

Cold perception as a key endpoint in human challenge trials with respiratory viruses



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INTRODUCTION

Human viral challenge studies are generally developed to quickly test efficacy of vaccines, prophylactics and treatments in a relatively small number of participants compared to Phase 2a/b field studies. hVIVO has developed multiple challenge agents for use in humans and have collated data on RSV, influenza, and SARS-CoV-2. In addition to typical measures of disease (temperature, symptoms, directed physical exam, tissue mucous weights and counts), some participants have been given daily cold perception questionnaires. Here we present the incidence of participant perceived colds, when they occur, and how this may impact the ability to use this measure for vaccine and treatment efficacy testing as well as for triggering treatment.

CLINICAL DESIGN

Viral Challenge and Assessments

Influenza H3N2, RSV Memphis 37b, and SARS-CoV-2 challenge viruses were tested clinically in separate virus studies. Volunteers were screened and attended outpatient follow-up visits in hVIVO's outpatient clinical unit. Viral challenge was conducted in hVIVO's viral challenge unit quarantine with extensive monitoring 24/7 (Figure 1 & 2).

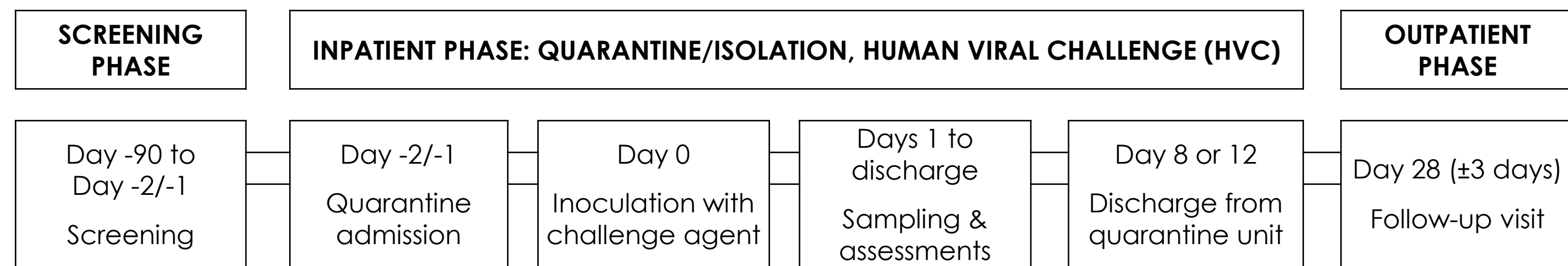


Figure 1: Clinical study schematic: screening to quarantine to discharge and final follow up outpatient visit.

Key Inclusion and Exclusion Criteria

- ✓ 18 – 55 years (SARS-2 18-30 years)
- ✓ Serosuitable for challenge
- ✓ Healthy
- ✓ Contraception adherence

Key Assessments

- ✓ Virology: qRT-PCR & culture
- ✓ Self-reported symptom diary cards 3x/day
- ✓ Cold perception questionnaire 1x/day
- ✓ Tissue mucous weights and counts
- ✓ Vital signs & safety assessments

hVIVO Subject symptom diary card

Patient perception of illness



Objective measure of temperature/fever



Paper tissues, mucous weight



Figure 2: Clinical assessments of participants through quarantine.

PERCEIVED COLDS & SYMPTOMS

Symptomatic profile of participants with perceived colds

For each challenge agent (RSV-NW, RSV-NPS, influenza H3N2, and SARS-CoV-2), symptom profiles were generated for infected participants perceiving colds and were compared to those infected participants not perceiving a cold with mean total symptom scores presented in bar charts in Figure 5. Pie charts were also created for the participants that perceived a cold to show the relative contribution of each symptom type to the total sum of all the diary cards.

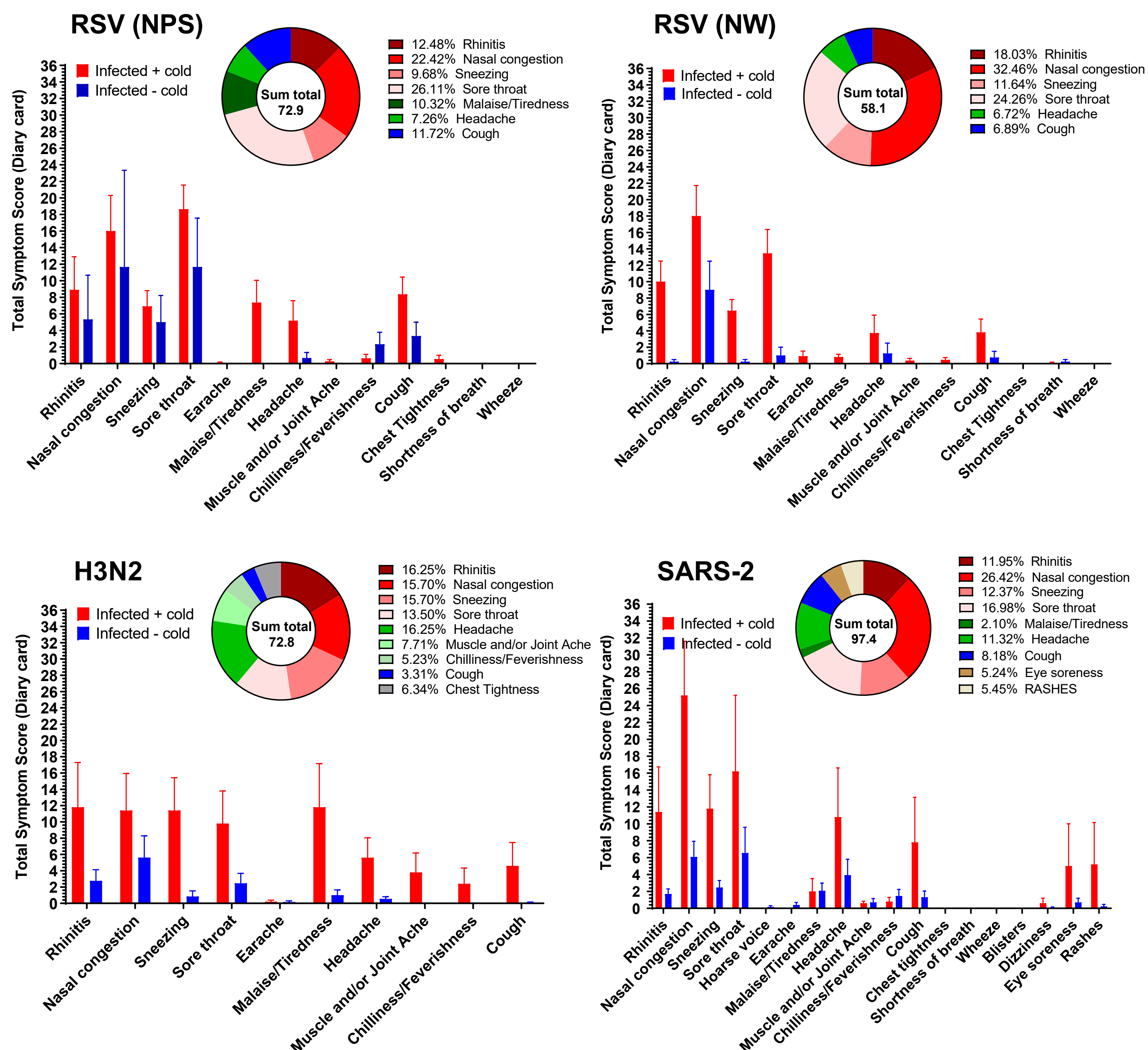


Figure 5: Symptom distributions in participants perceiving colds: Bar charts show the mean (\pm SEM) total sum of symptom diary cards for each symptom within the symptom diary construct for both infected with a cold (red), as well as infected without a cold (blue). Pie charts show the relative contribution of key symptoms to the overall total sum of symptoms for those participants perceiving colds (Red variations: URT symptoms; Blue variations: LRT symptoms; Green variations: systemic symptoms; Brown variations: other symptoms).

VIRAL CURVES AND ENDPOINT MEASURES

Viral Curves

Viral curves by qRT-PCR for infected participants were generated from hVIVO's database for the following viruses and plotted over time in Figure 3.

- H3N2 influenza from nasopharyngeal swabs (NPS), n=150
- RSV from nasal washes (NW), n=160
- RSV from nasopharyngeal swabs (NPS), n=15
- SARS-CoV-2 from mid-turbinate swabs (MidTurb), n=18

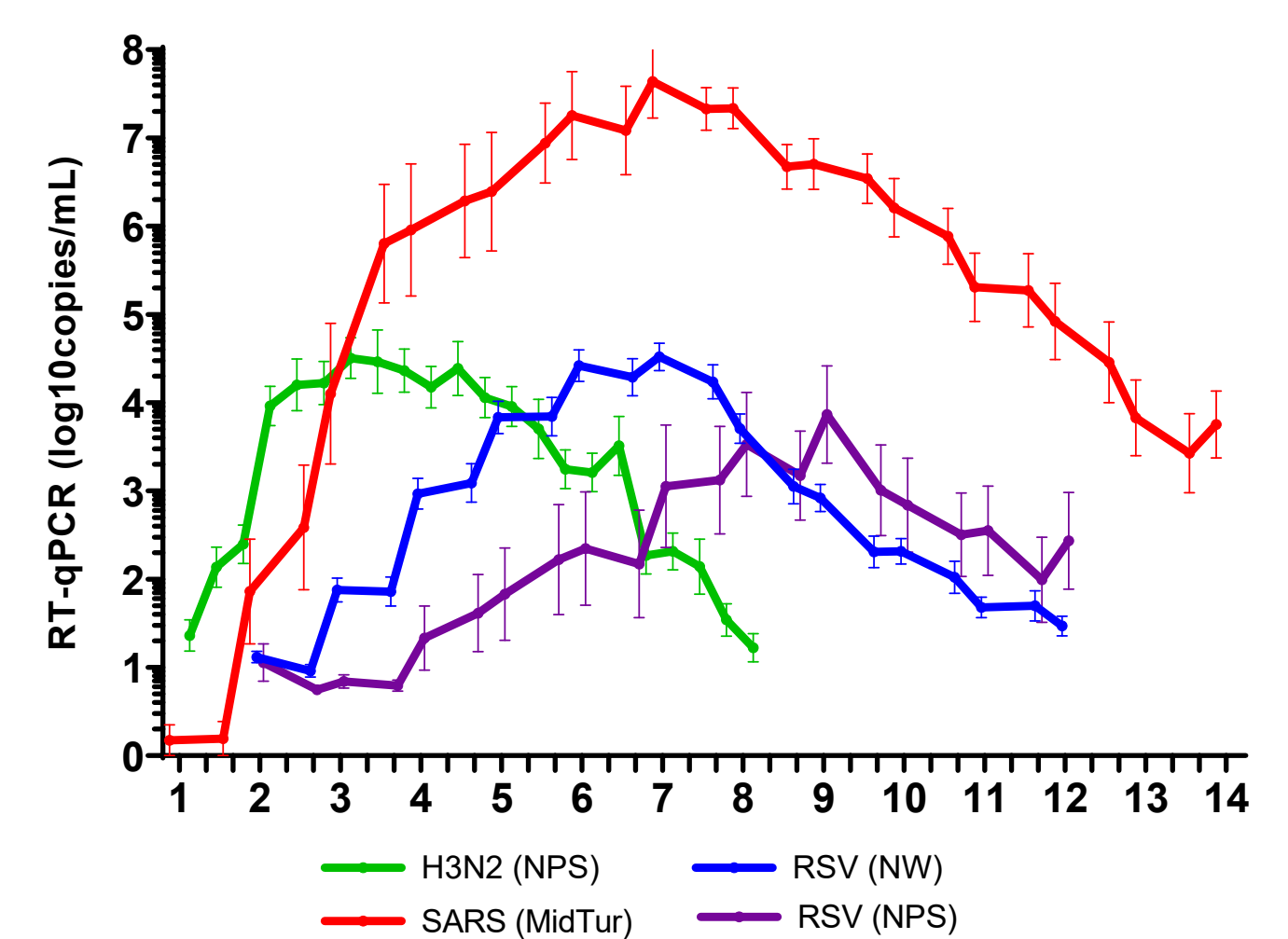


Figure 3: Viral time course from hVIVO's database of challenge agents: qRT-PCR. Infected were defined as 2 detectable PCR samples over 48 hours.

Cold Perception Incidence

Participants from the database received their daily cold perception questionnaire. The incidence relating to infection and relative incidence compared to symptomatic infection and febrile illness are shown in Table 1 and Figure 4.

Cold Perception Sub-Analysis Group		
Challenge Agents	Quantifiable Infection % (n/n)	Cold Perception % of infected
Influenza H3N2 A/Perth/16/2009	45% (18/40)	28%
RSV Memphis 37b (NW)	50% (15/30)	73%
RSV Memphis 37b (NPS)	52% (13/25)	85%
SARS-CoV-2	53% (18/34)	28%

Table 1: hVIVO's viral challenge subgroup that received daily cold perception questionnaires. Infection rate based on 2 quantifiable PCR over 48 hours.

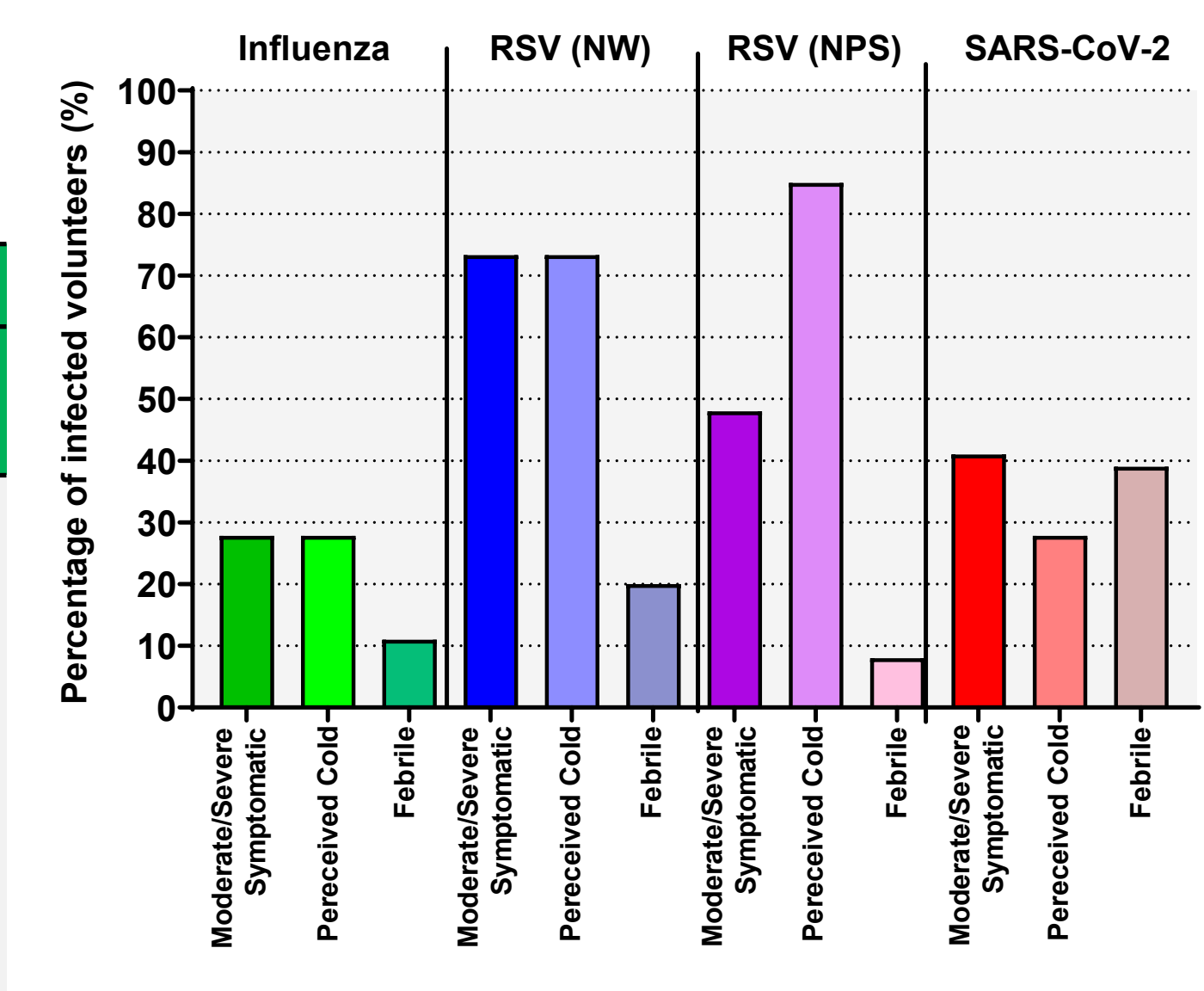


Figure 4: Incidence of moderately severe symptomatic infection, cold perception and febrile illness in challenge studies.

COLDS: ENDPOINTS, TREATMENTS & ONSET

Timing of onset of cold perception and treatment opportunities

The cumulative incidence of perceptions of cold within infected participants (% of infected) after inoculation with each challenge agent is shown in Figure 6. Furthermore, the timing relative to the viral curves (as shown in Figure 3 above) are shown in Figure 7.

- **Influenza H3N2:** Perceived colds occur after viral onset and around peak viral shedding
- **SARS-CoV-2:** Perceived colds occur several days after virus onset and close to peak viral shedding
- **RSV:** Relative to viral curves RSV-NPS participants mostly perceive their colds around viral onset and prior to peak virus shedding, while RSV-NW is closer to peak viral shedding

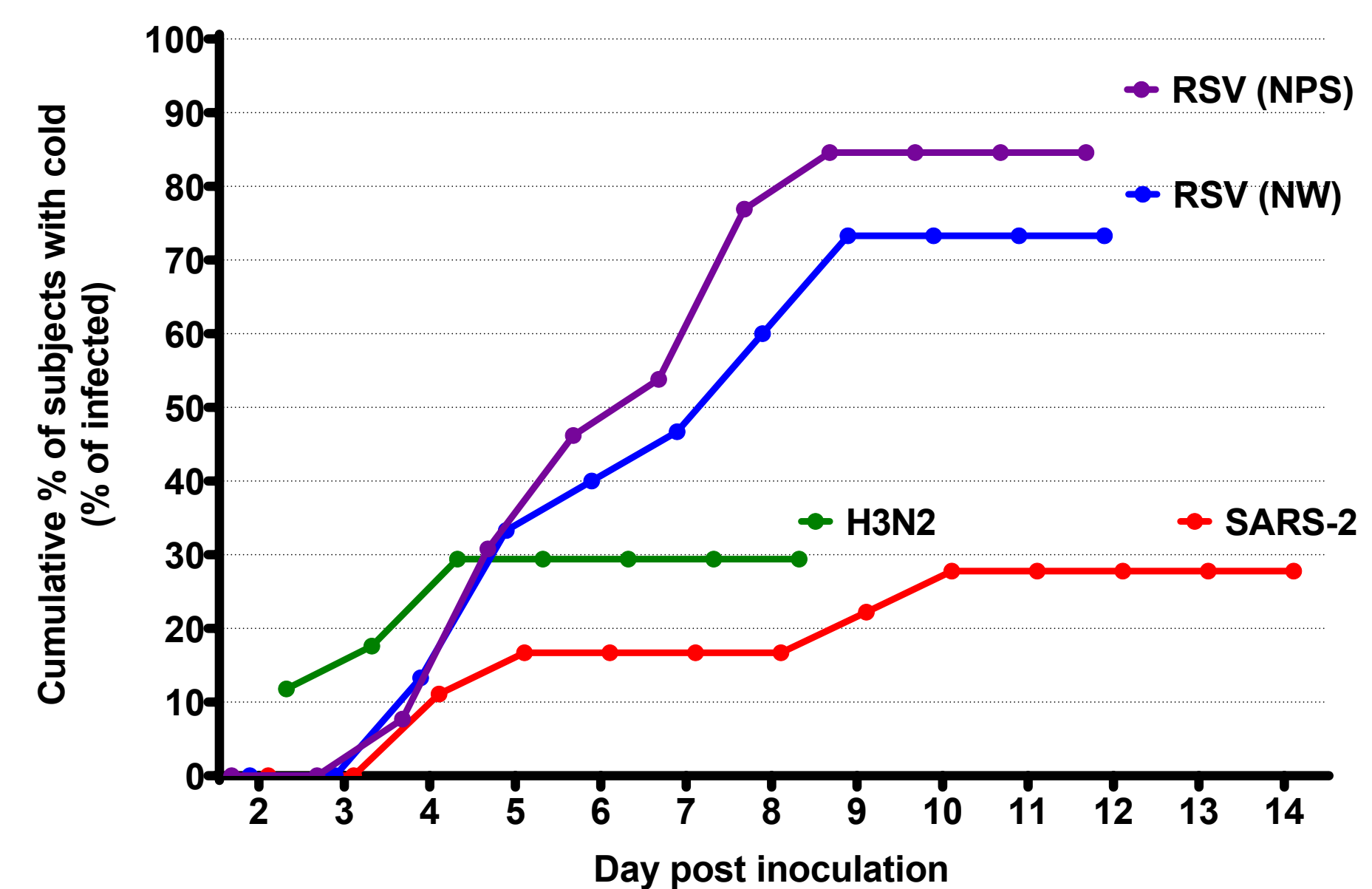


Figure 6: Onset of cold perception (percentage of infected); cumulative incidence by time point through quarantine for RSV-NPS (purple, n=), RSV-NW (blue), influenza H3N2 (green), and SARS-CoV-2 (red).

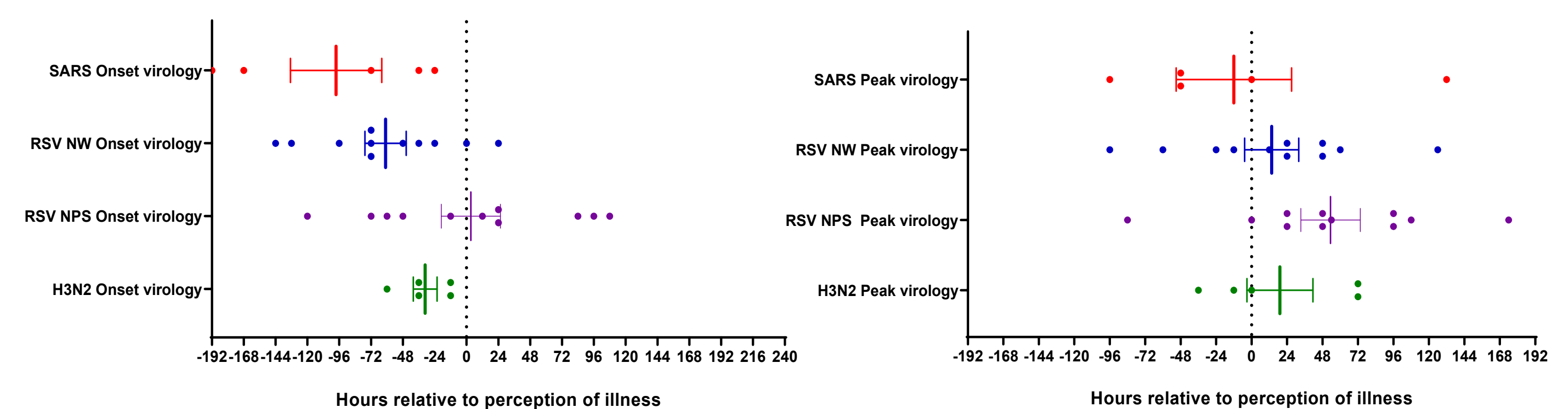


Figure 7: Timing of cold perception onset and relative timing (hours) to viral shedding onset (left) and viral peak shedding (right) for each challenge agent.

CONCLUSIONS

- Participants perceive having colds after respiratory viral challenge
- RSV has a high rate of incidence of cold perception
- Vaccines endpoints can include cold perception, especially for RSV
- Sore throat and URT symptoms mostly associate with cold perception
- Cold perception is not overtly linked to magnitude of total symptoms
- Febrile participants perceived having a cold
- Utility of cold perception for treatment upon onset of cold, especially for RSV when viral sampling by NPS

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