Appendix 2 (as supplied by the authors): Exposure misclassification bias sensitivity analysis

In this study we performed a number of sensitivity analyses to evaluate areas of uncertainty in using administrative data. The area of greatest concern was immunization status ascertainment and the misclassification bias arising from using physician billing claims as the data source.

A great deal of attention gets paid to random error in epidemiological research.[9, 10] It is accepted standard of practice to quantitatively report random error through 95% confidence intervals and p-values. However, it is much less common to quantitatively report systematic errors. This is particularly important when authors make claims regarding effect sizes or the results have policy implications.[11] One source of information bias leading to systematic error is misclassification bias, which is present to some degree in most observational studies.[12] It is expected that non-differential misclassification will bias associations towards the null, however this may not always be true.[13, 14]

In our study, we used the Ontario Health Insurance Plan (OHIP) database to assess immunization status. This has been used previously to assess influenza[15] and vaccine coverage in children.[16] This database is known to have variable sensitivity and specificity for influenza, as well as infant, immunization status.[3, 17] To support the validity of our findings we sought to validate the use of these data specifically for pertussis immunization and incorporate the performance measures into a multidimensional sensitivity analysis.

Fox *et al*. designed a SAS macro that uses record-level corrections for bias. This tool provides a probabilistic method for conducting a sensitivity analysis to correct for misclassification bias of a dichotomous variable.[11] By inputting ranges for sensitivity and specificity, the macro incorporates both systematic and random error. The macro simulates data

that would have been observed had the misclassified variable, in our case immunization status, been correctly classified given a range of sensitivity and specificity.

This macro has been described in more detail elsewhere and is available online.[11, 18] Knowing exact values of sensitivity and specificity is typically unrealistic. Even in our context the cohort contains a variety of ages and we demonstrated how these values change with age in Appendix 1. The macro allows inputs of a minimum and maximum sensitivity and specificity. Outside of this range the probability is equal to zero. It also allows up to two modes of sensitivity and specificity. The modes represent the zone of indifference (i.e., the range of values between which the probability is equal).

We inputted values for sensitivity and specificity based on our validation analysis described in Appendix 1. For the first three strata, we used a trapezoidal probability density function for the plausible ranges of sensitivity and specificity. This implies a minimum, a maximum, and two modes based on the overlap in age categories from the validation analysis. In the last strata there were no children younger than eight years of age, therefore a triangular probability density function was assumed and only one mode was used (Table e2).
The vaccine effectiveness in this sensitivity analysis, adjusted for the same covariates in the primary analysis, was 95% (95%CI, 87% to 100%), 98% (95%CI, 94% to 100%), 63% (95%CI, 35% to 82%), and 22% (95%CI, -70% to 73%) at 15-364 days, 1-3 years, 4-7 years, and ≥8 years, respectively. This equated to a change in vaccine effectiveness from the primary analysis of 15%, 14%, 1%, and -19% for each strata, respectively (Table e2).

The results of this sensitivity analysis demonstrated that the non-differential misclassification bias tended to skew the results towards the null hypothesis and therefore underestimate vaccine effectiveness within four years since last immunization. However, the

decrease in vaccine effectiveness from 1-3 years to 4-7 years, and from 4-7 years to ≥8 years, was larger than the primary analysis. At ≥8 years the estimate was 19% lower than the primary analysis, however neither were significantly different from zero. This suggests that despite the underestimation of vaccine effectiveness in the first three years post-immunization, the waning immunity effect is maintained, or potentially more pronounced.

This sensitivity analysis achieved a number of important objectives. First we confirmed that non-differential misclassification bias of immunization status tended to bias our results towards the null and underestimated vaccine effectiveness in the earlier years. This assumption is often made, but is not necessarily accurate.[13, 14] This analysis also permitted quantification of the level of uncertainty in our estimates, based on the known degree of systematic bias present in our exposure variable while simultaneously accounting for random error.[11] These findings strengthen our conclusions of waning immunity. We acknowledge the need for caution in interpreting results using data with an unknown amount of systematic error. However, by validating this data source and quantifying the change in our estimates, we can confidently conclude that the observed findings are not a result of underlying bias in the dataset.

Table e2: The sensitivity and specificity inputs used for each misclassification bias analysis. Each strata requires a minimum and maximum sensitivity and specificity with up to 2 modes (i.e. the zone of indifference). The bottom of the table contains the results of the sensitivity analysis with vaccine effectiveness estimates adjusted for the misclassification bias compared to the primary analysis.

	15 days – 1 year	1-3 years	4-7 years	8+ years
Misclassification bias sensitivity analysis inputs				
Minimum Sensitivity	0.545	0.545	0.545	0.545
Mode 1 Sensitivity	0.573	0.573	0.573	0.573
Mode 2 Sensitivity	0.879	0.659	0.659	-
Maximum Sensitivity	0.896	0.689	0.689	0.6
Minimum Specificity	0.778	0.778	0.778	0.778
Mode 1 Specificity	0.828	0.828	0.828	0.828
Mode 2 Specificity	0.967	0.975	0.975	-
Maximum Specificity	0.992	0.988	0.988	0.878
Misclassification bias sensitivity analysis results				
Crude %VE (95% CI)	95.8 (88.8-99.7)	97.6 (92.6-99.9)	55.6 (26.8-79.6)	13.6 (-60.6-67.0)
Crude % change from primary analysis	11.6	18.5	23.0	11.0
Adjusted %VE (95% CI)	95.4 (86.8-99.8)	98.1 (93.7-99.9)	63.3 (35.1-82.0)	22.0 (-69.6-73.1)
Adjusted % change from primary analysis	15.1	13.7	1.3	-19.4

VE=vaccine effectiveness, CI=confidence interval

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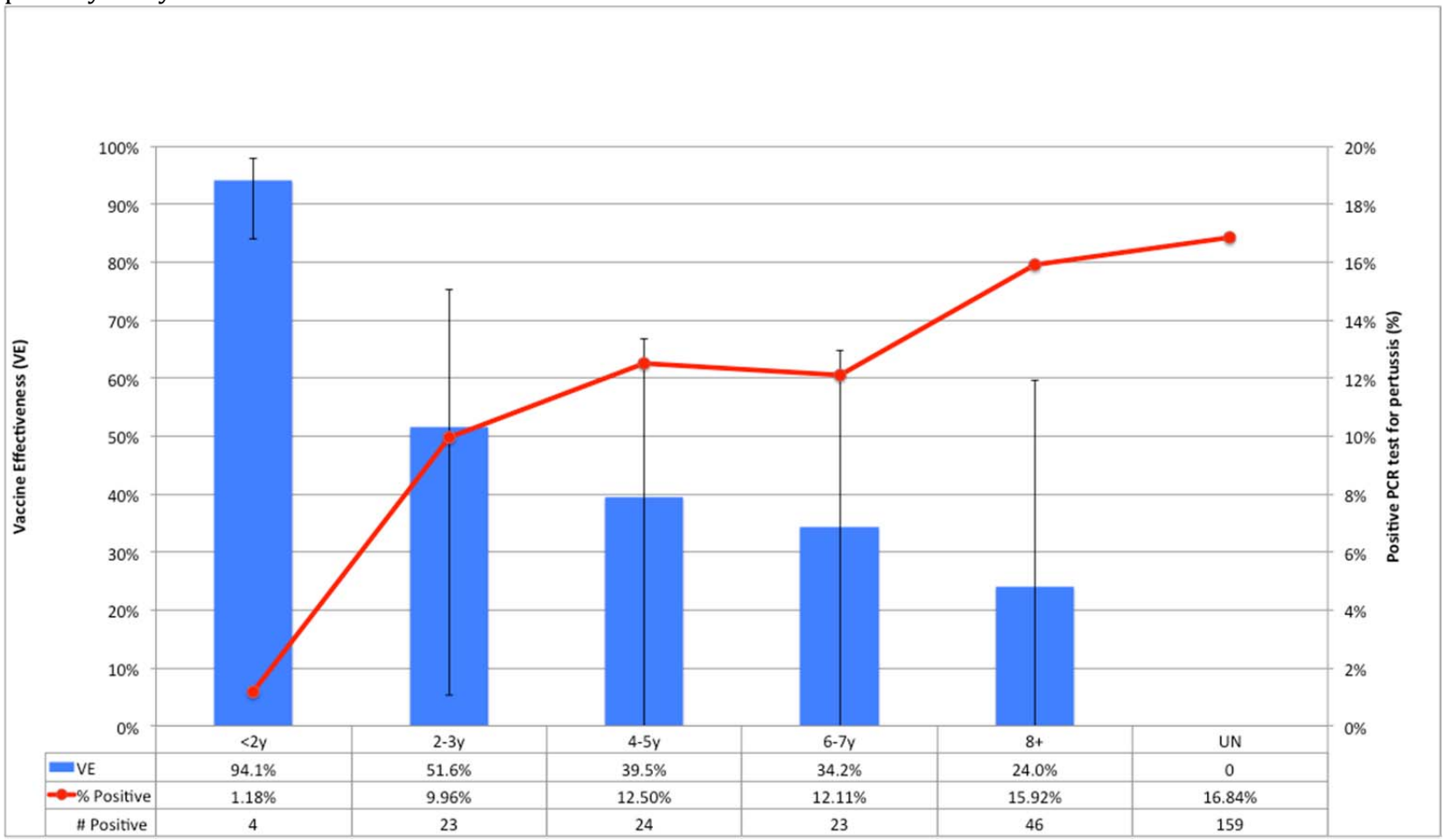
Figure e1: Pertussis vaccine effectiveness (left axis) and percentage of pertussis tests positive (right axis) since last vaccination. This figure is limited to those who have received 5 or more doses of vaccine demonstrating the same trend as the primary analysis.



	<2y	2-3y	4-5y	6-7y	8+	UN
VE	94.1%	51.6%	39.5%	34.2%	24.0%	0
% Positive	1.18%	9.96%	12.50%	12.11%	15.92%	16.84%
# Positive	4	23	24	23	46	159

Table a1: Multivariable logistic regression model predicting pertussis-positive cases compared to pertussis-negative controls for strata receiving their last immunization between 15 and 364 days from index date compared to those unimmunized.

Variable	**Adjusted OR (95% CI)**	**Test statistic**	**p-value**
Omnibus Likelihood Ratio, $\chi 2$(df)		209.03 (13)	<0.01
Up-to-date Immunizations vs unimmunized	0.20 (0.14, 0.286)	72.94	<0.01
Partial Immunizations vs unimmunized	0.25 (0.14, 0.46)	20.00	<0.01
Age (years)	1.04 (1.00, 1.079)	3.53	0.06
Sex (male vs female)	1.26 (0.95, 1.69)	2.49	0.12
Rural residence (yes vs no)	1.18 (0.84, 1.65)	0.93	0.34
Income quintile (2 vs 1)	1.47 (0.94, 2.29)	2.91	0.09
Income quintile (3 vs 1)	1.42 (0.91, 2.21)	2.37	0.12
Income quintile (4 vs 1)	0.85 (0.52, 1.36)	0.48	0.49
Income quintile (5 vs 1)	1.46 (0.94, 2.27)	2.83	0.09
Physician office visits in previous 12 months (≥8 vs <8)	0.84 (0.55, 1.09)	0.92	0.34
Hospitalizations in previous 12 months (≥1 vs 0)	0.77 (0.55, 1.20)	2.13	0.14
Emergency department visits in previous 12 months (≥2 vs <2)	0.56 (0.4, 0.78)	11.51	<0.01
Any chronic medical condition (yes vs no)	0.58 (0.23, 1.48)	1.3	0.26

Hosmer-Lemeshow p-value=0.304

Table a2: Multivariable logistic regression model predicting pertussis-positive cases compared to pertussis-negative controls for strata receiving their last immunization between 1 and 3 years from index date compared to those unimmunized.

Variable	**Adjusted OR (95% CI)**	**Test statistic**	**p-value**
Omnibus Likelihood Ratio, $\chi 2$(df)		166.54 (13)	<0.01
Up-to-date Immunizations vs unimmunized	0.16 (0.11, 0.23)	94.72	<0.01
Partial Immunizations vs unimmunized	0.32 (0.20, 0.50)	24.81	<0.01
Age (years)	1.05 (1.02, 1.09)	8.81	<0.01
Sex (male vs female)	1.06 (0.79, 1.41)	0.14	0.71
Rural residence (yes vs no)	1.15 (0.83, 1.61)	0.69	0.41
Income quintile (2 vs 1)	1.23 (0.78, 1.93)	0.81	0.37
Income quintile (3 vs 1)	1.29 (0.83, 1.99)	1.28	0.26
Income quintile (4 vs 1)	0.77 (0.48, 1.23)	1.19	0.28
Income quintile (5 vs 1)	1.28 (0.83, 1.98)	1.25	0.26
Physician office visits in previous 12 months (≥8 vs <8)	0.94 (0.67, 1.32)	0.13	0.72
Hospitalizations in previous 12 months (≥1 vs 0)	0.48 (0.32, 0.73)	11.90	<0.01
Emergency department visits in previous 12 months (≥2 vs <2)	0.68 (0.49, 0.95)	5.16	0.02

Any chronic medical condition (yes vs no)	0.32 (0.08, 1.37)	2.36	0.13

Hosmer-Lemeshow p-value=0.421

Table a3: Multivariable logistic regression model predicting pertussis-positive cases compared to pertussis-negative controls for strata receiving their last immunization between 4 and 7 years from index date compared to those unimmunized.

Variable	**Adjusted OR (95% CI)**	**Test statistic**	**p-value**
Omnibus Likelihood Ratio, $\chi 2$(df)		75.56 (13)	<0.01
Up-to-date Immunizations vs unimmunized	0.38 (0.25, 0.58)	20.09	<0.01
Partial Immunizations vs unimmunized	0.44 (0.28, 0.70)	12.17	<0.01
Age (years)	1.03 (0.99, 1.07)	1.96	0.16
Sex (male vs female)	1.11 (0.83, 1.48)	0.47	0.49
Rural residence (yes vs no)	1.14 (0.83, 1.56)	0.62	0.43
Income quintile (2 vs 1)	1.63 (1.02, 2.62)	4.1	0.04
Income quintile (3 vs 1)	1.58 (0.99, 2.52)	3.69	0.06
Income quintile (4 vs 1)	1.30 (0.81, 2.07)	1.19	0.28
Income quintile (5 vs 1)	1.52 (0.97, 2.38)	3.29	0.07
Physician office visits in previous 12 months (≥8 vs <8)	0.62 (0.42, 0.91)	5.86	0.02
Hospitalizations in previous 12 months (≥1 vs 0)	0.44 (0.28, 0.68)	13.36	<0.01
Emergency department visits in previous 12 months (≥2 vs <2)	0.72 (0.51, 1.01)	3.61	0.06
Any chronic medical condition (yes vs no)	0.69 (0.20, 2.35)	0.35	0.56

Hosmer-Lemeshow p-value=0.536

Table a4: Multivariable logistic regression model predicting pertussis-positive cases compared to pertussis-negative controls for strata receiving their last immunization between ≥8 years from index date compared to those unimmunized.

Variable	**Adjusted OR (95% CI)**	**Test statistic**	**p-value**
Omnibus Likelihood Ratio, $\chi 2$(df)		62.35 (13)	<0.01
Up-to-date Immunizations vs unimmunized	0.59 (0.34, 1.00)	3.83	0.05
Partial Immunizations vs unimmunized	0.64 (0.39, 1.06)	3.01	0.08
Age (years)	1.01 (0.98, 1.06)	0.50	0.48
Sex (male vs female)	0.95 (0.72, 1.25)	0.14	0.71
Rural residence (yes vs no)	0.93 (0.68, 1.27)	0.21	0.65
Income quintile (2 vs 1)	1.44 (0.91, 2.28)	2.46	0.12
Income quintile (3 vs 1)	1.54 (0.99, 2.40)	3.66	0.06
Income quintile (4 vs 1)	1.02 (0.65, 1.60)	0.01	0.94
Income quintile (5 vs 1)	1.41 (0.91, 2.16)	2.41	0.12

Physician office visits in previous 12 months (≥8 vs <8)	0.57 (0.40, 0.83)	8.54	<0.01
Hospitalizations in previous 12 months (≥1 vs 0)	0.44 (0.28, 0.68)	13.44	<0.01
Emergency department visits in previous 12 months (≥2 vs <2)	0.84 (0.61, 1.16)	1.09	0.30
Any chronic medical condition (yes vs no)	0.44 (0.10, 1.92)	1.19	0.28

Hosmer-Lemeshow p-value=0.495