Measles, mumps, and rubella vaccine at age 6 months and hospitalisation for infection before age 12 months: randomised controlled trial

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ABSTRACT

OBJECTIVE

To test for potential non-specific effects of an additional, early measles, mumps, and rubella (MMR) vaccine at age 5-7 months on risk of infection related hospitalisation before age 12 months.

DESIGN

Randomised, double blinded, placebo controlled trial.

SETTING

Denmark, a high income setting with low exposure to MMR.

PARTICIPANTS

6540 Danish infants aged 5 to 7 months.

INTERVENTIONS

Infants were randomly allocated 1:1 to intramuscular injection with standard titre MMR vaccine (M-M-R VaxPro) or placebo (solvent only).

MAIN OUTCOME MEASURES

Hospitalisations for infection, defined as all hospital contacts of infants referred from primary care for hospital evaluation and with an infection diagnosed, analysed as recurrent events, from randomisation to 12 months of age. In secondary analyses implications of censoring for date of subsequent diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type B, and immunisation with pneumococci conjugate vaccine (DTaP-IPV-Hib+PCV), potential effect modification by sex, prematurity (‹37 weeks' gestation), season, and age at randomisation were tested, and the secondary outcomes of hospitalisations ≥12 hours and antibiotic use were evaluated.

RESULTS

6536 infants were included in the intention-to-treat analysis. 3264 infants randomised to MMR vaccine experienced 786 hospitalisations for infection before age 12 months compared with 762 for the 3272 infants randomised to placebo. In the intention-to-treat analysis the rate of hospitalisations for infection did not differ between the MMR vaccine and placebo groups (hazard ratio 1.03, 95% confidence interval 0.91 to 1.18). For infants randomised to MMR vaccine compared with those randomised to placebo, the hazard ratio of hospitalisations for infection with a duration of at least 12 hours was 1.25 (0.88 to 1.77), and for prescriptions of antibiotics was 1.04 (0.88 to 1.23). No significant effect modifications were found by sex, prematurity, age at randomisation, or season. The estimate did not change when censoring at the date infants received DTaP-IPV-Hib+PCV after randomisation (1.02, 0.90 to 1.16).

CONCLUSION

Findings of this trial conducted in Denmark, a high income setting, do not support the hypothesis that live attenuated MMR vaccine administered early to infants aged 5-7 months decreases the rate of hospitalisations for non-targeted infection before age 12 months.

TRIAL REGISTRATION

EU Clinical Trials Registry EudraCT 2016-001901-18 and ClinicalTrials.gov NCT03780179.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Observational studies suggest that vaccines containing measles virus have beneficial non-specific effects on childhood mortality and morbidity

Sufficiently powered randomised controlled studies in low income countries have tested the hypothesis of non-specific effects of vaccines containing measles virus but results were unclear or non-significant

WHAT THIS STUDY ADDS

This well powered randomised controlled trial does not support the hypothesis of a non-specific effect of MMR vaccination on infection related hospitalisations in infants in a high income setting

Early implementation of MMR vaccination should be based on the specific, protective effect against the vaccine targeted diseases

Introduction

Vaccines are designed to protect against targeted infections. The specific effect of vaccines are of paramount importance for disease prevention and child health worldwide.[1] In the late 1970s, observational studies from low income countries reported a general decrease in child mortality among children vaccinated against measles that exceeded the expected decrease in measles related deaths.[2-4] Later, randomised studies reported increased non-measles related mortality among children who had received high titre measles vaccine.[5 6] Since then the hypothesis of non-specific or heterologous effects of vaccines has been pursued. For live attenuated vaccines such as those containing the measles virus, the hypothesis currently states that besides generating specific protection against the targeted pathogens, vaccination also leads to general beneficial health effects such as decreased risk of morbidity and mortality. In contrast, inactivated vaccines, such as the combined diphtheria, tetanus, and pertussis vaccine, have been suggested to have detrimental effects.[7-9] In both cases the strongest effects have been suggested in girls.[10-12]

However, based on our systematic review and meta-analysis of 22 randomised controlled trials

testing the potential non-specific effects of measles vaccines,[5 6 10 12-30] no such beneficial effects were identified for non-measles related overall mortality or morbidity. A systematic review and meta-analysis published in 2016 came to the same conclusion.[8]

Observational study results from high income countries suggest an association between measles vaccines and reduced mortality and morbidity.[31] Because child mortality in Denmark is low, the outcome of mortality would require a large and therefore impractical number of trial participants. However, high prevalence of infectious disease in infants and small children makes this a relevant and feasible trial outcome. Therefore, we tested the hypothesis of non-specific effects of the measles, mumps, and rubella (MMR) vaccine on hospitalisation of infants for infection—that is, all hospital contacts of infants referred from primary care for hospital evaluation and with an infection diagnosed, in a randomised, double blinded, placebo controlled trial.

Methods

Setting and study population

We performed a randomised, double blinded, placebo controlled trial (the Danish MMR trial) in healthy infants aged 5 to 7 months in Denmark recruited between April 2019 and October 2021. The trial protocol is available elsewhere.[32 33] In Denmark, the measles vaccine is routinely given in combination with mumps and rubella at ages 15 months and 4 years.[34] Recruited infants were randomly allocated 1:1 either to intramuscular vaccination with the live attenuated M-M-R VaxPro vaccine containing measles virus (Edmonston strain, standard titre), mumps virus (Jeryl Lynn strain), and rubella virus (Wistar RA 27/3 strain)[35] or to intramuscular vaccination with placebo (solvent only) at age 5-7 months. Regardless of randomisation status, the caregivers of all infants were encouraged to follow the routine child vaccination programme with MMR vaccines scheduled at 15 months and 4 years. Randomisation was carried out in the online research data system REDCap[36] in 2:4:6 blocks stratified by site (Rigshospitalet or Herlev Hospital), sex (boy or girl), and prematurity, defined as gestational age <37 weeks. Allocation and intervention took place on the same day. Study staff handled randomisation and preparation of syringes and blinded the syringes with coloured tape for parents and for staff who administered the injections. Immediately after allocation, randomisation was blinded in the electronic case report form until unblinding after last randomisation, complete data collection, and data validation. Participating families remained blinded until the infant reached at least 12 months of age.

Baseline characteristics were collected through online questionnaires filled out by the caregivers, and the Danish National health registers.

Outcome definition

We chose the outcome of infection related hospitalisations to test a potential non-specific effect of MMR vaccine against non-targeted infection. The Danish healthcare system comprises primary (family doctors) and secondary (hospitals) healthcare sectors. No paediatric patients enter hospitals without referral from healthcare professionals. All children are assessed in primary care during practice hours or by healthcare professionals in out-of-hours urgent care services. We only included infants in the analysis if their infection was severe enough for a healthcare professional after telephone contact or clinic visit to refer them to hospital for further observation or treatment. None of the infants observed in hospital were therefore referred or brought directly by caregivers.

The primary outcome of our study was hospitalisations for infection. We defined the follow-up period as being from the date of randomisation to age 12 months, when the third diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type B, and pneumococci conjugate vaccine (DTaP-IPV-Hib+PCV) is scheduled in the Danish childhood vaccination programme.[34] No other vaccines were routinely scheduled during the follow-up period. We measured hospitalisations for infection as recurrent events during follow-up. To best reflect a pragmatic clinical situation,[37] we obtained prospective data on hospitalisations for infection from the Danish National Patient Register,[38] which, independently of the trial and trial staff, routinely registers individual information on dates of admission, discharge, and diagnosis codes (ICD-10, international classification of diseases, 10th revision).[39] Hospitalisations were included if an ICD-10 code for infection, excluding measles, mumps, or rubella infections, was recorded as the primary or secondary diagnosis. Supplementary table S1 shows the ICD-10 codes used to define hospitalisation for infection. A new version of the Danish National Patient Register was introduced after we had planned the trial. In the previous version, hospital admissions were identified using a specific code, but in the new version admissions were identified using the duration of hospital contact.[40] Consequently, the trial data safety monitoring board redefined the primary trial outcome from admission coded hospital contacts to all hospitalisations for infection. Based on guidelines provided by the Danish Health Data Authority, if the interval between discharge and re-hospitalisation was more than four hours, we defined these as two separate events.[40]

Original power calculation

Sample size estimates for the primary outcome of hospitalisations were based on a 5% significance level and 80% power. Based on our observations from a previous vaccine trial in Danish infants, we expected the event rate to be 10%.[41] To detect a 20% reduction in hospitalisations, we determined that 6426 infants would need to be included using a 1:1 allocation ratio. The trial was not powered for subgroup analyses.

Statistical analysis

To account for known potential confounders[42-50] and to increase power, we performed an analysis adjusted

for all baseline characteristics. We did not include the measles immunisation status of mothers (wild type infection, measles vaccine, or not immunised) because the non-immunised group was too small.

The main analysis of hospitalisation for infection was based on the intention-to-treat principle in which recurrent hospitalisations for infection were analysed at the time from randomisation. We also conducted a per protocol analysis in which infants were excluded if the allocated intervention had not been adhered to, and the time scale was defined as time since intervention for both groups. Cox proportional hazard models were used to estimate hazard ratios between groups. Dependence between recurrent events was handled using robust standard errors for the estimated hazard ratios, obtained by using a clustered sandwich estimator assuming that events are only independent across but not within individuals. We censored infants at the first of the following events: migration, age 12 months, or death (no deaths occurred). In accordance with the randomisation procedure, all analyses were stratified by site (Rigshospitalet or Herlev Hospital), sex (boy or girl), and prematurity (<37 weeks). Results were presented as hazard ratios with 95% confidence intervals, and the mean number of events over time was presented graphically using the Nelson-Aalen method. All analyses were performed using Stata/MP version 17.0.

Secondary analyses

Sensitivity analyses

To test if MMR vaccine would affect the rate of hospitalisations for more severe infections, we defined the secondary outcome as hospitalisations with a duration of at least 12 hours. We also performed an analysis where only hospitalisations recurring at least seven days after latest discharge counted as a new event.

An additional secondary analysis was carried out with the outcome of filled prescriptions of systemic antibiotics (including antivirals) between randomisation and 12 months of age. Anatomical Therapeutic Chemical codes used to define this outcome were obtained from the Danish Register of Pharmaceutical Sales. Supplementary table S1 shows a list of the included codes. We also performed an analysis in which the outcome was defined as time to first event instead of recurrent events. In this analysis an infant only contributed one record for either the event time or the time of censoring.

In Denmark, the first three doses of DTaP-IPV-Hib+PCV are scheduled at 3, 5, and 12 months of age—that is, the first two doses were administered before randomisation and the third dose at the end of follow-up. To account for a possible effect of diphtheria, tetanus, and pertussis as the latest administered

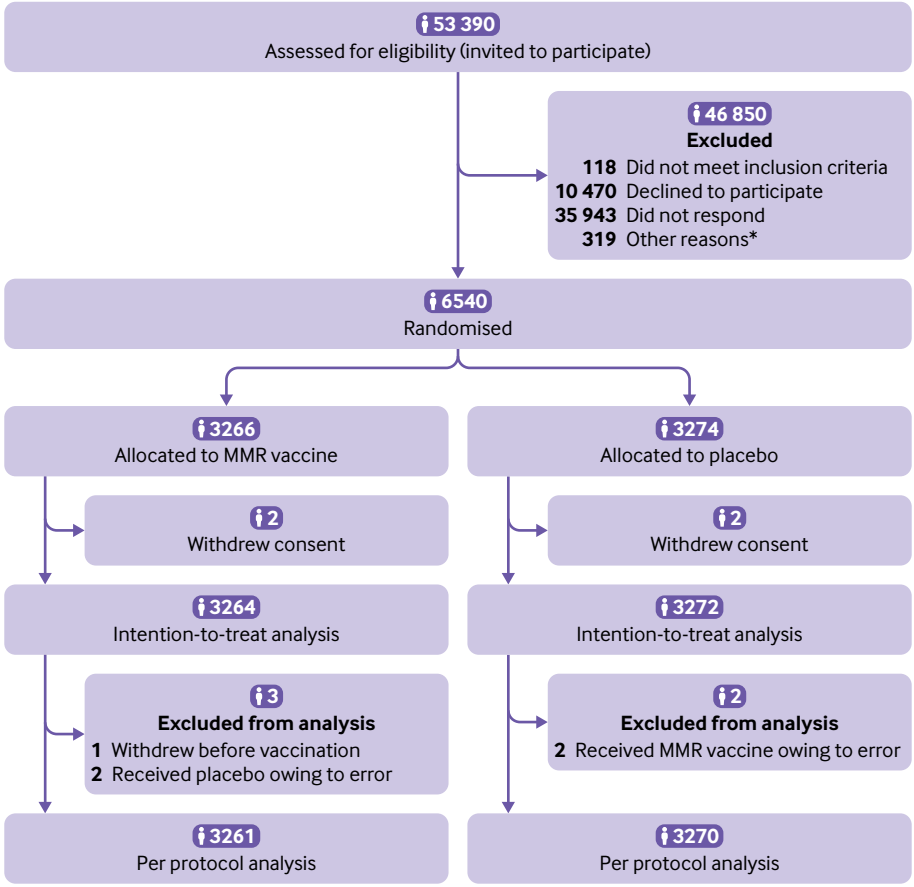

Fig 1 | Flow of participants through trial. Data collection was by invitations, telephone interviews, clinical examinations, and health registers. See supplementary table S4 for baseline characteristics by participation or non-participation. *Primarily because of cancelled visits for inclusion

Table 1 | Baseline characteristics of infants randomised to measles, mumps, and rubella (MMR) vaccine or placebo at age 5-7 months, Denmark. Values are number (percentage) unless stated otherwise

Characteristics	MMR vaccine	Placebo
Total	3264	3272
Sex:		
Boys	1693 (52)	1696 (52)
Girls	1571 (48)	1576 (48)
Gestational status:		
Premature (<37 weeks)	147 (5)	146 (4)
Mature (≥37 weeks)	3112 (95)	3109 (95)
Missing	5 (0)	17 (1)
Mean (SD) birthweight (kg)	3.53 (0.53)	3.55 (0.53)
Missing	11 (0)	22 (1)
Age at randomisation:		
Mean (SD) age (days)	187 (13.66)	187 (13.67)
<6 months	1245 (38)	1281 (39)
≥6 months	2019 (62)	1991 (61)
Season at randomisation:		
Spring	785 (24)	791 (24)
Summer	875 (27)	877 (27)
Autumn	880 (27)	878 (27)
Winter	724 (22)	726 (22)
Singleton and multiple births:		
Singletons	3198 (98)	3200 (98)
Twins	66 (2)	72 (2)
Siblings:		
Yes	1654 (51)	1620 (50)
No	1583 (49)	1622 (50)
Missing	27 (1)	30 (1)
Mean (SD) No of previous hospitalisations for infection	0.09 (0)	0.09 (0)
Mean (SD) No of past prescriptions for systemic antibiotic	0.49 (0)	0.04 (0)
Ethnicity (at least one parent with other ethnicity than Danish):		
Yes	505 (15)	505 (15)
No	2650 (81)	2671 (82)
Missing	109 (3)	96 (3)
Maternal measles immunisation status:		
Vaccinated, no infection	2645 (81)	2648 (81)
Wildtype, infection	290 (9)	289 (9)
No vaccine, no infection	17 (1)	14 (0)
Missing or unknown	312 (10)	321 (10)
Maternal education:		
No higher education	366 (11)	356 (11)
Short or medium higher education	1007 (31)	964 (29)
Long higher education	1853 (57)	1915 (59)
Missing	38 (1)	37 (1)
Annual household income (DKK):		
<200 000	75 (2)	72 (2)
200 000-400 000	488 (15)	409 (13)
>400 000	2627 (80)	2729 (83)
Missing	74 (2)	62 (2)

1DKK=£0.1; $0.1; €0.1.

vaccine,[9] we performed an analysis where the infants were censored at the date of immunisation with DTaP-IPV-Hib+PCV after randomisation. We also tested the inclusion of twins as clusters.

Adjustments and effect modification

We performed an analysis adjusting the main intention-to-treat analysis of hospitalisations for infection for all baseline characteristics, except maternal immunisation status. Previous randomised studies suggested stronger non-specific effects of the measles vaccine in girls and during the dry season in tropical climates. We therefore tested potential effect modification by sex and season at randomisation. Furthermore, we tested effect modification by prematurity and age at randomisation (≤6 months).[51 52] Finally, as the study was conducted during the covid-19 pandemic, we performed an interaction analysis to examine the potential influence of this event, dividing the study duration into three periods: first randomisation to first lockdown (15 April 2019-10 March 2020), full and partial lockdown (11 March 2020-21 May 2021), and post-lockdown, defined as the reopening of society until the end of the study period (21 May 2021-15 May 2022).

Patient and public involvement

Caregivers of participating infants were asked to give feedback on how they experienced phone calls and visits during the study, to optimise their feeling of inclusion and safety as participating families and

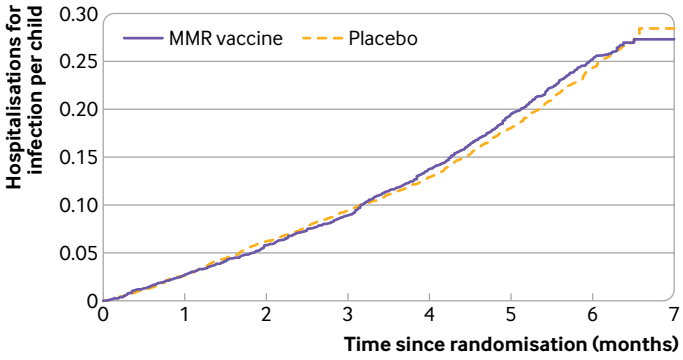

Fig 2 | Intention to treat analysis showing mean number of hospitalisations for infection according to allocation as a function of time since random assignment among 6536 Danish infants randomly assigned to either measles, mumps, and rubella (MMR) vaccine at 5-7 months of age or placebo (Nelson-Aalen method)

to ensure that we obtained the required sample size. Also, to increase our understanding of the public's perspective on an MMR vaccine being administered early, including that of the parents or caregivers of participating infants, we invited a subgroup of caregivers, health visitors, nurses, and general practitioners to take part in a qualitative study.[53]

Results

Randomisation, baseline, and follow-up

Between March 2019 and August 2021, we invited 53 390 mothers of infants aged 3 months who had been born in the Capital region of Denmark to take part in the study. Overall, 10 470 families declined to participate, 35 943 did not respond to the invitation or could not be contacted by telephone, 118 did not meet the inclusion criteria, and 319 were excluded for other reasons, primarily owing to the parents cancelling the inclusion visit. At the two study sites, Rigshospitalet and Herlev Hospital, 6540 infants were randomised: 3266 were allocated to MMR vaccine and 3274 to placebo. Three infants randomised to MMR vaccine did not receive the intervention: one infant's family withdrew from the study before vaccination and two infants received placebo owing to a procedural error. Two infants randomised to placebo received MMR vaccine owing to a procedural error. These five infants were excluded from the per protocol analysis. All the infants were followed-up in the Danish health registries. Four infants (two from each intervention group were), however, were excluded from all analyses because the parents withdrew consent after intervention, leaving 6536 infants for the primary intention-to-treat analysis of hospitalisations for infection and 6531 for the per protocol analysis (fig 1).

Baseline characteristics were balanced between both the intervention groups (table 1). Mean age of infants at randomisation was 187 days for both groups.

Primary outcome: hospitalisations for infection

Before 12 months of age, 6536 infants included in the primary intention-to-treat analysis had experienced a total of 1548 events (mean 0.24 events per infant). Overall, 786 hospitalisations for infection occurred in 3264 infants in the MMR vaccine group compared with 762 in 3272 infants in the placebo group (mean 0.24 and 0.23 events per infant, respectively). Figure 2 shows the mean number of events over time for the intention-to-treat analysis (see supplementary figure S1 for the results of the per protocol analysis). The rate of hospitalisations did not differ between the MMR vaccine group and placebo group in intention-to-treat analysis (hazard ratio 1.03, 95% confidence interval 0.91 to 1.18), and the results of the per protocol analysis were almost identical (1.03, 0.91 to 1.17; table 2).

Secondary analyses

The results for infection related hospitalisations did not change after adjusting for baseline characteristics in the main intention-to-treat analysis: 1.04 (0.91 to 1.18) (table 3). Infants with hospitalisations lasting at least 12 hours experienced a total of 165 events (mean 0.03 events per infant). Infants in the MMR vaccine group experienced 92 events versus 73 in the placebo group (mean 0.03 and 0.02 events per infant, respectively), resulting in a crude hazard ratio of 1.25 (0.88 to 1.77) and an adjusted hazard ratio of 1.24 (0.87 to 1.76). When time from discharge to rehospitalisation for all hospitalisations was set to at least seven days, the hazard was 1.02 (0.91 to 1.15). When the outcome of all hospitalisations for infection was changed to time to first hospitalisation for infection, the hazard ratio was 1.01 (0.90 to 1.13). Overall, 499 filled prescriptions for a systemic antibiotic were recorded in the MMR vaccine group compared with 481 in the placebo group (hazard ratio 1.04, 0.88 to 1.23).

No effect modification was observed by prematurity, age at randomisation, or season, nor by sex: the hazard ratio for boys in the MMR vaccine group versus placebo

Table 2 | Effect of measles, mumps, and rubella (MMR) vaccination on number of infection related hospitalisations among children randomised to MMR vaccine or placebo at age 5-7 months, Denmark. Values are number of admissions (number of children in analysis) unless stated otherwise

	Hospitalisations		
Analyses	MMR vaccine*	Placebo*	Hazard ratio (95% CI)†
Intention to treat (n=6536)	786 (3264)	762 (3272)	1.03 (0.91 to 1.18)
Per protocol (n=6531)‡	784 (3261)	762 (3270)	1.03 (0.91 to 1.17)

Intention-to-treat and per protocol analyses were stratified for sex, prematurity, and site in accordance with randomisation procedure.
*Infants were followed from randomisation to 12 months of age and analysed according to randomisation group using Cox regression.
†Supplementary table S2 presents analyses of crude hazard ratio including complete cases only.
‡Infants who did not follow the allocation were excluded and the time scale defined as time since injection.

Table 3 Sensitivity analyses and tests for effect modifications on infection related hospitalisations in infants randomised to measles, mumps, and rubella (MMR) vaccine or placebo at age 5-7 months, Denmark. Values are number of admissions (number of children in analysis)

Analyses	Hospitalisations		Hazard ratio (95% CI)†‡
	MMR vaccine*†	Placebo*†	
Hospitalisation ≥12 hours	92 (3264)	73 (3272)	1.25 (0.88 to 1.77)
Readmission to hospital >7 days from latest discharge	693 (3264)	678 (3272)	1.02 (0.91 to 1.15)
Twins analysed as clusters	786 (3264)	762 (3272)	1.03 (0.91 to 1.18)
Time to first hospitalisation for infection	564 (3264)	562 (3272)	1.01 (0.90 to 1.13)
Prescriptions for systemic antibiotics	499 (3264)	481 (3272)	1.04 (0.88 to 1.23)
DTaP-IPV-Hib+PCV censoring	751 (3264)	735 (3272)	1.02 (0.90 to 1.16)
Adjustments and effect modification			
Adjusted for baseline characteristics§	735 (3066)	703 (3084)	1.04 (0.91 to 1.18)
Sex:			
Boys	453 (1693)	444 (1696)	1.02 (0.86 to 1.22)
Girls	333 (1571)	318 (1576)	1.05 (0.87 to 1.26)
Gestational status:			
Premature	73 (147)	49 (146)	1.55 (0.90 to 2.68)
Mature	713 (3112)	703 (3109)	1.01 (0.89 to 1.15)
Age at randomisation:			
<6 months of age	282 (1245)	327 (1281)	0.89 (0.73 to 1.09)
>6 months of age	504 (2019)	435 (1991)	1.14 (0.96 to 1.34)
Season at randomisation:			
Spring	153 (785)	192 (791)	0.82 (0.63 to 1.06)
Summer	211 (875)	219 (877)	0.96 (0.76 to 1.20)
Autumn	274 (880)	216 (878)	1.26 (0.98 to 1.61)
Winter	148 (724)	135 (726)	1.10 (0.82 to 1.48)
Effects of covid-19 lockdown¶:			
Pre-lockdown	252 (1249)	286 (1255)	0.88 (0.71 to 1.08)
Lockdown	295 (1504)	259 (1505)	1.13 (0.92 to 1.38)
Post-lockdown	239 (511)	217 (512)	1.10 (0.86 to 1.39)

Intention-to-treat and per protocol analyses were stratified for sex, prematurity, and site in accordance with randomisation procedure.
*Infants were followed from randomisation to 12 months of age and analysed according to randomisation group using Cox regression.
†Intention-to-treat analyses were stratified for sex, gestational status, and site in accordance with the randomisation procedure.
‡Adjusted for baseline characteristics: sex, gestational status, multiple births, siblings, birthweight (in grams), age at randomisation (in days), season at randomisation (winter, spring, summer, autumn), number of previous hospitalisations for infection, ethnicity (at least one parent with other ethnicity than Danish), maternal education (primary, secondary, tertiary), annual household income (DKK: <200 000, 200 000-400 000, >400 000).
§Pre-lockdown defined as first randomisation to first lockdown (15 April 2019-10 March 2020), full and partial lockdown from 11 March 2020-20 May 2021, and post-lockdown defined as reopening of society to end of study period (21 May 2021-15 May 2022).

group was 1.02 (0.86 to 1.22) and for girls was 1.05 (0.87 to 1.26) (table 3). The inclusion in the analysis of twins as clusters did not have any effect on the estimates, nor did censoring for DTaP-IPV-Hib+PCV (table 3).

We observed a mean 0.20 events per infant in the MMR vaccine group and 0.17 in the placebo group during the covid-19 lockdown compared with 0.20 events and 0.23, respectively, pre-lockdown and 0.47 and 0.42, respectively, post-lockdown (table 3 and supplementary figure S2). The test for effect modification showed no statistical difference between the MMR vaccine group and placebo group for any of the three covid-19 lockdown periods (table 3).

Discussion

In this pragmatic randomised controlled trial in the high income setting of Denmark, a live attenuated MMR vaccine administered to infants at 5-7 months of age did not decrease the rate of hospitalisations for non-targeted infection before age 12 months.

Strengths and limitations of this study

One strength of this trial was the randomised controlled design with adequate power. All study participants were followed in the Danish National Patient Register, ensuring complete follow-up. The collection of outcome data was also independent of the trial staff, decreasing the risk of bias.

Because infants needed to be included at a particular age, we prioritised families who responded to the invitation letter, resulting in an inclusion rate of 12%. Understanding Danish was an inclusion criterion, therefore more families of Danish ethnicity were included compared with non-participants. This should not affect the validity of the trial results.[54]

Multiple secondary analyses were carried out without correction for multiple comparisons. Such results should be interpreted cautiously.

Comparisons with other studies

Most trials on the non-specific effects of vaccines containing the measles virus in low income countries have used mortality as the primary outcome, and many of these with a high titre measles vaccine as the comparator. As high titre measles vaccines were excluded from immunisation programmes in 1992 because of concerns about harmful non-specific effects,[55] comparison with these studies is of little relevance. We identified six studies from trials testing the non-specific effects of standard titre measles vaccines on mortality, that reported no significant

non-specific effects on non-measles related overall mortality.[12 20 23 24 27 28] Trials with mortality as the primary outcome are not directly comparable to our trial. However, even in high income settings, viral and bacterial infections have personal and financial implications for families and society. Hospitalisation for infection is also a plausible predictor for infections that, especially in countries with suboptimal treatment options, might lead to death.

Our findings corroborate the non-significant overall results of eight studies carried out in low income countries on the potential non-specific effects of standard titre measles vaccines on non-measles related hospitalisation and outpatient contacts.[10 11 17 22 23 25 27 28] One of these studies reported beneficial effects on hospital admissions in a subgroup analysis of girls (hazard ratio 0.59, 95% confidence interval 0.36 to 0.97).[10] No sex specific effects were, however, observed in the present trial.

Observational studies have suggested beneficial non-specific effects of vaccines that contain the measles virus, but there is concern about the limitations of using a non-randomised design.[31] The inherent risk of bias in observational studies, such as healthy vaccinee bias, makes observational studies unsuitable for drawing causal inference. Notably, randomised trials for outcomes of both overall mortality and morbidity consistently result in non-significant beneficial non-specific effects.[10-12 17 19-28 56]

Implications

A clinically relevant non-specific beneficial effect of stimulating the immune system with a vaccine containing measles virus, here an early MMR vaccine, has not been confirmed in trials in low income or high income settings. Besides the potential protective effect of the MMR vaccine against MMR, based on our findings we do not find justification for earlier implementation of MMR vaccination.

Conclusions

This randomised controlled trial carried out in the high income setting of Denmark did not support the hypothesis that administering live attenuated MMR vaccine at 5-7 months of age decreases the rate of hospitalisations for non-targeted infection before age 12 months.

Members of the Danish Health Authority Vaccine Advisory Board, the two paediatric departments at the recruitment sites, and the University of Copenhagen were represented on the trial steering committee. This trial was monitored by a data safety monitoring board consisting of Gorm Greisen (paediatrics) and Niels Frimodt-Møller (clinical microbiology). Data manager Jakob Hjort (Department of Clinical Medicine, Aarhus) helped structure and maintain data collection in REDCap. Study nurses Tina Bonita Redhead, Julie Elkjær Møller, Caroline Flemming Bendixen, and Anna Wandahl helped with participant inclusion and data collection.

Contributors: LGS conceived the trial. LGS and JS supervised the trial. LGS, AJ, and ACZ planned the analyses of the co-primary outcome of hospitalisations for infections. LGS developed the baseline questionnaires. DV, JKS, MM, EHH, and ACZ planned, coordinated, and participated in the data collection at the study site and trained and supervised study nurses. AJ, DV, JKS, MM, and ACZ cleaned and validated the data. AJ analysed the data with input from ACZ and LGS. ACZ drafted the original manuscript with help from AJ and LGS. All authors critically revised the manuscript and approved the final version for publication, had full access to all the data (including statistical reports and tables) in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. ACZ and LGS are guarantors and attest that all listed authors meet authorship criteria.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: no support from Innovation Fund Denmark; no financial relationships with any organisation that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This trial was approved by the regional biomedical research ethics committee and hospital boards at the study sites. The trial was monitored by the Copenhagen Good Clinical Practice Unit and the independent data safety monitoring board. A statistical analysis plan of the study was worked out and submitted to the data safety monitoring board before the initiation of data management and the statistical analyses. Written informed consent was collected from all parents. Besides essential trial permissions from the Danish authorities, the Danish Health Authority and Statens Serum Institut, which monitor public health, infectious diseases, and vaccination in Denmark, were informed about the trial.

Data sharing: In 2025, 18 months after the trial has been finalised, a pseudonymised data copy will be stored in Dansk Data Arkiv (https://www.sa.dk/da/brug-arkivet/ddd/) for other researchers to access and re-use data.

The lead author (ACZ) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: All published papers from the trial will be presented with hyperlinks on the study website, and participating families have been encouraged to follow results here. Dissemination of the findings on social media or in the press will be by request.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Supplementary information: Supplementary figures, tables, and supporting material