/cases to detection of the signal is largely determined by the time required to have at least one case in the reference category (i.e., for the products not associated with the ADR). As this may result in a delayed detection of the safety signal, the quantitative method could therefore not be relied upon alone. Apart from this, it should be noted that quantitative signal detection methods are only used to highlight potential signals for further (manual) review. For the actual confirmation of the safety signal, a careful review of the individual case reports is required, including a clinical assessment of the strength and likelihood of the causal association. For such case-by-case evaluations of ADR reports, it will be important to have reliable data on the product-specific exposure, and the impact of misattributed reports has not been evaluated.

In this study, we made several assumptions for the data simulation procedure, which should be taken into account when interpreting the results. First, we assumed the ADR reporting patterns to be similar across similar biological products, because no differences in reporting probabilities can be expected when reporters are unaware of the product-specific exposure status. The actual reporting pattern may in practice, however, very well differ between similar biological products, as shown by a recent analysis of the Italian pharmacovigilance database.[12] Patients and health professionals may particularly be triggered to report ADRs for novel biosimilars, as these products will be under increased scrutiny, which could lead to the generation of false positive product-specific signals. Also, the overall underreporting rate was considered 90% in this study, irrespective of the drug-event combination. In clinical practice, the underreporting may, however, be highly variable, ranging from 36% up to >99%, as shown by a systematic review.[42] As shown in Figure S1, the absolute impact of exposure misclassification will be higher in scenarios of higher levels of underreporting, though the relative impact was unaffected in our simulation model.

A second point to consider is that we did not include the underlying discrete probability distribution for the expected number of ADR reports in our model. As shown in a previous simulation study,[23] the expected variance in reporting may result in the reporting of non-causal associations (i.e., false positive signals). Thirdly, we assumed the misclassification to occur exclusively in one direction and to be non-differential of the type of ADR reported. These assumptions were made because we specifically aimed to explore the impact of the previously reported finding that reporters may tend to misattribute generic-associated ADRs to innovator products. Exposure information may, however, instead also be misclassified in two directions or reported on active substance level rather than product level. The latter will

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resemble the effect of underreporting, for which the impact has been evaluated elsewhere.[43]

In conclusion, the present study is, to our knowledge, the first study to evaluate the direction and magnitude of the effect of incorrect exposure attribution in spontaneous ADR reports on the time to detection of product-specific safety signals. The largest effect was observed in the detection of weak drug–event associations, although the absolute public health impact of exposure misclassification was highly dependent on the characteristics of the drug–event combination, such as the patient exposure, and background incidence of the event. Because the extent of potential exposure misclassification in spontaneous ADR reports is currently unknown, no recommendation on how to correct for this issue in signal detection procedures can be provided, other than raising awareness for this potential phenomenon. With the increasing availability and use of biologicals, including biosimilars, product-specific safety evaluations will become increasingly important in the near future. When product-specific signal detection will be implemented in the upcoming years and methods are refined for use in daily practice, it is therefore important to keep in mind the challenges that we identified.

CONFLICT OF INTEREST

N. S. Vermeer, H. C. Ebbers, A. C. G. Egberts, H. G. M. Leufkens, and M. L. De Bruin have no conflicts of interest that are directly relevant to the content of this research.

KEY POINTS

- Signal detection procedures for biologicals should be specific to the product, apart from to the active substance, because differences in the safety profile may emerge between products containing the same active substance. Previous studies have, however, suggested that reporters may tend to misattribute generic-associated ADRs to innovator products.
- This simulation study shows the direction and magnitude of the effect of exposure misclassification (i.e., incorrect exposure attribution) in ADR reports on the time to detection of product-specific risks in spontaneous reporting systems.
- We show that exposure misclassification results in the largest delay in identification of risks that have a weak association with the product of interest (RR $<$ 2 or 3) and in situations where the product associated with the unique risk has a large ($>$50%) market share.

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