Maternal vaccination and neonatal benefits

Focus on RSV and CMV

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Overview

- RSV
  - Burden of disease
  - Key areas to target
  - Vaccine trials
- CMV
  - Congenital CMV
  - Screening, Vaccination or antenatal treatment
  - Vaccine trials

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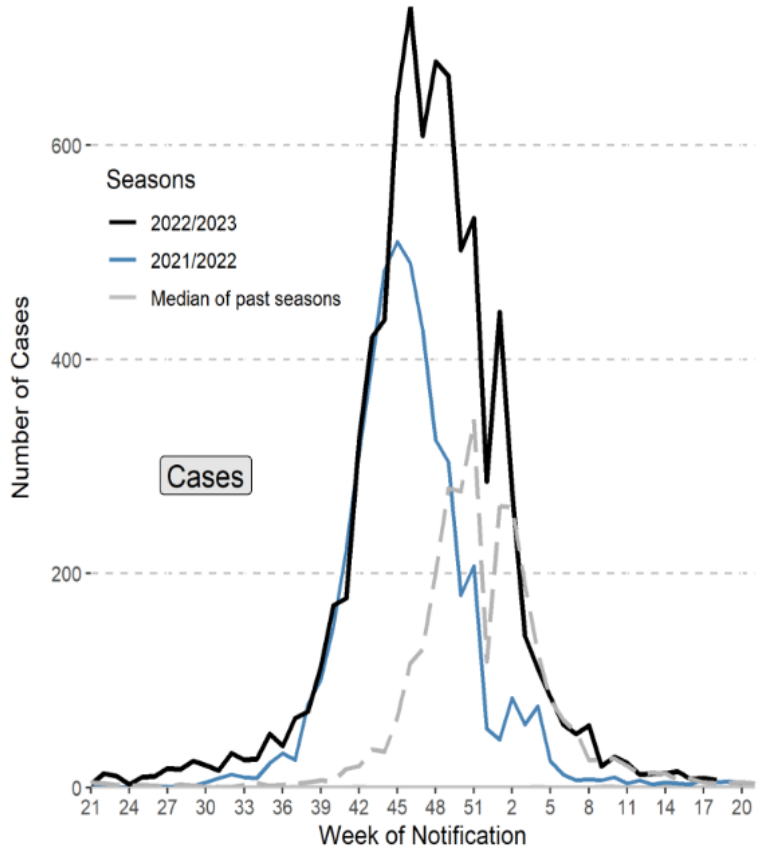
RSV

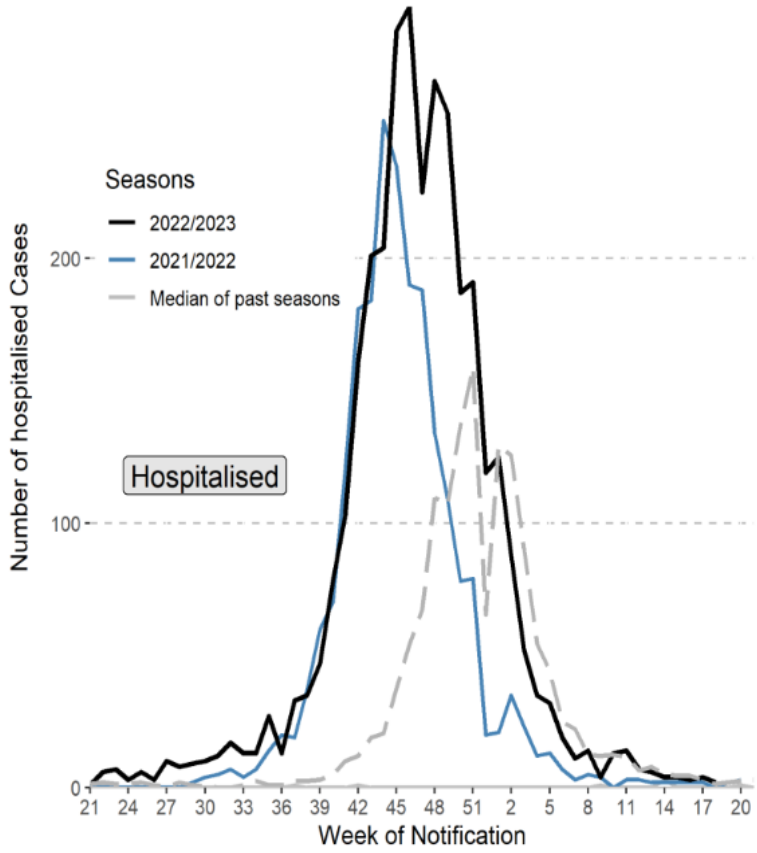
- Common cause of URTI and bronchiolitis
- Cause of medical admissions to hospitals in the Winter, usually September to December
- Can cause infections in adults, but usually mild apart from in at-risk patients.
- Risk factors for RSV hospitalization are[1]:
  - White ethnicity, Born between July and December
  - Older siblings or relatives with asthma
  - Neonatal respiratory morbidity

1. Sheridan Pereira et al PIDJ 2016

HSE Winter Infection Report

RSV cases and hospitalisation trends





RSV vaccine programme

- Aims:
  - To reduce PICU admissions?
  - To reduce hospital admissions?
  - To reduce community illness?
- Extreme premature babies won't get significant transplacental immunity from vaccinated mothers, yet these are the highest risk
- Costs: Could you drop palivizumab prophylaxis?

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The Journal of Infectious Diseases
MAJOR ARTICLE
IDSA Infectious Diseases Society of America
hivma hiv medicine association
OXFORD

Safety and Immunogenicity of an Investigational Respiratory Syncytial Virus Vaccine (RSVPreF3) in Mothers and Their Infants: A Phase 2 Randomized Trial

- Observer blinded, Placebo controlled, RCT
- Placebo Vs 60microg Vs 120microg RSV PreF3 vaccine in late second or third trimester
- Watched for side effects and laboratory evidence of immunity
- GSK vaccine

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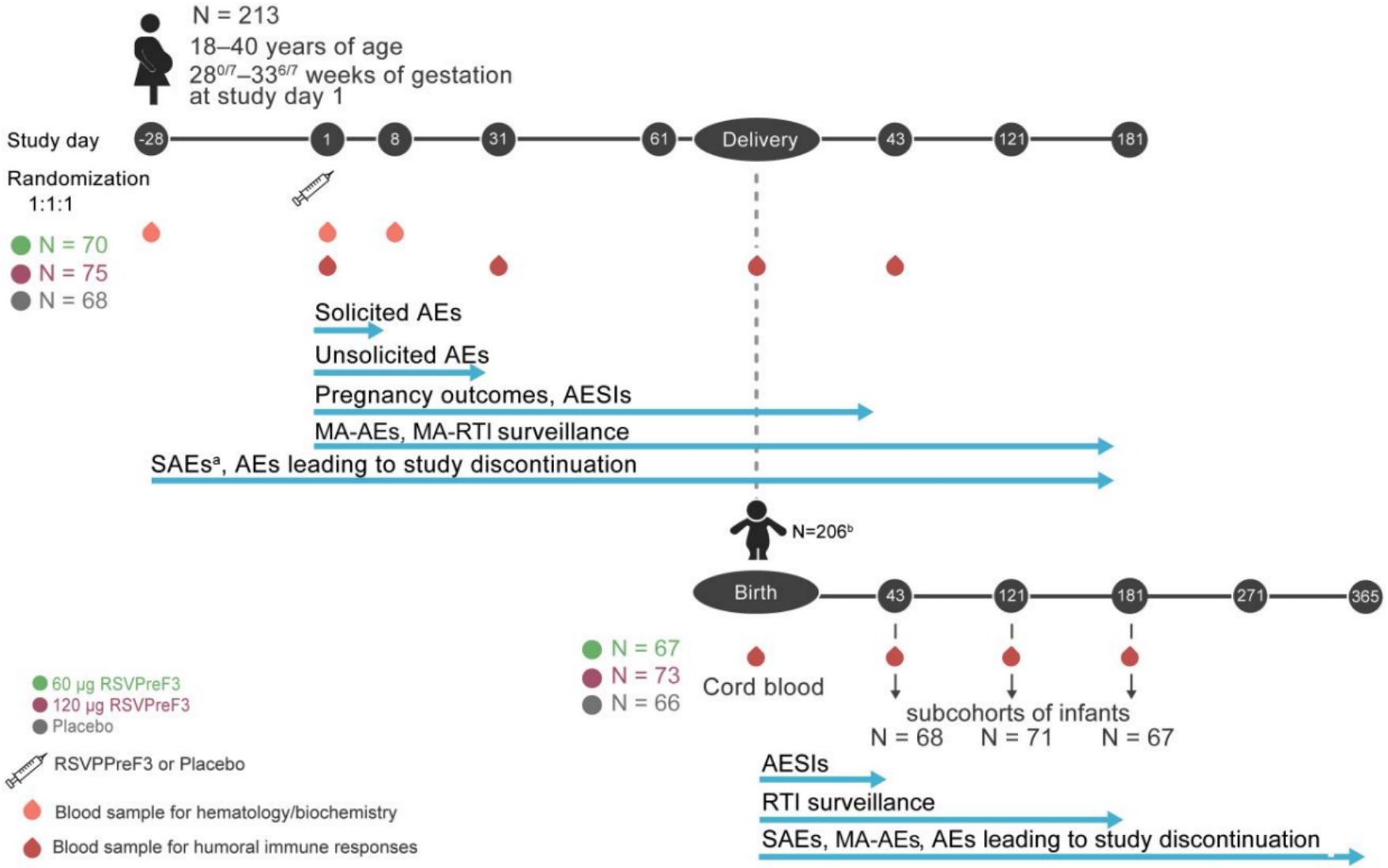

Figure 1. Study design. Abbreviations: AE, adverse event; AESI, adverse event of special interest; MA-AE, medically attended AE; MA-RTI, medically attended respiratory tract infection; N, number of participants; RSVPreF3, respiratory syncytial virus prefusion protein vaccine; RTI, respiratory tract infection; SAE, serious adverse event. [a]Only SAEs related to study participation were recorded from day −28 until vaccination; from vaccination through study end, all SAEs were recorded; [b]207 infants were delivered but 1 woman refused infant participation.

Bebia et al, JID 2023

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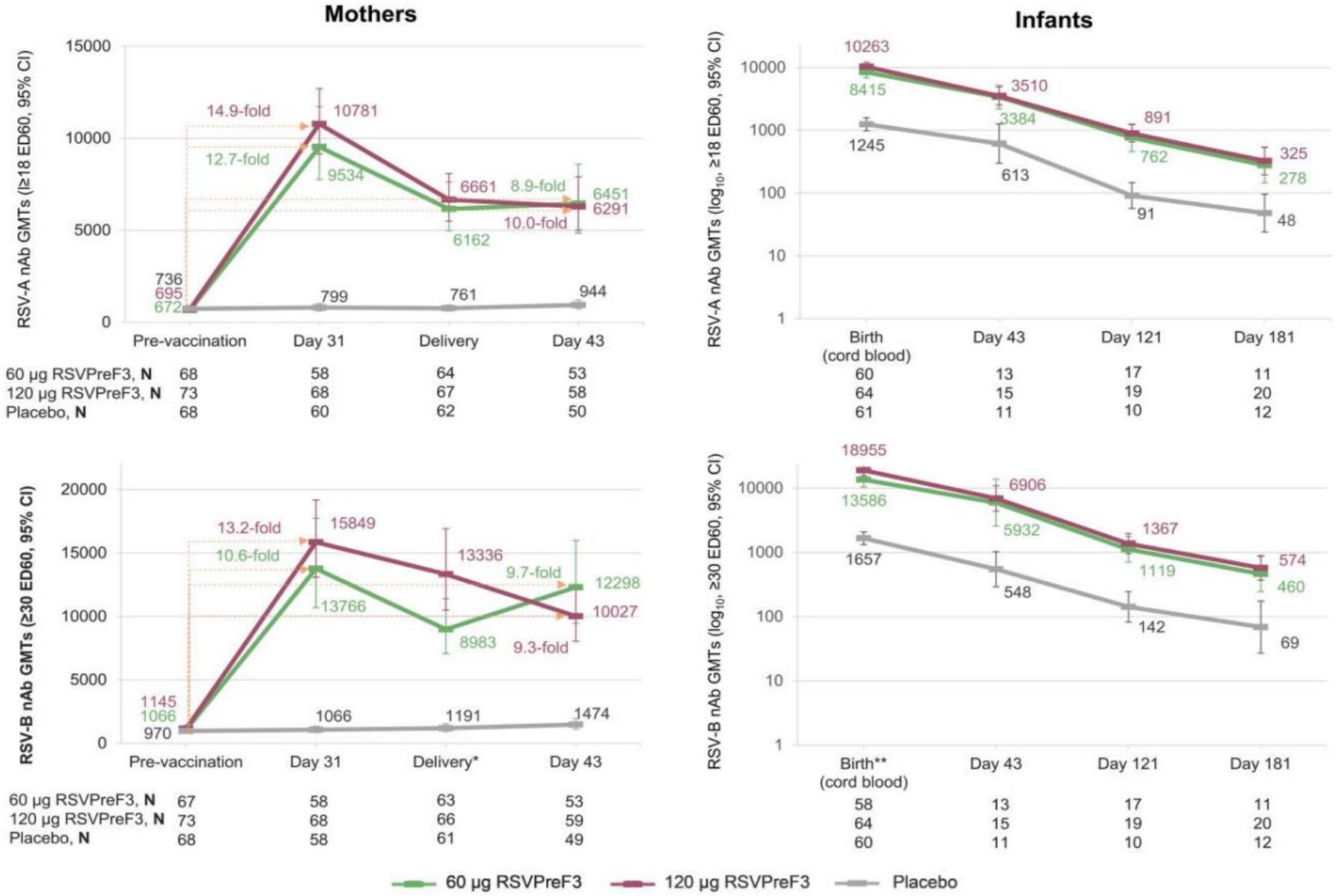

Figure 5. RSV-A and RSV-B nAb GMTs in mothers and infants. *, ** Difference statistically significant between the 60 and 120 µg RSVPreF3 groups (GMT ratios, *1.49 [95% CI, 1.11–2.01] and **1.41 [95% CI, 1.07–1.86]). Abbreviations: CI, confidence interval; ED, estimated dilution; GMT geometric mean titer; N, number of participants; nAb, neutralizing antibody; RSVPreF3, respiratory syncytial virus prefusion protein vaccine.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 20, 2023 VOL. 388 NO. 16

Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants

B. Kampmann, S.A. Madhi, I. Munjal, E.A.F. Simões, B.A. Pahud, C. Llapur, J. Baker, G. Pérez Marc, D. Radley, E. Shittu, J. Glanternik, H. Snaggs, J. Baber, P. Zachariah, S.L. Barnabas, M. Fausett, T. Adam, N. Perreras, M.A. Van Houten, A. Kantele, L.-M. Huang, L.J. Bont, T. Otsuki, S.L. Vargas, J. Gullam, B. Tapiero, R.T. Stein, F.P. Polack, H.J. Zar, N.B. Staerke, M. Duron Padilla, P.C. Richmond, K. Koury, K. Schneider, E.V. Kalinina, D. Cooper, K.U. Jansen, A.S. Anderson, K.A. Swanson, W.C. Gruber, and A. Gurtman, for the MATISSE Study Group*

- Phase 3, Double Blinded, Multinational
- Placebo Vs 120microg bivalent RSV prefusion F protein based vaccine
- Given 24-36 weeks pregnant
- Pfizer

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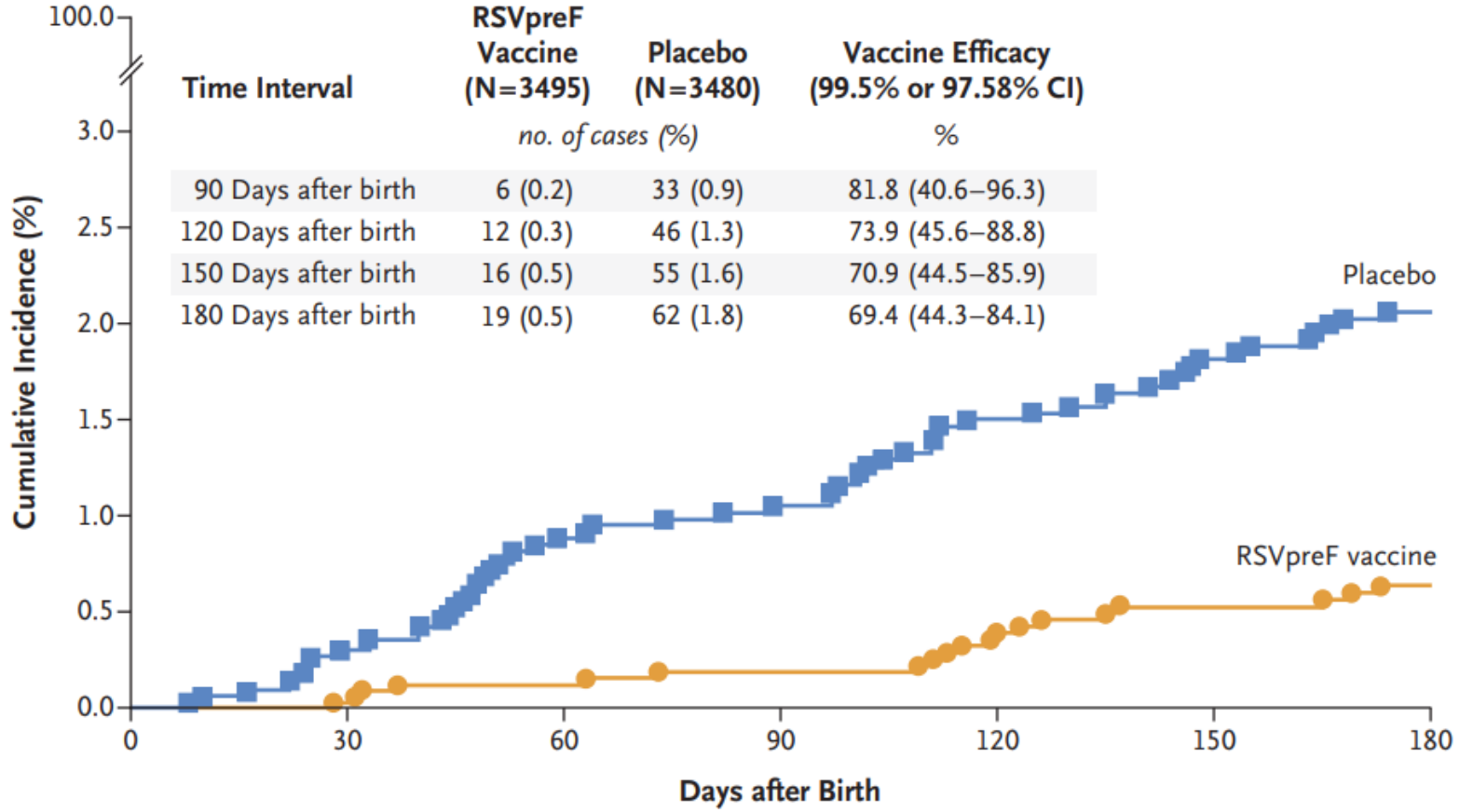
Kampmann et al. NEJM 2023,

A Medically Attended Severe RSV-Associated Lower Respiratory Tract Illness

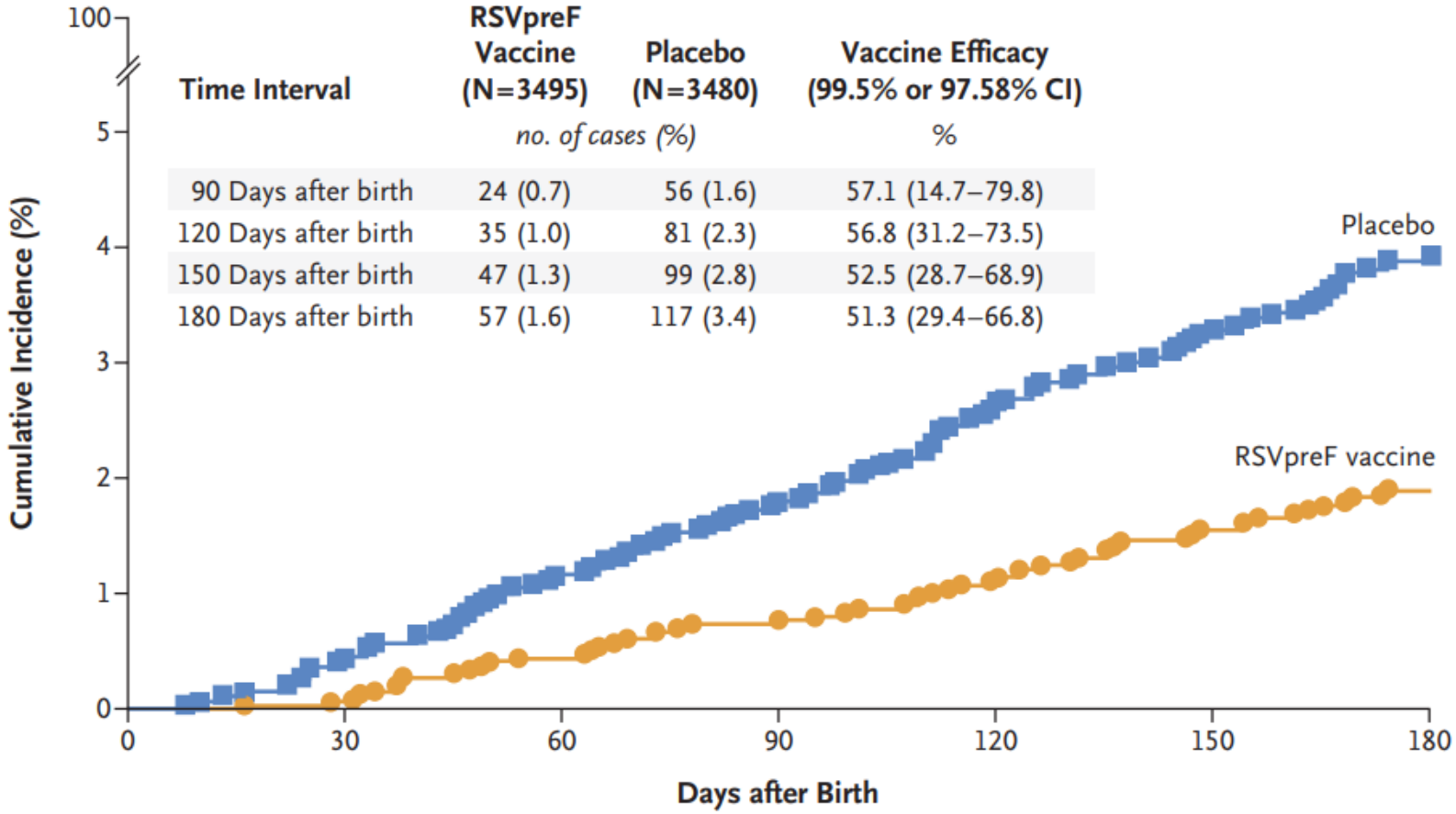
Time Interval	RSVpreF Vaccine (N=3495)	Placebo (N=3480)	Vaccine Efficacy (99.5% or 97.58% CI)
	no. of cases (%)		%
90 Days after birth	6 (0.2)	33 (0.9)	81.8 (40.6–96.3)
120 Days after birth	12 (0.3)	46 (1.3)	73.9 (45.6–88.8)
150 Days after birth	16 (0.5)	55 (1.6)	70.9 (44.5–85.9)
180 Days after birth	19 (0.5)	62 (1.8)	69.4 (44.3–84.1)



No. at Risk							
Placebo	3480	3292	2973	2899	2833	2776	2749
RSVpreF vaccine	3495	3349	3042	2981	2916	2867	2820

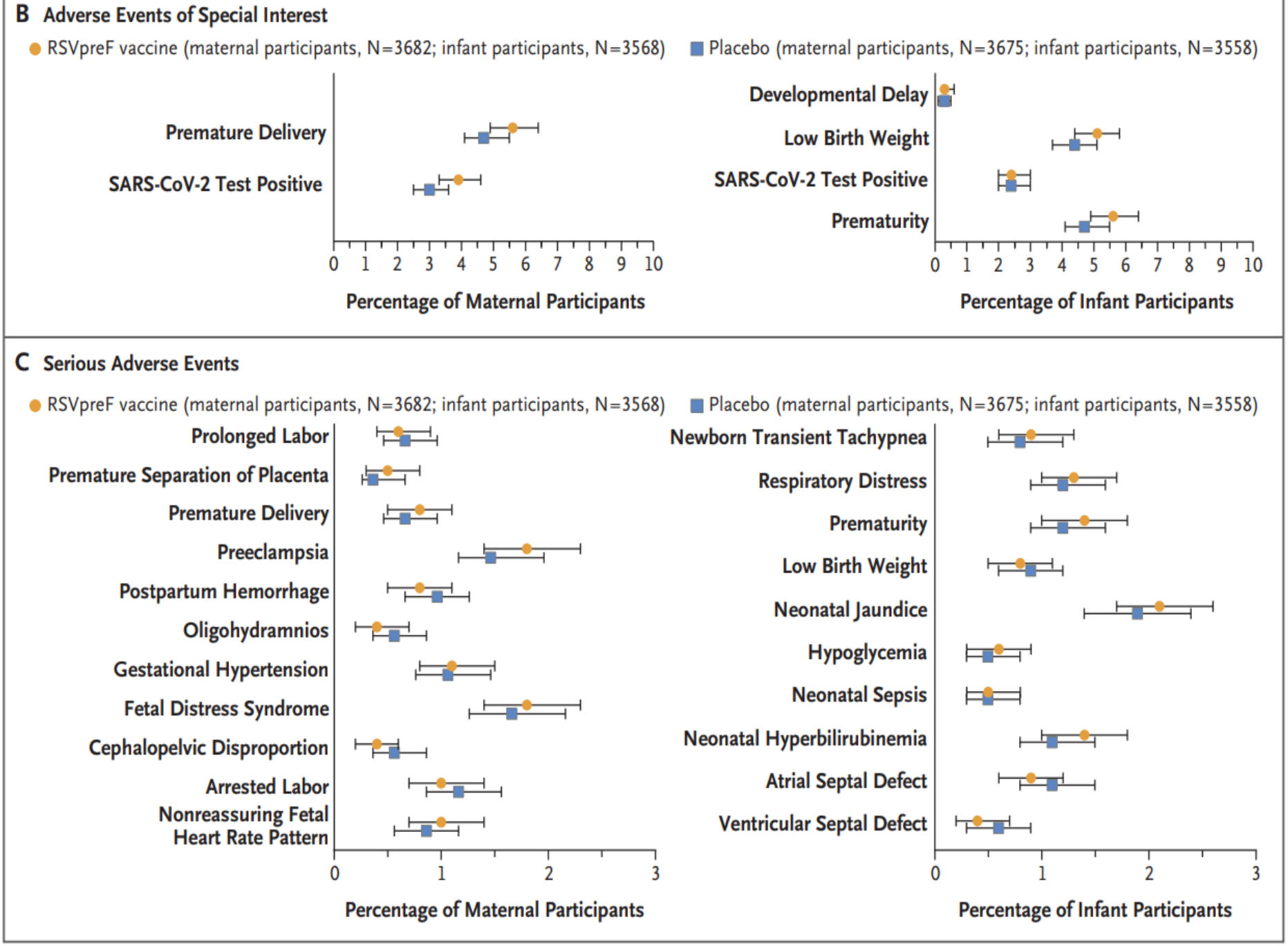
B Medically Attended RSV-Associated Lower Respiratory Tract Illness

Time Interval	RSVpreF Vaccine (N=3495)	Placebo (N=3480)	Vaccine Efficacy (99.5% or 97.58% CI)
	no. of cases (%)		%
90 Days after birth	24 (0.7)	56 (1.6)	57.1 (14.7–79.8)
120 Days after birth	35 (1.0)	81 (2.3)	56.8 (31.2–73.5)
150 Days after birth	47 (1.3)	99 (2.8)	52.5 (28.7–68.9)
180 Days after birth	57 (1.6)	117 (3.4)	51.3 (29.4–66.8)



No. at Risk

Placebo	3480	3288	2964	2879	2804	2738	2700
RSVpreF vaccine	3495	3348	3035	2968	2898	2845	2792


B Adverse Events of Special Interest
RSVpreF vaccine (maternal participants, N=3682; infant participants, N=3568)
Placebo (maternal participants, N=3675; infant participants, N=3558)
Premature Delivery
SARS-CoV-2 Test Positive
0 1 2 3 4 5 6 7 8 9 10
Percentage of Maternal Participants
Developmental Delay
Low Birth Weight
SARS-CoV-2 Test Positive
Prematurity
0 1 2 3 4 5 6 7 8 9 10
Percentage of Infant Participants
C Serious Adverse Events
RSVpreF vaccine (maternal participants, N=3682; infant participants, N=3568)
Placebo (maternal participants, N=3675; infant participants, N=3558)
Prolonged Labor
Premature Separation of Placenta
Premature Delivery
Preeclampsia
Postpartum Hemorrhage
Oligohydramnios
Gestational Hypertension
Fetal Distress Syndrome
Cephalopelvic Disproportion
Arrested Labor
Nonreassuring Fetal Heart Rate Pattern
0 1 2 3
Percentage of Maternal Participants
Newborn Transient Tachypnea
Respiratory Distress
Prematurity
Low Birth Weight
Neonatal Jaundice
Hypoglycemia
Neonatal Sepsis
Neonatal Hyperbilirubinemia
Atrial Septal Defect
Ventricular Septal Defect
0 1 2 3
Percentage of Infant Participants

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Respiratory Syncytial Virus Vaccination during Pregnancy and Effects in Infants

S.A. Madhi, F.P. Polack, P.A. Piedra, F.M. Munoz, A.A. Trenholme, E.A.F. Simões, G.K. Swamy, S. Agrawal, K. Ahmed, A. August, A.H. Baqui, A. Calvert, J. Chen, I. Cho, M.F. Cotton, C.L. Cutland, J.A. Englund, A. Fix, B. Gonik, L. Hammitt, P.T. Heath, J.N. de Jesus, C.E. Jones, A. Khalil, D.W. Kimberlin, R. Libster, C.J. Llapur, M. Lucero, G. Pérez Marc, H.S. Marshall, M.S. Masenya, F. Martinón-Torres, J.K. Meece, T.M. Nolan, A. Osman, K.P. Perrett, J.S. Plested, P.C. Richmond, M.D. Snape, J.H. Shakib, V. Shinde, T. Stoney, D.N. Thomas, A.T. Tita, M.W. Varner, M. Vatish, K. Vrbicky, J. Wen, K. Zaman, H.J. Zar, G.M. Glenn, and L.F. Fries, for the Prepare Study Group*

- RSV Fusion F protein Nanoparticle vaccine Vs Placebo
- RCT, Placebo controlled, Given 28-36 weeks
- Novavax

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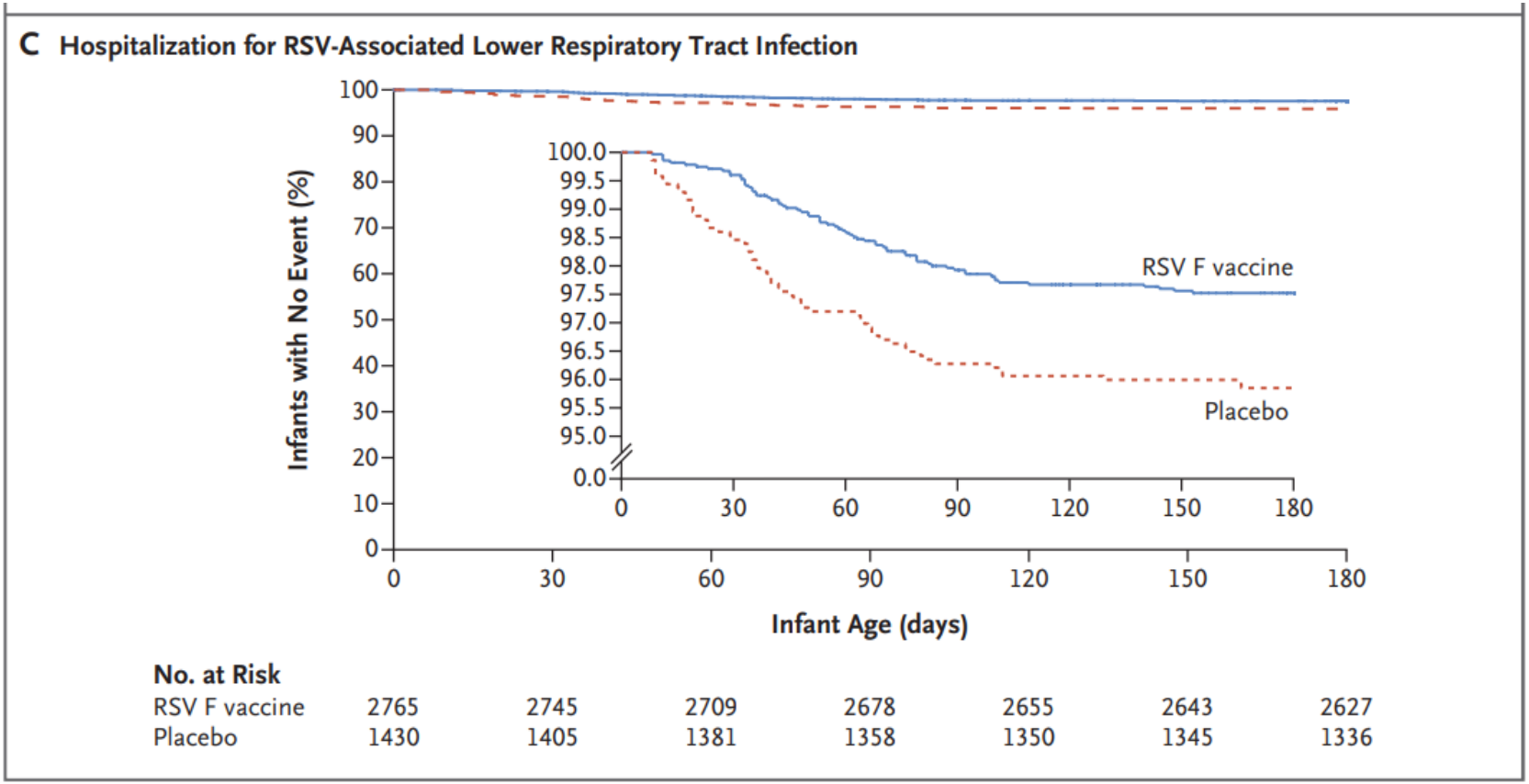
Madhi et al, NEJM



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Antibiotic Stewardship

- Lewnard et al ., PNAS 2022
- Double blind RCT, 11 countries
- Placebo vs Experimental RSV vaccine
- Statistically significant reduction in antimicrobial prescriptions in first 3 months of life
- Higher effect in high income countries

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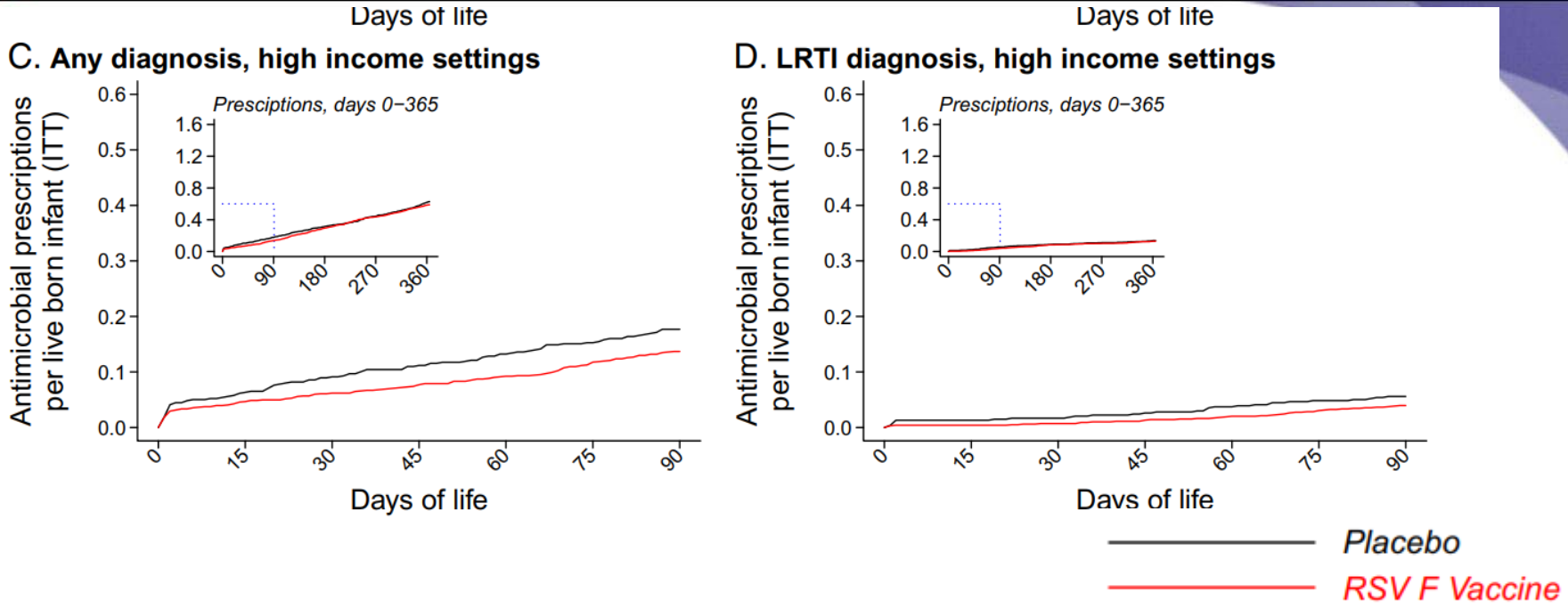

Table 2. VE against antimicrobial prescriptions among infants within the ITT population

	Through 90 d from birth			Through end of follow-up		
Setting and end point	RSV F vaccine, no. of events per 100 person-y (no. of events)	Placebo, no. of events per 100 person-y (no. of events)	VE (95% CI), %	RSV F vaccine, no. of events per 100 person-y (no. of events)	Placebo, no. of events per 100 person-y (no. of events)	VE (95% CI), %
All countries, person-y	730	379		2,908	1,504	
All antimicrobial prescriptions	133.7 (976)	148.7 (563)	12.9 (1.3–23.1)	111.2 (3,234)	112.8 (1,696)	3.4 (–4.8–11.1)
All antimicrobial prescriptions for LRTI*	71.0 (518)	82.2 (311)	16.6 (1.4–29.4)	61.8 (1,797)	62.4 (939)	3.3 (–7.6–13.1)
HICs	242	132		953	516	
All antimicrobial prescriptions	55.8 (135)	72.2 (95)	20.2 (–10.1–42.2)	62.8 (599)	66.1 (341)	5.2 (–14.2–21.3)
All antimicrobial prescriptions for LRTI*	10.3 (25)	20.5 (27)	49.4 (3.5–73.5)	10.4 (99)	12.6 (65)	13.2 (–30.6–42.4)
LMICs	488	247		1,955	988	
All antimicrobial prescriptions	172.3 (841)	189.5 (468)	10.9 (–2.1–22.2)	134.8 (2,635)	137.1 (1,355)	2.8 (–6.5–11.3)
All antimicrobial prescriptions for LRTI*	101.0 (493)	115.0 (284)	12.8 (–3.6–26.7)	86.9 (1,698)	88.5 (874)	2.2 (–9.2–12.5)

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RSV vaccines

- Several in development (i.e. Pfizer, Novavax, GSK)
- No clear safety warnings to date
- Will be given late second trimester or third
- Reduction in RSV bronchiolitis requiring
  - Medical attention
  - Supplemental oxygen
  - Antibiotic usage
  - This would have huge impact on paediatric services
- Unclear what benefit for extreme premature infants (i.e. 24-28 weeks)
- Cost analysis will need to also consider palivizumab for this at risk-group

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CMV vaccines

- Most common cause of hearing loss, and also can lead to severe developmental delay
- Four main options to reduce disease
  - Screening mothers: May miss cases if only screen at 14 weeks gestation
  - Antenatal treatment: Concerns over tolerability of high dose aciclovir, risk with ganciclovir
  - Screening babies: Time consuming and large volume of work
  - Vaccines?

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ORIGINAL ARTICLE

Vaccine Prevention of Maternal Cytomegalovirus Infection

Robert F. Pass, M.D., Changpin Zhang, M.D., Ashley Evans, M.D., Tina Simpson, M.D., William Andrews, M.D., Meei-Li Huang, Ph.D., Lawrence Corey, M.D., Janie Hill, R.N., Elizabeth Davis, R.N., M.P.H., Cynthia Flanigan, B.S., and Gretchen Cloud, M.S.

- Phase 2, Randomised, Double Blind
- Placebo Vs recombinant CMV envelope glycoprotein B with MF59 adjuvant
- Done on non-pregnant women

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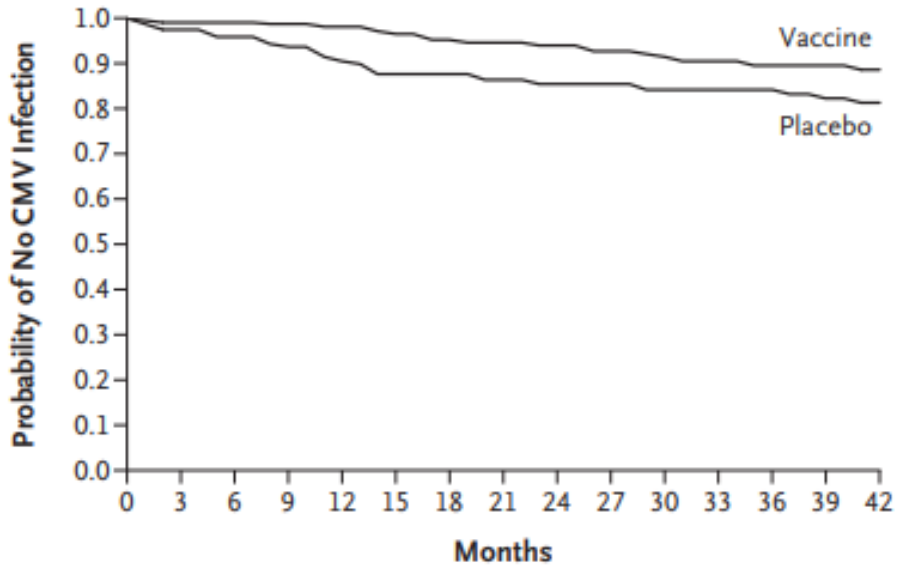
Benefit of CMV vaccine



No. at Risk

Vaccine	225	213	211	204	195	178	160	154	145	136	127	116	112	98	88
Placebo	216	193	185	178	169	153	141	128	121	114	108	104	97	87	75

Figure 2. Kaplan–Meier Estimates of Probability of Remaining Free of CMV Infection.

Up to 42 months after study enrollment, subjects in the vaccine group were more likely to remain free of CMV infection than were subjects in the placebo group (P=0.02). In the vaccine group, 18 subjects were found to have CMV infection, as compared with 31 in the placebo group.

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Table 1. Results of CMV vaccination in the guinea pig model of cCMV and women of child-bearing age.

Vaccine Platform	Efficacy in the guinea pig model of cCMV	Vaccine-elicited responses and protection in women of child-bearing age
Live-attenuated Vaccines [1,12]	*Reduced the rate of congenital infection (of live pups) by up to 51% [18]	Elicited short-lived, humanCMV-neutralizing antibody responses in healthy, seronegative women (peak geometric mean titer = 349)
	Reduced the rate of pup mortality by up to 55%	Did not protect against primary HCMV infection of women with infants actively shedding HCMV
Recombinant Protein Vaccines (gB) [1,7]	Reduced the rate of congenital infection (of live pups) by up to 36%	Elicited HCMV-neutralizing antibody responses in seronegative adults when given in three doses with MF59 adjuvant, which exceeded the levels found in naturally seroimmune individuals (peak geometric mean titer = 14,098)
	Reduced the rate of pup mortality by up to 62%	Proved to be 50% efficacious at preventing primary HCMV infection in women of child-bearing age
Viral Vector Vaccines (Alphavirus) [13,14]	Studies conducted using replicon expressing HCMV pp65 homolog guinea pig CMV (GPCMV) UL83	Studies conducted using replicon expressing HCMV gB or pp65/IE1 fusion protein
	Reduced the rate of congenital infection by 38%	Elicited HCMV-neutralizing antibodies (peak GMT = 218) and functional, HCMV-specific T cell responses (peak mean SFC = 138 gB; 504 pp65; 113 IE1) in healthy, seronegative adults
	Reduced the rate of pup mortality by 44%	
CMV DNA Vaccines [1,15,16]	Studies conducted using GPCMV gB or HCMV pp65 homolog GPCMV UL83	Administration of bivalent HCMV gB/pp65 vaccine alone to HCMV-seronegative subjects resulted in modest, gB-specific antibody responses in 22% of vaccinees and T cell responses in 29% and 38% for gB and pp65, respectively
	Reduced the rate of congenital infection by 9% and 36% for gB and UL83 vaccines, respectively	Vaccination of HCMV-seronegative adults with a trivalent HCMV gB/pp65/IE1 vaccine effectively primed memory T cell responses to live-attenuated vaccines
	Neither gB or UL83 vaccine had an effect on the rate of pup mortality	
Antibody Infusion [11,17,18]	Studies used hyperimmune anti-gB serum or anti-gH/gL monoclonal antibody	HCMV hyperimmune globulin was administered to women who acquired primary HCMV infection between five and 26 weeks of gestation every four weeks
	Infusion with anti-gB serum reduced the rate of congenital infection by up to 39%	Treatment with HCMV hyperimmune globulin reduced the rate of congenital CMV transmission by 14% (95% CI = -3, 31; $p = 0.13$)
	Infusion with anti-gB serum and gH/gL monolconal antibody reduced the rate of pup mortality by 100% and 35%, respectively	

*Reduced rates of congenital infection and pup mortality in guinea pigs was calculated by subtracting the rates observed in treated dams from untreated dams.

doi:10.1371/journal.ppat.1005355.t001

CMV vaccines

- Vaccine appears to reduce CMV related disease, with no major safety flags to date
- CMV vaccination programme would face several challenges
  - Timing of vaccine: Needs to be pre-conception
  - Is antenatal screening or infants screening more cost-effective?
  - Is antenatal treatment a better strategy?

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Head to Head

	CMV	RSV
Timing	Pre-conception	Late T2 or T3
Vaccine options	Limited	Several
Best strategy	Need to compare to screening or treatment options (both antenatal or postnatal)	Need to compare to palivizumab, or possibly a hybrid model
Health benefits to child	Reduction in developmental delay and hearing loss	Reduced severity of bronchiolitis
Health benefits to the system	Savings on long term care	Reduction in hospitalization and medical attendances.
"Achilles Heel"	Is vaccination the best strategy, compared to treatment or screening?	What about extreme prems 24-28 weeks who are the highest risk? Role for Palivizumab?

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Way forward

- Critical to have robust cost effectiveness and technical assessments done of the potential CMV and RSV vaccines
- Important to consider both benefit to the individual but also to the entire health system
- Important to consider how it fits in to a schedule with other maternal vaccines
  - Pertussis, influenza, SARS Cov2,
  - Group B Strep vaccine on the horizon
  - Pre-conception/Postnatal vaccines: Rubella, Varicella

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Thank you!

Rotunda in the 1800s

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