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

Sørup, Signe; Benn, Christine Stabell; Stensballe, Lone Graff; Aaby, Peter; Ravn, Henrik

Published in:
Vaccine

DOI:
10.1016/j.vaccine.2014.07.110

Publication date:
2015

Document version
Final published version

Vaccine 33 (2015) 237–245

Contents lists available at ScienceDirect

Vaccine

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

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

Signe Sørup[a,*], Christine Stabell Benn[a,b], Lone Graff Stensballe[a,d], Peter Aaby[a,c], Henrik Ravn[a,b,c]

[a] Research Centre for Vitamins and Vaccines (CVIVA), Bandim Health Project, Statens Serum Institut, Copenhagen, Denmark
[b] Institute of Clinical Research, University of Southern Denmark and Odense University Hospital, Odense, Denmark
[c] Bandim Health Project, Indepth Network, Bissau, Guinea-Bissau
[d] The Child & Adolescent Clinic, Rigshospitalet, Copenhagen, Denmark

ARTICLE INFO

Article history:
Received 23 May 2014
Received in revised form 1 July 2014
Accepted 21 July 2014
Available online 1 November 2014

Keywords:
Heterologous immunity
Immunization
Non-specific effects
Non-targeted effects
Measles–mumps–rubella vaccination
Respiratory syncytial virus

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.

* Corresponding author. Tel.: +45 32 68 36 75.
E-mail address: sgs@ssi.dk (S. Sørup).

http://dx.doi.org/10.1016/j.vaccine.2014.07.110

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),

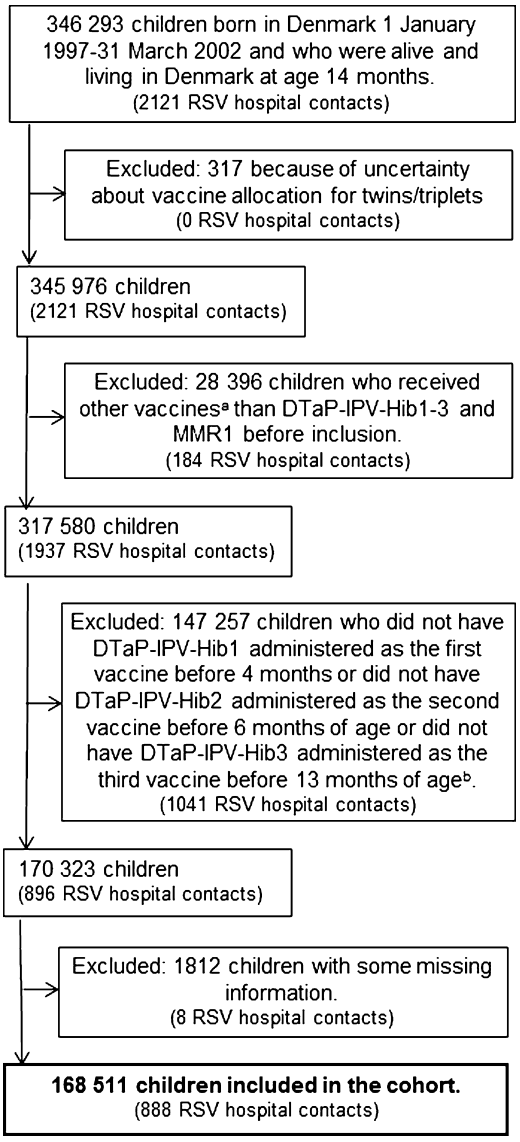

Fig. 1. Flowchart of the cohort. Abbreviations: RSV respiratory syncytial virus; DTaP-IPV-Hib vaccination against diphtheria tetanus pertussis (acellular) polio and *Haemophilus influenzae* type b; MMR vaccination against measles mumps and rubella. In the parentheses, number of hospital contacts related to RSV from 14 months and until date of censoring for the children included in the study or until 2 years of age for the children excluded from the study. [a] DTaP-IPV or Hib alone (N = 17,882; 63.0%), not recommended combination of vaccines (N = 5348; 18.8%), fourth dose of DTaP-IPV-Hib (N = 3371; 11.9%), whole cell pertussis vaccine (N = 1011; 3.6%), OPV (N = 435; 1.5%), booster dose against diphtheria and tetanus (N = 252; 0.9%), vaccine against hepatitis B (N = 87; 0.3%), and second dose of MMR (N = 10; 0.0%). [b] Children receiving MMR before DTaP-IPV-Hib3 were excluded.

parental place of birth (Denmark, Denmark-Foreign, or Foreign), adult composition of the household (two adults, single parent, or no parents), other children in the household (no or yes) and the time-varying variable chronic diseases (no or yes) coded according to Kristensen et al., 2012 [33]. In additional analyses described in the supplementary appendix further adjustment was made for maternal smoking in pregnancy, childcare, household income, and maternal education.

2.5.1. Interactions

Nonspecific effects of vaccines have previously been found to interact with sex and vitamin A supplementation [2,3]; other interactions might also be important. For this reason and to assess the generalizability of the results, we introduced interaction terms between MMR and dichotomised forms of the variables adjusted for in the main analysis. The interaction terms were introduced in the model one at a time and statistical significance was examined with Wald test statistics.

2.5.2. Sensitivity

The assumption of proportional hazards between vaccination groups was evaluated by Schoenfeld residuals and no violation was detected. We examined if the effect of MMR was immediate by splitting the time period with MMR at 30 days after MMR vaccination. In addition we examined for trend in the association according to time since MMR vaccination. The stability of the results was examined by continuing follow-up until 3 years of age. In a subgroup analysis, we excluded children who had been admitted to hospital with RSV before inclusion in the study to limit the potential effect of immunity to RSV. We examined the generalizability of the results by using a cohort which also included the children who had not received the first three doses of DTaP-IPV-Hib on time.

We do not believe that accidents are related to vaccination and we therefore performed an analysis in which the outcome was accidents registered at emergency room visits to check for possible registration bias in our data material.

All analyses were performed in Stata 12.

3. Results

A total of 168,511 children were followed until the first of the following events: age 2 years (N = 129,333; 76.8%), 1 June 2003 (N = 25,475; 15.1%), administration of other vaccines than the first MMR (mainly OPV) (N = 13,370; 7.9%), migration (N = 296; 0.2%), death (N = 31; 0.0%), unknown whereabouts for the Danish authorities (N = 4; 0.0%), and uncertainty about vaccinations for twins (N = 2; 0.0%).

Overall 60.6% were vaccinated with MMR by 16 months of age and 91.8% at 2 years of age. There was little variation in the likelihood of being MMR-vaccinated, but children of single parents, younger mothers, and children who lived together with other children were less likely to be MMR-vaccinated, particularly at 16 months of age (Table 1).

In 128,588 person years of follow-up 888 RSV hospital contacts occurred (rate, 6.8/1000 person years); 886 children had one RSV hospital contact each, while one child had two RSV hospital contacts during follow-up. The rate of RSV hospital contact according to the vaccination status and age are given in Supplementary Table 1. The median duration of RSV hospital contacts was 3 days (inter quartile range, 2–5 days) in both DTaP-IPV-Hib3 and MMR-vaccinated children.

Compared with children having DTaP-IPV-Hib3 as the most recent vaccination, having MMR as the most recent vaccination was associated with a reduced rate of RSV hospital contacts (IRR, 0.75; 95% CI, 0.63–0.89; Table 2); the adjusted IRR was 0.78 (95% CI, 0.66–0.93; Table 2). Further adjustment for maternal smoking in pregnancy, childcare, household income, and maternal education did not alter the results (Supplementary Table 3). In males, the adjusted IRR of RSV hospital contacts for MMR compared with DTaP-IPV-Hib3 as the most recent vaccine was 0.74 (95% CI, 0.60–0.92), while the adjusted IRR for females was 0.84 (95% CI, 0.66–1.06; P Interaction, 0.42; Table 3). Also, none of the other examined interactions were statistically significant (Table 3).

The main results of the sensitivity analyses are given here; further data is available on request. In the first month after MMR vaccination, the adjusted IRR for MMR compared with DTaP-IPV-Hib3 was 0.97 (95% CI, 0.76–1.24) but this changed significantly after one month to an adjusted IRR of 0.70 (95% CI, 0.58–0.85). There was a significant trend for lower IRRs with longer time since

Table 1
Distribution of most recent vaccine and risk ratios of being MMR-vaccinated at 16 months and 2 years of age according to background factors.

Characteristics	16 months of age				2 years of age			
	DTaP-IPV-Hib3% (*N*)[a]	MMR % (*N*)[a]	Adjusted RR[b] (95%-CI)	*P* value[c]	DTaP-IPV-Hib3% (*N*)[a]	MMR % (*N*)[a]	Adjusted RR[b] (95%-CI)	*P* value[c]
Sex								
Male	39.7% (33,700)	60.3% (51,136)	1 (Ref)	.03	8.3% (6486)	91.7% (71,693)	1 (Ref)	.10
Female	39.1% (32,328)	60.9% (50,369)	1.01 (1.00–1.02)		8.0% (6147)	92.0% (70,357)	1.00 (1.00–1.01)	
Birth weight, gram								
≤2000	40.8% (834)	59.2% (1208)	1.02 (0.98–1.06)	.01	8.0% (152)	92.0% (1738)	1.01 (0.99–1.02)	.44
2001–2500	39.5% (2027)	60.5% (3107)	1.02 (1.00–1.05)		8.3% (396)	91.7% (4378)	1.00 (0.99–1.01)	
2501–3000	38.3% (7978)	61.7% (12,856)	1.02 (1.01–1.04)		8.2% (1568)	91.8% (17,664)	1.00 (1.00–1.01)	
3001–3500	39.5% (21,049)	60.5% (32,298)	1 (Ref)		8.2% (4043)	91.8% (45,178)	1 (Ref)	
3501–4000	39.4% (22,254)	60.6% (34,200)	1.01 (1.00–1.02)		8.2% (4264)	91.8% (47,878)	1.00 (1.00–1.01)	
4001–4500	40.1% (9634)	59.9% (14,377)	1.01 (0.99–1.02)		8.0% (1781)	92.0% (20,395)	1.01 (1.00–1.01)	
>4500	39.4% (2252)	60.6% (3,459)	1.03 (1.00–1.05)		8.2% (429)	91.8% (4819)	1.01 (1.00–1.01)	
Gestational age, weeks								
<37	40.3% (3465)	59.7% (5139)	0.99 (0.96–1.01)	.18	7.8% (622)	92.2% (7366)	1.01 (1.00–1.02)	.04
≥37	39.4% (62,563)	60.6% (96,366)	1 (Ref)		8.2% (12,011)	91.8% (134,684)	1 (Ref)	
Caesarean section								
No	39.5% (56,015)	60.5% (85,886)	1 (Ref)	.60	8.2% (10,755)	91.8% (120,192)	1 (Ref)	.53
Yes	39.1% (10,013)	60.9% (15,619)	1.00 (0.99–1.01)		7.9% (1878)	92.1% (21,858)	1.00 (1.00–1.01)	
Chronic diseases								
No	39.3% (64,154)	60.7% (98,899)	1 (Ref)	.03	8.1% (12,242)	91.9% (138,144)	1 (Ref)	.40
Yes	41.8% (1874)	58.2% (2606)	0.97 (0.95–1.00)		9.1% (391)	90.9% (3906)	1.00 (0.99–1.01)	
Number of admissions between 1 month of age and date of DTaP-IPV-Hib3 vaccination								
None	39.1% (55,540)	60.9% (86,521)	1 (Ref)	<.001	8.0% (10,439)	92.0% (120,777)	1 (Ref)	<.001
One	40.8% (7858)	59.2% (11,393)	0.98 (0.97–0.99)		9.1% (1617)	90.9% (16,127)	0.99 (0.98–0.99)	
Two	42.5% (1747)	57.5% (2367)	0.96 (0.93–0.99)		10.3% (392)	89.7% (3400)	0.98 (0.97–0.99)	
Three or more	41.9% (883)	58.1% (1224)	0.98 (0.94–1.02)		9.6% (185)	90.4% (1746)	0.99 (0.98–1.00)	
Admission from date of DTaP-IPV-Hib3 vaccination until 14 months of age								
No	39.3% (64,073)	60.7% (98,879)	1 (Ref)	<.001	8.1% (12,212)	91.9% (138,262)	1 (Ref)	.001
Yes	42.7% (1955)	57.3% (2626)	0.95 (0.92–0.97)		10.0% (421)	90.0% (3788)	0.98 (0.97–0.99)	
Maternal age at birth of the child, years								
≤19	41.4% (1027)	58.6% (1452)	0.94 (0.91–0.98)	<.001	11.9% (277)	88.1% (2043)	0.95 (0.94–0.97)	<.001
20–24	37.1% (8509)	62.9% (14,411)	1.01 (1.00–1.02)		8.9% (1858)	91.1% (19,077)	0.98 (0.98–0.99)	
25–29	38.1% (24,434)	61.9% (39,708)	1.01 (1.00–1.02)		7.5% (4443)	92.5% (54,593)	1.00 (0.99–1.00)	
30–34	40.7% (22,732)	59.3% (33,069)	1 (Ref)		8.0% (4132)	92.0% (47,519)	1 (Ref)	
35–39	42.0% (8231)	58.0% (11,357)	0.99 (0.98–1.01)		9.1% (1673)	90.9% (16,635)	0.99 (0.99–1.00)	
≥40	42.1% (1095)	57.9% (1508)	0.99 (0.95–1.02)		10.3% (250)	89.7% (2183)	0.98 (0.96–0.99)	
Parental place of birth								
Denmark	39.2% (55,129)	60.8% (85,372)	1 (Ref)	.004	8.2% (10,583)	91.8% (119,060)	1 (Ref)	<.001
Denmark and foreign	40.5% (5539)	59.5% (8150)	0.98 (0.96–0.99)		8.4% (1063)	91.6% (11,629)	1.00 (0.99–1.00)	
Foreign	40.2% (5360)	59.8% (7983)	1.01 (0.99–1.02)		8.0% (987)	92.0% (11,361)	1.01 (1.01–1.02)	
Adult composition of the household								
Two adults	39.2% (61,640)	60.8% (95,795)	1 (Ref)	<.001	7.9% (11,517)	92.1% (133,767)	1 (Ref)	<.001
Single parent	43.5% (4293)	56.5% (5573)	0.92 (0.91–0.94)		11.9% (1089)	88.1% (8088)	0.96 (0.95–0.97)	
No parents	40.9% (95)	59.1% (137)	1.03 (0.92–1.15)		12.2% (27)	87.8% (195)	0.98 (0.93–1.03)	
Other children in the household								
No	34.9% (27,558)	65.1% (51,327)	1 (Ref)	<.001	6.7% (4892)	93.3% (67,715)	1 (Ref)	<.001
Yes	43.4% (38,470)	56.6% (50,178)	0.87 (0.86–0.88)		9.4% (7741)	90.6% (74,335)	0.97 (0.96–0.97)	

Abbreviations: RR—risk ratio; MMR, vaccination against measles, mumps, and rubella.

[a] The number of children do not add to the total number of children in the study, because some children were censored before the specified age.

[b] RR of being MMR vaccinated at the specified age estimated by Poisson regression with robust variance and adjusted for all variables in the table.

[c] *P* values for the test of the association between the specified variable and vaccination status.

Table 2
Incidence and incidence-rate-ratios of RSV hospital contact according to vaccination status.

Characteristics	RSV hospital contacts per 1000 person years (RSV hospital contacts/person years[a])		Unadjusted IRR[b] (95%-CI)	*P* Value[c]	Adjusted IRR[d] (95%-CI)	*P* Value[c]
Vaccination status						
DTaP-IPV-Hib3	8.9	(320/35,995)	1 (Ref)	.001	1 (Ref)	.006
MMR	6.1	(568/92,593)	0.75 (0.63–0.89)		0.78 (0.66–0.93)	

Abbreviations: RSV—respiratory syncytial virus; IRR—incidence-rate-ratio; DTaP-IPV-Hib3—vaccination with the third dose against diphtheria, tetanus, pertussis (acellular), polio, and *Haemophilus influenzae* type b; MMR, vaccination against measles, mumps, and rubella.

[a] The distribution of person years for each category indicates the demographic features of the included children.

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

[c] *P* values for the test of the association between the most recent vaccine and RSV hospital contacts.

[d] Cox proportional hazards model with age as underlying time, stratified by date of birth and adjusted for sex, birth weight, gestational age, caesarean section, chronic diseases, number of admissions between 1 month of age and date of DTaP-IPV-Hib3 vaccination, admission from date of DTaP-IPV-Hib3 vaccination until 14 months of age, maternal age at birth of the child, parental place of birth, adult composition of the household, and other children in the household (the IRR estimates for these variables are given in Supplementary Table 2).

MMR vaccination (Table 4). In the sensitivity analysis in which the children were followed to 3 years of age, an additional 129 cases of RSV hospital contacts were included and the estimate was unchanged (adjusted IRR, 0.78; 95% CI, 0.66–0.93). The adjusted IRR of RSV hospital contact was 0.75 (95% CI, 0.63–0.90) when the 3243 children who had been admitted with RSV before 14 months of age were excluded. The results were also stable when all children were included in the analysis irrespective of whether they had DTaP-IPV-Hib at the recommended ages (adjusted IRR, 0.79; 95% CI, 0.71–0.89).

There was no statistically significant association between MMR vaccination and emergency room visits resulting from accidents (adjusted IRR, 1.02; 95% CI, 0.98–1.06).

4. Discussion

As hypothesised children who had received MMR as their most recent vaccine had a lower rate of RSV hospital contacts compared with children who had DTaP-IPV-Hib3 as their most recent vaccination. The association was only apparent from 1 month after MMR vaccination. The association was similar for females and males and did not vary significantly according to any other background factors.

The main analyses of the present study included only children who had been vaccinated on time with DTaP-IPV-Hib to limit the possibility for confounding by factors related both to delayed vaccination and RSV hospital contact. There were too few RSV hospital contacts among children reversing the sequence of DTaP-IPV-Hib3 and MMR to perform an analysis in this group. It is important to emphasize that the statistical model had age in days as the underlying time scale securing elimination of any potential confounding by age by comparing the incidence of RSV hospital contacts between children of the exact same age but with different vaccination status. Inclusion of a wide range of additional potential confounders did not change the main estimate appreciably, indicating that confounding was limited in the present study.

Since there was no association between MMR vaccination and accidents, it seems unlikely that the association between MMR vaccination and RSV hospital contacts can be explained by a bias in health-seeking behavior.

Vaccinations were registered by GPs to obtain reimbursement; this provides an economic incentive to report all vaccines [24]. However, there might have been some underreporting of vaccines [34] and travel vaccines are not reimbursed and therefore not reported [24], but we believe travel vaccines are limited before two years of age. Any misclassification or underreporting of MMR vaccinations would bias the estimates toward no association. The outcome was RSV detected by ELISA or immunofluorescence and included in the RSV database, which cover 96% of RSV hospital contacts in Denmark [26]. RSV tests performed by ELISA or immunofluorescence are not as specific and sensitive as tests performed by PCR [35] indicating that some misclassification is present in the current study. However, there is no reason to believe that the sensitivity and specificity is affected by vaccination status; any misclassification would bias the results toward no association. There was a minimum of loss to follow-up because of the high quality of the Danish population-based registries [23].

Our previous observation of reduction in the rate of all-cause lower respiratory infections following MMR vaccination [19] can now partly be explained by a reduced rate of RSV hospital contacts. However, reduction in hospital contacts related to bacterial pathogens might also be important; a British self-controlled case-series study reported the risk of lobar pneumonia to be reduced 0–90 days following MMR vaccination [36]. In a similarly designed study of premature children from the US, the risk of wheezing lower respiratory disease in the first 30 days following MMR vaccination was reduced compared with 45–90 days after MMR vaccination [37]. These studies indicate a short-lived association. However, in the present study the association between MMR vaccination and RSV hospital contacts was only present from 30 days after MMR vaccination and continued throughout the third year of life.

In contrast to studies from West Africa of measles vaccination [38,39], we did not find any statistically significant interaction between MMR vaccination and sex. MMR was associated with significant reduction in RSV hospital contacts in boys but not in girls. Boys have a higher risk of severe RSV infection [40,41] as also seen in the present study; therefore there is greater statistical power to detect differences in boys. Furthermore, MMR vaccination may benefit boys more because of their higher risk of severe RSV infection. Also, there are numerous differences between high and low-income settings that might interact with the nonspecific and sex-differential effects of vaccinations, including family size, nutritional status, micronutrient supplementation, sex-differential access to care, the presence of atopic disease, exposure to infections in public child care institutions, and genetic differences.

The present study suggests that the MMR vaccine may have beneficial nonspecific effects by reducing the rate of hospital contacts related to RSV in a high-income setting. Only the most severe cases of RSV are cared for at the hospital, so the reduction in hospital contacts could be related to a reduction in the severity of RSV infection, enhanced resistance to RSV infection or both. The finding contradicts the current perception of vaccines as an intervention with a disease-specific effect only. Our observation might be interpreted as a chance finding or a finding resulting from uncontrolled confounding of factors related to delay in vaccination and the risk of RSV hospital contact. However, there were hardly any difference in characteristics between children who were and were not MMR-vaccinated at 16 and 24 months of age (Table 1). Furthermore, if

Table 3
Results for two-way-interactions between vaccination status and dichotomised forms of the variables included in the main analysis.

Characteristics	RSV hospital contacts per 1000 person years (RSV hospital contacts/person years)		Unadjusted IRR[a] (95%-CI)	Adjusted IRR[b] (95%-CI)
Female				
DTaP-IPV-Hib3	7.7	(136/17,637)	1 (Ref)	1 (Ref)
MMR	5.8	(265/45,774)	0.82 (0.65–1.04)	0.84 (0.66–1.06)
Male				
DTaP-IPV-Hib3	10.0	(184/18,358)	1 (Ref)	1 (Ref)
MMR	6.5	(303/46,819)	0.70 (0.57–0.87)	0.74 (0.60–0.92)
P interaction[c]			.28	.42
No other children in the household				
DTaP-IPV-Hib3	8.5	(132/15,580)	1 (Ref)	1 (Ref)
MMR	6.0	(270/44,896)	0.78 (0.61–0.99)	0.82 (0.65–1.04)
Other children in the household				
DTaP-IPV-Hib3	9.2	(188/20,415)	1 (Ref)	1 (Ref)
MMR	6.2	(298/47,696)	0.74 (0.60–0.91)	0.76 (0.61–0.94)
P interaction[c]			.70	.57
No single parenthood				
DTaP-IPV-Hib3	8.7	(294/33,604)	1 (Ref)	1 (Ref)
MMR	5.9	(519/87,445)	0.74 (0.62–0.89)	0.77 (0.64–0.92)
Single parenthood				
DTaP-IPV-Hib3	10.9	(26/2391)	1 (Ref)	1 (Ref)
MMR	9.5	(49/5148)	0.96 (0.59–1.57)	1.00 (0.61–1.63)
P interaction[c]			.30	.30
Only Danish born parents				
DTaP-IPV-Hib3	9.7	(294/30,157)	1 (Ref)	1 (Ref)
MMR	6.4	(502/77,870)	0.72 (0.60–0.86)	0.75 (0.63–0.90)
At least one parent born outside Denmark				
DTaP-IPV-Hib3	4.5	(26/5838)	1 (Ref)	1 (Ref)
MMR	4.5	(66/14,723)	1.11 (0.69–1.77)	1.12 (0.70–1.80)
P interaction[c]			.08	.10
Maternal age <30 years				
DTaP-IPV-Hib3	8.9	(168/18,871)	1 (Ref)	1 (Ref)
MMR	6.3	(313/50,078)	0.76 (0.61–0.94)	0.79 (0.64–0.98)
Maternal age ≥30 years				
DTaP-IPV-Hib3	8.9	(152/17,124)	1 (Ref)	1 (Ref)
MMR	6.0	(255/42,514)	0.74 (0.59–0.93)	0.77 (0.62–0.97)
P Interaction [c]			.86	.88
Normal birth weight (>2500 g)				
DTaP-IPV-Hib3	8.5	(294/34,484)	1 (Ref)	1 (Ref)
MMR	5.9	(522/88,670)	0.75 (0.63–0.90)	0.79 (0.66–0.94)
Low birth weight (≤2500 g)				
DTaP-IPV-Hib3	17.2	(26/1511)	1 (Ref)	1 (Ref)
MMR	11.7	(46/3923)	0.69 (0.42–1.13)	0.73 (0.44–1.22)
P interaction[c]			.71	.79
Term (gestational age≥37 weeks)				
DTaP-IPV-Hib3	8.6	(293/34,173)	1 (Ref)	1 (Ref)
MMR	5.8	(512/87,914)	0.74 (0.62–0.88)	0.77 (0.64–0.92)
Premature (gestational age<37 weeks)				
DTaP-IPV-Hib3	14.8	(27/1822)	1 (Ref)	1 (Ref)
MMR	12.0	(56/4679)	0.87 (0.54–1.40)	0.94 (0.58–1.52)
P interaction[c]			.53	.42
No caesarean section				
DTaP-IPV-Hib3	8.5	(260/30,582)	1 (Ref)	1 (Ref)
MMR	5.6	(441/78,714)	0.72 (0.60–0.87)	0.75 (0.62–0.90)
Caesarean section				
DTaP-IPV-Hib3	11.1	(60/5413)	1 (Ref)	1 (Ref)
MMR	9.2	(127/13,879)	0.88 (0.63–1.22)	0.94 (0.67–1.31)
P interaction[c]			.25	.21
No chronic diseases				
DTaP-IPV-Hib3	8.6	(301/34,985)	1 (Ref)	1 (Ref)
MMR	5.9	(528/90,110)	0.74 (0.62–0.89)	0.77 (0.65–0.93)
Chronic diseases				
DTaP-IPV-Hib3	18.8	(19/1010)	1 (Ref)	1 (Ref)
MMR	16.1	(40/2483)	0.90 (0.51–1.57)	0.94 (0.53–1.67)
P interaction[c]			.52	.50

Table 3 (*Continued*)

Characteristics	RSV hospital contacts per 1000 person years (RSV hospital contacts/person years)		Unadjusted IRR[a] (95%-CI)	Adjusted IRR[b] (95%-CI)
No admissions between 1 month of age and date of DTaP-IPV-Hib3 vaccination				
DTaP-IPV-Hib3	7.4	(225/30,285)	1 (Ref)	1 (Ref)
MMR	4.9	(385/78,784)	0.72 (0.59–0.88)	0.74 (0.60–0.90)
Admissions during 1 month of age and date of DTaP-IPV-Hib3 vaccination				
DTaP-IPV-Hib3	16.6	(95/5710)	1 (Ref)	1 (Ref)
MMR	13.3	(183/13,809)	0.86 (0.65–1.12)	0.89 (0.68–1.17)
P interaction[c]			.28	.23
No admission from date of DTaP-IPV-Hib3 vaccination until 14 months of age				
DTaP-IPV-Hib3	8.5	(298/34,936)	1 (Ref)	1 (Ref)
MMR	5.8	(523/90,193)	0.74 (0.62–0.88)	0.76 (0.64–0.91)
Admission from date of DTaP-IPV-Hib3 vaccination until 14 months of age				
DTaP-IPV-Hib3	20.8	(22/1059)	1 (Ref)	1 (Ref)
MMR	18.7	(45/2400)	1.06 (0.62–1.80)	1.12 (0.66–1.92)
P interaction[c]			.19	.16

Abbreviations: RSV—respiratory syncytial virus; IRR—incidence-rate-ratio; DTaP-IPV-Hib3—vaccination with the third dose 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 age and season.

[b] Cox proportional hazards model with age as underlying time, stratified by date of birth and adjusted for sex, birth weight, gestational age, caesarean section, chronic diseases, number of admissions between 1 month of age and date of DTaP-IPV-Hib3 vaccination, admission from date of DTaP-IPV-Hib3 vaccination until 14 months of age, maternal age at birth of the child, parental place of birth, adult composition of the household, and other children in the household.

[c] *P* value for the interaction term between vaccination status and the specified variables. This corresponds to testing if the IRR for MMR varies between categories of the other variables; for example, if the IRR for MMR differs between females and males.

the beneficial effect of MMR resulted from confounding, the same benefit should have been observed in the first month after vaccination. Several randomized trials from low-income countries have documented that nonspecific effects of vaccines are indeed possible [1]. In one of these trials from Guinea-Bissau [5] measles vaccine was particularly effective in reducing hospital admissions related to respiratory infections [17].

Nonspecific effects of vaccines have often been dismissed as biologically implausible. However, immunological studies have shown that a pathogen encounter may alter the subsequent resistance toward other infections [2,3]. These changes can occur at the level of the innate immune system; for example, BCG may enhance the nonspecific innate resistance through epigenetic reprogramming of monocytes [42]. Numerous animal studies have shown that pathogens can also induce nonspecific alterations of the adaptive immune system, through cross-reacting T-cell epitopes [43]. Notably, measles virus, mumps virus, and RSV all belong to the family paramyxoviridae and one study in mice found T-cell cross reactivity between these viruses [44] and a study in children found that prior RSV infection was related to higher antibody titres against measles, mumps, and rubella following vaccination with MMR [45]. Further studies on the biological mechanisms are clearly needed, in particular whether antigen-specific responses or non-specific inflammatory/innate mechanisms are more important for the protection we observed in the present study.

The current WHO recommendations do not consider nonspecific effects of vaccines. However, WHO's Strategic Advisory Group of Experts has recently recommended further research into nonspecific effects of vaccines [46]. Ideally, the age schedule for vaccinations should be evaluated in trials testing both the specific effect and the nonspecific effects on overall morbidity and mortality. In high-income countries it might reduce the risk of hospital contacts and reduce health care costs to lower the age of MMR vaccination or introduce an additional dose of MMR vaccination at an earlier age, particularly bearing in mind that the greatest burden of RSV occurs in children below 12 months of age [21]. If confirmed in further studies in high-income settings, the nonspecific beneficial effect of MMR vaccination could be used as an additional incentive for parents to have their children vaccinated on time.

In conclusion, the present nationwide cohort study showed that the rate of RSV hospital contact was reduced in Danish children who had received MMR rather than DTaP-IPV-Hib3 as their most recent vaccination. The finding has major public health implications. Further studies are needed to test this observation and to examine whether earlier administration of MMR might be beneficial.

Table 4
Results according to time since MMR vaccination.

Characteristics	RSV hospital contacts per 1000 person years (RSV hospital contacts/person years)		Unadjusted IRR[a] (95%-CI)	Adjusted IRR[b] (95%-CI)
Vaccination status				
DTaP-IPV-Hib3	8.9	(320/35,989)	1 (Ref)	1 (Ref)
Days since MMR vaccination				
0–30	8.7	(105/12,107)	0.98 (0.77–1.25)	1.01 (0.79–1.28)
31–90	7.0	(164/23,469)	0.78 (0.62–0.97)	0.82 (0.65–1.03)
91–210	5.6	(239/42,461)	0.62 (0.49–0.79)	0.64 (0.50–0.82)
>210	4.1	(60/14,546)	0.40 (0.27–0.60)	0.43 (0.29–0.64)
P trend			<0.001	<0.001

Abbreviations: RSV—respiratory syncytial virus; IRR—incidence-rate-ratio; DTaP-IPV-Hib3—vaccination with the third dose 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 age and season.

[b] Cox proportional hazards model with age as underlying time, stratified by date of birth and adjusted for sex, birth weight, gestational age, caesarean section, chronic diseases, number of admissions between 1 month of age and date of DTaP-IPV-Hib3 vaccination, admission from date of DTaP-IPV-Hib3 vaccination until 14 months of age, maternal age at birth of the child, parental place of birth, adult composition of the household, and other children in the household.

Funding

This work was supported by the Health Foundation [2009B132 to S.S.]; Rosalie Petersens Foundation [to S.S.]; Danish National Research Foundation [DNRF108 to S.S., C.S.B., L.G.S. and H.R.]; European Research Council [ERC-2009-StG, grant agreement no. 243149 to C.S.B.]; and the Novo Nordisk Foundation [research professorship grant to P.A.]. The funders had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication

Author's contributions

S.S. conceptualized and designed the study, acquired the vaccination and confounder data, analyzed and interpreted the data, drafted the initial manuscript. C.S.B. and P.A. conceptualized and designed the study, interpreted the data and reviewed and revised the manuscript. L.G.S. conceptualized and designed the study, acquired the RSV hospital contact data, interpreted the data, reviewed and revised the manuscript. H.R. conceptualized and designed the study, acquired the vaccination and confounder data, interpreted the data, reviewed and revised the manuscript, All authors read and approved the final manuscript.

Acknowledgements

The authors thank Tyra G Krause from Department of Infectious Disease Epidemiology, Statens Serum Institut, Denmark, for her valuable comments on the draft for this article.

Conflict of interest statement

All authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.07.110.

References

[1] Aaby P, Whittle H, Stabell Benn C. Vaccine programmes must consider their effect on general resistance. BMJ 2012;344:e3769 [10.1136/bmj.e3769].
[2] Flanagan KL, van Crevel R, Curtis N, Shann F, Levy O, Optimmunize N. Heterologous ("nonspecific") and sex-differential effects of vaccines: epidemiology, clinical trials, and emerging immunologic mechanisms. Clin Infect Dis 2013;57:283–9 [10.1093/cid/cit209].
[3] Benn CS, Netea MG, Selin LK, Aaby P. A small jab—a big effect: nonspecific immunomodulation by vaccines. Trends Immunol 2013;34:431–9 [10.1016/j.it.2013.04.004].
[4] Aaby P, Samb B, Simondon F, Seck AM, Knudsen K, Whittle H. Non-specific beneficial effect of measles immunisation: analysis of mortality studies from developing countries. BMJ 1995;311:481–5 [10.1136/bmj.311.7003.481].
[5] Aaby P, Martins CL, Garly ML, Bale C, Andersen A, Rodrigues A, et al. Non-specific effects of standard measles vaccine at 4.5 and 9 months of age on childhood mortality: randomised controlled trial. BMJ 2010;341:c6495 [10.1136/Bmj.C6495].
[6] Aaby P, Roth A, Ravn H, Napirna BM, Rodrigues A, Lisse IM, et al. Randomized trial of BCG vaccination at birth to low-birth-weight children: beneficial nonspecific effects in the neonatal period? J Infect Dis 2011;204:245–52 [10.1093/infdis/jir240].
[7] Biering-Sorensen S, Aaby P, Napirna BM, Roth A, Ravn H, Rodrigues A, et al. Small randomized trial among low-birth-weight children receiving bacillus Calmette–Guerin vaccination at first health center contact. Pediatr Infect Dis J 2012;31:306–8 [10.1097/INF.0b013e3182458289].
[8] Shann F. The non-specific effects of vaccines. Arch Dis Child 2010;95:662–7 [10.1136/adc.2009.157537].
[9] Aaby P, Jensen H, Gomes J, Fernandes M, Lisse IM. The introduction of diphtheria–tetanus–pertussis vaccine and child mortality in rural Guinea-Bissau: an observational study. Int J Epidemiol 2004;33:374–80 [10.1093/ije/dyh005].
[10] Aaby P, Benn CS, Nielsen J, Lisse IM, Rodrigues A, Ravn H. Testing the hypothesis that diphtheria-tetanus-pertussis vaccine has negative non-specific and sex-differential effects on child survival in high-mortality countries. BMJ Open 2012;2:e000707 [10.1136/bmjopen-2011-000707].
[11] Aaby P, Ravn H, Roth A, Rodrigues A, Lisse IM, Diness BR, et al. Early diphtheria-tetanus-pertussis vaccination associated with higher female mortality and no difference in male mortality in a cohort of low birthweight children: an observational study within a randomised trial. Arch Dis Child 2012;97:685–91 [10.1136/archdischild-2011-300646].
[12] Aaby P, Benn CS. Non-specific and sex-differential effects of routine vaccines: what evidence is needed to take these effects into consideration in low-income countries? Hum Vaccin 2011;7:120–4 [10.4161/hv.7.1.13848].
[13] Veirum JE, Sodemann M, Biai S, Jakobsen M, Garly ML, Hedegaard K, et al. Routine vaccinations associated with divergent effects on female and male mortality at the paediatric ward in Bissau, Guinea-Bissau. Vaccine 2005;23:1197–204 [10.1016/j.vaccine.2004.02.053].
[14] Valentiner-Branth P, Perch M, Nielsen J, Steinsland H, Garly ML, Fischer TK, et al. Community cohort study of *Cryptosporidium parvum* infections: sex-differential incidences associated with BCG and diphtheria-tetanus-pertussis vaccinations. Vaccine 2007;25:2733–41 [10.1016/j.vaccine.2006.01.035].
[15] Rodrigues A, Fischer TK, Valentiner-Branth P, Nielsen J, Steinsland H, Perch M, et al. Community cohort study of rotavirus and other enteropathogens: are routine vaccinations associated with sex-differential incidence rates? Vaccine 2006;24:4737–46 [10.1016/j.vaccine.2006.03.033].
[16] Stensballe LG, Nante E, Jensen IP, Kofoed PE, Poulsen A, Jensen H, et al. Acute lower respiratory tract infections and respiratory syncytial virus in infants in Guinea-Bissau: a beneficial effect of BCG vaccination for girls community based case-control study. Vaccine 2005;23:1251–7 [10.1016/j.vaccine.2004.09.006].
[17] Martins CL, Benn CS, Andersen A, Bale C, Schaltz-Buchholzer F, Do VA, et al. A randomized trial of a standard dose of Edmonston–Zagreb measles vaccine given at 4.5 months of age: effect on total hospital admissions. J Infect Dis 2014;209:1731–8 [10.1093/infdis/jit804].
[18] Sorup S, Villumsen M, Ravn H, Benn CS, Sorensen TI, Aaby P, et al. Smallpox vaccination and all-cause infectious disease hospitalization: a Danish register-based cohort study. Int J Epidemiol 2011;40:955–63 [10.1093/ije/dyr063].
[19] Sorup S, Benn CS, Poulsen A, Krause TG, Aaby P, Ravn H. Live vaccine against measles, mumps, and rubella and the risk of hospital admissions for nontargeted infections. JAMA 2014;311:826–35 [10.1001/jama.2014.470].
[20] Garcia-Garcia ML, Calvo C, Pozo F, Villadangos PA, Perez-Brena P, Casas I. Spectrum of respiratory viruses in children with community-acquired pneumonia. Pediatr Infect Dis J 2012;31:808–13 [10.1097/INF.0b013e3182568c67].
[21] Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet 2010;375:1545–55 [10.1016/S0140-6736(10)60206-1].
[22] Law BJ, Carbonell-Estrany X, Simoes EA. An update on respiratory syncytial virus epidemiology: a developed country perspective. Respir Med 2002;96(Suppl B):S1–7 [10.1053/rmed.2002.1294].
[23] Pedersen CB. The Danish Civil Registration System. Scand J Public Health 2011;39:22–5 [10.1177/1403494810387965].
[24] Andersen JS, Olivarius NDF, Krasnik A. The Danish National Health Service Register. Scand J Public Health 2011;39:34–7 [10.1177/1403494810394718].
[25] Pedersen PA, Hollnagel H, Olivarius NF, Reusch S, Sorensen M, Thorsen H. Individual registration of children in the national health service. New possibilities for epidemiological research in primary health care. Ugeskr Laeger 1999;161:6351–4.
[26] Stensballe LG, Kristensen K, Nielsen J, Aaby P. Diagnosis coding in The Danish National Patient Registry for respiratory syncytial virus infections. Scand J Infect Dis 2005;37:747–52 [10.1080/00365540510012107].
[27] Knudsen LB, Olsen J. The Danish Medical Birth Registry. Dan Med Bull 1998;45:320–3.
[28] Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health 2011;39:30–3 [10.1177/1403494811401482].
[29] Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. Scand J Public Health 2011;39:103–5 [10.1177/1403494811405098].
[30] Jensen VM, Rasmussen AW. Danish Education Registers. Scand J Public Health 2011;39:91–4 [10.1177/1403494810394715].
[31] Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. BMC Med Res Methodol 2003;3:21 [10.1186/1471-2288-3-21].
[32] Okiro EA, White LJ, Ngama M, Cane PA, Medley GF, Nokes DJ. Duration of shedding of respiratory syncytial virus in a community study of Kenyan children. BMC Infect Dis 2010;10:15 [10.1186/1471-2334-10-15].
[33] Kristensen K, Hjuler T, Ravn H, Simoes EA, Stensballe LG. Chronic diseases, chromosomal abnormalities, and congenital malformations as risk factors for respiratory syncytial virus hospitalization: a population-based cohort study. Clin Infect Dis 2012;54:810–7 [10.1093/cid/cir928].
[34] Wojcik OP, Simonsen J, Molbak K, Valentiner-Branth P. Validation of the 5-year tetanus, diphtheria, pertussis and polio booster vaccination in the Danish childhood vaccination database. Vaccine 2013;31:955–9 [10.1016/j.vaccine.2012.11.100].
[35] Henrickson KJ, Hall CB. Diagnostic assays for respiratory syncytial virus disease. Pediatr Infect Dis J 2007;26:S36–40 [10.1097/INF.0b013e318157da6f].
[36] Stowe J, Andrews N, Taylor B, Miller E. No evidence of an increase of bacterial and viral infections following measles, mumps and rubella vaccine. Vaccine 2009;27:1422–5 [10.1016/j.vaccine.2008.12.038].
[37] Mullooly JP, Schuler R, Mesa J, Drew L, DeStefano F, team V.S.D. Wheezing lower respiratory disease and vaccination of premature infants. Vaccine 2011;29:7611–7 [10.1016/j.vaccine.2011.08.022].

[38] Aaby P, Garly ML, Bale C, Martins C, Jensen H, Lisse I, et al. Survival of previously measles-vaccinated and measles-unvaccinated children in an emergency situation: an unplanned study. Pediatr Infect Dis J 2003;22:798–805 [10.1097/01.inf.0000083821.33187.b5].
[39] Desgrees du LA, Pison G, Aaby P. Role of immunizations in the recent decline in childhood mortality and the changes in the female/male mortality ratio in rural Senegal. Am J Epidemiol 1995;142:643–52.
[40] Sommer C, Resch B, Simoes EA. Risk factors for severe respiratory syncytial virus lower respiratory tract infection. Open Microbiol J 2011;5:144–54 [10.2174/1874285801105010144].
[41] Stensballe LG, Kristensen K, Simoes EA, Jensen H, Nielsen J, Benn CS, et al. Atopic disposition, wheezing, and subsequent respiratory syncytial virus hospitalization in Danish children younger than 18 months: a nested case-control study. Pediatrics 2006;118:e1360–8 [10.1542/peds.2006-0907].
[42] Kleinnijenhuis J, Quintin J, Preijers F, Joosten LA, Ifrim DC, Saeed S, et al. Bacille Calmette-Guerin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. Proc Natl Acad Sci USA 2012;109:17537–42 [10.1073/pnas.1202870109].
[43] Welsh RM, Che JW, Brehm MA, Selin LK. Heterologous immunity between viruses. Immunol Rev 2010;235:244–66 [10.1111/j.0105-2896.2010.00897.x].
[44] Ziola B, Smith RH. T cell cross-reactivity among viruses of the paramyxoviridae. Viral Immunol 1987;1:111–9.
[45] Ziola B, Karvonen B, Stewart J. Prior infection by respiratory syncytial virus or parainfluenza viruses augments virus-specific IgG responses induced by the measles/mumps/rubella vaccine. Viral Immunol 1994;7:205–14.
[46] Meeting of the Strategic Advisory Group of Experts on immunization, April 2014—conclusions and recommendations. *Wkly Epidemiol Rec* 2014;89:221–36.