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Association between socioeconomic status and adverse events following immunization at 2, 4, 6 and 12 months

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Using a population-based self-controlled case series design, we examined data on children born between the years 2002 and 2009 in the province of Ontario, Canada. We specifically examined how socioeconomic status (SES) influences rates of adverse events following immunization (AEFI), defined as emergency room visits and / or hospital admissions. For vaccination at 2, 4 and 6 mo combined, the relative incidence of AEFI (95% CI) in the first 72 h after vaccination was 0.69 (0.67 to 0.71). For all three vaccinations combined, we observed no relationship between the relative incidence of an event and quintile of socioeconomic status (p = 0.1433). For the 12-mo vaccination alone, the relative incidence of events (95% CI) on days 4 to 12 following immunization was 1.35 (1.31 to 1.38). We observed a significant relationship between socioeconomic status and vaccination at 12 mo, with lower SES being associated with a higher relative incidence of events (p = 0.0075). When the lowest 2 quintiles of income combined were compared with the highest 3 quintiles, the relative incidence ratio (95% CI) was 0.94 (0.89 to 0.99, p = 0.02). These results translate to 150 additional adverse events in the lower SES quintiles as compared with the higher SES quintiles for every 100,000 children vaccinated, or 1 additional event for every 666 individuals vaccinated. Future studies should explore potential explanations for this observation.

Introduction

In Ontario, Canada, the routine pediatric immunization schedule includes vaccines against diphtheria, pertussis, tetanus, polio, hemophilus influenzae type b (Hib) and pneumococcus administered at 2, 4 and 6 mo of age, and vaccines against measles, mumps and rubella (MMR vaccine) and meningococcal disease (type C) administered at 12 mo of age. These vaccines have been demonstrated to be safe and highly effective in reducing incidence of the targeted diseases. However, in the process of conferring immunity, these vaccines can produce physiological reactions. Inactivated vaccines administered at 2, 4 and 6 mo typically produce reactions within 24 to 48 h.[1] The live attenuated MMR vaccine administered at 12 mo of age can produce a physiological reaction one to two weeks after immunization.[2,3]

Identifying risk factors for AEFI is important as they may provide clues to the etiology of these events, may assist health care providers in communicating potential risks and could allow for the development of interventions to reduce these events. Together, the outcomes of these investigations could help to alleviate concerns about vaccination by better preparing parents for expected mild AEFI.

When examining predictors of emergency room (ER) visits and hospitalization following immunization, we have previously shown that event rates were increased at 2 mo of age in lower birth weight, full term infants and were reduced in premature infants, after adjusting for weight.[4,5] In this study we examine how socioeconomic status (SES) influences rates of AEFI as measured by ER visits and hospital admissions following immunization.

VISION (Vaccine and Immunization Surveillance in Ontario)

We have previously utilized linked health services data to evaluate the safety of pediatric vaccines in Ontario. We defined adverse events following immunization (AEFI) as ER visits and admissions occurring within a specified at-risk period, an outcome that we have previously identified as being more comprehensive than looking at specific endpoints.[6] For the diphtheria, pertussis, tetanus, polio, hemophilus influenzae type b (Hib) and pneumococcus vaccinations administered at 2, 4 and 6 mo of age, we physiologically expect reactions to the vaccine to occur within 24 to 48 h and thus we examined for risk of events in the immediate 3 d post-vaccination. Our analysis showed a reduced rate of events in the risk period compared with the control period, which we attributed to the healthy vaccinee effect: the decision to forgo vaccination in unhealthy children. This effect results in the child being particularly healthy at the time of vaccination and thus

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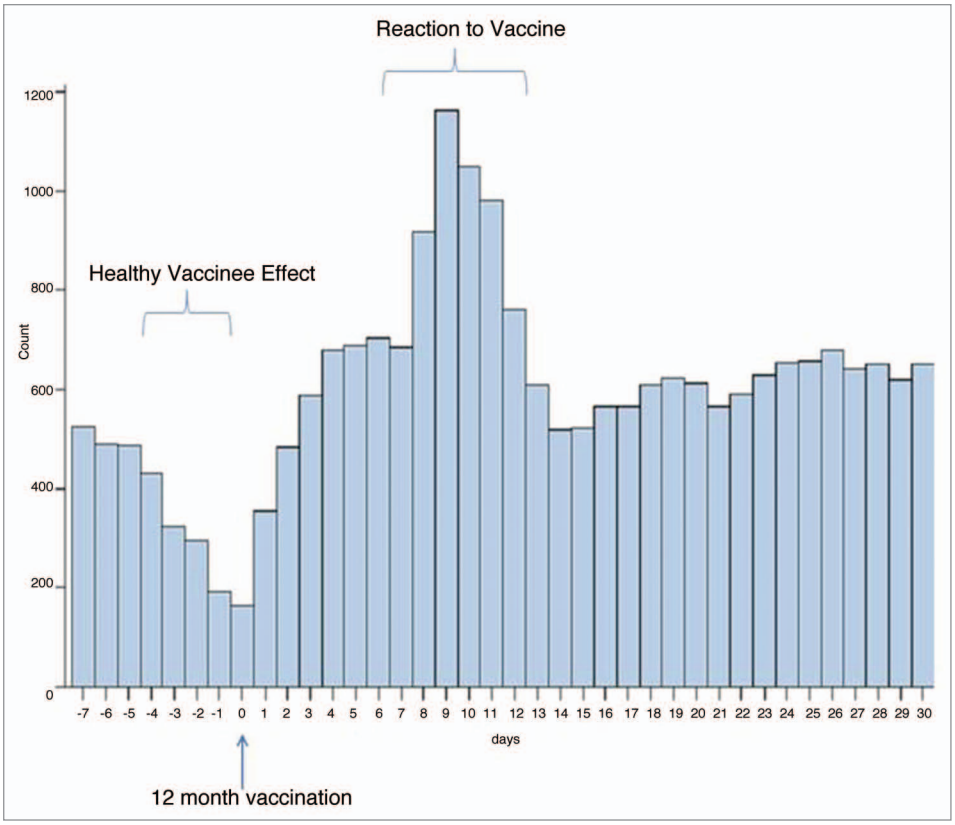

Figure 1. Emergency room visits and hospital admissions before and after 12 mo vaccination. Count, number of combined endpoints of emergency room visit or hospitalization; Days, number of days before or after vaccination, day 0 being the day of vaccination. Adapted with permission from Wilson et al.[2]

having a reduced rate of events in the immediate post-vaccination period. 12-mo vaccinations contain the live attenuated MMR vaccine which can produce a physiological reaction one to two weeks after immunization.[2,3] We identified the at-risk period as being 4 to 12 d post-vaccination which consisted of combined days with a statistically significant elevated risk compared with a baseline level. This is demonstrated in **Figure 1**.

Results

In our analysis, we examined data on children born between the years of 2002 and 2009. For our combined 2, 4 and 6 mo analysis, data was available for 1,862,263 vaccinations in 701,496 unique children. For our 12-mo analysis, data was available for 547,470 vaccinated children.

For vaccination at 2, 4 and 6 mo combined, the relative incidence of events (95% CI) in the first 72 h after vaccination was 0.69 (0.67 to 0.71). We observed no relationship between relative incidence of an event and quintile of socioeconomic status (p = 0.1433). When examining the vaccinations separately, we observed a nominally statistically significant difference among income quintiles at 4 mo, with lower SES being associated with an increased risk of an event (p = 0.03) (**Table 1A, B and C**).

For the 12-mo vaccination, the relative incidence of events (95% CI) on days 4 to 12 following vaccination was 1.35 (1.31 to 1.38) (**Table 1D**). We observed a significant relationship between socioeconomic status and vaccination, with lower SES being associated with a higher relative incidence of events (p = 0.0075). The relative incidence ratio (95% CI) comparing the highest SES quintile to the lowest SES quintile was 0.96 (0.88 to 1.05). When the lowest two quintiles of income combined were compared with the highest 3 quintiles, the relative incidence ratio was 0.94 (0.89 to 0.99, p = 0.02) which translates into 150 additional events for every 100,000 vaccinated for lower income, vs. higher income, or 1 additional event for every 666 individuals vaccinated. The vast majority of these events were ER visits (~95%). The mean CTAS score in both the lowest and highest income quintile was 3.4 suggesting similar acuity of presentation. In the lowest SES quintile, the top 5 main diagnoses for ER visits and/or admissions within the risk period following the 12-mo vaccination, based on ICD-10 codes, were acute respiratory infections (n = 406), otitis media (n = 357), unspecified fever (n = 289), non-infective colitis/gastroenteritis (n = 187) and unspecified viral infection (n = 183). These top 5 main diagnoses represent 45.3% of the events observed in the risk period. The same diagnoses were in the top 5 in the highest income quintile and represented 46.3% of the events observed in the risk period: otitis media (n = 288), acute respiratory infections (n = 262), unspecified fever (n = 217), unspecified viral infection (n = 129) and non-infective colitis/gastroenteritis (n = 93).

Discussion

Our analysis of the association between SES and adverse events following immunization, defined as ER visits and hospital admissions during the pre-defined risk period, found that overall, there was no association following vaccination at 2, 4 and 6 mo of age. Examination of each vaccination separately revealed a significant association between SES and the risk of AEFI at 4 mo, although this association would not remain significant after adjustment for multiple testing. A significant association was observed following the 12-mo vaccination, with lower socioeconomic status being associated with a higher risk of an event. The risk difference between low / moderate and higher SES, using neighborhood income quintiles as a proxy, translated into 150 additional events per 100,000 children vaccinated.

Table 1A. Adverse events following immunization at 2 mo

Income quintile	Vaccinated children	Events during risk period (days 0–2)	Events during control period (days 9–18)	Relative incidence	Relative incidence ratio (RIR)	RIR p-value
Overall	643 636	2309	8798	0.79 (0.75–0.82)		
1	136031	590	2194	0.81 (0.74–0.88)	1 (ref)	
2	126936	473	1870	0.76 (0.69–0.84)	0.94 (0.82–1.08)	
3	132794	456	1727	0.79 (0.71–0.88)	0.98 (0.86–1.13)	
4	136609	448	1747	0.77 (0.69–0.85)	0.95 (0.83–1.09)	
5	111266	342	1260	0.81 (0.72–0.92)	1.01 (0.87–1.17)	0.862

Table 1B. Adverse events following immunization at 4 mo

Income quintile	Vaccinated children	Events during risk period (days 0–2)	Events during control period (days 9–18)	Relative incidence	Relative incidence ratio (RIR)	RIR p-value
Overall	621366	1790	7972	0.67 (0.64–0.71)		
1	129185	499	2021	0.74 (0.67–0.82)	1 (ref)	
2	122058	393	1742	0.68 (0.61–0.77)	0.91 (0.79–1.06)	
3	128485	349	1536	0.68 (0.61–0.77)	0.92 (0.79–1.07)	
4	133074	328	1479	0.67 (0.59–0.75)	0.90 (0.77–1.05)	
5	108564	221	1194	0.56 (0.48–0.64)	0.75 (0.63–0.89)	0.0308

Socioeconomic status is an indicator of other related factors that could potentially explain the association between SES and AEFI. Some of the concepts theoretically related to SES include education level, nutrition and access to a family doctor. It could be hypothesized that lower SES parents would have reduced access to primary care and therefore may be more likely to utilize the hospital system if an event were to occur following vaccination. If this hypothesis were correct, we would have expected to observe lower acuity scores in the lower SES children, which was inconsistent with our findings. We also would have expected to observe the same association between SES and AEFI with the 2, 4 and 6 mo vaccinations, which was not the case. This may partly be due to the comparatively lower rate of AEFI following these vaccinations making it more difficult to identify an association. As further evidence against this hypothesis, the literature in this area does not support an association between low SES and reduced access to primary care in Ontario.[7,8]

Given the known relationship between SES and education level, it could be hypothesized that the effect we observed was mediated by parental education level.[9] Parents of lower SES may have less education which could reduce their understanding of the information about AEFI given to them by physicians. This could result in expected physiological reactions being perceived as abnormal with resultant seeking of medical care. However, we observed the same acuity scores for presentation in all SES quintiles, which argues against this hypothesis.

Perhaps most interesting is the possibility that there is a real physiological difference between lower SES and higher SES children. This is most likely mediated through nutritional status. Low income is a known risk factor for micronutrient deficiencies including Vitamin A deficiency which can depress immune function.[10,11] Vitamin A deficiency has been shown to affect the immune response by decreasing the number of T and B lymphocytes, and by altering the innate immunity response via the mucosal epithelia, natural killer cells, macrophages and monocytes.[12] Data from the 2004 Canadian Community Health Survey indicated that Canadian children aged 1–3 y had a prevalence of inadequate Vitamin A consumption of under 5%, whereas the prevalence was approximately 35% for Canadian adults over the age of 19 y.[13,14] It is plausible that vitamin A deficiencies in lower income Canadian mothers could result in their infants having similar deficiencies. While nutritional status has not been found to be associated with seroconversion, nutritional status can be associated with response to measles infection.[15] In children who are Vitamin A deficient, measles infection results in increased morbidity and mortality.[16,17] For this reason, Vitamin A supplementation is given with MMR vaccination in parts of the developing world.[17,18] An MMR vaccination simulates a mild measles infection through the administration of a live attenuated virus which undergoes controlled replication. Given the current state of evidence, it is plausible that children of lower SES have subclinical nutritional deficiencies that could magnify the mild viral illness produced by the vaccine. This, however, is a hypothesis that would require further exploration.

Our study has important strengths and limitations. The strengths include the fact that this is the first study, to the best of our knowledge that examines the association between SES and AEFI. Our large sample size permitted us to identify small effect sizes. The population-based nature of our study reduced the likelihood of selection bias. Utilizing the self-controlled case series design allowed us to adjust for all fixed confounding variables. Using relative incidence ratios permitted us to compare relative incidence rates across quintiles of SES, and adjust for the healthy vaccinee effect. Our study also has some important limitations.

Table 1C. Adverse events following immunization at 6 mo

Income quintile	Vaccinated children	Events during risk period (Days 0–2)	Events during control period (Days 9–18)	Relative incidence	Relative incidence ratio (RIR)	RIR p-value
Overall	597261	1735	8767	0.59 (0.56–0.63)		
1	122641	455	2134	0.64 (0.58–0.71)	1 (ref)	
2	116800	361	1875	0.58 (0.52–0.65)	0.90 (0.78–1.05)	
3	123843	337	1764	0.57 (0.51–0.64)	0.90 (0.77–1.05)	
4	128964	311	1673	0.56 (0.49–0.63)	0.87 (0.74–1.02)	
5	105013	271	1321	0.62 (0.54–0.70)	0.96 (0.82–1.14)	0.409

Table 1D. Adverse events following immunization at 12 mo

Income quintile	Vaccinated children	Events during risk period (days 4–12)	Events during control period (days 20–28)	Relative incidence	Relative incidence ratio (RIR)	RIR p-value
Overall	547470	12959	9629	1.35 (1.31–1.38)		
1	111348	2937	2221	1.32 (1.25–1.40)	1 (ref)	
2	106504	2775	1874	1.48 (1.40–1.57)	1.12 (1.00–1.16)	
3	113990	2635	1981	1.33 (1.25–1.41)	1.01 (0.93–1.09)	
4	118461	2622	1991	1.32 (1.24–1.40)	1.00 (0.92–1.08)	
5	97167	1990	1562	1.27 (1.19–1.36)	0.96 (0.88–1.05)	0.0075
1,2 combined*	217852	5712	4095	1.39 (1.34, 1.45)		
3,4,5 combined*	329618	7247	5534	1.30 (1.26, 1.36)	0.94 (0.89, 0.99)	0.0201

*Note, multiple events in a risk period were only counted once, therefore events in combined quintiles will not necessarily sum to the same totals as in individual quintiles.

As mentioned, we did not investigate primary care visits following immunization. These are less specific for identifying adverse events and would dilute any signal. The main diagnoses associated with ER visit and hospital admission were not validated. Furthermore, we used general Ontario Health Insurance Plan (OHIP) billing codes for vaccination, which most likely represent the recommended vaccines provided at each age we studied, but it is possible that the general billing codes represented other vaccinations.

Methods

Using VISION (Vaccine and Immunization Surveillance in Ontario), an analysis infrastructure created using linked health administrative data to monitor vaccine safety and efficacy in Ontario, we examined whether rates of ER visits and hospital admissions within pre-defined risk periods following immunizations at 2, 4, 6 and 12 mo varied by quintile of socioeconomic status.[19] During our study period, standard pediatric vaccines administered at 2, 4 and 6 mo of age included those against diphtheria, pertussis, tetanus, polio, hemophilus influenzae type b (Hib) and pneumococcus. At 12 mo of age, immunizations consisted of a vaccine against measles, mumps and rubella (MMR vaccine) throughout the entire study period and in addition, a vaccine against meningococcal disease (type C) was added to the schedule as of September 2004. To conduct this analysis, we utilized the self-controlled case series (SCCS) method in which individuals serve as their own control.[20,21] Vaccinated and unvaccinated individuals differ in important ways that could influence the outcome of interest and in most instances the proportion of unvaccinated children is low. The SCCS design, which is emerging as a primary method for assessing safety of vaccines, overcomes these challenges by implicitly adjusting for all fixed confounding variables, since individuals serve as their own controls, and only requiring data on observed cases. We defined our composite primary endpoint as ER visits or hospital admissions. The rate of events per day in an "at-risk" period is compared with the rate of events in a control period, defined as a period of time during which it would be unlikely that the exposure produced the outcome.[21] In the SCCS method, only individuals who were both vaccinated and had an event of interest during the observation period contribute to the analysis. The date of vaccination serves as the index date for exposure for each patient. Each individual's follow-up time is divided into distinct intervals: an initial exposed period, an unexposed period, and a washout period in between the exposed and unexposed periods. Our choice of the 'at-risk' and control periods was based on previous analyses we conducted examining adverse events following immunization at these time periods.[22] For the 2-, 4- and 6-mo vaccinations, the "at-risk" period was 0 to 2 d after vaccination and the control period was 9 to 18 d after vaccination. For 12-mo vaccination, the "at-risk" period was 4 to 12 d after vaccination and the control period was 20 to 28 d after vaccination. The relative incidence rate of the composite endpoint of ER visit or hospitalization during the exposed period compared with the unexposed period was computed using a fixed effects conditional Poisson regression model that included indicator variables for exposure

period and for individual patients, thereby allowing each individual to serve as his / her own control. To address the correlation of multiple events occurring close together in time (e.g., an ER visit leading to an admission, or serial ER visits), the occurrence of events were classified as "one or more events" or "no events" in each of the "at-risk" and control periods.

We compared incidence rates of the composite endpoint across quintiles of SES by calculating relative incidence ratios with the highest SES quintile serving as the reference group.[21] We conducted a test for interaction in the SCCS model using a likelihood ratio test to examine whether the relative incidence of the composite endpoint changed significantly across the levels of SES. We used a significance test cut-off adjusted for multiple testing using a Bonferroni correction. In a post-hoc analysis we compared the rates of events in the lowest 2 quintiles of SES to the highest 3 for the 12 mo vaccination. This was based on the hypothesis that there was a threshold effect of SES, where above the 2nd quintile the additional impact of increasing SES on events was negligible.

The study included all children born in Ontario between April 1st, 2002 and March 31st, 2009, who were present in the Institute for Clinical Evaluative Sciences' Registered Persons Database. Vaccination events at 2, 4, 6 and 12 mo of age were identified using billing codes for general vaccination in the OHIP Database dated on the exact vaccine due date (for example, at 2 mo we captured vaccinations occurring 60 d after birth) as well as occurring up to 14 d before, or 40 d after the due date. We identified data on hospital admissions from the Canadian Institute for Health Information's Discharge Abstract Database and data on ER visits from the National Ambulatory Care Registration System. To assess the relative severity of ER visits, we compared the Canadian Triage and Acuity Scale (CTAS) score across SES groups.[23] For this study, we defined SES by neighborhood income quintile. Using methodology developed at Statistics Canada, neighborhood income quintiles were derived based on the average of "single-person-equivalent" income in enumeration areas or dissemination areas from Canadian Census data. The postal code for each child at 6 mo of age was used to determine usual place of residence, and then neighborhood income quintile was assigned based on data from the closest Canadian Census. This methodology has been described in detail elsewhere.[24]

Conclusion

Our study identified that lower SES increased the likelihood of an AEFI, defined as an ER visit or hospital admission, after 12-mo vaccination. Future research should examine for potential explanations for this observation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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