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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

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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

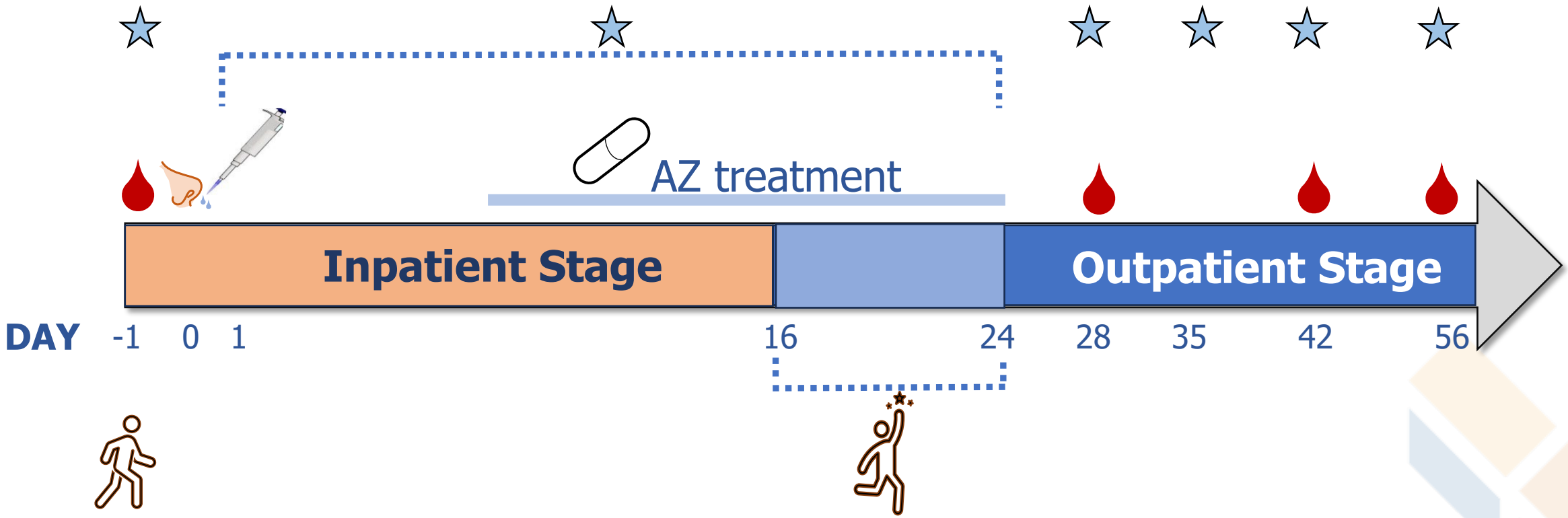
- **Experimental design:** To determine **HID70-90** by safe dose escalation phase, followed by dose confirmation phase.
- **Inoculation schedule:** A single dose of challenge inoculum administered intranasally.
- **Rescue/eradication therapy:** All participants were treated with azithromycin regardless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

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

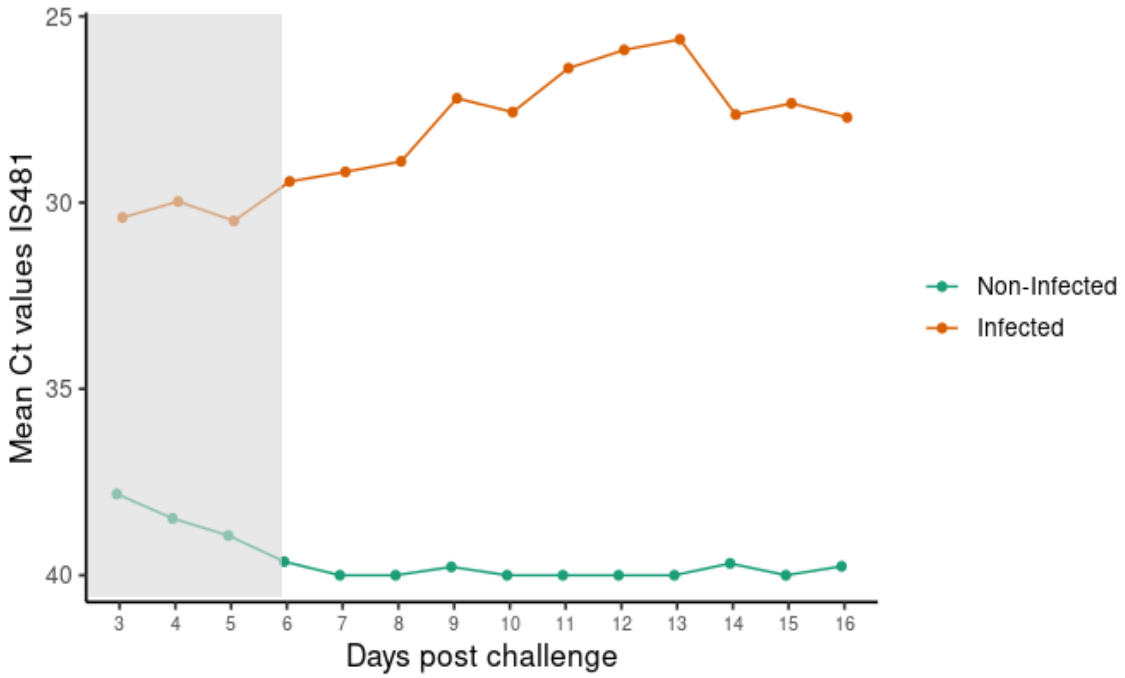
No Symptoms → **ASYMPTOMATIC INFECTION**

Symptoms → **SYMPTOMATIC INFECTION**

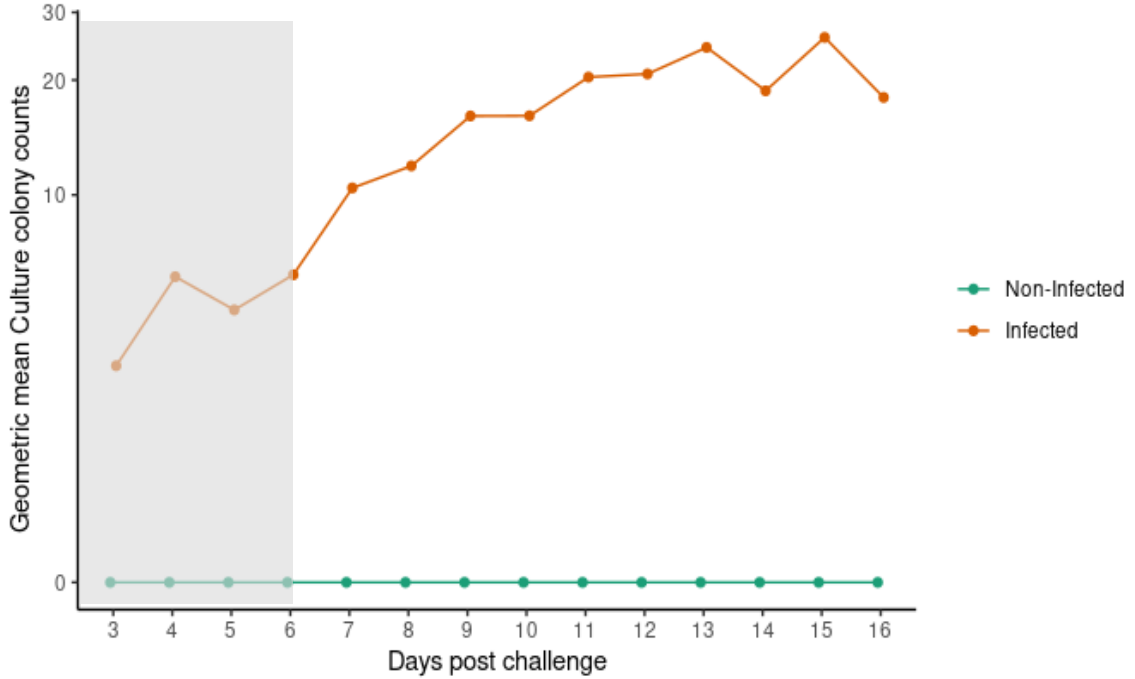
RATIONALE for Rule 1

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

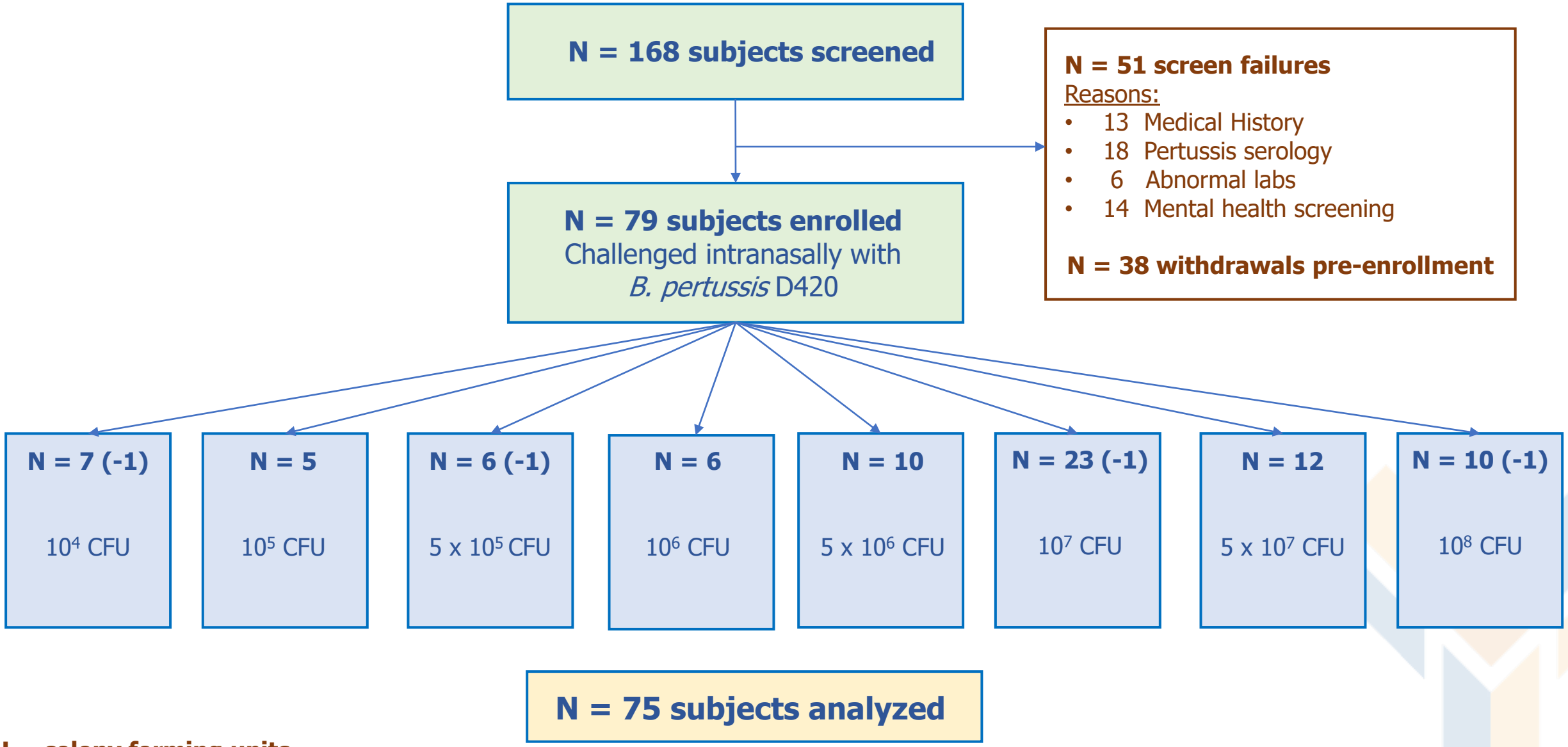
RATIONALE for Rule 2

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:

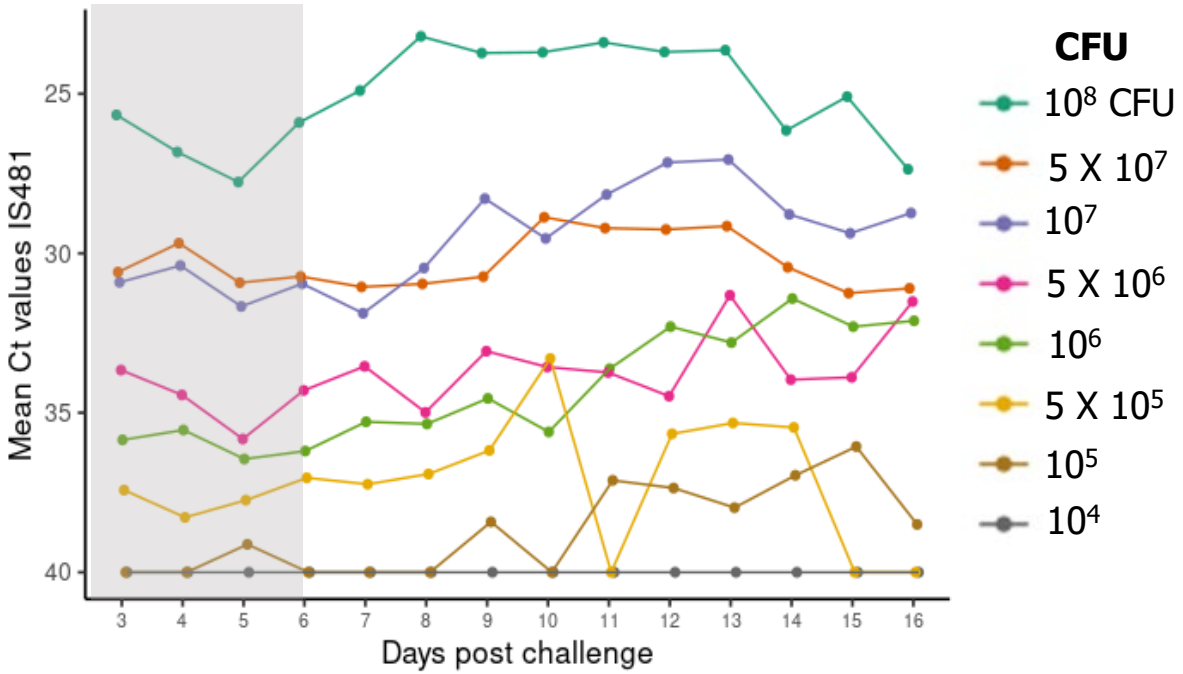
- Excludes symptoms not associated with infection (baseline/background "noise")
- Aligns with the symptoms typically reported in the catarrhal stage of natural infection
- Acknowledges the non-specific, protean nature of the catarrhal stage clinical manifestations (avoids over-reporting of symptomatic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

Participant Selection and Dose Cohorts

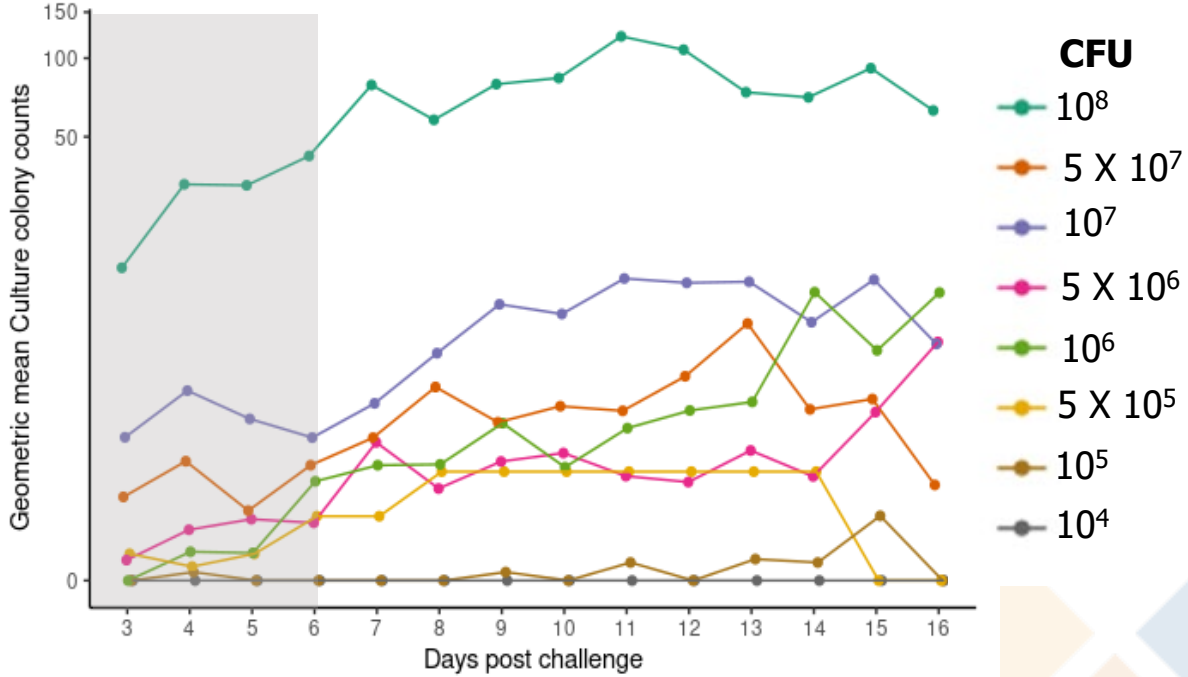


CFU = colony forming units

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

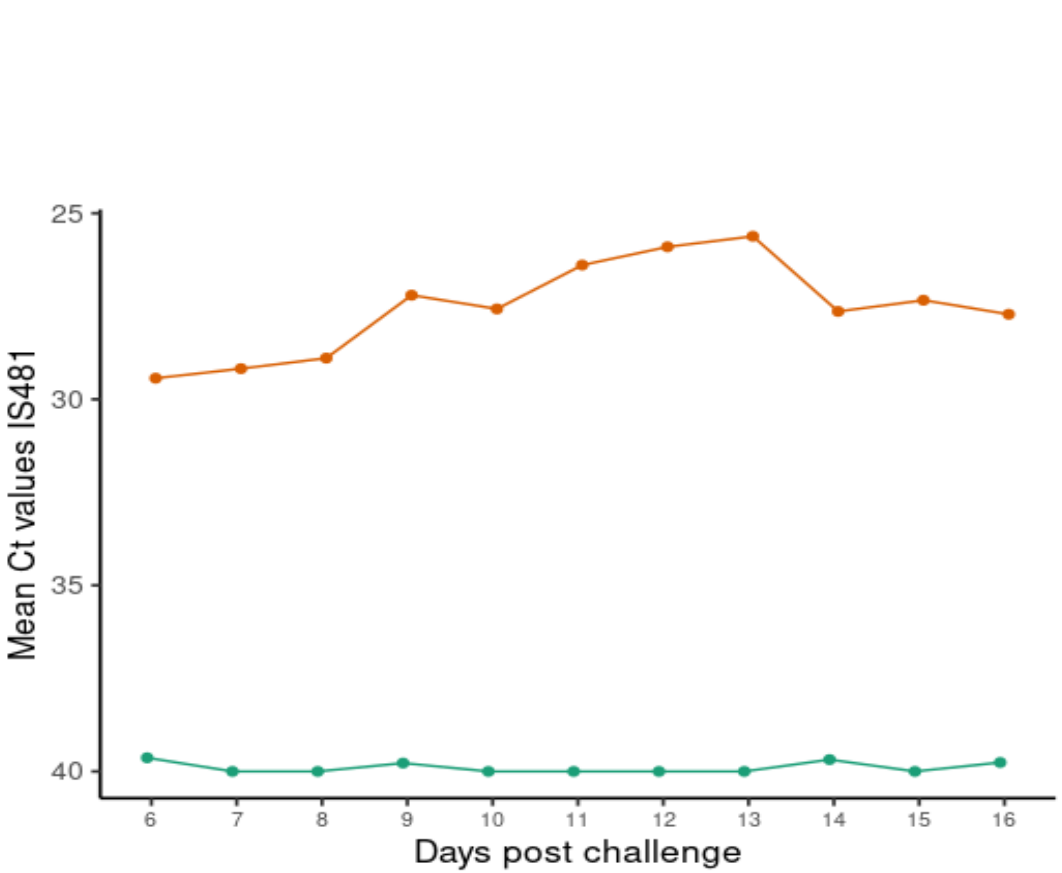


Mean PCR IS481 CT values comparing all dose groups, days post challenge

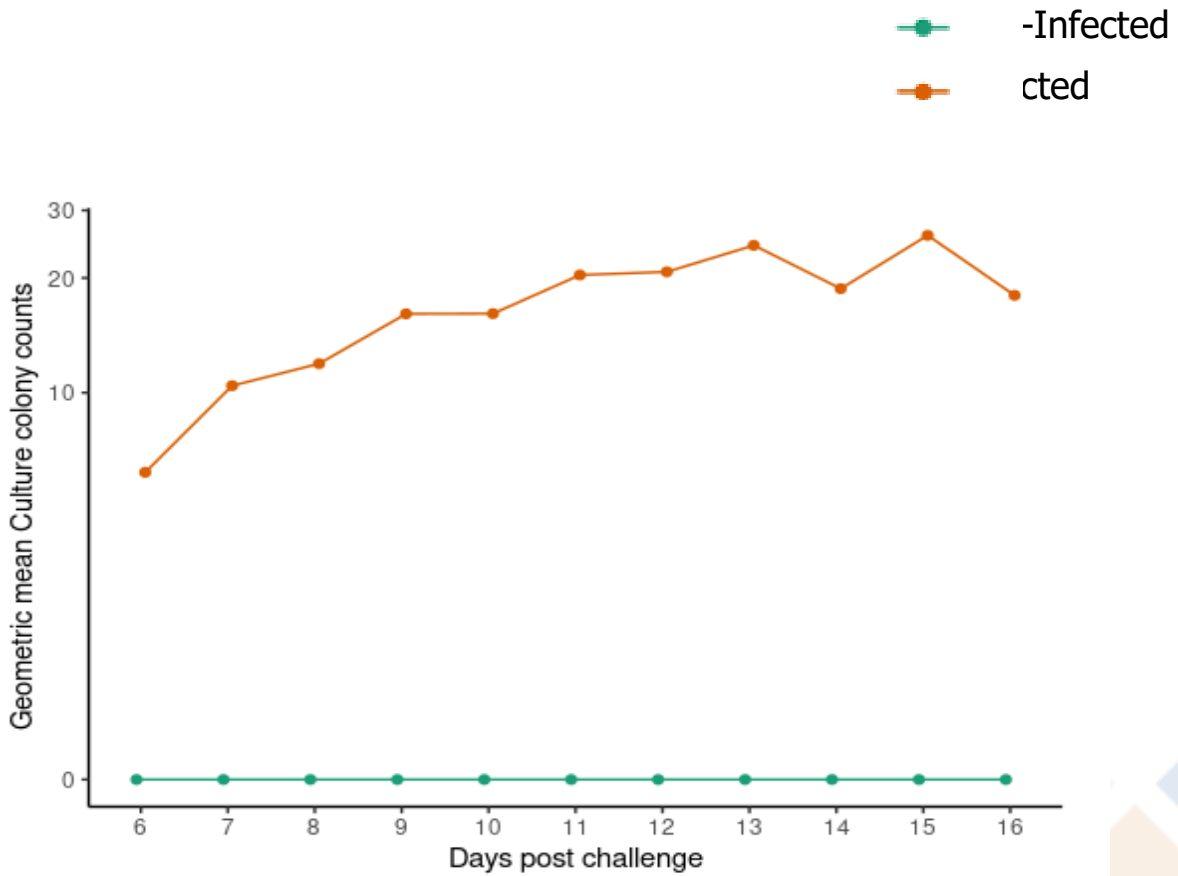


Geometric mean colony counts comparing all dose groups, days post challenge

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



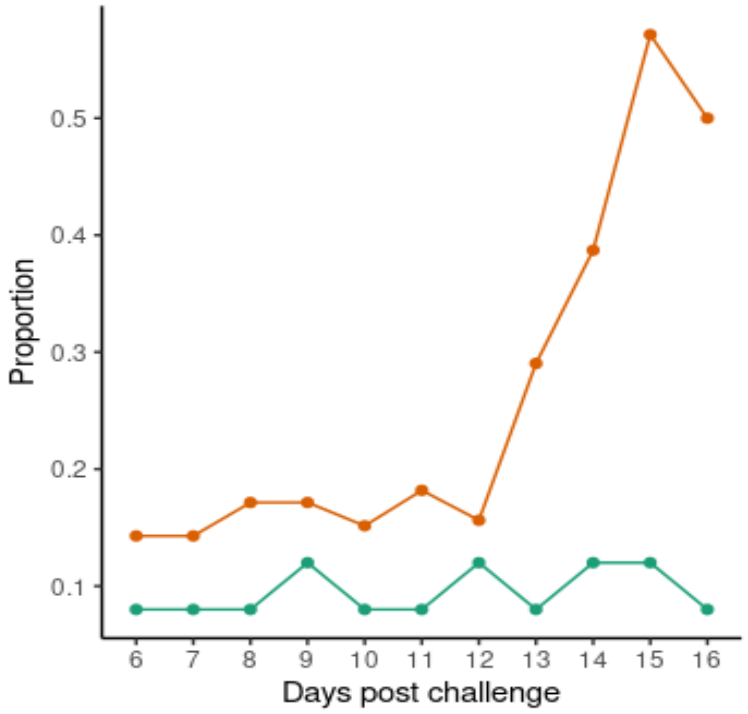
Mean PCR IS481 CT values comparing Infected to Non-Infected, days post challenge

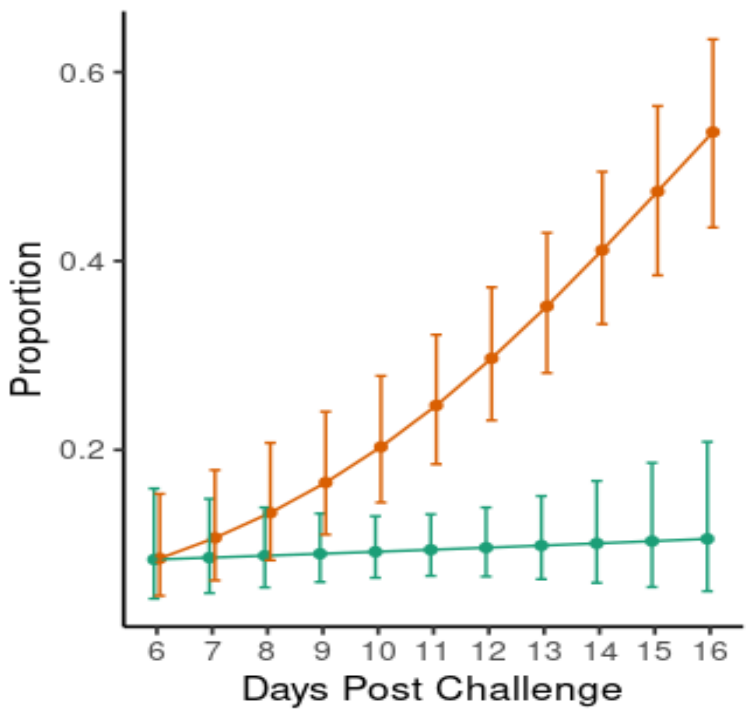


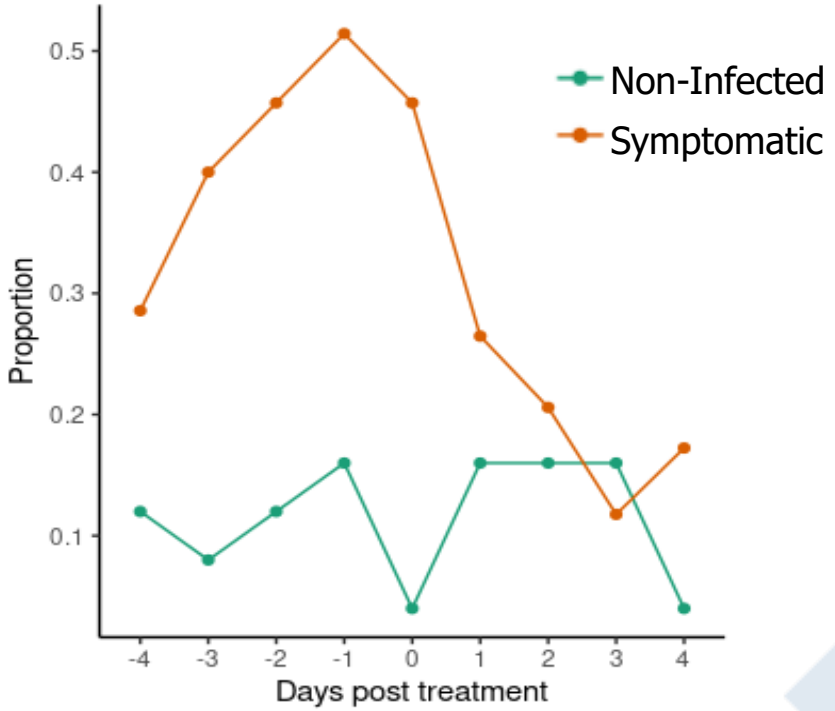
Geometric mean colony counts comparing Infected to Non-Infected, days post challenge

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

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







A

B

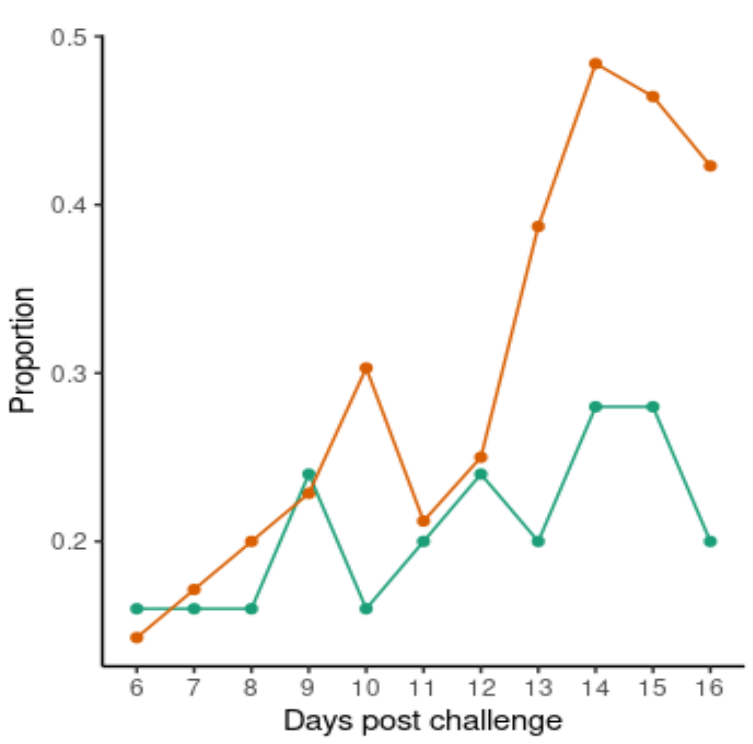
C

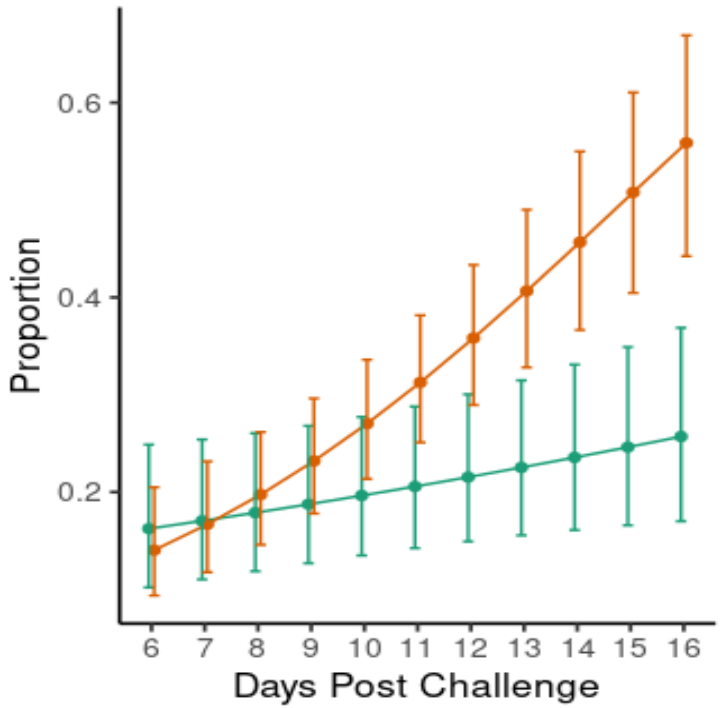
**Systemic symptoms by days post challenge and outcome:
A – rate per day; B – modelled to assess rate of change in reporting**

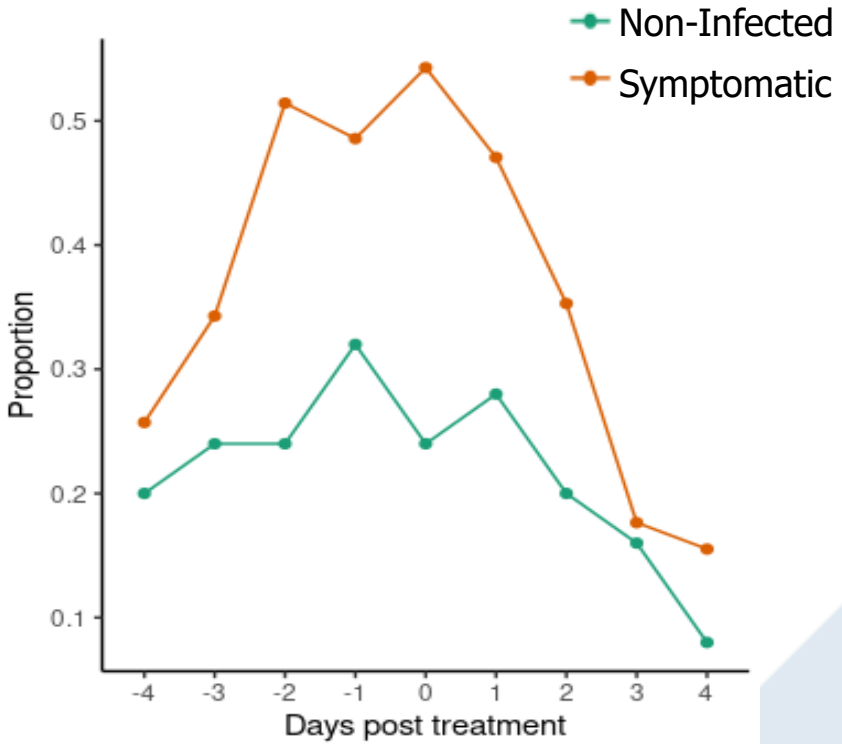
C. Effect of treatment (Day 0) by days pre/post treatment and outcome

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

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







A B

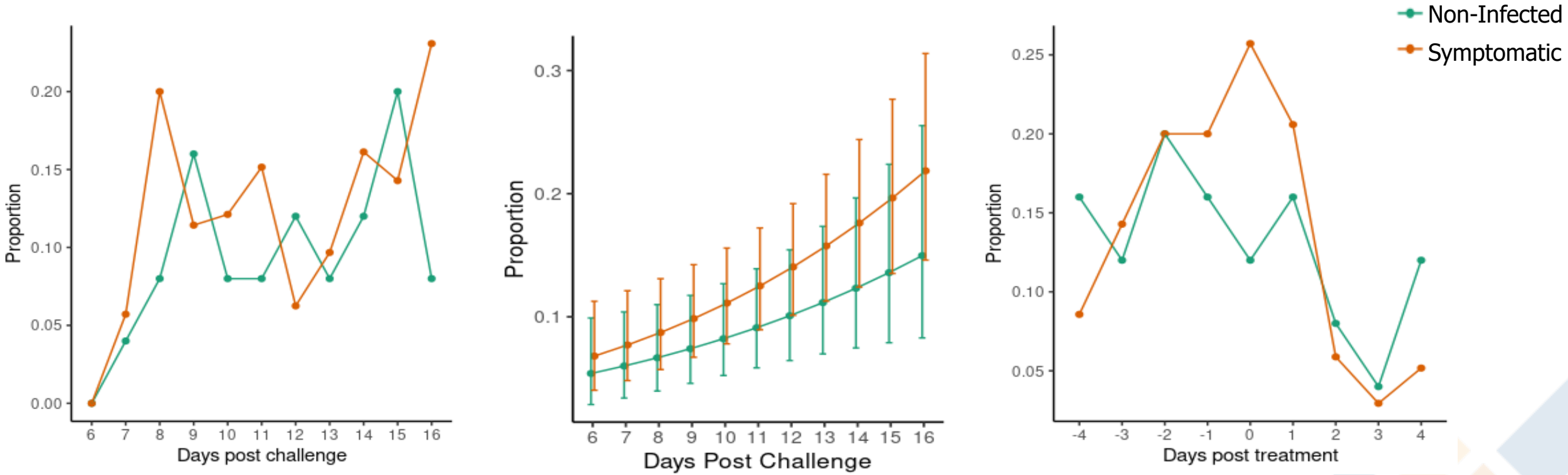
**Nasal symptoms by days post challenge and outcome:
A – rate per day; B – modelled to assess rate of change in reporting**

C

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

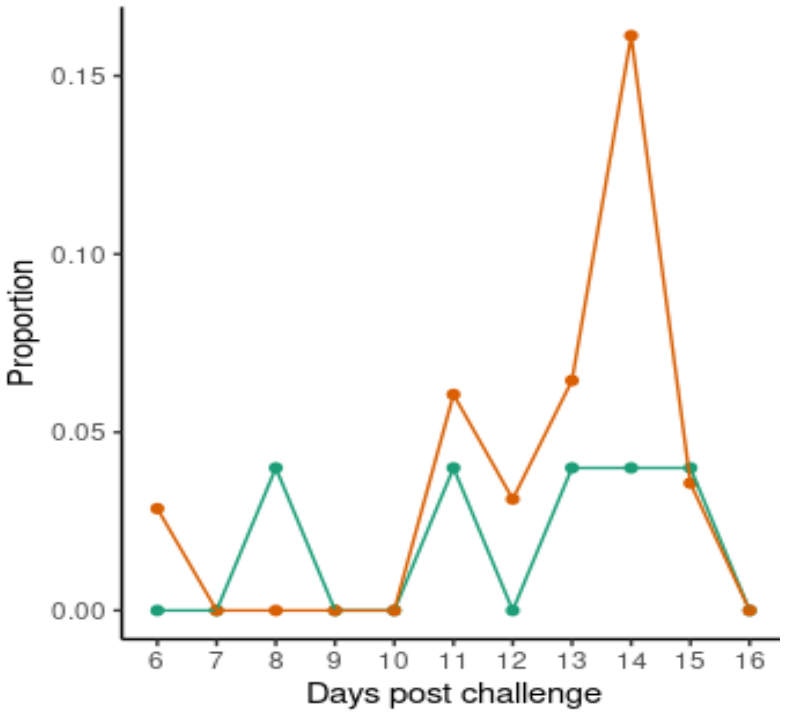
C

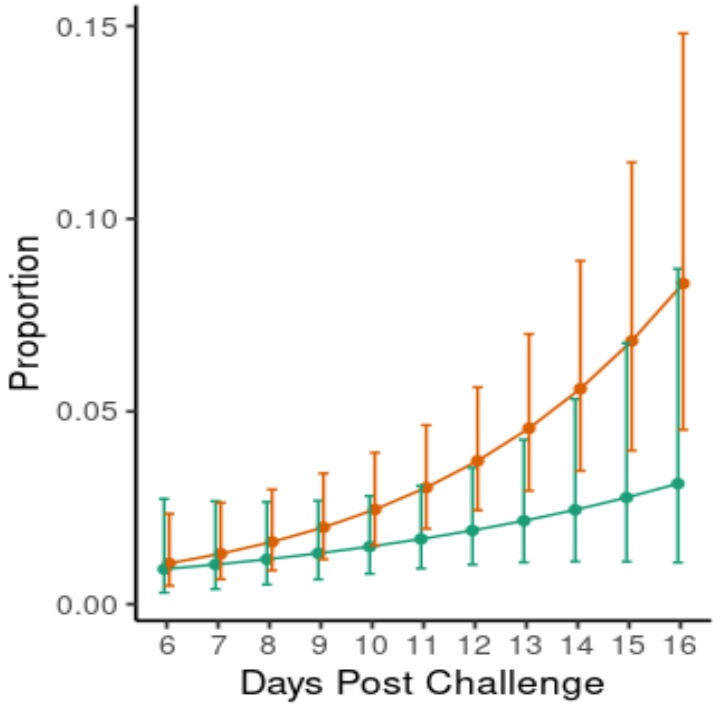
Pharyngeal symptoms by days post challenge and outcome:
A – rate per day; B – modelled to assess rate of change in reporting

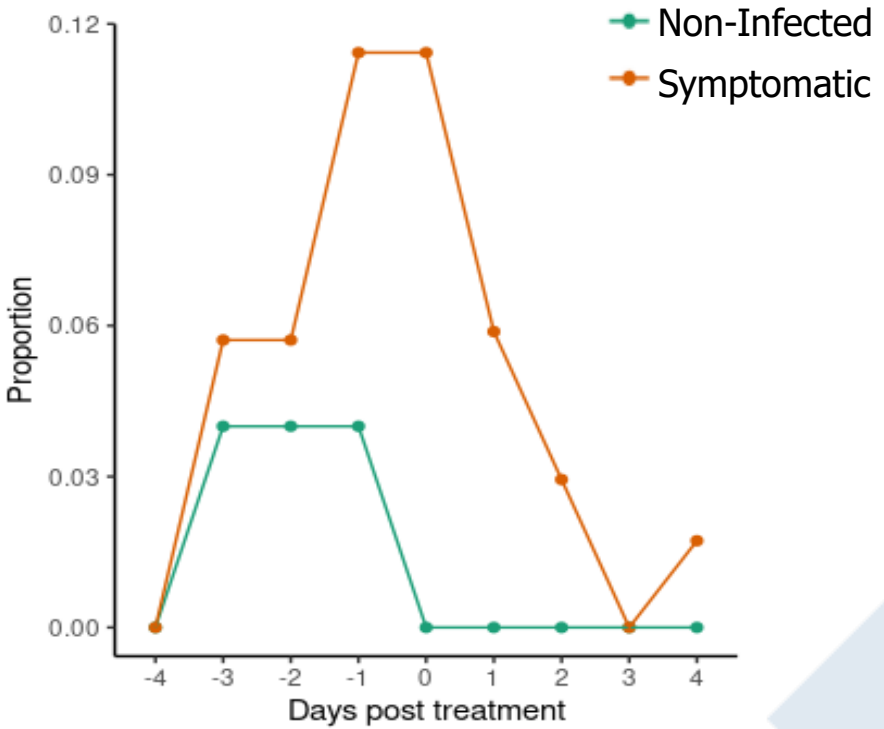
C. Effect of treatment (Day 0) by days post treatment and outcome

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

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







A

B

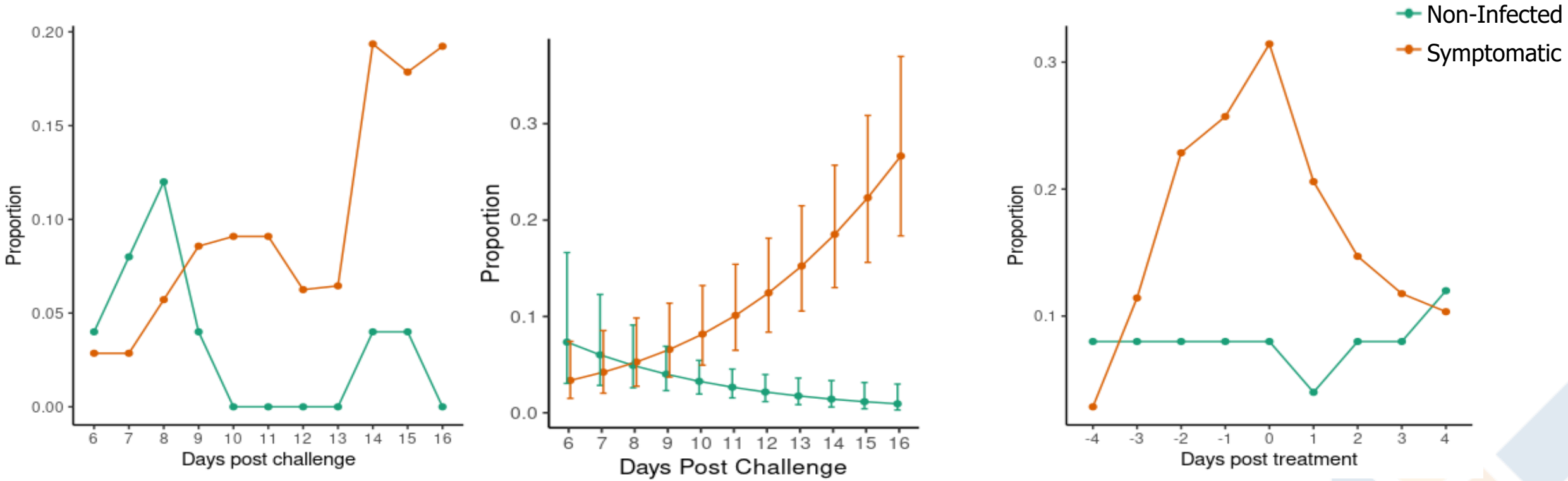
C

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

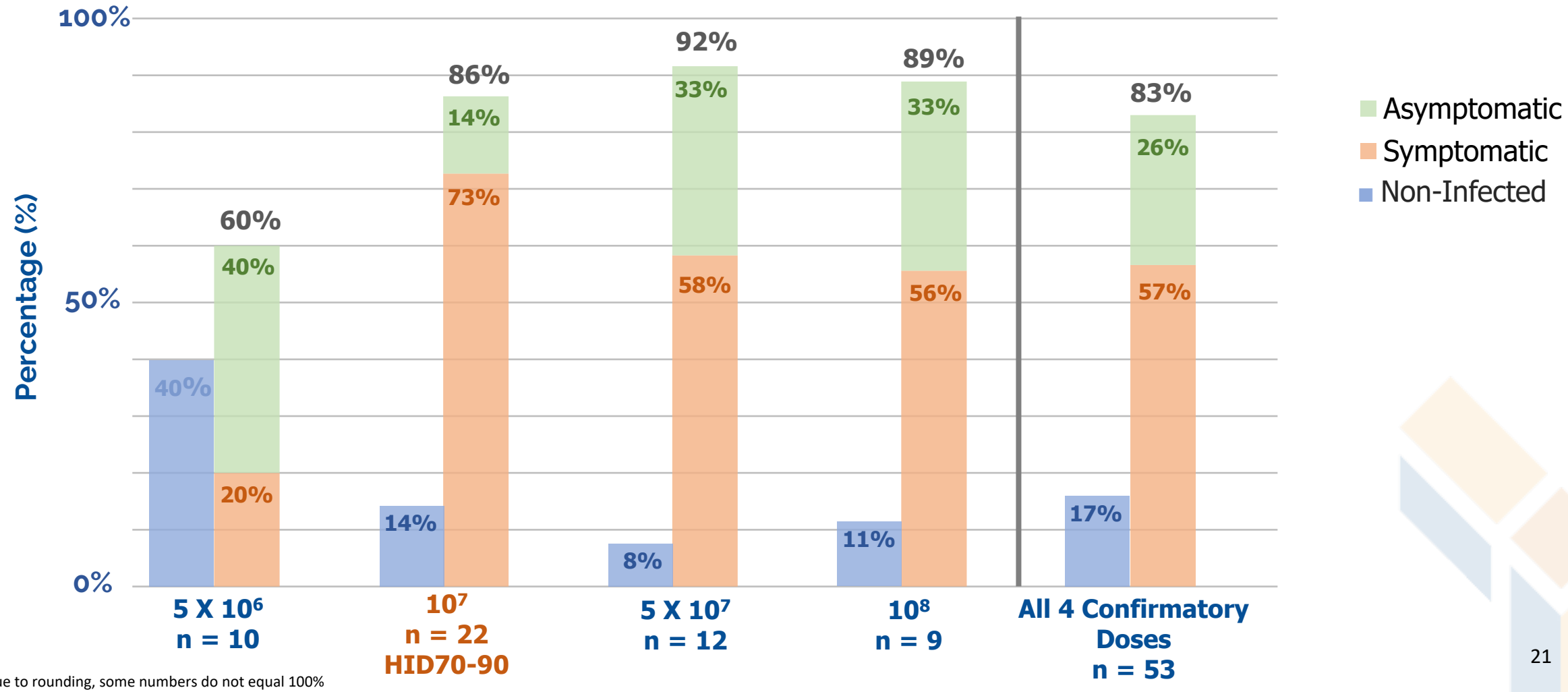
Rates* of Clinical Outcomes per Dose

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%)
5×10^5	5	4 (80%)	1 (20%)	0 (0%)	1 (20%)
10^6	6	3 (50%)	3 (50%)	0 (0%)	3 (50%)
5×10^6	**10**	**4 (40%)**	**6 (60%)**	**4 (40%)**	**2 (20%)**
10^7	**22**	**3 (14%)**	**19 (86%)**	**3 (14%)**	**16 (73%)**
5×10^7	**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

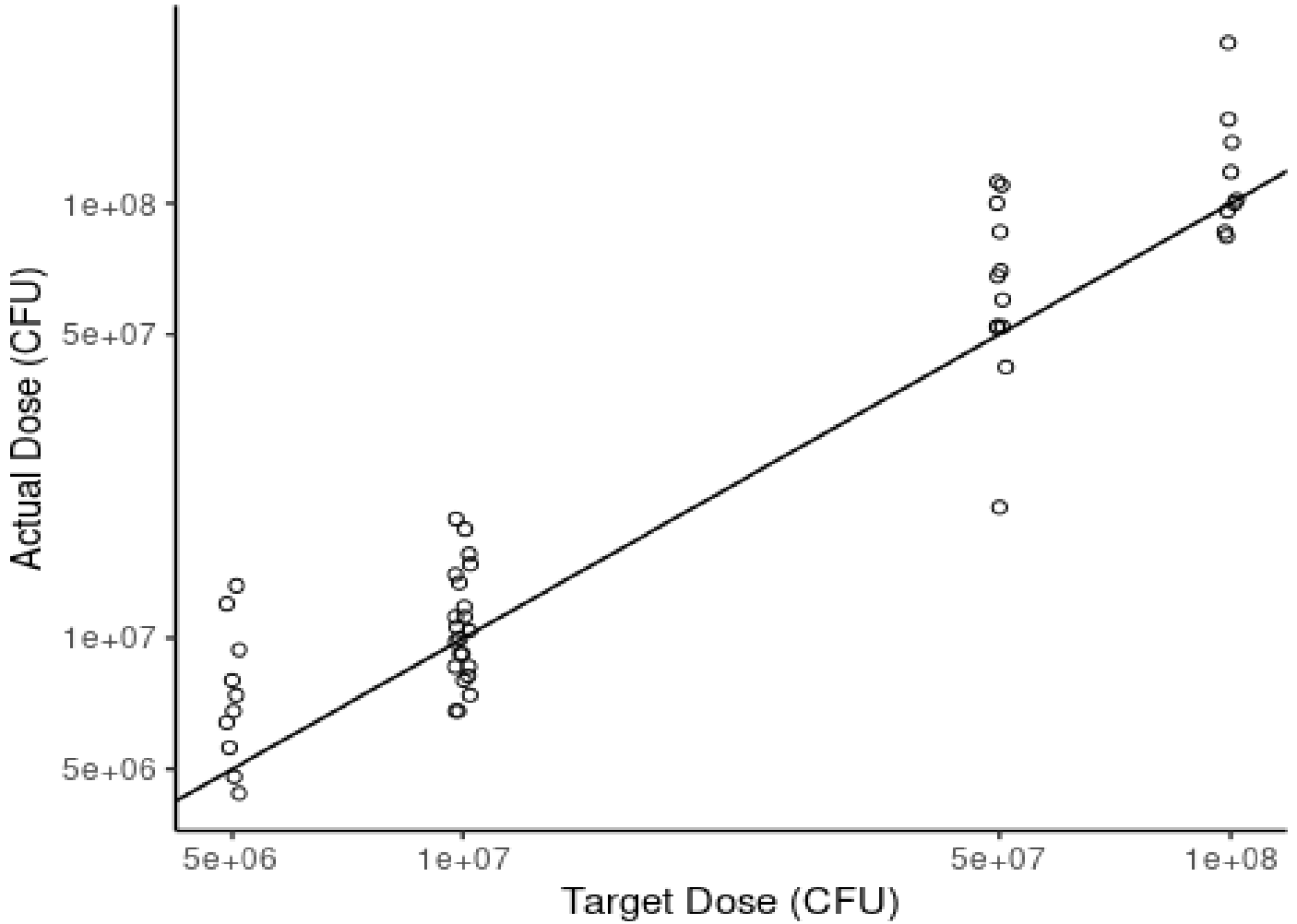
5 X 10^6
Mean: 7.3 x 10^6

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

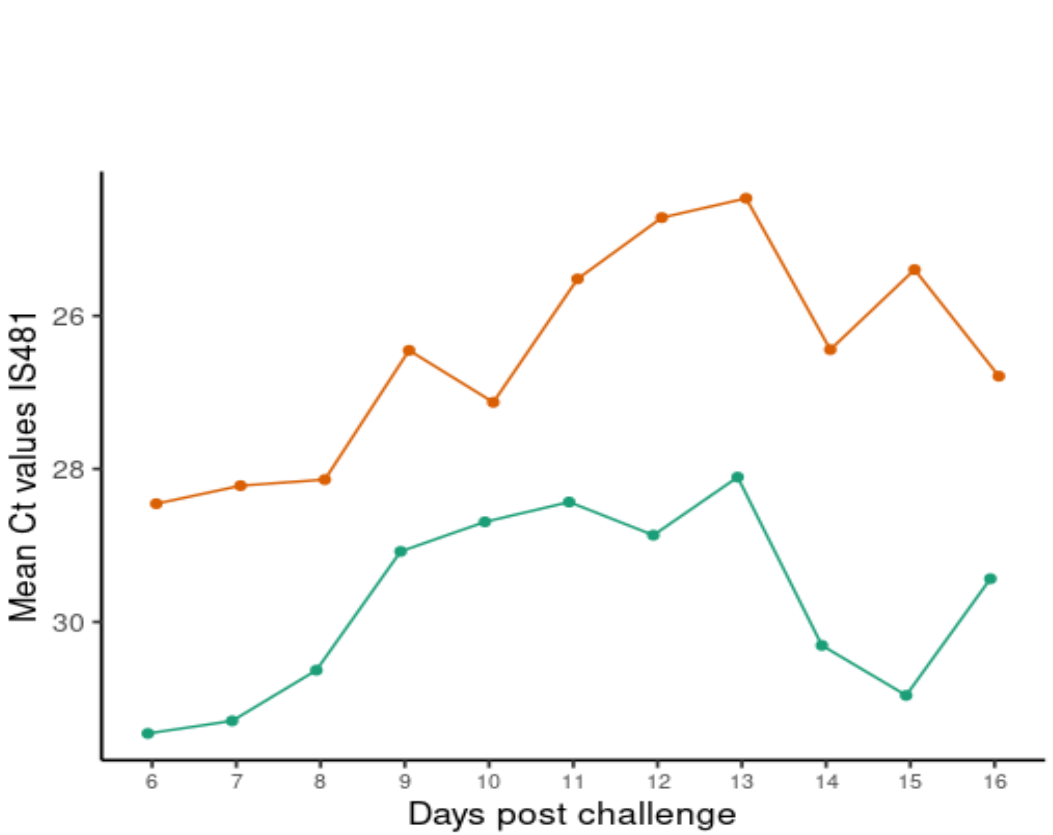
5 X 10^7
Mean: 6.3 x 10^7

10^8
Mean: 1.2 x 10^8

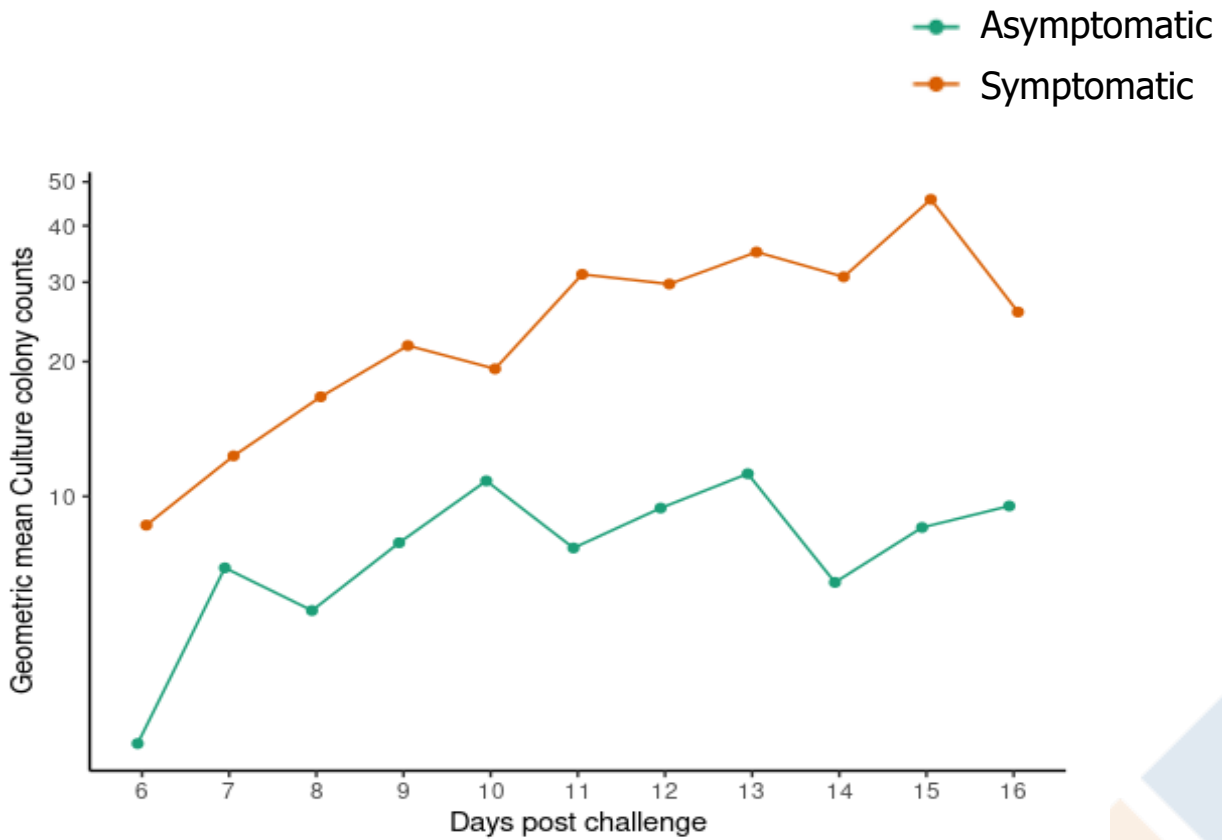
All four confirmatory doses
Mean: 2.2 x 10^7



Symptomatic Infection correlates with higher bacterial shedding by PCR & Culture

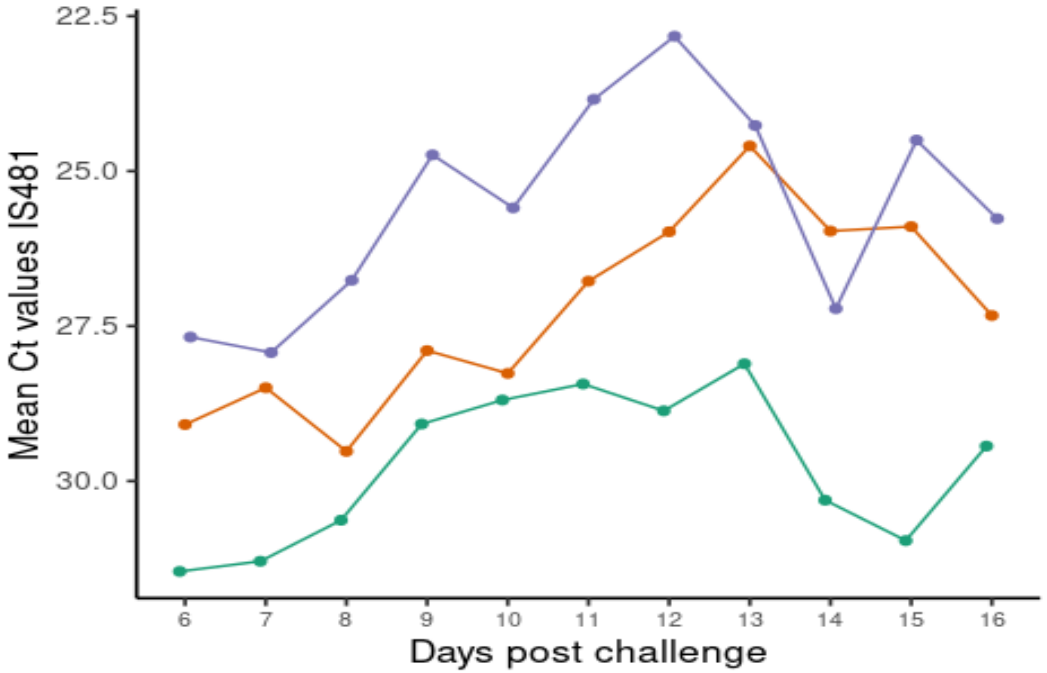


Mean PCR IS481 CT values comparing Asymptomatic and Symptomatic outcomes in confirmatory doses, days post challenge

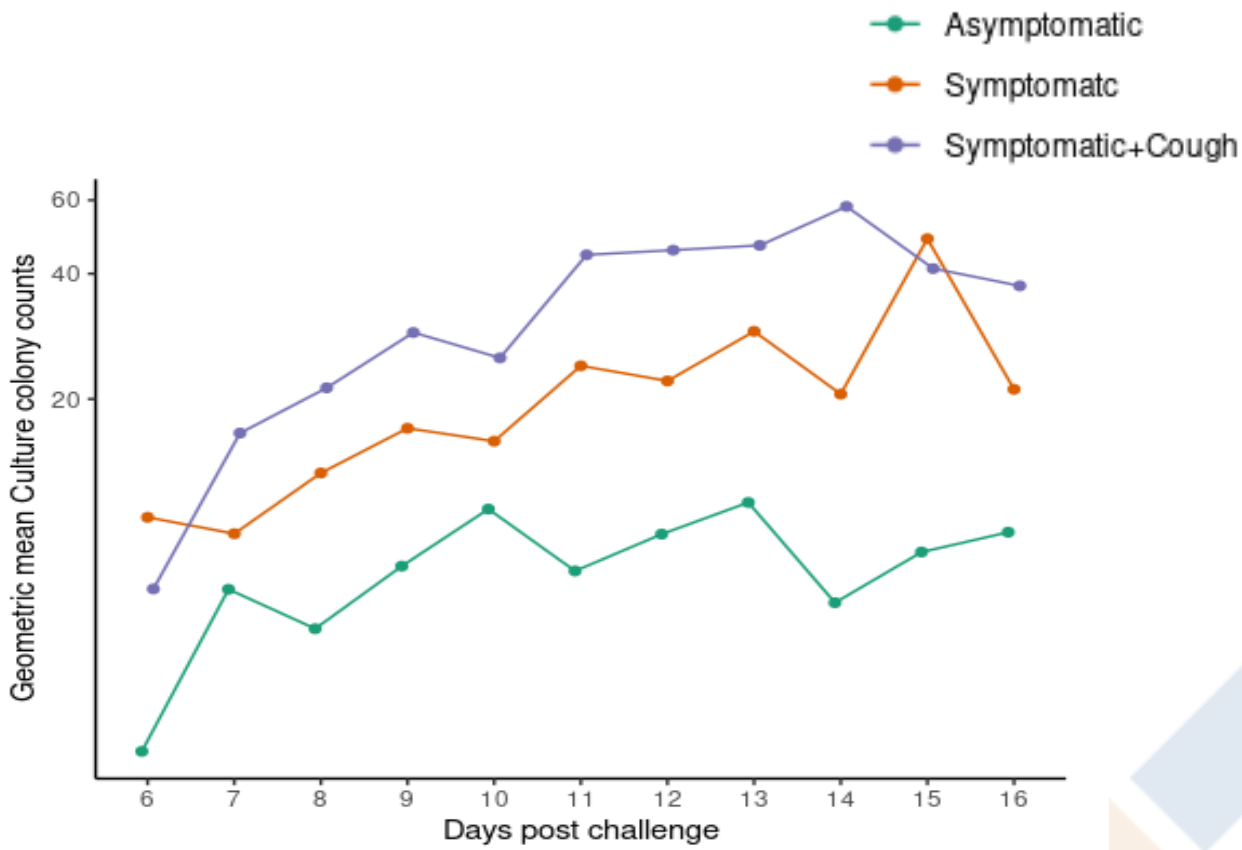


Geometric mean colony counts comparing Asymptomatic and Symptomatic outcomes in confirmatory doses, days post challenge

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



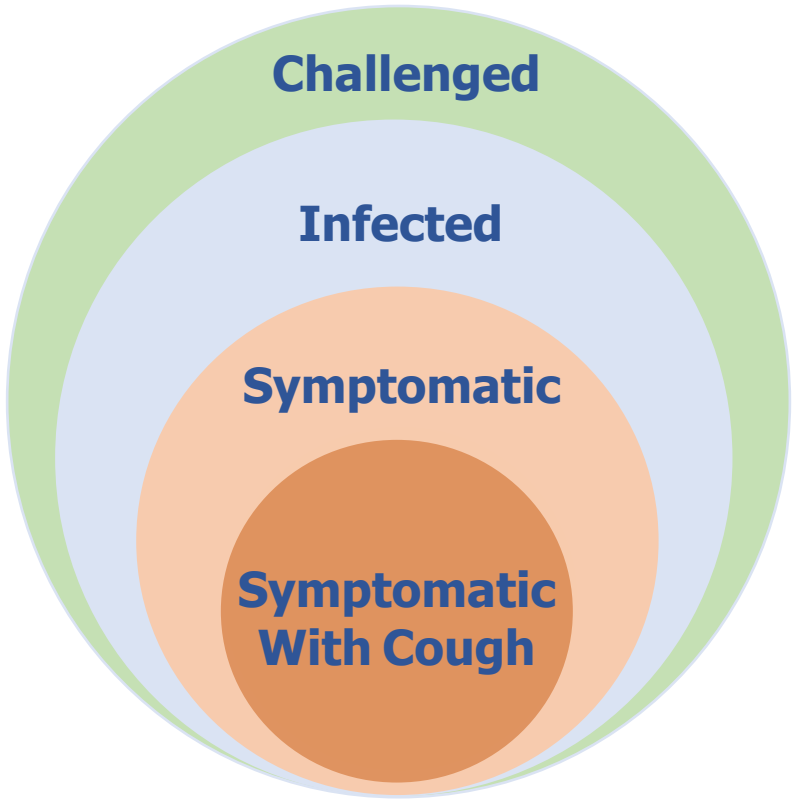
Geometric mean colony counts comparing Symptomatic (with & without cough) and Asymptomatic outcomes over days post challenge

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



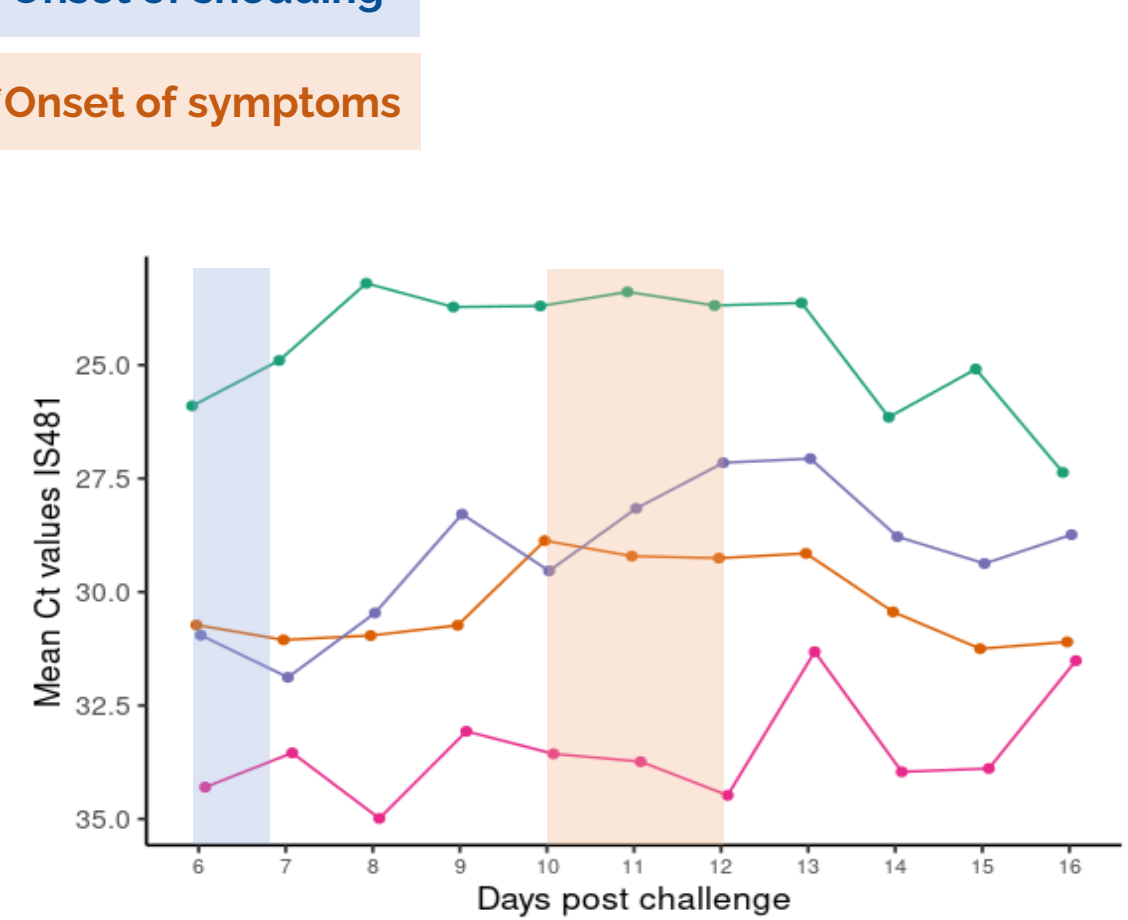
Endpoints (N = no. challenged)	5×10^6 (N = 10)	10^7 (N = 22)	5×10^7 (N=12)	10^8 (N=9)
	n (%)	n (%)	n (%)	n (%)
Infected	6 (60%)	19 (86%)	11 (92%)	8 (89%)
Symptomatic	2 (20%)	16 (73%)	7 (58%)	5 (56%)
Symptomatic with cough	1 (10%)	8 (36%)	3 (25%)	3 (33%)

HID70-90

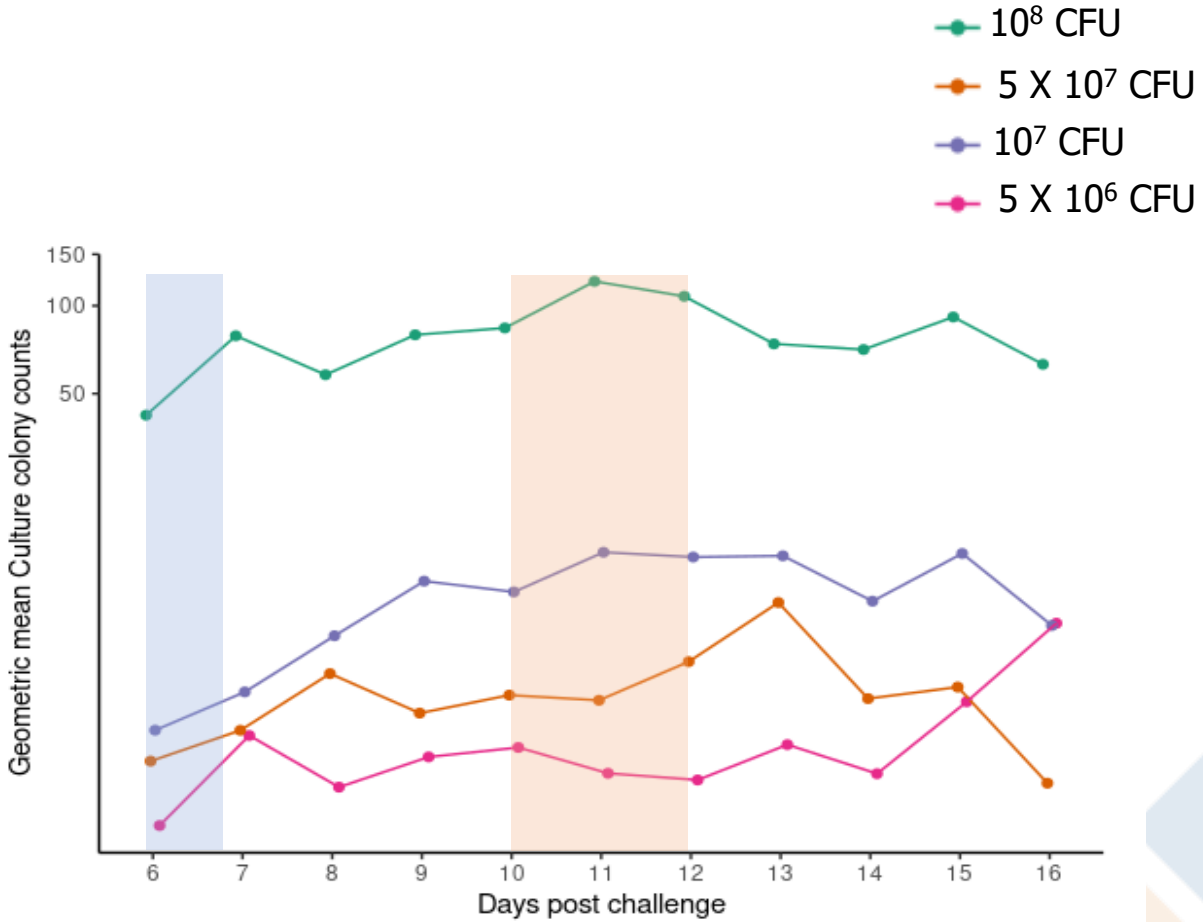
Clinical Events: Onset of shedding precedes onset of clinical symptoms

*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.

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Thank you