Vaccine 34 (2016) 6172–6180

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

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ARTICLE INFO

Article history:
Received 27 June 2016
Received in revised form 31 October 2016
Accepted 1 November 2016
Available online 10 November 2016

Keywords:
Heterologous immunity
Nonspecific effects
Non-targeted effects
Simultaneous immunization
Infectious disease admissions

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.

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.

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http://dx.doi.org/10.1016/j.vaccine.2016.11.005
0264-410X/

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 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.

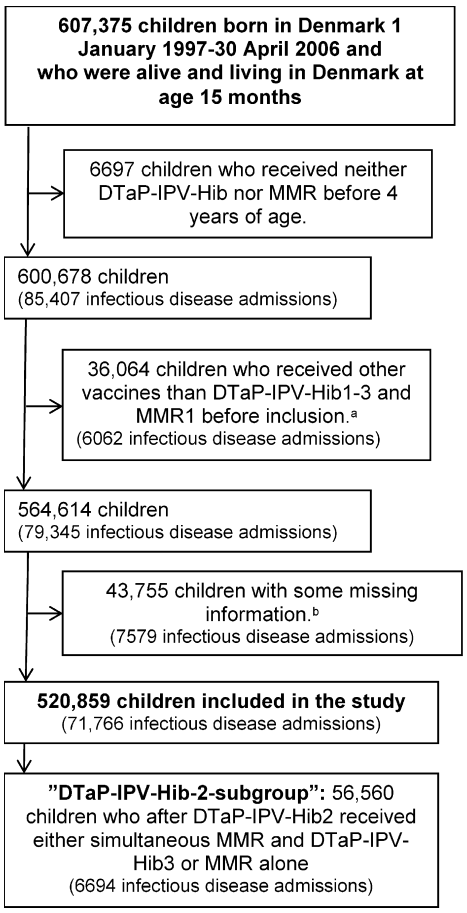

Fig. 1. Flowchart of inclusion in the study. Abbreviations: DTaP-IPV-Hib, vaccination against diphtheria, tetanus, pertussis (acellular), polio, and *Haemophilus influenzae* type b; MMR, vaccination against measles, mumps, and rubella. Notes: Infectious disease admissions are counted from the latest 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.

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

on births, deaths, and emigration from the Danish Civil Registration System which also contain information about a child's parents, siblings, and household [11]. Information about maternal smoking during pregnancy, mode of delivery, birth weight, and gestational age was obtained from the Danish Medical Birth Register [18]. Information on household equivalence income [19], and maternal education [20] was obtained from Statistics Denmark.

2.4. Follow-up

We started follow-up at 15 months of age, when MMR was recommended, or from the date when a child received the first dose of either DTaP-IPV-Hib or MMR if it occurred after 15 months of age. The children were followed until the earliest of the following events: 4 years of age, administration of other vaccines than DTaP-IPV-Hib1-3 or MMR1, death, migration, unknown whereabouts for the Danish authorities, uncertain vaccine allocation, or end of the study on 1 January 2009.

Factors related to receiving vaccines out-of-sequence may also be related to the risk of admissions for infectious diseases. Therefore, we defined a subgroup of children, the "DTaP-IPV-Hib-2-sub group", who had been compliant with the vaccination program up to DTaP-IPV-Hib-2, and then subsequently received vaccines out-of-sequence – either simultaneous MMR and DTaP-IPV-Hib3 or MMR alone instead of the recommended DTaP-IPV-Hib3 alone. We redid some of the analyses in the "DTaP-IPV-Hib-2-subgroup" to minimise the risk of bias related to out-of-sequence vaccination.

2.5. Statistical methods

We used Cox regression to estimate the incidence rate ratios (IRRs) and 95% CIs of infectious disease hospital admissions according to the most recent vaccine by including vaccination status as a time-varying variable. This means that the children changed vaccination group at the date of vaccination. The main comparison was between simultaneous MMR and DTaP-IPV-Hib vs. MMR alone as most recent vaccine, but we also compared simultaneous MMR and DTaP-IPV-Hib vs. DTaP-IPV-Hib alone as most recent vaccine and DTaP-IPV-Hib alone vs. MMR alone as most recent vaccine. The assumption of proportional hazards between simultaneous MMR and DTaP-IPV-Hib and MMR alone was evaluated by Schoenfeld residuals, and no violations were detected. We used age as the underlying timescale and stratified by date of birth (day, month, and year) to control completely for any effect of age, season, and calendar year. All infectious disease admissions were included, so children may contribute with several admissions. However, several admissions within a short time period could be related to the same infection, therefore we defined admissions occurring within 14 days after a previous discharge as the same episode. Accordingly, person time during admission and 14 days after discharge was not included in the count of person years. To account for recurrent admissions for infections, we used the Andersen-Gill model, where the main assumption is, that the effects of covariates on the intensity (incidence rate) for events, is similar for the first event, second event and so forth. Notably, we employ a Markov version of the Andersen-Gill model because we assume that time since previous events does not affect the intensity of future events in our model [21]. We performed both unadjusted and adjusted analyses in Stata 13.

We performed the analyses separately according to type of infection, duration of admission, and age groups. Furthermore, we examined whether the association between vaccination status and admissions with infections differed according to determinants of simultaneous MMR and DTaP-IPV-Hib and tested for homogeneity with Wald test statistics.

2.5.1. Sensitivity analyses

We performed a number of sensitivity analyses further described in supplemental methods.

2.5.2. Negative control outcome

We do not believe vaccination status is causally related to emergency room visits due to unintentional accidents and would not expect any association. Therefore, we performed an analysis with emergency room visits due to unintentional accidents as negative control outcome [22] to examine if differential health seeking behaviour could explain any association between vaccination status and infectious disease admissions.

3. Results

3.1. Inclusion and censoring

The study included 520,859 children (Fig. 1); the majority were followed from age 15 months, but 1991 (0.4%) received their first vaccine after 15 months of age and were followed from the date of the first vaccination. Follow-up ended at age 4 years (N = 305,802; 58.7%), administration of other vaccines than MMR1 and DTaP-IPV-Hib (mainly OPV) (N = 140,554; 27.0%), 1 January 2009 (N = 72,022; 13.8%), migration (N = 2274; 0.4%), death (N = 144; 0.0%), unknown whereabouts for the Danish authorities (N = 50; 0.0%), and uncertain vaccine allocation for twins or triplets (N = 13; 0.0%).

The vaccination history of the children is presented in Fig. 2. The MMR group consisted mainly of children who followed the recommended schedule and first received three doses of DTaP-IPV-Hib and later MMR. The group receiving simultaneous MMR and DTaP-IPV-Hib consisted mainly of children who received MMR and DTaP-IPV-Hib3 simultaneously.

56,560 children were included in the "DTaP-IPV-Hib-2-sub group" receiving either MMR alone (N = 51,256; 90.6%) or simultaneous MMR and DTaP-IPV-Hib3 (N = 5304; 9.4%) after DTaP-IPV-Hib2.

3.2. Determinants of vaccination

By 2 years of age, most children had reached their final vaccination group; 4965 children had simultaneous MMR and DTaP-IPV-Hib (1.0%), 411,518 had MMR alone (83.7%) and 74,959 had DTaP-IPV-Hib alone (15.3%) as the most recent vaccine. The distribution of background factors according to the most recent vaccine at 2 years of age are given in Table 1.

3.3. Hospital admissions due to infectious diseases

The study included 71,766 infectious disease admissions during 1,119,757 person-years at risk (rate, 6.4 admissions per 100 person-years). The rates of admissions according to vaccination history are given in Fig. 2. The rate of infectious disease admissions declined with age for all three vaccine groups (Supplemental Fig. 1).

Compared with MMR alone, simultaneous administration of MMR and DTaP-IPV-Hib was associated with a higher rate of infectious disease admissions for all children (adjusted IRR, 1.07; 95% CI, 1.00–1.15; Table 2a). The estimate was the same in the "DTaP-IPV-Hib-2-subgroup" (adjusted IRR, 1.07; 95% CI, 0.98–1.16; Table 2b).

For all children, comparing simultaneous MMR and DTaP-IPV-Hib with DTaP-IPV-Hib alone there was no difference (adjusted IRR, 0.95; 95% CI, 0.89–1.02; p, 0.166).

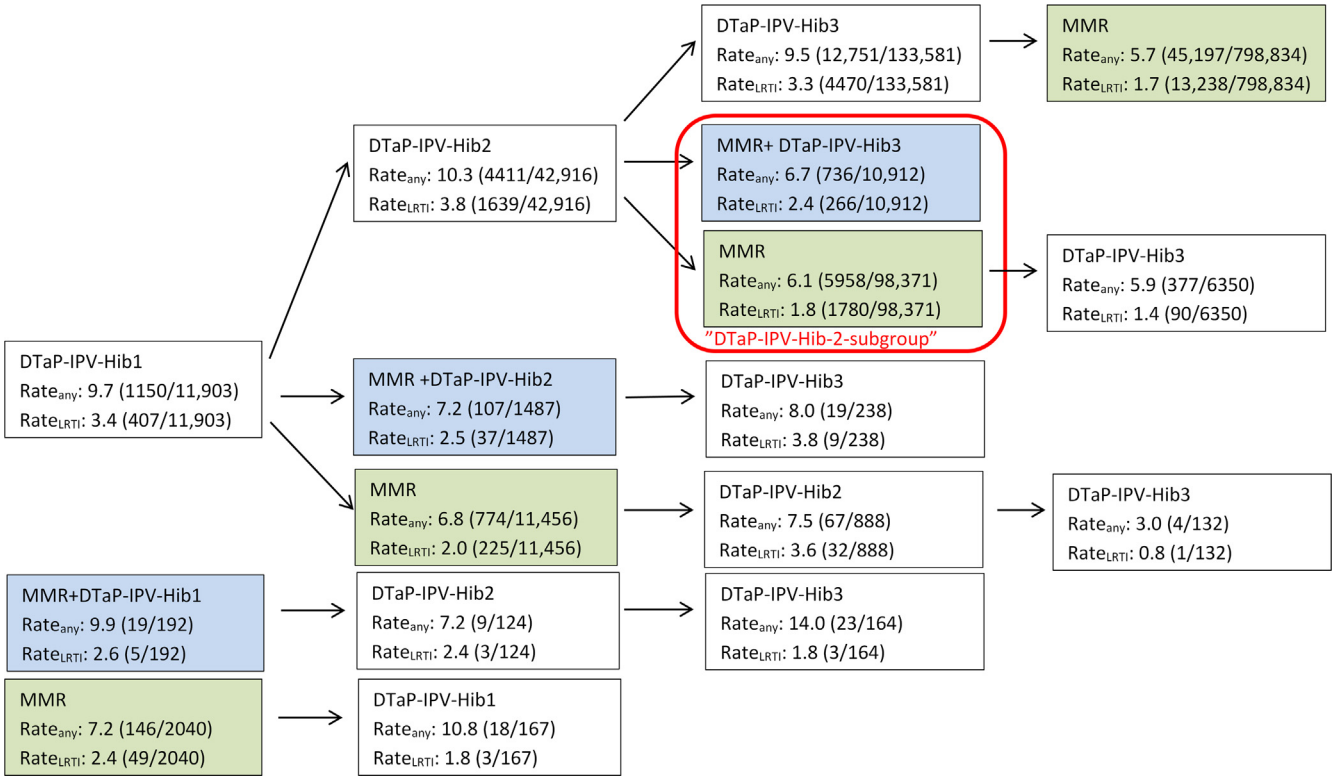

Fig. 2. Rate of infectious disease admissions according to most recent vaccine and vaccination history. Abbreviations: DTaP-IPV-Hib, vaccination against diphtheria, tetanus, pertussis (acellular), polio, and *Haemophilus influenzae* type b; MMR, vaccination against measles, mumps, and rubella; LRTI, admissions with lower respiratory tract infections. The rate is the incidence rate of infectious disease admissions (any) and separately for admissions with lower respiratory tract infections (LRTI) per 100 person-years according to the most recent vaccine and previous vaccination history for the children included in the study. In brackets number of admission/person-years. The figure only includes admissions and person-years from the date of inclusion in the study (15 months of age for the majority). Thus for instance the incidence rate in the box DTaP-IPV-Hib1 are the rate in the age interval 15 months–4 years for children who have not yet received any other vaccines. Light blue boxes mark the cases and person years included in the overall MMR + DTaP-IPV-Hib group; Light green boxes mark the cases and person years included in the overall MMR group; the "DTaP-IPV-Hib-2-subgroup" box contains the individuals included in the subgroup analyses. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.4. Type of infection, duration of admission, age groups and interactions

The rate of admission for lower respiratory tract infections was significantly higher for simultaneous MMR and DTaP-IPV-Hib compared with MMR alone for all children (adjusted IRR, 1.27; 95% CI, 1.13–1.42; Table 3a) and in the "DTaP-IPV-Hib-2-subgroup" (adjusted IRR, 1.22; 95% CI, 1.05–1.42; Table 3b). There were no significant differences between the two vaccine groups for any other types of infections (Table 3a and b).

26,621 admissions lasted less than one day (37.1%). IRRs comparing simultaneous MMR and DTaP-IPV-Hib with MMR alone as most recent vaccine were similar irrespective of duration of admission, both when considering admissions with any type of infection (Supplemental Table 2a) or only admissions with lower respiratory tract infections (Supplemental Table 2b).

Effect estimates for any infection and for lower respiratory tract infections were similar in all age groups during follow-up (Supplemental Table 3a and b).

Interactions were only examined in relation to admissions due to lower respiratory tract infections as this was the only type of infection with significant association to simultaneous administration of MMR and DTaP-IPV-Hib. The association between simultaneous administration of MMR and DTaP-IPV-Hib and admissions with lower respiratory tract infections was significantly stronger for children who had been admitted with infections before 15 months of age (IRR = 1.59; 95% CI, 1.35–1.87) compared with those not admitted (IRR = 1.13; 95% CI, 0.96–1.34; Supplemental Table 4). The association was also significantly stronger for children of mothers with an educational level above vocational training (IRR = 1.61; 95% CI, 1.32–1.95) compared with children of less educated mothers (IRR = 1.14; 95% CI, 0.98–1.31; Supplemental Table 4). The association was stronger for children from high-income households (IRR = 1.56; 95% CI, 1.30–1.87) compared with low-income households (IRR = 1.11; 95% CI, 0.95–1.30; Supplemental Table 4). Furthermore, the association was only present in children from areas with less than 2000 inhabitants per km^2 (IRR = 1.36; 95% CI, 1.19–1.55) compared with areas with more inhabitants (IRR = 1.03; 95% CI, 0.80–1.31; Supplemental Table 4).

3.5. Sensitivity analyses

None of the sensitivity analyses altered the results considerably as further described in Supplemental results.

3.6. Negative control outcome

There was no difference in the rate of emergency room visits due to accidents for children who had simultaneous MMR and DTaP-IPV-Hib compared with MMR alone (adjusted IRR, 1.00; 95% CI, 0.95–1.04; Table 4).

Table 1
Distribution of vaccinations at 2 years of age according to background factors.

	All Children			"DTaP-IPV-Hib-2-subgroup"[a]	
	Simultaneous MMR and DTaP-IPV-Hib % (N)	DTaP-IPV-Hib alone % (N)	MMR alone % (N)	Simultaneous MMR and DTaP-IPV-Hib3 % (N)	MMR alone % (N)
Maternal smoking during pregnancy					
No	76.8%	74.0%	82.7%	77.1%	82.0%
	(3815)	(55,465)	(340,486)	(3323)	(35,603)
Yes	23.2%	26.0%	17.3%	22.9%	18.0%
	(1150)	(19,494)	(71,032)	(988)	(7799)
Sex					
Male	53.2%	52.3%	50.9%	53.2%	51.6%
	(2643)	(39,208)	(209,376)	(2295)	(22,406)
Female	46.8%	47.7%	49.1%	46.8%	48.4%
	(2322)	(35,751)	(202,142)	(2016)	(20,996)
Birth weight, g					
⩽2000	2.4%	2.0%	1.8%	2.2%	2.0%
	(117)	(1531)	(7415)	(96)	(863)
2001–2500	3.1%	3.4%	3.2%	3.2%	3.3%
	(156)	(2572)	(13,216)	(137)	(1421)
2501–3000	12.4%	12.3%	12.0%	12.2%	12.0%
	(616)	(9254)	(49,431)	(526)	(5222)
3001–3500	31.2%	31.3%	31.6%	31.0%	31.6%
	(1550)	(23,447)	(129,903)	(1335)	(13,726)
3501–4000	32.4%	33.0%	33.6%	32.9%	33.3%
	(1609)	(24,747)	(138,098)	(1417)	(14,447)
4001–4500	15.2%	14.4%	14.4%	15.3%	14.3%
	(753)	(10,790)	(59,358)	(659)	(6214)
>4500	3.3%	3.5%	3.4%	3.3%	3.5%
	(164)	(2618)	(14,097)	(141)	(1509)
Gestational age, weeks					
<37	7.1%	6.3%	6.0%	6.9%	6.3%
	(354)	(4747)	(24,875)	(298)	(2730)
⩾37	92.9%	93.7%	94.0%	93.1%	93.7%
	(4611)	(70,212)	(386,643)	(4013)	(40,672)
Caesarean section					
No	81.8%	83.0%	82.3%	81.7%	81.7%
	(4062)	(62,238)	(338,734)	(3522)	(35,473)
Yes	18.2%	17.0%	17.7%	18.3%	18.3%
	(903)	(12,721)	(72,784)	(789)	(7929)
Chronic diseases					
No	96.3%	96.0%	97.0%	96.3%	96.7%
	(4779)	(71,971)	(398,975)	(4153)	(41,988)
Yes	3.7%	4.0%	3.0%	3.7%	3.3%
	(186)	(2988)	(12,543)	(158)	(1414)
Number of admissions due to infections before 15 months of age					
None	82.6%	84.4%	87.7%	82.7%	86.9%
	(4099)	(63,285)	(360,981)	(3567)	(37,733)
One	14.0%	12.6%	10.4%	13.9%	11.1%
	(694)	(9430)	(42,941)	(601)	(4798)
Two	2.4%	2.2%	1.5%	2.3%	1.6%
	(121)	(1669)	(6016)	(99)	(681)
Three or more	1.0%	0.8%	0.4%	1.0%	0.4%
	(51)	(575)	(1580)	(44)	(190)
Admitted to hospital for any cause within the last month					
No	98.8%	98.8%	99.1%	98.9%	99.0%
	(4906)	(74,039)	(407,741)	(4262)	(42,961)
Yes	1.2%	1.2%	0.9%	1.1%	1.0%
	(59)	(920)	(3777)	(49)	(441)
Maternal age at birth of the child, years					
⩽19	1.8%	2.0%	1.3%	1.8%	1.5%
	(91)	(1522)	(5327)	(78)	(651)
20–24	12.1%	13.0%	11.6%	11.7%	12.0%
	(602)	(9722)	(47,603)	(503)	(5210)
25–29	32.8%	32.5%	36.2%	32.4%	35.4%
	(1631)	(24,363)	(148,876)	(1398)	(15,378)
30–34	36.3%	34.6%	35.6%	37.0%	35.5%
	(1804)	(25,938)	(146,585)	(1596)	(15,401)
35–39	14.4%	15.3%	13.4%	14.5%	13.7%
	(716)	(11,458)	(55,238)	(626)	(5939)
⩾40	2.4%	2.6%	1.9%	2.6%	1.9%
	(121)	(1956)	(7889)	(110)	(823)

Table 1 (*continued*)

	All Children			"DTaP-IPV-Hib-2-subgroup"[a]	
	Simultaneous MMR and DTaP-IPV-Hib % (N)	DTaP-IPV-Hib alone % (N)	MMR alone % (N)	Simultaneous MMR and DTaP-IPV-Hib3 % (N)	MMR alone % (N)
Highest educational level for the female adult in the household					
Primary school	26.7% (1328)	27.9% (20,883)	18.7% (76,975)	25.4% (1096)	20.2% (8779)
High school examination	9.9% (494)	9.9% (7410)	9.8% (40,448)	9.8% (422)	9.8% (4234)
Vocational training	28.5% (1415)	31.0% (23,235)	34.7% (142,751)	29.1% (1254)	33.5% (14,530)
Bachelor or academy profession	26.1% (1294)	24.7% (18,504)	28.1% (115,660)	26.9% (1158)	27.8% (12,054)
Master's degree or higher	8.7% (434)	6.6% (4927)	8.7% (35,684)	8.8% (381)	8.8% (3805)
Parental place of birth					
Denmark	78.8% (3911)	82.7% (61,981)	83.6% (343,912)	79.7% (3435)	82.6% (35,856)
Denmark and foreign	10.4% (515)	9.6% (7163)	8.8% (36,251)	10.0% (430)	9.0% (3903)
Foreign	10.9% (539)	7.8% (5815)	7.6% (31,355)	10.3% (446)	8.4% (3643)
Adults in the household					
Two adults	88.7% (4403)	88.5% (66,327)	93.6% (385,021)	88.9% (3831)	92.5% (40,161)
Single parent	11.3% (560)	11.5% (8601)	6.4% (26,418)	11.1% (478)	7.4% (3228)
No parents	0.0% (2)	0.0% (31)	0.0% (79)	0.0% (2)	0.0% (13)
Income quintiles for the household					
1st (lowest)	26.3% (1305)	26.5% (19,877)	17.2% (70,966)	25.2% (1087)	19.4% (8401)
2nd	20.2% (1004)	22.2% (16,647)	19.0% (78,374)	20.0% (862)	19.2% (8353)
3rd	19.4% (964)	19.1% (14,327)	20.8% (85,481)	19.9% (858)	20.3% (8799)
4th	17.3% (857)	16.9% (12,634)	21.6% (88,933)	17.8% (767)	20.6% (8930)
5th (highest)	16.8% (835)	15.3% (11,474)	21.3% (87,764)	17.1% (737)	20.5% (8919)
Other children in the household					
No	26.0% (1291)	28.0% (20,965)	42.8% (176,099)	26.5% (1142)	41.1% (17,857)
Yes	74.0% (3674)	72.0% (53,994)	57.2% (235,419)	73.5% (3169)	58.9% (25,545)
Population density, inhabitants per km^2					
<50	5.1% (253)	8.2% (6152)	6.6% (27,188)	5.0% (214)	6.7% (2918)
50–499	56.2% (2788)	59.9% (44,871)	58.9% (242,240)	56.6% (2440)	60.2% (26,144)
500–1999	16.3% (811)	16.7% (12,553)	18.7% (76,926)	16.3% (704)	17.6% (7654)
2000–4999	5.6% (278)	4.2% (3178)	4.5% (18,629)	5.5% (237)	4.4% (1927)
⩾5000	16.8% (835)	10.9% (8205)	11.3% (46,535)	16.6% (716)	11.0% (4759)

Abbreviations: MMR, vaccination against measles, mumps, and rubella; DTaP-IPV-Hib, vaccination against diphtheria, tetanus, pertussis (acellular), polio, and *Haemophilus influenzae* type b.

[a] Children who have received DTaP-IPV-Hib1 and DTaP-IPV-Hib2 previously and thereafter either simultaneous MMR and DTaP-IPV-Hib3 or MMR alone.

4. Discussion

The rate of hospital admissions related to infectious diseases was higher when the most recent vaccination was simultaneous MMR and DTaP-IPV-Hib compared with MMR alone as the most recent vaccine. This was due to a higher rate of lower respiratory tract infections, but not other types of infections. There was no difference in the rate of hospital admission for any infectious disease or for lower respiratory tract infections when comparing simultaneous MMR and DTaP-IPV-Hib with DTaP-IPV-Hib alone.

The present study included all children born in Denmark and follow-up was nearly complete due to the high quality of the Danish population based registries [11]. We believe that the vaccination information is reliable because it was reported by general practitioners for reimbursement purposes, but we cannot exclude some underreporting [23].

Several issues indicate that bias is unlikely to explain the association between simultaneous administration of MMR and DTaP-IPV-Hib and admissions due to lower respiratory tract infections. First, we took several steps to minimize confounding. We adjusted

Table 2
Incidence and incidence rate ratios of admissions with infections according to the most recent vaccination.

	Admissions per 100 person-years (Admissions/Person-years)		Unadjusted IRR[a] (95% CI)	*P* value	Adjusted IRR[b] (95% CI)	*P* value
(a) All children						
Simultaneous MMR and DTaP-IPV-Hib	6.8	(862/12,591)	1.24 (1.16–1.33)		1.07 (1.00–1.15)[c]	
DTaP-IPV-Hib alone	9.6	(18,829/196,464)	1.26 (1.24–1.29)	<0.001	1.13 (1.11–1.15)	<0.001
MMR alone	5.7	(52,075/910,702)	1(ref)		1(ref)	
(b) "DTaP-IPV-Hib-2-subgroup"[d]						
Simultaneous MMR and DTaP-IPV-Hib3	6.7	(736/10,912)	1.19 (1.10–1.29)	<0.001	1.07 (0.98–1.16)	0.139
MMR alone	6.1	(5958/98,371)	1(ref)		1(ref)	

Abbreviations: DTaP-IPV-Hib, vaccination against diphtheria, tetanus, pertussis (acellular), polio, and *Haemophilus influenzae* type b; MMR, vaccination against measles, mumps, and rubella; IRR, incidence rate ratio; CI, confidence interval.

[a] Cox proportional hazards model with age as underlying time scale and stratified by date of birth thereby controlling for age and season.

[b] Cox proportional hazards model with age as underlying time, stratified by date of birth and adjusted for mother smoking during pregnancy, sex, birth weight, gestational age, caesarean section, chronic diseases, number of infectious disease admissions before 15 months of age, admitted to hospital for any cause within the last 30 days, maternal age at birth of the child, highest educational level for the female adult in the household, parental place of birth, adults in the household, income quintiles for the household, other children in the household, and population density.

[c] p-value 0.045.

[d] Children who have received DTaP-IPV-Hib1 and DTaP-IPV-Hib2 previously and thereafter either simultaneous MMR and DTaP-IPV-Hib3 or MMR alone.

Table 3
Results for admissions with different types of infections according to most recent vaccine.

	Admissions per 100 person-years (Admissions/Person-years)		Unadjusted IRR[a] (95% CI)	Adjusted IRR [b] (95% CI)
(a) All children				
Upper respiratory tract infections				
Simultaneous MMR and DTaP-IPV-Hib	2.6	(329/12,591)	1.16 (1.04–1.29)	1.01 (0.90–1.13)
DTaP-IPV-Hib alone	3.8	(7453/196,464)	1.24 (1.20–1.28)	1.12 (1.08–1.15)
MMR alone	2.3	(21,129/910,702)	1 (ref)	1 (ref)
Lower respiratory tract infections				
Simultaneous MMR and DTaP-IPV-Hib	2.4	(308/12,591)	1.58 (1.41–1.77)	1.27 (1.13–1.42)
DTaP-IPV-Hib alone	3.4	(6657/196,464)	1.43 (1.38–1.47)	1.22 (1.18–1.26)
MMR alone	1.7	(15,292/910,702)	1 (ref)	1 (ref)
Gastrointestinal infections				
Simultaneous MMR and DTaP-IPV-Hib	0.8	(106/12,591)	1.01 (0.84–1.23)	0.94 (0.77–1.14)
DTaP-IPV-Hib alone	1.3	(2494/196,464)	1.13 (1.08–1.19)	1.07 (1.01–1.12)
MMR alone	0.8	(7573/910,702)	1 (ref)	1 (ref)
Other types				
Simultaneous MMR and DTaP-IPV-Hib	1.5	(189/12,591)	1.13 (0.98–1.31)	1.00 (0.87–1.16)
DTaP-IPV-Hib alone	2.1	(4138/196,464)	1.22 (1.18–1.27)	1.07 (1.03–1.12)
MMR alone	1.3	(12,266/910,702)	1 (ref)	1 (ref)
(b) "DTaP-IPV-Hib-2-subgroup"[c]				
Upper respiratory tract infections				
Simultaneous MMR and DTaP-IPV-Hib3	2.6	(285/10,912)	1.12 (0.99–1.28)	1.04 (0.90–1.19)
MMR alone	2.5	(2440/98,371)	1 (ref)	1 (ref)
Lower respiratory tract infections				
Simultaneous MMR and DTaP-IPV-Hib3	2.4	(266/10,912)	1.49 (1.29–1.70)	1.22 (1.05–1.42)
MMR alone	1.8	(1780/98,371)	1 (ref)	1 (ref)
Gastrointestinal infections				
Simultaneous MMR and DTaP-IPV-Hib3	0.9	(94/10,912)	1.03 (0.82–1.28)	0.99 (0.79–1.25)
MMR alone	0.9	(878/98,371)	1 (ref)	1 (ref)
Other types				
Simultaneous MMR and DTaP-IPV-Hib3	1.4	(154/10,912)	1.04 (0.88–1.24)	0.93 (0.77–1.12)
MMR alone	1.4	(1390/98,371)	1 (ref)	1 (ref)

Abbreviations: IRR, incidence rate ratio; CI, confidence interval; DTaP-IPV-Hib, vaccination against diphtheria, tetanus, pertussis (acellular), polio, and *Haemophilus influenzae* type b; MMR, vaccination against measles, mumps, and rubella.

[a] Cox proportional hazards model with age as underlying time and stratified by date of birth thereby controlling for season.

[b] Cox proportional hazards model with age as underlying time, stratified by date of birth and adjusted for mother smoking during pregnancy, sex, birth weight, gestational age, caesarean section, chronic diseases, number of infectious disease admissions before 15 months of age, admitted to hospital for any cause within the last 30 days, maternal age at birth of the child, highest educational level for the female adult in the household, parental place of birth, adults in the household, income quintiles for the household, other children in the household, and population density.

[c] Children who have received DTaP-IPV-Hib1 and DTaP-IPV-Hib2 previously and thereafter either simultaneous MMR and DTaP-IPV-Hib3 or MMR alone.

for a long range of potential confounders including complete adjustment for age. However, there might be other factors associated both with lack of compliance with the recommended vaccination schedule and infectious disease admissions which we had no information about. Therefore, we performed a separate analysis for the "DTaP-IPV-Hib-2-subgroup" of children who received vaccines out-of-sequence after DTaP-IPV-Hib2 and found a similar association. There were however still marked differences in

Table 4
Incidence and incidence rate ratios of unintentional accidents according to the most recent vaccination.

Characteristics	Accidents per 100 person-years (Accidents/Person-years)		Unadjusted IRR[a] (95% CI)	*P* value	Adjusted IRR[b] (95% CI)	*P* value
Simultaneous MMR and DTaP-IPV-Hib	14.9	(1872/12,557)	1.08 (1.03–1.13)		1.00 (0.95–1.04)	
DTaP-IPV-Hib alone	14.7	(28,926/196,220)	1.04 (1.03–1.05)	<0.001	1.01 (0.99–1.02)	0.721
MMR alone	14.1	(128,166/908,150)	1(ref)		1(ref)	

Abbreviations: DTaP-IPV-Hib, vaccination against diphtheria, tetanus, pertussis (acellular), polio, and *Haemophilus influenzae* type b; MMR, vaccination against measles, mumps, and rubella; IRR, incidence rate ratio; CI, confidence interval.

[a] Cox proportional hazards model with age as underlying time scale and stratified by date of birth thereby controlling for age and season.

[b] Cox proportional hazards model with age as underlying time, stratified by date of birth and adjusted for mother smoking during pregnancy, sex, birth weight, gestational age, caesarean section, chronic diseases, number of infectious disease admissions before 15 months of age, admitted to hospital for any cause within the last 30 days, maternal age at birth of the child, highest educational level for the female adult in the household, parental place of birth, adults in the household, income quintiles for the household, other children in the household, and population density.

background factors between those who received MMR alone and those who received simultaneous MMR and DTaP-IPV-Hib3 within this subgroup. This might be related to underreporting of DTaP-IPV-Hib-3 leading to some children being included in the "DTaP-IPV-Hib-2-subgroup" although they have received DTaP-IPV-Hib-3. Such children would only be eligible to receive MMR, while children truly delayed on DTaP-IPV-Hib-3 would be eligible to receive MMR and DTaP-IPV-Hib-3 simultaneously. If this should influence the results delay on DTaP-IPV-Hib-3 should be related to some health or other background factor, which is not already captured by the many background factors we adjust for. Second, the association was only observed for admissions with lower respiratory tract infections, but not for other infectious disease groups. It is difficult to imagine a confounder or other social, economic, cultural or health bias, which would lead to simultaneous administration of MMR and DTaP-IPV-Hib being associated with higher admission rates due to lower respiratory tract infections, but not with other types of infections. Third, it is unlikely that the results could be explained by differences in health seeking behaviour, as vaccination status was not related to emergency room visits due to unintentional accidents.

Similar results have been observed in other settings. A randomized trial from Guinea-Bissau showed detrimental effects of simultaneous administration of DTP, OPV, and measles vaccine compared with OPV and measles vaccine alone on "febrile disease with vesicular rash" reported by the mother (IRR, 1.86; 95% CI, 1.00–3.47); this trial also found a tendency toward increased risk of hospital admission for any cause (IRR, 1.70; 95% CI, 0.70–4.07) [24]. Several observational studies from low-income countries have found detrimental effects on mortality and admissions with simultaneous administration of live measles vaccine and inactivated DTP vaccine [6–8,25–27]. Previous studies, including a randomized trial, have shown that measles vaccine has the strongest effects related to the prevention of admissions for lower respiratory tract infections [1,28,29].

The biological mechanisms explaining the present findings have not been determined, but the non-specific effects of vaccines have been linked to both heterologous immunity due to cross-reactive T- and B-cell epitopes and training of the innate immune system [2,4,5,30]. For example, the live Bacille Calmette-Guerin vaccine can induce epigenetic changes which reprograms monocytes to enhanced protection against unrelated pathogens [31]. It is unknown whether simultaneous administration of MMR and DTaP-IPV-Hib may neutralise the beneficial effect of MMR vaccine for lower respiratory tract infections or DTaP-IPV-Hib increases susceptibility to pathogens of the lower respiratory tract.

Vaccination schedules have been designed based on studies of specific immune responses [32], and assessment of specific vaccine efficacy and not on studies of impact on overall morbidity and mortality [33]. Vaccines are often administered together due to convenience and to achieve higher vaccination coverage. However, in the context of herd immunity toward the targeted diseases it might also affect the overall health of children as suggested by the present study. WHO's Strategic Advisory Group of Experts on immunization (SAGE) has stated that further research into non-specific effects of vaccines are warranted and particularly recommend randomized trials [34]. The present study suggests that in countries where the vaccination schedule includes simultaneous administration of MMR and DTaP-IPV-Hib it would be important to test the recommended schedule against a schedule with MMR administered after DTaP-IPV-Hib. However, additional observational studies are also needed to examine non-specific effects in other settings and to help optimize the design of subsequent randomized trials.

5. Conclusions

As hypothesized, simultaneous administration of MMR and DTaP-IPV-Hib vaccine was associated with a higher rate of infectious disease admissions compared with MMR alone as the most recent vaccine. The association was only significant for lower respiratory tract infections, but not for other types of infections. Even though it might be convenient to administer vaccines together, it may have negative effects on the overall health of children compared with the live vaccine alone in the context of herd immunity to the targeted diseases. This needs to be examined further in observational studies and randomized trials.

Conflict of interest

None.

Funding

This work was supported by the Danish Council for Independent Research [DFF – 4183-00316 to S.S.]; the Health Foundation (Helsefonden) [2009B132 to S.S.]; Rosalie Petersens Foundation [to S.S.]; the Novo Nordisk Foundation [research professorship grant to P.A.]; European Research Council (ERC) Starting Grant [ERC-StG-243149 to C.S.B]; and the Danish National Research Foundation (DNRF) supports the Research Center for Vitamins and Vaccines [DNRF108]. The funding bodies had no role in the design of the study and collection, analysis, and interpretation of data and in writing of the manuscript.

Authors' contributions

S.S., C.S.B., A.P., T.G.K., P.A., and H.R. conceptualized and designed the study. S.S. and H.R. acquired the data and performed

the statistical analyses. S.S., C.S.B., A.P., T.G.K., P.A., and H.R. analysed and interpreted the data. S.S. drafted the initial manuscript. C.S.B., A.P., T.G.K., P.A., and H.R. critically revised the manuscript for important intellectual content. All authors approved the final submitted version.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2016.11.005.

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