Mæslinge-fåresyge-røde hunde (MFR)-vaccination i 5-7-måneders-alderen: Immunogenicitet og reaktogenicitet

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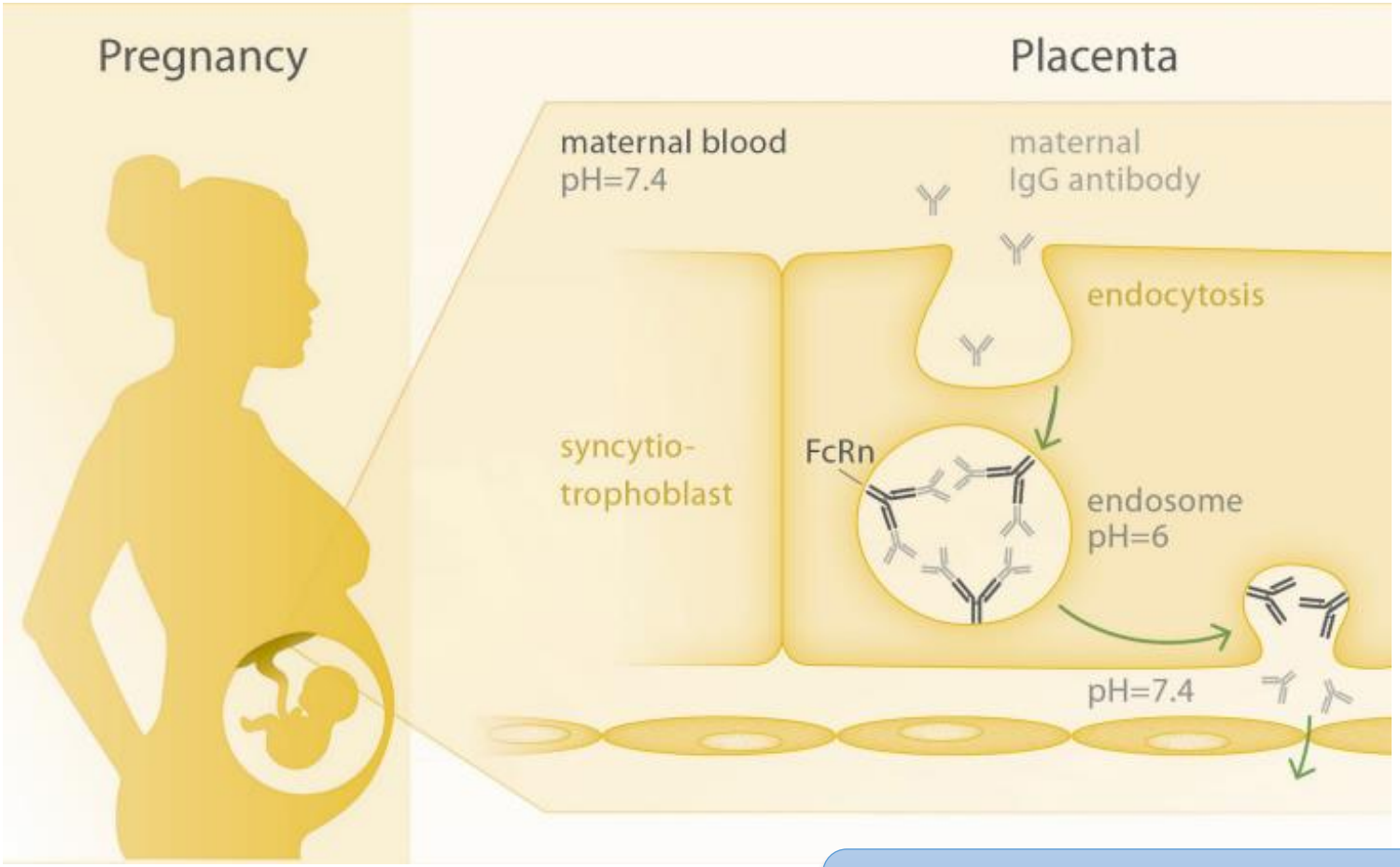
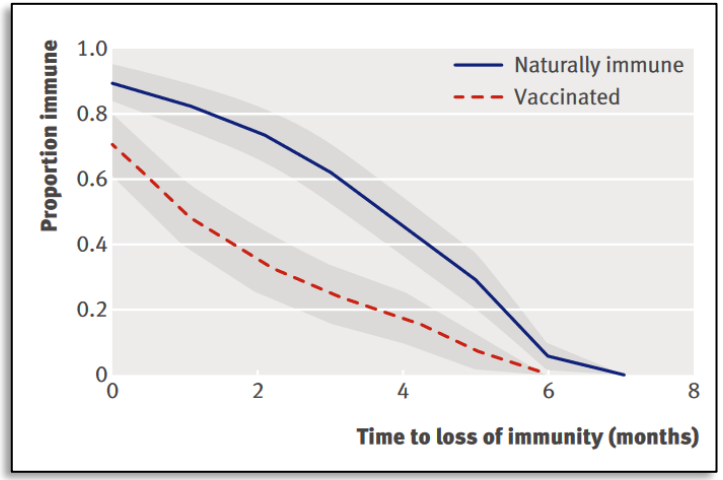
Medvejleder: Jannet Svensson

Børnedage, Juni 2024, Helsingør

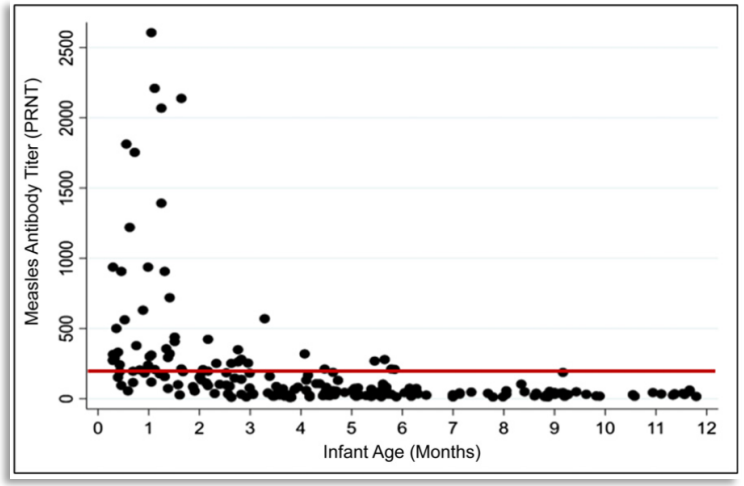
Hvorfor?



Vertically Transferred Immunity in Neonates:
Mothers, Mechanisms and Mediators
Albrecht M et al., Front. Immunology, 2020



Leuridan et al., BMJ, 2010

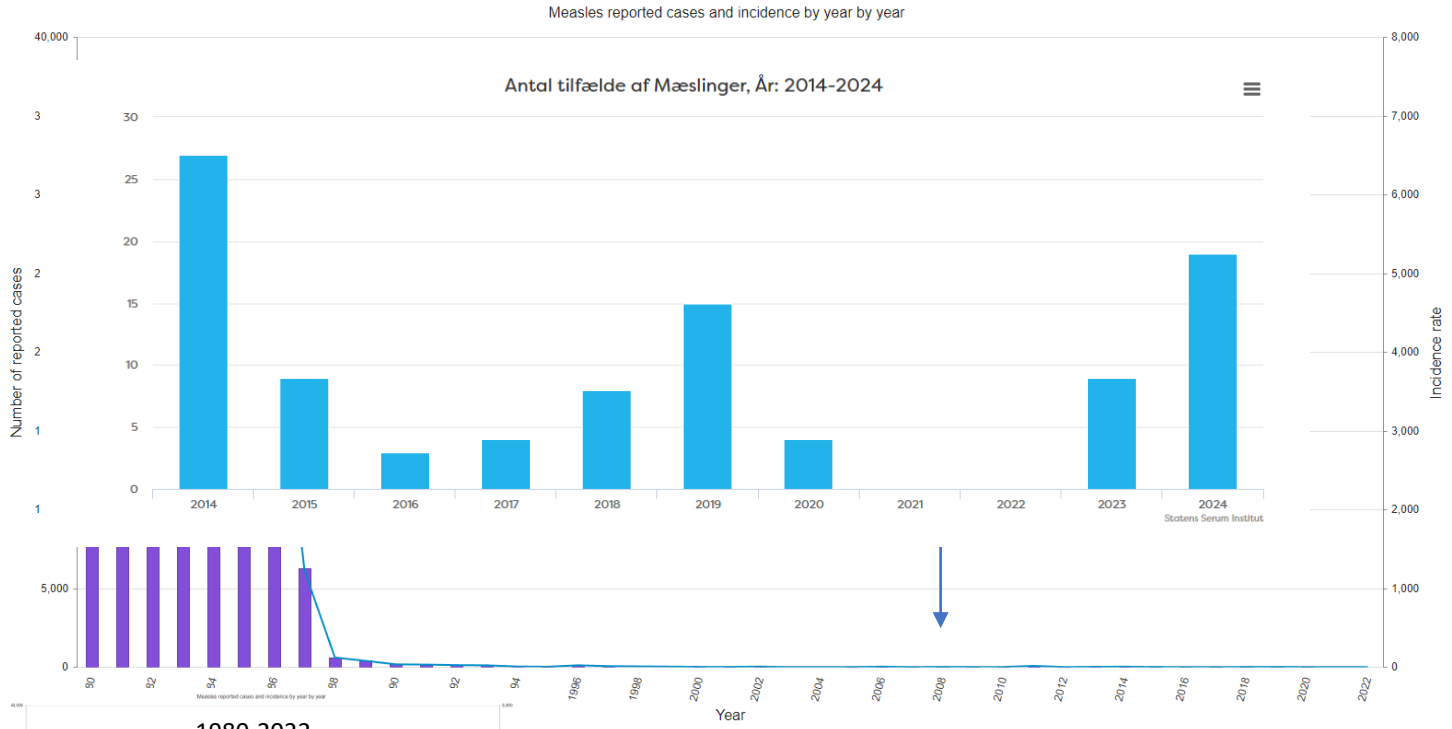


Measles Antibody Levels in Young Infants, Science M et al., Pediatrics, 2019

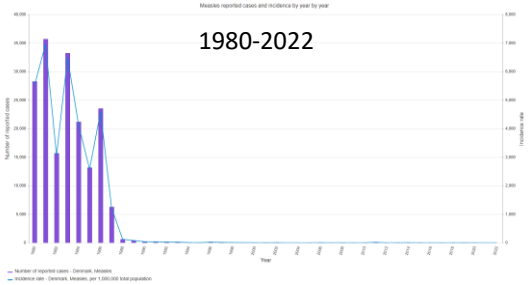
- Beskyttelse mod mæslinger
- Hæmning af vaccinerespons

Er vi helt ovre det der med mæslinger?

1980-2022



1980-2022



Nearly 40 million children are dangerously susceptible to growing measles threat

23 November 2022 | Joint News Release | Reading time: 4 min (1042 words)

Measles vaccination coverage has steadily declined since the beginning of the COVID-19 pandemic. In 2021, a record high of nearly 40 million children missed a measles vaccine dose: 25 million children missed their first dose and an additional 14.7 million children missed their second dose, a joint publication by the World Health Organization (WHO) and the United States Centers for Disease Control and Prevention (CDC) reports. This decline is a significant setback in global progress towards achieving and maintaining measles elimination and leaves millions of children susceptible to infection.

In 2021, there were an estimated 9 million cases and 128 000 deaths from measles worldwide. Twenty-two countries experienced large and disruptive outbreaks. Declines in vaccine coverage, weakened measles surveillance, and continued interruptions and delays in immunization activities due to COVID-19, as well as persistent large outbreaks in 2022, mean that measles is an imminent threat in every region of the world.

https://immunizationdata.who.int/pages/incidence/MEASLES.html?CODE=DNK&YEAR=

Besøgt 030624:
https://statistik.ssi.dk//sygdomsdata#!/?sygdomskode=MEAS&xaxis=Aar&show=Graph&aar=2014%7C2024&datatype=Individual

Deltagere

- 5-7 måneder gamle
- Raske børn
- Inklusionskriterier:
  - GA $\geq$ 32+0
  - FV $\geq$ 1000g
- Eksklusionskriterier:
  - Overlappende med vanlig brug af MFR-vaccine

Vist med skriftligt samtykke fra forældre

Studiedesign

MFR

Placebo

Immunogenicitet (10%)

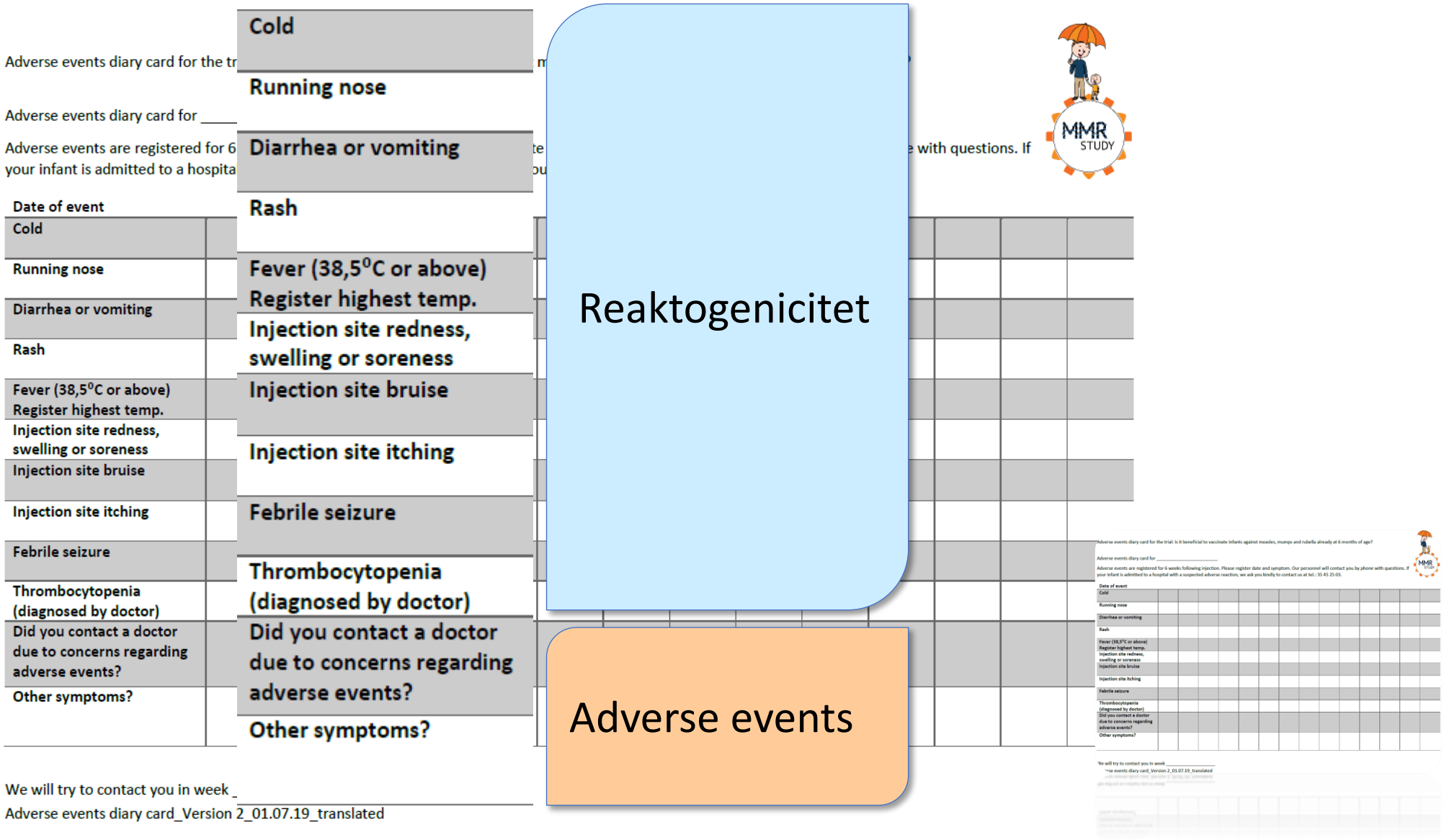
4 år

Trials. 2020; 21: 1015. PMCID: PMC7727227
Published online 2020 Dec 10. doi: 10.1186/s13063-020-04845-7 PMID: 33303011

Measles-mumps-rubella vaccine at 6 months of age, immunology, and childhood morbidity in a high-income setting: study protocol for a randomized controlled trial

Dorthe Maria Vittrup,[✉1] Anne Cathrine Lund Laursen,[2] Michelle Malon,[2] Jesper Kiehn Soerensen,[2] Jakob Hjort,[3] Soren Buus,[4] Jannet Svensson,[1] and Lone Graff Stensballe[2,5]

Reaktogenicitet

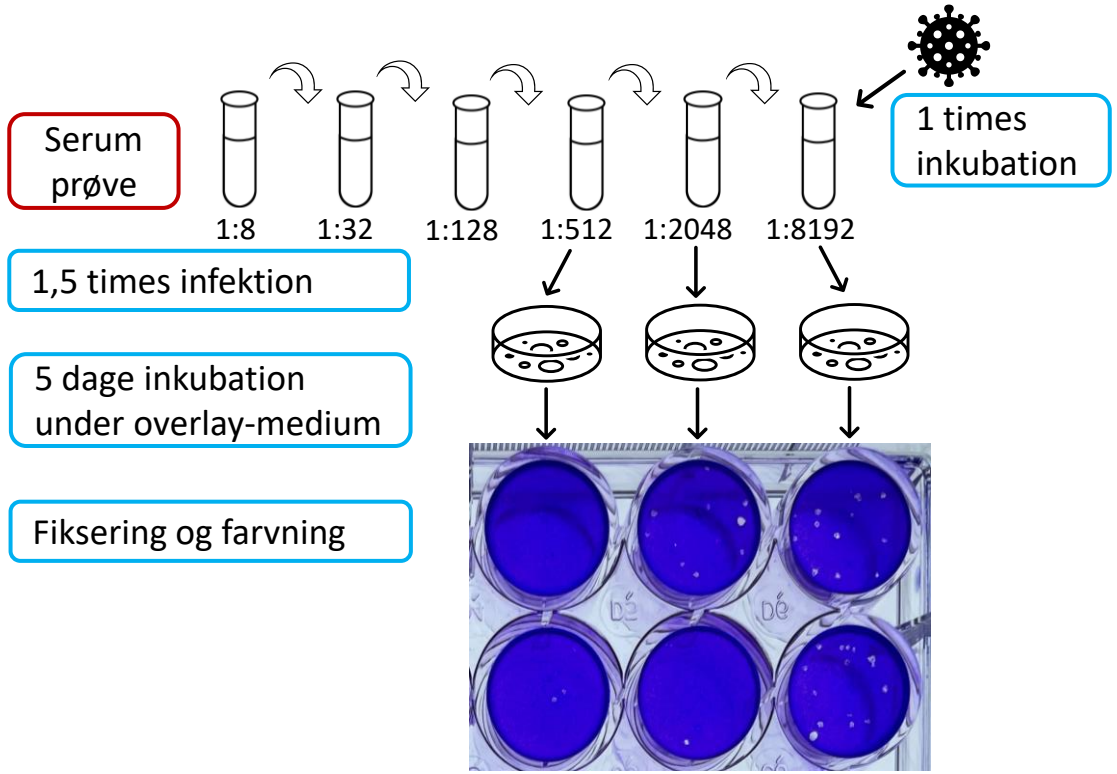


6-ugers follow-up

Metoder immunogenicitet: Antistofkorrelater for klinisk beskyttelse

Mæslinge plaque-reduction neutralisation test (PRNT)

Serobeskyttelsesgrænse: ≥ 120 mIU/mL•



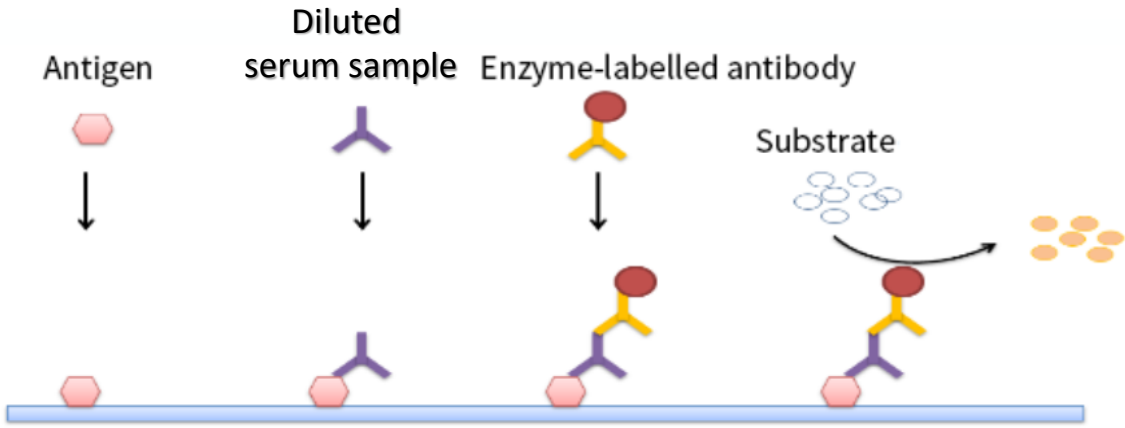
Mæslinger, fåresyge og røde hunde IgG ELISA

Serobeskyttelsesgrænser:

≥ 220 mIU/mL i mæslinge IgG

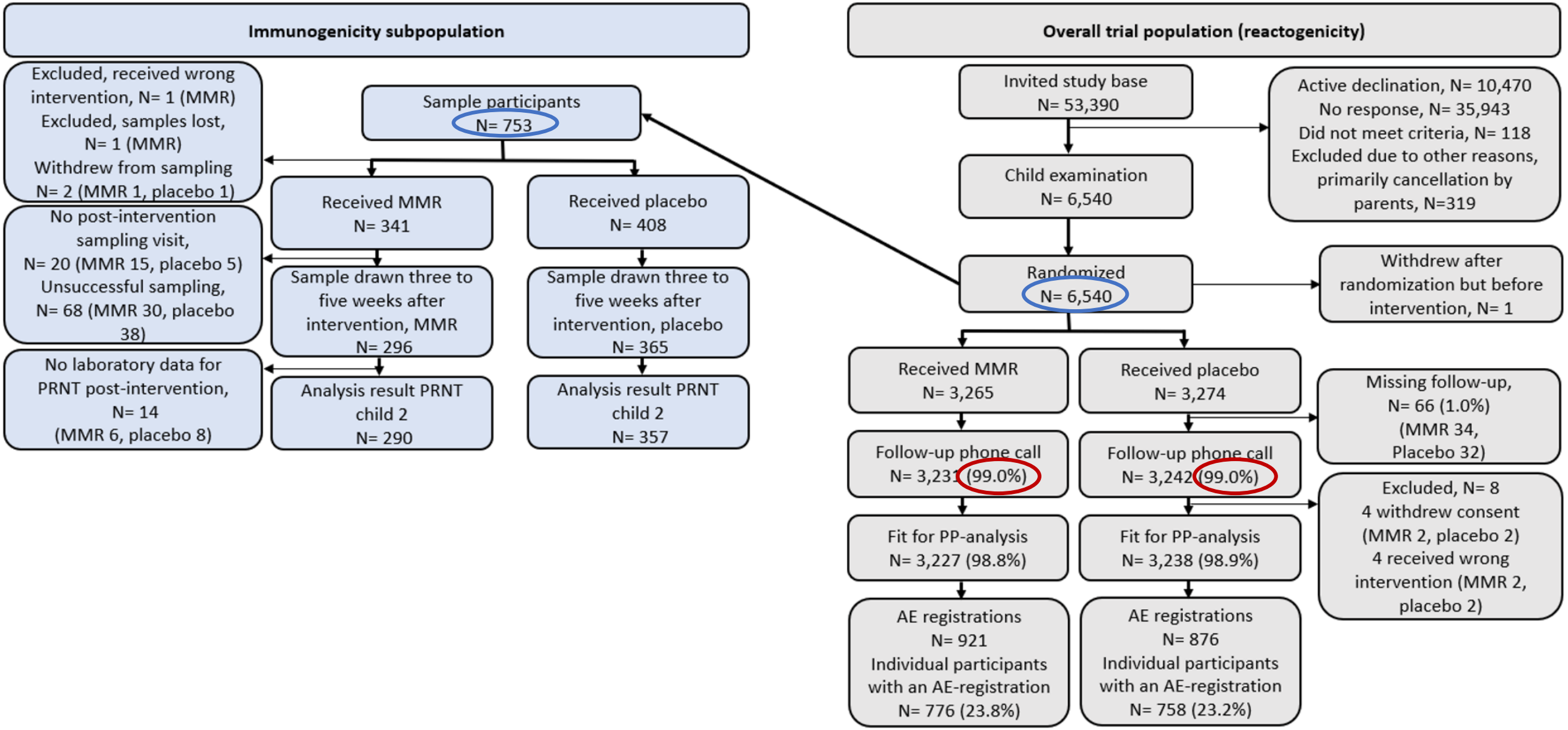
≥ 10 IU/mL i rubella IgG

Usikkert for fåresyge, men seropositivitet >10 NTU/ml



•Chen *et al.*, 1990, The Journal of Infectious Diseases

Resultater


Immunogenicity subpopulation
Excluded, received wrong intervention, N= 1 (MMR)
Excluded, samples lost, N= 1 (MMR)
Withdrew from sampling N= 2 (MMR 1, placebo 1)
Sample participants N= 753
Received MMR N= 341
Received placebo N= 408
No post-intervention sampling visit, N= 20 (MMR 15, placebo 5)
Unsuccessful sampling, N= 68 (MMR 30, placebo 38)
Sample drawn three to five weeks after intervention, MMR N= 296
Sample drawn three to five weeks after intervention, placebo N= 365
No laboratory data for PRNT post-intervention, N= 14 (MMR 6, placebo 8)
Analysis result PRNT child 2 N= 290
Analysis result PRNT child 2 N= 357
Overall trial population (reactogenicity)
Invited study base N= 53,390
Active declination, N= 10,470
No response, N= 35,943
Did not meet criteria, N= 118
Excluded due to other reasons, primarily cancellation by parents, N=319
Child examination N= 6,540
Randomized N= 6,540
Withdrew after randomization but before intervention, N= 1
Received MMR N= 3,265
Received placebo N= 3,274
Missing follow-up, N= 66 (1.0%) (MMR 34, Placebo 32)
Follow-up phone call N= 3,231 (99.0%)
Follow-up phone call N= 3,242 (99.0%)
Excluded, N= 8
4 withdrew consent (MMR 2, placebo 2)
4 received wrong intervention (MMR 2, placebo 2)
Fit for PP-analysis N= 3,227 (98.8%)
Fit for PP-analysis N= 3,238 (98.9%)
AE registrations N= 921
Individual participants with an AE-registration N= 776 (23.8%)
AE registrations N= 876
Individual participants with an AE-registration N= 758 (23.2%)

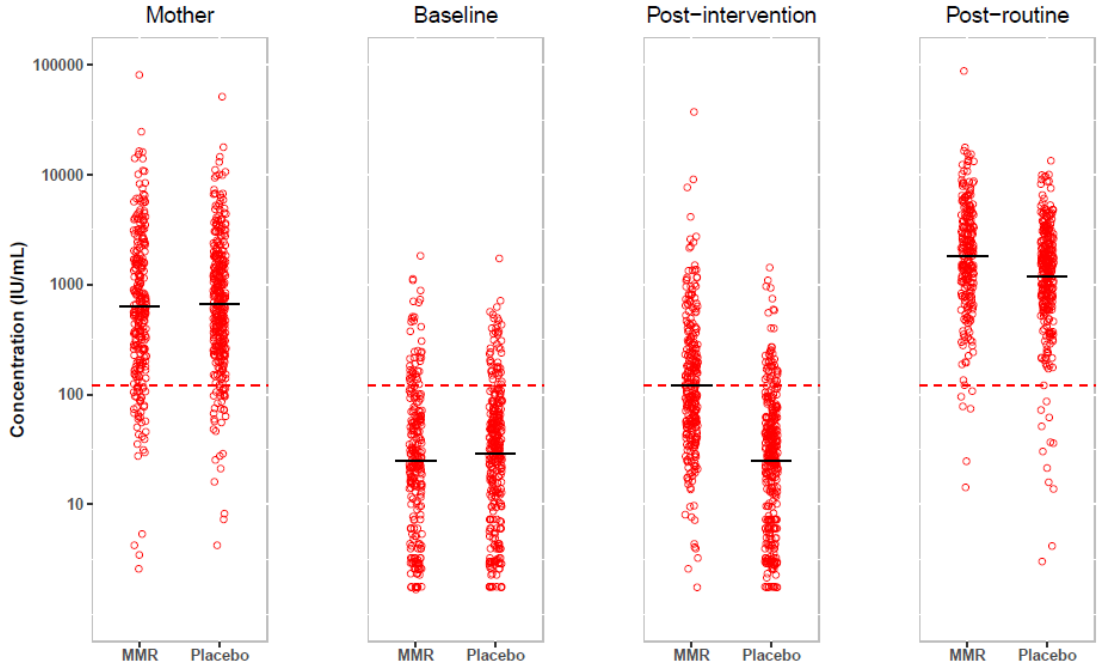
	Total N	MMR N (%)	Placebo N (%)
Baseline characteristics	6465	3227 (**49.9**)	3238 (**50.1**)
Study site	6465		
Rigshospitalet		3189 (98.8)	3199 (98.8)
Herlev Hospital		38 (1.2)	39 (1.2)
Sex boys	6465	1675 (51.9)	1673 (51.7)
Mean infant age months	6465	**6.2** (6.1-6.2)	**6.2** (6.1-6.2)
Age at randomisation < 6 months	6465	1236 (**38.3**)	1274 (**39.4**)
Mean time from intervention to follow-up phone call in days	6465	**44.5**	**44.4**
Premature (GA<37 weeks)	6415	211 (**6.6**)	203 (**6.3**)
Number of siblings	6411		
0		1568 (**49.0**)	1601 (**49.9**)
1		1169 (**36.5**)	1121 (**34.9**)
2 or more		466 (**14.6**)	486 (**15.1**)
Mean maternal age years	6405	**33.1** (32.9-33.2)	**33.1** (33.0-33.3)
Household income per year (USD)	6331		
Less than 27000		72 (**2.3**)	68 (**2.1**)
Between 27000-54000		485 (**15.4**)	402 (**12.7**)
More than 54000		2598 (**82.4**)	2706 (**85.2**)
Parents living together	6366	3003 (94.5)	3032 (94.8)
Mother's educational level	6399		
≤ High-school education		153 (**4.8**)	138 (**4.3**)
Vocational education-bachelor's degree		1207 (**37.8**)	1169 (**36.5**)
≥ Master's degree		1832 (**57.3**)	1894 (**59.2**)
Maternal measles immunization status (self-reported)	5839		
Previously infected		126 (**4.3**)	119 (**4.1**)
Vaccinated		2618 (**89.6**)	2621 (**89.7**)
Both previously infected and vaccinated		158 (**5.4**)	166 (**5.7**)
Not immunised		17 (**0.6**)	14 (**0.5**)

[a] Time was defined as time from intervention until follow-up phone call or censoring on day 49 after intervention, whichever came first. Reactogenicity data were however only systematically registered and collected until 42 days after intervention. This interval was perceived as the true follow-up time.
[b] Age was reported as mean (95% CI).
Table presented in paper 2, slightly modified.

Resultater: Immunogenicitet

Mæslinge-neutraliserende antistoffer (PRNT)

	MMR				Placebo			
	Mother	Baseline	Post interv.	Post routine	Mother	Baseline	Post interv.	Post routine
	N=336	N=294	N=290	N=266	N=400	N=356	N=357	N=339
GMC	668 (563-793)	24 (20-29)	120 (102-141)	1815 (1552-2123)	709 (622-809)	30 (25-34)	25 (22-29)	1184 (1041-1347)
AMC	2725 (3-119513)	79 (1-1828)	455 (2-37295)	3595 (4-87948)	1637 (4-51366)	73 (2-1731)	67 (2-1429)	1936 (3-13407)
SCR (%)	-	-	47.0	83.8	-	-	7.3	94.6
SPR (%)	87.5	15.3	46.9	97.0	90.8	14.3	12.9	95.6



Mæslinger, fåresyge, and rubella IgG ELISA

	MMR				Placebo			
	Mother	Baseline	Post interv.	Post routine	Mother	Baseline	Post interv.	Post routine
Mæslinger	N=335	N=285	N=293	N=279	N=404	N=352	N=361	N=356
Titer	37.2 (0.1-291.5)	2.5 (0.0-26.4)	11.6 (0.4-82.0)	52.0 (1.1-198.3)	37.2 (0.8-254.8)	2.7 (0.0-62.5)	2.3 (0.0-44.0)	36.5 (0.1-281.2)
SPR (%)	75.8	2.1	34.5	92.1	73.3	3.7	1.7	88.8
Fåresyge	N=317	N=275	N=276	N=262	N=377	N=330	N=334	N=329
Titer	49.1 (0.1-493.8)	2.9 (0.2-35.8)	12.2 (0.3-169.2)	140.3 (1.4-960.3)	52.5 (0.8-360.3)	3.1 (0.0-29.3)	3.2 (0.0-114.3)	24.6 (0.2-342.7)
SPR (%)	87.4	1.1	33.0	92.0	85.7	3.0	2.1	50.5
Rubella	N=335	N=297	N=293	N=270	N=404	N=363	N=361	N=353
AMC	49.0 (0.0-610.1)	6.0 (0.0-127.0)	24.8 (0.0-117.6)	89.0 (0.1-1066)	45.9 (0.0-519.8)	4.6 (0.0-90.3)	3.8 (0.0-65.1)	48.6 (0.0-1470)
SPR (%)	76.0	11.4	60.7	92.2	75.8	10.4	10.1	65.3

eClinicalMedicine
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eClinicalMedicine. 2024 Feb; 68: 102421. PMCID: PMC10825632
Published online 2024 Jan 12. doi: 10.1016/j.eclinm.2023.102421 PMID: 38292039

Immunogenicity and reactogenicity following MMR vaccination in 5–7-month-old infants: a double-blind placebo-controlled randomized clinical trial in 6540 Danish infants

Dorthe Maria Vittrup,[a,b,*] Andreas Jensen,[b] Jesper Kiehn Sørensen,[b] Anne Cathrine Zimakoff,[b] Michelle Malon,[b] Salma Charabi,[c] Marie Ryberg Johansen,[d] Eric A.F. Simões,[e] Nikolai Søren Kirkby,[f] Søren Buus,[g] Jannet Svensson,[a,h,i] and Lone Graff Stensballe[b,i,j]

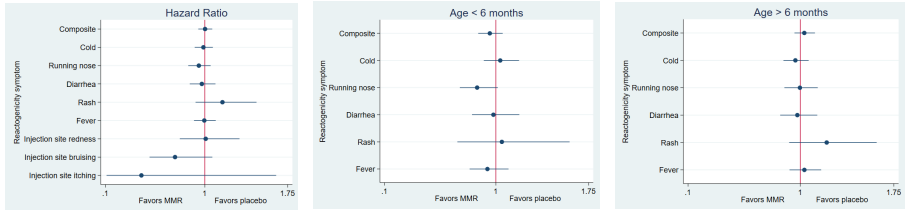
Geometric mean concentration ratios (GMR)

	Post intervention (MMR/placebo)				Post routine vaccine	
	N	GMR	N	Adjusted GMR	N	GMR
Measles PRNT						
GMR	647	4.3 (3.4-5.3)	591	4.2 (3.5-5.1)	563	1.5 (1.3-1.9)
Effect modification						
Sex						
Male	345	3.7 (2.8-5.0)	318	4.0 (3.1-5.3)	301	1.3 (1.0-1.8)
Female	302	5.0 (3.6-6.8)	273	4.4 (3.4-5.9)	262	1.8 (1.3-2.4)
Prematurity						
GA <37	35	13.4 (4.9-36.1)	32	11.0 (4.4-28.0)	28	1.0 (0.4-2.4)
GA ≥37	598	4.0 (3.2-4.9)	547	4.0 (3.3-4.9)	522	1.6 (1.3-1.9)
Age at intervention						
< 6 months	71	2.5 (1.3-4.6)	68	2.7 (1.6-4.7)	66	1.1 (0.6-2.0)
≥ 6 months	576	4.6 (3.7-5.7)	523	4.5 (3.7-5.5)	497	1.6 (1.3-2.0)
ELISA IgG						
Measles GMR	646	3.9 (3.4-4.5)	584	3.8 (3.3-4.4)	584	1.4 (1.2-1.6)
Mumps GMR	603	3.3 (2.9-3.8)	548	3.5 (3.1-4.0)	541	9.3 (7.3-11.9)
Rubella GMR	646	21.7 (14.6-32.2)	591	24.0 (18.0-32.0)	578	7.3 (5.2-10.4)

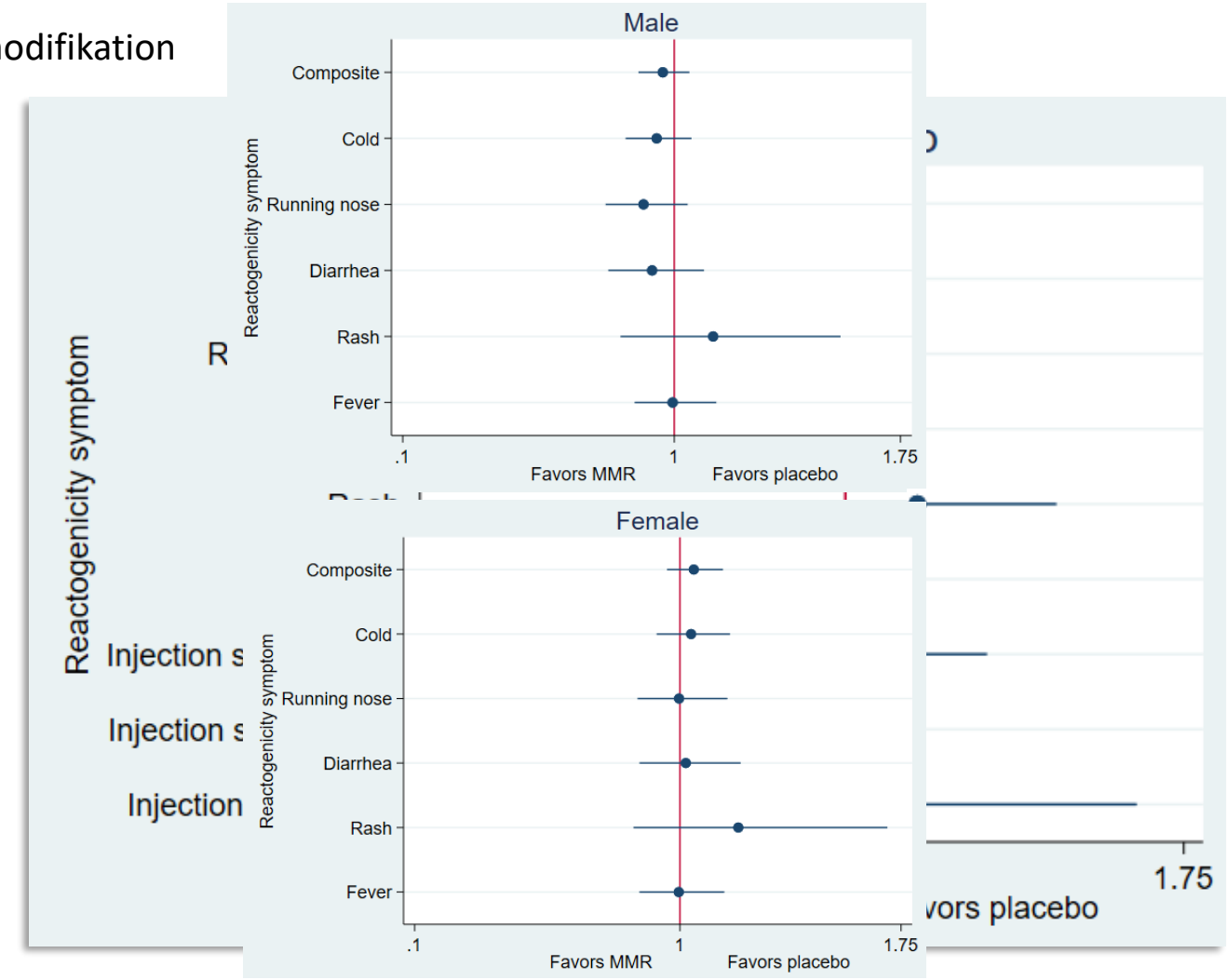
Adjusted for baseline level

Resultater: Reaktogenicitet

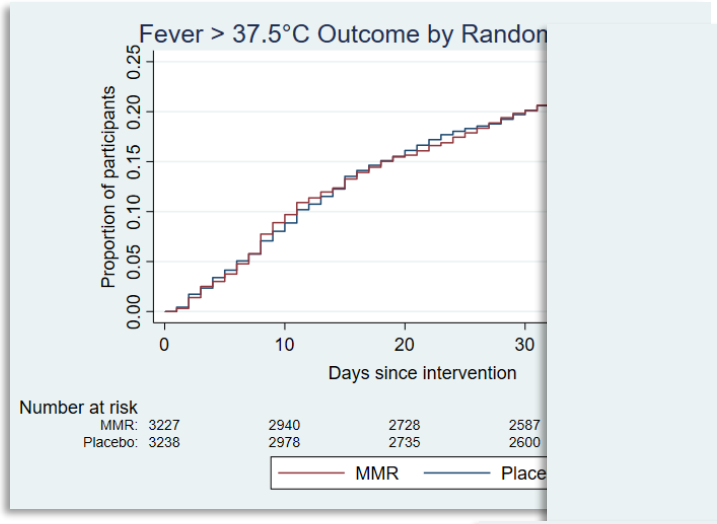
Reaktogenicitet	N (%) event	N (%, 95% CI) event - MMR	N (%, 95% CI) event - placebo
Komposit outcome	3,879 (60)	1,935 (60, 58-62)	1,944 (60, 58-62)
Forkølelse	2,225 (34)	1,103 (34, 33-36)	1,122 (35, 33-36)
Løbenæse	1,342 (21)	652 (20, 19-22)	690 (21, 20-23)
Diare eller opkastning	1,079 (17)	532 (17, 15-18)	547 (17, 16-18)
Generaliseret udslæt	278 (4.3)	149 (4.6, 3.9-5.4)	129 (4.0, 3.4-4.7)
Feber (>37,5°C)	1,575 (24)	784 (24, 23-26)	791 (24, 23-26)
Feber (≥39,0°C)	630 (9.6)	327 (10.0, 9.0-11.1)	303 (9.3, 8.3-10.3)
Injektionssted rødme	219 (3.4)	110 (3.4, 2.8-4.1)	109 (3.4, 2.8-4.0)
Injektionssted blåt mærke	109 (1.7)	46 (1.4, 1.1-1.9)	63 (1.9, 1.5-2.5)
Injektionssted kløe	10 (0.15)	3 (0.1, 0.0-0.3)	7 (0.2, 0.1-0.4)
Feberkramper	1 (0.02)	1 (0.03, 0.01-0.18)	0 (0.00, 0.00-0.12)
Trombocytopeni	0 (0.00)	0 (0.00, 0-0.12)	0 (0.00, 0-0.12)

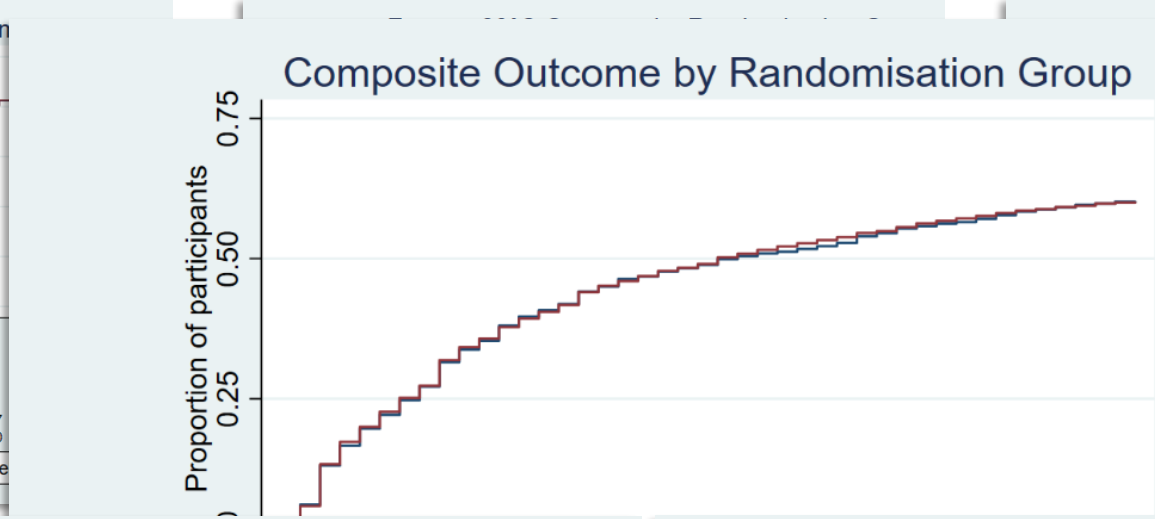


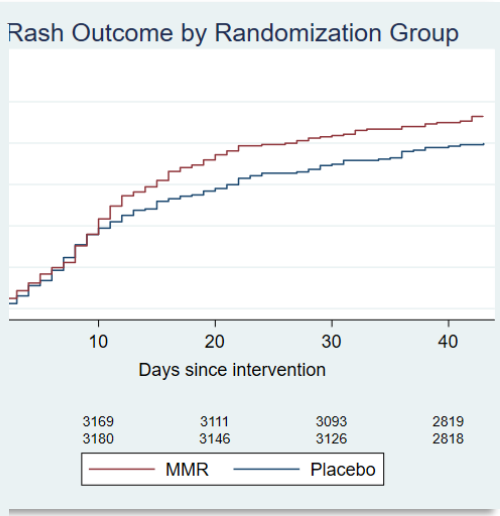
Effektmodifikation



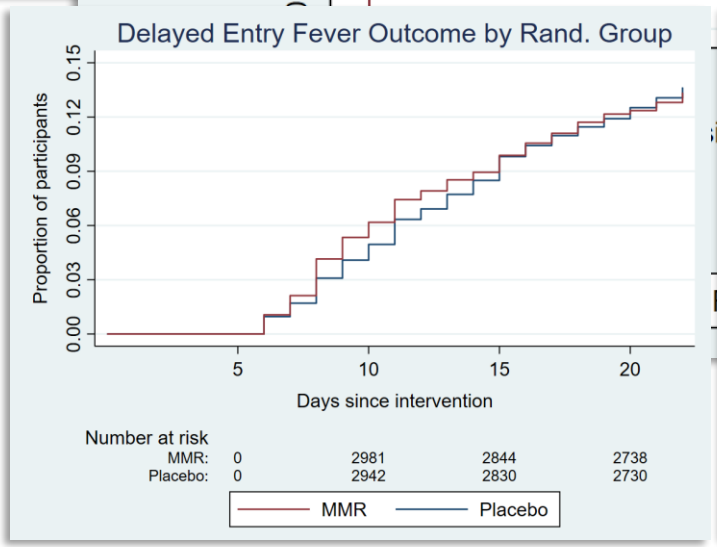
Timing af events..

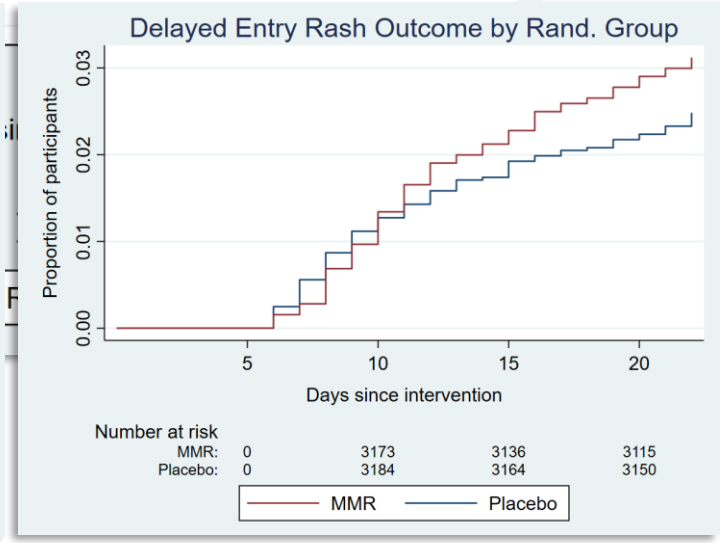






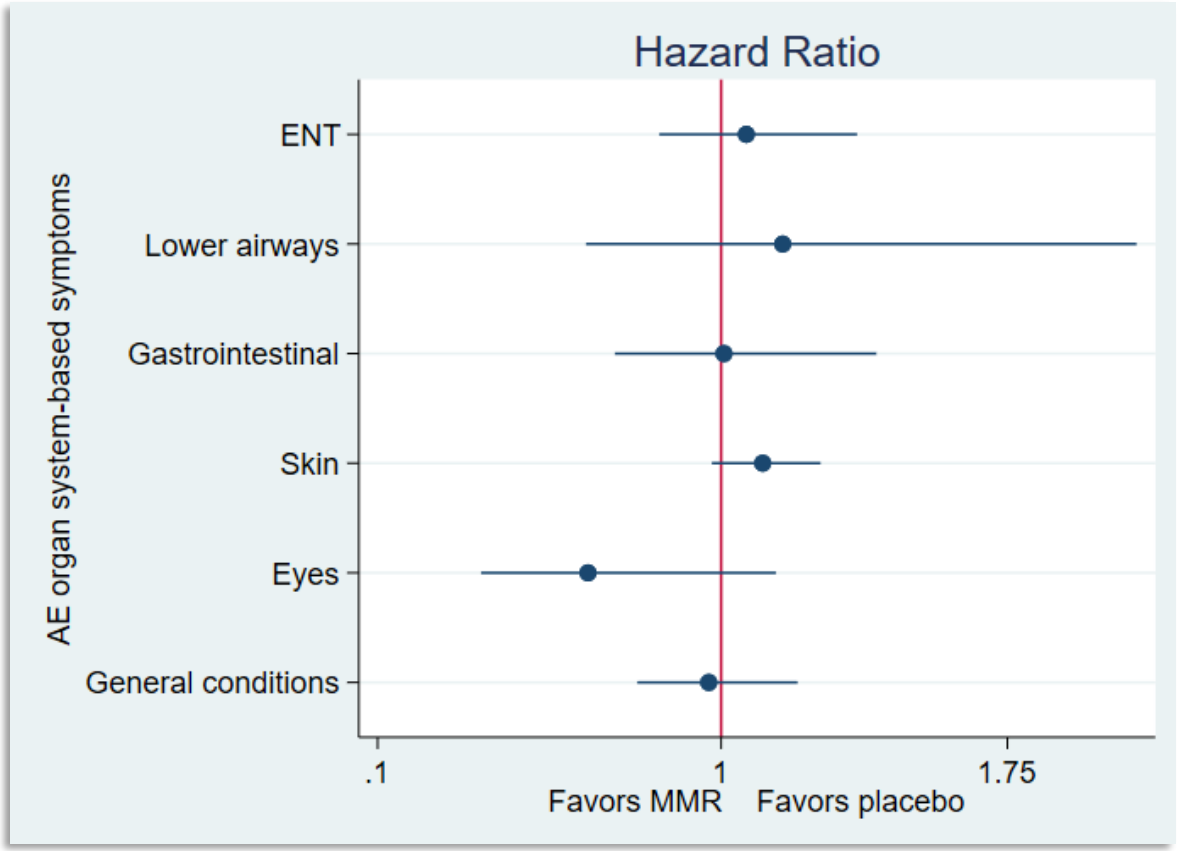
Selv når vi zoomer ind på timing..





Resultater: Adverse events

Adverse events	N (%) event	N (%, 95% CI) event - MMR	N (%, 95% CI) event - placebo	HR (95% CI) – placebo as reference
Ear-nose-throat	266 (4.1)	137 (4.2, 3.6-5.0)	129 (4.0, 3.4-4.7)	1.07 (0.84-1.36)
Lower airways	45 (0.70)	24 (0.74, 0.50-1.10)	21 (0.65, 0.42-0.99)	1.16 (0.65-2.09)
Gastro-intestinal	138 (2.1)	69 (2.1, 1.7-2.7)	69 (2.1, 1.7-2.7)	1.01 (0.72-1.41)
Skin	941 (15)	492 (15, 14-17)	449 (14, 13-15)	1.11 (0.98-1.26)
Eyes	51 (0.79)	20 (0.62, 0.40-0.95)	31 (0.96, 0.67-1.35)	0.65 (0.37-1.14)
General conditions	331 (5.12)	163 (5.05, 4.35-5.86)	168 (5.19, 4.48-6.01)	0.97 (0.78-1.20)
Severe	25 (0.39)	16 (0.50, 0.31-0.80)	9 (0.28, 0.15-0.53)	1.77 (0.78-4.01)



Serious adverse events (SAE)

	MMR	Placebo
Total population (N=6,465)	3,227	3,238
Events (N=27)	17	10
Individuelle deltagere (N=25)	16	9
Tid til SAE*, middel (95% CI)	26.0 (12.3-39.7)	21.8 (11.1-32.5)
(Spredning i dage siden intervention)	(2-40)	(5-44)
Indlæggelse (N = 27)	17	10
Luftvejsinfektion (N = 14)	10	4
Gastrointestinel (N = 3)	1	2
Urinvejsinfektion (N = 5)	3	2
Andet (N = 5)	3	2
Tid til luftvejsinfektion event*, middel (95% CI)	19.5 (11.2-27.8)	33.75 (18.4-49.1)
Feberkramper (N = 1)	1	0
Tid til feberkrampe*	33	-

*Tid i dage siden administration af intervention

	MMR	Placebo
Antigen test positivitet		
Rhinovirus	1	1
RSV	4	2
Intet swap resultat, klinisk diagnose		
Bronchitis	4	0
Pseudocroup	1	1
Total	10	4

Samme sikkerhed i de præmaturt fødte spædbørn!

Interaktionsanalyser er blevet udført for præmature for alle reactogenicitetssymptomer and SAE'r (SAE N=1 for MMR, N=1 for placebo). Alle disse analyser viste lignende eller lavere risiko for adverse outcomes for de præmature spædbørn sammenlignet med spædbørn født til termin.

1

MFR vaccination ved 5-7-måneders-alderen er **sikkert. Ingen significant forskel i bivirkningshyppighed!**

3

Immunogenicitet er **lavere i yngre spædbørn**, men kan boostes.
MFR < 12 måneder skal betragtes som en MFR0-dosis

2

Symptomer er almindelige og rapportering påvirkes af deltagelse i et studie.

4

Klinisk beskyttelse mod mæslinger kunne ikke evalueres i dette trial – men immunogenicitet er en god proxy (mæslinger og rubella)

MMR STUDY

Involverede

Trial-personale og kollegaer (fotorækkefølge): Jesper Kiehn Sørensen, Julie Elkjær Møller, Anna Wandahl, Jannet Svensson, Dorthe M. Vittrup, Lone Graff Stensballe, Tina Bruun, Anne Cathrine Zimakoff, Michelle Malon, Caroline Fleming and Andreas Jensen (ikke på billedet)

Medicinstuderende og assisterende læger: Ann-Britt Kirkedal, Rikke Svensson, Emma Bay, Emma Hatley, Emma Hoppe, Marie Ryberg, Salma Charabi og Ida Lind

Samarbejdspartnere: Søren Buus (KU), Nikolai S. Kirkby (Rigshospitalet), Eric Simoes (CU Anschutz), Susette Audet (US FDA), Jakob Hjort (AU) og Sektion for Eksterne Projekter, Biokemi, RH

Slide overview

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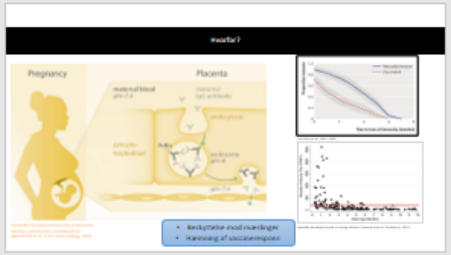

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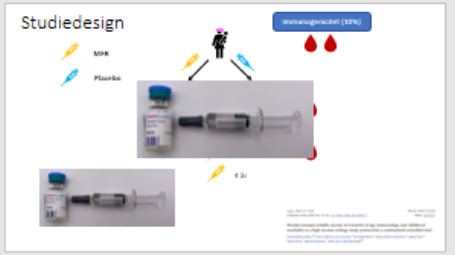

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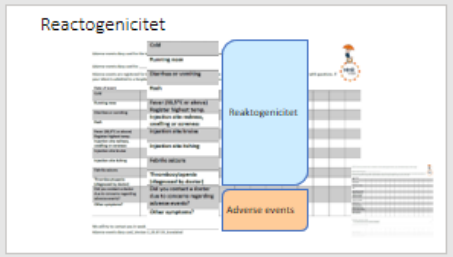

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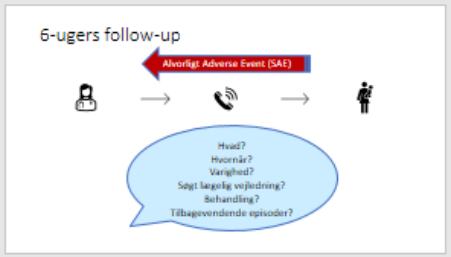

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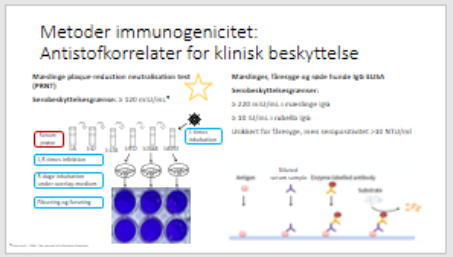

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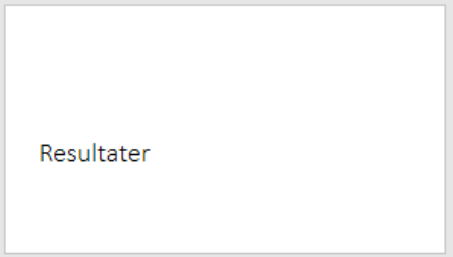

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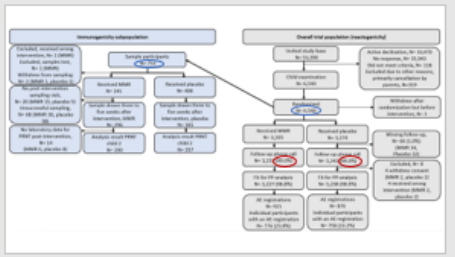

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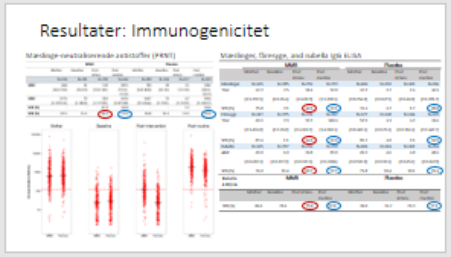

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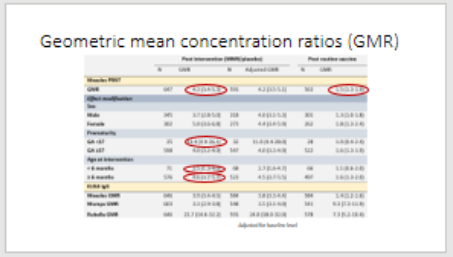

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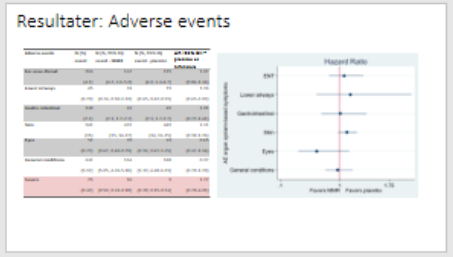

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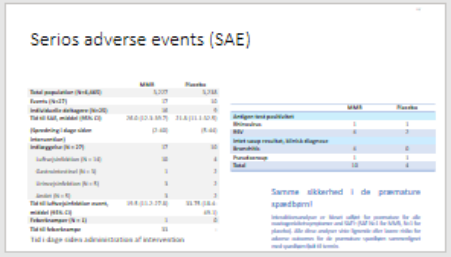

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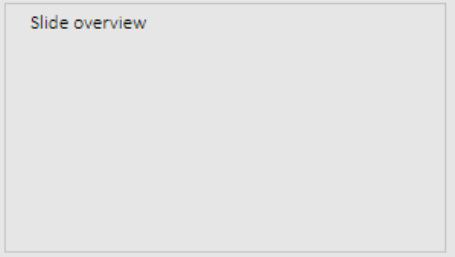

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