 International Journal of Epidemiology 2000;**29**:757–763

Vaccine-associated paralytic poliomyelitis: a retrospective cohort study of acute flaccid paralyses in Brazil

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Background	At the present time, in Brazil and other countries in the Americas, the only cases of paralytic poliomyelitis due to poliovirus are caused by vaccine strains. The recognition of possible determinants of vaccine-associated paralytic poliomyelitis (VAPP) by public health surveillance and immunization programmes is relevant to inform the debate on criteria for case definition and vaccination strategies.
Methods	A retrospective cohort study based on the cases of acute flaccid paralysis (AFP) reported to the Ministry of Health (MoH) was designed, with the objective of studying cases of VAPP in Brazil between 1989 and 1995. Clinical, laboratory and epidemiological data from 3656 acute flaccid paralysis (AFP) cases, 30 of them diagnosed as VAPP, were analysed.
Results	An 8.88 risk ratio of VAPP (95% CI : 4.37–18.03) was found when comparing individuals who received oral poliovirus vaccine (OPV) between 4 and 40 days before the onset of paralysis and individuals who did not receive the vaccine within this period. A risk of 1 case/2.39 million first doses and 1 case/13.03 million OPV doses administered was estimated for the general population.
Conclusions	Cases of AFP who received OPV between 4 and 40 days before the onset of paralysis and had fever, a prodrome of gastrointestinal symptoms, history of first dose of OPV, isolation of vaccine poliovirus type 2, and young age deserve careful investigation, since they are at increased risk for the condition studied.

Keywords	Vaccine, poliomyelitis, oral poliomyelitis vaccine, adverse effect
Accepted	2 February 2000

In 1994, the International Commission for the Certification of Poliomyelitis Eradication, after analysing epidemiological and immunization data, concluded that the circulation of wild poliovirus was interrupted in Brazil and in the other countries of the Americas.[1] Thus, at the present time the only cases of poliomyelitis occurring in the region are vaccine-related.[2] The oral poliovirus vaccine (OPV) may cause a rare event, a case of vaccine-associated paralytic poliomyelitis (VAPP), due to the ability of attenuated strains to revert towards neurovirulence. Vaccine-associated paralytic poliomyelitis can occur both in vaccine recipients and in their contacts.[3] With the exception of immunodeficiency, no conditions identify individuals at greater risk for this adverse event.[2]

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In Brazil and other countries most VAPP cases are due to type 2 and 3 strains.[4] Although the reversal towards neurovirulence happens frequently in strains 2 and 3, recent studies have confirmed the isolation of type 1 poliovirus from samples from patients with VAPP, demonstrating the occurrence of mutations in this strain.[5]

Vaccine-associated paralytic poliomyelitis was observed soon after the introduction of attenuated poliovirus vaccines. In the US, between 1980–1994, it was demonstrated that the risk of VAPP was of approximately 1 case/2.4 million OPV doses; this has remained relatively constant since 1965. With regard to the first dose, it is estimated that there is one case of VAPP per 750 000 doses distributed.[6] In individuals with immunodeficiency, a 7- to 21-fold higher risk is reported for first doses in comparison to subsequent ones.[2]

Until 1989 in Brazil, cases of acute flaccid paralysis (AFP) with (1) neurological sequellae compatible with poliomyelitis still present 60 days after the onset of paralysis, (2) isolation of vaccine poliovirus from stool samples and (3) a history of vaccination between 4 and 30 days before the onset of the

paralysis were classified as VAPP. In 1990, the criteria were changed, excluding the history of vaccination (since contacts of vaccinees can develop VAPP), and determining that the isolation of vaccine poliovirus strains should be done from stool samples collected up to 14 days after the onset of paralysis.[7]

This study aimed to estimate the incidence of VAPP in infants and the risk of this condition in relation to the first dose and to the total number of doses of OPV administered, and to analyse VAPP cases in Brazil, comparing OPV recipients (exposed) with contacts of vaccinees (non-exposed). Predictive models were designed, based on a cohort of individuals with AFP, trying to identify possible risk factors for this condition.

Methods

Data source

In Brazil, detection of VAPP cases is based on reporting of AFP cases to the epidemiological surveillance system of the Ministry of Health (MoH) Poliomyelitis Eradication Program.[7] A total of 3636 cases of AFP of the extremities in children <15 years and 20 observations in subjects aged $\geqslant 15$ years, reported to the MoH and included in the Poliomyelitis Eradication Surveillance System/Pan American Health Organization between 1989 and 1995 were analysed. Out of this total, 30 were classified as VAPP.

Study design, variables and biases

The study design proposed is a retrospective cohort of the AFP cases where the outcome observed is the occurrence of VAPP. The main exposure variable ('exposed') was having received OPV between 4 and 40 days before the onset of AFP.[8] All individuals who had not received the vaccine or who received it outside of this period were classified as 'non-exposed'. The other independent variables analysed were: gender, fever, gastrointestinal (GI) and upper respiratory signs and/or symptoms, month of onset, extremit(y/ies) paralysed, number of OPV doses received before the paralysis (in the 'exposed' individuals), type of vaccine poliovirus isolated and age in years.

Since the database analysed was a secondary source, it had some limitations, mainly related to the lack of information concerning some variables. As to the possibility of selection bias, given the underreporting of AFP, the likelihood of inclusion in this cohort is related to the quality of the epidemiological surveillance and not to the exposure or the disease. As to classification bias, since the classification criteria for VAPP are very strict, they could only lead to a smaller number of VAPP cases, probably randomly distributed between exposed and non-exposed, and to an underestimation of the effect.

Statistical analysis

The incidence of VAPP in infants, the risk of VAPP occurrence in relation to the first OPV dose and the total number of vaccine doses given, and the crude relative risk (RR) of VAPP in relation to exposure to OPV and other covariates were calculated.

The construction of a parsimonious multivariate model to study the determination of VAPP occurrence from the covariates observed was done using logistic regression.[9] The adequacy of the regression models proposed was investigated using the diagnosis of deviance residuals.[9,10] The logistic regression model allows the estimation of the odds ratio (OR) as a measure of association, which provides a good approximation of the relative risk in studies with rare outcomes like the present one.[11]

In the logistic regression models used in this study, the dichotomous dependent variable represents the occurrence of VAPP, while exposure to the vaccine is the independent main variable, also analysed dichotomously. The other independent variables included in the predictive model were categorical, with the exception of age, which was treated as a continuous variable. The option was made for building models including the main independent variable and two or three covariates, with the objective of obtaining more robust models and more accurate estimates. Later, the multivariate models were selected on the basis of the statistical tests, accuracy of the estimates found, and the biological plausibility of each model.

For each variable in the model the regression coefficient and its standard error, the exponential of the regression coefficient and its CI, and the deviance were calculated, as well as statistical significance tests to evaluate the adjustment of the models.[9] For the association between age and the occurrence of VAPP, the generalized additive model (GAM)[10] was also used. Figures containing the observed values and the probability predicted by the model for the occurrence or non-occurrence of VAPP were used to evaluate the predictive models chosen.

The statistical analyses considered 95% CI and a 5% $\propto$ error[9–12] and used the S-Plus software, version 3.3, Copyright 1988 (1995 Math Soft, Inc. S. Copyright AT&T).

Results

Incidence and the risk of occurrence

In the period studied, 1989–1995, the estimated infant population was 22 669 368.[13] The incidence of VAPP in infants under one year old (16 cases) corresponded to 0.71/1 000 000 or 1 case/1 416 835 children in this age group.

Table 1 shows that about 50% of VAPP had no exposure to OPV between 4 and 40 days prior to paralysis. On the other hand, 90% of individuals without VAPP had no exposure to OPV in this time. Fever appeared in 60% of AFP cases, albeit in 93% of VAPP.

To calculate the risk of VAPP in relation to the total number of OPV doses administered, doses of the vaccination campaigns (occurring biannually in the country) and routine vaccination doses were added. An estimated risk of 1:2.39 million for first doses and 1:13.03 million for the total number of OPV doses given was found.

Table 2 shows that individuals with AFP have an increased risk of VAPP under certain conditions. When the crude RR were analysed, exposure to OPV, a history of fever and particularly the isolation of type 2 vaccine poliovirus were shown to be significantly associated to the condition studied.

Multivariate analysis

The models considered more appropriate, among those tested, for analysing the association between VAPP and OPV exposure will be presented. The model summarized in Table 3 shows that exposure to the first dose of OPV is an important risk factor for the occurrence of VAPP, while the subsequent doses appear to be protective factors. Fever is a covariate associated with VAPP, albeit with a wide CI.

Table 1 Acute flaccid paralysis (AFP) according to outcome, age, exposure to oral polio vaccine (OPV) and fever

	VAPP[a]				No VAPP					
	Age <1 year		Age ⩾1 year		Age <1 year		Age ⩾1 year		Total	
Variable	No.	%	No.	%	No.	%	No.	%	No.	%
Exposure[b]										
Fever[c]	7	43.75	4	28.57	43	18.38	160	5.20	214	6.40
No Fever	1	6.25	2	14.29	13	5.56	78	2.53	94	2.81
No exposure[d]										
Fever[c]	8	50.00	7	50.00	140	59.83	1702	55.28	1857	55.55
No Fever	0	0.00	1	7.14	38	16.24	1139	36.99	1178	35.24
Total	16	100.00	14	100.00	234	100.00	3079	100.00	3343	100.00

[a] Vaccine-associated paralytic poliomyelitis.

[b] Exposure to OPV between 4 and 40 days prior to paralysis.

[c] 313 AFP with variable fever ignored.

[d] No exposure to OPV between 4 and 40 days prior to paralysis.

Table 2 Estimated crude relative risks (RR) for vaccine-associated paralytic poliomyelitis (VAPP) occurrence, according to the variables studied

Variable	RR	95% CI	*P*-value
Oral polio vaccine[a]	8.88	4.37–18.03	<0.01
Gender	0.61	0.29–1.24	0.16
Fever	3.99	1.40–11.41	<0.01
GI[b] symptoms	2.05	0.96–4.37	0.06
Upper respiratory symptoms	1.41	0.35–5.63	0.62
March–August[c]	1.43	0.68–3.00	0.33
Lower limbs	1.40	0.67–2.93	0.37
Virus 1[d]	4.18	1.02–17.07	0.03
Virus 2[d]	30.83	15.39–61.76	<0.01
Virus 3[d]	19.71	9.18–42.36	<0.01

[a] Exposure to OPV between 4 and 40 days prior to paralysis.

[b] Gastrointestinal.

[c] Reference category: September to February.

[d] Reference category: isolation of other polioviruses, other enteroviruses or no isolation.

Table 3 Estimated relative risk of vaccine-associated paralytic poliomyelitis by multivariate logistic regression (OR), regression coefficient, standard error of the coefficient and *P*-value of the deviance, according to number of vaccine doses and fever

Variable	OR	95% CI	Coefficient	SE	*P*-value
1st dose	3.00	1.42–6.35	1.099	0.382	<0.01
2nd dose	0.08	0.03–0.19	–2.486	0.446	<0.01
⩾3rd dose	0.78	0.29–2.08	–0.247	0.499	<0.01
Fever	3.45	1.22–9.80	1.239	0.532	<0.01

Figure 1, corresponding to the model in Table 2, shows the greatest risk of 0.20 and a mean of 0.05.

In Table 4, age appears to be a protective factor in a model also including the variables vaccine exposure (categorized in first and ⩾2 doses) and fever. Individuals who took the first dose of OPV and had fever have a VAPP risk approximately 2.5 times higher; however, the CI for the estimated measure of association for fever includes one.

Figure 2 shows the effect of age on VAPP in a GAM model which also includes the variables vaccine exposure (first dose and ⩾2 doses) and fever. A decreasing effect, attributable to age, is observed. This effect becomes more intense between 10 and approximately 15 years old. After this point, the number of observations becomes too small, and estimates are inaccurate.

Figure 3 shows the predictive probability of the model presented in Table 3. The median risk predicted by the model for subjects developing VAPP was around 0.03, with a mean around 0.05. The peak estimated risk for the occurrence of disease was 0.18.

In comparison with previous models, the model with the variables vaccine exposure (first dose and ⩾2 doses), fever and GI symptoms showed an increased risk of the first dose for the occurrence of VAPP. The variable GI symptoms appeared to be a risk factor, although the CI includes the null value (Table 5).

Figure 4 presents the predictive probability of the model presented in Table 4. The model predicted a median risk of around 0.01 for a subject developing VAPP, with a mean of 0.03. The maximum risk of developing VAPP was 0.12.

Discussion

Since 1989 there have been no cases of paralytic poliomyelitis caused by wild poliovirus in Brazil.[14] The same happens in the Americas, where the last isolation of wild poliovirus occurred in 1991, in Peru, and in 1979 in the US. Thus, the only cases of paralytic poliomyelitis identified in the Western Hemisphere since then are vaccine-related.[15]

The results found in this study corroborate data in the international literature concerning the low risk of VAPP occurrence. Nonetheless, the risks and incidence rates found in Brazil are even lower than those found in other studies,[6,16–18] even when compared to the Latin American study,[19] which includes the Brazilian data. However, one must take into account the heterogeneity of the diagnostic criteria used throughout the world for the classification of VAPP.

Moreover, other plausible hypotheses must be considered so that these discrepancies can be understood. Considering that sometimes there are double entries, with doses distributed in vaccine campaigns also recorded as routine doses due at that

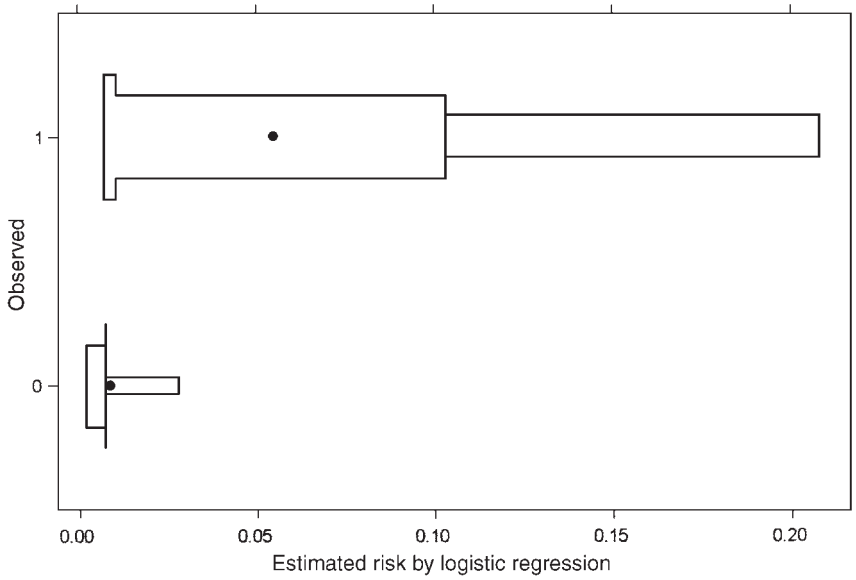

Figure 1 Quartile distribution of the probability of vaccine-associated paralytic poliomyelitis occurrence, according to logistic model, including number of vaccine doses and fever

* The point on the graph represents the mean.

Table 4 Estimated relative risk of vaccine-associated paralytic poliomyelitis by multivariate logistic regression (OR), regression coefficient, standard error of the coefficient and *P*-value of the deviance, according to number of vaccine doses, fever and age

Variable	OR	95% CI	Coefficient	SE	*P*-value
1st dose	2.66	1.49–4.76	0.979	0.297	<0.01
⩾2nd dose	0.34	0.13–0.86	–1.072	0.473	<0.01
Fever	2.45	0.83–7.16	0.897	0.547	<0.01
Age	0.56	0.42–0.75	–0.568	0.148	<0.01

time, one can hypothesize an underestimation of risk, secondary to an overestimation of the number of doses distributed. Underclassification of VAPP cases is also possible, since Brazil follows strict criteria requiring isolation of vaccine poliovirus from stool samples collected up to 14 days after the onset of paralysis.

In addition to these factors, the vaccination campaigns carried out since 1980, with wide dissemination of vaccine poliovirus in the population, must be considered. This assumes that, at the time of case analysis, older individuals already had several opportunities for contact with the vaccine poliovirus and were likely to be immunized. The effect of the frequent vaccination campaigns could overcome the decreased seroconversion to polioviruses seen in warm climates and in developing countries, as well as the interference created by diarrhoeal diseases mentioned in several studies.[3,20–25]

The results of vaccine poliovirus isolation demonstrate a larger association with the isolation of type 2 vaccine poliovirus. These findings agree with reports in the literature concerning the greater occurrence of poliovirus types 2 and 3 in VAPP, while the type 1 strain is considered more stable in the attenuation/virulence process.[4,16,26]

The analysis of risk of VAPP occurrence in relation to vaccine exposure demonstrated a significant association, i.e. the risk of individuals exposed to the vaccine was significantly higher than that of individuals who did not receive the vaccine between 4 and 40 days before the onset of paralysis. Few references in the literature use this approach. Nevertheless, other studies, presenting percentage data, are consistent with the results found in Brazil. In these studies it can be noted that most cases of VAPP occur in vaccine recipients, when compared to contacts of vaccinees.[6,17,27–29] Some discrepancies in relation to these findings were found in studies in Romania,[29] in the US, analysing the 1973–1984 historical series[16] and in Washington,[30] where the largest number of cases was among contacts of vaccinees.

As to the age group of VAPP occurrence, the risk decreases with increasing age. This finding agrees with the literature, where it is noted that most cases occur in the youngest age groups.[16,29,31]

In the models presented, an approximately three times higher risk is observed for the first dose of OPV in relation to subsequent doses. When the first, second, third or more vaccine doses were analysed, the last two appear to be protective factors for the condition. The increased risk for the first dose of OPV has already been clearly demonstrated in several other studies analysing cases of VAPP.[16–18,29,31]

Acute flaccid paralyses presenting with a prodromic phase of fever and GI symptoms are associated with VAPP. The studies reviewed lacked this analysis, which prevented their comparison with the present results. Nevertheless, the literature describes, among the clinical manifestations of poliomyelitis, the 'minor illness', characterized by fever, vomiting, diarrhoea, etc.[32] This description alone allows us to consider them relevant when faced with a case of paralytic poliomyelitis.

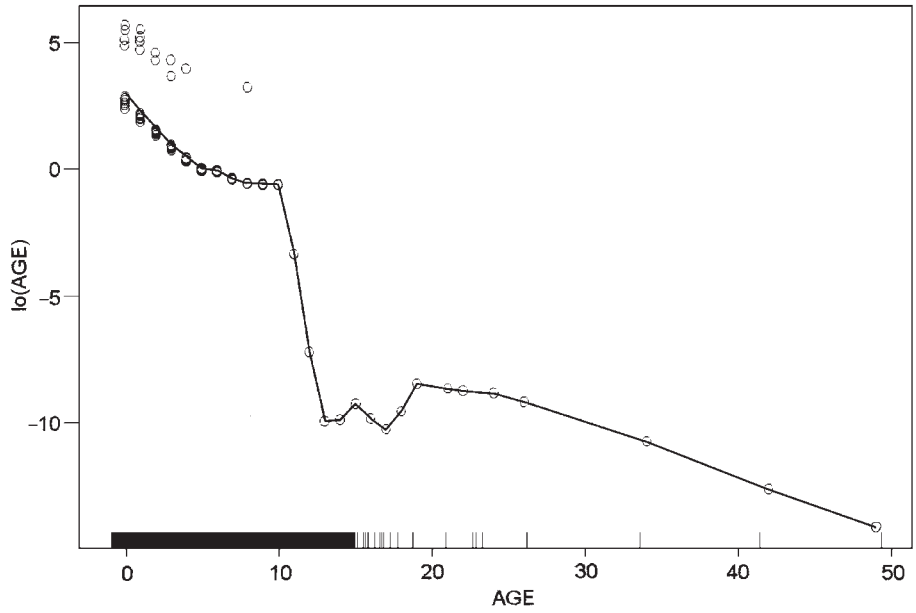

Figure 2 Relation between vaccine-associated paralytic poliomyelitis and age, according to logistic model, adjusted by the generalized additive model (GAM) function, including number of vaccine doses and fever

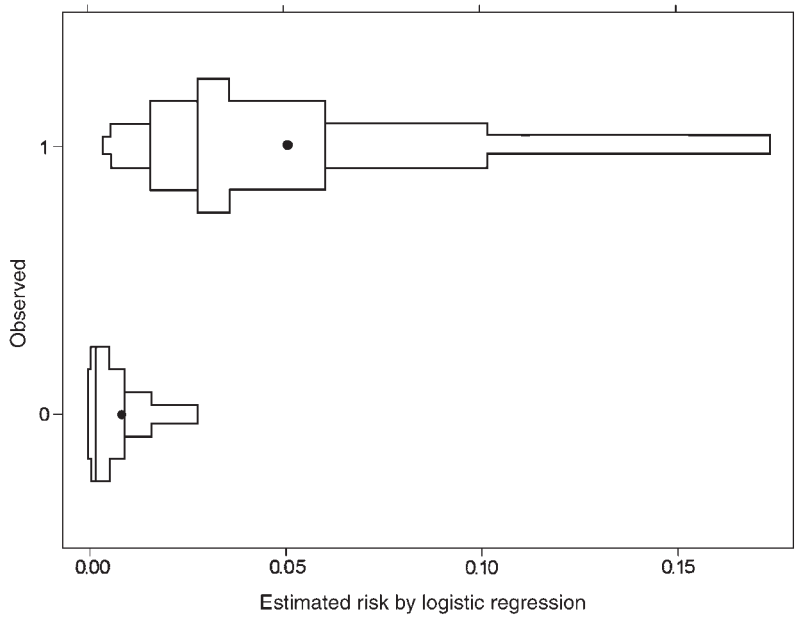

Figure 3 Quartile distribution of the probability of vaccine-associated paralytic poliomyelitis occurrence, according to logistic model, including number of vaccine doses (first and two or more), fever and age* The point on the graph represents the mean.

* The point on the graph represents the mean.

The other variables analysed did not show statistical significance when the crude relative risk data were analysed and when they were included in the models.

The construction of a predictive model for the outcome studied had some limiting factors. Since the event studied is rare, and therefore has a small number of cases, estimates are not very accurate, and several analyses demonstrated a lack of statistical significance of the factors examined. However, the analysis of the data demonstrated that some variables are important, allowing us to identify which, among the risk factors studied, are more relevant for the occurrence of the condition.

To our knowledge, no other studies using multivariate analysis for determining the occurrence of VAPP have been conducted, rendering the comparison of our findings to published data hard to achieve.

The important risk factors to be considered when a case of AFP is reported are: previous exposure to the vaccine (between 4 and 40 days before the onset of paralysis), presence of fever and a GI prodrome, number of vaccine doses and age group. Given the results found, it seems evident that the first dose of OPV is more strongly associated with the occurrence of VAPP than the others, while two or more doses of vaccine would appear to be a protective factor, as previously commented.

For almost all the observations, the predictive probability of the multivariate models developed was too low. In all the models, the predicted risk of developing VAPP was very close to zero, even among those who had actually become ill. The predictive model which included vaccine exposure, first dose of vaccine, fever and age had the highest median and a peak probability of 0.18. However, when the model included only the number of vaccine doses and fever, the peak estimated risk, by logistic regression, was 0.20. Among the models tested, these would be the best for predicting the risk of VAPP when AFP is reported.

The results found are consistent with the literature, in spite of the limitations mentioned before. As to the validity of our findings, it must be considered that, at least in principle, the whole population of AFP occurring in the period 1989–1995 in the country was analysed. This allows us to believe that our results faithfully portray events in this population in this period regardless of the statistical significance or precision of the model parameter estimates.

Table 5 Estimated relative risk of vaccine-associated paralytic poliomyelitis by multivariate logistic regression (OR), regression coefficient, standard error of the coefficient and *P*-value of the deviance, according to number of vaccine doses (first and two or more), gastrointestinal (GI) symptoms and fever

Variable	OR	95% CI	Coefficient	SE	*P*-value
1st dose	3.89	2.21–6.86	1.359	0.290	<0.01
≥2nd dose	0.24	0.09–0.58	–1.435	0.461	<0.01
GI Symptoms	1.61	0.74–3.53	0.477	0.400	<0.06
Fever	3.27	1.13–9.50	1.187	0.543	0.02

Acknowledgements

The authors gratefully acknowledge Drs Luiz Antônio Bastos de Camacho and João Baptista Risi Junior for their comments and suggestions. This paper was supported by the National Epidemiology Center, National Health Foundation, Ministry of Health, Brazil. CJS was partially supported by CNP, PRONEX/FINEP, FAPERJ.

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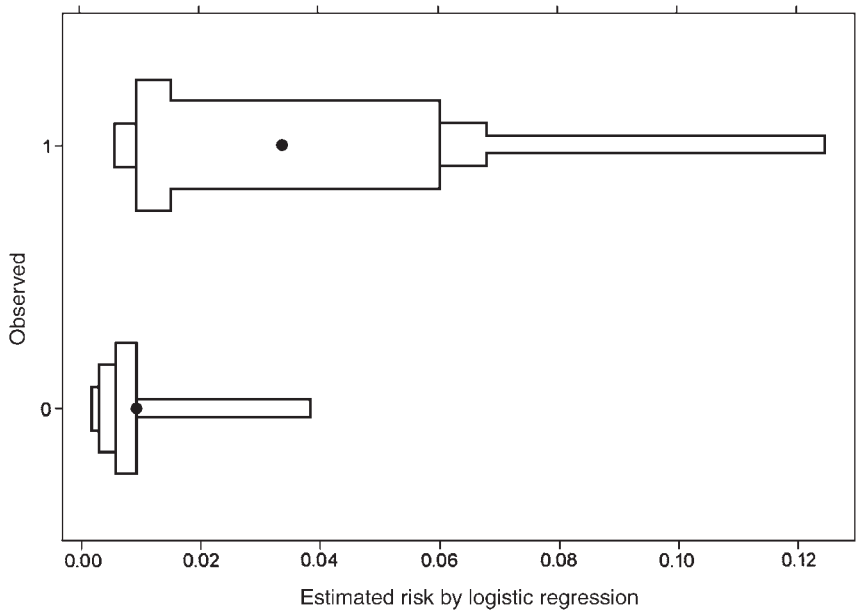

Figure 4 Quartile distribution of the probability of vaccine-associated paralytic poliomyelitis occurrence, according to logistic model, including number of vaccine doses (first and two or more), fever and gastrointestinal symptoms

* The point on the graph represents the mean.

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