Supplementary Materials

Supplement to: J. Terstappen et al., 2025. Intranasal monoclonal antibodies do not prevent respiratory infection in a randomized, controlled experimental infection trial. *Npj Drug Discovery*.

This appendix has been provided by the authors to give readers additional information about the work.

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Section S1: Intranasal antibodies to prevent respiratory infections

Candidate	Description	Latest development	Studies				
			Study design	**Dose**	**Administration**	**Results**	**Trial registration**
F61	mAb (IgG1) neutralizing SARS-CoV-2	Phase 1 and real-world study	Mice model: placebo-controlled challenge study	Single dose of 5-20 mg/kg two hours before challenge	Drops; 50 µL	Prophylactic effect observed for range of SAR-CoV-2 variants at 20 mg/kg dose [1]	N.A.
			Randomized, double-blind, placebo-controlled trial; n=2008 healthy adults; 7 day follow-up	Single or daily dose of 24 mg	Spray; 0·8mL/dose	Laboratory confirmed efficacy at day 7 was 3·8% in the one-dose cohort and 72·2% in the multiple dose cohort [2]	[3,4]
Palivizumab	mAb (IgG1) neutralizing RSV	Phase 1/2b	Mice model: challenge study	Single dose of 0·005-0·5 mg/kg one to seven days before challenge	Drops; 50 µL	Intranasal palivizumab protected mice against RSV infection in a dose-dependent manner and this protection lasted at least 1 week [5]	N.A.
			Randomized, double-blind, placebo-controlled trial; n=268 healthy late-preterm infants; 1 year follow-up	Daily dose of 50 µg palivizumab (1 mg/mL) per nostril	Drops; 50 µL/dose	Any RSV infection in infants in palivizumab arm (18/47 (38·3%) was similar to placebo arm (11/47 (23·4%); aOR 2·2, 95% CI 0·7–6·5) [6]	[7,8]
BI-767551 *DZIF-10c*	mAb (IgG1) neutralizing SARS-CoV-2	Phase 1/2a	Mice model: isotype-controlled challenge study	Single dose of 40 mg/kg one day before challenge	Drops; max 30 µL into the lungs	No infection in the prophylactically treated arm versus high infectious titers in the isotype-controlled arm [9]	N.A.
			Open-label dose escalation trial rolled-over into randomized placebo-	..	Inhalation	..	[10]

			controlled expansion cohort; n=45 healthy adults				
35B5	mAb (IgG1) neutralizing SARS-CoV-2	Phase 1	Pharmacokinetic study; n=30 healthy adults	Single dose of 1 mg/mL	Spray; volume unknown.	Single dose of 35B5 conveys ex-vivo neutralization of SARS-CoV-2 variants at least 24 hours after administration [11].	Clinical trial registration missing.
IGM-6268 *IgM-14*	mAb (IgM) neutralizing SARS-CoV-2	Phase 1	Mice model: Isotype-controlled challenge study	Single dose of 0·044-3·5 mg/kg six hours before challenge	Drops; 40-50 µL	Enhanced potency of IgM over IgG confirmation. Lung viral load after challenge reduced at least 5-fold compared to isotype arm [12,13]	N.A.
			Two randomized, double-blind, placebo-controlled trials; n=54 and 26; 60 day follow-up	1-7·5 mg once or twice per day for 5 days	Atomizer	Both trials were terminated by sponsor decision	[14,15]
RBD IgY	Chicken-derived IgY binding SARS-CoV-2	Phase 1	Mice and hamster model: placebo-controlled challenge study; 3-4 day follow-up	Mice: Single dose of 2 mg (100 mg/kg) 30 minutes before challenge. Hamsters: 1.7 mg (0·017 mg/kg) one day before challenge and twice daily for five days after challenge Syrian golden hamsters: 100 µL of 1 mg/50 mL of the 20 mg/mL solution per nare four hours before challenge.	Mice: 0·1 mL Hamsters: volume unknown. Syrian golden hamsters: 100 µL	Mice: >100-fold reduction in viral RNA in lungs and trachea compared with placebo [16]. Hamsters: RBD IgY treatment protected against significant weight loss and reduced viral load [17]. Syrian golden hamsters: No *in vivo* efficacy [18]	N.A.

			Randomized, double-blind, placebo-controlled trial; n=48; 21 day follow up	2-8 mg once, twice or three times daily (total daily dose 2-24 mg)	Drops; 100 µL/drop	Similar safety events between RBD IgY and placebo groups [18]	[19]
HH-120	IgM-like ACE2 fusion protein neutralizing SARS-CoV-2	Clinical trial of unknown phase	Single arm clinical trial; n=14. Randomized, single-blinded, placebo-controlled trial; n=268	5-8 doses of 2 mg/dose per day for three consecutive days post-exposure	Spray; 0·2 mL	Well tolerated and reduced the risk of SARS-CoV-2 infection in individuals with varying levels of exposure to the virus [20].	[21,22]
IgG1 Antibody cocktail	Human mAb cocktail (IgG1) against SARS-CoV-2	Clinical trial of unknown phase	Randomized, double-blind, placebo-controlled trial; n=36; 14 day follow up	2 doses per nostril, three times daily for 7 days	Spray; volume unknown	..	[23]
MY-586	SARS-CoV-2 nAb	Clinical trial of unknown phase	Randomized, double-blind, placebo-controlled trial; n=72; 1 year follow up	5 mg/mL; different doses and intervals	Spray; volume unknown	..	[24]
CR9114 *PanFlu*	Pan-influenza mAb targeting H5 hemagglutinin	Mice model	Mice model: placebo controlled challenge study in naïve and immunized mice; 21 days follow-up	Single dose of 0·2-5 mg/kg 24 hours before challenge	100 µL	Complete reduction of weight loss and mortality in both dose groups compared with placebo [25].	N.A.
			Randomized, placebo-controlled dose escalation trial; n=75	..	..	..	Trial announced[26]
TriSb92 *Covidin*	Trimeric antibody-mimetic sherpabody against SARS-CoV-2	Mice model	Open-label untreated-controlled challenge study; n=22; 2 day follow-up	Single dose of 5-50 µg (0·250-2·50 mg/kg) 1-8 hours before challenge.	Drops; 50 µL	Reduction in viral RNA in lung tissue compared with untreated controls [27].	N.A.
WKS13	mAb (IgG1) neutralizing SARS-CoV-2	Hamster model	Mock-controlled challenge study; n=44; 4 day follow-up	Single dose of 500 µg (5 mg/kg) one day before challenge	Drops; 100 µL	Significantly lower infectious viral titers in lung and nasal wash	N.A.

						samples compared with control group [28].	
Anti-RSV Ig	Hyper-enriched anti-RSV IgG	Mice model	Isotype-controlled challenge study; n=8; 4-day follow-up.	Single dose of 0·1 or 1 mg/kg one day before challenge	50 µL	Full protection against RSV replication in the lungs with high dose and some protection at low dose [29]	N.A.
EU126-M2 *Invisimask*	SARS-CoV-2	Mice model	Untreated-controlled challenge study; 7-day follow-up.	Single dose of 25-200 µg (1·25-10 mg/kg) 10 hours before challenge*	40 mL*	Significant reductions in virus detection in both nose and lung areas 7 days after virus dosing [30]*	N.A.
M336	mAb (IgG1) neutralizing MERS-CoV	Rabbit model	Ig-controlled challenge study; 1-3-day follow-up.	Single dose of 1-10 mg/kg one day before challenge	0·2-2 mL	> 1000-9000 fold reduction in viral RNA titers compared with controls [31]	N.A.
6F12	mAbs neutralizing influenza HA	Mice model	Ig-controlled challenge study; 14-day follow-up.	Single dose of 0·3-3 mg/kg 2-120 hours before challenge	Droplets or aerosol; volume unknown	Local administration is superior to systemic administration in a prophylaxis regimen [32].	N.A.
Mab 62	mAb (IgG1) neutralizing influenza H7 strains	Mice model	Mock-controlled challenge study; n=20; 14-day follow-up.	Single dose of 2·5-10 mg/kg one day before challenge.	100 µL	Immunization with 2.5 mg/kg was sufficient for full protection against weight loss and mortality [33].	N.A.
DPJY01	mAb (IgA) neutralizing influenza H5 strains	Mice model	Isotype- and mock-controlled challenge study, 14-day follow-up.	Single dose of 10-50 mg/kg 24-72 hours before challenge	Drops; 50 µL	Full protection against mortality with 50 mg/kg 24-72 hours before challenge [34].	N.A.

Table S1. Intranasal mAbs in development to prevent respiratory infections.
Summary of mAbs in development for mucosal administration in the last 15 years to prevent respiratory infections. mAbs are ordered by development stage and then by publication year. If antibody dosing in animal models was not expressed as mg/kg, we calculated it assuming a mouse weighs 20 grams and a hamster weighs 100 grams. *study was not peer-reviewed as it was only published on bioRxiv. Abbreviations: aOR, adjusted odds ratio; Ig; immunoglobuline; mAb, monoclonal antibody; MERS-CoV, Middle-Eastern respiratory syndrome coronavirus; N.A., not applicable; nAb, neutralizing antibody; RBD, receptor binding domain; RNA, ribonucleic acid; RSV; respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; .., not available.

Section S2: Supplementary Tables and Figures

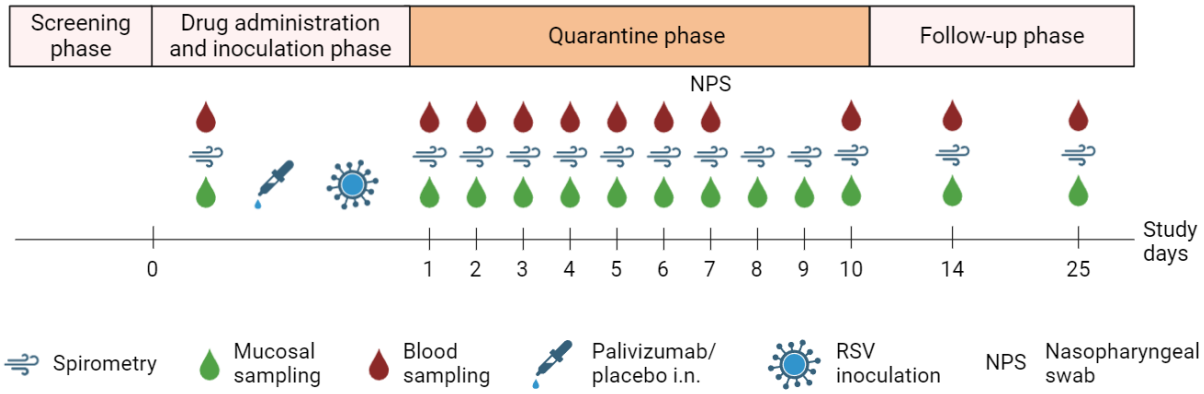


Fig. S1. Study Design.

After screening, participants were randomized 1:1 to palivizumab or placebo group (n=14 per group). Predose sampling included nasal and blood sampling as well as spirometry. One hour after drug administration, participants were challenged with 10^4 PFU of RSV-A Memphis 37b and released for home-quarantine. During home-quarantine, participants logged their symptoms and temperature daily in symptom diaries. Research personnel performed daily home-visits for sample collection and spirometry. On day 7, participants were released from quarantine if their nasal pharyngeal swab tested negative on RSV. (Serious) adverse events were monitored throughout the entire study duration. i.n., intranasal; NPS, nasopharyngeal swab; PFU, plaque-forming unit; RSV, respiratory syncytial virus. Figure was created using Biorender.com.

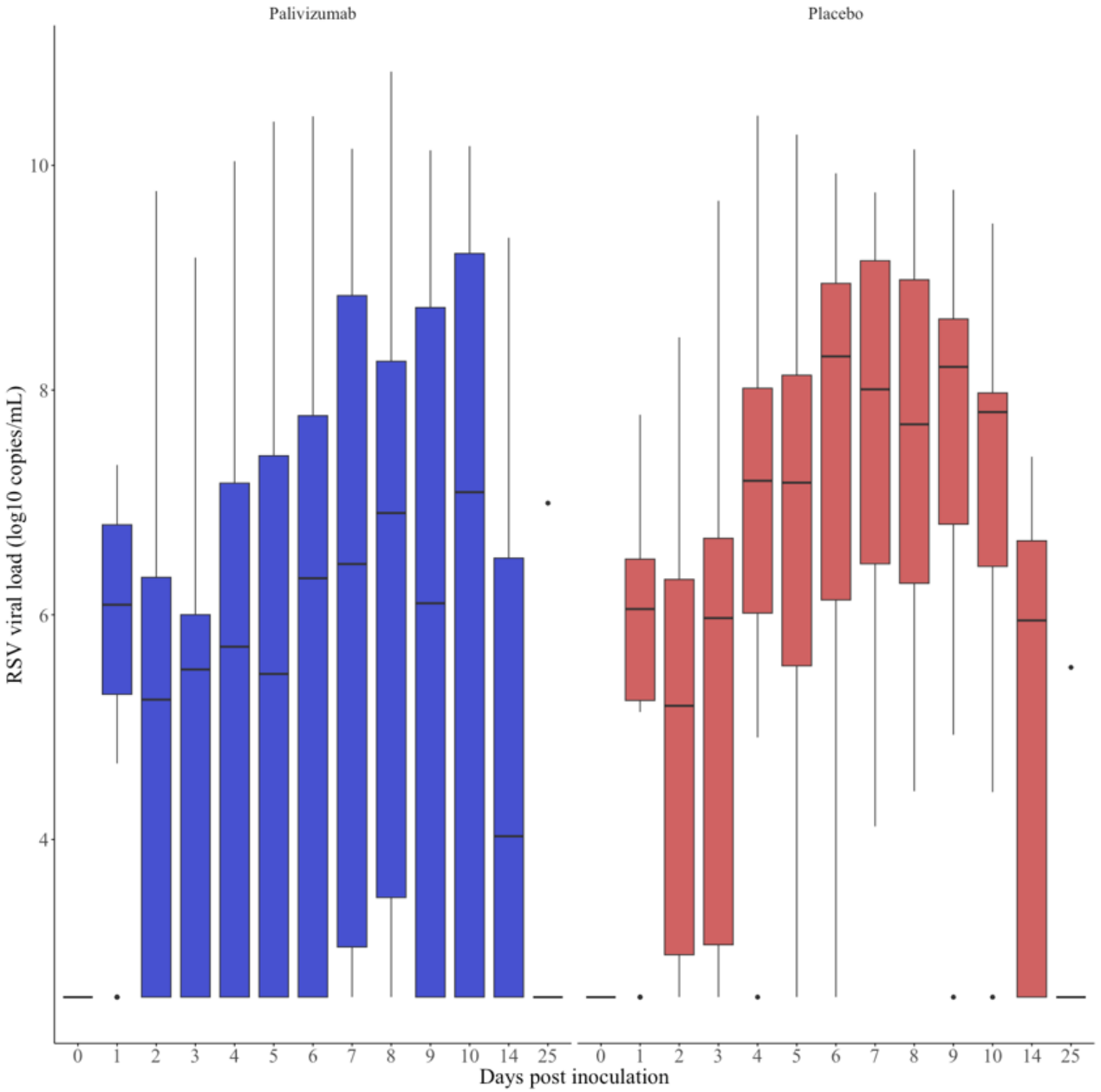
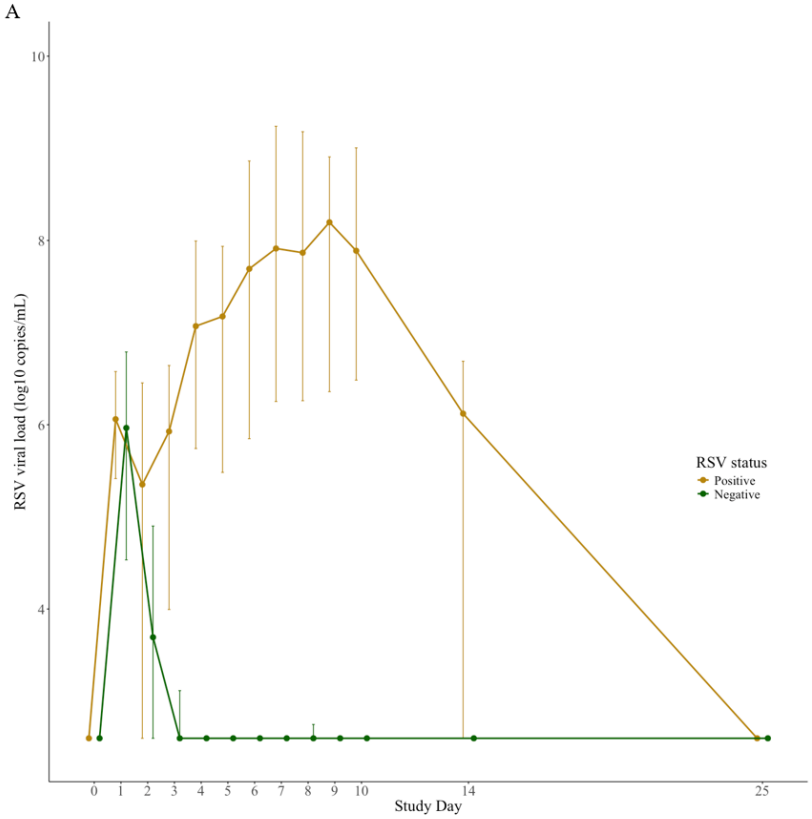


Fig S2. Boxplot of RSV viral copies/mL over time per treatment group.

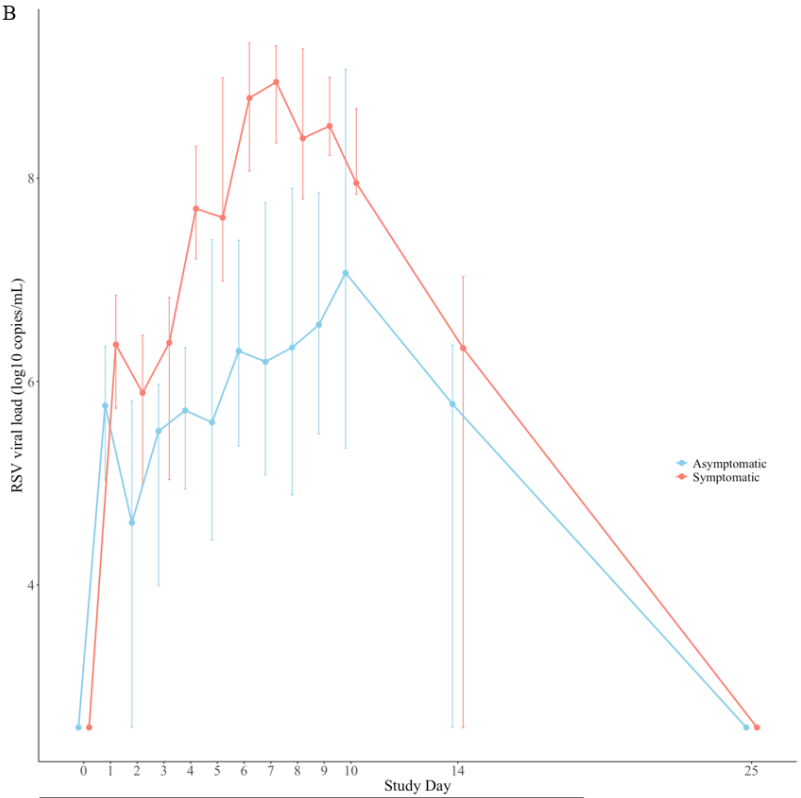
The boxes in the plots represent the interquartile range (IQR), with the median marked by a line inside the box. The whiskers extend from the box to the minimum and maximum values. Outliers are depicted as individual points beyond the whiskers.

A



RSV status	n	Median AUC	1st quartile	3rd quartile
Positive	24	9.57	7.99	10.22
Negative	4	4.30	3.68	4.78

B



Symptom status	n	Median AUC	1st quartile	3rd quartile
Symptomatic	12	8.19	7.01	10.02
Asymptomatic	12	9.82	9.52	10.22

Fig. S3. Viral load per RSV and symptom status

Viral load per RSV and symptom status. Descriptive statistics of RSV copies/mL (log10) area under the curve from day 2-14 per treatment group are provided in the table. **A.** Viral load (median + IQR) over time for RSV positive and negative participants. **B.** Viral load (median + IQR) over time of symptomatic and asymptomatic RSV positive participants.

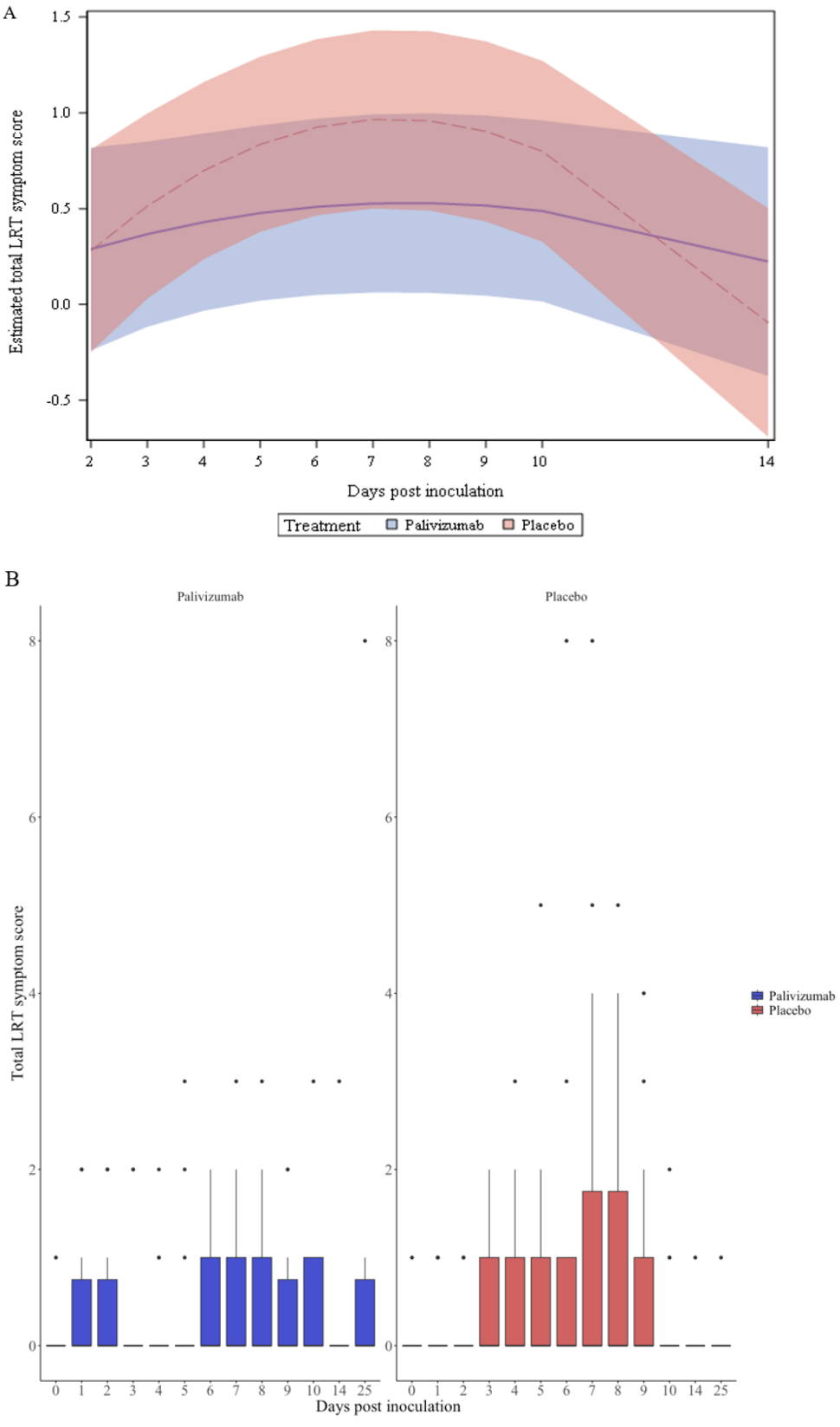
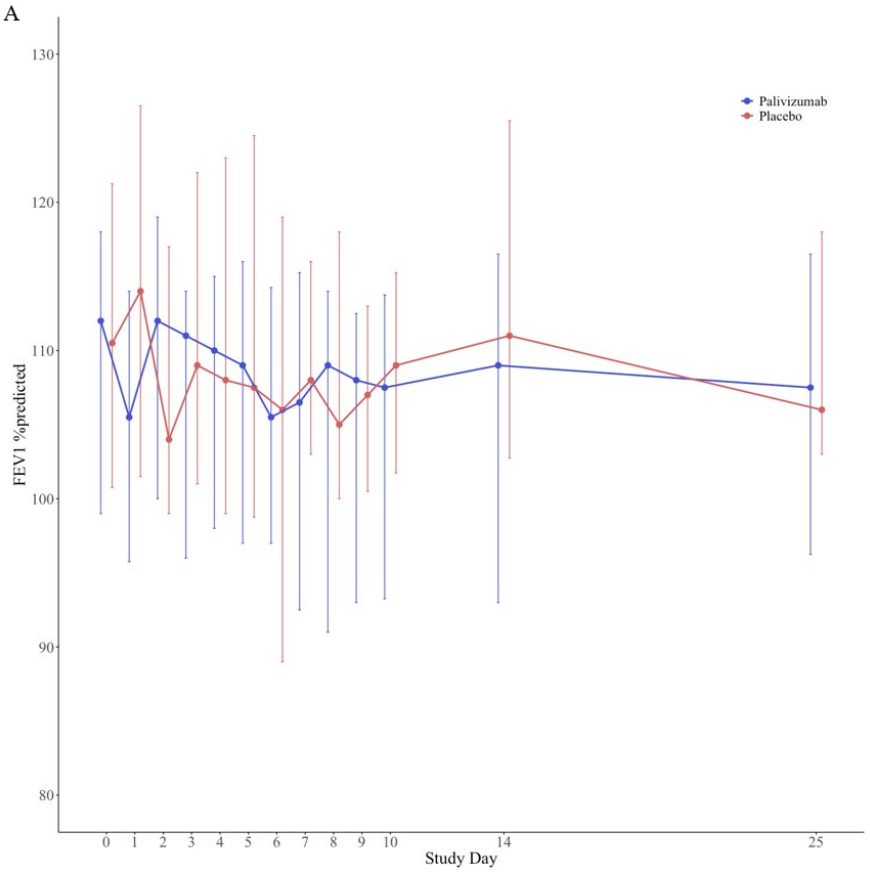
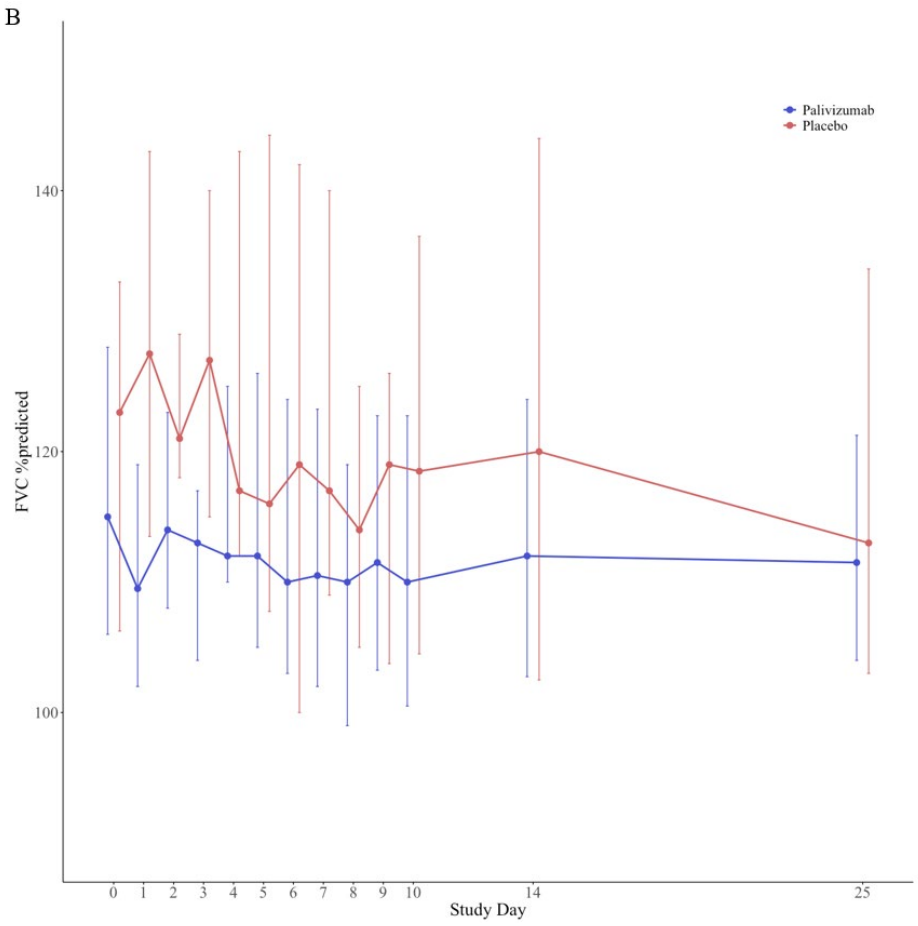


Fig. S4. Lower respiratory tract symptoms after RSV challenge

A. Mean estimates of regression model for lower respiratory tract symptom score on days 2-14 per treatment group (line with 95%CI in shaded area). No significant interaction was observed (p=0·07). Linear mixed model using treatment group, time of recording the symptoms, quadratic effect of the time of recording, interaction between treatment group, and time and interaction between treatment group and time squared as fixed effects, and intercept as random effect. **B**. Boxplot of daily lower respiratory tract symptom score over time per treatment group. The LRT total symptom score is the sum of the scores for all 5 LRT symptoms that were listed in the symptom diary and self-reported by participants once daily (see Supplementary material section S3). The score for each symptom ranged from 0 (absent) to 3 (severe). The boxes in the plots represent the interquartile range (IQR), with the median marked by a

line inside the box. The whiskers extend from the box to the minimum and maximum values. Outliers are depicted as individual points beyond the whiskers. LRT, lower respiratory tract.





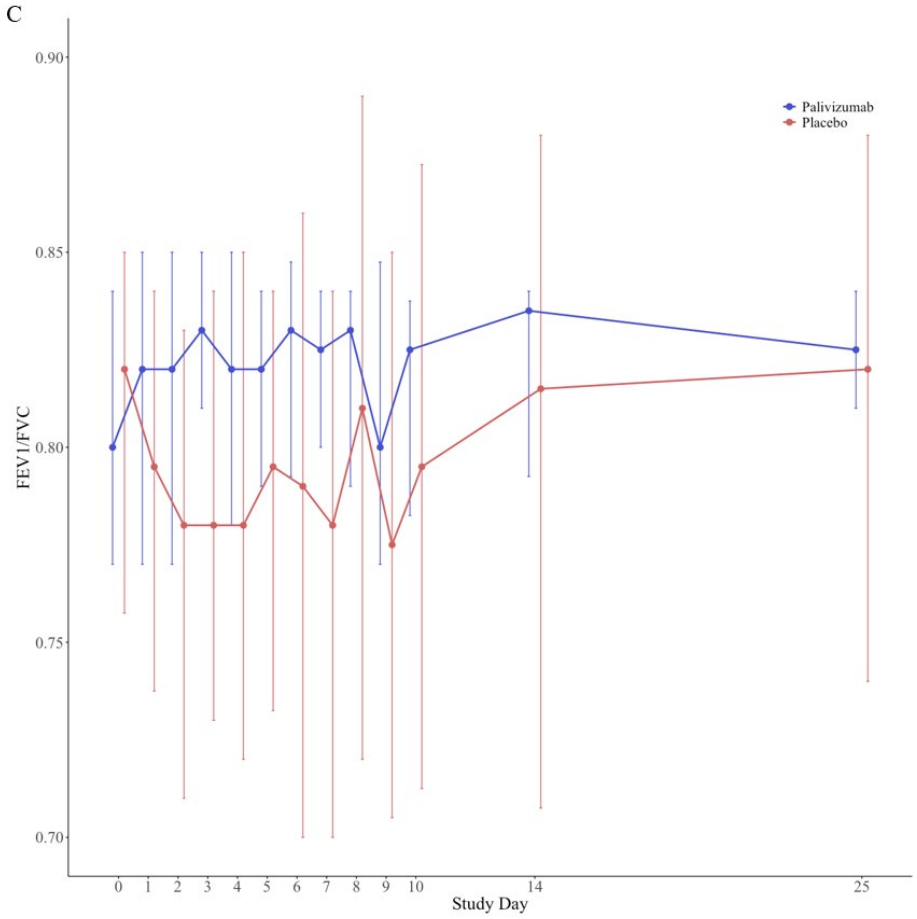


Fig. S5. Lung function over time per treatment group

A. FEV1 %predicted (median + IQR). FEV1 is the volume that has been exhaled at the end of the first second of forced expiration. FEV1 %predicted is the FEV1 value expressed as a percentage of the predicted value for participants age, sex, and height. **B.** FVC %predicted (median + IQR). FVC is the amount of air that can be forcibly exhaled from your lungs after taking the deepest breath possible. FVC %predicted is the FVC value expressed as a percentage of the predicted value for participants age, sex, and height. **C.** FEV1/FVC (median + IQR). Abbreviations: FEV1, forced expiratory volume; FVC, forced vital capacity.

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