Leids Universitair Medisch Centrum

CHDR Centre for Human Drug Research

RSV Summit: The Burden of Disease and New intervention Strategies
Brussels 5 Mar 2024

Early Career Scientist:

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LEIDEN UNIVERSITY CENTRE OF INFECTIOUS DISEASES

Early Career Scientist: Johan van der Plas

2017 Master of Medicine Leiden University Medical Centre

2018 - 2022 research physician and project leader Centre of Human Drug Research (CHDR)
Clinical pharmacologist in training

2022 Resident Internal Medicine Amstelland general hospital (Amsterdam area)

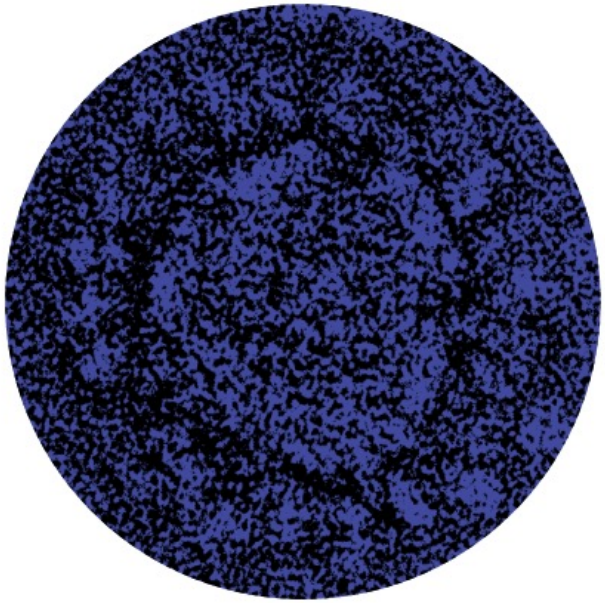
2022 Interim Study Manager CHDR

2023 PhD '*Advances in clinical development for vaccines and therapeutics against respiratory virus infections*'

Current position (Leiden University Medical Centre):

- Medical specialist in training medical microbiology
- Clinical pharmacologist
- Clinical scientist

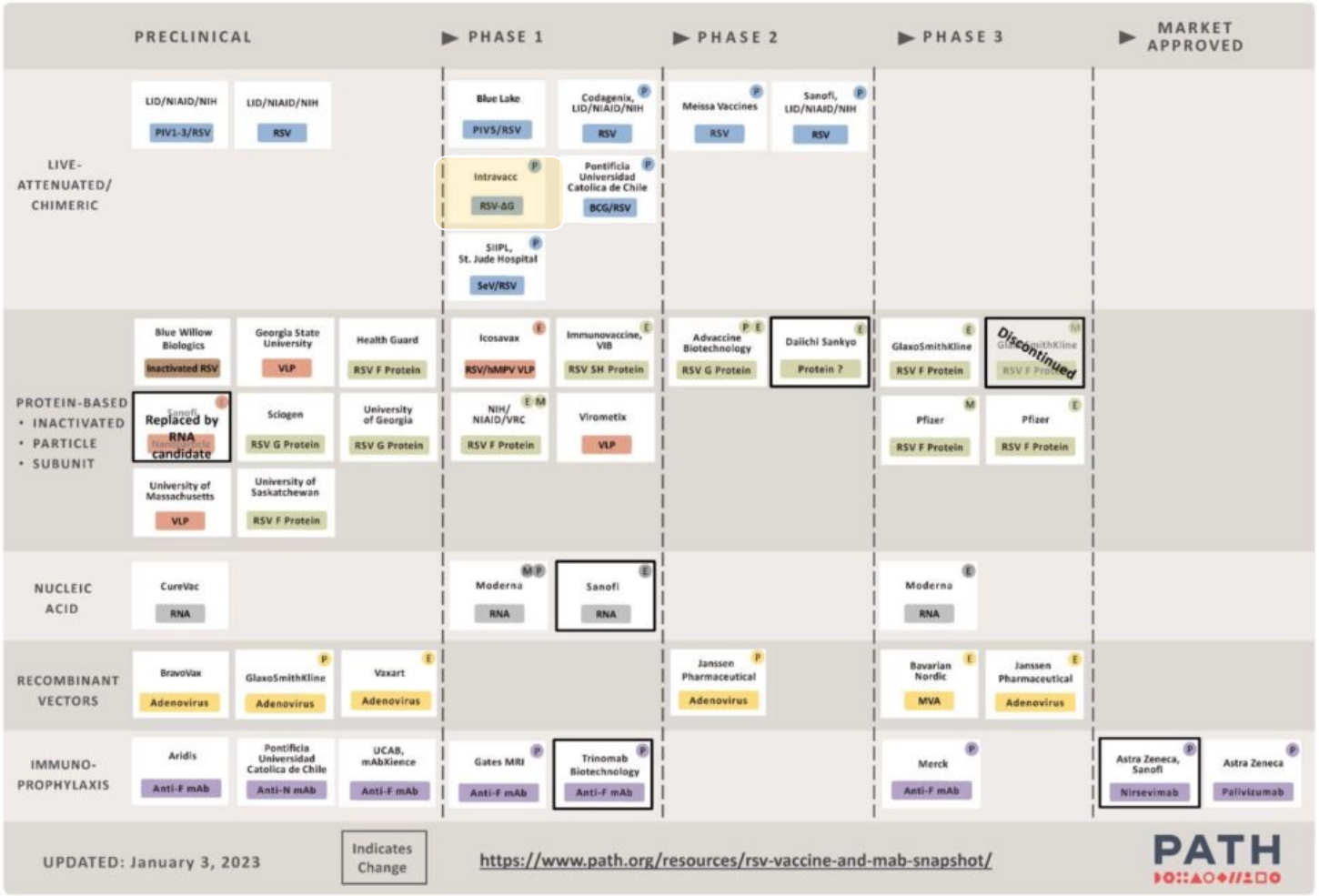
Previous work in RSV



ADVANCES IN CLINICAL DEVELOPMENT FOR VACCINES AND THERAPEUTICS AGAINST RESPIRATORY VIRUS INFECTIONS

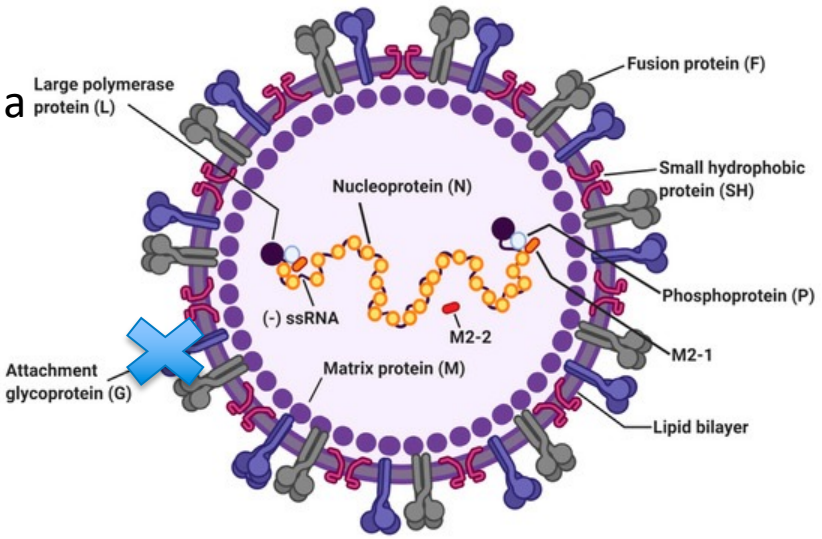
J.L. van der Plas

RSV Vaccine and mAb Snapshot



Vaccine candidate: RSVdeltaG

- Intravacc (Bilthoven, the Netherlands) developed a live-attenuated recombinant RSV vaccine.
- Genomic sequence for the attachment protein G deleted
- Hypothesis: recombinant RSV will have impaired binding to host cells and reduced infectivity, but still able to induce protective immunity against wt-RSV
- F protein preserved as major neutralizing antigen + other surface proteins

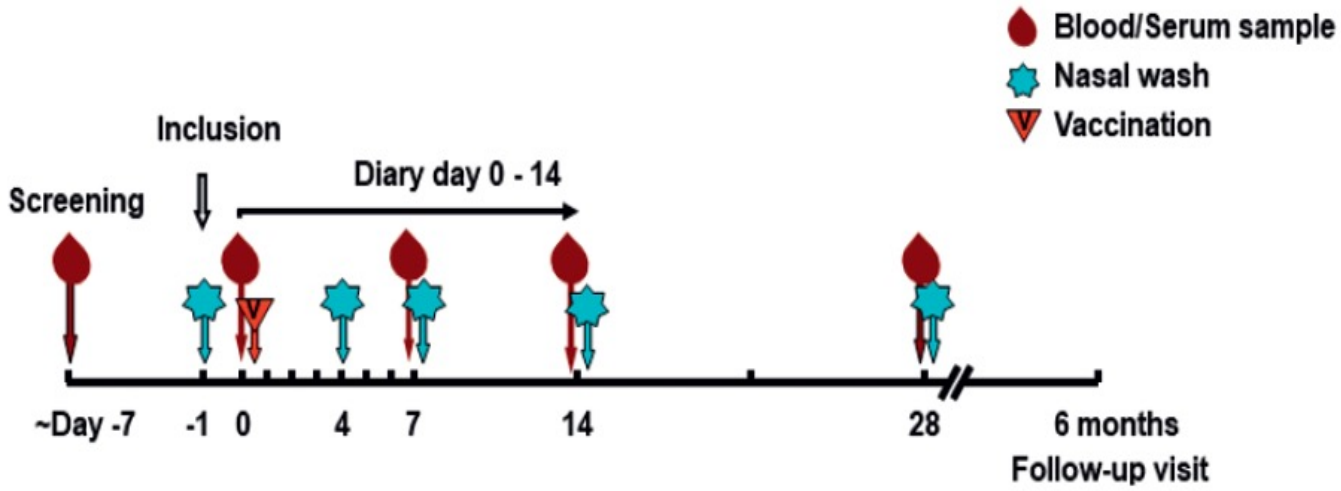


Study design: randomized, double-blind, placebo-controlled

- Randomization: active versus placebo: 3:1
- Population: male and female healthy adult volunteers (n=48)
  - Virus neutralization antibody titers ≤9.6log2 (titer)
  - Immune competent
  - Non smoking (90 days prior to vaccination) + no chronic lung diseases
  - No nasal abnormalities
- Treatment:
  - Active: RSVΔG (dose: 6.5 log10 CCID50) & formulation buffer
  - Placebo: formulation buffer only

- Route of administration: intra nasally (0.2 ml: 0.1ml each nostril)

Study Design



Safety & Tolerability

- No difference in amount of solicited adverse events between placebo and active group

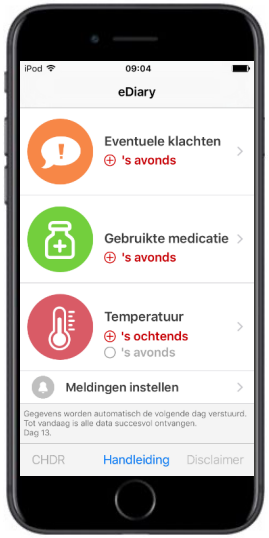


Table 2. Solicited adverse events during first 14 days after inoculation

Symptoms	RSVΔG *N* = 36 Number of subjects *(%)*	Placebo *N* = 12 Number of subjects *(%)*
≥1 symptom	29 (80.6)	9 (75.0)
Nasal congestion	11 (30.6)	5 (41.7)
Sneezing	15 (41.7)	5 (41.7)
Rhinorrhea	16 (44.4)	4 (33.3)
Epistaxis	4 (11.1)	-
Coughing	11 (30.6)	2 (16.7)
Sore throat	11 (30.6)	7 (58.3)
Dyspnea	2 (5.6)	2 (16.7)
Eye irritation/complaints	4 (11.1)	-
Earache	2 (5.6)	1 (8.3)
Myalgia/arthralgia	12 (33.3)	4 (33.3)
Malaise	13 (36.1)	6 (50.0)
Fever	1 (2.7)	1 (8.3)

RSVΔG = respiratory syncytial virus lacking the G protein

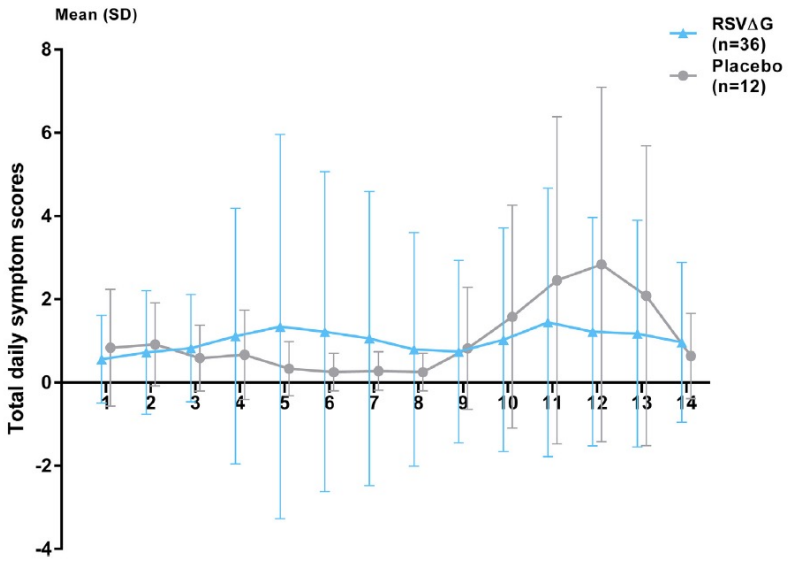


Fig. 3. Mean and SD of total symptom scores (range 0–32) during days 1–14 for RSVΔG and placebo treatment. SD = standard deviation.

Viral shedding of RSVΔG & immunogenicity

- qPCR: RSV-specific RNA was detected on day 4 post-vaccination in 3/36 (8.3%) in the RSVΔG group. Samples were below the LLOQ
- Positive qPCR results did not coincide with positive qCulture read-out
- RSV majority of IgA in nasal washes were below the lower limit of quantification (no IgA detected in placebo group)
- RSV serum nAbs < 2-fold response in adults

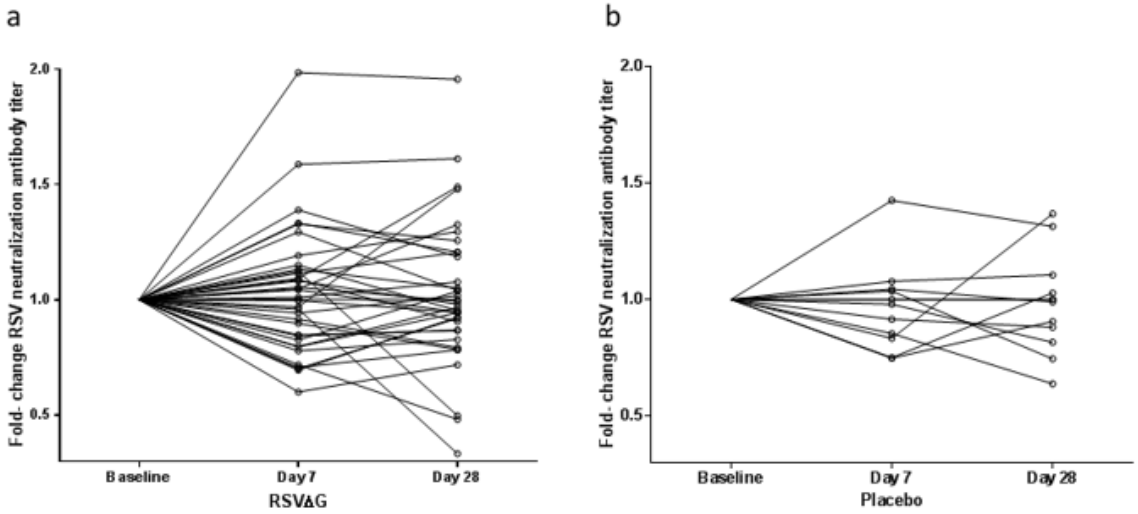


Figure 3. Fold-change in RSV neutralization antibody titer, day 7 and day 28 post-inoculation versus baseline. (*a*) Fold-change in RSVΔG group (n=36). (*b*) Fold- change in placebo group (n= 12). RSV = respiratory syncytial virus.

Lessons learned from the RSVΔG first-in-human trial

- Deletion of G-protein leads to a highly attenuated vaccine strain (in healthy adults)
- Safety and shedding results clear the way for further assessment in pediatric population
- Immunogenicity results not ideal?
- Back to the drawing board

- Clear advantages for intranasal vaccination
- Variant strain: G-RSVΔG → Virus will be able to attach to host cell via its G-protein, increasing infection potential, progency virions identical to RSVΔG and sufficiently attenuated
- Live-attenuated virusses, historically safe option for intranasal vaccination → sustaining pre-fusion state of viral fusion protein (F)

FUTURE PROJECTS FOR RESPIRATORY VIRUSES

- Development of viral challenge strains and application in clinical trials
- Unit for respiratory virus challenges opened in December 2023
- Validation of rhinovirus strain ongoing
- Development of influenza and RSV (A, B) strains
- INNO4VAC. Ingrid de Visser Kamerling (CHDR), Meta-Roestenberg (LUMC)