



**WITS VIDA**  
UNIVERSITY OF THE WITWATERSRAND  
VACCINES & INFECTIOUS DISEASES ANALYTICS



**KEMRI** | Wellcome Trust

# Cracking the Code: Identifying RSV Correlates of Protection in a South African Vaccine Effectiveness Trial

Alane Izu

2025 December

Montreal, Canada

UNIVERSITY OF THE  
WITWATERSRAND,  
JOHANNESBURG

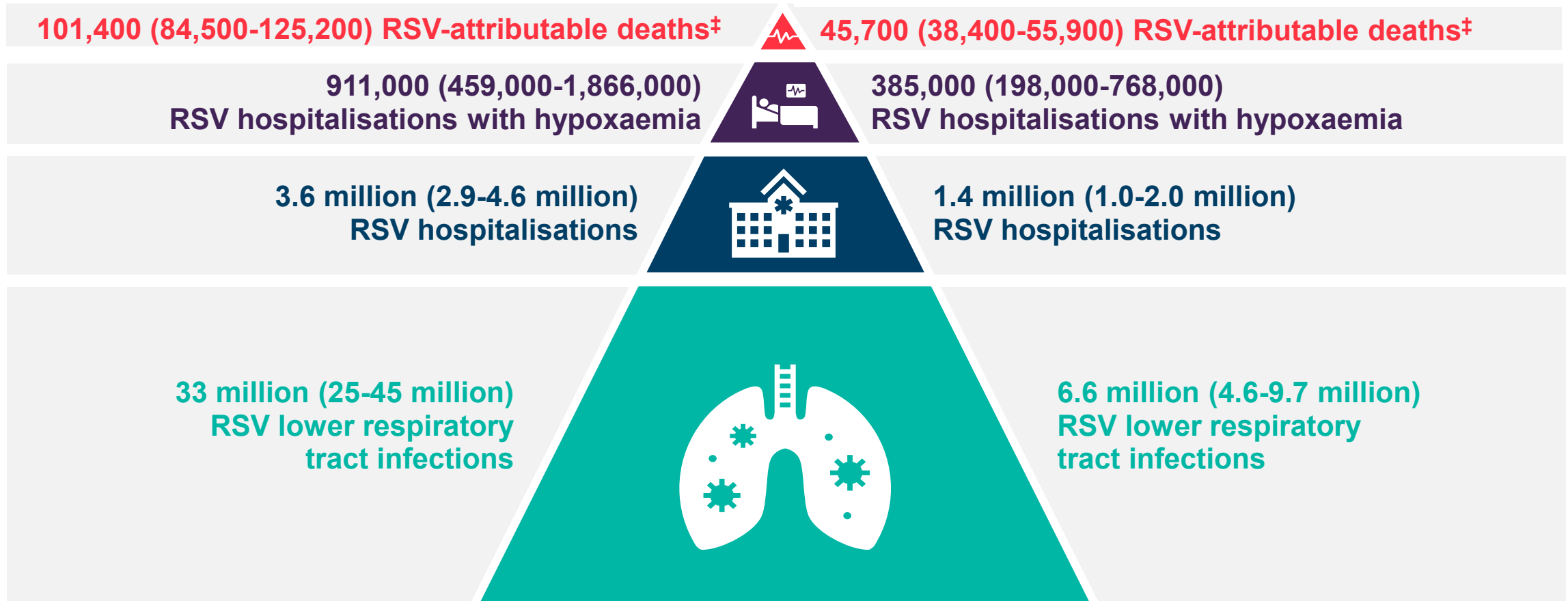


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# RSV leads to substantial annual global burden of disease\*†

## Children aged 0-60 months

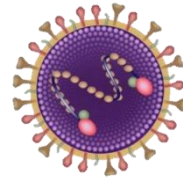
## Infants aged 0-6 months



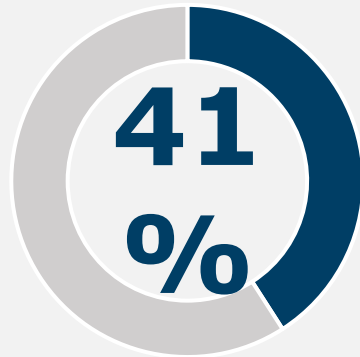
\*The burden of RSV-associated acute lower respiratory infection morbidity and mortality in 2019 for children aged 0-60 months was estimated using a generalised linear mixed-effects model based on a systematic literature review including a total of 481 global studies. †Estimated number of infections, hospitalisations, and deaths for RSV-associated acute LRTI are reported as estimates (uncertainty range). ‡Hospital + community; estimated RSV-attributable in-hospital deaths=26,300 in children aged 0-60 months and 13,300 in infants aged 0-6 months. RSV, respiratory syncytial virus. Li Y ... et al. *Lancet*. 2022;399:2047-2064.

# RSV contributes to significant healthcare system burden

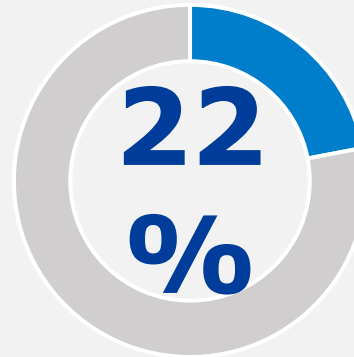
RSV-LRTI hospitalisation data from the first 5 years of the Drakenstein Child Health Study



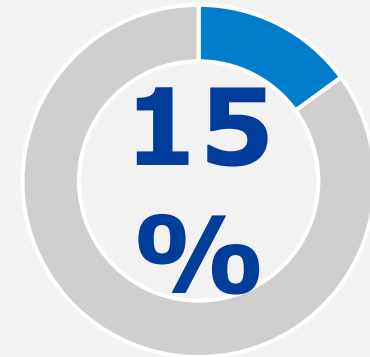
RSV-LRTI accounted for



**LRTI-associated hospitalisations in first 6 months**

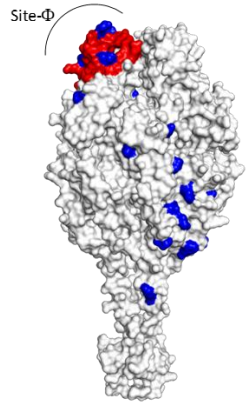


**All-cause hospitalisations in first 6 months**



**All-cause hospitalisations in first 2 years**

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



Stabilized **RSV Bivalent vaccine** can elicit polyclonal vaccine-specific antibodies to protect infants through **6 months** of age<sup>3-6</sup>

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## 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\*



## MATISSE Study

Highly Efficacious **against severe LRTI**

**Final Efficacy:**

**82%**  
3 months


**70%**  
6 months


Efficacy also observed for less severe disease and against RSV A and B


LRTI=Lower Respiratory Tract Infection

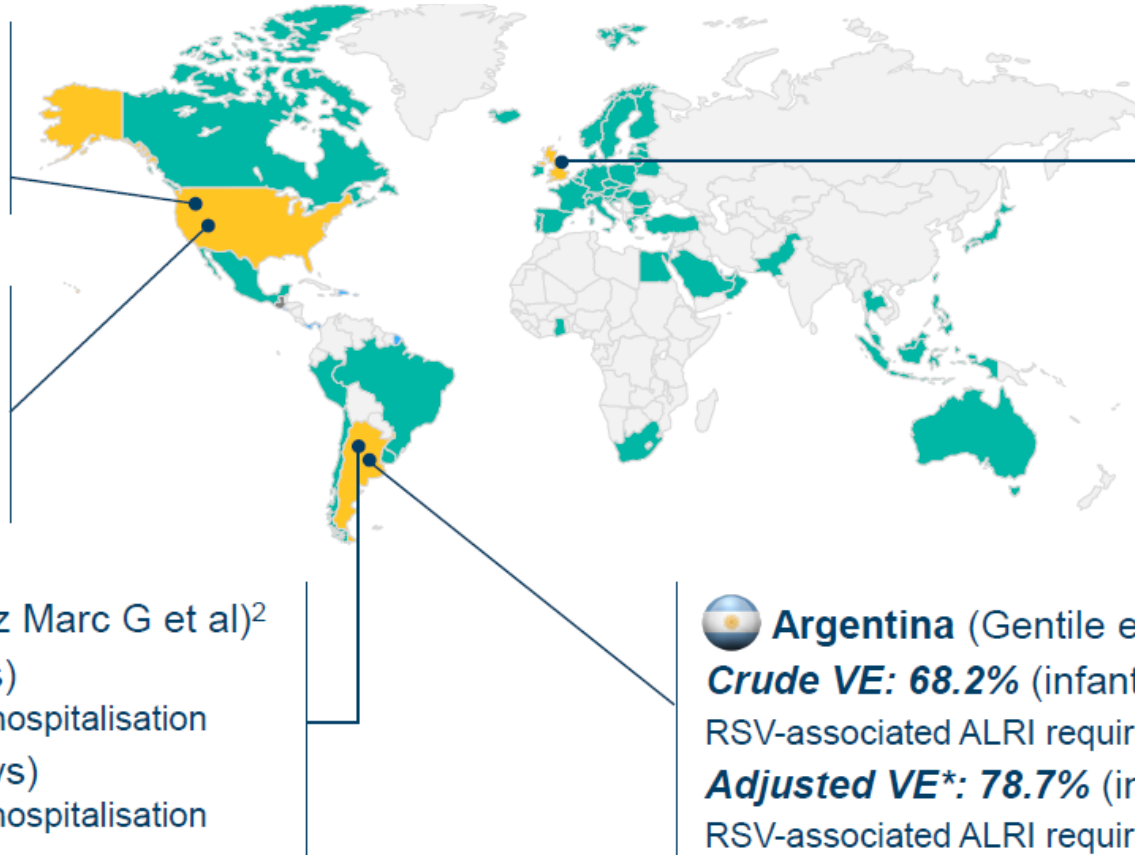
1. Meissner HC. *N Engl J Med.* 2016; 2. Shi T et al., *Lancet.* 2017; 3. Crank et al, *Science* 2019, 365:505-9; 4. Hall et al., *J Infect Dis* 1990; 162:1283-90  
5. Langedijk et al., *Rev Med Virol.* 2021;e2284. <https://doi.org/10.1002/rmv.2284> 6. Simoes E et al. *N Engl J Med* 2022; 386:1615-1626.


# RSVpreF real-world evidence of vaccine effectiveness in helping prevent RSV-associated outcomes in infants.


 **USA (NVSN, ACIP)<sup>1</sup>**  
**Adjusted VE: 70%**  
 (infants <6 months)  
 RSV-associated hospitalisation

 **USA (VISION, ACIP)<sup>1</sup>**  
**Adjusted VE: 79%**  
 RSV-associated hospitalisation  
**Adjusted VE: 54%**  
 RSV-associated ED visits

 **Argentina (BERNI, Pérez Marc G et al)<sup>2</sup>**  
**VE: 78.6%** (infants 0-90 days)  
 RSV-associated LRTD requiring hospitalisation  
**VE: 71.3%** (infants 0-180 days)  
 RSV-associated LRTD requiring hospitalisation



 **UK (Williams TC et al)<sup>4</sup>**  
**Adjusted VE: 58%**  
 RSV-associated ALRI requiring hospitalisation  
 Mothers vaccinated at any time before delivery  
**Adjusted VE: 72%**  
 RSV-associated ALRI requiring hospitalisation  
 Mothers vaccinated >14 days before delivery

 **Argentina (Gentile et al)<sup>3</sup>**  
**Crude VE: 68.2%** (infants <6 months)  
 RSV-associated ALRI requiring hospitalisation  
**Adjusted VE\*: 78.7%** (infants <6 months)  
 RSV-associated ALRI requiring hospitalisation

Jurisdictions that have approved RSVpreF are shown in teal on the map.<sup>5</sup>

\*The effectiveness was adjusted for the independent predictors of RSV infection, including age under 3 months, a history of prematurity, and chronic respiratory disease.<sup>3</sup>

ACIP, Advisory Committee on Immunization Practices; ALRI, acute lower respiratory infection; BERNI, Real-World Impact and Effectiveness of ABRYSV0 Vaccination During Pregnancy Against RSV Illness in Infants; ED, emergency department; LRTD, lower respiratory tract disease; NVSN, New Vaccine Surveillance Network; RSV, respiratory syncytial virus; RSVpreF, respiratory syncytial virus prefusion F; VE, vaccine effectiveness; VISION, Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network

1. MacNeil A. Effectiveness and impact of RSV prevention products in infants during the 2024–2025 RSV season. Presented at ACIP, June 25, 2025. <https://www.cdc.gov/acip/downloads/slides-2025-06-25-26/03-MacNeil-Mat-Peds-RSV-5> [Unpublished]. Accessed July 20, 2025; 2. Pérez Marc G et al. *Lancet Infect Dis*. 2025;May 5 [Online ahead of print]. doi:10.1016/S1473-3099(25)00156-2; 3. Gentile A et al. *Pediatr Infect Dis J*. 2025;May 28 [Online ahead of print]. doi:10.1097/INF.0000000000004878 4. Williams TC et al. *Lancet Child Adolesc Health*. 2025;July 18 [Online ahead of print]. doi:10.1016/S2352-4642(25)00155-5 5. Please slides 25-27 for full references and details on licensures and recommendations.

ORIGINAL ARTICLE

PREPARE

## 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. Martínón-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, and the Prepare Study Group\*

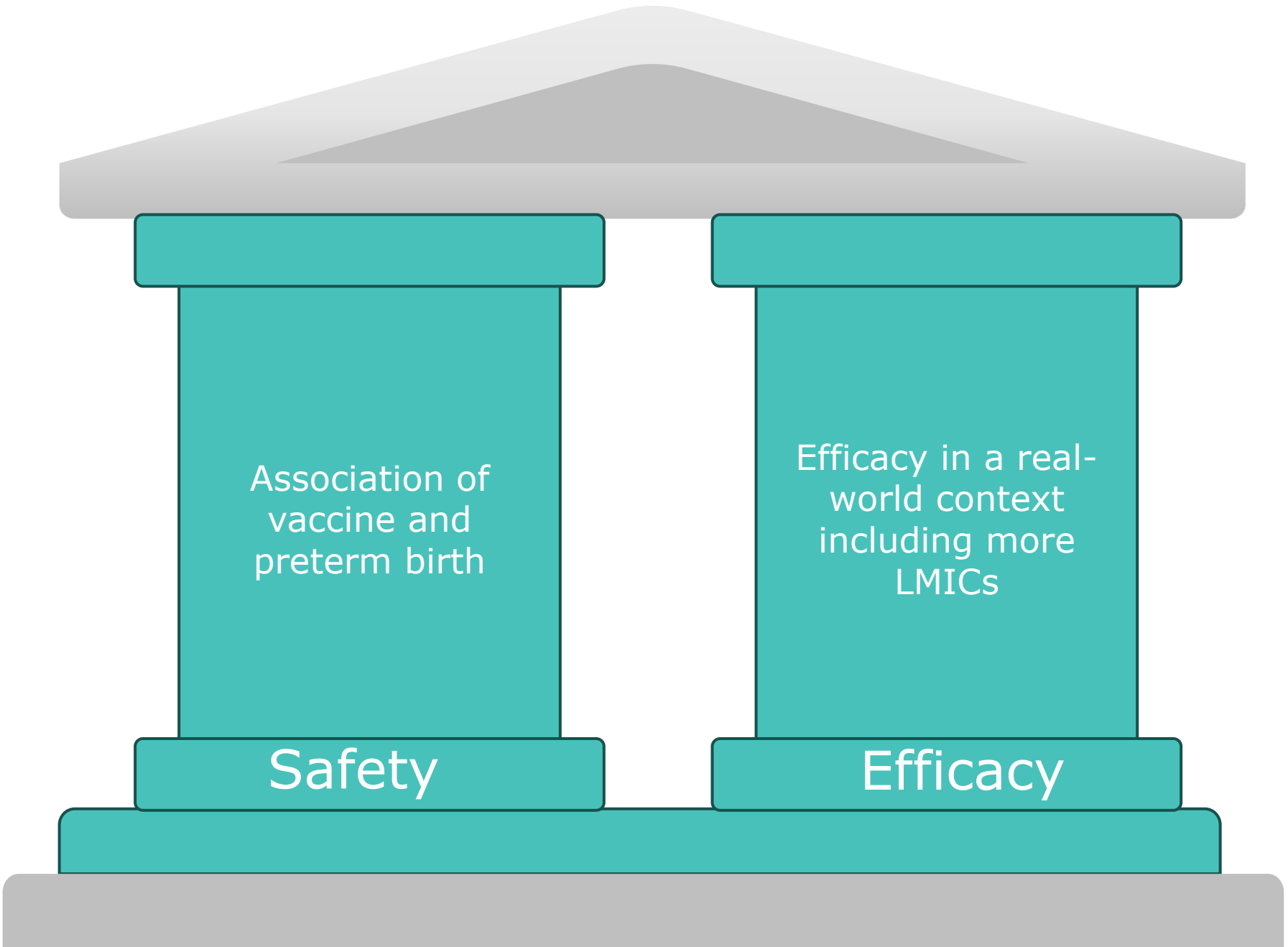
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## RSV Prefusion F Protein–Based Maternal Vaccine — Preterm Birth and Other Outcomes

Ilse Dieussaert, I.R., Joon Hyung Kim, M.D., Sabine Luik, M.D., Claudia Seidl, M.Sc., Wenji Pu, Ph.D., Jens-Ulrich Stegmann, M.D., Geeta K. Swamy, M.D., Peggy Webster, M.D., and Philip R. Dormitzer, M.D., Ph.D.

RSV MAT-009



# Safety ?and? Efficacy

**Safety**

Exclude anyone at higher risk of preterm birth

Include only those that have acceptable ANC



Include everyone!

# Safety and Efficacy

## GA staging

Women need to have ultrasound in first or second trimester

## Preterm risk

Exclude women with history of risk factors associated with preterm birth



## Comorbidities

Not restricting to comorbidities

## Vaccine tolerance

Exclude women experienced SAE associated with vaccine

## Primary objectives:

Evaluate the safety of RSVA/B-preF in relation to preterm births (born at <37 weeks GA) in women with GA staging Level of Certainty (LOC) 1 to 2B at time of enrolment. (US at first or second trimester)

Evaluate the efficacy of RSVA/B-preF against RSV-A or RSV-B subgroup confirmed severe LRTI through to 180 days of age.

# Considerations

## Scientific

- Inclusion/exclusion criteria

## Statistical

- Event driven
- Non-inferior criteria
- Powered for safety (power for efficacy follows)
- Interim analysis

## Operational

- Standard of care
- Data collection
- Licensure of vaccine
- Cultural context

# Sample size consideration re: preterm safety endpoint

Hypothesis: Maternal RSV vaccination does not increase risk of preterm birth by more than 20%.

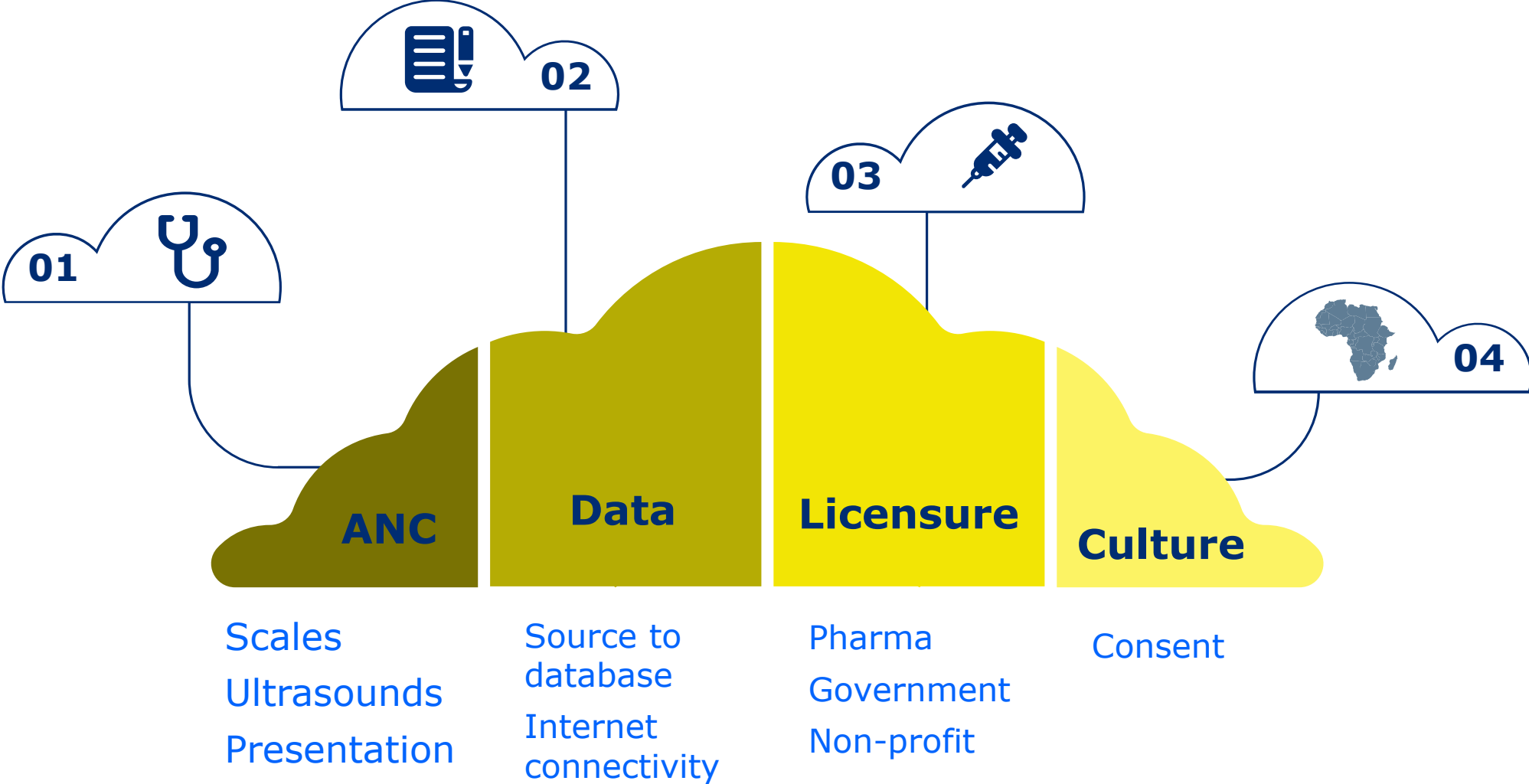
Background preterm birth rate	Type I error = 0.025 Total cases: 949 Total cases in vaccinated: 474	Type I error = 0.05 Total cases: 746 Total cases in vaccinated: 373
5	21089	16578
5.5	19172	15071
6	17574	13815
6.5	16222	12752
7	15063	11841
7.5	14059	11052
<b>8</b>	<b>13181</b>	10361
8.5	12405	9752
9	11716	9210
<b>9.5</b>	<b>11099</b>	8725
10	10544	8289

- Need 949 preterm births (474 in the vaccinated) to accept the null hypothesis with 80% power and a type I error rate of 2.5%, assuming a true RR=1.
- Criterion: Accept hypothesis if upper bound of 95%CI I < 1.2.

# Sample size consideration re efficacy endpoint

Attack rate in placebo	RSV-confirmed severe LRTI (VE = 70%)	All-cause severe LRTI (VE = 40%)
	Total participants 1:1 Expected total cases 40 (9 vaccine arm)	Total participants 1:1 Expected total cases 398 (149 vaccine arm)
<b>5</b>	<b>1369</b>	11056
5.5	1245	10052
6	1140	9214
6.5	1054	8505
7	978	7898
7.5	914	7372
8	856	6912
8.5	805	6505
9	760	6143
9.5	720	5820
<b>10</b>	<b>685</b>	<b>5529</b>

# Operational considerations



# Planning study



Feasibility of enrolment



Preterm birth rate



Assessment of birth outcome



Follow-up of participants



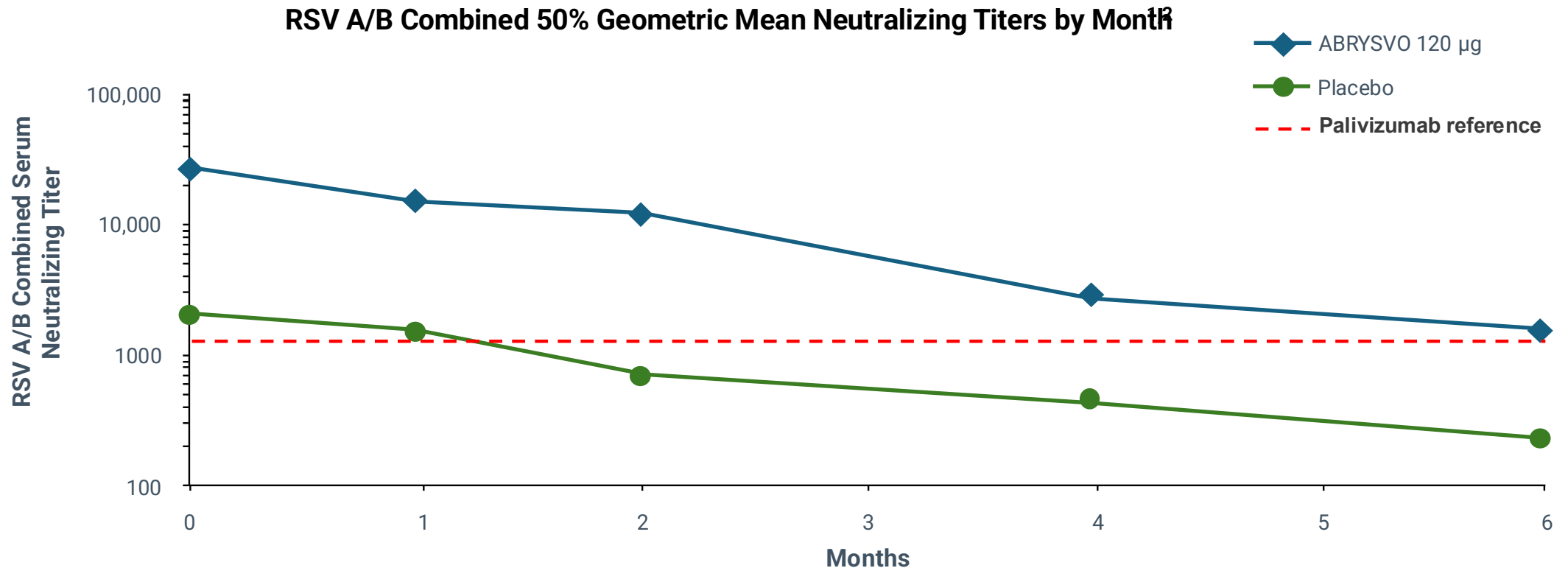
Laboratory, Data, Ethics

# Immunogenicity objectives

Immune response in  
women between  
vaccination and delivery

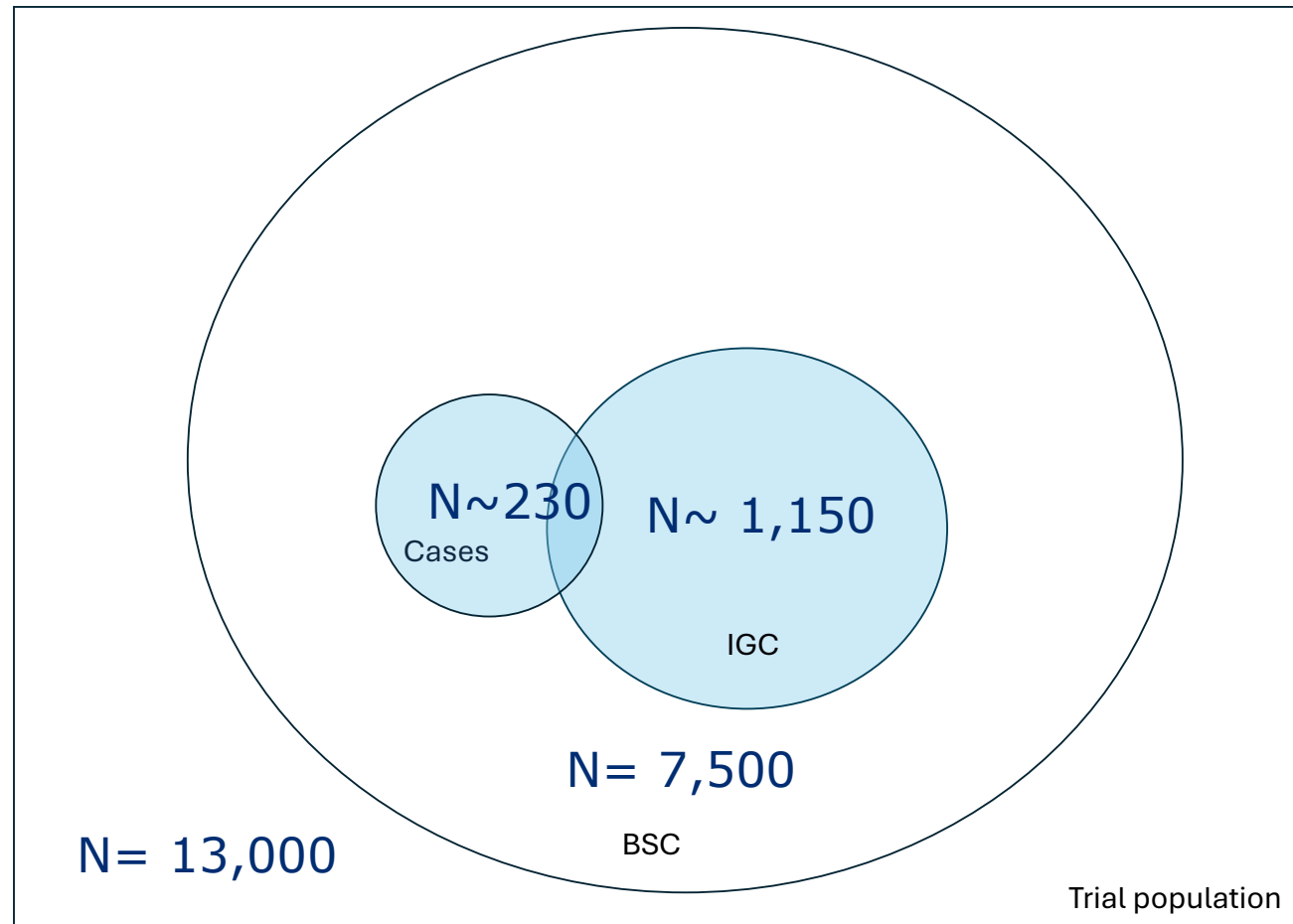
Transplacental transfer  
ratio in newborns born  
to WLHIV

# Infant RSV Pooled Neutralizing Titers Persist, Remaining Higher Than Placebo Through 6 Months of Age



Palivizumab reference line = 50% A/B neutralizing titer of a 100ug/mL palivizumab dose, demonstrated to be efficacious in preventing infant RSV-associated ICU admission (Forbes ML, Kumar VR, Yogev R, et al. *Hum Vaccin Immunother* 2014;10:2789-94.)

# Case-Cohort nested study to investigate for Correlate of Protection against severe RSV-LRTI.



BSC= Birth Sampled Cohort. IGC= Immunogenicity Cohort (Cases and Controls)

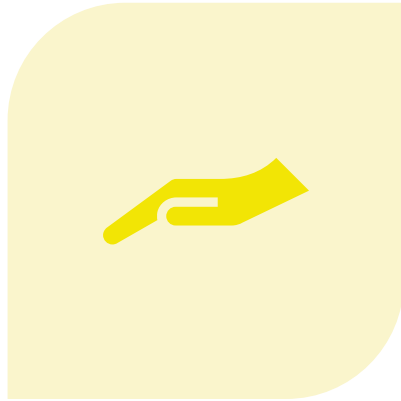
# Expected number of severe RSV LRTI cases in the trial by HEU, Preterm HIV- and Term HIV-

Country	Expected enrolment				Expected cases placebo			Expected cases vaccinated		
	Overall	HEU	Preterm HIV-	Term HIV-	HEU	Preterm HIV-	Term HIV-	HEU	Preterm HIV-	Term HIV-
South Africa	5000	1125	500	3375	43	20	85	18	9	27
Kenya	3000	226	263	2513	8	10	63	4	4	19
Ghana	3000	113	226	2663	4	8	67	2	4	20
Gambia	2000	10	250	1740	0	9	44	0	4	13
Total	13000	1474	1239	10291	55	47	259	24	21	79
	<b>7500</b>	<b>850</b>	<b>714</b>	<b>5937</b>	<b>32</b>	<b>27</b>	<b>148</b>	<b>13</b>	<b>11</b>	<b>44</b>

BSC= Birth Sampled Cohort; HEU=HIV exposed uninfected; HIV-= HIV-uninfected

# Participants safety and stopping rules.

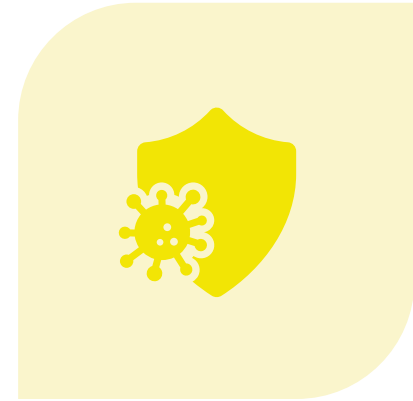
- Scientific Advisory Committee (SAC) has been constituted to advise on the trial.
- Data and Safety Monitoring Board (DSMB) has been constituted with a set of pre-defined stopping rules for an excess in adverse birth outcomes.
- The DSMB will be provided quarterly data to evaluate safety, although data will be provided more frequently if requested by the DSMB.
- In order to safeguard against an increased risk in preterm birth rate in vaccinated mothers, an interim analysis will be done at the recommendation of the DSMB.



**SAFETY**



**EFFICACY**



**CORRELATE OF  
PROTECTION**

# Thank you

[alane.izu@wits-vida.org](mailto:alane.izu@wits-vida.org)  
[www.wits-vida.org](http://www.wits-vida.org)



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