Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Evidence of MMR Vaccination Receipt

Criteria		Code	Code Type	Description	
A	**1**	90704	CPT	Mumps virus vaccine, live, for subcutaneous use	OR
		99.46	ICD-9 proc	Vaccination against mumps	
				AND	
	2	90705	CPT	Measles virus vaccine, live, for subcutaneous use	OR
		99.45	ICD-9 proc	Vaccination against measles	
				AND	
	3	90706	CPT	Rubella virus vaccine, live, for subcutaneous use	OR
		99.47	ICD-9 proc	Vaccination against rubella	
OR					
B	**1**	90704	CPT	Mumps virus vaccine, live, for subcutaneous use	OR
		99.46	ICD-9 proc	Vaccination against mumps	
				AND	
	2	90708	CPT	Measles and rubella virus vaccine, live, for subcutaneous use	
OR					
C	**1**	90705	CPT	Measles virus vaccine, live, for subcutaneous use	OR
		99.45	ICD-9 proc	Vaccination against measles	
				AND	
	2	90709	CPT	Rubella and mumps virus vaccine, live, for subcutaneous use	
OR					
D	**1**	90707	CPT	Measles, mumps and rubella virus vaccine (MMR), live, for subcutaneous use	OR
		99.48	ICD-9 proc	Administration of measles-mumps-rubella vaccine	
OR					
E	**1**	90710	CPT	Measles, mumps, rubella, and varicella vaccine (MMRV), live, for subcutaneous use	

eTable 2. *ICD-9* Codes Used to Define Seizures, Vaccination-Related Allergies, and Allergic Contraindication to Vaccinations

ICD-9 Dx Code	Condition
Seizures	
345.xx	Epilepsy and recurrent seizures
780.3x	Convulsions
Vaccination-related allergies	
995.68	Anaphylactic reaction due to eggs
999.39	Complications of medical care, NEC, infection following other infusion, injection, transfusion, or vaccination
999.42	Anaphylactic reaction due to vaccination
E948.4	Tetanus vaccine causing adverse effect in therapeutic use
E948.5	Diphtheria vaccine causing adverse effect in therapeutic use
E948.6	Pertussis vaccine, including combinations with pertussis component, causing adverse effect in therapeutic use
E948.8	Other and unspecified bacterial vaccines causing adverse effect in therapeutic use
E948.9	Mixed bacterial vaccines, except combinations with pertussis component, causing adverse effect in therapeutic use
E949.4	Measles vaccine causing adverse effect in therapeutic use
E949.5	Poliomyelitis vaccine causing adverse effect in therapeutic use
E949.6	Other and unspecified viral and rickettsial vaccines causing adverse effect in therapeutic use
E949.7	Mixed viral-rickettsial and bacterial vaccines, except combinations with pertussis component, causing adverse effect in therapeutic use
E949.9	Other and unspecified vaccines and biological substances causing adverse effect in therapeutic use
V14.7	Personal history of allergy to serum or vaccine
V15.03	Personal history of allergy to eggs
V64.04	Vaccination not carried out because of allergy to vaccine or component
Pre-term birth	
362.20	Retinopathy of prematurity, unspecified
362.22	Retinopathy of prematurity, stage 0
362.23	Retinopathy of prematurity, stage 1
362.24	Retinopathy of prematurity, stage 2
362.25	Retinopathy of prematurity, stage 3
362.26	Retinopathy of prematurity, stage 4
362.27	Retinopathy of prematurity, stage 5

ICD-9 Dx Code	Condition
765.00	Extreme fetal immaturity, unspecified (weight)
765.01	Extreme fetal immaturity, less than 500 grams
765.02	Extreme fetal immaturity, 500-749 grams
765.03	Extreme fetal immaturity, 750-999 grams
765.04	Extreme fetal immaturity, 1,000-1,249 grams
765.05	Extreme fetal immaturity, 1,250-1,499 grams
765.06	Extreme fetal immaturity, 1,500-1,749 grams
765.07	Extreme fetal immaturity, 1,750-1,999 grams
765.08	Extreme fetal immaturity, 2,000-2,499 grams
765.09	Extreme fetal immaturity, 2,500 or more grams
765.10	Other preterm infants, unspecified (weight)
765.11	Other preterm infants, less than 500 grams
765.12	Other preterm infants, 500-749 grams
765.13	Other preterm infants, 750-999 grams
765.14	Other preterm infants, 1,000-1,249 grams
765.15	Other preterm infants, 1,250-1,499 grams
765.16	Other preterm infants, 1,500-1,749 grams
765.17	Other preterm infants, 1,750-1,999 grams
765.18	Other preterm infants, 2,000-2,499 grams
765.19	Other preterm infants, 2,500 or more grams
765.21	Less than 24 completed weeks of gestation
765.22	24 completed weeks of gestation
765.23	25-26 completed weeks of gestation
765.24	27-28 completed weeks of gestation
765.25	29-30 completed weeks of gestation
765.26	31-32 completed weeks of gestation
765.27	33-34 completed weeks of gestation
765.28	35-36 completed weeks of gestation
776.6	Anemia of neonatal prematurity
V21.30	Low birth weight status, unspecified
V21.31	Low birth weight status, less than 500 grams
V21.32	Low birth weight status, 500-999 grams
V21.33	Low birth weight status, 1000-1499 grams
V21.34	Low birth weight status, 1500-1999 grams
V21.35	Low birth weight status, 2000-2500 grams

Sensitivity Analyses for Exposure and Outcome Misclassification

Because it is unlikely that claims-based indicators of MMR immunization status or ASD status are completely accurate, sensitivity analyses were undertaken to explore the potential impact of misclassification on estimated relative risks (RR). The general approaches followed were for simple, multidimensional, and multiple bias analyses, making use of the publicly available spreadsheet tools, developed by, and described in, Lash et al. *Applying Quantitative Bias Analysis to Epidemiologic Data* (2009).[1] Select results are summarized in eTable3 and discussed below.

eTable 3. Uncorrected and Misclassification-Corrected Relative Risks for the Effect of One-Dose MMR Exposure on ASD Risk at 5 Years of Age

	Unadjusted RR for one MMR dose at 5 years of age	
	Older sibling without ASD	**Older sibling with ASD**
Uncorrected	1.16	0.69
Corrected for non-differential exposure misclassification	1.40	0.60
Further corrected for non-differential outcome misclassification	1.48	0.60
Further corrected for differential outcome misclassification – Scenario 1: Sn|MMR+ = 0.75; Sn|MMR- = 0.60*	1.18	0.48
Further corrected for differential outcome misclassification – Scenario 2: Sn|MMR+ = 0.45; Sn|MMR- = 0.30*	0.99	0.40

* Sn|MMR+ is assumed sensitivity among those receiving MMR and Sn|MMR- is assumed sensitivity among those unvaccinated

Exposure Misclassification

MMR immunization rates in index children included in this study (i.e., having at least 60 months of continuous enrollment and at least one older sibling who were privately insured and captured in the ORD research database) were between 4% and 14% percentage points lower than the rates reported in the National Immunization Survey, depending on year of birth between 2001-2010.[2] Under the assumption that these differences reflect misclassification of MMR exposure in study data, a simple bias analysis was conducted. The specificity of claims to identify MMR-immunized children was assumed to be 100%. In other words, the assumption is that there were no false positives identified with the claims algorithm – if the claims indicated a child received MMR, they actually did receive it. Making this assumption about specificity, and further assuming that the NIS data reflect the true prevalence of MMR exposure in our sample, the sensitivity of claims identification of MMR immunization can be estimated as the ratio of the claims-based MMR immunization prevalence to the NIS MMR prevalence. The logic here flows from the fact that the ratio of two prevalences that apply to the same population simplifies to a ratio of their numerators – which here would be the ratio of those identified in claims as receiving MMR divided by all those actually receiving MMR. Because 100% specificity is assumed, those identified by claims as receiving MMR include only true positives. Therefore this ratio estimates the number of true positives identified with claims divided by those believed to have actually received MMR – the sensitivity of the claims based approach. The average of the ratios of claims-to-NIS MMR prevalences over the 2001-2010 period, or 0.908, was used as our sensitivity estimate for this bias analysis. It was also assumed that any misclassification, here related only to imperfect sensitivity, would be non-differential with respect to ASD status. In other words, true MMR immunized children with and without ASD would be equally likely to be misclassified as unimmunized by the claims data. Further, it was assumed that the non-differential misclassification at this sensitivity and specificity applied to both children with and without older siblings with ASD.

The specificity (100%) and sensitivity (0.908) estimates were then applied to the unadjusted data for the one-dose MMR effect on ASD status at age five years. As expected, this non-differential misclassification suggests that true RRs are further from the null then the estimates. In the case of subjects with older siblings not having ASD, the misclassification-corrected RR is 1.4 indicating that the reported RR could be an 18% underestimate of the true RR. For subjects with older siblings that have ASD, the corrected estimate was 0.60, 13% lower than the RR estimate that was reported.

Outcome Misclassification

We previously published a chart-based validation study[3] of the claims-based ASD case identification approach implemented in this study. In the validation study, the sampling was conditional on presence or absence of claims with ASD ICD-9 codes, so the reported validity

statistics presented there were predictive values (as opposed to sensitivity and specificity). The two-ASD-claims case definition used here was shown in the validation study to have a positive predictive value of 87.4% (95% CI 81.7%, 91.8%). Because of validation study cost and design-constraints, only 60 subjects without ASD claims were included; consequently, the negative predictive value estimate 98.3% should be interpreted with caution. If it is assumed that the true ASD prevalence in the source populations for the validation study (children between ages 2 and 20 years old in the ORD database between 2001 and 2009 with at least 12 months continuous enrollment) and this study (children in the ORD between 2001 and 2007 with at least five years of continuous enrollment and an older sibling in the database) are roughly comparable, we can then consider for use in bias analysis assumed sensitivities and specificities for claims-based ASD classification that are consistent with the observed predictive values from the validation study. Thinking first about specificity, it seems reasonable to assume a value substantially higher than 99%. If the true prevalence of ASD in the study population is consistent with the latest CDC estimates (1.47%),[4] 99% specificity implies that 1% of those without ASD (or 0.985% of the total population) are false-positives. That suggests that there are nearly as many false positives as true ASD cases – which seems implausible. If 99.9% specificity is assumed there would then be approximately 1 false positive for every 10 true cases - which seems more reasonable. With this specificity and the assumed true ASD prevalence of 1.47%, Bayes Theorem can be applied to estimate the sensitivity (45%) that leads to a positive predictive value roughly equal to that observed in our validation study. Sensitivity estimates of 30% and 75% generate positive predictive values at the lower and upper bounds of the 95% CI for the validation study's PPV. Consequently, we ran a multidimensional bias analysis varying sensitivity from 0.30 to 0.75, holding specificity constant at 0.999. Note that while these sensitivities, at face value, seem worryingly low, because ASD is an uncommon condition, the impact of imperfect outcome sensitivity should be much less than that of imperfect outcome specificity. We considered the scenarios introduced above and utilized the multiple bias analysis approach described in Lash et al (2009)[1] beginning analyses here with the data already "corrected" for exposure misclassification as described above.

First, the situation where misclassification is non-differential was considered. For subjects with older siblings without ASD, correction for outcome misclassification moves the RR from 1.40 (the exposure misclassification corrected estimate) to 1.48, regardless of assumed sensitivity. For subjects with older siblings that have ASD, correcting for non-differential outcome classification does not change the RR estimate any further from the exposure-misclassification corrected estimate. This suggests only a small additional underestimation of the true RR associated with non-differential outcome misclassification. However, it might be reasonable to expect some differential misclassification here, with the sensitivity of the claims approach perhaps greater in children that have been MMR vaccinated; ostensibly, because these families are inherently more inclined to use services and therefore have ASD identified and/or because some of them may become more attentive to their child's developmental status post immunization. Correcting for differential misclassification in this direction results in smaller RR estimates. So, in subjects with

unaffected older siblings, when sensitivity is assumed to be 0.75 in the MMR immunized and 0.6 in the unvaccinated the RR estimate moves from 1.40 to 1.14 (the corrected RR estimate becomes 0.99 when sensitivity is assumed to be 0.45 and 0.30 in the vaccinated and unvaccinated, respectively). In subjects with affected older siblings, the RR estimates become more protective.

Conclusions

The bias analyses conducted here are informative but need to be cautiously interpreted because they rely on assumptions that might be inaccurate, are based on unadjusted cumulative incidence rate ratio measures (as opposed to adjusted hazard rate ratio measures), and focus attention on point estimates at the expense of confidence intervals (in other words a corrected RR estimate still carries as much imprecision as was associated with the original estimate's 95% confidence interval). Under assumptions regarding potential under-reporting of MMR immunization in the claims data informed by a comparison of NIS and claims-based MMR vaccination prevalences, bias analysis suggests the magnitude of the resulting misclassification would be modest. Moreover, it is also quite plausible that some of the differences between the claims-based MMR prevalences and the NIS estimates are real and do not reflect misclassification. Differences might be related to birth order (our index child sample by definition exclude first-born children who are included in the NIS) or socioeconomic status (our index child sample are all privately insured and thus tend to be of higher socioeconomic status, whereas the NIS also includes publicly insured and uninsured children who tend to be of lower socioeconomic status). In different studies, socioeconomic status has been positively associated with unvaccinated status[5,6] and negatively associated with delayed vaccination.[7,8,9]

Non-differential outcome misclassification, if present, would appear to have a very small additional biasing effect toward the null. Differential outcome misclassification, which most likely would manifest as greater outcome detection sensitivity among those vaccinated then among those not vaccinated, would make actual RRs smaller than those reported. Applied to the one-dose effect at 5 years scenario selected here, in subjects who do not have affected older siblings where the original point estimates were above 1.0 this bias would countervail the impact of exposure misclassification but in those with ASD-affected older siblings where the original point estimates were below 1.0 this compounds exposure misclassification suggesting that the corrected effect is even further protective. However, here it is important to emphasize that confidence intervals are wider for this group and that adjustment for confounders tended to move estimated effects in this group toward 1.0.

eTable 4. Relative Risk of ASD (1+ diagnoses)[a] by Index Child MMR Vaccination Status, Fully Adjusted[b] With Time Interaction, Older Sibling ASD Status, and Older Sibling ASD Status Interacted With MMR Vaccination Status

Time-/Age-Specific Hazard Ratios	Older sibling without ASD (N=94,090)				Older sibling with ASD (N=1,964)			
	N[d]	ASD Cases[e]	hazard ratio (95% CI)	p-value	N[d]	ASD Cases[e]	hazard ratio (95% CI)	p-value
Exactly one MMR[c] dose by age 2	78071	72	0.98 (0.76-1.26)	0.86	1415	11	0.82 (0.54-1.24)	0.34
Exactly one MMR dose by age 3	79925	298	1.00 (0.82-1.22)	0.97	1484	46	0.83 (0.57-1.22)	0.34
Exactly one MMR dose by age 4	79949	492	1.02 (0.82-1.25)	0.89	1519	75	0.85 (0.58-1.25)	0.40
Exactly one MMR dose by age 5	40630	415	1.03 (0.78-1.37)	0.81	884	66	0.86 (0.56-1.32)	0.50
Exactly two MMR doses by age 5	45706	317	1.06 (0.79-1.42)	0.70	807	35	0.52 (0.31-0.88)	0.01

[a] Index child was defined as 1+ ASD diagnoses; older sibling ASD status was defined as 2+ ASD diagnoses. The total sample size in this table is 96,054. Tables 1 and 2 in the manuscript are limited to index children with no ASD diagnoses or 2+ ASD diagnoses (n=95,727).

[b] Adjusted for birth year, gender, region, race/ethnicity, maternal/paternal highest education level, household income, age of mother at index infant date of birth, age of father at index infant date of birth, continuous enrollment with mental health carve-out benefit, Childhood Chronic Conditions Score, seizure, allergies, pre-term birth

[c] MMR vaccination doses captured after year 1 birthday

[d] Number of index children who have exactly the number of MMR doses given at any time between birth and each age given

[e] Number of index children who have been diagnosed with ASD at any time between birth and each age given.

eTable 5. Relative Risk of ASD[a] by Index Child MMR Vaccination Status, Fully Adjusted[b] With Time Interaction, Older Sibling ASD Status, and Older Sibling ASD Status Interacted With MMR Vaccination Status – Excluding Index Children With Unknown Sociodemographic Data

Time-/Age-Specific Hazard Ratios	Older sibling without ASD (N=76,014)				Older sibling with ASD (N=1,607)			
	N[d]	ASD Cases[e]	hazard ratio (95% CI)	p-value	N[d]	ASD Cases[e]	hazard ratio (95% CI)	p-value
Exactly one MMR[c] dose by age 2	63458	43	0.90 (0.65-1.24)	0.71	1165	4	0.82 (0.48-1.39)	0.42
Exactly one MMR dose by age 3	64918	185	0.98 (0.76-1.26)	0.91	1218	30	0.89 (0.55-1.44)	0.48
Exactly one MMR dose by age 4	64933	315	1.06 (0.80-1.40)	0.82	1242	53	0.97 (0.60-1.57)	0.61
Exactly one MMR dose by age 5	33103	275	1.15 (0.78-1.70)	0.67	728	43	1.05 (0.61-1.82)	0.77
Exactly two MMR doses by age 5	36902	193	1.10 (0.73-1.66)	0.80	652	26	0.60 (0.31-1.19)	0.04

[a] Index child and older sibling ASD status was defined as 2+ ASD diagnoses

[b] Adjusted for birth year, gender, region, race/ethnicity, maternal/paternal highest education level, household income, age of mother at index infant date of birth, age of father at index infant date of birth, continuous enrollment with mental health carve-out benefit, Childhood Chronic Conditions Score, seizure, allergies, pre-term birth.

[c] MMR vaccination doses captured after year 1 birthday.

[d] Number of index children who have exactly the number of MMR doses given at any time between birth and each age given.

[e] Number of index children who have been diagnosed with ASD at any time between birth and each age given

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