Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

Canadian Center for Vaccinology

Dalhousie University
IWK Health
Nova Scotia Health

# The First North American Pertussis Controlled Human Infection Model (CHIM) Using the Pertactin-Producing D420 Isolate

**Scott A. Halperin, MD**

Professor of Pediatrics and Microbiology & Immunology

Director, Canadian Center for Vaccinology

Dalhousie University, IWK Health Centre

# CCFV RESEARCH TEAM

Scott Halperin, MD

*Director*

May ElSherif, MD, MPH, BSc

*Clinical Scientist, Director - Laboratory Operations*

Kara Redden, BNI, MScN

*Challenge Unit Manager*

Wade Blanchard, PhD

*Senior Biostatistician*

Lingyun (Peter) Ye, MSc

*Director - Research Data & Analytics*

**Open-label, phase 1, dose-escalation clinical trial to establish a Controlled Human Infection Model (CHIM) by determining and confirming the optimal and safe *Bordetella pertussis* dose administered intranasally to healthy adults 18–40 years of age that induces detection of *B. pertussis* in nasopharyngeal samples with mild symptomatic infection**

- PRN-producing, US strain *B. pertussis* D420 isolate
- Funding: NIH R34 writing grant, CDC Broad Agency Announcement contract
- Health Canada and FDA approved

# LITERATURE REVIEW: Early pertussis disease in adults is characterized by mild, non-specific respiratory symptoms

## Incubation Stage:

- 5-10 days, up to 21 days (up to 28 days)

## Early Symptomatic Catarrhal Stage:

- Mostly mild symptoms that mimic other respiratory illness, e.g. influenza, coronavirus
- Difficult to diagnose pertussis at catarrhal stage by symptoms alone
- Hallmark paroxysmal pertussis cough is absent

## Mild catarrhal symptoms can include:

- Runny Nose
- Any cough
- Sore Throat
- Sneezing
- Mild Coryza
- Low grade or absence of fever

## Supporting the case for *early* clinical pertussis diagnosis

- Recent exposure to whooping cough
- Not recently vaccinated
- Laboratory confirmation by culture and/or PCR

These criteria are met in our experimental pertussis CHIM.

*References: CDC. 2024.https://www.cdc.gov/pertussis/hcp/clinical-overview/index.html; Craig et al. 2020. Clin Infect Dis 70:152-161; Kilgore et al. 2016. Clin Microbiol Rev 29:449-486; Moore et al. 2017. Chest 152:353-367; Ward et al. 2006. Clin Infect Dis 43:151-157.*

# Participants were challenged in a safe dose-escalation design

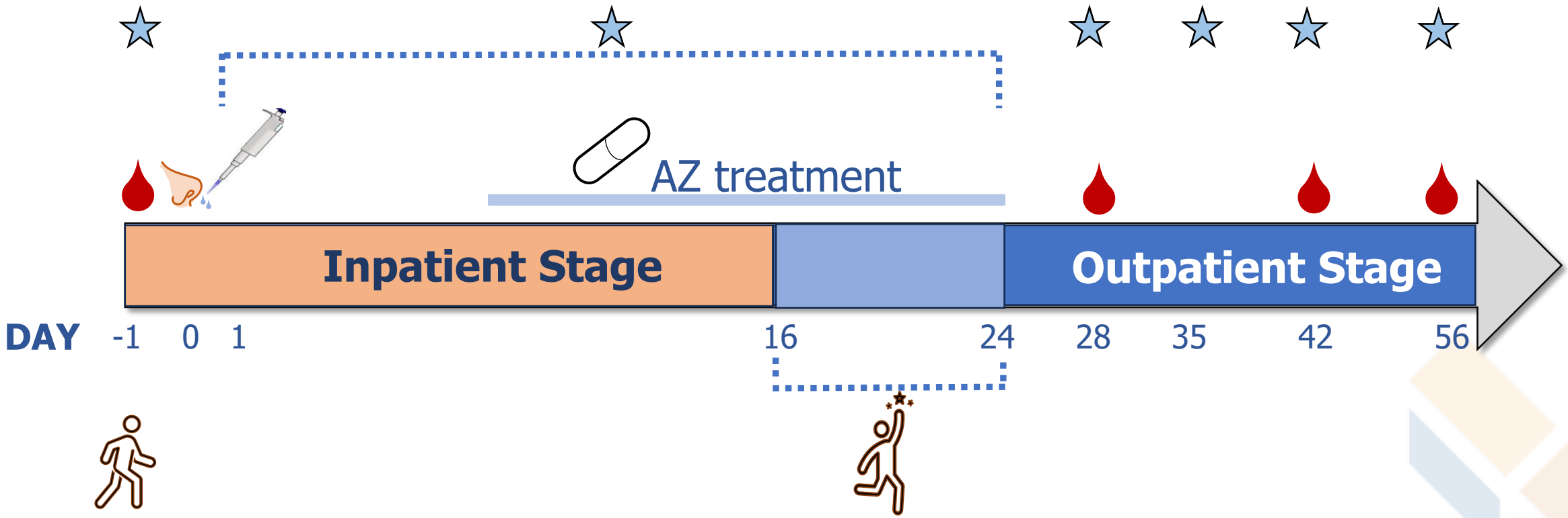
- **Experimental design:** To determine **HID70-90** by safe dose escalation phase, followed by dose confirmation phase.
- **Inoculation schedule:** A single dose of challenge inoculum administered intranasally.
- **Rescue/eradication therapy:** All participants were treated with azithromycin regardless of individual outcome.

| *B. pertussis* CFU Dose in 0.2 mL | | |
|---|---|---|
| **Dose #** | **Colony forming units (CFU)** | |
| 1 | 1000 | $10^3$ |
| 2 | 5000 | $5 \times 10^3$ |
| *3* | **10000* | *$10^4$* |
| 4 | 50000 | $5 \times 10^4$ |
| 5 | 100000 | $10^5$ |
| 6 | 500000 | $5 \times 10^5$ |
| 7 | 1000000 | $10^6$ |
| 8 | 5000000 | $5 \times 10^6$ |
| 9 | 10000000 | $10^7$ |
| 10 | 50000000 | $5 \times 10^7$ |
| 11 | 100000000 | $10^8$ |

*** Starting dose**

# Study Eligibility and Schedule

**Nasal wash and/or Nasopharyngeal aspirate**




PARTICIPANTS: 18-40 years old, eligibility criteria, wP and aP status, sex/gender

# Blinded Adjudication

## Adjudication exercise

- 3 adjudicators (R3, R4, R5)
- Participant snapshots
- Blinded to dose level per participant & treatment start
- Outcomes assigned were compared using the **Cohen's Kappa (chance corrected agreement)**

**Outcome groups:**

1. Non-Infected
2. Infected without Symptoms
3. Infected with Symptoms

| VARIABLES | Day -1 | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9... | ...Day 16 | Day 17 | Day 18 | Day 19 | Day 20 | Day 21 | Day 22 | Day 23 | Day 28 | Day 35 | Day 42 | Day 56 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PCR is481(NW) | | | | | xxx | xxx | N/E | xxx | N/E | xxx | xxx | xxx | xxx | xxx | xx | xx | xx | | | Neg | Neg | Neg | Neg |
| PCR ptxs1(NW) | | | | | xx | xx | N/E | xxx | N/E | xxx | xxx | xxx | xxx | x | Neg | Neg | Neg | | | | | | |
| Culture(NW) | Neg | | | | + | + | +++ | ++ | ++ | +++ | +++ | +++ | +++ | Neg | Neg | Neg | Neg | | | | | | |
| PCR is481(NPA) | | | | | Neg | xxx | xxx | xxx | xxx | xxx | xxx | xx | xxx | xxx | xx | xxx | Neg | | | | | | |
| PCR ptxs1(NPA) | | | | | Neg | xx | xxx | xxx | xxx | xxx | xxx | Neg | xxx | xxx | xx | xx | Neg | | | Neg | Neg | Neg | Neg |
| Culture(NPA) | Neg | | | | Neg | + | +++ | ++ | +++ | +++ | +++ | Neg | ++ | + | Neg | Neg | Neg | | | Neg | Neg | Neg | Neg |
| Fever | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | | | | | |
| Malaise | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | | | | | |
| Fatigue | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | | | | | |
| Runny Nose | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | | | | | |
| Nasal Congestion | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | | | | | | | |
| Sneezing | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | | | | | | | |
| Watery Eyes | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | | | | | |
| Red Eyes | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | | | | | |
| Sore throat | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | | | | | | | |
| Cough | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | | | | | | | |
| Anti-PT IgG (EU/mL) | <10 | <10 | <10 | | <10 | | <10 | | <10 | | | | | | | | | | | | 54 | 59 | 26 |
| FHA IgG (IU/mL) | 22 | | | | | | | | | | | | | | | | | | | | | 65 | 71 |
| PRN IgG (IU/mL) | 196 | | | | | | | | | | | | | | | | | | | | | 350 | 311 |
| FIM IgG (EU/mL) | <16 | | | | | | | | | | | | | | | | | | | <16 | | <16 | <16 |

SHEDDING

SYMPTOMS

SEROLOGY

# Blinded Adjudication

## 1. Adjudication results

- No specific criteria, only clinical judgement
- Moderate – substantial agreement

## 2. Investigator assessment

- 2 Investigators (R1, R2)
- Established criteria for clinical events (infection, symptoms)

## 3. Automated algorithm

- Did not adversely affect specificity of clinician outcomes
- Algorithm adopted

**Table 1**

| Comparison | *Kappa |
|---|---|
| R3 with R4 | 0.62 |
| R3 with R5 | 0.56 |
| R4 with R5 | 0.67 |

**Table 2**

| Comparison | *Kappa |
|---|---|
| R1 with R2 | 0.92 |

**Outcome groups:**

1. Non-Infected
2. Infected without Symptoms
3. Infected with Symptoms

***Kappa**

**$< 0.2$ poor agreement**

**$0.2 - 0.4$ fair agreement**

**$0.4 - 0.6$** *moderate agreement*

**$0.6 - 0.8$** *substantial agreement*

**$> 0.8$ great agreement**

**Table 3**

| Agreement with Automated Algorithm | | *Kappa |
|---|---|---|
| R1 | 96% | 0.94 |
| R2 | 93% | 0.90 |
| R3 | 69% | 0.57 |
| R4 | 74% | 0.61 |
| R5 | 86% | 0.79 |

# Automated Algorithm for Determining Clinical Outcome

**RULE 1:**

**INFECTION STATUS**

Bacterial detection is determined from Day 6 post challenge to first day of treatment:

- 1 or more culture **OR**
- 3 or more PCR

**No Bacterial Detection** → **NON-INFECTED**

**Bacterial Detection** → **INFECTED**

**RULE 2:**

**PERTUSSIS SYMPTOM STATUS**

Solicited symptoms starting or worsening with confirmed infection status meeting the following complement:

- 2 or more symptoms, at least one of which must be a respiratory specific symptom

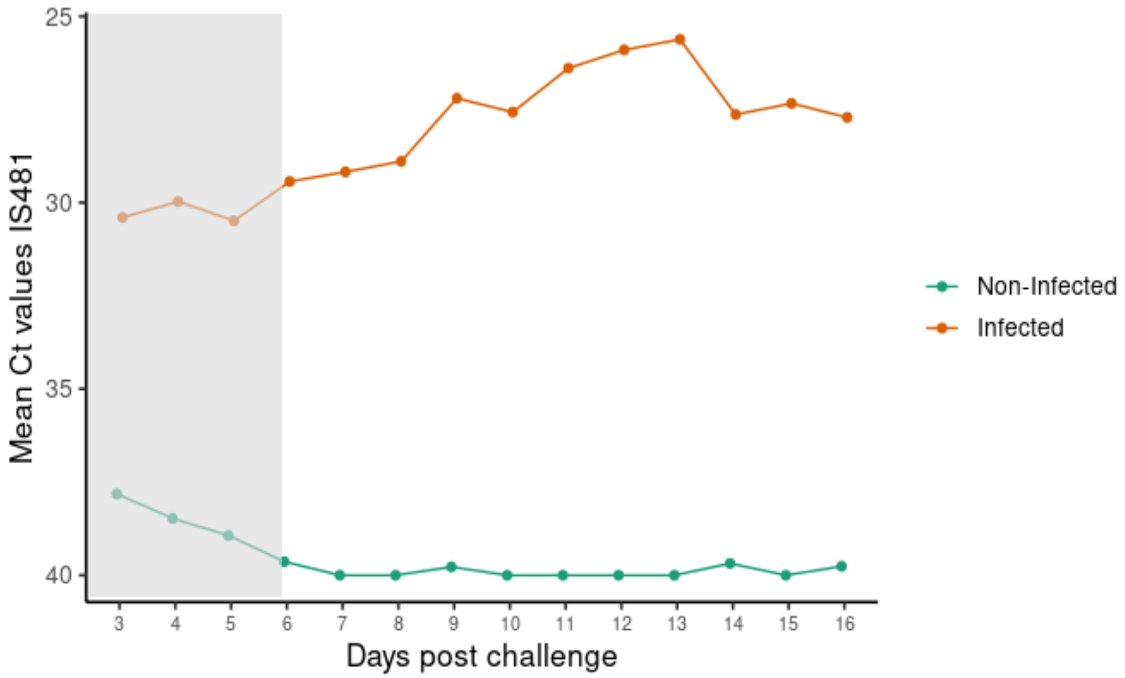
**No Symptoms** → **ASYMPTOMATIC INFECTION**

**Symptoms** → **SYMPTOMATIC INFECTION**

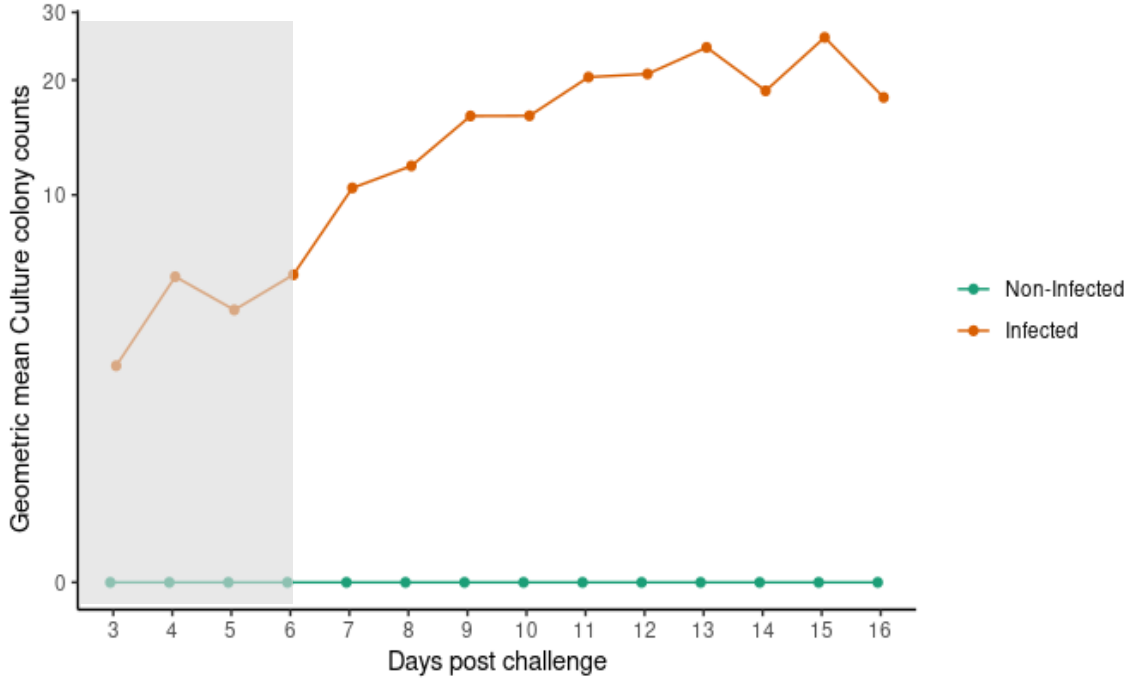
# RATIONALE for Rule 1

**Day 6 start for assessment of bacterial shedding:**

- Avoids potential confounding (over reporting) from residual dose effect on Days 3 to 5
- Established shedding accounts for known incubation period




**Mean PCR IS481 CT values comparing all dose groups, days post challenge**




**Geometric mean colony counts comparing all dose groups, days post challenge**

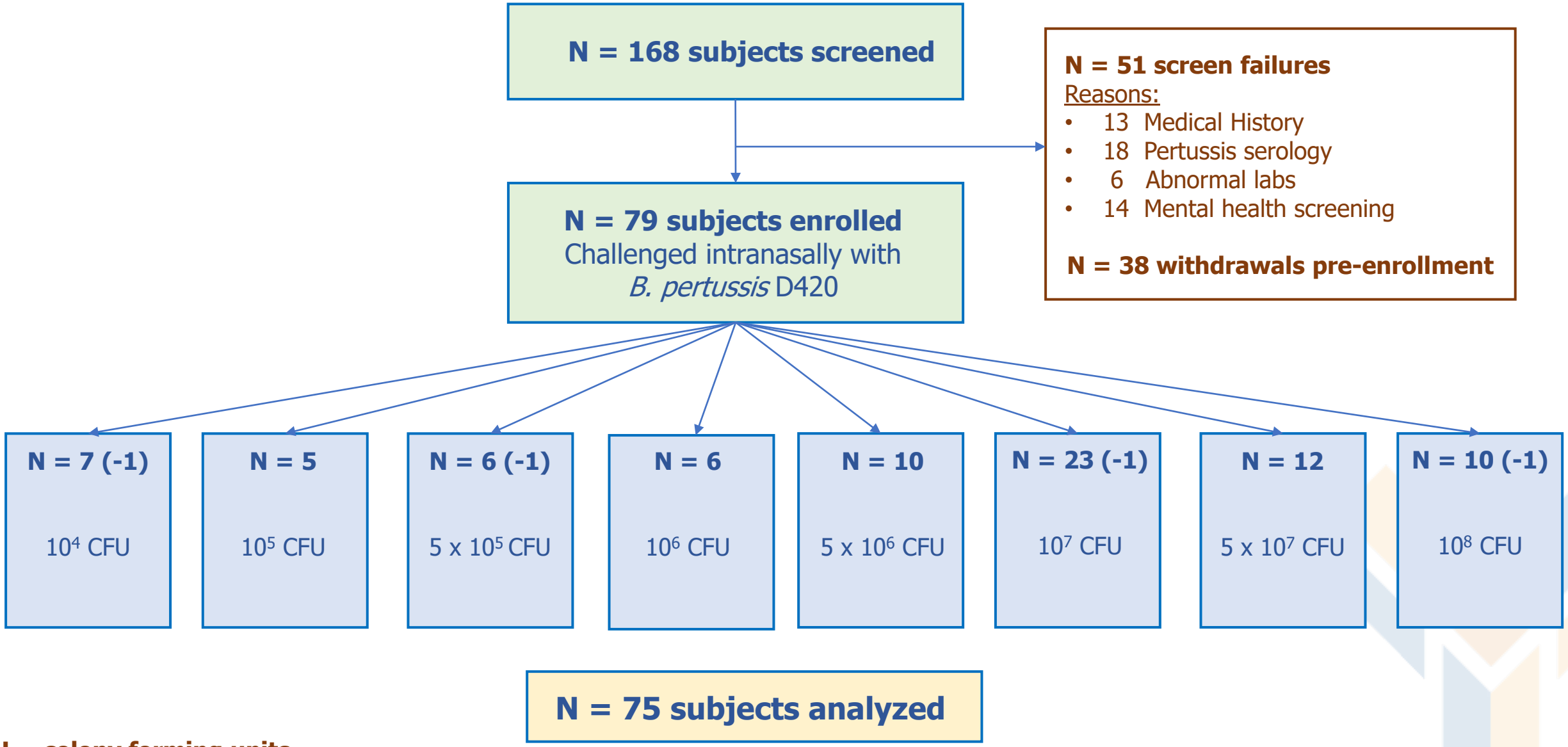
# RATIONALE for Rule 2

| Body System | Solicited Symptoms | Respiratory Association |
|---|---|---|
| Systemic | Fatigue, Malaise | Non-Respiratory |
| Nasal | Nasal Congestion, Runny Nose, Sneezing | Respiratory |
| Pharyngeal | Sore Throat | Respiratory |
| Ocular | Watery Eyes, Red Eyes | Respiratory |
| Pulmonary | Cough | Respiratory |

**2 or more symptoms, at least one of which is a respiratory symptom with shedding**:

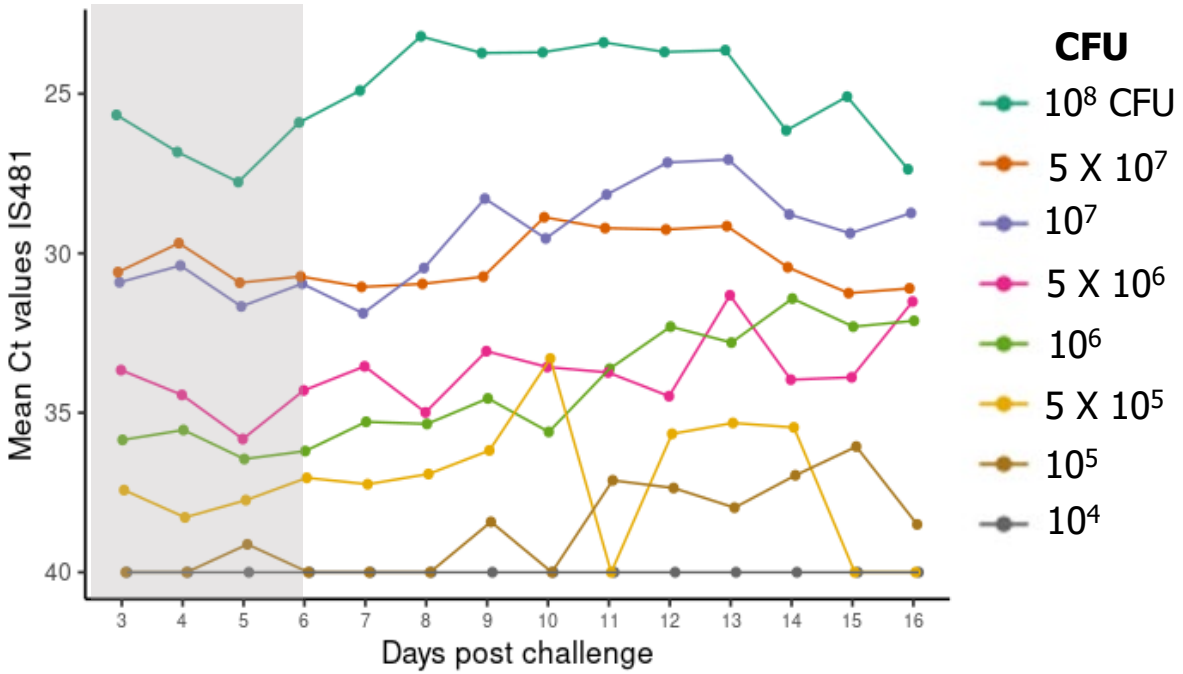
- Excludes symptoms not associated with infection (baseline/background "noise")
- Aligns with the symptoms typically reported in the catarrhal stage of natural infection
- Acknowledges the non-specific, protean nature of the catarrhal stage clinical manifestations (avoids over-reporting of symptomatic outcome )

# Participant Selection and Dose Cohorts

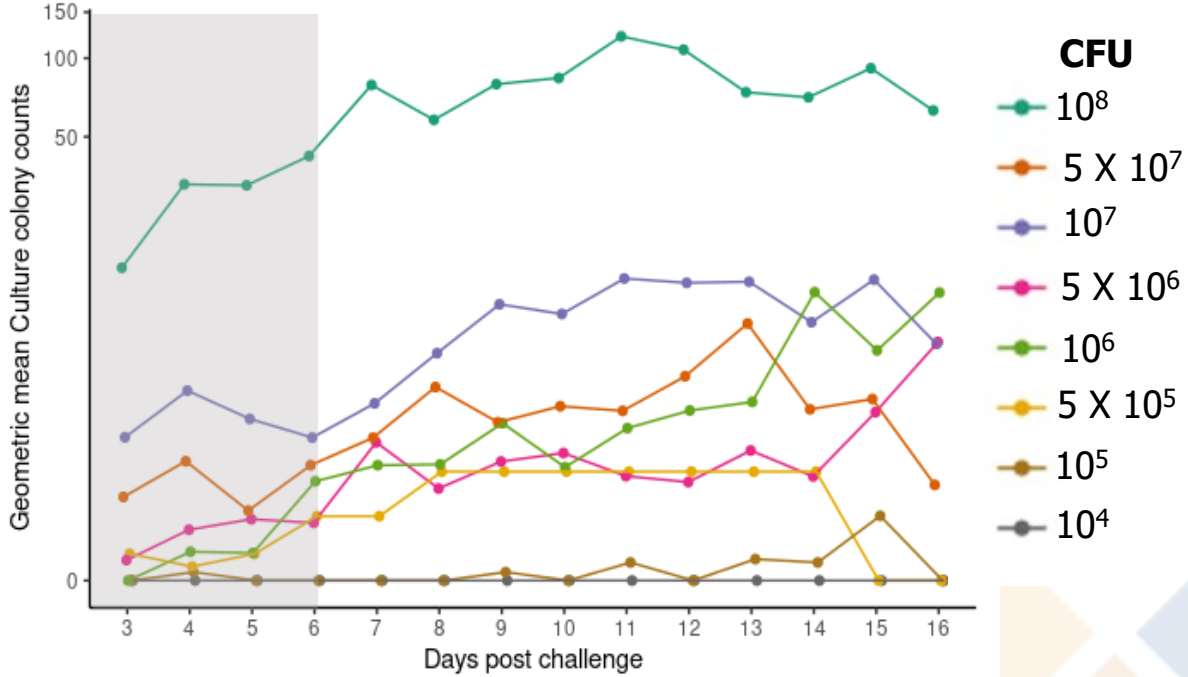



**CFU = colony forming units**

# A dose response of bacterial shedding is observed by PCR & Culture

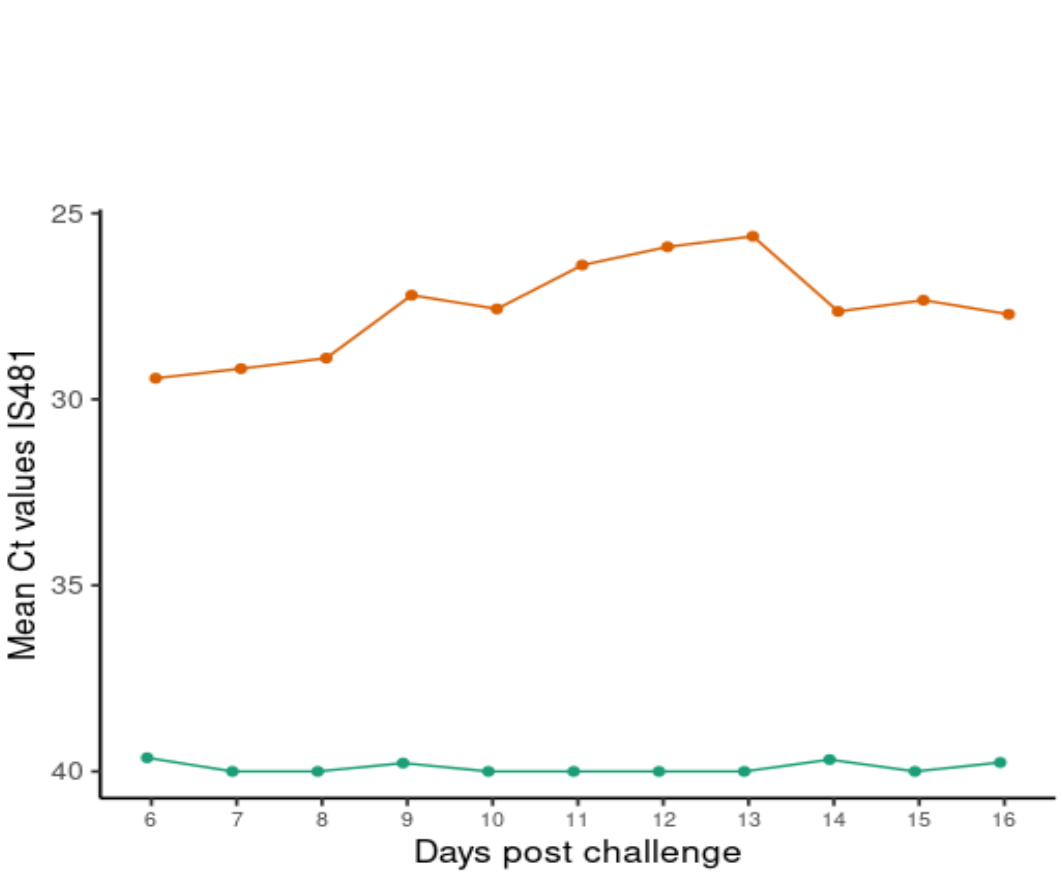



Mean PCR IS481 CT values comparing all dose groups, days post challenge

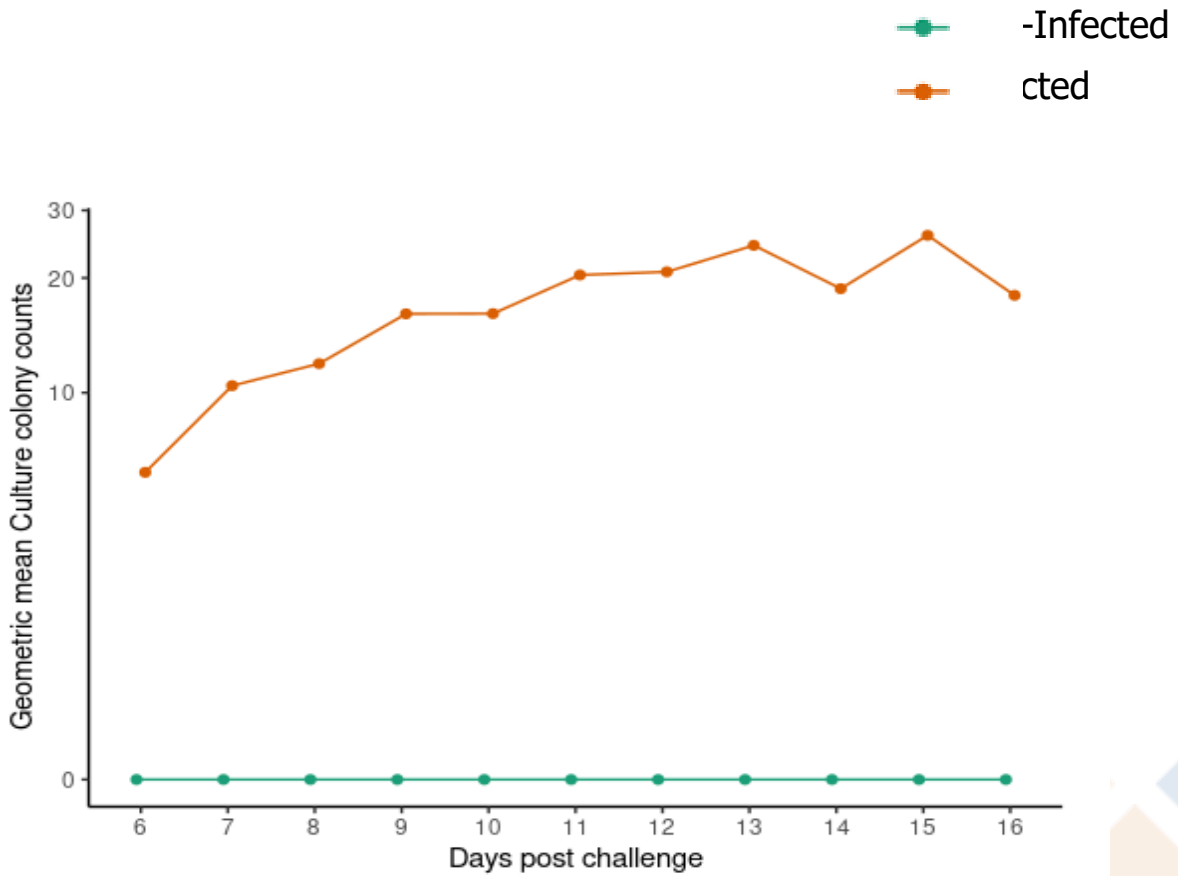



Geometric mean colony counts comparing all dose groups, days post challenge

# Bacterial shedding signals by PCR & Culture are sustained beyond Day 6



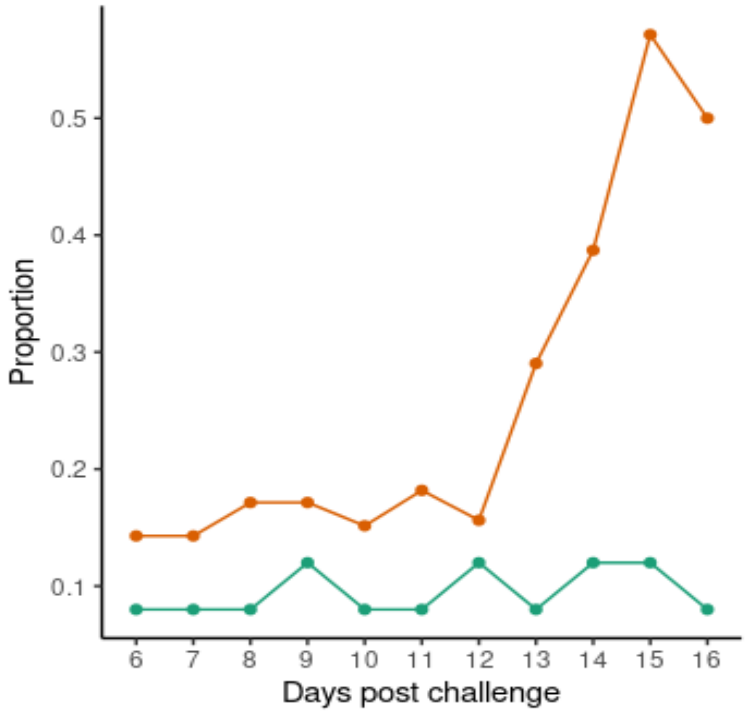

Mean PCR IS481 CT values comparing Infected to Non-Infected, days post challenge

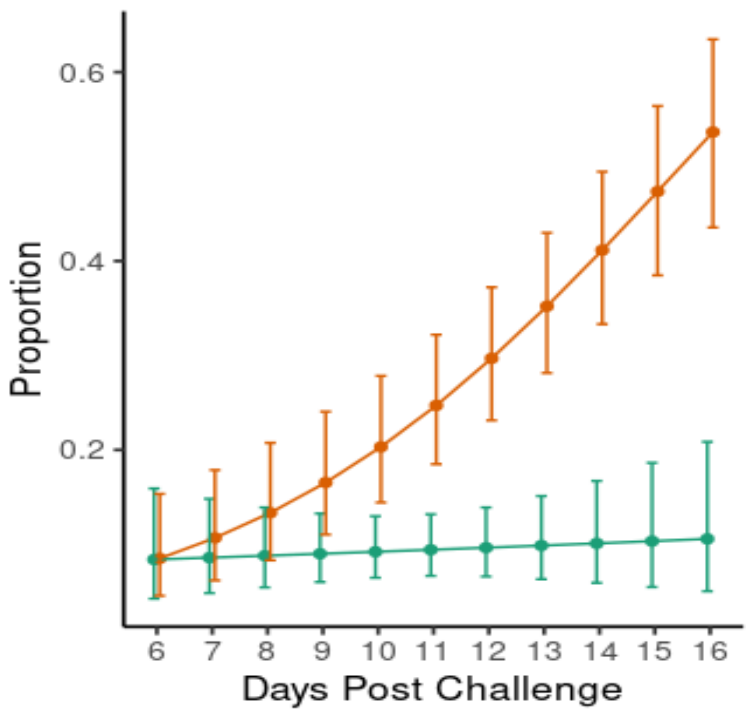


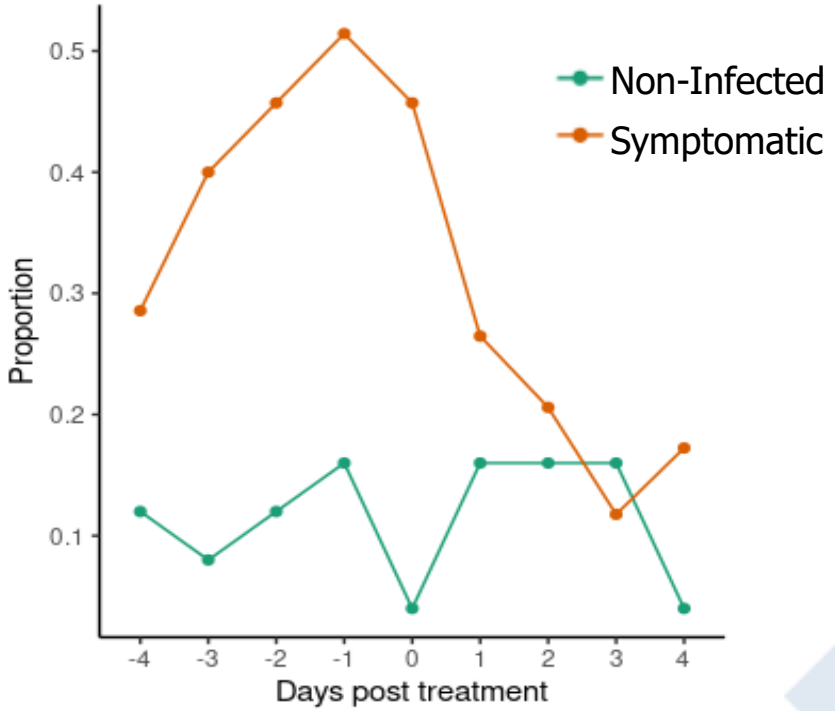

Geometric mean colony counts comparing Infected to Non-Infected, days post challenge

# Outcomes: All doses Symptomatic (n=35) vs Non-Infected (n=25)

## Variable(s): Systemic Symptoms (Fatigue and Malaise)




A

B

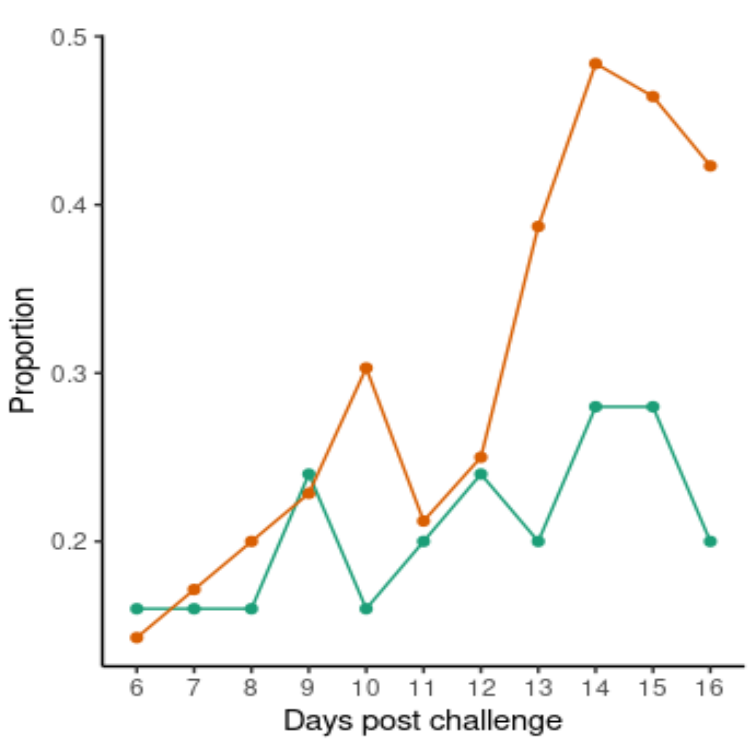
C

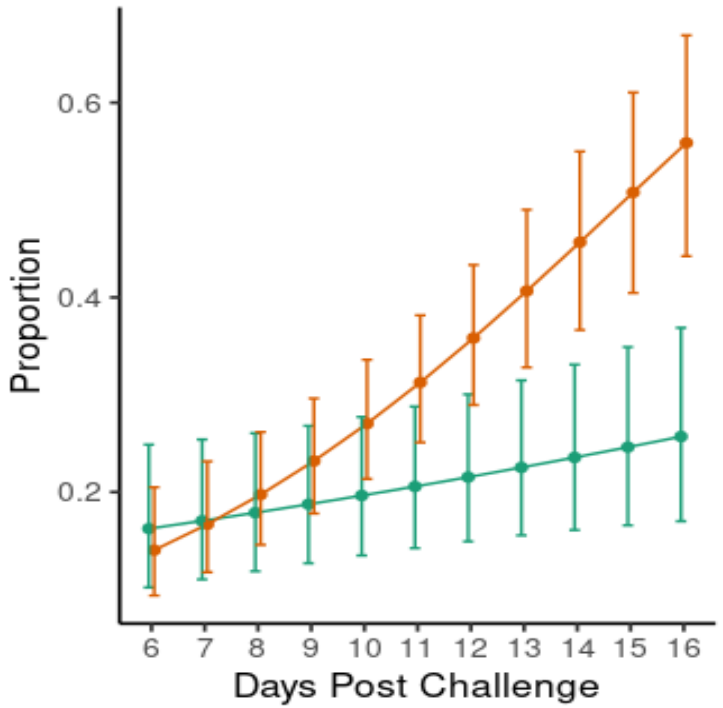
**Systemic symptoms by days post challenge and outcome:
A – rate per day; B – modelled to assess rate of change in reporting**

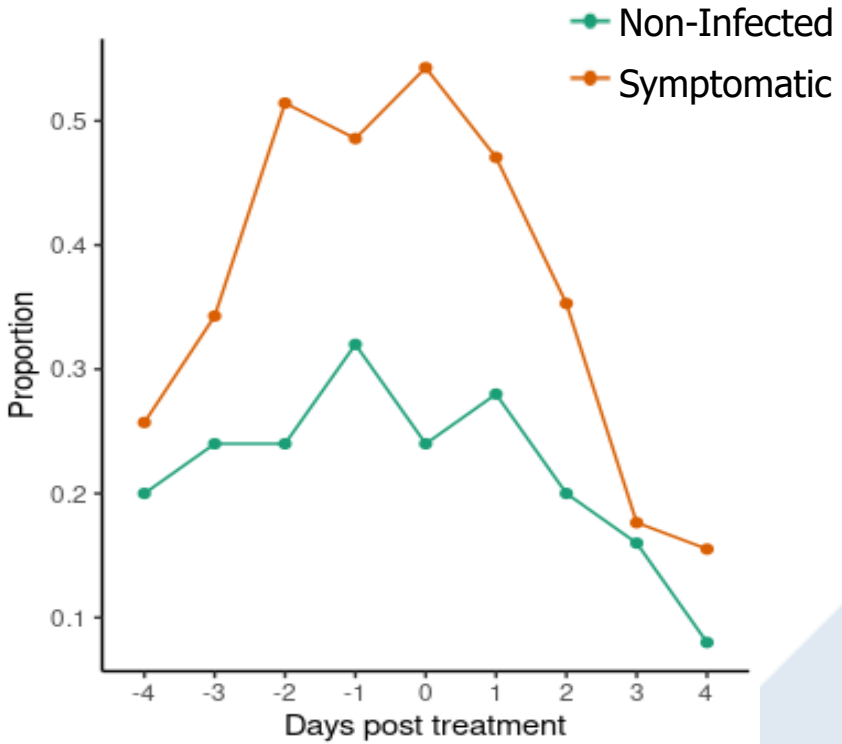
**C. Effect of treatment (Day 0) by days pre/post treatment and outcome**

# Outcomes: All doses Symptomatic (n=35) vs Non-Infected (n=25)

## Variable(s): Nasal Symptoms (Nasal Congestion, Rhinorrhea, and Sneezing)



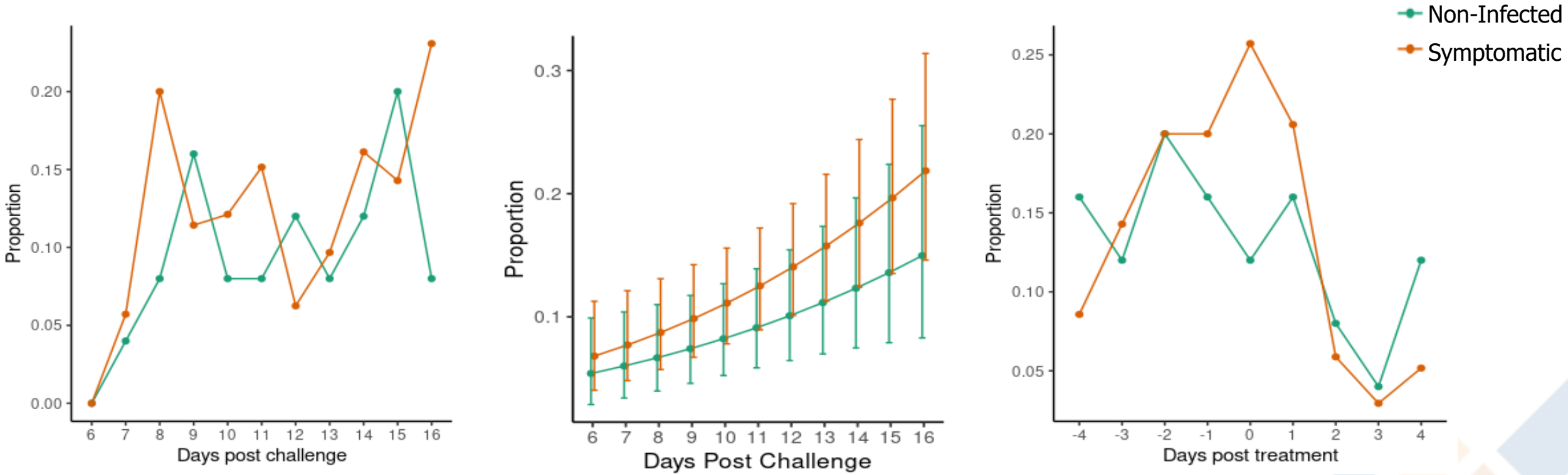

A B C

**Nasal symptoms by days post challenge and outcome:
A – rate per day; B – modelled to assess rate of change in reporting**

**C. Effect of treatment (Day 0) by days post treatment and outcome**

## Outcomes: All doses Symptomatic (n=35) vs Non-Infected (n=25)

## Variable(s): Pharyngeal Symptoms (Sore Throat)




A

B

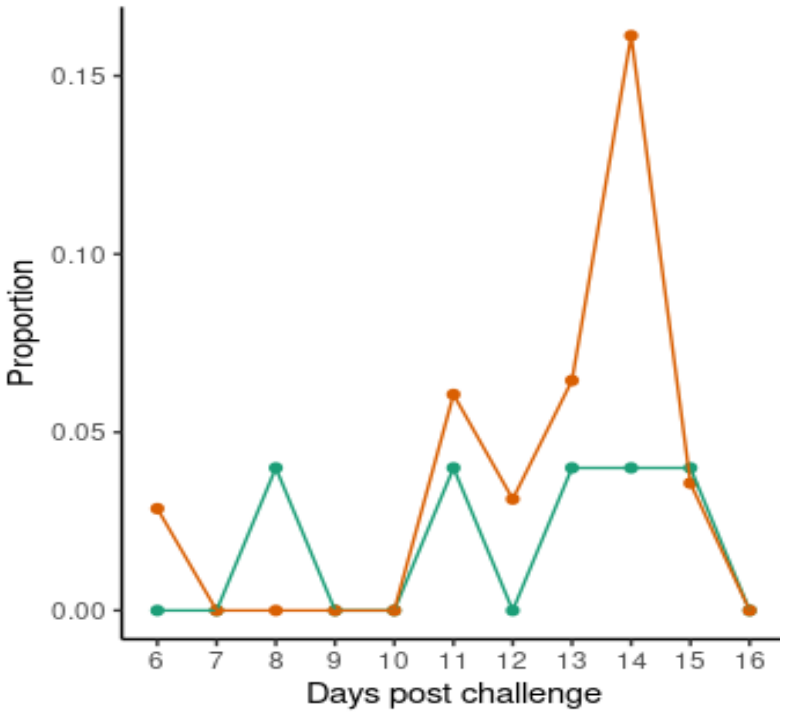
C

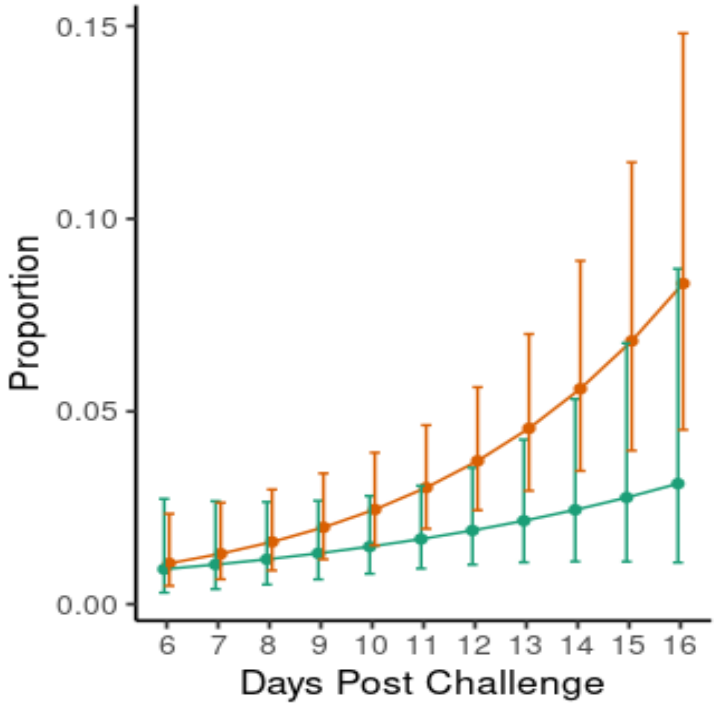
**Pharyngeal symptoms by days post challenge and outcome:**
**A – rate per day; B – modelled to assess rate of change in reporting**

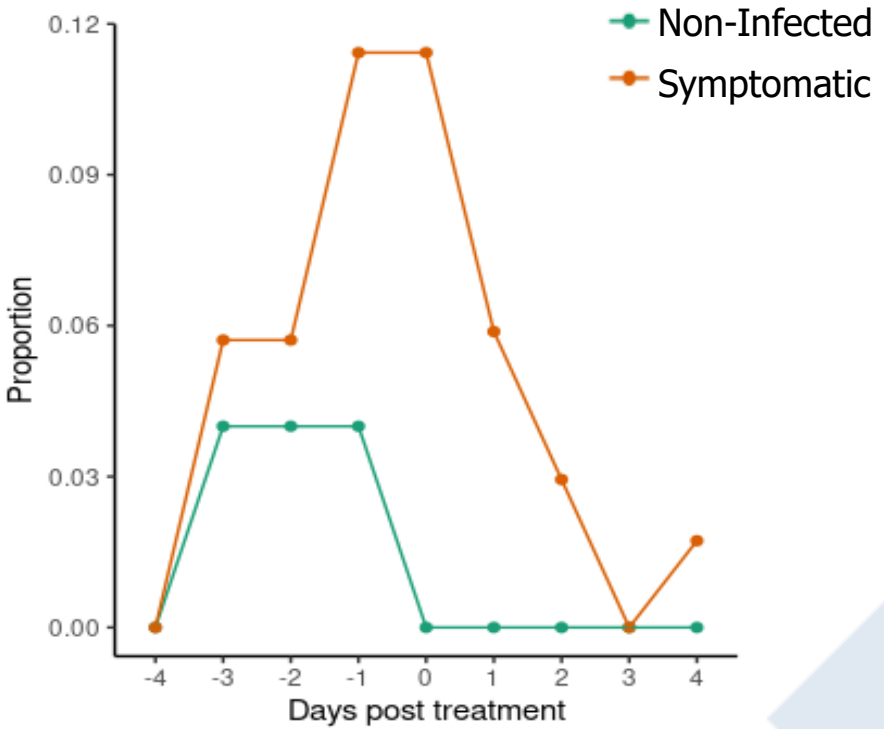
**C. Effect of treatment (Day 0) by days post treatment and outcome**

# Outcomes: All doses Symptomatic (n=35) vs Non-Infected (n=25)

## Variable(s): Ocular Symptoms (Watery Eyes, Red Eyes)




A

B

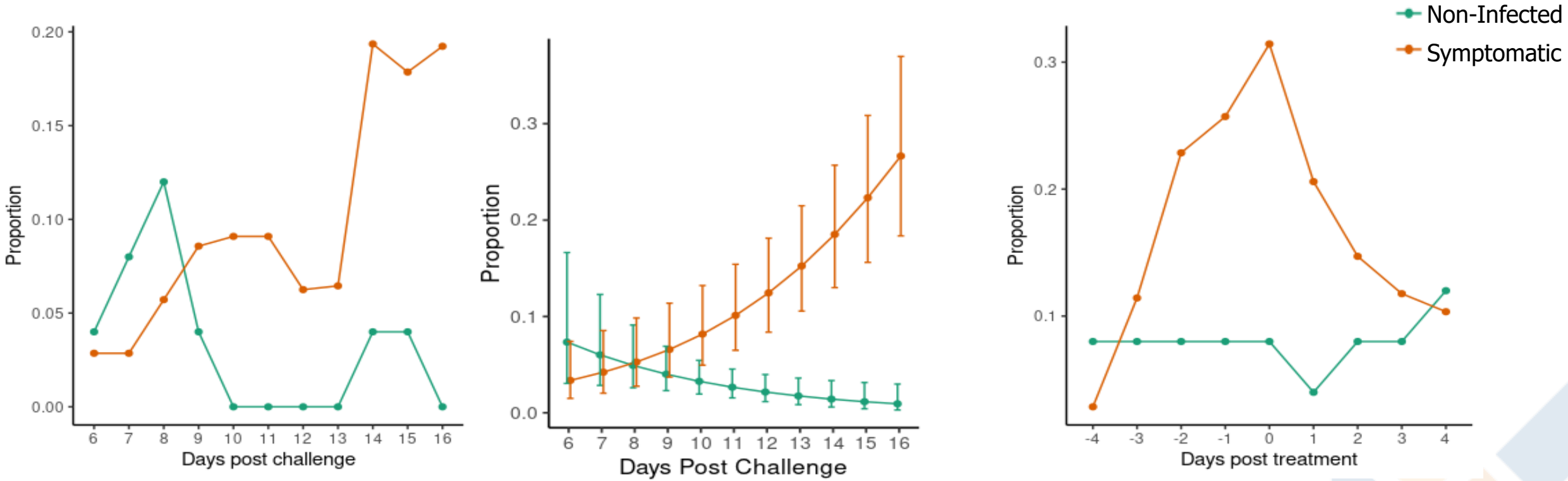
C

Ocular symptoms by days post challenge and outcome:
A – rate per day; B – modelled to assess rate of change in reporting

C. Effect of treatment (Day 0) by days post treatment and outcome

# Outcomes: All doses Symptomatic (n=35) vs Non-Infected (n=25)

## Variable(s): Pulmonary Symptoms (Cough)




A

B

C

**Pulmonary symptoms by days post challenge and outcome:**
**A – rate per day; B – modelled to assess rate of change in reporting**

**C. Effect of treatment (Day 0) by days post treatment and outcome**

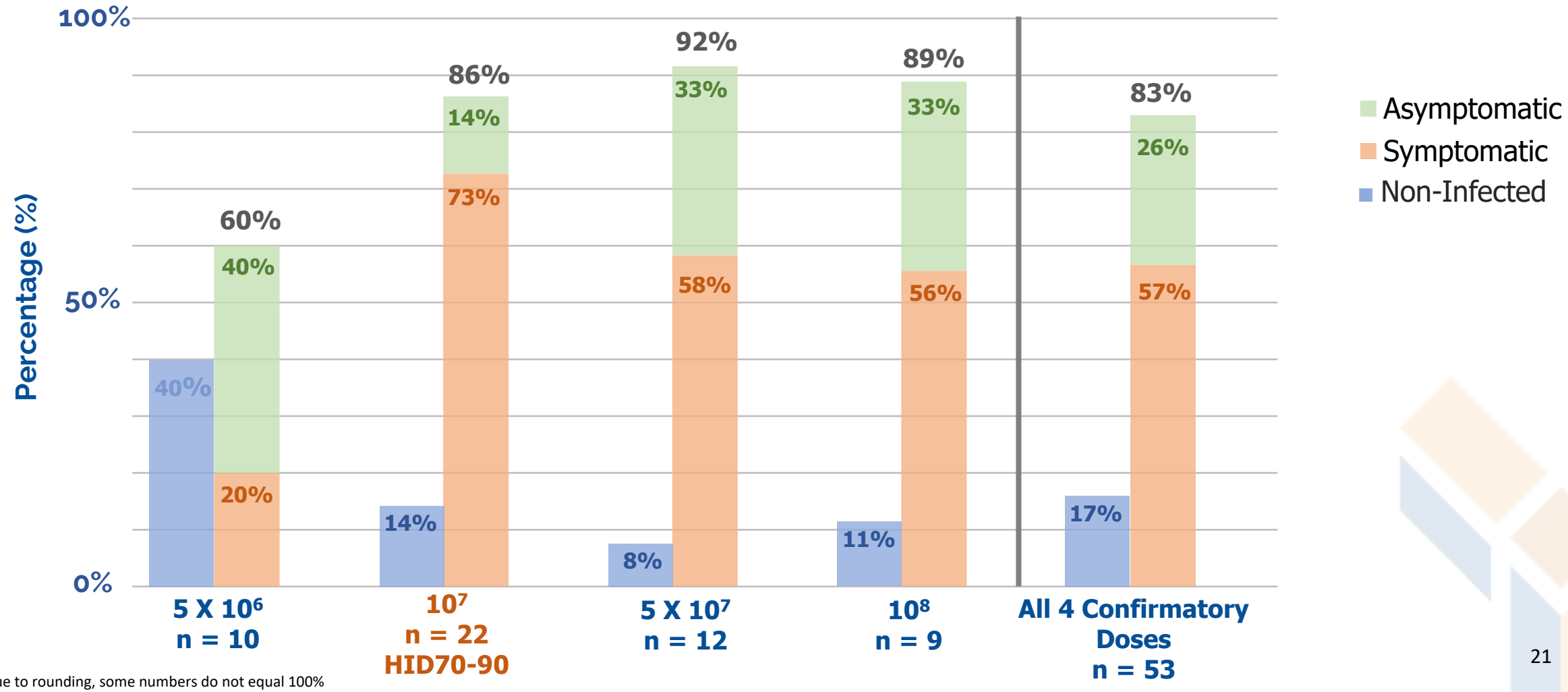
# Rates* of Clinical Outcomes per Dose

| Dose CFU | N | No Bacterial detection | Bacterial detection | | |
|---|---|---|---|---|---|
| | | Non-infected n (%) | Infected n (%) | Asymptomatic n (%) | Symptomatic n (%) |
| $10^4$ | 6 | 6 (100%) | 0 (0%) | 0 (0%) | 0 (0%) |
| $10^5$ | 5 | 3 (60%) | 2 (40%) | 1 (20%) | 1 (20%) |
| $5 \times 10^5$ | 5 | 4 (80%) | 1 (20%) | 0 (0%) | 1 (20%) |
| $10^6$ | 6 | 3 (50%) | 3 (50%) | 0 (0%) | 3 (50%) |
| **$5 \times 10^6$** | **10** | **4 (40%)** | **6 (60%)** | **4 (40%)** | **2 (20%)** |
| **$10^7$** | **22** | **3 (14%)** | **19 (86%)** | **3 (14%)** | **16 (73%)** |
| **$5 \times 10^7$** | **12** | **1 (8%)** | **11 (92%)** | **4 (33%)** | **7 (58%)** |
| **$10^8$** | **9** | **1 (11%)** | **8 (89%)** | **3 (33%)** | **5 (56%)** |

*Due to rounding, some numbers do not equal 100%

Infected = Asymptomatic + Symptomatic

# Rates* of Clinical Outcomes by Confirmatory Doses




*Due to rounding, some numbers do not equal 100%

# Accuracy of Confirmatory Doses

## 5 X $10^6$ | $10^7$ | 5 x $10^7$ | $10^8$ (CFU )

**Actual vs Target Doses**
Geometric means

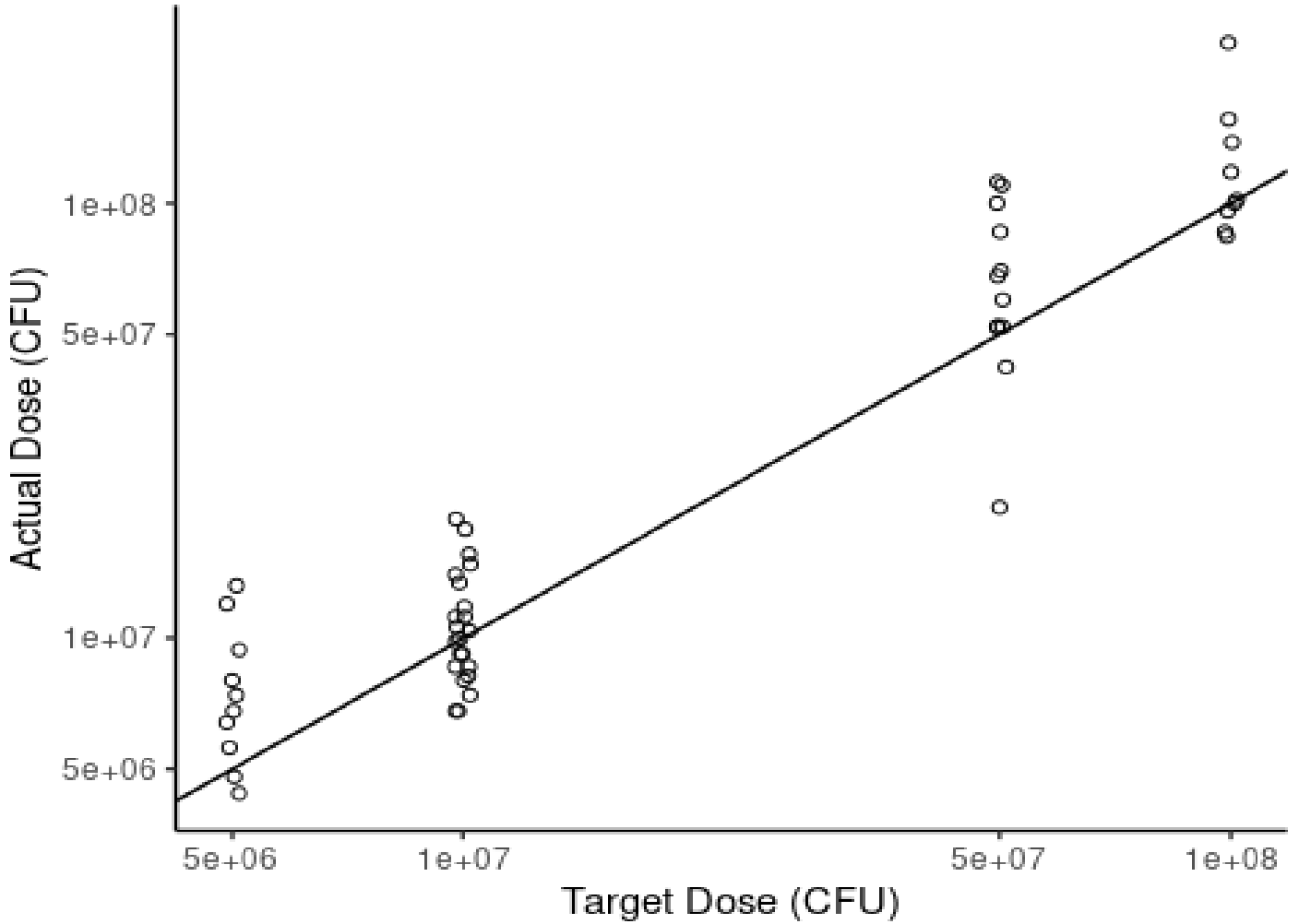
**5 X $10^6$**
Mean: 7.3 x $10^6$

**$10^7$ HID70-90**
Mean: 1.1 x $10^7$

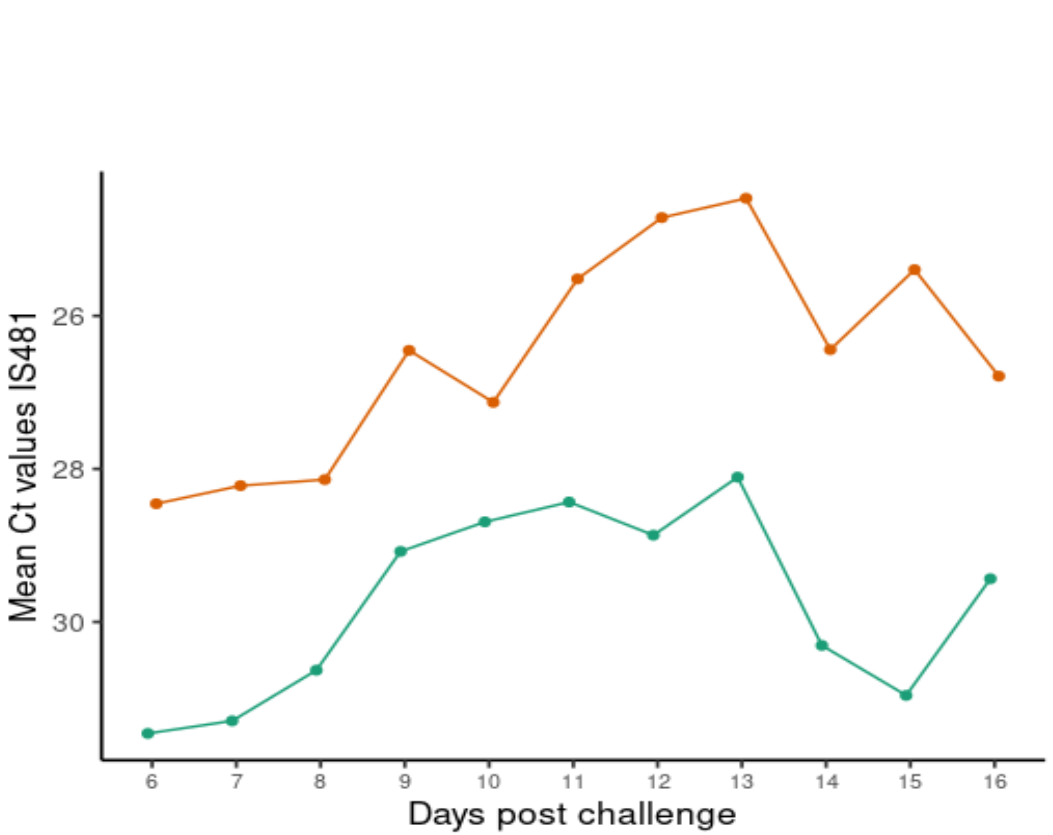
**5 X $10^7$**
Mean: 6.3 x $10^7$

**$10^8$**
Mean: 1.2 x $10^8$

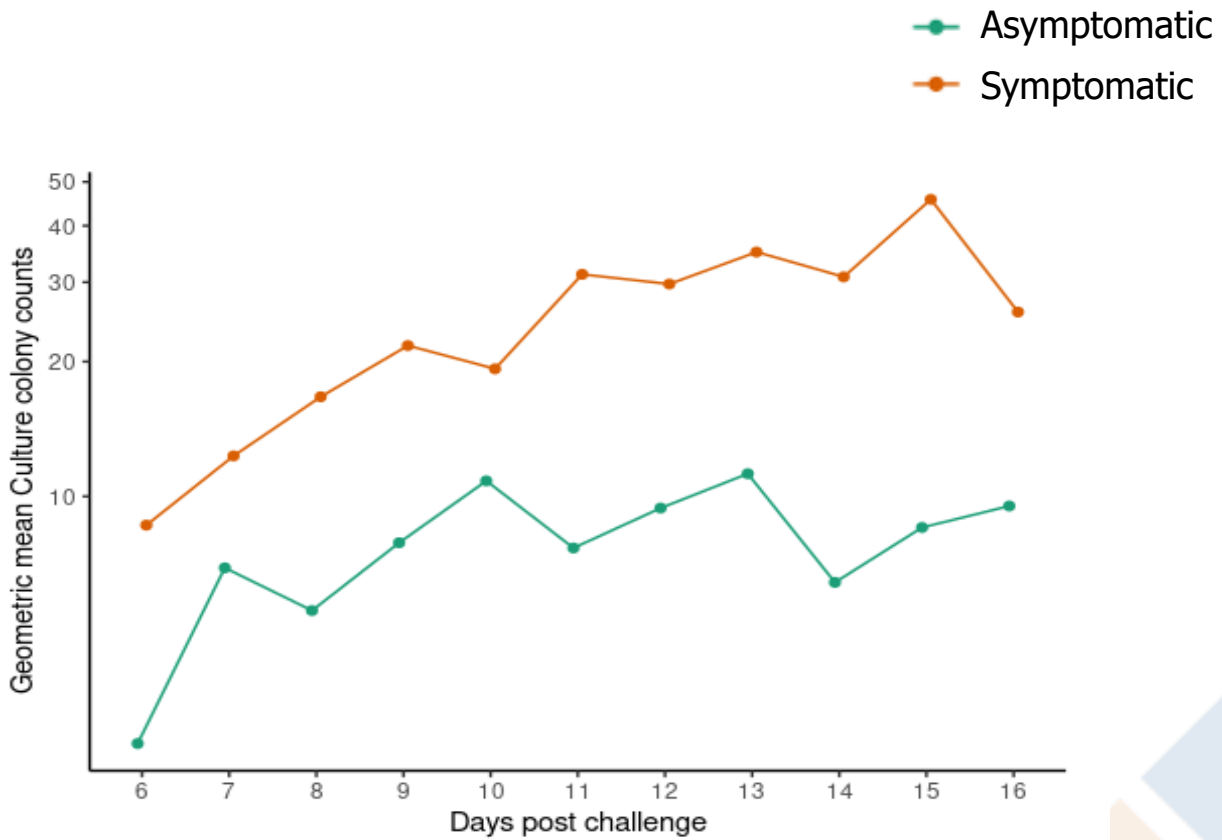
**All four confirmatory doses**
Mean: 2.2 x $10^7$



# Symptomatic Infection correlates with higher bacterial shedding by PCR & Culture

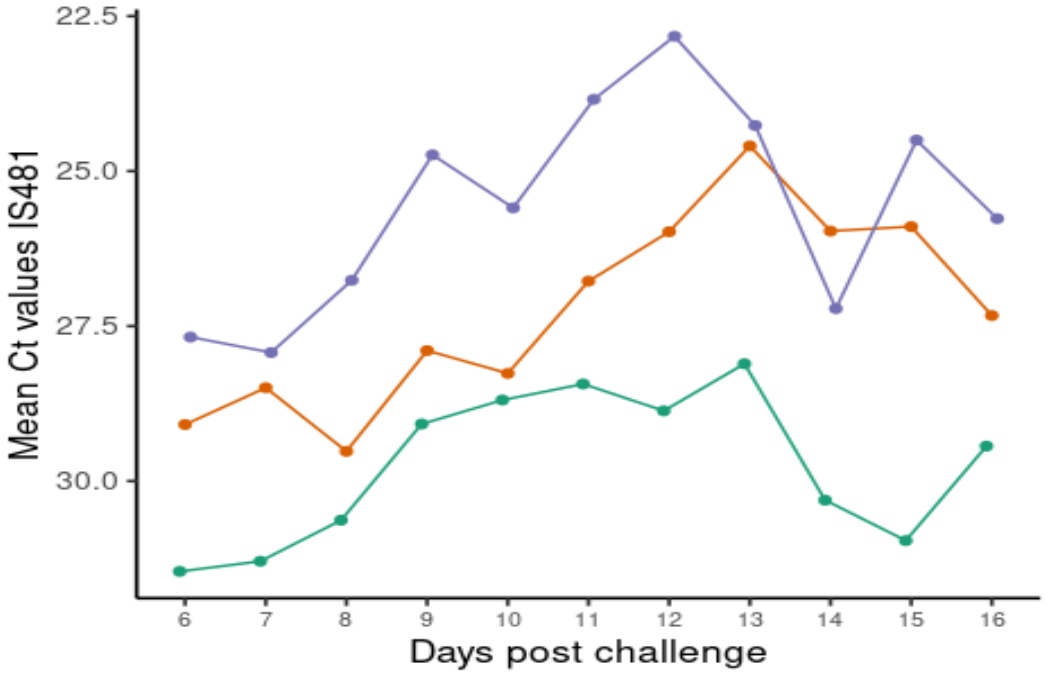



Mean PCR IS481 CT values comparing Asymptomatic and Symptomatic outcomes in confirmatory doses, days post challenge

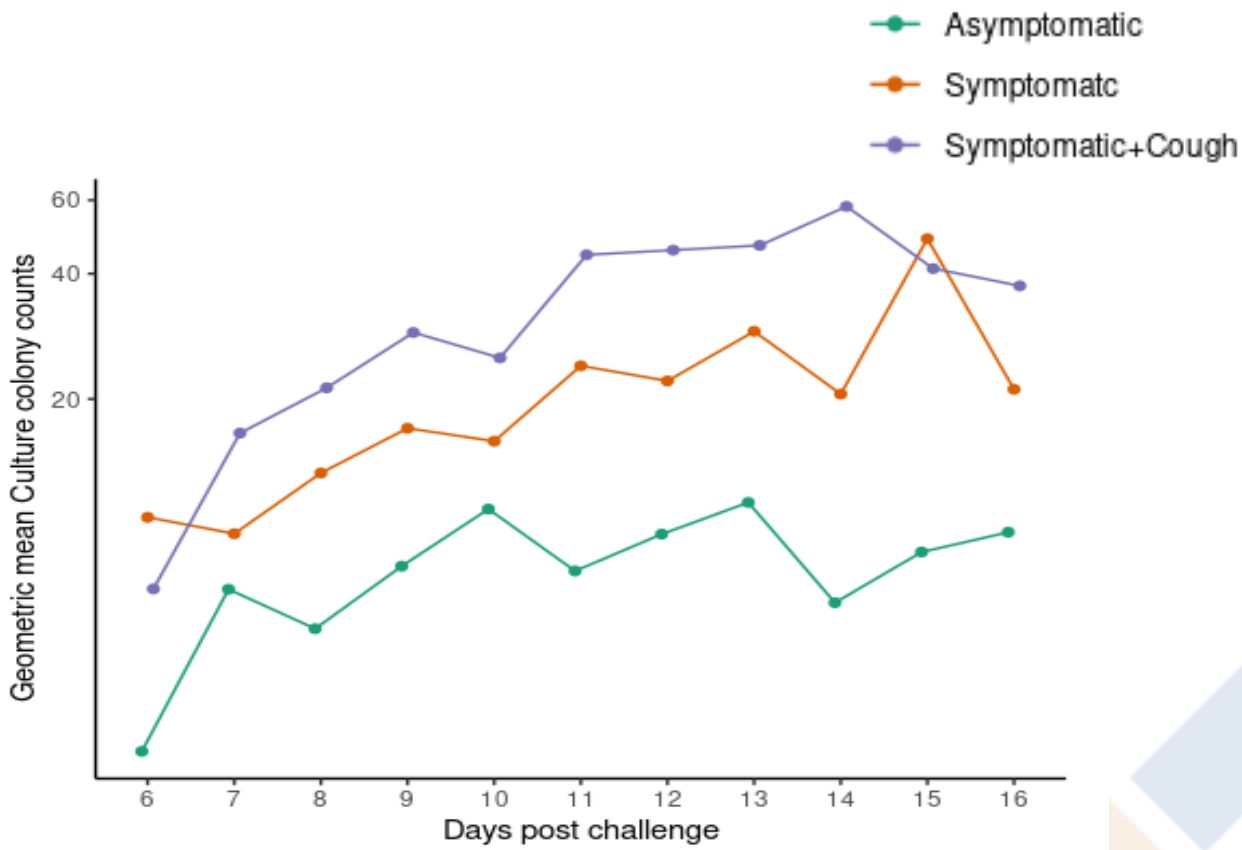



Geometric mean colony counts comparing Asymptomatic and Symptomatic outcomes in confirmatory doses, days post challenge

# Cough correlates with higher bacterial shedding by PCR & Culture




Mean PCR IS481 CT values comparing Symptomatic (with & without cough) and Asymptomatic outcomes over days post challenge



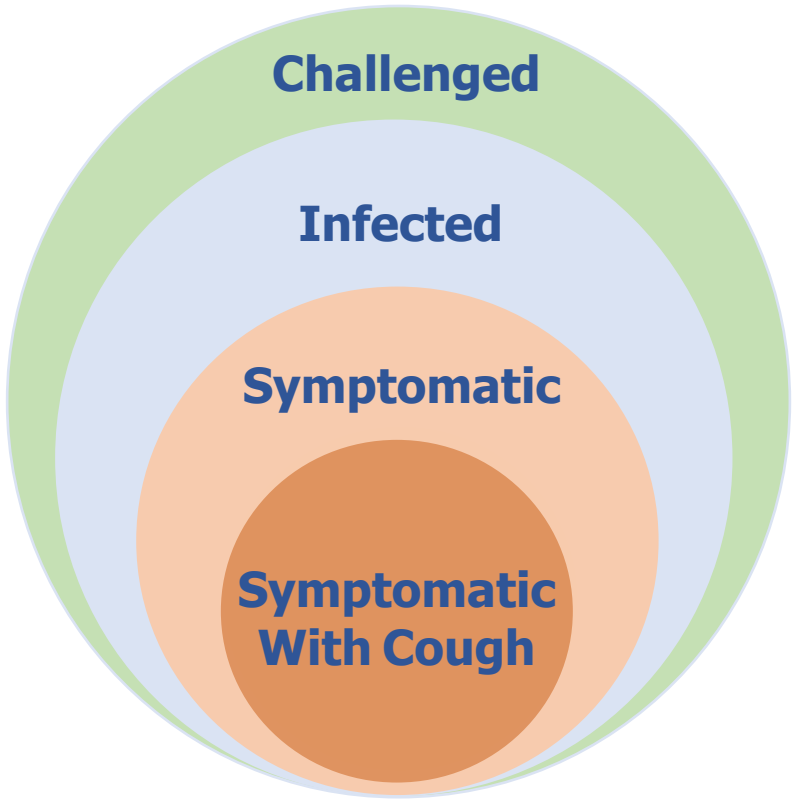

Geometric mean colony counts comparing Symptomatic (with & without cough) and Asymptomatic outcomes over days post challenge

# Frequency of Symptoms in Symptomatic Infection

| Body system | $10^7$ CFU – HID70-90 (*n= 16) | 5 X $10^6$ \| $10^7$ \|5 x $10^7$ \| $10^8$ (CFU ) (*n = 30) |
|---|---|---|
| | n (%) | n (%) |
| *Systemic* | *12 (75% )* | *25 (83% )* |
| *Nasal* | *15 (94% )* | *25 (83% )* |
| Ocular | 3 (19%) | 8 (27%) |
| Pharyngeal (ST) | 9 (56%) | 15 (50%) |
| *Cough* | *8 (50% )* | *15 (50% )* |

*n, the number of symptomatic participants in that group

# D420 Pertussis CHIM
# Endpoint Rates with Confirmatory Doses



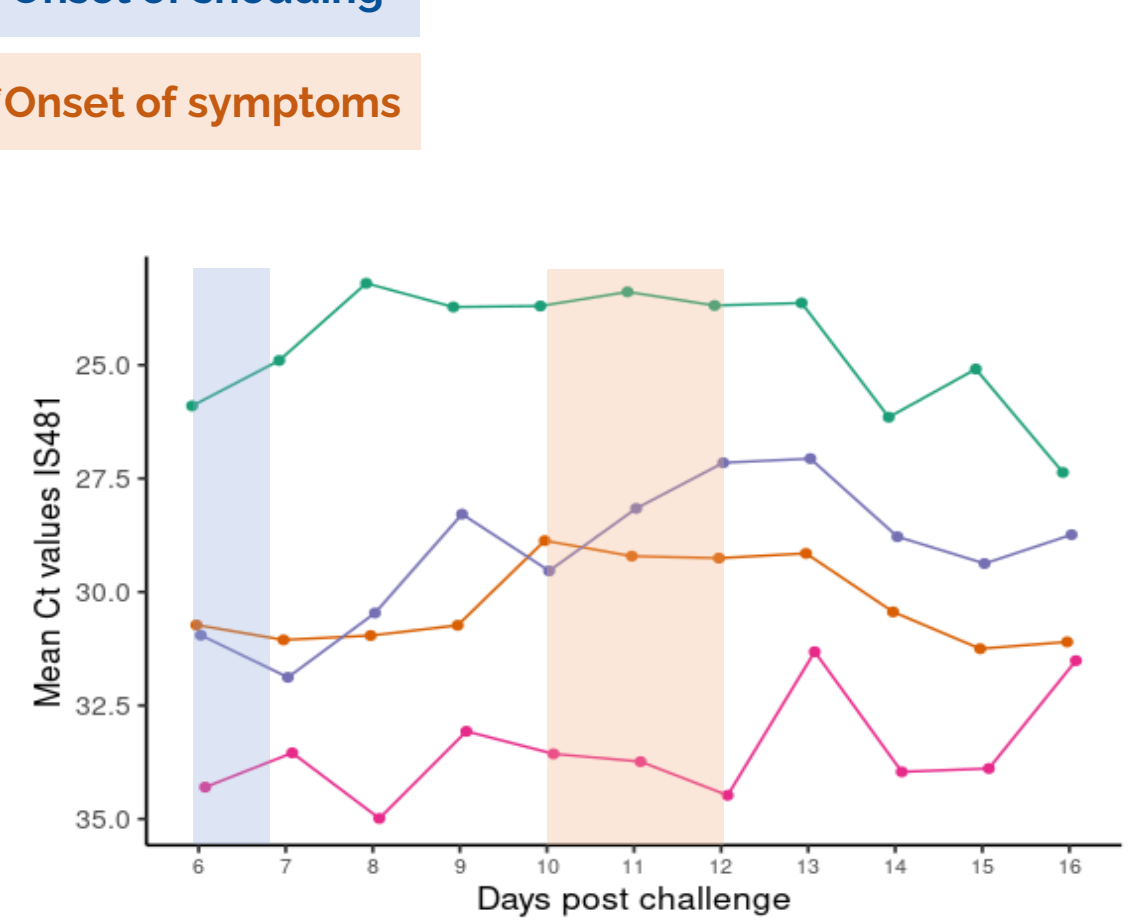

| Endpoints (N = no. challenged) | $5 \times 10^6$ (N = 10) | $10^7$ (N = 22) | $5 \times 10^7$ (N=12) | $10^8$ (N=9) |
|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (%) |
| **Infected** | 6 (60%) | 19 (86%) | 11 (92%) | 8 (89%) |
| **Symptomatic** | 2 (20%) | 16 (73%) | 7 (58%) | 5 (56%) |
| **Symptomatic with cough** | 1 (10%) | 8 (36%) | 3 (25%) | 3 (33%) |

**HID70-90**

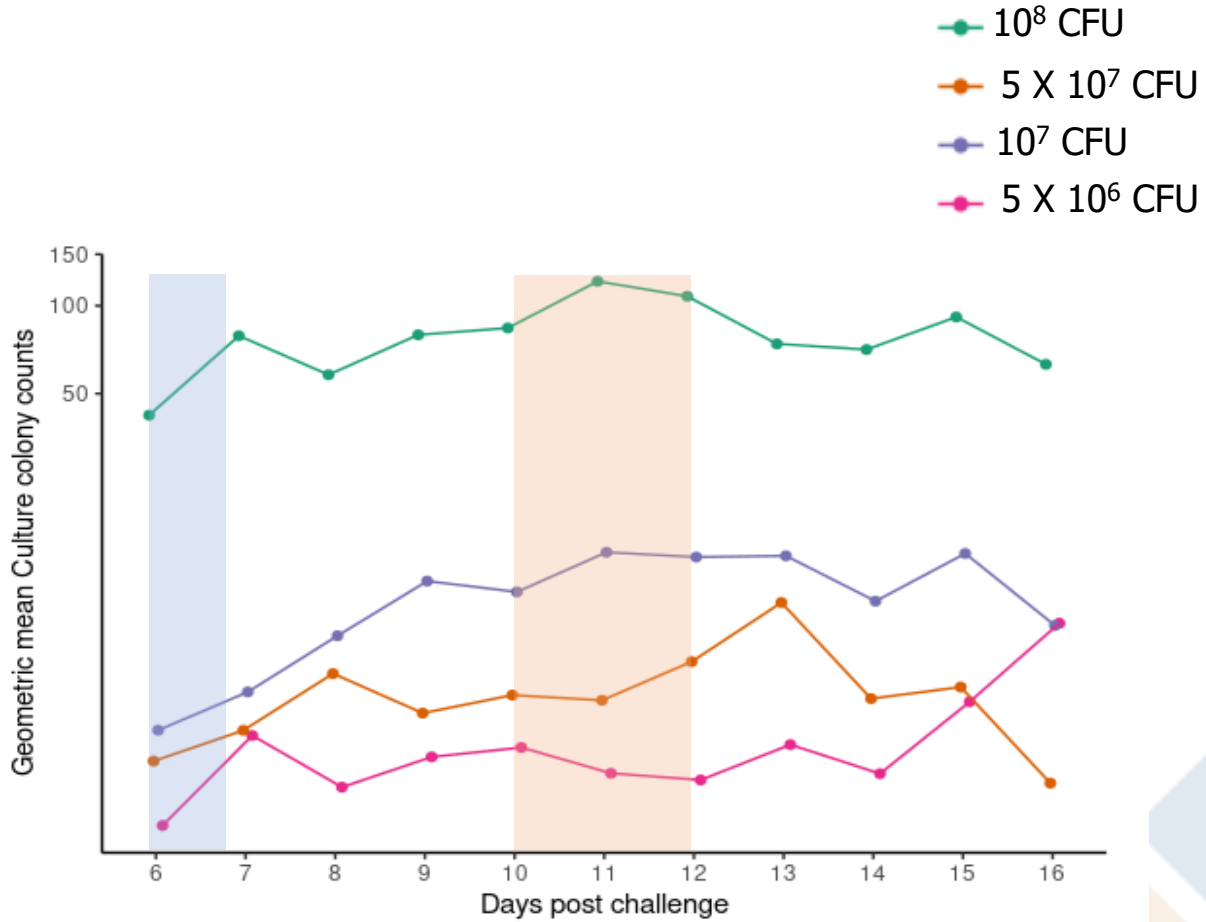
# Clinical Events: Onset of shedding precedes onset of clinical symptoms

*Onset of shedding

*Onset of symptoms




Mean PCR IS481 CT values comparing confirmatory doses over days post challenge




Geometric mean colony counts comparing confirmatory doses over days post challenge

# Conclusion

1. We present a controlled human infection model (CHIM) of D420 that can be used as a model of infection or mild symptomatic illness:
    - HID70-90 @ $10^7$ CFU
        - ➢ Overall infected, 86%
        - ➢ Mild symptomatic infection, 73%
        - ➢ Mild symptomatic infection with cough, 36% (where 50% of all symptomatic participants present with cough)
2. This adult pertussis CHIM model produces similar catarrhal symptoms to natural disease.
3. This model provides the potential for evaluating candidate vaccines for the prevention of pertussis infection and symptomatic illness.
4. We are currently evaluating this model for its performance with a pertactin-deficient isolate representing the current epidemiology in North America and worldwide.

CCFV
Canadian Center for Vaccinology

Dalhousie University
IWK Health
Nova Scotia Health

# The First North American Pertussis Controlled Human Infection Model (CHIM) Using the Pertactin-Producing D420 Isolate

# Thank you