Incidental Myocarditis in Healthy Adults Following RSV Inoculation: Insights from a Decade of Controlled Human Infection Studies

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INTRODUCTION & OBJECTIVES

Respiratory Syncytial Virus (RSV) is typically associated with respiratory infections, but rare cardiac effects such as myocarditis may also occur. Over a decade of controlled human infection studies involving more than 2,000 participants, we identified six cases (0.3% incidence) of myocarditis with RSV-related symptoms that were either mild or asymptomatic following inoculation. Here, we present a case series of mild subclinical myocarditis linked to RSV infection during viral challenge studies, highlighting the rarity of this condition and its incidental detection. These findings offer valuable insights into the likely frequency of such events in RSV infection that would not be detected in other clinical settings.

METHODS

Symptoms Please report the highest level of symptoms you have experienced since completing the last diary card (if appplicable), including any symptoms you currently have (tick ONE in each row)	I have NO symptoms	Just noticeable	It's clearly bothersome from time-to-time, but it doesn't interfere with me doing my normal daily activities	It's quite bothersome most or all of the time, and it stops me from participating in activities	Symptoms at rest
Runny Nose	☐ 0	☐ 1	☐ 2	☐ 3	
Stuffy Nose	☐ 0	☐ 1	☐ 2	☐ 3	
Sneezing	☐ 0	☐ 1	☐ 2	☐ 3	
Sore Throat	☐ 0	☐ 1	☐ 2	☐ 3	
Earache	☐ 0	☐ 1	☐ 2	☐ 3	
Malaise/Tiredness	☐ 0	☐ 1	☐ 2	☐ 3	
Headache	☐ 0	☐ 1	☐ 2	☐ 3	
Muscle and/or Joint Ache	☐ 0	☐ 1	☐ 2	☐ 3	
Chilliness/Feverishness	☐ 0	☐ 1	☐ 2	☐ 3	
Cough	☐ 0	☐ 1	☐ 2	☐ 3	
Chest Tightness	☐ 0	☐ 1	☐ 2	☐ 3	
Shortness of Breath	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Wheeze	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Figure 1: hVIVO Subject symptom diary card.

We conducted a retrospective assessment of our historical data, which included participants from RSV challenge studies conducted between 2013 and 2021 who had myocarditis reported as serious adverse event during their 12-day quarantine period.

This included analysing the investigational medicinal product, infection onset, viral load, and clinical aspects of myocarditis.

Participants self-reported and rated symptom severity three times daily during quarantine using the hVIVO SDC on paper forms (Figure 1).

Symptoms score grading:

0 (none) to 3 (severe, activity-limiting); 4 (at rest) for shortness of breath and wheeze only.

- runny nose **(RN)**
- stuffy nose **(STN)**
- sneezing **(SNZ)**
- sore throat **(ST)**
- earache **(EA)**
- malaise/tiredness **(MAL)**
- headache **(HA)**
- muscle and joint ache **(MJA)**
- chills/feverishness **(Chil)**
- cough **(CO)**
- chest tightness **(CT)**
- shortness of breath **(SOB)**

Viral Challenge Model

This study adhered to hVIVO's standard operating procedures for viral challenge trials. Eligible participants, identified through initial screening, were admitted to a dedicated hVIVO quarantine unit for approximately 15 days (Day -2/-1 to Day 12). To ensure the absence of pre-existing respiratory infections, participants underwent additional screening before receiving an intranasal inoculation of the RSV-A M37b challenge virus on Day 0.

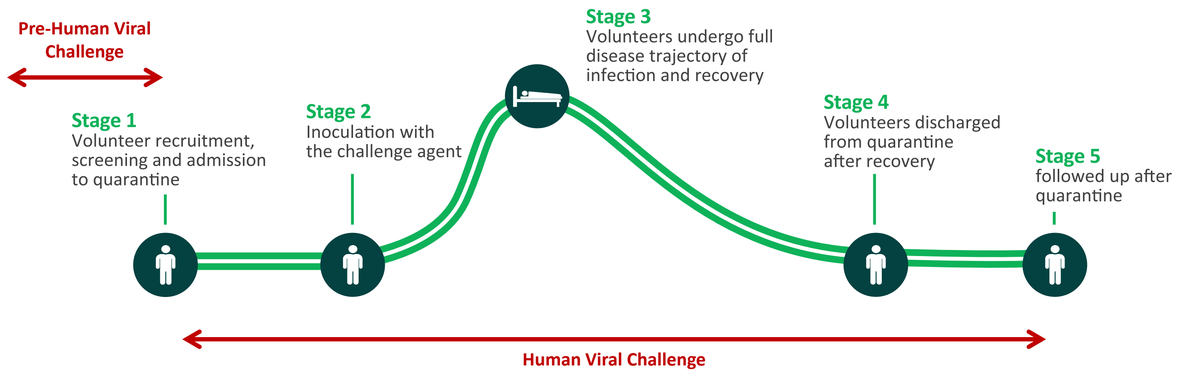
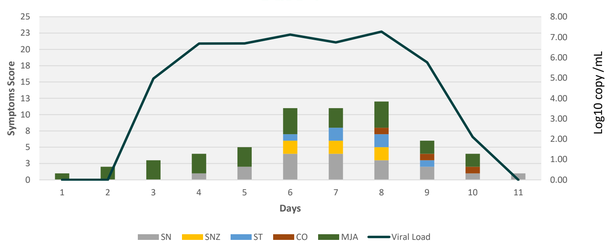


Figure 2: This methodology ensures a controlled environment for studying viral challenge responses while prioritising participant safety and data integrity.

RESULTS

Case 1



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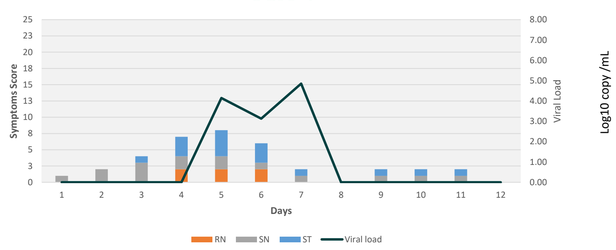

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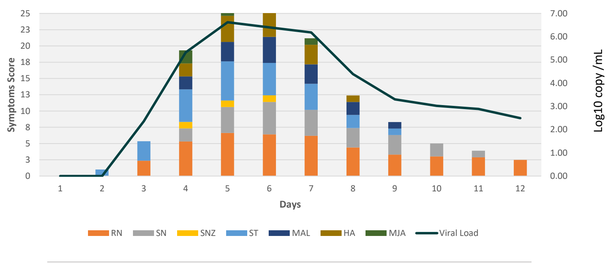

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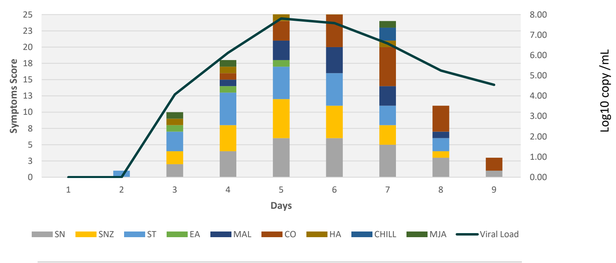

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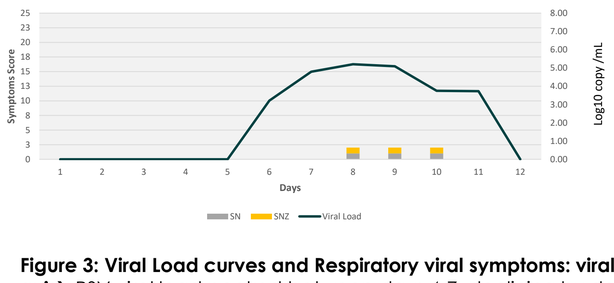

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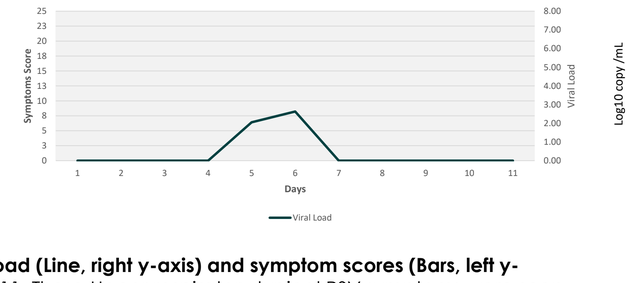
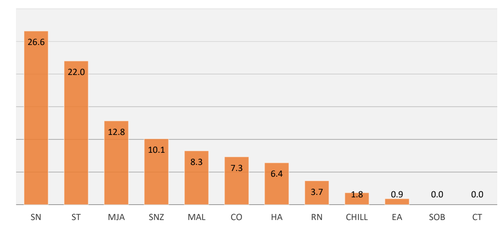


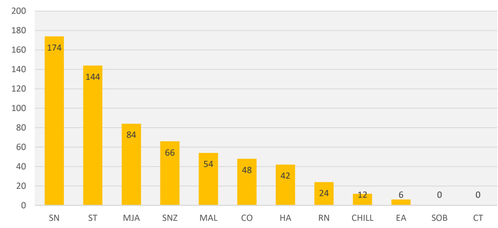
Figure 3: Viral Load curves and Respiratory viral symptoms: viral load (Line, right y-axis) and symptom scores (Bars, left y-axis). RSV viral load peaked between days 4-7, declining by day 11. These Upper respiratory typical RSV symptoms were seen in 5 subjects between days 2-5

Symptoms Score Prevalence (%)



The most common respiratory symptoms were stuffy nose (SN) and sore throat (ST).

Absolute Symptom Score Prevalence



Peak Total Symptom Score from SDC ranged from 0 to 30, indicating wide variation in clinical presentation.

Figure 4: Prevalence of various RSV respiratory symptoms.

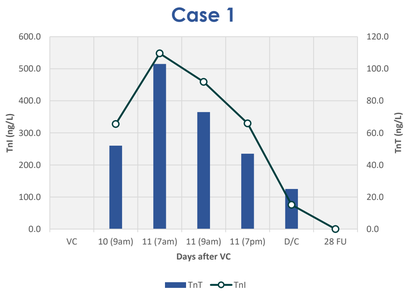
CLINICAL AND DIAGNOSTIC CHARACTERISTICS

Case	Age/Sex	Type of IMP	Quarantine Days	Day of Troponin Peak	Peak Troponin T / Troponin I (ng/L)	Duration of Elevated Troponin (days)	ECG Findings	Peak Daily Symptom Score	Peak CRP (<5.0 mg/L)	MRI Findings
1	24M	Active vaccine	11	Day 11	103 / 548	5	Concave STE in the inferior leads and in V3-6 with subtle inferior leads PR depression	12	2.9	Report suggested previous myocarditis
2	28M	Placebo vaccine	12	Day 12	78 / 314	4	No ECG changes	25	Not reported	Normal
3	21M	Placebo vaccine	13	Day 11	17 / 121	5	No ECG changes	2	5.2	1° MRI: suggestive of previous myocarditis 2° MRI (6 months after): Normal
4	19M	Active antiviral	12	Day 11	461 / TnI not reported	3	Inferolateral TWI in leads II, III, V5 & V6	8	12.9	Viral Myocarditis confirmed
5	30M	Placebo vaccine	10	Day 9	45 / 225	6	Unspecific for pericarditis	30	1.7	Normal
6	18F	Active clinical trial drug	13	Day 12	28 / 243	4	Temporary biphasic TWI V2-V4	0	2.3	Normal

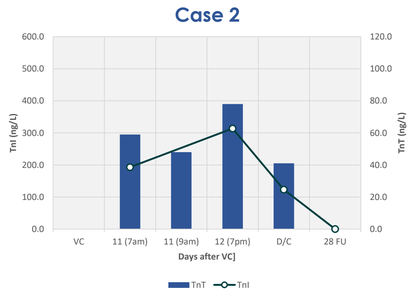
Table 1: Clinical and diagnostic characteristics of myocarditis in each participant.

TROPONIN T AND I BLOOD TESTS

Case 1



Case 2



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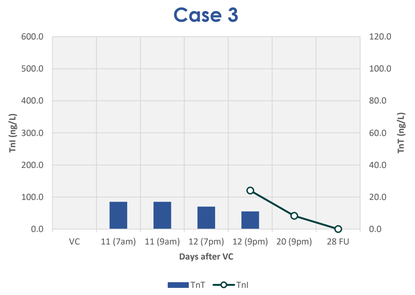

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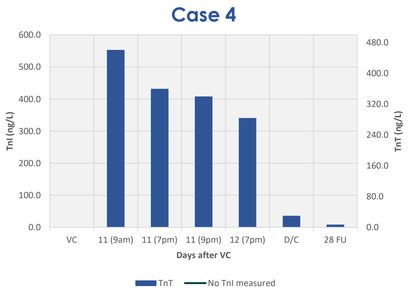

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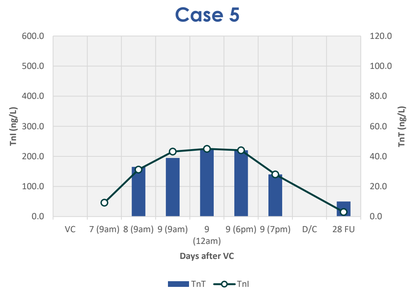

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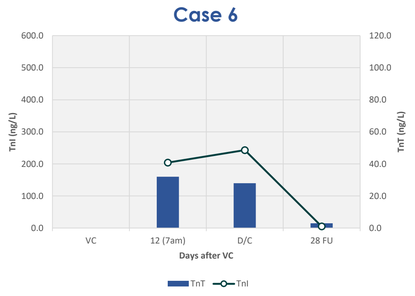

Figure 5: Routine troponin and ECG testing on day 11 post-inoculation incidentally revealed subclinical myocarditis. Troponin levels were elevated, peaking at 17-461 ng/L for Troponin T (TnT, right y-axis) and 121-548 ng/L for Troponin I (TnI, left y-axis), persisting for 3-6 days. These findings were supported by ECG results (see Table 1), despite the absence of typical myocarditis symptoms in all participants.

CLINICAL FINDINGS IN RSV-INDUCED MYOCARDITIS

ECG Findings

- Range: No changes to specific abnormalities
- Observed abnormalities: ST-segment elevation, T-wave inversion

Laboratory Findings

- Generally: No clinically significant abnormalities
- Exception: Elevated troponin levels
- CRP levels: Ranged from 1.7 to 12.9 mg/L

Cardiac MRI Results

- Normal results: 3 cases
- Suggested/confirmed myocarditis: 2 cases
- Initial suggestion of myocarditis with normal follow-up: 1 case (Follow-up MRI at 6 months was normal)

Additional Findings

- RSV-induced myocarditis may occur subclinically in healthy adults
- Detection facilitated by close monitoring in challenge study setting

Outcome

- All subjects followed up
- No long-term complications or adverse impacts from mild viral-induced myocarditis

CONCLUSIONS

Our data demonstrates a very low incidence (0.3%) of myocarditis events following experimental RSV infection, likely mirroring natural event rates. The subclinical presentation often prevents detection in routine clinical settings, highlighting the value of controlled studies. With no long-term complications observed in this small proportion of subjects, experimental RSV infection remains a safe and effective tool for evaluating RSV antiviral drugs or vaccines.

ACKNOWLEDGEMENTS

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