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# Cumulative incidence of cardiac surgery associated with exposure to benfluorex: A retrospective analysis based on compensation claims data

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Data on retrospective compensation claims for injuries caused by pharmaceutical drugs are prone to selection and reporting biases. Nevertheless, this case study of the antidiabetic drug benfluorex shows that such data can be used to estimate the cumulative incidence of drug-related injury, and to provide insights into its epidemiology. To this end, we develop a modelling framework for under-reporting of retrospective claims for compensation arising from drug damage. The model involves a longitudinal component related to attrition of cases over time, and a cross-sectional component related to incomplete reporting. We apply this model to cardiac valve surgery necessitated by exposure to benfluorex. Benfluorex was marketed in France between 1976 and 2009, when it was withdrawn because it caused valvular heart disease. A scandal erupted in 2010 over the scale of the damage caused by the drug. Since then, no further estimates of cumulative incidence have been published, though thousands of claims for compensation have been processed. The analysis combines compensation claims data and sociological survey data on benfluorex users, together with data on benfluorex sales and duration of treatment. We find a threshold of toxicity at about 6 months' exposure, and that at least 1690 individuals (95% CI 1290 to 2320) needed heart surgery to replace or repair valves damaged by exposure to benfluorex in France: a cumulative incidence of 3.68 per 10,000 (95% CI 2.68 to 5.34) benfluorex users or 3.22 per 10,000 (95% CI 2.48 to 4.39) person-years at risk above the exposure threshold. While these findings are tentative, they are consistent with those obtained previously using very different methods.

## KEYWORDS

benfluorex, compensation claim, cumulative incidence, pharmacoepidemiology, under-reporting, valvular heart disease

## 1 | INTRODUCTION

When a pharmaceutical drug is known to cause an adverse event, it is of interest to estimate the cumulative incidence of serious adverse events in persons exposed to the drug. This may be done prospectively in controlled epidemiological

**Abbreviations:** AFSSAPS, Agence française de sécurité sanitaire des produits de santé; AIC, Akaike information criterion; ANSM, Agence nationale de sécurité du médicament et des produits de santé; CI, confidence interval; CNAM, Caisse nationale de l'assurance maladie; DI-VHD, drug-induced valvular heart disease; ONIAM, Office national d'indemnisation des accidents médicaux; VHD, valvular heart disease.

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studies, but is more difficult to achieve retrospectively when contemporaneous records are unavailable, particularly if the drug has been withdrawn. Databases of claims and compensation payments for drug damage or medical errors may provide a source of data upon which to base such estimates, but these data are likely to be prone to severe under-reporting and selection bias.<sup>1</sup>

We develop a simple model to estimate the cumulative incidence of adverse events from retrospective compensation claims data, taking into account the two major sources of bias: under-reporting to the database by prevalent cases, and differential under-reporting within the database of claims relating to exposures that occurred in the more distant past. The model is motivated by the Mediator affair in France, in which the assessment of cumulative incidence of drug damage played a major part.

## 2 | THE MEDIATOR AFFAIR

Benfluorex, a pharmaceutical drug structurally related to fenfluramine, was licensed for the treatment of hyperlipidaemia and as an add-on treatment for type 2 diabetes in overweight patients, though it later came to be used off-label for weight loss, predominantly by women. It was manufactured by *Laboratoires Servier* and marketed in France under the trade name Mediator between 1 September 1976 and 30 November 2009, when it was withdrawn by the then French medicines agency AFSSAPS, several epidemiological studies having confirmed an association with valvular heart disease (VHD).<sup>2-4</sup>

From 2010, a controversy which was to have many ramifications erupted in France.<sup>5</sup> Central to it were reports of the likely burden of VHD caused by benfluorex over the period it was commercialised: thousands of admissions to hospital for treatment or surgery, and between 500 and 1300 deaths depending on duration of follow-up.<sup>6,7</sup> These estimates were contested by *Laboratoires Servier* and some cardiologists.<sup>8,9</sup> The scandal took on a political dimension relating to conflicts of interest, leading to reform of the French medicines agency (which was reconstituted as ANSM), parliamentary enquiries, and protracted litigation right up to the Court of Appeal in 2023.<sup>10,11</sup>

Prior to the Mediator affair, ONIAM (the French office for compensation of medical accidents) did not deal with adverse events caused by pharmaceutical drugs other than compulsory vaccines. But in 2011, its remit was widened to include claims for compensation from victims of benfluorex. The benefit for potential victims was that the procedure is out-of-court, free of charge, and quicker than legal action. In subsequent years, further evidence that benfluorex caused drug-induced VHD (DI-VHD) emerged.<sup>12,13</sup> A better understanding was gained of its clinical features and of why the link had not been uncovered earlier: it became apparent that DI-VHD related to benfluorex exposure had been incorrectly classified as being of rheumatic origin.<sup>14,15</sup> This led to a further change in the law in 2016 to allow ONIAM to reconsider previously rejected claims for compensation. By 2022, over 10,000 claims had been submitted to ONIAM, of which over 4,000 were validated.<sup>16</sup> Research was also undertaken to explore the epistemological aspects of the Mediator affair and its socio-political implications.<sup>17,18</sup> In contrast, despite the controversy surrounding the original reports, no new estimates of the damage caused by the drug have been published to date.

The case study presented in this paper was undertaken in an attempt to evaluate the burden of severe VHD caused by the drug, independently of earlier estimates. It is based on data from a survey of users of benfluorex undertaken between 2014 and 2017, which formed part of a wider sociological study of benfluorex in France including its use and its impacts, and the largest existing case series of DI-VHD, assembled between 2012 and 2020 and published by experts advising ONIAM.<sup>17,19</sup> The precise context of this evaluation is set out in the declaration of interest at the end of the paper.

## 3 | METHOD

Consider a pharmaceutical drug introduced at time  $t = 0$  and withdrawn at some later time  $t = T$ . The adverse event of interest may occur at any moment after an individual was first exposed at time  $t$ ,  $0 \leq t < T$ , right up to the present time  $U$ . Compensation claims for adverse events caused by the drug may only be lodged after  $T$  up until  $U$ ; it is assumed that sufficient time has elapsed between  $T$  and  $U$  for all adverse events to have occurred and claims to have been made.

There are two distinct sources of under-reporting to take into account. First, exposed patients who have experienced the event (whom we shall refer to as cases) must be present after  $T$  to be able to make a claim, whether or not they do so. (In rare instances, claims may also be made on behalf of patients who have died.) Second, only a proportion of cases present after  $T$  will make a claim. We shall refer to these two sources of under-reporting, respectively, as longitudinal (relating to attrition of cases over time) and cross-sectional (relating to under-reporting of cases present after  $T$ ). The longitudinal

component may result, for example, from patients dying; the cross-sectional component reflects the propensity of cases to lodge a claim, some perhaps choosing not to do so because of the complexity of the procedure.

Let  $m(t)$  be the mean duration of exposures for patients first exposed at time  $t$ ,  $P(t)$  the frequency density of first exposures at  $t$  (integrating to the total number of persons exposed over  $[0, T]$ ), and  $\lambda$  the event rate per unit person-time at risk. The rate is assumed to be low, and only one event occurs per case. Let  $m \geq 0$  be the threshold exposure, below which the risk is zero, so that  $m'(t) = \max\{m(t) - m, 0\}$  is the mean time at risk for exposures starting at  $t$ . The expected number of cases with first exposure in  $[t, t + dt)$  is  $v(t)dt = \lambda P(t)m'(t)dt$ . We want to estimate  $N = \int_0^T v(t)dt$ .

As described above, cases need to be present after  $T$  in order to be reported to the claims database. Define the following probabilities for  $0 \leq t < T$ :

$$\begin{aligned} \pi(t) &= P(\text{case present after } T \mid \text{case first exposed at time } t), \\ \theta(t) &= P(\text{case reported} \mid \text{case present after } T, \text{ case first exposed at time } t). \end{aligned}$$

The function  $\pi(t)$ , or more precisely its complement  $1 - \pi(t)$ , measures the attrition between  $t$  and  $T$  of cases first exposed at  $t$ . Accordingly we would expect  $\pi(t)$  to decrease (or at least to be non-increasing) as  $T - t$  increases, and to tend to 1 as  $t$  tends to  $T$ . Similarly, if  $\theta(t)$  depends on  $t$ , we might expect it to be greatest at  $t = T$  and decrease as  $T - t$  increases, events relating to exposures in the more distant past being less likely to be reported. Combining these probabilities, we obtain

$$\theta(t)\pi(t) = P(\text{case reported} \mid \text{case first exposed at time } t),$$

since to be reported, the case needs to be present after  $T$ .

The estimable quantities include the proportions reported  $\theta(t)$  and the reported event rate  $\mu(t) = \lambda\theta(t)\pi(t)$ . Furthermore,  $\pi(t) \leq 1$  and  $\pi(T) = 1$ . We may express  $\pi(t)$  in terms of these quantities as follows:

$$\pi(t) = \frac{\mu(t)/\theta(t)}{\mu(t_0)/\theta(t_0)},$$

where  $t_0$  is the value of  $t \in [0, T]$  that maximises  $\mu(t)/\theta(t)$ , so that  $\pi(t_0) = 1$ . While we expect  $t_0 = T$ , we do not require it to be so a priori, to allow for random fluctuation in the location of the maximum. Suppose that  $C(t)dt$  cases with first exposure starting in  $[t, t + dt)$  are reported (and are thus also present after  $T$ ). Then  $C(t)$  has expectation  $c(t) = v(t)\theta(t)\pi(t)$ . Setting  $\pi'(t) = \mu(t)/\mu(t_0)$ , we obtain

$$\begin{aligned} N &= \frac{1}{\theta(t_0)} \int_0^T \frac{c(t)}{\pi'(t)} dt \\ &= \frac{\mu(t_0)}{\theta(t_0)} \times \Delta, \end{aligned}$$

where  $\Delta = \int_0^T P(t)m'(t)dt$  is the total person-time at risk. The latter displayed expression helps to bring into focus the key quantities involved:  $\mu(t_0)$ ,  $\theta(t_0)$ , and  $\Delta$ .

Simplifications arise when  $\theta(t)$  does not depend on time of first exposure  $t$ , but takes the constant value  $\theta$ . As we shall see, this applies to the present case study. In this setting,

$$\begin{aligned} \theta &= P(\text{case reported} \mid \text{case present after } T), \\ \pi(t) &= \pi'(t) = \frac{\mu(t)}{\mu(t_0)}, \end{aligned}$$

where  $t_0$  is now the value of  $t \in [0, T]$  that maximises  $\mu(t)$ , and

$$N = \frac{1}{\theta} \int_0^T \frac{c(t)}{\pi(t)} dt. \tag{1}$$

$N$  is estimated by substituting estimators for  $c(t)$ ,  $\theta$  and  $\pi(t)$  in Equation (1). This development takes no account of any attrition of cases after  $T$ , and in particular between  $T$ , the time the drug was withdrawn, and  $T' \geq T$ , the time at which

**TABLE 1** Quarter after benfluorex initiation in which treatment ended: Data from 1075 persons starting treatment in 2005–2007, and fitted values from the modified geometric model.

Quarter	Proportion	Count	Fitted
1	0.41	445	445.00
2	0.10	109	109.00
3	0.05	54	47.10
4	0.04	43	42.84
5	0.03	33	38.97
6	0.03	33	35.45
> 6	0.33	358	356.64

reports to the claims database began. In the present case study,  $T' > T$  and cases need to be present after  $T'$ , rather than after  $T$ , to be reported. If there is such attrition, then  $\pi(t)$  may be strictly less than 1 on  $[0, T]$ , and setting its maximum to 1 as we have done would then underestimate the total number of cases  $N$ .

In the present case study, we will estimate the number of individuals undergoing cardiac surgery for DI-VHD necessitated by exposure to benfluorex. Time  $t = 0$  corresponds to 1 September 1976, and time  $t = T$  to 30 November 2009. The decree setting up the compensation scheme was issued on 29 July 2011, which corresponds to  $T'$ , and the analysis includes data up to June 2020, which corresponds to  $U$ . The following stages are involved in the analysis.

We begin with data on treatment duration and sales figures, to derive by back-calculation the number of new users of benfluorex in each year from 1976 to 2009. We also calculate the mean person-time of exposure in each annual cohort, to provide denominators for the reporting rates. Next, we estimate  $\theta(t)$ , using a separate survey. Then, we develop a model for the numbers of users who underwent cardiac valve surgery owing to valvular disorders caused by benfluorex, as assessed by ONIAM. This model is used to estimate the function  $\pi(t)$ . The two sources of under-reporting are then combined to estimate the total number  $N$  of operated cases of DI-VHD caused by benfluorex exposure. Finally, confidence intervals are obtained by bootstrapping the entire procedure as will be explained in Section 10, where the key assumptions underlying the method are also assessed critically.

#### 4 | DURATION OF TREATMENT WITH BENFLUOREX

We begin by estimating the distribution of durations of treatment with benfluorex, based on a sample of 1075 women who started on benfluorex in 2005–2007.<sup>7</sup> The data, in the form of proportions by quarter in which treatment ended, are in Table 1; the counts were deduced from these proportions.

These data are well fitted by a three-parameter modified geometric distribution on  $\{n : n = 1, 2, \dots\}$ ,  $n$  being the quarter in which treatment ended, with probability mass function  $p(1) = p_1$ ,  $p(2) = (1 - p_1)p_2$ , and  $p(n) = (1 - p_1)(1 - p_2)(1 - p_3)^{(n-3)}p_3$  for  $n \geq 3$ . The mean of this distribution is:

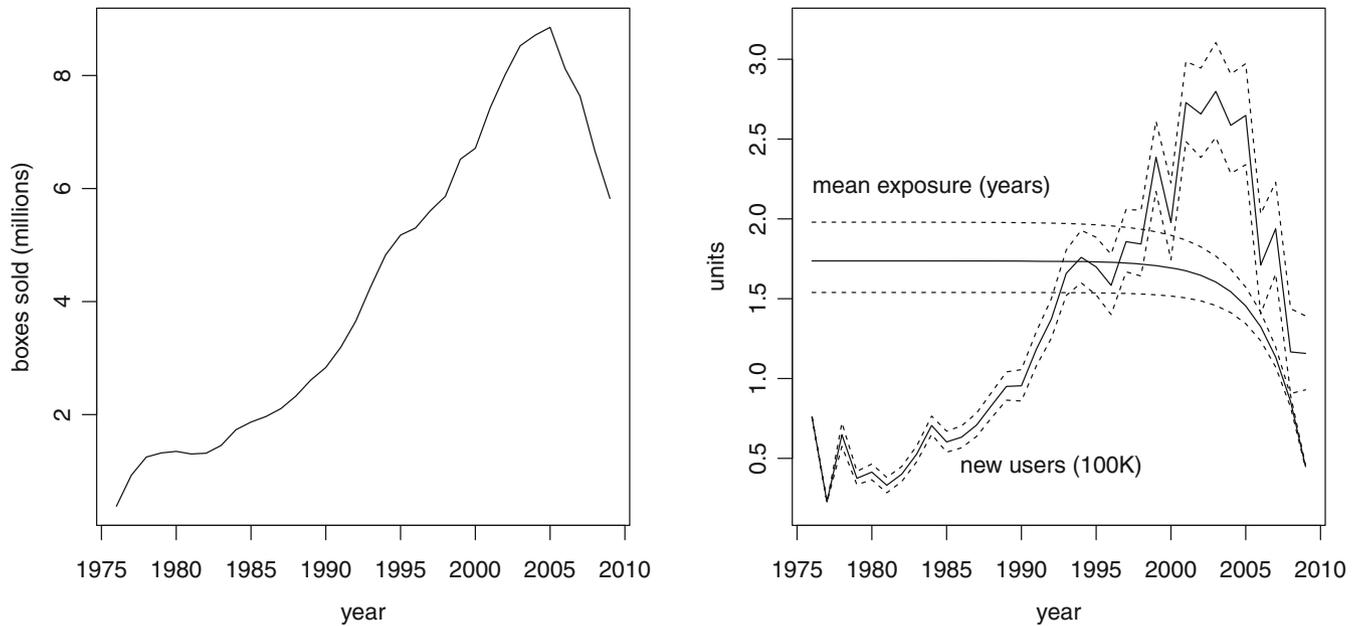
$$\delta = (2 - p_1) + (1 - p_1)(1 - p_2)/p_3.$$

Note that this mean is likely to be larger than the mean of the actual treatment durations, because it is not restricted by the withdrawal of the drug.

The maximum likelihood estimates are  $\hat{p}_1 = 0.414$ ,  $\hat{p}_2 = 0.173$ ,  $\hat{p}_3 = 0.0904$ . The estimated (unrestricted) mean is  $\hat{\delta} = 6.95$  quarters, 95% CI (6.16, 7.92). The fitted values are shown in Table 1. The Pearson chi-squared goodness of fit statistic is 2.10 on 3 degrees of freedom,  $p = 0.552$ .

#### 5 | PERSON-YEARS OF EXPOSURE TO BENFLUOREX BY ANNUAL COHORT

The number of boxes of Mediator sold each year in France are shown in the left panel of Figure 1. The sales figure for 2009 pertains to the first three quarters of 2009, so was extrapolated (by multiplying by 334/273) to the period up until



**FIGURE 1** Left: Annual sales of boxes of Mediator in France. Right: Estimated new users by year, and estimated mean duration of benfluorex exposure (full lines), with pointwise 95% confidence bands (dashed lines).

the drug’s withdrawal on 30 November that year. We also know that, per person, five boxes of Mediator correspond to 3 months’ treatment.<sup>7</sup> Using the treatment duration distribution derived in the previous section, we may derive the numbers starting treatment by back-calculation, based on the relation:

$$N_j = 5 \times \sum_{i=1}^j B_i S_{j-i} \tag{2}$$

for  $j = 1, \dots, 133$ . The subscript  $j$  represents quarters; quarter  $j = 1$  is the last quarter of 1976 (when sales of Mediator began) and quarter  $j = 133$  is the last quarter of 2009 (when it was withdrawn). In Equation (2),  $N_j$  is the numbers of boxes sold in quarter  $j$ ,  $B_j$  is the number of users starting in quarter  $j$ , and  $S_j$  is the probability that treatment does not end in quarters  $1, \dots, j$ , with  $S_0 = 1$ .

We work in discrete time with quarters as units. If treatment starts in quarter  $j$ , we assume it starts at the beginning of the quarter; if it ends in quarter  $j$ , it ends just before the end of that quarter.

Since the sales data are annual, we define  $T_1 = N_1$ ,  $T_k = N_{4k-6} + N_{4k-5} + N_{4k-4} + N_{4k-3}$  to represent the annual sales with  $k = 1$  corresponding to 1976 and  $k = 34$  to 2009. Similarly, to reduce dimensionality, we set  $D_1 = B_1$ ,  $D_k = B_{4k-6} = B_{4k-5} = B_{4k-4} = B_{4k-3}$  for  $2 \leq k \leq 34$ . The numbers of new starters on benfluorex in year  $k$  are  $P_1 = D_1$ ,  $P_k = 4D_k$  for  $k = 2, \dots, 34$ . Equation (2) then leads to the following recurrence relation for the  $P_k$ :

$$\begin{aligned} P_1 &= \frac{1}{5} T_1, \\ P_2 &= \left\{ \frac{4}{5} T_2 - 4P_1(S_1 + S_2 + S_3 + S_4) \right\} \times (4 + 3S_1 + 2S_2 + S_3)^{-1}, \\ P_k &= \left\{ \frac{4}{5} T_k - 4P_1(S_{4(k-1)-3} + S_{4(k-1)-2} + S_{4(k-1)-1} + S_{4(k-1)}) \right. \\ &\quad \left. - \sum_{i=2}^{k-1} P_i(S_{4(k-i)-3} + 2S_{4(k-i)-2} + 3S_{4(k-i)-1} + 4S_{4(k-i)} + 3S_{4(k-i)+1} + 2S_{4(k-i)+2} + S_{4(k-i)+3}) \right\} \\ &\quad \times (4 + 3S_1 + 2S_2 + S_3)^{-1} \text{ for } k = 3, \dots, 34. \end{aligned}$$

The estimated annual numbers of patients  $P_k$  starting on benfluorex in years  $k = 1$  (1976) to  $k = 34$  (2009) are shown in the right panel of Figure 1. The total number of users over this period is estimated to be 4.58 million, 95% CI (4.08, 5.10).

We also need the total consumption of benfluorex by each annual cohort of new users. The average duration (in quarters) of benfluorex exposure for a person starting treatment in quarter  $j$  is:

$$\eta_j = \sum_{i=1}^{133-j+1} ip(i) + (133-j+1)S_{133-j+1} \text{ for } j = 1, \dots, 133,$$

where  $p(i)$  is the probability mass function estimated in Section 4. Thus the average duration of exposure, in years, for persons starting benfluorex in year  $k$  is:

$$m_1 = \frac{1}{4}\eta_1,$$

$$m_k = \frac{1}{16}(\eta_{4k-6} + \eta_{4k-5} + \eta_{4k-4} + \eta_{4k-3}) \text{ for } k = 2, \dots, 34.$$

The  $m_k$  change little up to the year 2000, then decline rapidly as a result of the censoring induced by withdrawal of the drug (Figure 1, right panel). The total person-years of exposure in each annual cohort are  $P_k m_k$ ,  $k = 1, \dots, 34$ . The weighted mean duration of treatment with benfluorex over the lifetime of the drug,  $\sum_k P_k m_k / \sum_k P_k$ , is estimated to be 1.59 years, 95% CI (1.43, 1.78).

## 6 | ESTIMATION OF CROSS-SECTIONAL UNDER-REPORTING

The cross-sectional under-reporting function  $\theta(t)$  introduced in Section 3 was estimated from an independent survey of users of benfluorex.<sup>17</sup> This survey was added on to a case-control study of benfluorex users, in which the cases were users who had developed VHD attributable to benfluorex and the controls were users who had not developed VHD. The purpose of the survey was to investigate, from a sociological perspective, the factors influencing patients' attitudes, and their awareness of and involvement with mechanisms for obtaining redress, including ONIAM.

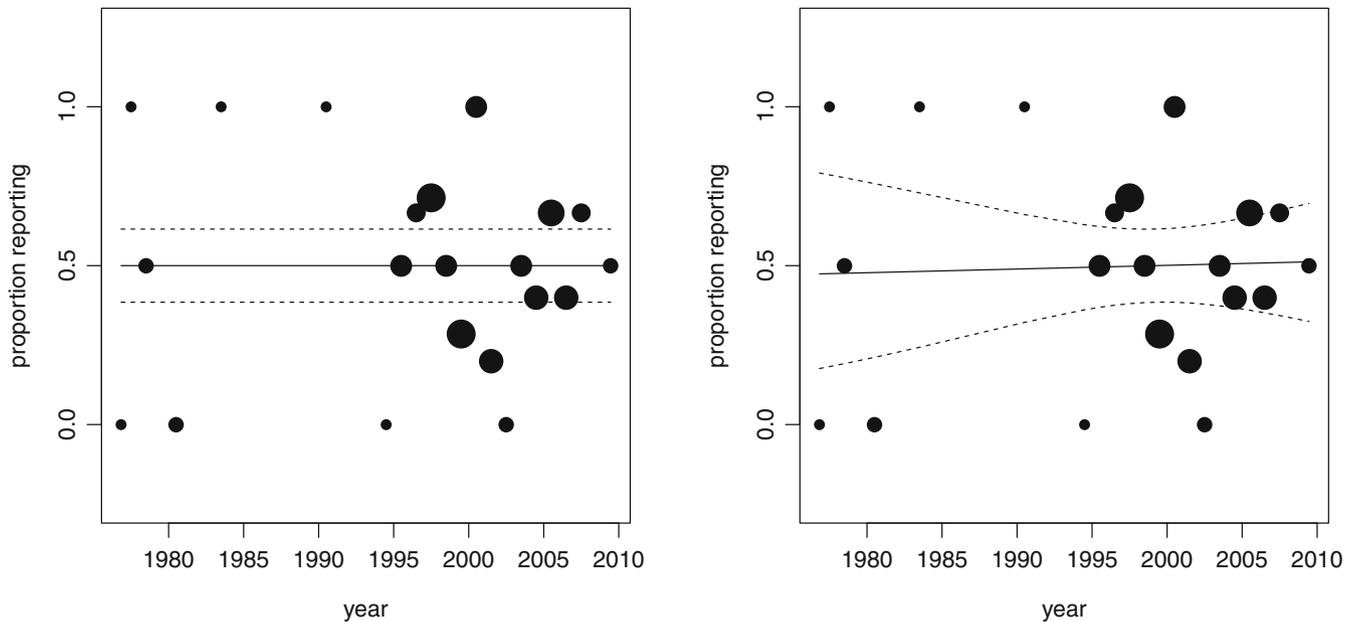
Recruitment for the survey began in June 2014 and ended in November 2015, and included the 109 cases within the case-control study who had been contacted by that time. Cases were recruited within participating centres or with the help of associations of victims of benfluorex. For context, by the end of May 2015 ONIAM had received 8787 compensation claims relating to benfluorex, 92% of the 9584 claims on which the surgery data (to be described in Section 7) are based.<sup>19,20</sup>

We focus on the 81 cases who agreed to participate in this survey, out of the 109 cases contacted, a response rate of 74%. Of these 81, 40 had lodged a claim with ONIAM. The main motivations for lodging a claim were that the procedure was free of charge, the hope of obtaining a quick result, and having been advised to do so by an association of victims of benfluorex. A commonly expressed reason for not pursuing a claim was discouragement when confronted with a complex procedure.<sup>17</sup>

These data may be used to estimate cross-sectional under-reporting. However, in line with the model described in Section 3, we need to check whether the proportion of persons making a claim varies with the year they started on benfluorex.

Of the 81 cases, 70 had information on year of first exposure to benfluorex; within this subgroup, 35 made a claim to ONIAM and 35 did not. For 21 of the 34 years there was at least one person starting on benfluorex in that year (including 1976 and 2009). We fitted logistic regression models with binomial error to the proportions making a claim for each year of first exposure. The model with just the grand mean gave a deviance of 24.368 on 20 degrees of freedom; the model with time trend had deviance 24.345 on 19 degrees of freedom. The deviance difference of 0.0225 on 1 degree of freedom does not indicate the presence of a trend ( $p = 0.881$ ). The Pearson goodness of fit statistic for the model without trend was 19.1 on 20 degrees of freedom,  $p = 0.515$ . This suggests a good fit, with no overdispersion. The two fitted models (with and without time trend) are shown in Figure 2.

Neither the formal test nor the estimated trend line in the right panel of Figure 2 suggest that  $\theta(t)$  varies with  $t$ . We therefore estimate its constant value  $\theta$  from the full data set as  $\hat{\theta} = 40/81$ , and derive its confidence interval by bootstrapping as part of the overall estimation method. We obtain  $\hat{\theta} = 0.494$ , 95% CI (0.383, 0.605).



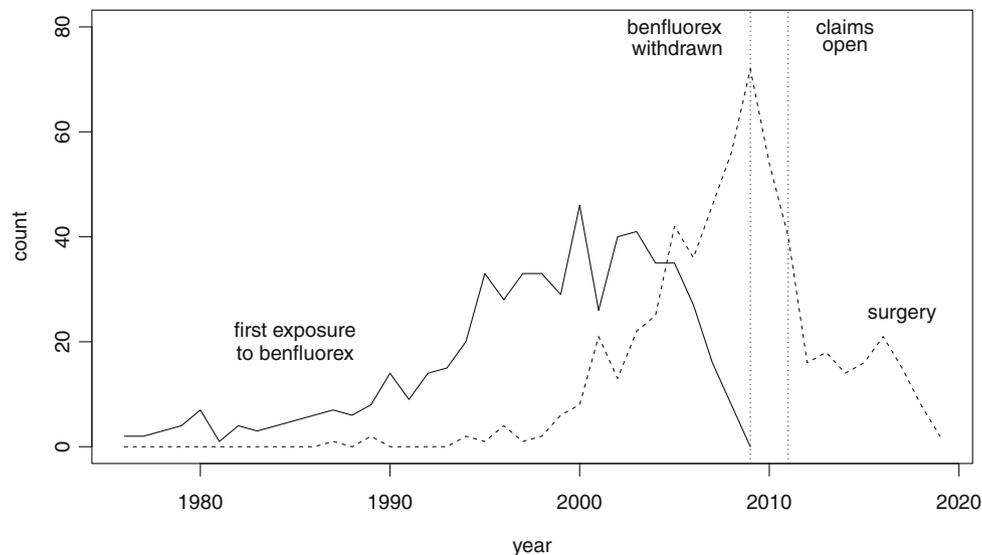
**FIGURE 2** Proportion reporting a claim to ONIAM by year of first exposure to benfluorex. The circles are the data points; circle areas are proportional to the denominators. Left panel: Grand mean model (full line) with 95% confidence interval (dashed lines). Right panel: Model with trend (full line), with pointwise 95% confidence band (dashed lines).

## 7 | LONGITUDINAL ATTRITION AND DOSE RESPONSE

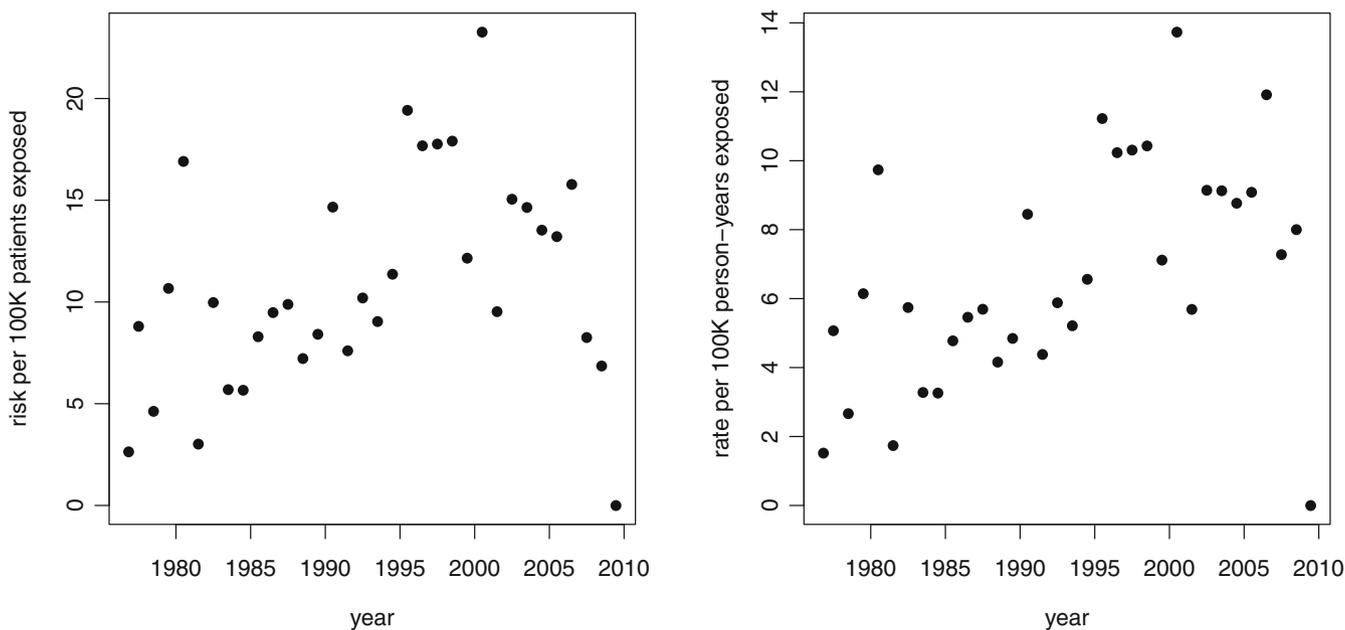
In this section we describe the data underpinning the estimation of the longitudinal attrition function  $\pi(t)$  defined in Section 3. These data also provide information on dose response. We use data on 564 validated compensation claims for benfluorex-related DI-VHD requiring surgical valve replacement or repair.<sup>19</sup> Validation was undertaken by a panel of experts from ONIAM in an adversarial procedure with lawyers and experts from *Laboratoires Servier*. The diagnostic procedure for DI-VHD included pathology analysis of the valves, which was available for 276 patients; echocardiography examination; and evaluation of evidence of VHD causes other than benfluorex exposure. Of the 564, 530 (94%) had at least one valve replaced; 34 had valve repairs only (not including redo surgery). The patients were identified from a review of the 9584 benfluorex-related claims to ONIAM up to June 2020, of whom 1031 underwent cardiac surgery. 467 patients with surgery were excluded, 453 because benfluorex exposure was deemed not to be the cause and 14 owing to lack of data or consent. Figure 3 shows the distribution of year of first exposure to benfluorex for the 564 validated cases, and the year surgery was undertaken.

Among the 564 reported (and validated) cases, let  $C_k$ ,  $k = 1, \dots, 34$  denote the number of individuals starting benfluorex in year  $k$  who went on to have a surgical intervention that resulted in a valid claim. The left-hand panel of Figure 4 shows the observed risk  $\rho_k = C_k/P_k$  per 100,000 persons first exposed in year  $k$ . The risk increases to a maximum in 2000, then declines. We interpret the increase in  $\rho_k$  as being the result of more complete reporting in the more recent past, and the decline as being the result of reduced cumulative exposure to benfluorex in the post-2000 cohorts, owing to its withdrawal in 2009. The right-hand panel of Figure 4, on the other hand, shows the observed rate  $\sigma_k = C_k/(P_k m_k)$  per 100,000 person-years of exposure: the upward trend now continues to 2008. We interpret the increase in the rate  $\sigma_k$  up to 2008 as the result of more complete reporting in more recent cohorts.

The rate for 2009 is zero: there were no surgeries in this cohort, and this year appears as a clear outlier in the right-hand panel of Figure 4. There are two possible interpretations of this observation. One is that the zero count for 2009 is a random zero, resulting from the comparatively low duration of exposure for that cohort: 0.448 year on average, 95% CI (0.437, 0.459). The alternative is that the zero count is structural, owing to a threshold of exposure below which DI-VHD either does not develop, or does not progress to the point where surgery is required. These interpretations, and the estimation of  $\pi(t)$ , will be explored further in the next section.



**FIGURE 3** Details of 564 DI-VHD surgery cases from ONIAM. Full line: Distribution by year of first exposure to benfluorex. Dashed line: Distribution by year of surgery. The vertical dotted lines indicate the year benfluorex was withdrawn (2009), and the year ONIAM began accepting compensation claims relating to benfluorex exposure (2011).



**FIGURE 4** Surgery for DI-VHD by year of first exposure to benfluorex. Left panel: Risk per 100K persons exposed. Right panel: Rate per 100K person-years of exposure.

## 8 | QUASI-POISSON MODELS

The risks and rates of Section 7 may be represented by quasi-Poisson models. The risks  $\rho_k$  were modelled using a quasi-Poisson log-linear model with offset  $\log(P_k)$  and two linear trends, one for the cohorts up to 2000, the other for the post-2000 cohorts; this was implemented as a  $\text{linear} \times \text{period}$  term in the linear predictor. We also fitted the reduced model with just a single trend. The deviance for the full model ( $\text{linear} \times \text{period}$ ) was 60.473 on 30 degrees of freedom; and for the reduced model (single trend) it was 100.52 on 32 degrees of freedom. The  $F_{2,30}$  test statistic was 9.93,  $p = 0.000489$ . We concluded that the decline in risk for the post-2000 cohorts is a genuine effect, most likely reflecting reduced cumulative exposure in these cohorts.

We modelled the person-time rates  $\sigma_k$  also using a quasi-Poisson log-linear model, but with person-time offset  $\log(P_k m_k)$ , a linear term (for the under-reporting) and an indicator variable (for 2009), then tested the reduced model without the indicator variable. The deviance for the full model (trend + indicator) was 48.232 on 31 degrees of freedom; and for the reduced model (trend only) it was 59.720 on 32 degrees of freedom. The  $F_{1,31}$  statistic was 7.38,  $p = 0.0107$ . We also fitted a quadratic model, with and without the indicator for 2009. The deviances were 43.059 on 30 degrees of freedom for the full model and 51.963 on 31 degrees of freedom for the reduced model. The  $F_{1,30}$  statistic was 6.20,  $p = 0.0185$ . We concluded that the data do not support the null hypothesis of a random zero, and that the 2009 zero count is more likely due to a threshold effect at around 6 months' exposure.

The post-2000 decline in risk suggests that above the threshold, the risk increases with average duration of exposure, at least up to the plateau at about 1.74 years (21 months) shown in Figure 1 (right panel); beyond that there is insufficient information owing to lack of variation in mean duration of exposure.

Since there is a threshold effect at  $m = m_{34} = 0.448$  year, the average time at risk for individuals starting benfluorex in year  $k$  is  $m'_k = m_k - m$ ,  $k = 1, \dots, 33$ . The corresponding rates are  $\tau_k = C_k / (P_k m'_k)$ ; these will be used to estimate the function  $\pi(t)$ , in line with Section 3.

To this end, we fitted two further quasi-Poisson log-linear models with person-time at risk offset  $\log(P_k m'_k)$  for  $k = 1, \dots, 33$ : the first with a linear trend, the second with an additional quadratic term. The quadratic model was fitted to check for evidence of curvature in  $\pi(t)$ , and to assess sensitivity to modelling assumptions.

The deviances were 44.752 on 31 degrees of freedom for the linear model, and 42.682 on 30 degrees of freedom for the quadratic model. The  $F_{1,30}$  statistic was 1.46,  $p = 0.237$ . Thus, including a quadratic term did not significantly improve model fit. The dispersion parameters were similar:  $\phi = 1.50$  for the linear model and  $\phi = 1.51$  for the quadratic model. Figure 5 shows the fitted trends  $\hat{c}_k / P_k m'_k$  with 95% pointwise confidence bands under each of the two models;  $\hat{c}_k$  is the estimated expected value of the count  $C_k$ . Both trend lines are monotone increasing.

From these models, parameterised in terms of the time interval  $T - t$  where  $T$  corresponds to 30 November 2009, we derive the following estimates of  $\pi(t)$ . For the linear model,  $\hat{\pi}(t) = \exp(\hat{\beta}(T - t))$  with  $\hat{\beta} = -0.0362$ , 95% CI  $(-0.0495, -0.0238)$ . For the quadratic model,  $\hat{\pi}(t) = \exp(\hat{\beta}(T - t) + \hat{\gamma}(T - t)^2)$  with  $\hat{\beta} = -0.00583$ , 95% CI  $(-0.0522, 0.0437)$ , and  $\hat{\gamma} = -0.00102$ , 95% CI  $(-0.00266, 0.000389)$ . The correlation between the two parameter estimates was  $-0.959$ .

While there is little difference between the linear and quadratic trends shown in Figure 5, their maximal values on  $[0, T]$  (both attained at  $t = T$ ) are different. This will affect the estimation of the cumulative incidences, to be discussed in Section 9.

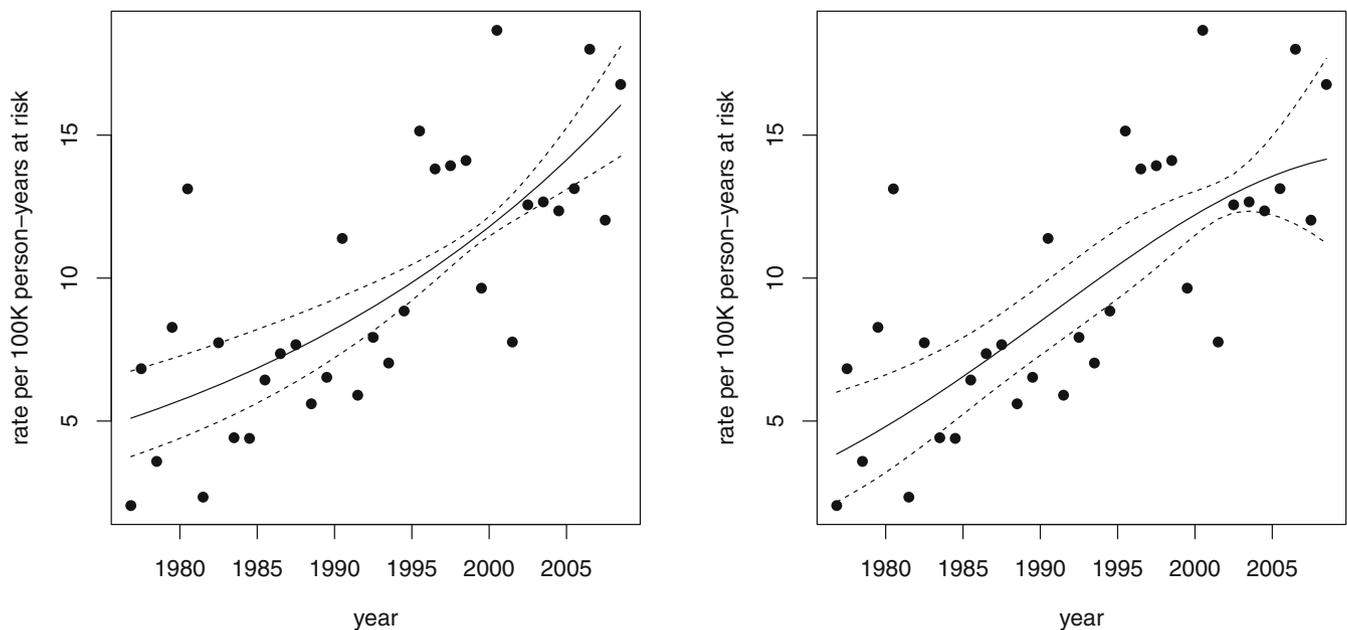


FIGURE 5 Rate of surgery for DI-VHD per 100K person-years at risk (exposure over the 0.448 year threshold), by year of first exposure to benfluorex: Data, fitted models (full lines) and pointwise 95% confidence bands (dashed lines). Left panel: Linear model; Right panel: Quadratic model.

**TABLE 2** Estimates of cumulative incidence of surgery, cumulative incidence risk (per 10,000 benfluorex users), and cumulative incidence rate (per 10,000 person-years of benfluorex exposure beyond 0.448 year): Linear and quadratic models, and model averages, with 95% confidence intervals.

Quantity	Linear model	Quadratic model	Model average
AIC <sub>c</sub>	191.29	192.27	—
Weight	0.620	0.380	—
Cumulative incidence	1790	1520	1690
95% CI	(1400, 2390)	(1190, 2190)	(1290, 2320)
Cumulative risk	3.91	3.31	3.68
95% CI	(2.92, 5.50)	(2.48, 5.06)	(2.68, 5.34)
Cumulative rate	3.42	2.90	3.22
95% CI	(2.70, 4.53)	(2.29, 4.15)	(2.48, 4.39)

## 9 | ESTIMATED CUMULATIVE INCIDENCE OF SURGERY

Putting these various estimates together we obtain the total number of cases, from Equation (1) suitably modified for grouped data:

$$\hat{N} = \frac{1}{\hat{\theta}} \sum_{k=1}^{34} \frac{\hat{c}_k}{\hat{\pi}(k)},$$

where  $k$  denotes the year of first exposure. We obtained two sets of estimates, according to whether the linear or the quadratic model was used to obtain  $\hat{\pi}(t)$ . These estimates, along with 95% confidence intervals, are displayed in Table 2. The linear model for  $\pi(t)$  yields  $\hat{N} = 1790$ , and the quadratic model yields  $\hat{N} = 1520$ , even though there is little difference between the model fits reported in Section 8. The reason for the difference in the estimates of  $N$ , as noted in Section 8 and demonstrated in Section 3, is that while the trend lines are similar, the endpoints at  $t = T$  are different.

The standard model choice approach would lead us to select the linear model over the quadratic model, as the former is more parsimonious. Instead, we chose to acknowledge the model uncertainty and adopted a model averaging approach using AIC weights. The Poisson AIC, corrected for overdispersion, is:

$$\text{AIC}_c = -2 \log(L) + 2p\phi,$$

where  $L$  is the maximised Poisson likelihood,  $p$  is the number of estimated parameters in the linear predictor, and  $\phi \geq 1$  is the dispersion.<sup>21</sup> The AIC weights are proportional to  $\exp(-\text{AIC}_c/2)$  and sum to 1. These are shown in Table 2, along with the resulting model averages for the cumulative incidence. Using the person denominators  $\sum_k P_k$  and the person-time at risk denominators  $\sum_k P_k m'_k$ , we obtained the cumulative incidence risk and rate, also shown in Table 2. The model average estimates are as follows. The cumulative incidence of surgery is 1690 cases, with 95% CI (1290, 2320); the cumulative incidence risk of surgery is 3.68 per 10,000 benfluorex users, 95% CI (2.68, 5.34); the cumulative incidence rate is 3.22 per 10,000 person-years at risk (ie, beyond 0.448 year's exposure to benfluorex), 95% CI (2.48, 4.39). These quantities represent the excess number of cases, along with the corresponding risk and rate, caused by exposure to benfluorex over the years during which it was marketed in France.

## 10 | UNCERTAINTY AND KEY ASSUMPTIONS

With the exception of the logistic regression of Section 6, statistical uncertainty of the parameter estimates and derived quantities was assessed by bootstrapping. Confidence intervals were obtained as percentile intervals from samples drawn with replacement from (a) the 1075 benfluorex treatment durations in Table 1, (b) the survey sample of size 81 from Section 6, and (c) the 564 validated surgeries with exposures starting in the years 1976–2009 from Section 7. The complete

estimation process was rerun with these three bootstrap samples, and this procedure was repeated 20,000 times to obtain percentile confidence intervals. This bootstrapping procedure was also applied to the model averages; in 79.4% of bootstrap samples, the linear model scored a lower AIC<sub>c</sub>, and hence a higher weight, than the quadratic model.

The method we have described depends on several key assumptions. We discuss the impact of these assumptions in the context of parameter uncertainty, with sensitivity analyses to illustrate the direction and magnitude of potential biases where these are not evident.

The first assumption is that the distribution of benfluorex treatment duration, based on a sample of women starting benfluorex in 2005–2007, applies to the whole population of benfluorex users. It is striking that over half of the women sampled stopped benfluorex within 6 months. It is possible that this treatment pattern was specifically associated with use of the drug for weight loss, and that treatment duration was longer for those who used it to treat diabetes. This would affect the estimated cumulative incidence. For example, reducing the parameters  $p_1$  and  $p_2$  in Section 4 to 75% of their estimated values, thus reducing the proportion stopping benfluorex within 6 months to 40%, leads to a moderate rise in the cumulative incidence from  $\hat{N} = 1690$  to  $\hat{N} = 1750$ . The proportion stopping benfluorex within 6 months is estimated to be 0.515, 95% CI (0.485, 0.545). This confidence interval is too narrow to accommodate the potential selection bias noted above. If such a bias occurred, our results would underestimate the true incidence.

The second key assumption is that the independent survey which underpins the estimation of  $\theta$  correctly estimates the cross-sectional under-reporting. The sample included some patients with DI-VHD who did not require surgery. It could be that those who had not undergone surgery were less likely to lodge a claim with ONIAM than those who had. However, this did not transpire from the questionnaire: the main reasons given for not engaging with ONIAM were procedural.<sup>17</sup> On the other hand, the case-control population from which the survey was sampled was partly recruited with the help of associations of victims of benfluorex, which also advised victims to seek redress, whether through ONIAM or by legal action, thus possibly introducing a selection bias in the other direction.<sup>17</sup> The 95% confidence interval for  $\theta$  is (0.383, 0.605), which accommodates substantial uncertainty in its estimation in line with these considerations.

The third key assumption is that the indication for surgery did not vary substantially over the period, so that the trend apparent in Figure 5 is due primarily to longitudinal attrition rather than to changes in surgical practice. This assumption primarily affects the estimation of  $\pi(t)$  rather than the number of surgeries. Surgical practice undoubtedly evolved over the period, resulting in an increase in numbers of operations in persons over 70 years of age.<sup>22–24</sup> However, the 564 documented surgeries were for the most part undertaken in younger patients (median age 58 years, IQR 50–65), and so are unlikely to be affected by this trend.<sup>19</sup> Furthermore, data from France for 2006–2016 shows that most of the increase in hospitalisations for VHD (all ages combined) were for valvular stenosis rather than for valvular regurgitation.<sup>25</sup> Since most operations validated by ONIAM were for valvular regurgitation (718 valves out of 869 operated on, 82.6%), this does not suggest there was a major change in surgical practice for benfluorex-related surgeries.<sup>19</sup> Nevertheless, the function  $\pi(t)$  is estimated with substantial uncertainty. For example, the model average value of  $\pi(t)$  for the 1976 cohort is estimated to be 0.302, with 95% CI (0.173, 0.438).

The fourth key assumption is that the validated claims data on which these calculations are based are complete. This is manifestly not the case: the 564 validated surgery cases were from 9584 claims up to June 2020, whereas ONIAM reports that as of end 2022, 10,138 claims had been received.<sup>16</sup> In addition, some surgery cases could not be processed owing to missing data or lack of consent. Furthermore, some persons having already made a claim may require surgery in future: as shown by the upper tail in Figure 3, the induction time to surgery can be long. These factors are not accounted for by parameter uncertainty. Thus, the calculations most likely underestimate the true cumulative incidence of surgery associated with benfluorex.

The fifth assumption is that there is no attrition of cases after  $T$ . This might not be the case. As described in Section 3, surgery cases who died between  $T$ , when the drug was withdrawn in 2009, and  $T'$ , when ONIAM began accepting claims for compensation in 2011, will most likely not be counted, resulting in underestimation of the cumulative incidence. The likely size of this effect may be assessed by extrapolating the linear and quadratic models of Section 8 to  $T'$  (29 July 2011). This yields the model average estimate  $\hat{N} = 1760$  cases of surgery, a moderate increase over the estimated  $\hat{N} = 1690$  from Table 2.

The final assumption concerns the choice of the threshold exposure  $m$  below which the risk of surgery is zero. The choice of  $m$  is not helped by the granularity of the data: data to a finer temporal resolution would have been preferable. In keeping with the annual grouping of the sales and surgery data, we used  $m = m_{34} = 0.448$  year, which corresponds to the average exposure for patients first exposed in 2009. An alternative choice is  $m = \eta_{130}/4 = 0.628$  year, corresponding to the average exposure for patients first exposed in the first quarter of 2009. This value yields the model average  $\hat{N} = 1840$ , 95% CI (1380, 2480), which is appreciably higher than  $\hat{N} = 1690$  obtained with  $m = m_{34}$ . The difference

cannot be accommodated through parameter uncertainty, since the 95% confidence interval for  $m_{34}$  is a narrow one: (0.437, 0.459).

In conclusion, the model average estimates quoted in Table 2 are generally based on conservative modelling choices, and are thus best regarded as lower bounds for the cumulative incidence, as well as for the cumulative incidence risk and rate.

## 11 | DISCUSSION

We have presented a new model to adjust for under-reporting of adverse events based on retrospective data from validated claims for compensation, motivated and exemplified by a detailed case study on cardiac valve surgery resulting from DI-VHD caused by exposure to benfluorex. The estimation method is simple, but relies on a long deductive chain using data which inevitably are incomplete and may be subject to bias, as set out in Section 10. As a consequence, the estimates are tentative, and come with wide confidence intervals. A drawback of the model from a statistical point of view is its dependence on  $\mu(t_0)$ , as shown in Section 3. In our case, this corresponds to the upper endpoint  $\mu(T)$ . As shown in Figure 5, this is model-dependent, so we used contrasting parametric models and obtained a compromise estimate using frequentist model averaging. For convenience, we used bootstrap confidence intervals for these estimates, which admittedly are ad-hoc.<sup>21</sup> For the reasons set out in Section 10, the estimates are best regarded as lower bounds for the cumulative incidence. Nevertheless, these analyses confirm some earlier findings and throw new light on other issues.

Using back-calculation, we derived annual estimates of first users of benfluorex. We estimate that there were 4.58 million users of benfluorex, 95% CI (4.08, 5.10). This is consistent with the round figure of 5 million quoted in the literature.<sup>6,26</sup> The mean duration of treatment with benfluorex was estimated to be 1.59 years, 95% (1.43, 1.78), which is in line with the “approximately 18 months” reported in the literature.<sup>7</sup> Our analyses suggest that there was a threshold of about 6 months’ exposure to benfluorex below which patients did not develop DI-VHD requiring surgery, and that subsequently the risk increased with average duration of exposure, at least to about 21 months’ exposure. This is consistent with the dose-response relationships previously found in other studies.<sup>3,12</sup>

It is instructive to compare the present estimate of the total cumulative incidence of surgery of at least 1690 cases, 95% CI (1290, 2320), to the others available. Two estimates were published in 2011–2012, using methods that are very different from those used in the present paper.<sup>6,7</sup> These estimates, which we shall take at face value, were based on two studies by CNAM, the French national health insurance scheme: a controlled cohort study in persons with diabetes of the association between benfluorex and hospitalisation for VHD and valve replacement surgery, and an uncontrolled study of hospitalisation, valve replacement surgery, and mortality in a cohort of benfluorex users.<sup>3,6,7</sup>

The first calculation, which assumed no threshold effect, estimated that 2,450 patients needed surgery.<sup>6</sup> The method used no data in common with the present paper other than the total number of Mediator boxes sold. This value lies above the upper 95% confidence limit for our own minimum estimate (namely 2320), but is of the same order of magnitude. The second calculation assumed that there was a threshold at 18 months’ exposure.<sup>7</sup> An estimate for the number of surgeries was not quoted (only hospital admissions and deaths were projected), but this is easily derived using the authors’ method for hospitalisations, by substituting into their formula the sample of 298 surgical valve replacements and a relative risk of cardiac valve replacement surgery of 3.9.<sup>3,6</sup> This gives:

$$\begin{aligned} \text{cardiac valve surgeries} &= \frac{298}{10317567} \times 78300000 \times \frac{3.9 - 1}{3.9} \\ &\approx 1680. \end{aligned}$$

This estimate of 1680 surgeries is very similar to ours (namely 1690). The only data in common with the present paper are those on duration of treatment in Section 4, and the total number of Mediator boxes sold.

Much of the controversy around the damage caused by benfluorex was focused on mortality. Comprehensive data on deaths caused by benfluorex are unavailable, and in any case the method we have described may not be applicable to deaths: the selection biases and under-reporting involved are likely to be overwhelming, especially as far as early deaths in the longer term are concerned. However, the estimates obtained in the present paper, while confined to severe DI-VHD cases requiring surgery, confirm the orders of magnitude obtained using different methods in 2011–2012.

Indeed, the present findings further underline the potential severity of benfluorex-associated DI-VHD and, albeit indirectly, its adverse impact on survival. Studies from several European countries of heart valve replacement surgery

relating to the period of interest (1976–2020) show that it did not fully restore life expectancy, especially in patients under 70 years.<sup>27–31</sup> One Swedish study found that patients aged 50–59 years undergoing aortic valve replacement surgery in 1995–2013 lived on average 3.8 years less than expected of the reference population.<sup>32</sup> In addition, recent evidence on mitral valve surgery from France suggests that operative and short-term mortality are appreciable.<sup>33</sup> A precise quantitative assessment of likely excess mortality in operated benfluorex patients is beyond the scope of this paper, and would require adjustment for age, comorbidities, and time trends in operative and post-operative mortality. Nevertheless, the number of cardiac surgeries along with their cumulative incidence risk or rate give a broad indication of the surgery-related health burden and mortality attributable to benfluorex. This is likely to include many years of life lost and many years lived with disability, even though the full human scale of this avoidable disaster remains hidden to this day.

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## CONFLICT OF INTEREST STATEMENT

Paddy Farrington served as expert witness to the Court, appointed by the examining magistrates in litigation relating to benfluorex, for which he received payment from the French Ministry of Justice.

## DATA AVAILABILITY STATEMENT

Data other than those given in the paper are not publicly available, though the Mediator sales data and the data on surgeries have been published in graphical form.<sup>6,17,19</sup> The R analysis file is available upon request.

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## REFERENCES

1. Tilma J, Nørgaard M, Mikkelsen KL, Johnsen SP. Existing data sources for clinical epidemiology: the Danish patient compensation association database. *Clin Epidemiol*. 2015;7:347–353.
2. Frachon I, Etienne Y, Jobic Y, Le Gal G, Humbert M, Leroyer C. Benfluorex and unexplained valvular heart disease: a case-control study. *PLoS One*. 2010;5(4):e10128.
3. Weill A, Païta M, Tuppin P, et al. Benfluorex and valvular heart disease: a cohort study of a million people with diabetes mellitus. *Pharmacoepidemiol Drug Saf*. 2010;19(12):1256–1262.
4. Derumeaux G, Ernande L, Serusclat A, et al. Echocardiographic evidence for valvular toxicity of benfluorex: a double-blind randomised trial in patients with type 2 diabetes mellitus. *PLoS One*. 2012;7(6):e38273.
5. Mullard A. Mediator scandal rocks French medical community. *Lancet*. 2011;377(9769):890–892.
6. Hill C. Mortalité attribuable au benfluorex (Mediator®). *Presse Med*. 2011;40:462–469.
7. Fournier A, Zureik M. Estimate of deaths due to valvular insufficiency attributable to the use of benfluorex in France. *Pharmacoepidemiol Drug Saf*. 2012;21(4):343–351.
8. Vincent L, Guardiola B, Tsouderos Y, Canet E. Mediator: who's to blame? (letter). *Lancet*. 2011;377(9782):2003.
9. Acar J. Benfluorex-induced cardiac valve injury (letter). *Pharmacoepidemiol Drug Saf*. 2012;21(11):1243–1244.
10. Casassus B. Drug scandals in France: have the lessons been learnt? *Lancet*. 2016;388(10044):550–552.
11. Frachon I, Benkimoun P. Tough ruling for Servier in the Mediator trial. *Lancet*. 2024;403(10433):1235–1236.
12. Tribouilloy C, Rusinaru D, Maréchaux S, et al. Increased risk of left heart valve regurgitation associated with benfluorex use in patients with diabetes mellitus: a multicenter study. *Circulation*. 2012;126(24):2852–2858.
13. Tribouilloy C, Maréchaux S, Jobic Y, et al. Frequency of drug-induced valvular heart disease in patients previously exposed to benfluorex: a multicentre prospective study. *Eur Heart J*. 2013;34(46):3580–3587.
14. Szymanski C, Andréjak M, Peltier M, Maréchaux S, Tribouilloy C. Adverse effects of benfluorex on heart valves and pulmonary circulation. *Pharmacoepidemiol Drug Saf*. 2014;23(7):679–686.
15. Le Ven F, Alavi Z, Jobic Y, Etienne Y, Didier R, Porcher R. Drug-induced- or rheumatic- valvular heart disease in patients exposed to benfluorex? *PLoS One*. 2016;11(8):e0160011.

16. ONIAM. Rapport d'activité. 2022 <http://www.oniam.fr/indemnisation-accidents-medicaux/rapport-d-activite>
17. Lellinger S. *Innovation Thérapeutique et Accidents Médicamenteux: Socio-genèse du Scandale du Benfluorex (Mediator®) et Conditions de Reconnaissance d'une Pathologie Émergente: les Valvulopathies Médicamenteuses*. Thèse de doctorat de l'Université de Strasbourg; 2018 <http://theses.hal.science/tel-02426018>
18. Lellinger S, Bonah C. "This corporation has 'anethetized' the actors in the drug chain". Influence peddling and the normality of conflicts of interest in the Mediator® scandal. In: Hauray B, Boullier H, Gaudillière J-P, Michel H, eds. *Conflicts of Interest and Medicine: Knowledge, Practices, and Mobilizations*. London: Routledge; 2022:181-200.
19. Laurent M, Ennezat PV, Malergue M-C, Bruneval P. Cardiac valvular surgery and history of anorectic drug intake: a retrospective study of a large population of benfluorex-exposed patients. *Arch Cardiovasc Dis*. 2022;115(6-7):348-358.
20. Collège d'experts benfluorex. Expertise des pathologies liées au benfluorex: bilan à mi-parcours du Collège d'experts chargé de se prononcer sur les responsabilités. *Arch Mal Coeur Vaiss Prat*. 2015;2015(243):23-29.
21. Claeskens G, Hjort NL. *Model Selection and Model Averaging*. Cambridge: Cambridge University Press; 2008.
22. Acar J, Michel PL, Dorent R. Evolution des étiologies des valvulopathies opérées en France sur une période de 20 ans. *Arch Mal Coeur*. 1992;85(4):411-415.
23. Ghosh P. Changing trends in valve surgery in Europe: 1991-2000. *J Heart Valve Dis*. 2004;13(1):1-10.
24. Brown JM, O'Brien SM, Wu C, Sikora JAH, Griffith BP, Gammie JS. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. *J Thorac Cardiovasc Surg*. 2009;137(1):82-90.
25. Grave C, Tribouilloy C, Juillière Y, et al. Hospitalisations pour valvulopathie en France: caractéristiques des patients et évolution 2006-2016. *Bull Épidémiol Hebd*. 2019;(4):70-79.
26. Tribouilloy C, Jeu A, Maréchaux S, Jobic Y, Rusinaru D, Andréjak M. Benfluorex (Mediator®) et atteintes valvulaires. *Presse Med*. 2011;40:1008-1016.
27. Abdelnoor M, Nitter-Hauge S, Trettl S. Relative survival of patients after heart valve replacement. *Eur Heart J*. 1990;11(1):23-28.
28. Ståhle E, Kvidal P, Nyström SO, Bergström R. Long-term relative survival after primary heart valve replacement. *Eur J Cardiothorac Surg*. 1997;11(1):81-91.
29. Kvidal P, Bergström R, Hörte LG, Ståhle E. Observed and relative survival after aortic valve replacement. *J Am Coll Cardiol*. 2000;35(3):747-756.
30. Lassnigg A, Hiesmayr M, Frantal S, et al. Long-term absolute and relative survival after aortic valve replacement: a prospective cohort study. *Eur J Anaesthesiol*. 2013;30(11):695-703.
31. Rosato S, Biancari F, D'Errigo P, et al. Relative survival after adult cardiac surgery: analysis of the Italian nationwide registry data. *J Cardiothorac Vasc Anesth*. 2023;37(11):2223-2227.
32. Glaser N, Persson M, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Loss in life expectancy after surgical aortic valve replacement: SWEDHEART study. *J Am Coll Cardiol*. 2019;74(1):26-33.
33. Messika-Zeitoun D, Candolfi P, Enriquez-Sarano M, et al. Presentation and outcomes of mitral valve surgery in France in the recent era: a nationwide perspective. *Open Heart*. 2020;7(2):e001339.

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