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Measles–mumps–rubella vaccination and respiratory syncytial virus-associated hospital contact

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ABSTRACT

Background: The live measles vaccine has been associated with lower non-measles mortality and admissions in low-income countries. The live measles–mumps–rubella vaccine has also been associated with lower rate of admissions with any type of infection in Danish children; the association was strongest for admissions with lower respiratory infections.
Objective: To examine whether measles, mumps, and rubella (MMR) vaccination was associated with reduced rate of hospital contact related to respiratory syncytial virus (RSV) in a high-income country.
Methods: Nationwide cohort study of laboratory-confirmed RSV hospital contacts at age 14–23 months in all children born in Denmark 1997–2002 who had already received the vaccine against diphtheria, tetanus, pertussis (acellular), polio, and *Haemophilus influenzae* type b (DTaP-IPV-Hib) at the recommended ages of 3, 5, and 12 months.
Results: The study included 888 RSV hospital contacts in 128,588 person years of follow up (rate 6.8/1000 person years). Having MMR as the most recent vaccine was associated with a reduced rate of RSV hospital contacts compared with having DTaP-IPV-Hib as the most recent vaccine (Incidence rate ratio (IRR), 0.75; 95% confidence interval (CI), 0.63–0.89). After adjustment for potential confounders including exact age in days the IRR was 0.78 (95% CI, 0.66–0.93). The adjusted IRR was 0.74 (95% CI, 0.60–0.92) in males and 0.84 (95% CI, 0.66–1.06) in females (*P* Interaction, 0.42). There was no association in the first month after MMR vaccination (adjusted IRR, 0.97; 95% CI, 0.76–1.24) but the adjusted IRR was 0.70 (95% CI, 0.58–0.85) from one month after MMR vaccination.
Conclusions: MMR vaccination was associated with reduced rate of hospital contacts related to laboratory-confirmed RSV infection. Further research on the association between MMR vaccination and other unrelated pathogens are warranted.

1. Introduction

Besides the disease-targeted effects, vaccines may affect morbidity and mortality to unrelated infections by changing the general level of resistance toward infections, the so-called non-specific effects of vaccines [1–3]. In low-income countries, live vaccines like bacille Calmette–Guérin (BCG) against tuberculosis and measles vaccine have beneficial effects on all-cause child mortality [4–8]. In contrast, inactivated vaccines including diphtheria–tetanus–pertussis (DTP) vaccine may increase all-cause child mortality [9–11]. The nonspecific effects are often most marked in females [2,8,10–12]. Most findings from low-income countries relate to all-cause mortality. However, nonspecific effects of vaccinations on the incidence of infectious diseases and admission rates have been reported from both low-income [13–17] and high-income countries [18]. Recently, we found that the rate of admissions related to infections and particularly lower respiratory infections was reduced for Danish children following vaccination with the live MMR vaccine against measles, mumps, and rubella [19].

Abbreviations: CI, Confidence interval; DTaP-IPV-Hib, Inactivated vaccine against diphtheria, tetanus, pertussis (acellular), polio, and *Haemophilus influenzae* type b; GP, general practitioner; IRR, incidence rate ratio; MMR, Live vaccine against measles, mumps, and rubella; OPV, Oral polio vaccine; RSV, Respiratory syncytial virus.

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One of the most common causes of acute lower respiratory tract infections in infants is respiratory syncytial virus (RSV) [20–22]. Worldwide, an estimated 33.8 million new cases occur each year leading to 3.4 million hospital admissions of children under 5 years of age [21]. A study from Guinea-Bissau found that BCG vaccination reduced the risk of severe RSV infection [16]. The aim of the present study was to examine the association between MMR vaccine and the rate of hospital contacts resulting from RSV infection in a high-income setting. In the study period, the Danish recommendations were to administer MMR (Enders Edmonston, Jeryl Lynn, and Wistar RA 27/3) at 15 months of age after three doses of the inactivated vaccine against diphtheria, tetanus, pertussis (acellular), polio, and *Haemophilus influenzae* type b (DTaP-IPV-Hib) recommended at 3, 5 and 12 months of age (see Supplementary Fig. 1). The prespecified hypothesis was that children most recently vaccinated with MMR have a lower rate of RSV hospital contact compared with children vaccinated most recently with the third dose of DTaP-IPV-Hib (DTaP-IPV-Hib3).

2. Material and methods

The Danish Civil Registration System was established in 1968 and all Danish residents are assigned a unique personal identification number [23]. The personal identification number is used by all Danish national registers and was used to link the registers for the present study.

2.1. Vaccination register

In Denmark, all recommended childhood vaccinations are administered free-of-charge by the general practitioner (GP). For the purpose of reimbursement, the GPs report all vaccinations to the counties and from the counties the data are transferred to the Danish National Health Service Register [24]. Based on this information we created a database of childhood vaccinations. Most childhood vaccinations were registered in a child's name, but occasionally childhood vaccinations were registered in a parent's name (5.7%), particularly for young infants who only received their own medical card after they had been named [25]. The recommended childhood vaccinations were only reimbursed by the counties for persons below 18 years of age. Childhood vaccinations registered to an adult can therefore be assumed to have been administered to a child and we assigned such vaccinations to that adult's child, which was closest to the scheduled age of that vaccine. Vaccinations are only registered on a weekly basis. We coded date of vaccination as Wednesday of the registered week of vaccination.

2.2. RSV-database

Information on RSV-related hospital contacts was obtained from the Danish nationwide RSV-database, which was established for research purposes by collection of information from the 18 Danish laboratories testing for RSV among patients at the Danish hospitals, described in detail elsewhere [26]. The RSV-database covers the period 1 January 1996 to 1 June 2003 were RSV was examined by ELISA or immunofluorescence. During this period, all admitted children with symptoms consistent with RSV were tested for RSV to facilitate isolation of RSV cases from other admitted children to reduce the risk of transmission. In children born in Denmark and registered in the Danish Civil Registration System, the incidence rates of hospital contacts with RSV were 25.2, 27.5, 16.0, and 6.8 per 1000 person years among the age groups less than 6 weeks, 6 weeks-6 months, 6–14 months and 14–24 months, respectively. We only included information on children born on 1 January 1997 and onwards, because the vaccination schedule changed considerably from 1996 to 1997.

2.3. Other register information

The Danish Civil Registration System contains information on vital status and emigration which we used to define inclusion date and follow-up periods [23]. It was also possible to obtain information about the composition of each child's household, and age and country of birth of the parents. The Danish Medical Birth Register contains information about birth weight, mode of delivery, gestational age, and maternal smoking in pregnancy [27]. The Danish National Patient Register contains information about discharge diagnoses [28]; we used this register to obtain information on other types of hospital contacts, including accidents and chronic diseases. We obtained information on household equivalence income [29], maternal education [30], and public childcare from Statistics Denmark.

2.4. Design

The study was designed as a cohort study with retrospective identification of children born in Denmark during 1 January 1997 and 31 March 2002 and who were alive and living in Denmark at 14 months of age. In the main analysis we only included children who had followed the recommended vaccination schedule for the first three vaccination visits by receiving DTaP-IPV-Hib1 before 4 months of age, DTaP-IPV-Hib2 before 6 months of age, and DTaP-IPV-Hib3 before 13 months of age. The purpose of this selection was to include children who resemble each other with respect to determinants of vaccination and thereby reduce bias. Further details of the inclusion are given in Fig. 1. Follow-up was stopped at 2 years of age since oral polio vaccine (OPV) was scheduled at 2 years of age until July 1, 2001 (see Supplementary Fig. 1). The Danish Data Protection Agency approved the study.

2.5. Statistical methods

To describe determinants of MMR vaccination, we estimated the risk ratios (RRs) of being MMR-vaccinated at 16 months and 2 years of age according to different covariates using Poisson regression with robust variance [31].

To estimate incidence-rate-ratios (IRRs) and 95% confidence intervals (CIs) of RSV hospital contact according to most recent vaccination we used Cox proportional hazard regression analysis. Hence, the children changed vaccination status from DTaP-IPV-Hib3 to MMR on the date of MMR vaccination. We included all RSV hospital contacts, so one child could have several RSV hospital contacts. To minimize the risk that the same episode of RSV infection counted as two hospital contacts we defined the duration of one RSV infection to be 14 days based on the expected maximal period of shedding [32]. These 14 days were excluded from the count of person years.

We used age as the underlying timescale of the Cox regression model and stratified by date of birth such that cases were only compared with children born on the same date and at the same age; hence, we controlled completely for any potential confounding from age, season, and calendar year. Furthermore, the model was adjusted for: sex, birth weight in grams ($\leq$2000, 2001–2500, 2501–3000, 3001–3500, 3501–4000, 4001–4500, or >4500), gestational age (<37 weeks or $\geq$37 weeks of gestation), caesarean section (no or yes), number of admissions for any cause between 1 month of age and date of DTaP-IPV-Hib3 vaccination (none, one, two, or $\geq$three), admission for any cause from date of DTaP-IPV-Hib3 vaccination until 14 months of age (no or yes), maternal age at birth of the child in years ($\leq$19, 20–24, 25–29, 30–34, 35–39, or $\geq$40),