



Simultaneous vaccination with MMR and DTaP-IPV-Hib and rate of hospital admissions with any infections: A nationwide register based cohort study



Signe Sørup^{a,*}, Christine S. Benn^{a,b}, Anja Poulsen^c, Tyra G. Krause^d, Peter Aaby^{a,e}, Henrik Ravn^{a,b}

^a Research Center for Vitamins and Vaccines (CVIVA), Bandim Health Project, Statens Serum Institut, Copenhagen, Denmark

^b OPEN, Odense Patient Data Explorative Network, Odense University Hospital/Department of Clinical Research, University of Southern Denmark, Odense, Denmark

^c Department of Paediatrics and Adolescent Medicine, Rigshospitalet, Copenhagen, Denmark

^d Department of Infectious Disease Epidemiology, Statens Serum Institut, Copenhagen, Denmark

^e Bandim Health Project, Indepth Network, Bissau, Guinea-Bissau

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ABSTRACT

Background: In Denmark, live measles, mumps, and rubella vaccine (MMR) is associated with a reduced risk of infectious disease admissions, particularly for lower respiratory tract infections. In low-income countries, simultaneous vaccination (i.e. vaccination at the same visit) with live and inactivated vaccines may increase child mortality compared with the live vaccine alone. We examined the hypothesis that simultaneous administration of MMR and the inactivated DTaP-IPV-Hib vaccine compared with MMR alone is associated with higher incidence of infectious disease admissions.

Methods: Nationwide, retrospective, register based cohort study of 520,859 children born in Denmark 1997–2006, who were followed from 15 months to 4 years of age. Incidence rate ratios (IRRs) of hospital admissions were estimated by Cox regression and adjusted for background factors including exact age.

Results: By 2 years of age, 4965 children had simultaneous MMR and DTaP-IPV-Hib as their most recent vaccination. Compared with MMR alone, simultaneous administration was associated with a higher rate of lower respiratory tract infections (adjusted incidence rate ratio (IRR), 1.27; 95% confidence interval (CI), 1.13–1.42). There was no effect on other infections. Overall, simultaneous administration was associated with a 7% (95% CI, 0–15%) increase in infectious disease admissions.

Conclusions: Simultaneous administration of MMR and DTaP-IPV-Hib compared with MMR alone may increase the rate of hospital admissions related to lower respiratory tract infections. These findings require replication in other high-income settings.

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1. Introduction

We have previously shown that the rate of infectious disease admissions was related to the type of vaccine Danish children most recently had received. The live MMR-vaccine against measles, mumps, and rubella as the most recent was associated with

reduced rate of infectious disease admissions compared with the inactivated DTaP-IPV-Hib-vaccine against diphtheria, tetanus, pertussis (acellular), polio, and *Haemophilus influenzae* type b [1]. The association was particularly strong for lower respiratory tract infections. This finding supports evidence from randomized trials in low-income countries that live vaccines like measles vaccine have non-specific beneficial effects on the immune system by reducing infectious disease mortality more than expected from prevention of measles infections [2–4]. It has been proposed that non-specific effects of vaccines could be related to cross-protective antibodies or trained innate immunity [2,4,5].

The sequence and combination of vaccines may be very important for the magnitude and direction of the overall mortality and morbidity effects. Observational studies from low-income countries have found that compared with measles vaccine alone

Abbreviations: CI, confidence interval; DTaP-IPV-Hib, inactivated vaccine against diphtheria, tetanus, pertussis (acellular), polio, and *Haemophilus influenzae* type b; DTP, inactivated vaccine against diphtheria, tetanus, and pertussis; IRR, incidence rate ratio; LRTI, lower respiratory tract infections; MMR, live vaccine against measles, mumps, and rubella; OPV, live oral polio vaccine.

* Corresponding author at: Research Center for Vitamins and Vaccines (CVIVA), Bandim Health Project, Statens Serum Institut, Artillerivej 5, DK-2300 Copenhagen S, Denmark.

E-mail address: sgs@ssi.dk (S. Sørup).

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simultaneous administration (i.e. vaccination at the same visit) of the live measles vaccine and the inactivated DTP-vaccine against diphtheria, tetanus, and pertussis might be associated with higher mortality [6–8]. If the combination of live and inactivated vaccines has negative health effects compared with the live vaccine alone, it could have important consequences for health also in high-income countries. Some countries like Germany and Latvia administer MMR together with DTaP-IPV-Hib [9]. In the USA, MMR is recommended between 12 and 15 months of age as are several inactivated vaccines [10]. In countries that do not recommend simultaneous administration of live and inactivated vaccines many children receive the vaccines at the same visit if coming late for vaccinations.

In the present nationwide register based cohort study we tested the hypothesis that compared with MMR administered alone, simultaneous administration of MMR and DTaP-IPV-Hib is associated with higher rate of infectious disease admissions among Danish children aged 15 months to 4 years.

2. Methods

In Denmark all residents are assigned a unique personal identification number and are registered with date of birth and whereabouts in the Danish Civil Registration System [11] enabling identification of the study cohort. We included children who were born in Denmark between 1 January 1997 and 30 April 2006 and who were alive and living in Denmark at 15 months of age; further inclusion criteria are displayed in Fig. 1. The included cohort was recommended three doses of the DTaP-IPV-Hib vaccine at 3, 5, and 12 months of age and MMR at 15 months of age. The MMR vaccine consisted of Enders Edmonston, Jeryl Linn, and Wistar RA 27/3. Furthermore, three doses of oral polio vaccine (OPV) were recommended at 2, 3, and 4 years of age until 1 July 2001, thus it was mainly the birth cohorts 1997–1999 who had received OPV. The seven-valent pneumococcal conjugate vaccine was introduced on 1 October 2006; children born after 30 April 2006 were recommended a catch-up program and were not included in the present study [12].

All national Danish registries record the unique personal identification number [13] making it possible to retrieve additional information about the cohort as described below. The study was approved by the Danish Data Protection Agency.

2.1. Vaccinations

In Denmark, all recommended childhood vaccinations are administered free-of-charge by the general practitioners. For the purpose of reimbursement, vaccination information is reported to the Danish National Health Service Register [14]. Before 1997, all vaccines were registered on the personal identification number of the parents, but thereafter they were reported on the child's own personal registration number. Some childhood vaccines were still registered on parents (3.4%), but we have assigned such vaccines to the child who was closest to the recommended age for that vaccine.

2.2. Infectious disease hospital admissions

The Danish National Patient Register contains information about discharge diagnoses, which are coded according to the tenth revision of the International Classification of Diseases [15]. We identified date of admission and discharge for all inpatient contacts with a primary or secondary discharge diagnosis of any infection as previously described [1] and also given in Supplemental Table 1. In Denmark, emergency departments are rarely used for infectious

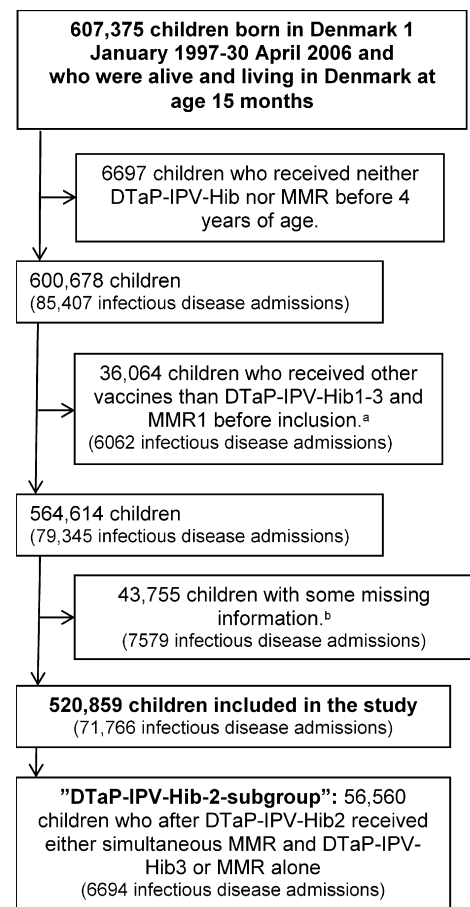


Fig. 1. Flowchart of inclusion in the study. Abbreviations: DTaP-IPV-Hib, vaccination against diphtheria, tetanus, pertussis (acellular), polio, and *Haemophilus influenzae* type b; MMR, vaccination against measles, mumps, and rubella. Notes: Infectious disease admissions are counted from the latest of the following events 15 months of age, received the first dose of either DTaP-IPV-Hib or MMR and until date of censoring for the children included in the study or until 4 years of age for the children excluded from the study. ^a DTaP-IPV or Hib alone (N = 18,149; 50.3%), not recommended combination of vaccines (N = 7113; 19.7%), fourth dose of DTaP-IPV-Hib (N = 6982; 19.4%), booster dose against different combinations of diphtheria, tetanus, pertussis (acellular), and polio (N = 1972; 5.5%), whole cell pertussis vaccine (N = 989; 2.7%), OPV (N = 500; 1.4%), second dose of MMR (N = 357; 1.0%) and pneumococcal conjugate vaccine (N = 2, 0.0%). ^b Some children had missing information on more than one variable. The number of children with missing information on each variable and in parentheses the percentage among the total number of children with missing information was: 23,391 (53.5%) with missing information on maternal smoking during pregnancy, 20,024 (45.8%) with missing information on educational level for the female adult in the household, 4698 (10.7%) with missing information on birth weight, 3610 (8.3%) with missing information on gestational age, 3371 (7.7%) with missing information on household income, 337 (0.8%) with missing information on parental place of birth, 330 (0.8%) with missing information on maternal age at birth of the child, 200 (0.5%) with uncertain vaccine allocation for twins or triplets, and 100 (0.2%) with missing information on population density.

diseases, because primary care service is available for 24 h, seven days a week to deal with infectious diseases [16]. As primary care has limited diagnostic tools like acute blood tests and X-rays, children with severe infections are usually admitted to the free-of-charge hospitals' paediatric wards for further diagnostics and monitoring; the mildest cases are often discharged the same day.

2.3. Other register based information

From the Danish National Patient Register we also obtained information on previous admissions, emergency room visits due to accidents and chronic diseases coded according to Kristensen et al. [17]. We defined inclusion and follow-up with information

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