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Risk of fatal adverse events associated with 17DD yellow fever vaccine

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SUMMARY

Yellow fever (YF), an acute infectious disease, is endemic in the north and central-west of Brazil. This disease can be prevented by the use of a vaccine. In Brazil, four fatal adverse events have been associated with the YF vaccine used in the country (17DD vaccine). We briefly describe the last two fatalities, and estimate the risk of 17DD-associated fatal adverse events under different epidemiological scenarios. Controversies regarding the appropriate denominator that enters the estimation of risk serve as a motivation for each proposed scenario. The statistical procedures used show optimum behaviour when assessing the risk of rare events. Risk estimates vary from 0·043 (95% CI 0·017–0·110) to 2·131 (95% CI 0·109–12·071) fatalities per million doses administered. The robust estimates of the risk of fatal adverse events we present constitute an important element in future risk–benefit analysis and point to the need for good quality vaccine coverage and adverse-events surveillance data to assess the risk of vaccination. Although vaccination of YF endemic regions is necessary to maintain low disease prevalence, preventive administration of YF vaccine to the entire population should be cautiously analysed.

INTRODUCTION

Yellow fever (YF) is endemic in tropical Africa and America. YF is transmitted through two major cycles. The sylvatic cycle (sYF), mostly restricted to wild and rural areas, has monkeys as its main host and wild mosquitoes as vectors (mainly *Haemagogus* spp. in Brazil). Urban YF is transmitted from human to human by the domestic mosquito *Aedes aegypti* (the same vector of dengue fever). In Brazil, YF is maintained in its sylvatic cycle, mainly in the west and north regions of the country (Fig. 1).

Although there is no specific treatment for YF, the disease can be prevented by the use of a vaccine. The YF vaccine has been considered one of the safest and most effective vaccines ever produced [1]. Worldwide, over 300 million doses of YF vaccine have been administered and adverse events are rarely reported. However, in 2001, the safety of YF vaccine was challenged by the reporting of fatal adverse events: three

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Fig. 1. Map of Brazil. Dark grey: states of Brazil were sylvatic yellow fever (sYF) is endemic. Light grey: transition area, i.e. areas sporadically affected by sYF. White: states where there is no sYF activity. Labelled states and their respective capitals (in italic) indicate the occurrence of a fatal adverse event. SP, São Paulo (*SP*, São Paulo); MG, Minas Gerais (*BH*, Belo Horizonte); RS, Rio Grande do Sul (*PA*, Porto Alegre); GO, Goiás (*GA*, Goiânia).

deaths in the United States, in January 1996, May 1998 and November 1998 [2], two in Brazil, occurring in October 1999 and February 2000 [3], and one in Australia, in February 2001 [4].

In the United States, starting in June 2001, an enhanced surveillance system for the identification of adverse events following YF vaccination was initiated [5]. By the end of 2002, this system had identified two non-fatal cases of YF vaccine-associated viscerotropic disease and four non-fatal cases of YF vaccine-associated neurotropic disease [5, 6]. No obvious correlation was found associating these events with a specific vaccine lot, risk factor or immunological characteristic [7, 8], although one study suggests that the elderly are at increased risk of systemic adverse event following YF vaccination [9]. In addition to the data presented above, two unpublished cases have been confirmed in Brazil and are briefly described in this paper.

Recommendation for the use of vaccines should be based on a dynamic balance between risks and benefits [1]. So far, YF vaccine recommendations were based on the assumption of null risk. The knowledge of the recent fatal events obligates the scientific community to evaluate the risk–benefit balance of vaccination. To make this analysis possible, an estimate of the risk of adverse events of YF vaccine must be calculated. In this paper, we present an estimate of YF vaccine risk of a fatal adverse event using data from Brazil. Our goal is to offer public health authorities and the scientific community an estimate of the risk of a fatal event, which could be used in risk–benefit analysis.

YF vaccination in Brazil

YF sylvatic activity follows a 7- to 10-year periodic cycle (Fig. 2), probably driven by the infection dynamics of its sylvatic hosts [10, 11]. In Brazil, YF vaccine trials began around the year 1936, with the YF vaccine 17DD. Since then, Brazil has maintained a vaccination strategy that targets the population in endemic and transition areas, as well as travellers to these areas. In 1998, with the overall spread of *Aedes aegypti* to most of the country and the increasing activity of sYF within the endemic and transition areas, the vaccination strategy was modified to include the entire Brazilian population [3, 12].

Despite this effort, the epizootic wave continued to grow, and reached its peak by the end of 2000. From January 1998 to December 2000, 181 and 14 cases were notified within and outside the endemic area respectively. The occurrence of two deaths associated with 17DD vaccine, in October 1999, in the state of Goiás (GO), and in February 2000, in the state of São Paulo (SP), halted the wide-scale campaign [3]. The original vaccination strategy was re-established in 2000, i.e. vaccination of endemic and transition areas, as well as travellers to these areas [13].

In 2001, a sYF epidemic emerged outside the endemic region, in the state of Minas Gerais (MG, see Fig. 1). In response, a large vaccination campaign was initiated, covering the capital and municipalities at risk. An active sentinel surveillance system was implemented in Belo Horizonte (BH), capital of MG, to detect potential fatal adverse events related to the vaccine. The BH campaign (BH_C) and its active sentinel surveillance programme lasted from February to May 2001. During this period, a total of 810 411 doses of the vaccine was administered. One fatal event associated with the vaccine was detected (described below). During this campaign, a significant but unknown proportion of the vaccine doses was administered to individuals who had already been vaccinated. Since 1998, MG was intensively

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Table. *For each of the states where a fatal adverse event occurred: (1) the number of 17DD vaccine doses administered from January 1991 to December 1997, and from January 1998 to December 2001, (2) the population in 2001; and (3) the month of fatal adverse event associated with YF vaccine*

State	Vaccine doses (1991–1997)	Vaccine doses (1998–2001)	Population in 2001	Month of YF vaccine fatal event occurrence
GO	4 421 455	4 777 556	5 116 395	October 1999
SP	5 781 130	6 593 659	37 630 105	February 2000
MG	2 301 427	16 177 853	18 127 024	March 2001
RS	15 549	469 307	10 310 021	September 2001

Source: National Programme of Immunizations, National Health Foundation.
GO, state of Goiás; MG, state of Minas Gerais; RS, state of Rio Grande do Sul; SP, state of São Paulo.
Percentage vaccinated can be obtained by dividing the number of doses by the population.
Vaccination coverage above 100% implies re-vaccination of individuals and/or underestimation of population size.

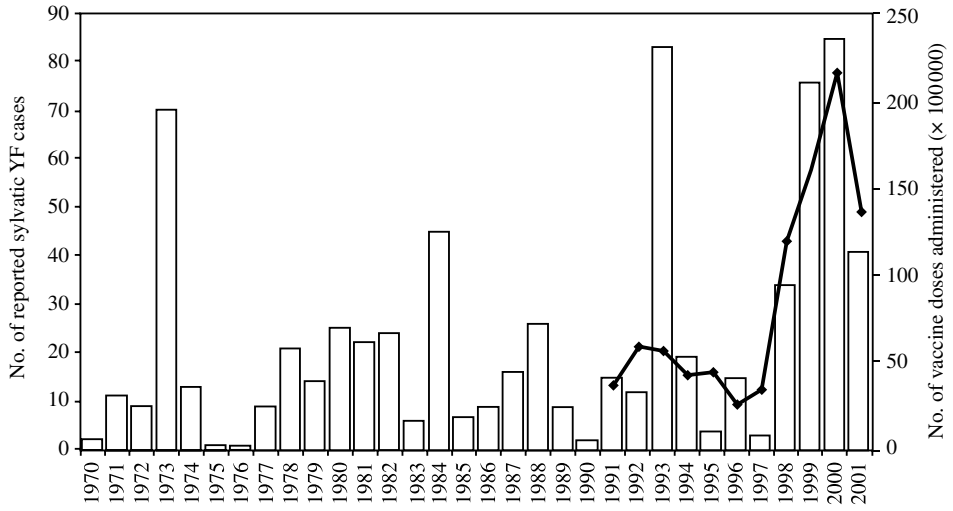

Fig. 2. On the left vertical axis: number of reported cases of sylvatic YF (yellow fever) in Brazil from 1970 to 2001. Note the 7- to 10-year periodic cycles. On the right vertical axis: number of 17DD vaccine doses administered in Brazil from January 1991 to December 2001. □, Cases; –◆–, doses applied.

vaccinating its population (see Table, note the number of doses administered in MG from 1991 to 1997 and the number of doses administered from 1998 to 2001).

Still in 2001, the state of Rio Grande do Sul (RS) reported YF activity in non-human hosts (monkeys found dead in nearby forests). A localized vaccination campaign covering municipalities at risk was carried out. The campaign started in July 2001, and ended in December 2001. Again, an active sentinel surveillance system was implemented, following the same guidelines as in MG. Almost 500 000 doses were applied (91% vaccination coverage), and one fatal event was detected, in September 2001 (described below). In contrast to MG, the majority of the RS population received the vaccine for the first time during this campaign.

In summary, in the last decade (from January 1991 to December 2001), a total of 93 567 028 doses of 17DD vaccine was administered to the Brazilian population, 43% to the four states where fatal events were reported (see Table). Approximately 70% of the doses were administered after the onset of the most recent epizootic wave, i.e. from the beginning of 1998 to the end of 2001. Four fatal events associated with 17DD vaccine were registered during this period of intense vaccination. The first two events have been described in the literature [3]. Following this, we briefly describe the two most recent fatalities.

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Case description

Case 1 was a 19-year-old woman who presented to a local health centre in March 2001, with fever. She had received YF 17DD vaccine in BH (lot no. 997FB050Z) 2 days before the onset of her illness. It was suspected to be a mild reaction following vaccination, and symptomatic treatment was administered. On 16 March (7 days after illness onset), she returned to the health centre feeling increasingly unwell. She was treated with antibiotics, paracetamol and *Saccharomyces boulardii* suspension. On 18 March she sought medical attention in another hospital. On examination she was conscious, prostrated, severely hypotensive, and had petechiae in her conjunctivae. The tentative diagnosis was haemorrhagic fever and sepsis. She was transferred to a larger hospital due to continuing deterioration. On admission she was severely ill, showing signs of haemodynamic instability and respiratory distress. On examination, the patient was bradycardic, febrile, sweating and vomiting. Physical signs included melaena, haematuria, jaundice, and bleeding affecting the genital, conjunctival and cutaneous areas.

On 19 March (10 days after vaccination), the patient died. No necropsy was performed. Visceral samples were collected from spleen and liver through viscerotomy. Histopathological findings of liver samples indicated acute viral hepatitis caused by hepatotropic virus. The immunoperoxidase technique was positive for YF. Reverse transcription PCR on RNA extracted directly from liver and spleen was positive for YF virus. Sequence analysis of the amplicons corresponding to the 3′ untranslated region revealed that the recovered virus was the 17DD vaccine virus.

Case 2 was a 4-year-old boy from Três Passos, RS, who was vaccinated against YF on 29 August 2001. Three days after vaccination, he experienced fever, prostration and right axilar lymphadenopathy. He sought medical assistance, and oral antibiotics were prescribed. On 3 September (5 days after vaccination), as the symptoms had not subsided, he returned to the health centre but was released with the same prescription. On 5 September (7 days after vaccination), he decompensated, with prostration, vomiting, anorexia and abdominal pain. Physical examination revealed right axilar and cervical adenomegaly, and significant oedema on the right side of his chest. On the following day, he was noted to be jaundiced, and physical examination revealed painful hepatomegaly and generalized lymphadenopathy. On 7 September (9 days after vaccination), he was transferred to the intensive care unit because of continuing deterioration. Physical examination revealed purpura in both ankles and feet. During that night he had hypothermia, severe hypoglycaemia, generalized seizures, abdominal distension and mild upper gastrointestinal bleeding. The following morning, he became dyspnoeic and anuric, presenting mild contractions in the arms and legs. During the night, it was noticed bilateral mydriasis, cyanosis and hypothermia.

On 8 September 2001 (10 days after vaccination), the patient died. Histopathological findings were characteristic of wild-type YF. Using immunohistochemistry, YF viral antigen was identified in liver, spleen, kidney, heart and axilar lymph node specimens. Sequence analysis of the RNA from the specimens revealed that the virus recovered from this patient was the 17DD vaccine virus.

METHODS

Epidemiological scenarios

The risk of fatal adverse events is defined as the ratio between the number of reported fatal events (X) and the number of doses administered (n). Since fatal events were not associated with a single vaccine lot, campaign or spatial location, there were doubts regarding the correct number of doses to be used in the denominator. Choices for the denominator (n) range from the total number of doses used in the last decade, over 90 million, to a few hundred thousand doses administered under a regime of strict surveillance of adverse events.

Epidemiological aspects regarding the disease and the vaccine are at the root of the problem concerning the correct choice of a numerator and a denominator. Lack of active surveillance data for fatal adverse events following vaccination in the past, possible misclassification of vaccine-induced YF cases (which could be confounded with sylvatic transmitted disease in endemic regions), as well as a large number of vaccine doses administered to individuals already vaccinated (believed not to suffer from vaccine-induced complications) in endemic areas cast doubts on the appropriate choice of a numerator and denominator for risk estimates. On the other hand, one may argue that out of the 26 Brazilian states, 22 have been vaccinating their populations and no

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fatal cases were detected. This observation favours the safety of the vaccine.

Given these controversies on the choice of a denominator, we have calculated the risk under eleven different scenarios based on the doses administered in specific locations. For each state where a fatal event was reported (GO, SP, MG, RS), we constructed one scenario restricted to the epizootic period, which lasted from January 1998 to December 2001 (scenarios GO_1, SP_1, MG_1 and RS_1), and one scenario considering the number of doses administered between January 1991 and December 2001 (scenarios GO_2, SP_2, MG_2 and RS_2). As mentioned above, the BH case (case 1) was detected through the use of an active sentinel surveillance protocol. Since this strict surveillance protocol provided access to very precise information regarding this location, we opted to construct a scenario for the vaccination campaign in BH, labelled scenario BH_C.

Finally, two other scenarios were constructed considering the country as a whole, since vaccination has also been performed in the other 22 states. In these states no fatal adverse events associated with the vaccine have been reported. The scenarios BR_1 and BR_2 consider the number of doses administered in the country from 1998 to 2001 and from 1991 to 2001 respectively. For these two scenarios the numerator includes the four deaths reported until now.

Confidence interval estimators

The standard Wald confidence interval for proportions performs poorly when risk is very close to zero [14]. The erratic behaviour of the coverage probability of this statistical procedure prompted us to use a set of alternative confidence intervals that are described in Appendix 1 [14]. Their technical properties assure better coverage probability and/or are narrower in comparison with the Wald interval. Since some of these intervals are quite conservative, the confidence intervals proposed here may be longer than necessary and thus allow us to adopt a cautious approach when further considering risk–benefit issues related to YF vaccination. Good minimum coverage probability also stands as an additional property found in the proposed intervals that place these estimates on the safe side. That is, they estimate a number of adverse fatal events above the nominal level of 95%, forcing additional caution in recommending future vaccination strategies.

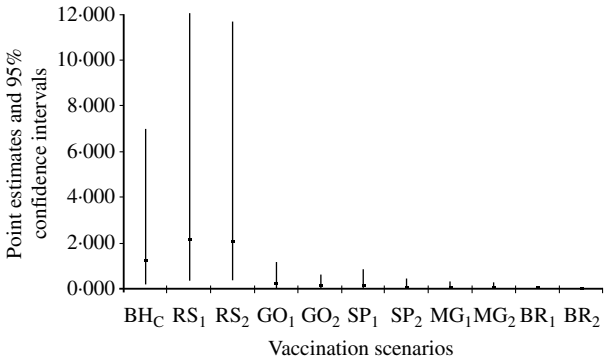

Fig. 3. Estimated risk of fatal adverse events per million doses administered and the 95% confidence intervals for each one of the vaccination scenarios proposed. In this figure the estimates obtained using the Clopper–Pearson confidence-interval estimator are plotted.

RESULTS

Figure 3 shows the estimated 95% confidence interval for each scenario, as predicted by the most conservative confidence interval (CI) for large n (the Clopper–Pearson). Risk estimates varied from 2·131 (95% CI 0·376–12·071) in scenario RS_1 to 0·043 (95% CI 0·012–0·109) deaths per million doses (scenario BR_2). Eight out of 11 scenarios predicted less than one death per million doses, an estimate that agrees with previous expectations [6, 15]. Three scenarios, however, resulted into higher estimates of risk: RS_1 (2·131, 95% CI 0·376–12·071), RS_2 (2·062, 95% CI 0·364–11·684), and BH_C (1·234, 95% CI 0·218–6·990).

Appendix 2 shows the estimated risk of fatal adverse event and the five confidence intervals for each scenario used in the analysis. The worst scenarios are those for RS (RS_1 and RS_2), which do not differ much (2·13 and 2·062 for RS_1 and RS_2 respectively). For these, the confidence interval of the expected number of deaths associated with 17DD vaccine ranges from 0 to 12 per million doses administered. They are followed by the BH_C scenario which predicts, at most, 7 deaths per million doses administered (upper limit of its confidence interval).

The first scenario for GO predicts, as an upper limit of its confidence interval, 1 death due to the vaccine per million doses administered. All other scenarios estimate, at most, 1–9 deaths per 10 million doses administered. The scenarios for the whole country, which assume a much higher number of doses administered, provided estimates similar to the lower risk scenarios (95% CI 0·017–0·162 for BR_1 and 95% CI 0·012–0·109 for BR_2).

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DISCUSSION

In this paper, we used data from Brazil to estimate the risk of fatal adverse events associated with YF 17DD vaccine. YF 17DD vaccine has been regarded as one of the safest and most effective vaccines ever developed [10]. Vaccine trials conducted in 1936 and 1937 in Brazil, concluded that the vaccine was well tolerated and efficacious [10]. However, four fatal adverse events associated with 17DD vaccine have occurred in the country [3].

We analysed 11 different scenarios, calculating for each five different confidence intervals. Some scenarios correspond to localized mass vaccination campaigns, where a relatively small number of doses were administered (RS_1 and BH_C). These result in smaller denominators for the risk estimation and lower precision. Scenarios BR_1 and BR_2 capture the uncertainty associated with risk estimates based on data pooled together for the whole country. Our results indicate that the risk of a fatal adverse event after vaccination with 17DD is no longer null. According to our analysis, in the worst scenario, an upper limit of 12 fatalities per million doses of vaccine administered could occur.

One of the limitations of the analysis of the risk associated with the vaccine is the uncertainty associated with the actual number of fatal adverse events. Surveillance programmes have changed over the years, and the awareness concerning fatal adverse events associated with 17DD is recent. Although this may suggest the occurrence of adverse events in the past, we cannot assess them.

It is known that YF resembles many other diseases of the tropics, and the disease caused by the vaccine strain is very similar to YF. Consequently, the number of fatal adverse events may go under-reported in endemic regions, just as the disease itself does. With the exception of GO, the states where fatalities were reported are not endemic for YF, and this could actually be the reason why the deaths were finally detected and reported. Moreover, when active surveillance programmes were implemented to detect fatal events, they found them. These facts justify restricting the scope of risk estimates to locations in space and time where active surveillance programmes were implemented.

One additional source of error leading to underestimation of the risk is the possibility that fatal adverse events only occur in individuals being vaccinated for the first time. Therefore, individuals who are being re-vaccinated should not be included for risk assessment. In most states, the number of re-vaccinations is likely to be high, as the number of doses per person exceeds 100%. Unfortunately, the number of re-vaccinated individuals is not known. The scenarios that can be considered free of this problem are RS_1 and RS_2 where the number of re-vaccinations is likely to be low or absent.

We believe these results indicate the need for caution when planning intervention strategies leading to YF vaccination of large susceptible populations. By no means do we believe that vaccination should not be delivered in endemic and transition areas. These areas suffer greatly from the disease and the case-fatality rate is high. The low activity of sYF seen in Brazil can be, at least partially, attributed to mass vaccination programmes in endemic regions for over 50 years. However, alternative strategies should be considered for urban areas which are free of the disease. Some of these strategies are: (1) intensive immunization of travellers migrating to risk areas, (2) better screening of individuals coming from endemic areas, (3) better immunization coverage in the endemic region, and (4) more effective vector control programs. It is not clear which strategy would be the most cost-effective and subject to lower risks.

In addition, we believe that a careful analysis should be done to determine which travellers should be vaccinated. YF cases do occur each year, but they are well associated with occupational hazard [11] and tourism [13]. Fortunately, since the epizootic activity of YF is currently diminishing, there is some time ahead for formulation of the best vaccination strategy for non-endemic areas.

It is important to stress the fact that surveillance programmes regarding YF endemic activity and 17DD adverse events must continue and be improved [9]. The estimates presented here can help in the planning of optimum disease control strategies. Known weaknesses of the present estimates will certainly benefit from improved practices of the surveillance of adverse events caused by YF vaccination.

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the study, and all the personnel involved in the identification of cases. We also thank the National Health Foundation (FUNASA) for making the data available at their internet site.

APPENDIX 1

We calculated the risk of fatal adverse events for eleven different vaccination scenarios. We assumed that the number of individuals dying from the vaccine follows a binomial distribution with parameters (n, p), where n is the vaccinated population size and p is the probability of death due to the vaccine (risk), the latter been estimated as the sampled proportion of fatal events, $\hat{p} = X/n$.

The estimated risk was always very close to zero, a situation in which the standard Wald confidence interval tends to perform poorly. This led us to use a set of alternative confidence intervals [14].

(1) The Wilson interval, which is based on inverting the acceptance region of the Wald large-sample normal test $|(\hat{\theta}-\theta)/se(\hat{\theta})| \leqslant \kappa$, where θ is a generic parameter, $\hat{\theta}$ is the maximum-likelihood estimate of θ, κ is the $100(1-\alpha/2)$th percentile of the standard normal distribution. The estimated standard error $(\hat{p}\hat{q})^{\frac{1}{2}}n^{-\frac{1}{2}}$, is replaced by the null standard error $(pq)^{\frac{1}{2}}n^{-\frac{1}{2}}$:

$$\mathrm{CI_W} = \frac{X+\kappa^2/2}{n+\kappa^2} \pm \frac{\kappa n^{\frac{1}{2}}}{n+\kappa^2}(\hat{p}\hat{q}+\kappa^2/(4n))^{\frac{1}{2}}.$$

We further followed [14, section 4.1.1, p. 112] and modified the lower bound of the above interval such that $\mathrm{CI_{MW}} = (\frac{1}{2})\chi^2_{2X,\alpha}$. Where $\chi^2_{2X,\alpha}$ denotes the 100αth percentile of the χ^2 distribution with $2X$ degrees of freedom.

(2) The Jeffrey's confidence interval is given by $\mathrm{CI_J} = [L_J(x), U_J(x)]$, where,

$$L_J(0) = 0, \; U_J(n) = 1, \quad \text{and}$$
$$L_J(x) = B(\alpha/2;\, X+\tfrac{1}{2},\, n-X+\tfrac{1}{2}),$$

$$U_J(x) = B(1-\alpha/2;\, X+\tfrac{1}{2},\, n-X+\tfrac{1}{2}), \text{ otherwise.}$$

$B(\alpha, m_1, m_2)$ denotes the α quantile of a binomial (m_1, m_2) distribution.

(3) The Clopper–Pearson (CP) confidence interval, which is the inversion of equal-tail binomial test rather than its normal approximation, is defined by $\mathrm{CI_{CP}} = [L_{CP}(x), U_{CP}(x)]$, where $L_{CP}(x)$ and $U_{CP}(x)$ are, respectively, the solutions in p to the equations $P_p(X \geqslant x) = \alpha/2$ and $P_p(X \leqslant x) = \alpha/2$.

(4) The Santner q-interval for a binomial given by:

$$\mathrm{CI_S} = \left[\frac{X}{n+\kappa^2} + \frac{\kappa^2}{n+\kappa^2}(0{\cdot}5) \pm \sqrt{\frac{(X/n)(1-X/n)(n^2\kappa^2)}{n(n+\kappa^2)^2} + \frac{\kappa^4}{(n+\kappa^2)^2/4}}\right].$$

(5) The Logit interval, modified by Anscombe [14], is obtained by inverting a Wald-type interval for the log odds $\hat{\lambda} = \log[(X+\frac{1}{2})/(n-X+\frac{1}{2})]$ and corresponding variance given by

$$\hat{V} = \frac{(n+1)(n+2)}{n(X+1)(n-X+1)}, \text{ yielding}$$

$$\mathrm{CI_L} = \left[\frac{e^{\hat{\lambda}-\kappa\hat{V}^{\frac{1}{2}}}}{1+e^{\hat{\lambda}-\kappa\hat{V}^{\frac{1}{2}}}}, \frac{e^{\hat{\lambda}+\kappa\hat{V}^{\frac{1}{2}}}}{1+e^{\hat{\lambda}+\kappa\hat{V}^{\frac{1}{2}}}}\right].$$

The interpretation of the expressions above requires the following additional notation: $\kappa \equiv Z_{\alpha/2} = \Phi^{-1}(1-\alpha/2)$, where Φ is the standard normal distribution; $\hat{p} = X/n$ is the sample proportion of 'successes' (fatal adverse events).

APPENDIX 2. Expected number of fatal adverse events and 95% confidence interval (CI) limits per million doses administered, for each vaccination scenario

Scenario	CI	Lower limit	Risk	Upper limit
BH_C	W	0·063	1·234	6·990
	J	0·000		5·768
	CP	0·218		6·990
	S	0·031		6·875
	L	0·695		4·932
RS_1	W	0·109	2·131	12·071
	J	0·000		9·960
	CP	0·376		12·071
	S	0·054		11·872
	L	1·200		8·516
RS_2	W	0·106	2·062	11·684
	J	0·000		9·640
	CP	0·364		11·684
	S	0·052		11·491
	L	1·161		8·243
GO_1	W	0·011	0·209	1·186
	J	0·000		0·978
	CP	0·037		1·186
	S	0·005		1·166
	L	0·118		0·837
GO_2	W	0·006	0·109	0·616
	J	0·000		0·508
	CP	0·019		0·616

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APPENDIX 2 (*cont.*)

Scenario	CI	Lower limit	Risk	Upper limit
	S	0·003		0·606
	L	0·061		0·434
SP_1	W	0·008	0·152	0·859
	J	0·000		0·709
	CP	0·027		0·859
	S	0·004		0·845
	L	0·085		0·606
SP_2	W	0·004	0·081	0·458
	J	0·000		0·378
	CP	0·014		0·458
	S	0·002		0·450
	L	0·045		0·323
MG_1	W	0·003	0·062	0·350
	J	0·000		0·289
	CP	0·011		0·350
	S	0·002		0·344
	L	0·035		0·247
MG_2	W	0·003	0·054	0·307
	J	0·000		0·253
	CP	0·010		0·307
	S	0·001		0·302
	L	0·030		0·216
BR_1	W	0·024	0·063	0·162
	J	0·021		0·150
	CP	0·017		0·161
	S	0·024		0·162
	L	0·048		0·105
BR_2	W	0·017	0·043	0·110
	J	0·014		0·102
	CP	0·012		0·109
	S	0·017		0·110
	L	0·032		0·071

W, Wilson; J, Jeffrey; CP, Clopper–Pearson; S, Santner; L, Logit. All CI estimators used are described in Appendix 1.

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