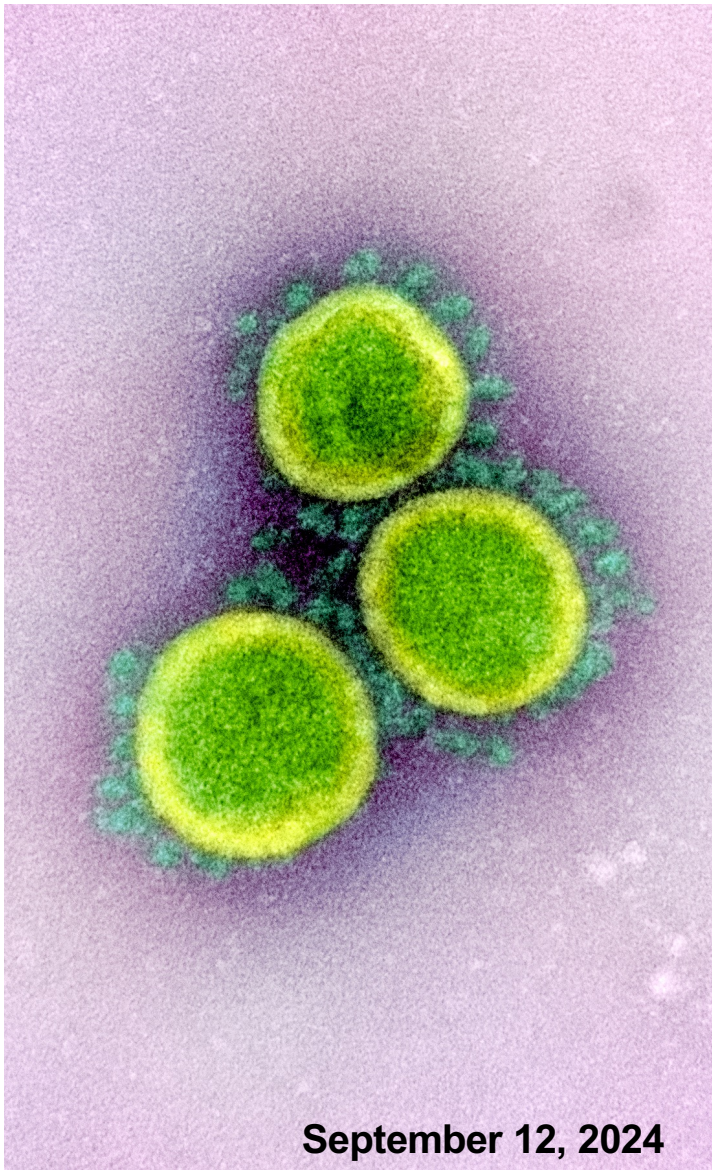
Simple Question, Complex Answer:
Determining the Duration of Contagiousness of Individuals with COVID-19

Yves Longtin MD
Associate Professor of Medicine, McGill University

Hosted by Jim Gauthier



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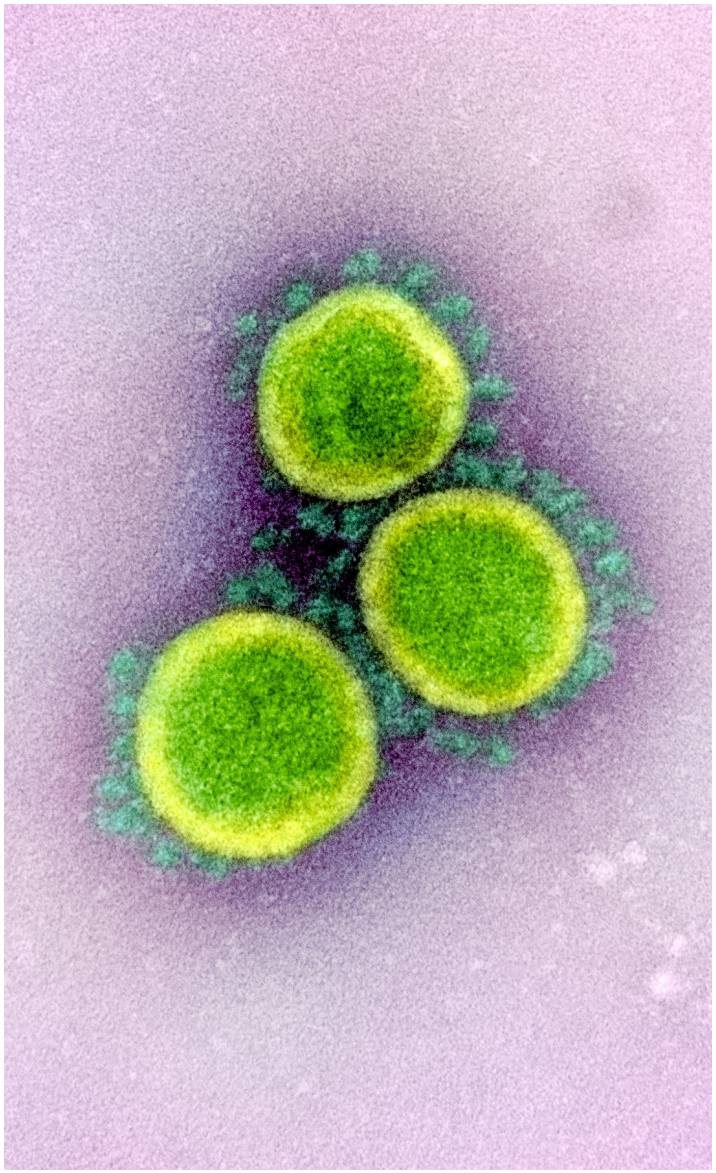
September 12, 2024

Objectives

1. Review the current knowledge regarding duration of infectivity of individuals with COVID-19

2. Identify current knowledge gaps that influences current recommendations



Disclosures

Yves Longtin

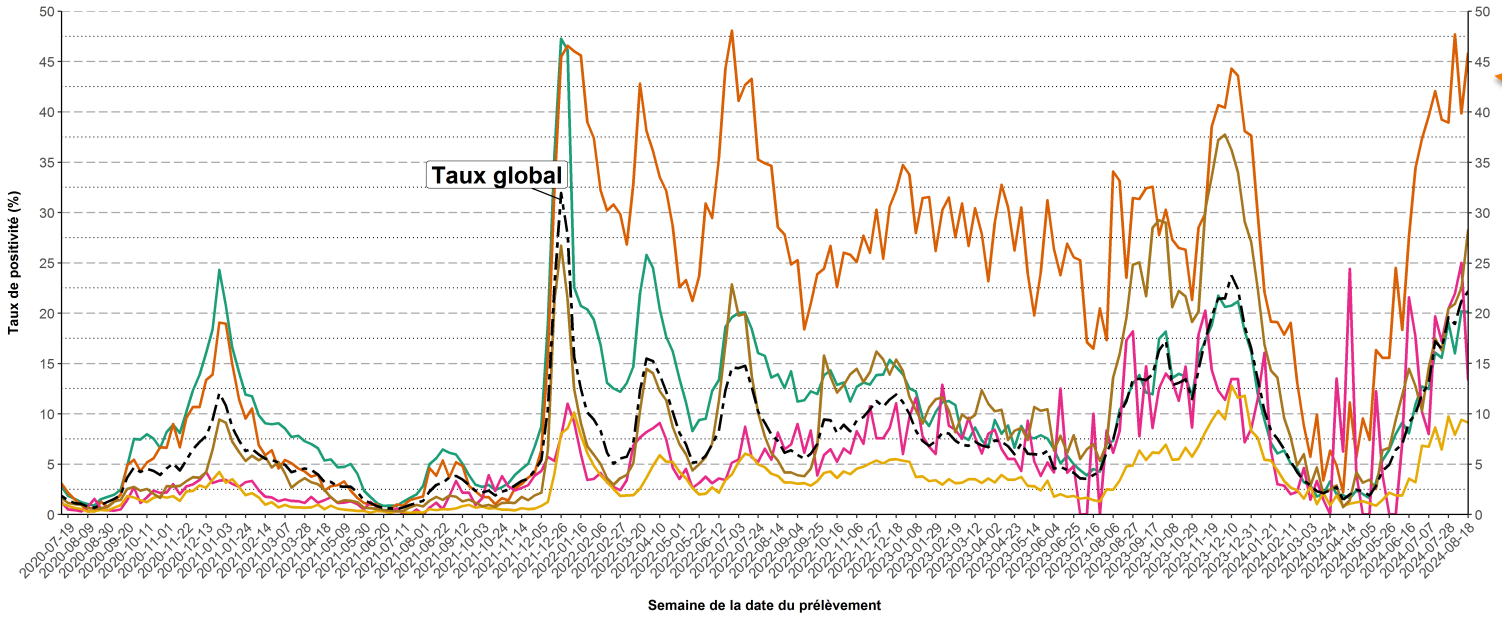
- Relationship with for-profit/ non-profit organizations:
  - Grant support:
    - Summit (Oxford)
  - Salary support:
    - Fonds de recherche en santé du Québec
  - Member of scientific committees:
    - WHO Antimicrobial Resistance TaskForce
    - AMMI Canada Council

Why talk about COVID-19 in 2024?

- Still prevalent
  - 1-2 peaks per year
- Still morbid in some populations
- HCWs with COVID-19 still subjected to work restrictions in some jurisdictions
- Because we are still being asked what to do with HCWs with COVID-19

Aug 18 2024
45% positivity among HCWs tested

Positivity rate (COVID-19) per week, by NAAT indication grouping, from February 25, 2020 to August 28, 2024



HCW
- 1. Personnes symptomatiques non TS (M1, M2, M7)
- 2. TS symptomatiques (M3)
- 4. Personnes asymptomatiques reliées à une éclosion (M5, M6, M14, M15)
- 6. Autres personnes asymptomatiques (M4, M8, M9, M10, M11, M12, M16, M18)
- 7. Autres ou inconnu (M19, M21, M22, M23, M24, M25)

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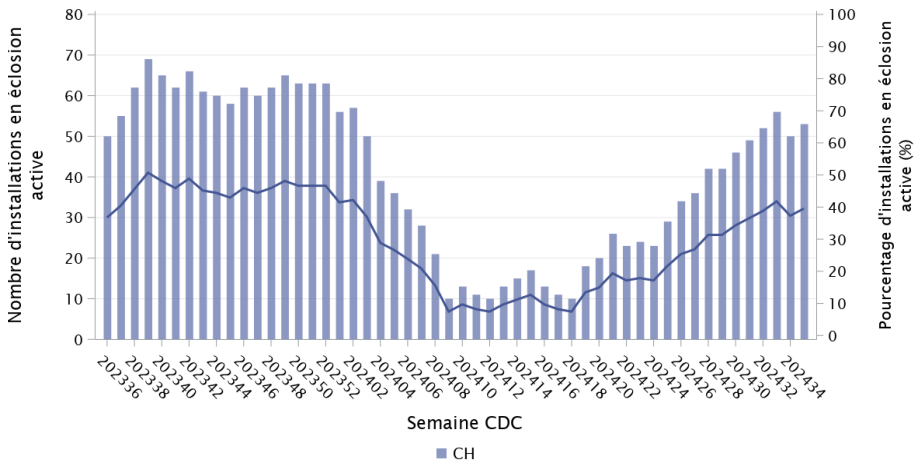
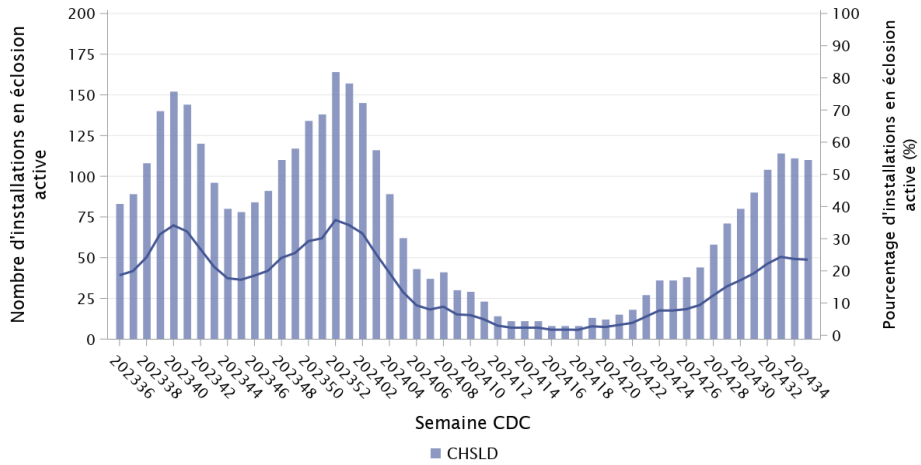
Number and proportion of hospitals and LTCF with active COVID-19 outbreaks





Notes :

- Une installation en éclosion active sera comptée chaque semaine où elle aura au moins une éclosion active pendant une journée.
- Le graphique est construit en utilisant la date de début de la plus ancienne éclosion et la date de fin de la plus récente éclosion, parmi la période d'éclosion de chaque installation.

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Should we still test HCWs for COVID-19?

- HCP with **even mild symptoms** of COVID-19 should be **prioritized for viral testing** with nucleic acid or antigen detection assays
- When testing a person with symptoms of COVID-19, negative results from at least one viral test indicate that the person most likely does not have an active SARS-CoV-2 infection at the time the sample was collected.
- If using NAAT (molecular), a single negative test is sufficient in most circumstances. If a higher level of clinical suspicion for SARS-CoV-2 infection exists, consider maintaining work restrictions and confirming with a second negative NAAT.
- If using an antigen test, a negative result should be confirmed by either a negative NAAT (molecular) or second negative antigen test taken 48 hours after the first negative test.

https://www.cdc.gov/covid/hcp/infection-control/guidance-risk-assesment-hcp.html

Infectivity of COVID-19

- COVID-19 Infectivity
  - May be up to 10 days in non-severe cases among non immunocompromised individuals
  - Wide interindividual variability
  - Assessed by viral culture (gold standard)
- Healthcare workers with COVID-19
  - Must be isolated until deemed non-infectious but can lead to staff shortages
  - Criteria to allow early return to work developed by several jurisdictions

Return to work criteria for HCWs with COVID-19

	CDC[1]	ECDC[2]	Victoria, AUS[4]
Without criteria	At least 10 days have past since onset of symptoms	At least 10 days	
With criteria			
	At least 7 days	At least > 6 days	At least 5 days off
	Symptom improvement	Symptom improvement	Resolution of acute symptoms
	No fever without antipyretic use x 24h	No fever	
	Negative viral testing last 48h (NAAT or RADT)*	Negative NAAT or RADT on Day 6	Negative RADT may be considered

1. Last updated Sept 2022, for nonsevere COVID-19 not immunocompromised
2. 3rd update, Jan 2022. https://www.ecdc.europa.eu/en/publications-data/covid-19-guidance-discharge-and-ending-isolation
3. https://www.inspq.qc.ca/publications/3141-covid-19-gestion-travailleurs-sante-milieux-soins
4. https://www.health.vic.gov.au/infectious-diseases/covid-19-coronavirus-disease-2019#control-measures-for-covid-19

* If test positive on days 5-7: extend to 10 days isolation in all cases

Downgrading COVID-19 measures?

Updates: Recommendations for duration of work exclusion for healthcare personnel with SARS-CoV-2 infection are being reviewed as part of updates to the Guideline for Infection Control in Healthcare Personnel, 1998. Once a draft is finalized by the Healthcare Infection Control Practices Advisory Committee (HICPAC), it will be posted in the federal register for a public comment period before being returned to HICPAC for additional review. Further information about HICPAC, the guideline development and public comment process, and future meetings is available at: Healthcare Infection Control Practices Advisory Committee (HICPAC).

Updates may be slow to come as fundamental questions arise re. how COVID-19 is managed

https://www.cdc.gov/covid/hcp/infection-control/guidance-risk-assesment-hcp.html

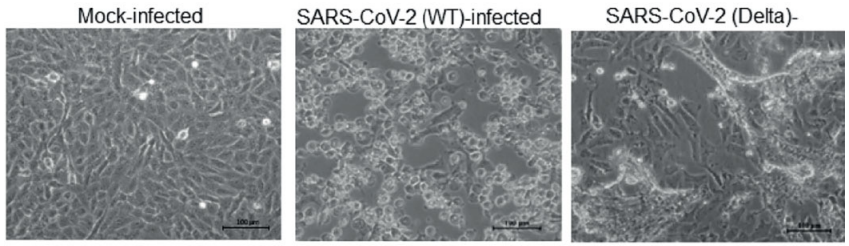
How are return-to-work criteria determined for HCWs?

- References that justify recommendations not always included in the recommendations

- Risk-benefit assessment must be conducted and influence recommendations
  - Zero risk = implicitly abandoned from societal point of view
  - No more screening or isolation in the community
  - Population at risk (patients)

Determination of SARS-CoV-2 infectivity

- Viral culture is the current gold standard
  - Growth of virus on cell culture is an indicator that viral particles have capacity to infect human cells
  - However, poorly standardized
    - Choice of cell line
    - Inoculation volume
    - Freeze-thaw vs fresh samples
    - Duration of incubation



Khandelwal N et al. *Frontiers in Cellular and Infection Microbiology*. 2021-November-23 2021;11doi:10.3389/fcimb.2021.771524

- Main cell line: Vero E6
  - Median tissue culture infectious dose (TCID50/ml) ranges between 2,0E+04 to 6.3E+06

100-fold variation in sensitivity

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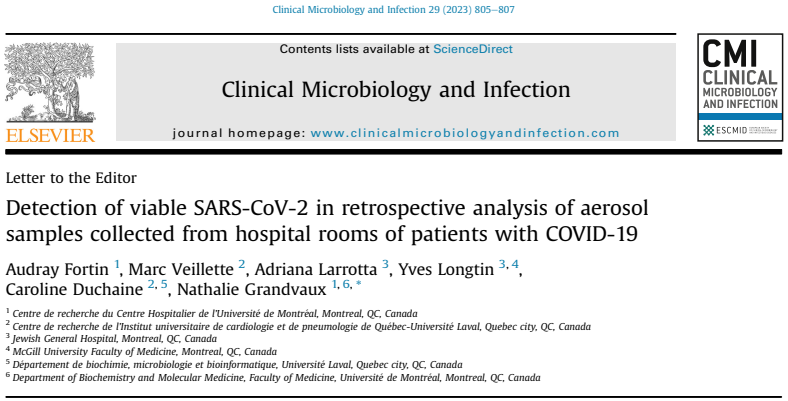
Wurtz N, Penant G, Jardot P, Duclos N, La Scola B. Culture of SARS-CoV-2 in a panel of laboratory cell lines, permissivity, and differences in growth profile. *Eur J Clin Microbiol Infect Dis*. Mar 2021;40(3):477-484.

Increasing sensitivity?



Clinical Microbiology and Infection 29 (2023) 805–807

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Letter to the Editor

Detection of viable SARS-CoV-2 in retrospective analysis of aerosol samples collected from hospital rooms of patients with COVID-19

Audray Fortin [1], Marc Veillette [2], Adriana Larrotta [3], Yves Longtin [3, 4], Caroline Duchaine [2, 5], Nathalie Grandvaux [1, 6, *]

[1] Centre de recherche du Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada
[2] Centre de recherche de l'Institut universitaire de cardiologie et de pneumologie de Québec-Université Laval, Quebec city, QC, Canada
[3] Jewish General Hospital, Montreal, QC, Canada
[4] McGill University Faculty of Medicine, Montreal, QC, Canada
[5] Département de biochimie, microbiologie et bioinformatique, Université Laval, Quebec city, QC, Canada
[6] Department of Biochemistry and Molecular Medicine, Faculty of Medicine, Université de Montréal, Montreal, QC, Canada

- Frozen air samples
- Conducting 2 successive cycles of infection on Vero E6 cells can lead to detectable CPE and expression of Spike (S) and nucleocapsid (N) proteins (indicative of de novo infctious virions)
- Detects virions in Frozen air samples with TCID50 3.6 x 10^2

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SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis

Muge Cevik, Matthew Tate, Ollie Lloyd, Alberto Enrico Maraolo, Jenna Schafers, Antonia Ho

Summary

Background Viral load kinetics and duration of viral shedding are important determinants for disease transmission. We aimed to characterise viral load dynamics, duration of viral RNA shedding, and viable virus shedding of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in various body fluids, and to compare SARS-CoV-2, SARS-CoV, and Middle East respiratory syndrome coronavirus (MERS-CoV) viral dynamics.

Lancet Microbe 2021; 2: e13–22
Published Online
November 19, 2020
https://doi.org/10.1016/
S2666-5247(20)30172-5

PRE-OMICRON

- 8 studies attempted to isolate live virus from resp samples
- No live virus isolated after day 9 of symptoms

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Cevik M et al. Lancet Microbe. 2021 Jan;2(1):e13-e22.

Previous studies

Study	Study design	Sample size	Population	Period	Culture method	Confirmation of replication
L'huillier EID 2020	Cross sectionnal	23	Children	2020	Vero E6	CPE and decrease in Ct value
Lescure Lancet ID 2020	Prospective cohort	5 patients	Inpatients	2020	Vero E6, 3 days	CPE only
Kujawski Nature Med 2020	Prospective cohort	12 patients	Inpatients/outpatient	2020	Vero CCL-81	CPE and RT-PCR, no quantification criteria
Bullard CID 2020	Cross sectional	90 samples	Outpatients	2020	Vero CCL-81, 4 days	CPE only
To Lancet ID 2020	Prospective cohort	23 patients	Inpatients	2020	Vero E6, 3 days	CPE only
Wolfel Nature 2020	Prospective cohort	9 patients,	Inpatients	2020	Vero E6, 6 days	CPE and RT-PCR, no quantification criteria
Arons NEJM 2020	Cross sectionnal	47 samples	LCTF	2020	Vero CCL-81	CPE and RT-PCR, no quantification criteria
La Scola (Raoult) Eur J Clin Microbiol Infect Dis 2020	Cross sectional	183 samples	Inpatient/outpatient	2020	Vero E6	CPE and RT-PCR, no quantification criteria
Le TQM EID 2020	Prospective cohort	12 patients	Returning travelers	2020	Vero	

This is the type of study on which current recommendations are based!

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LIMITATIONS

- Small sample sizes
- Some cross-sectional data
- Sensitivity of the culture technique
- Patient population: Heterogenous
- Early in the pandemic

This is the type of study on which current recommendations are based!

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International Journal of Infectious Diseases 129 (2023) 228–235

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Duration of viable virus shedding and polymerase chain reaction positivity of the SARS-CoV-2 Omicron variant in the upper respiratory tract: a systematic review and meta-analysis

Yu Wu, Zirui Guo, Jie Yuan, Guiying Cao, Yaping Wang, Peng Gao, Jue Liu, Min Liu*

Department of Epidemiology and Biostatics, School of Public Health, Peking University, Beijing, China

OMICRON

Interindividual Variation!

- 11 studies (n=384 patients) reported duration of viable virus shedding of Omicron
  - Pooled duration viable virus shedding: 5.16 days (95% CI, 4.2 to 6.14)
  - Maximum duration: 15 days
  - Boucau: 25% still shedding virus at 8 days

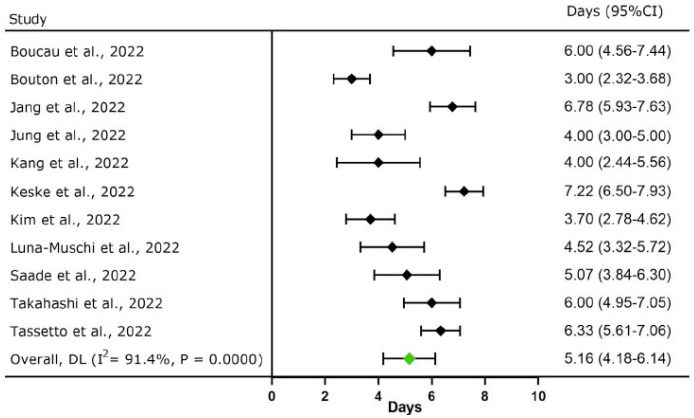

Figure 2. Forest plot for the meta-analysis of viable virus shedding duration of the SARS-CoV-2 Omicron variant in upper respiratory tract. CI, confidence interval; DL, DerSimonian and Laird method.

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How to count durations of infectivity

- Where does the timer start?
  - Day 0
    - Symptom onset n=8 studies
    - Symptom onset OR diagnosis n=4 studies
    - Diagnosis n=2 studies
- How do you call the day of onset?
  - Experts: Day 0
  - Non-experts: Day 1

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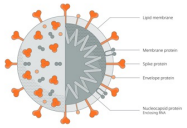
Oordt-Speets AM, Spinardi JR, Mendoza CF, Yang J, Del Carmen Morales G, Kyaw MH. Duration of SARS-CoV-2 shedding: A systematic review. J Glob Health. 2024 Mar 29;14:05005. doi: 10.7189/jogh.14.05005. PMID: 38547496; PMCID: PMC10978056.

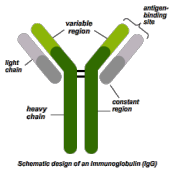
From Original virus to Omicron, many things changed

Δ → O



Virus

Vaccination



Natural immunity

Many potential confounders!

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Return-to-Work criteria

- Can they really distinguish infectious and non-infectious individuals?
- Could we improve them?
- What is their impact on absenteeism?

How could we Improve these rules?

- Need to find variables that are predictors of loss of infectivity!

The number of studies was too small and had insufficient statistical power to show clear trends of daily SARS-CoV-2 culture status or culture positivity for stratified groups, such as vaccinated vs unvaccinated persons; different SARS-CoV-2 variants of concern; symptomatic vs asymptomatic SARS-CoV-2 infected persons; and time since symptom onset vs time since diagnosis.

Oordt-Speets AM, Spinardi JR, Mendoza CF, Yang J, Del Carmen Morales G, Kyaw MH. Duration of SARS-CoV-2 shedding: A systematic review. J Glob Health. 2024 Mar 29;14:05005. doi: 10.7189/jogh.14.05005. PMID: 38547496; PMCID: PMC10978056.

Clinical Infectious Diseases

MAJOR ARTICLE

Timing and Predictors of Loss of Infectivity Among Healthcare Workers With Mild Primary and Recurrent Coronavirus Disease 2019 (COVID-19): A Prospective Observational Cohort Study

Stefania Dzieciolowska,[1] Hugues Charest,[2,3,4] Tonya Roy,[3,4] Judith Fafard,[3,4] Sara Carazo,[4,5] Ines Levade,[3,4] Jean Longtin,[6] Leighanne Parkes,[1,7] Sylvie Nancy Beaulac,[3,4] Jasmin Villeneuve,[4] Patrice Savard,[2,8] Jacques Corbeil,[5] Gaston De Serres,[4,5] and Yves Longtin[1,7,9]

[1]McGill University Faculty of Medicine, Montréal, Canada; [2]Faculté de médecine, Université de Montréal, Montréal, Canada; [3]Laboratoire de Santé Publique du Québec, Sainte-Anne-de-Bellevue, Canada; [4]Institut National de Santé Publique du Québec, Québec City, Canada; [5]Université Laval, Québec City, Canada; [6]CHU de Québec—Université Laval, Québec City, Canada; [7]Jewish General Hospital Sir Mortimer B. Davis, Montréal, Canada; [8]Centre Hospitalier de l'Université de Montréal (CHUM) and CHUM Research Center, Montréal, Canada; and [9]Lady Davis Research Institute, Montréal, Canada

Background. There is a need to understand the duration of infectivity of primary and recurrent coronavirus disease 2019 (COVID-19) and identify predictors of loss of infectivity.

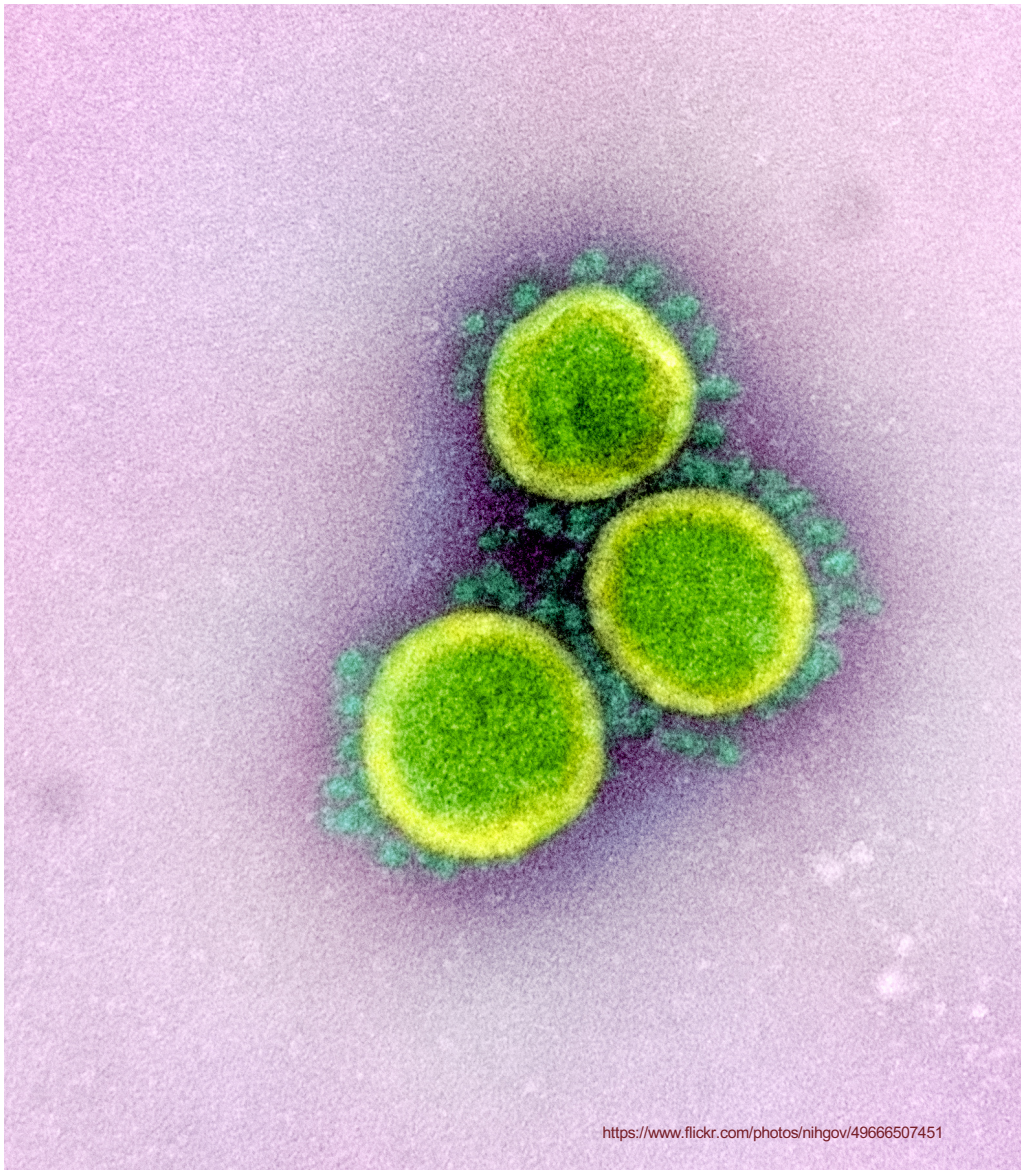
Methods. Prospective observational cohort study with serial viral culture, rapid antigen detection test (RADT) and reverse transcription polymerase chain reaction (RT-PCR) on nasopharyngeal specimens of healthcare workers with COVID-19. The primary outcome was viral culture positivity as indicative of infectivity. Predictors of loss of infectivity were determined using multivariate regression model. The performance of the US Centers for Disease Control and Prevention (CDC) criteria (fever resolution, symptom improvement, and negative RADT) to predict loss of infectivity was also investigated.

Results. In total, 121 participants (91 female [79.3%]; average age, 40 years) were enrolled. Most (n = 107, 88.4%) had received ≥3 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine doses, and 20 (16.5%) had COVID-19 previously. Viral culture positivity decreased from 71.9% (87/121) on day 5 of infection to 18.2% (22/121) on day 10. Participants with recurrent COVID-19 had a lower likelihood of infectivity than those with primary COVID-19 at each follow-up (day 5 odds ratio [OR], 0.14; $P < .001$]; day 7 OR, 0.04; $P = .003$]) and were all non-infective by day 10 ($P = .02$). Independent predictors of infectivity included prior COVID-19 (adjusted OR [aOR] on day 5, 0.005; $P = .003$), an RT-PCR cycle threshold [Ct] value <23 (aOR on day 5, 22.75; $P < .001$) but not symptom improvement or RADT result.

The CDC criteria would identify 36% (24/67) of all non-infectious individuals on day 7. However, 17% (5/29) of those meeting all the criteria had a positive viral culture.

Conclusions. Infectivity of recurrent COVID-19 is shorter than primary infections. Loss of infectivity algorithms could be optimized.

Dzieciolowska S, et al. Clin Infect Dis. 2024 Mar 20;78(3):613-624



https://www.flickr.com/photos/nihgov/49666507451

Objectives

- Primary objective:
  - Proportion of HCWs infected with COVID-19 (Omicron variants) who are shedding infectious viral particles on the 5th, 7th and 10th day of COVID-19 infection using viral culture as a marker of infectiousness
- Secondary objective:
  - To assess the value of various clinical variables such as fever, symptom resolution, rapid antigen test result and RT-PCR Ct value to predict loss of infectivity.

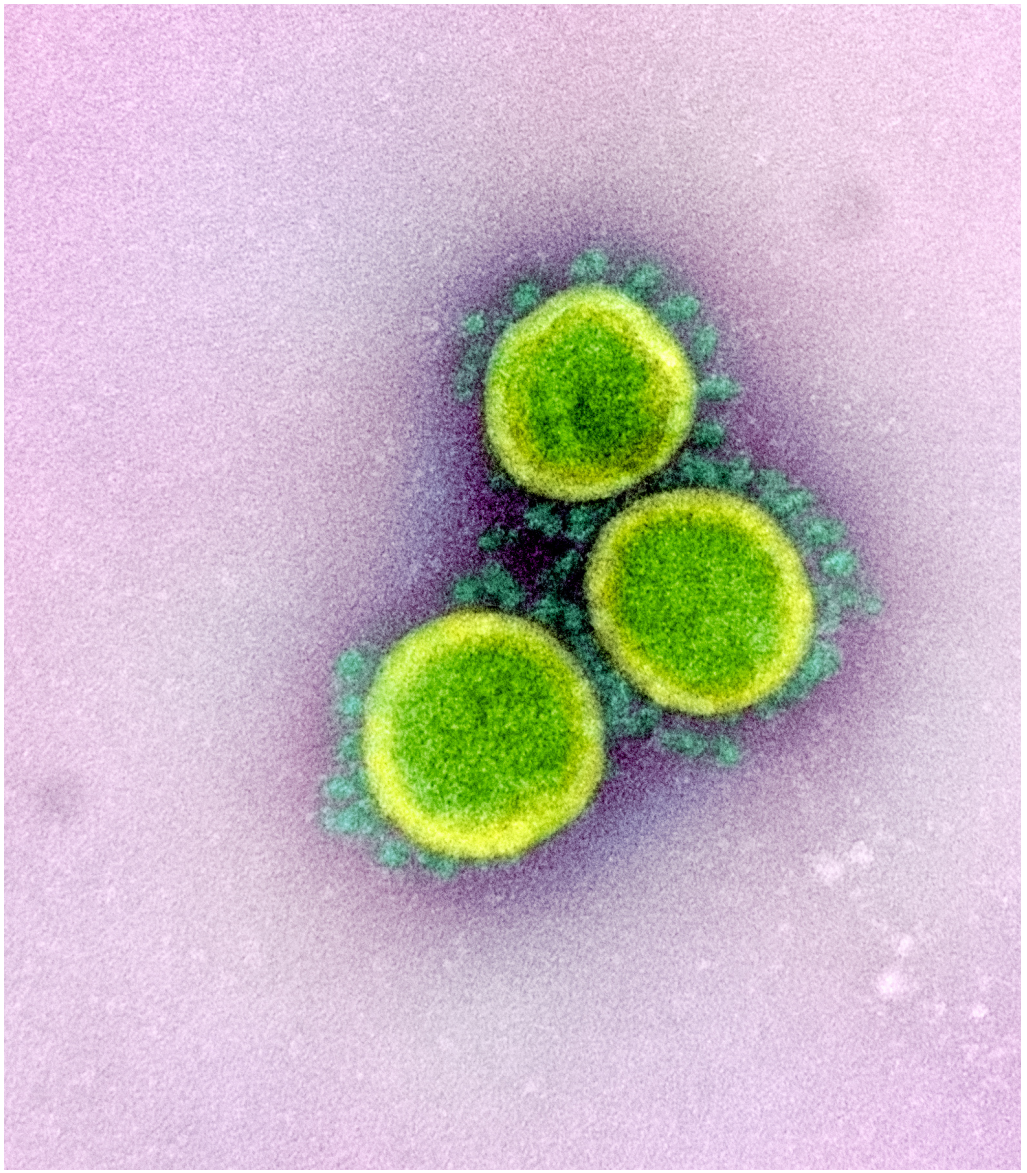
Primary outcome definition

- Definition of persistent viral infectivity
  - Presence of cytopathic effect (CPE) in viral culture

    PLUS

  - RT-PCR confirming presence of SARS-CoV-2 on the supernatant at least 3 Ct values lower than in the original sample

METHODS



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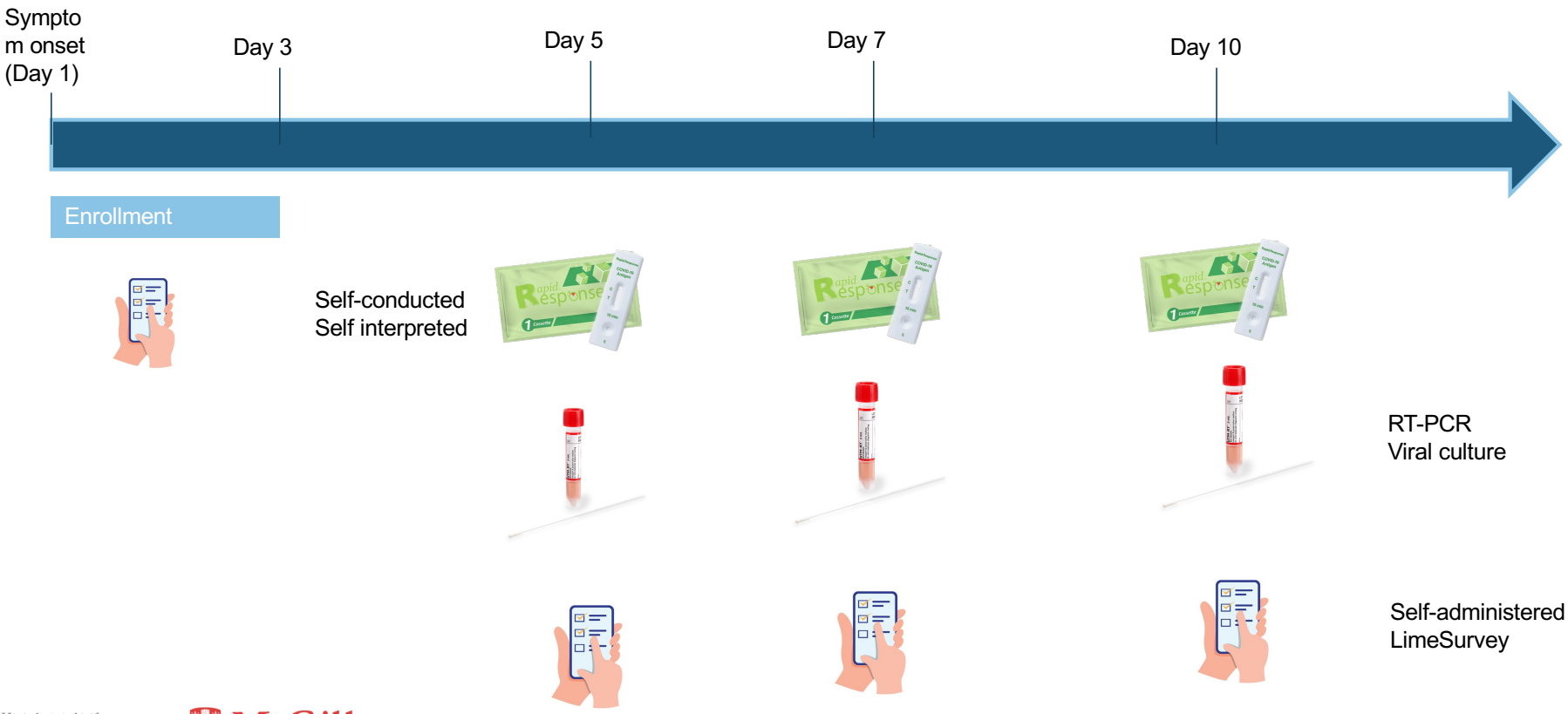
Methods

- Study design: Prospective observational study
- Population:
  - 121 HCWs with laboratory confirmed symptomatic COVID-19 (ID Now)
  - Identified through Occupational Health and Safety
- Recruitment and enrolment
  - Remotely within 72h of symptom onset
  - Follow-up visits on Day 5, 7 and 10 (CDD)
- REB approval (project 2022-3235)

- Inclusion criteria
  - ❑ Employee of CIUSS COMTL (or CIUSSS COMTL healthcare worker such as physician)
  - ❑ Acute symptomatic COVID infection with symptom onset less than 72 hours prior to enrollment.
- Exclusion criteria
  - ❑ Asymptomatic infection
  - ❑ Severe COVID (defined as hospitalization)
  - ❑ HCW eligible to get a COVID-specific treatment such as Paxlovid or Sotrovimab)
  - ❑ Contraindication to nasopharyngeal swab
  - ❑ Cannot commute to the Clinique de Dépistage for testing using a personal mode of transportation
  - ❑ Not fluent in French or English
  - ❑ No access to internet or to a cell phone

Methods



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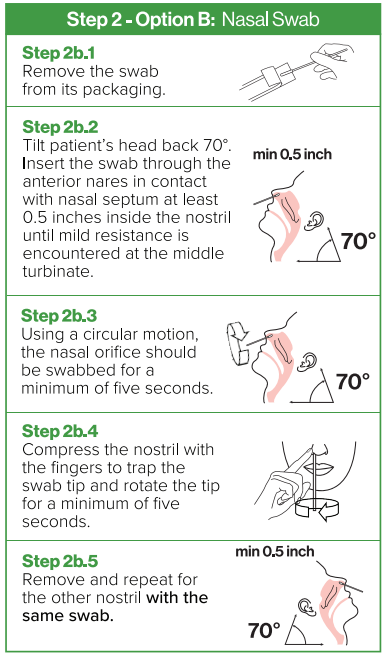
Rapid antigen detection assay

- Rapid Response COVID-19 Antigen (BTNX Inc) provided to each participant
- Performed by the participants at home on Days 5, 7 and 10 (before or after visit to CDD)
- Nasal swab
- 3 possible interpretations
  - Positive
  - Negative
  - Uncertain
- Picture uploaded



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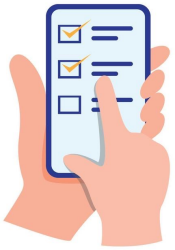
Clinical data

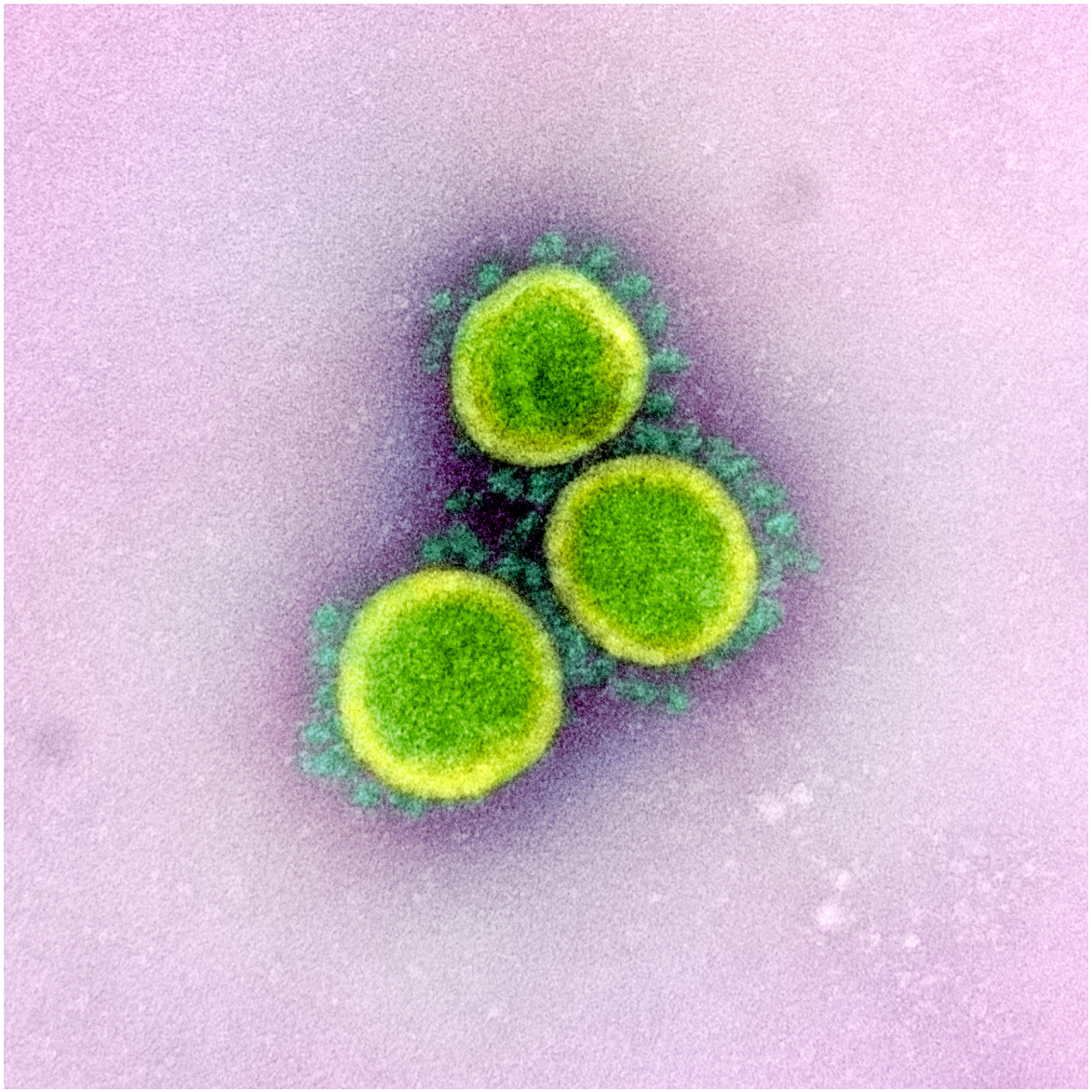


- 4 questionnaires
  - Baseline
    - Demographic data, comorbidity, vaccination status, history of previous COVID-19 infection, and symptomatology of current infection
  - Day 5, 7 and 10
    - Symptomatology (including evolution)
    - Tylenol and NSAID use in afebrile individuals
  - Online self-administered surveys (Limewire)

Statistical considerations

- Sample size calculation
  - 115 participants to recruit
    - Provides +/- 8% confidence interval for a proportion of 25% viral culture positivity at day 7
- Analyses
  - Standard descriptive analyses
  - Association between variable and persistent infectivity assessed by univariate and multivariate logistic regression
  - All tests were 2-tailed and a p-value < 0.05 was considered statistically significant

RESULTS



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Results

- 127 participants recruited between Feb 20th and June 30th, 2022
- 121 included in final analyses

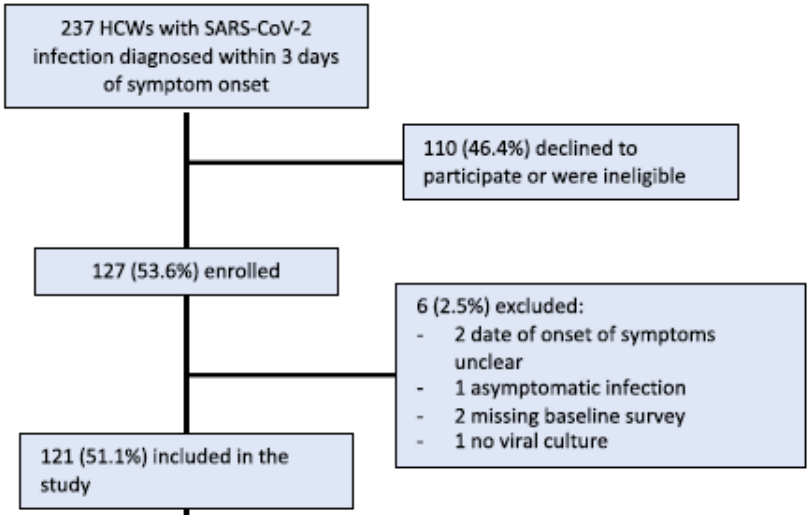

Figure 1. Flow diagram of participant selection into the study and proportion of infective participants at each follow-up visit. Abbreviations: HCW, healthcare worker; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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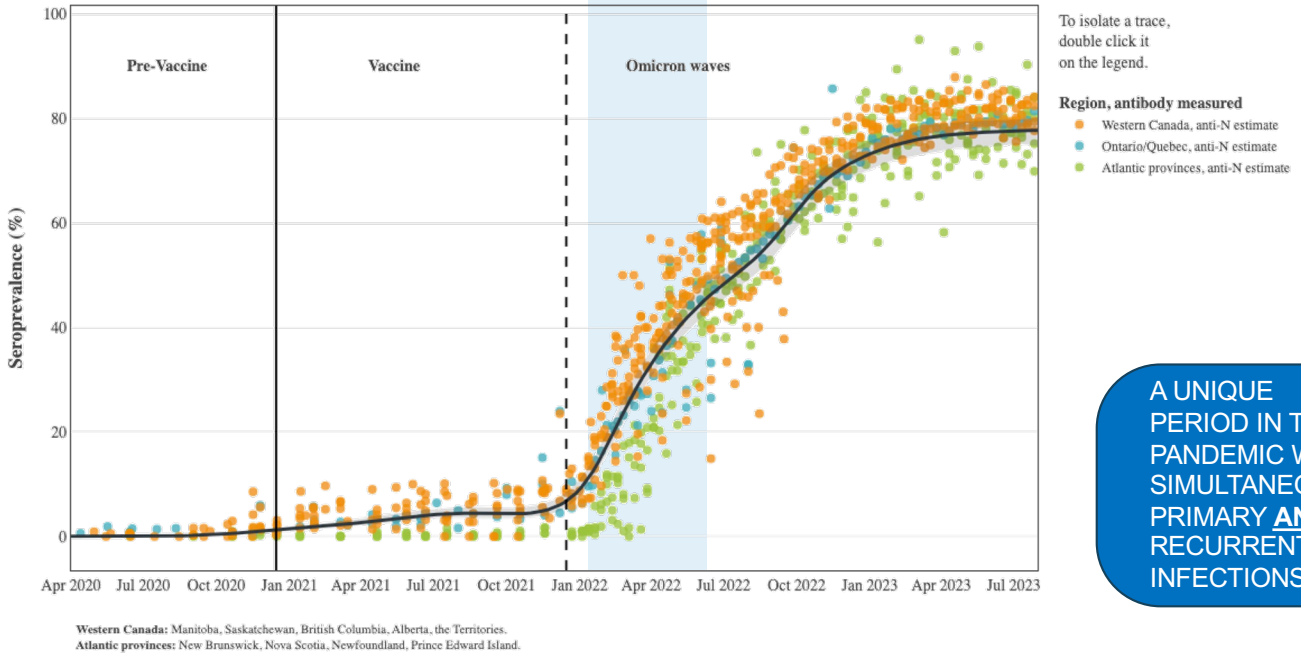
COVID-19 IMMUNITY TASK FORCE | GROUPE DE TRAVAIL SUR L'IMMUNITÉ FACE À LA COVID-19

STUDY PERIOD



Western Canada: Manitoba, Saskatchewan, British Columbia, Alberta, the Territories.
Atlantic provinces: New Brunswick, Nova Scotia, Newfoundland, Prince Edward Island.

A UNIQUE PERIOD IN THE PANDEMIC WITH SIMULTANEOUS PRIMARY **AND** RECURRENT INFECTIONS

Data notes:
Each point represents a seroprevalence estimate from a project at the mid-point of a sample collection period. The black line represents the estimated average seroprevalence weighted by sample size. The light grey bands represent the 95% credible confidence interval.

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https://www.covid19immunitytaskforce.ca/seroprevalence-in-canada/

Participant Characteristics

Table 1. Demographic and Clinical Characteristics of Healthcare Workers With COVID-19

Characteristic	Overall Population (n = 121)
Demographic characteristics	
Mean age—y (SD)	40.2 (12.0)
Female sex (%)	96 (79.3)
Workplace	
Acute care hospital (%)	56 (46.3)
Local community services centers (%)	16 (13.2)
Long term care facilities (%)	15 (12.4)
Rehabilitation center (%)	9 (7.4)
Private clinic, family medicine clinic (%)	7 (5.8)
Other[a] (%)	18 (14.9)
Occupation	
Nurse, nurse practitioner, patient care attendant (%)	45 (37.2)
Physician (%)	20 (16.5)
Administration (%)	13 (10.7)
Physiotherapy, occupational therapy, social worker, radiology technician (%)	22 (18.2)
Other (%)	21 (17.4)
Comorbidities and past medical history	
Immunocopromised condition[b] (%)	4 (3.3)

YOUNG

MOSTLY FEMALES

VARIOUS HC SETTINGS

ALL TYPES OF HCWs

NON-IMMUNOCOMPROMISED

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Participant Characteristics

20 REINFECTIONS (approx.. 1 year prior)

HIGHLY VACCINATED

MOSTLY Pfizer-BioNTech

Table 1. Demographic and Clinical Characteristics of Healthcare Workers With COVID-19

Characteristic	Overall Population (n = 121)
Previous COVID-19 episode (%)	20 (16.5)
Median elapsed time since last COVID-19 episode—d (IQR)	347.5 (264–454)
COVID-19 vaccination status	
Not vaccinated (%)	2 (1.7)
1 dose (%)	3 (2.5)
2 doses (%)	9 (7.4)
3 doses (%)	102 (84.3)
4 doses (%)	5 (4.1)
COVID-19 vaccine type (n = 347 doses)[d]	
Pfizer-BioNTech Comirnaty (%)	310 (89.3)
Moderna Spikevax (%)	30 (8.6)
AstraZeneca Vaxzevria (%)	7 (2.0)
Median elapsed time since last COVID-19 vaccine dose—d (IQR)	122 (95–175)

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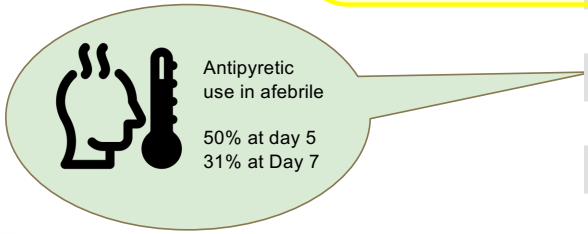
Participant Characteristics

MILD COVID-19

Table 1. Demographic and Clinical Characteristics of Healthcare Workers With COVID-19

Characteristic	Overall Population (n = 121)
Severity of COVID-19 infection[c]	
Very mild (Ambulatory, no limitation of activities) (%)	97 (80.2)
Mild (Ambulatory, with limitation of activities) (%)	24 (19.8)
SARS-CoV-2 specific therapy[e] (%)	1 (0.8)
COVID-19 symptomatology on enrollment	
Median number of symptoms (IQR)	5 (3–6)
Sore throat (%)	94 (77.7)
Rhinorrhea and/or nasal congestion (%)	88 (72.7)
Fatigue (%)	81 (66.9)
Headache (%)	77 (63.6)
Myalgia (%)	55 (45.5)
Chills (%)	50 (41.3)
Cough (%)	21 (17.4)
Fever (%)	18 (14.9)
Dizziness (%)	17 (14.0)
Diarrhea (%)	14 (11.6)
Nausea and/or vomiting (%)	10 (8.3)
Chest pain (%)	10 (8.3)
Dyspnea (%)	8 (6.6)

6 MAIN SYMPTOMS



OUTCOME

- No hospitalization
- No O_2 requirement
- A single participant received nirmatrelvir/ritonavir

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Participant Characteristics

Table 1. Demographic and Clinical Characteristics of Healthcare Workers With COVID-19

Characteristic	Overall Population (n = 121)
SARS-CoV-2 lineage	
BA.1 and sublineages (%)	14 (11.6)
BA.2 and sublineages (%)	73 (60.3)
BA.4 and sublineages (%)	3 (2.5)
BA.5 (%)	10 (8.3)
BQ.1 (%)	9 (7.4)
XBB (%)	1 (0.8)
Recombinants (%)	2 (1.7)
Unknown (%)	9 (7.4)

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Infectivity on Days 5, 7 and 10

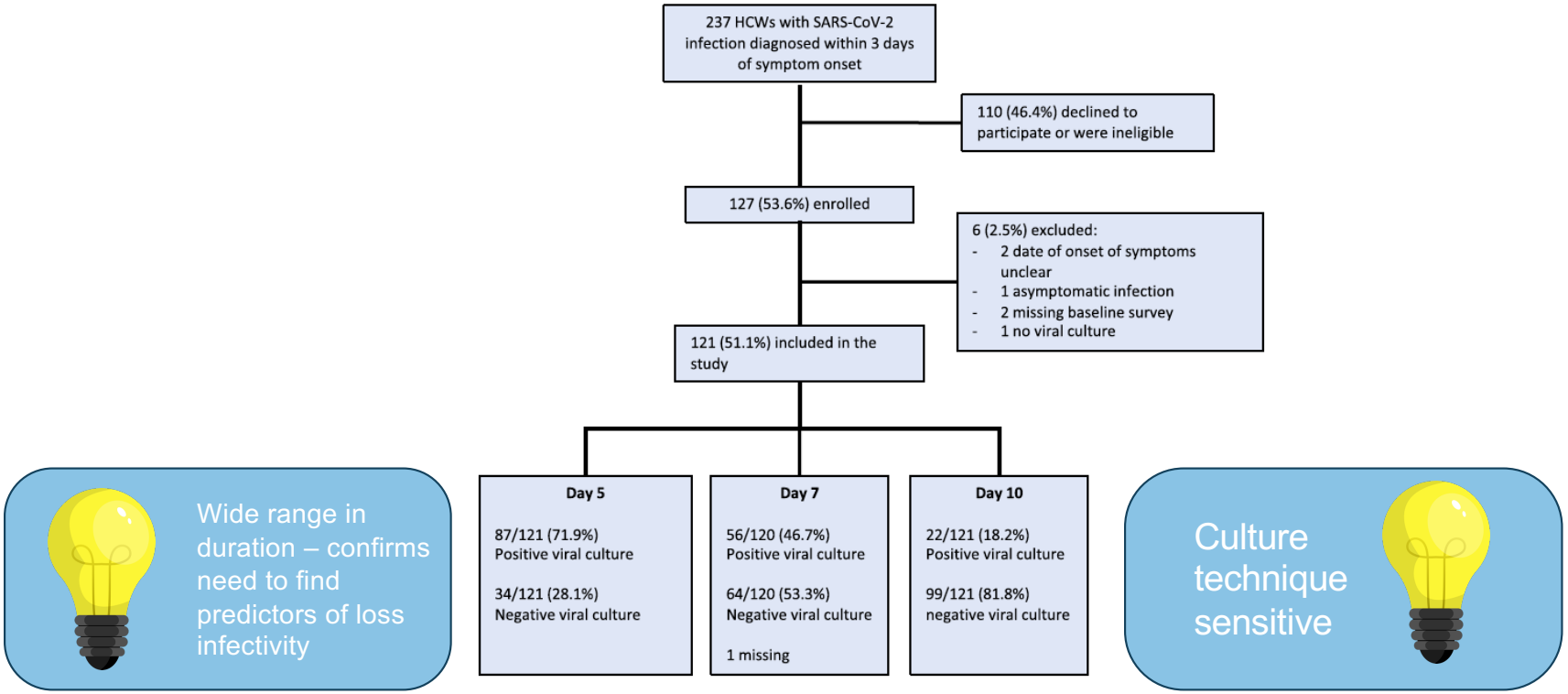


Figure 1. Flow diagram of participant selection into the study and proportion of infective participants at each follow-up visit. Abbreviations: HCW, healthcare worker; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Predictors of loss of infectivity

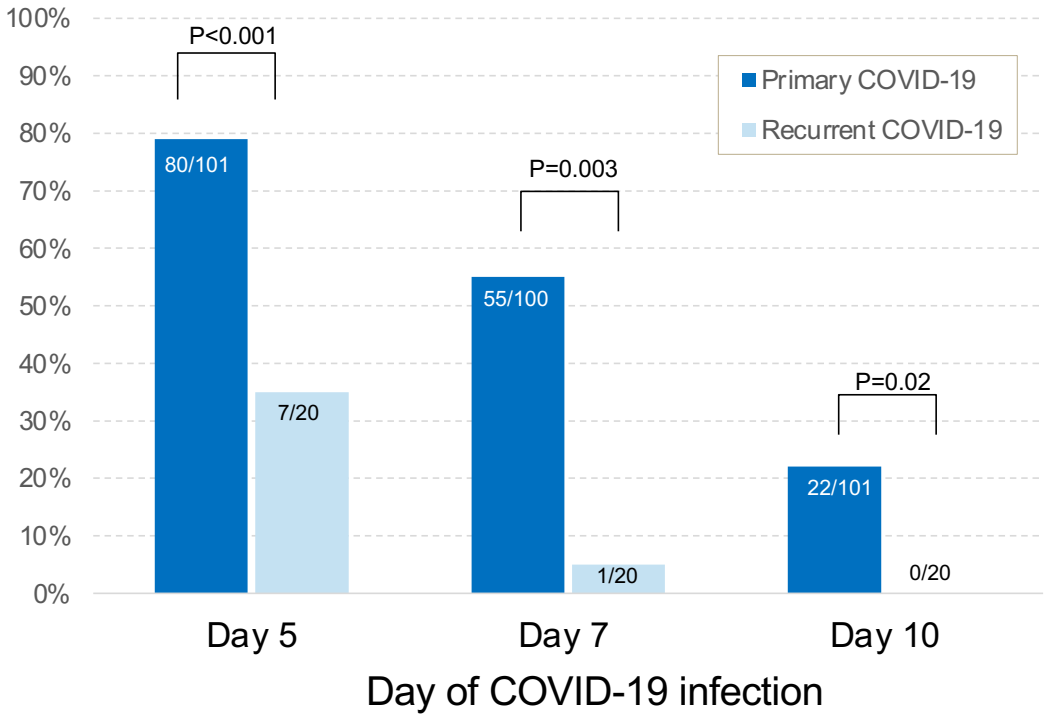
Bivariate analysis

Table 2. Predictors of Infectivity on Day 5, 7, and 10 of COVID-19 Among Healthcare Workers (Bivariate Analyses)

	Day 5[b]				Day 7[b]				Day 10[b]			
Explanatory Variable	Absence of Infectivity n (Line %)	Presence of Infectivity n (Line %)	OR (95% CI)	*P* Value[c]	Absence of Infectivity n (Line %)	Presence of Infectivity n (Line %)	OR (95% CI)	*P* Value[c]	Absence of Infectivity n (Line %)	Presence of Infectivity n (Line %)	OR (95% CI)	*P* Value[c]
Overall	34 (28.1)	87 (71.9)	…		64 (53.3)	56 (46.7)	…		99 (81.8)	22 (18.2)	…	
Demographics												
Median age (IQR)	40 (34–53)	38 (30–48)	NE	.12	38.5 (31.5–49)	39.5 (32–48)	NE	.99	38 (31–48)	39.5 (29–51)	NE	.84
Male sex (%)	7 (28.0)	18 (72.0)	Ref		13 (20.3)	11 (19.6)	Ref		21 (84.0)	4 (16.0)	Ref	
Female sex (%)	27 (28.1)	69 (71.9)	0.99 (.37–2.65)	.99	51 (53.1)	45 (46.9)	1.04 (.43–2.56)	.93	78 (81.3)	18 (18.8)	1.21 (.37–3.96)	.75
Previous infection status												
No previous COVID-19	21 (20.8)	80 (79.2)	Ref		45 (45.0)	55 (55.0)	Ref		79 (78.2)	22 (21.8)	Ref	
Previous COVID-19	13 (65.0)	7 (35.0)	0.14 (.05–.40)	<.001	19 (95.0)	1 (5.0)	0.04 (.01–.33)	.003	20 (100)	0 (0.0)	NE	.02
Vaccination: number of doses received												
No vaccination or 1 dose received	2 (40.0)	3 (60.0)	Ref		2 (40.0)	3 (60.0)	Ref		5 (100)	0 (0.0)	Ref	
≥ 2 doses received	32 (27.6)	84 (72.4)	1.75 (.28–10.96)	.55	62 (53.9)	53 (46.1)	0.57 (.09–3.54)	0.55	94 (81.0)	22 (19.0)	NE	.58
Immunity status stratified by timing of last vaccine and previous COVID-19												
No previous infection and last vaccine dose ≥6 m ago	2 (16.7)	10 (83.3)	Ref		7 (63.6)	4 (36.4)	Ref		11 (91.7)	1 (8.3)	Ref	
No previous infection and last vaccine dose <6 m ago	19 (21.3)	70 (78.7)	0.74 (.15–3.65)	.71	38 (42.7)	51 (57.3)	2.35 (.64–8.60)	.20	68 (76.4)	21 (23.6)	3.40 (.41–27.87)	.26
Previous infection, last vaccine dose> or <6 m ago[a]	13 (65.0)	7 (35.0)	0.11 (.02–.64)	.01	19 (95.0)	1 (5.0)	0.09 (.01–.97)	.047	20 (100)	0 (0.0)	NE	.38
RADT result												
Negative	8 (61.5)	5 (38.5)	Ref		29 (85.3)	5 (14.7)	Ref		64 (100)	0 (0)	Ref	
Positive	20 (20.6)	77 (79.4)	6.16 (1.82–20.88)	.004	26 (34.7)	49 (65.3)	10.93 (3.78–31.60)	<.001	22 (55.0)	18 (45.0)	NE	.03
Uncertain	6 (66.7)	3 (33.3)	0.80 (.13–4.75)	.81	7 (87.5)	1 (12.5)	0.83 (.08–8.27)	.87	11 (84.6)	2 (15.4)	NE	<.001
SARS-CoV2 RT-PCR												
Median Ct value (IQR)	28.5 (25.0–33.4)	21.8 (20.3–25.0)	…	<.001	31.3 (27.4–35.6)	24.7 (22.9–27.4)	…	<.001	35.5 (31.4–40.0)	26.7 (24.4–28.3)	…	.002
Negative result	6 (75.0)	2 (25.0)	Ref		13 (100)	0 (0.0)	Ref		46 (100)	0 (0.0)	Ref	
Positive result	28 (25.0)	84 (75.0)	9.00 (1.72–47.17)	.01	51 (47.7)	56 (52.3)	NE	<.001	52 (70.3)	22 (29.7)	NE	<.001
RT-PCR Ct (reference: negative RT-PCR)												
Ct value: 27–34	15 (57.7)	11 (42.3)	2.20 (.37–13.04)	.39	36 (69.2)	16 (30.8)	Ref (Ct ≥27)	…	40 (81.6)	9 (18.4)	Ref (Ct ≥27)	…
Ct value: 23–<27	9 (33.3)	18 (66.7)	6.00 (1.00–35.91)	.05	13 (33.3)	26 (66.7)	6.12 (2.56–14.66)	<.001	10 (47.6)	11 (52.4)	9.67 (1.21–77.12)	.03

Recurrent COVID-19

Proportion of healthcare workers with positive viral culture



Primary COVID-19 with Omicron = longer infectivity than previously described

i.e. day 4 after symptom onset

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Table 2. Predictors of Infectivity on Day 5, 7, and 10 of COVID-19 Among Healthcare Workers (Bivariate Analyses)

	Day 5[b]				Day 7[b]				Day 10[b]			
Explanatory Variable	Absence of Infectivity n (Line %)	Presence of Infectivity n (Line %)	OR (95% CI)	*P* Value[c]	Absence of Infectivity n (Line %)	Presence of Infectivity n (Line %)	OR (95% CI)	*P* Value[c]	Absence of Infectivity n (Line %)	Presence of Infectivity n (Line %)	OR (95% CI)	*P* Value[c]
Overall	34 (28.1)	87 (71.9)	…		64 (53.3)	56 (46.7)	…		99 (81.8)	22 (18.2)	…	
Demographics												
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Male sex (%)	7 (28.0)	18 (72.0)	Ref		13 (20.3)	11 (19.6)	Ref		21 (84.0)	4 (16.0)	Ref	
Female sex (%)	27 (28.1)	69 (71.9)	0.99 (.37–2.65)	.99	51 (53.1)	45 (46.9)	1.04 (.43–2.56)	.93	78 (81.3)	18 (18.8)	1.21 (.37–3.96)	.75
Previous infection status												
No previous COVID-19	21 (20.8)	80 (79.2)	Ref		45 (45.0)	55 (55.0)	Ref		79 (78.2)	22 (21.8)	Ref	
Previous COVID-19	13 (65.0)	7 (35.0)	0.14 (.05–.40)	<.001	19 (95.0)	1 (5.0)	0.04 (.01–.33)	.003	20 (100)	0 (0.0)	NE	.02
Vaccination: number of doses received												
No vaccination or 1 dose received	2 (40.0)	3 (60.0)	Ref		2 (40.0)	3 (60.0)	Ref		5 (100)	0 (0.0)	Ref	
≥ 2 doses received	32 (27.6)	84 (72.4)	1.75 (.28–10.96)	.55	62 (53.9)	53 (46.1)	0.57 (.09–3.54)	0.55	94 (81.0)	22 (19.0)	NE	.58
Immunity status stratified by timing of last vaccine and previous COVID-19												
No previous infection and last vaccine dose ≥6 m ago	2 (16.7)	10 (83.3)	Ref		7 (63.6)	4 (36.4)	Ref		11 (91.7)	1 (8.3)	Ref	
No previous infection and last vaccine dose <6 m ago	19 (21.3)	70 (78.7)	0.74 (.15–3.65)	.71	38 (42.7)	51 (57.3)	2.35 (.64–8.60)	.20	68 (76.4)	21 (23.6)	3.40 (.41–27.87)	.26
Previous infection, last vaccine dose> or <6 m ago[a]	13 (65.0)	7 (35.0)	0.11 (.02–.64)	.01	19 (95.0)	1 (5.0)	0.09 (.01–.97)	.047	20 (100)	0 (0.0)	NE	.38
RADT result												
Negative	8 (61.5)	5 (38.5)	Ref		29 (85.3)	5 (14.7)	Ref		64 (100)	0 (0)	Ref	
Positive	20 (20.6)	77 (79.4)	6.16 (1.82–20.88)	.004	26 (34.7)	49 (65.3)	10.93 (3.78–31.60)	<.001	22 (55.0)	18 (45.0)	NE	.03
Uncertain	6 (66.7)	3 (33.3)	0.80 (.13–4.75)	.81	7 (87.5)	1 (12.5)	0.83 (.08–8.27)	.87	11 (84.6)	2 (15.4)	NE	<.001
SARS-CoV2 RT-PCR												
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Negative result	6 (75.0)	2 (25.0)	Ref		13 (100)	0 (0.0)	Ref		46 (100)	0 (0.0)	Ref	
Positive result	28 (25.0)	84 (75.0)	9.00 (1.72–47.17)	.01	51 (47.7)	56 (52.3)	NE	<.001	52 (70.3)	22 (29.7)	NE	<.001
RT-PCR Ct (reference: negative RT-PCR)												
Ct value: 27–34	15 (57.7)	11 (42.3)	2.20 (.37–13.04)	.39	36 (69.2)	16 (30.8)	Ref (Ct ≥27)	…	40 (81.6)	9 (18.4)	Ref (Ct ≥27)	…
Ct value: 23–<27	9 (33.3)	18 (66.7)	6.00 (1.00–35.91)	.05	13 (33.3)	26 (66.7)	6.12 (2.56–14.66)	<.001	10 (47.6)	11 (52.4)	9.67 (1.21–77.12)	.03

RADT Result

RT-PCR Result

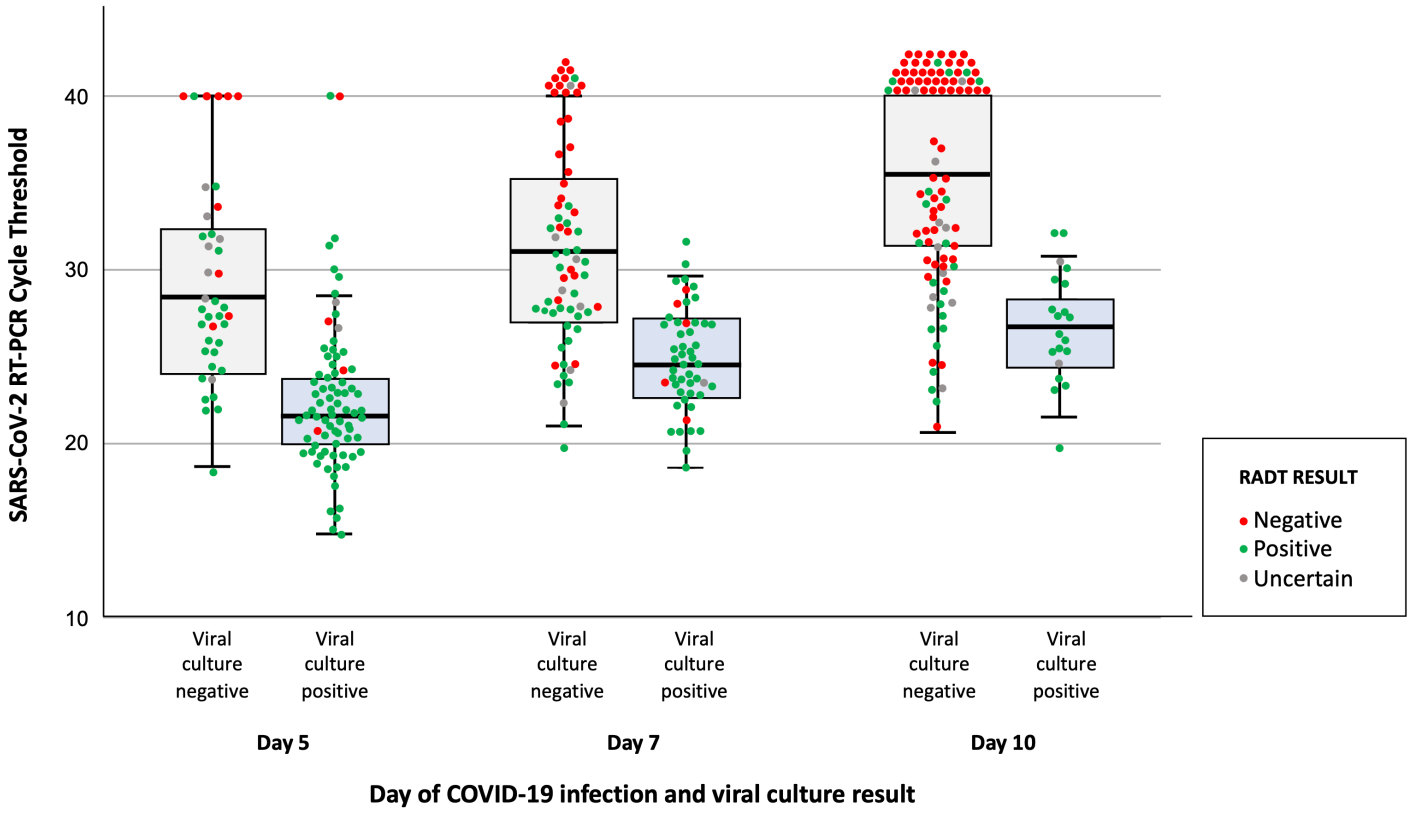
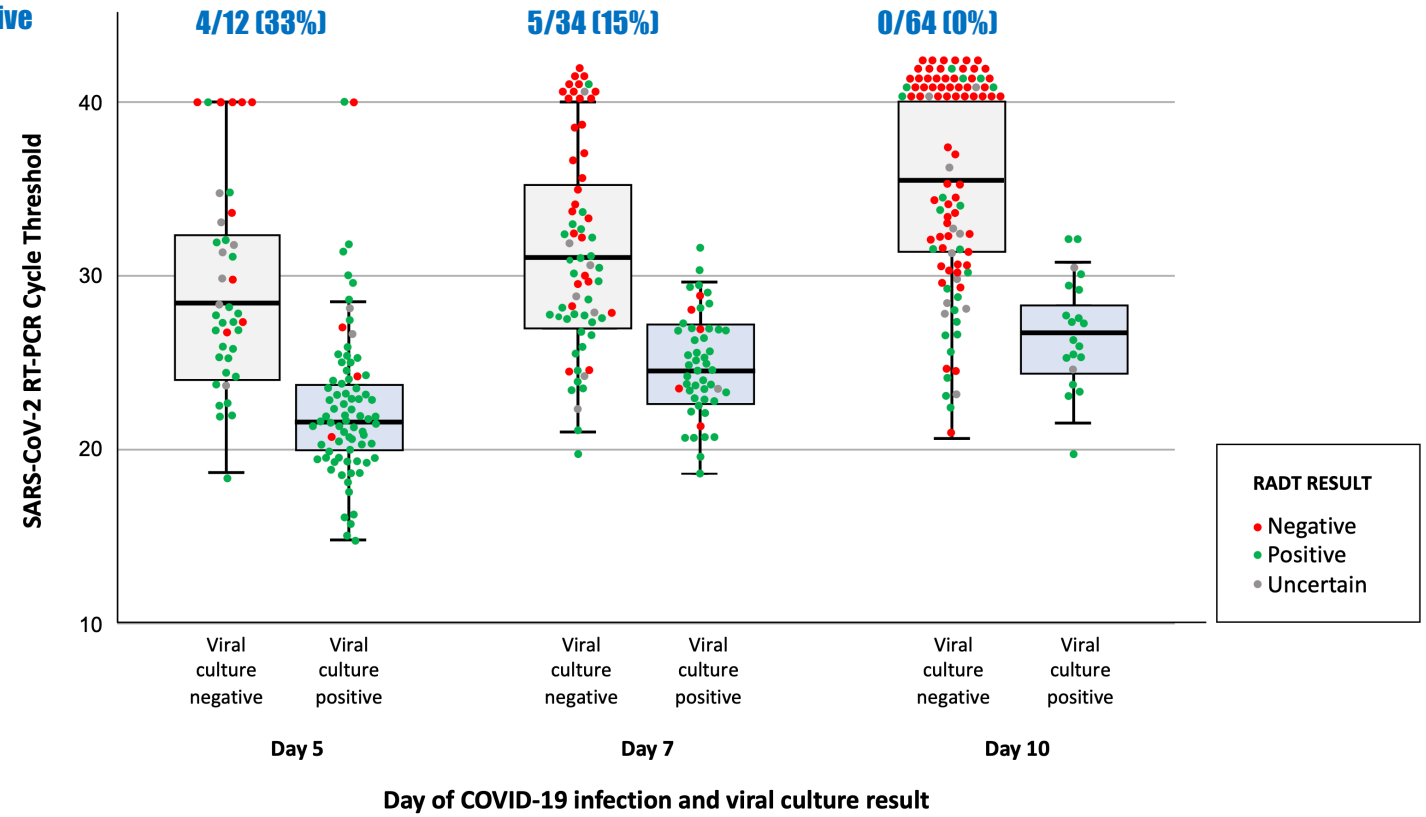


Figure 2. Box plot with overlaid jitter plot comparing SARS-CoV-2 RT-PCR Ct, RADT result, and viral culture positivity at day 5, 7, and 10 of COVID-19 among 121 healthcare workers. The horizontal line in each box indicates the median, whereas the top and bottom of the boxes represent the 75th and 25th percentile, respectively. Error bars represent 95% confidence intervals. Negative RT-PCR results were attributed a Ct value of 40 to facilitate data visualization. Abbreviations: COVID-19, coronavirus disease 2019; Ct, cycle threshold; RADT, rapid antigen diagnostic test; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

RADT False negative



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Recurrent COVID-19: Lower viral load throughout study

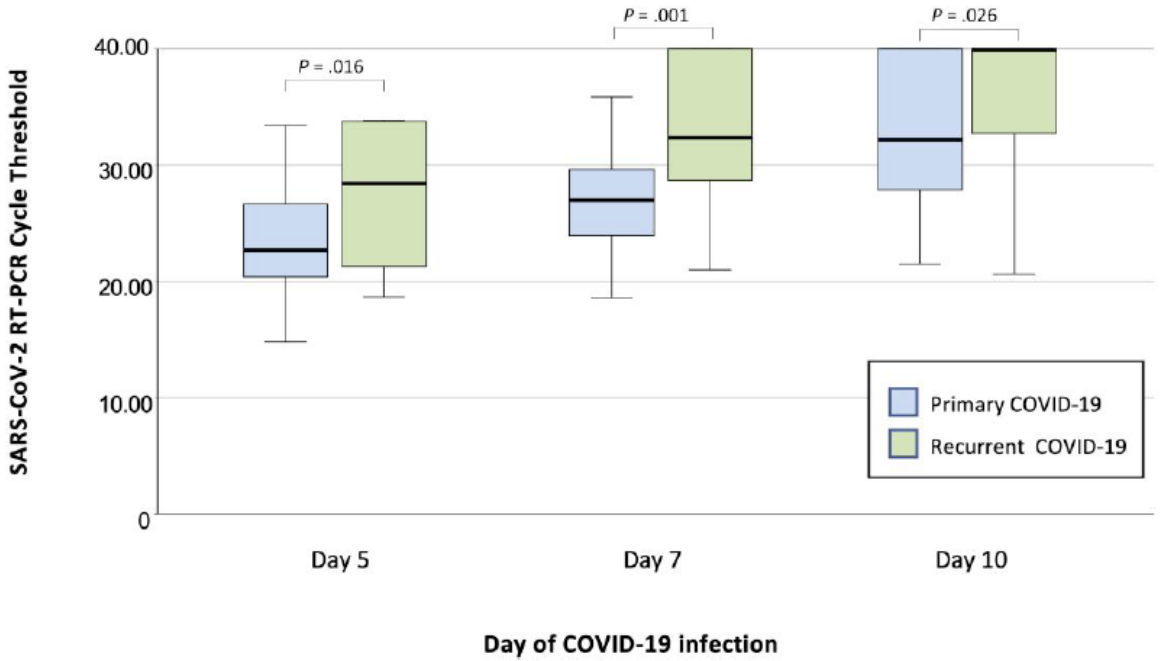
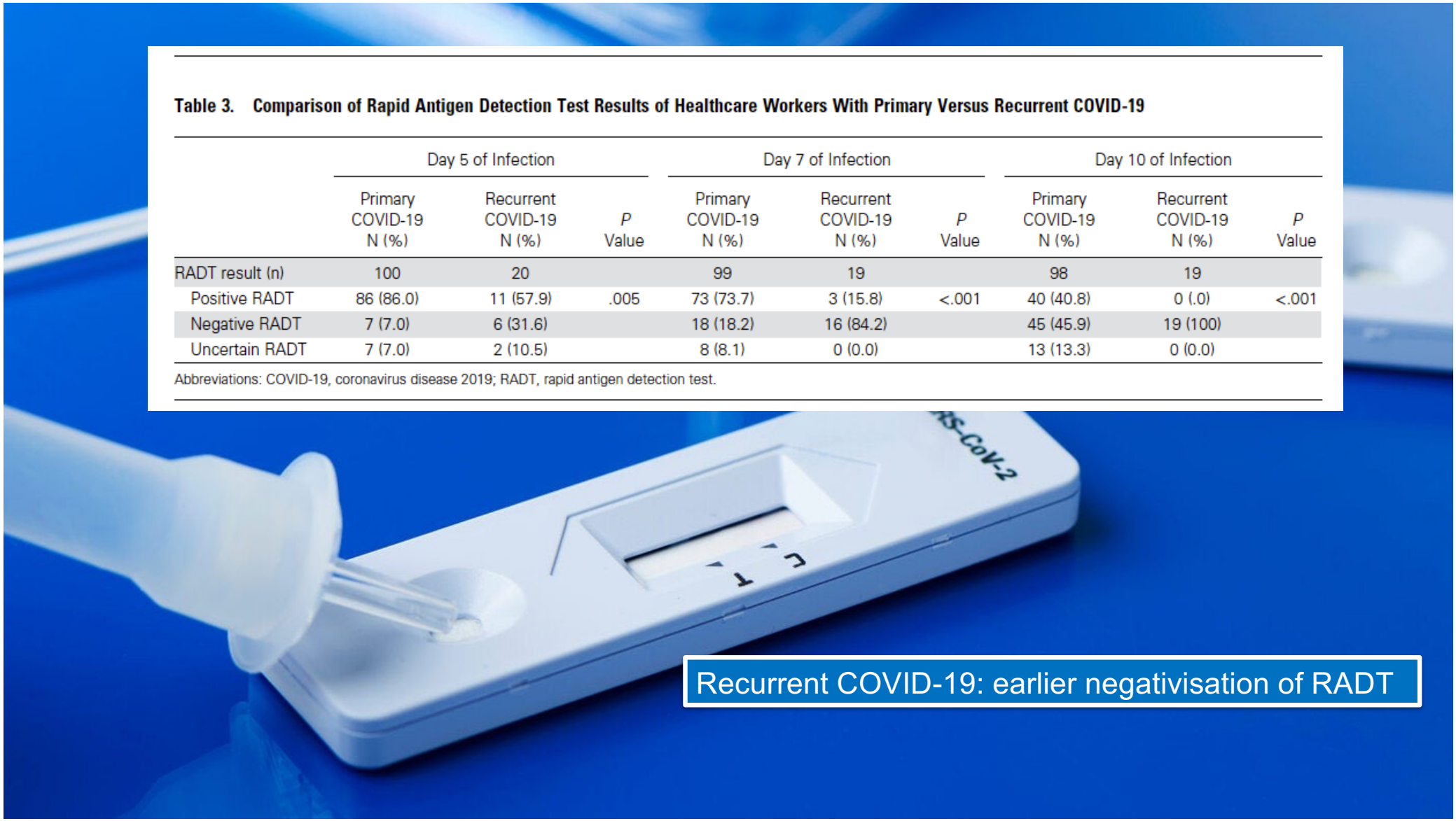


Figure 3. Box plot comparing SARS-CoV-2 RT-PCR Ct at day 5, 7, and 10 of primary versus recurrent COVID-19 infection. The horizontal line in each box indicates the median, whereas the top and bottom lines represent the 75th and 25th percentile, respectively. Error bars represent 95% confidence intervals. Negative RT-PCR results were attributed a Ct value of 40 to facilitate data visualization. Comparison between primary versus recurrent infections assessed by Mann-Whitney *U* test. Abbreviations: COVID-19, coronavirus disease 2019; Ct, cycle threshold; RADT, rapid antigen diagnostic test; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 3. Comparison of Rapid Antigen Detection Test Results of Healthcare Workers With Primary Versus Recurrent COVID-19

	Day 5 of Infection			Day 7 of Infection			Day 10 of Infection		
	Primary COVID-19 N (%)	Recurrent COVID-19 N (%)	*P* Value	Primary COVID-19 N (%)	Recurrent COVID-19 N (%)	*P* Value	Primary COVID-19 N (%)	Recurrent COVID-19 N (%)	*P* Value
RADT result (n)	100	20		99	19		98	19	
Positive RADT	86 (86.0)	11 (57.9)	.005	73 (73.7)	3 (15.8)	<.001	40 (40.8)	0 (.0)	<.001
Negative RADT	7 (7.0)	6 (31.6)		18 (18.2)	16 (84.2)		45 (45.9)	19 (100)	
Uncertain RADT	7 (7.0)	2 (10.5)		8 (8.1)	0 (0.0)		13 (13.3)	0 (0.0)	

Abbreviations: COVID-19, coronavirus disease 2019; RADT, rapid antigen detection test.



Recurrent COVID-19: earlier negativisation of RADT

Table 2. Continued

Explanatory Variable	Day 5[b] Absence of Infectivity n (Line %)	Day 5[b] Presence of Infectivity n (Line %)	Day 5[b] OR (95% CI)	Day 5[b] *P* Value[c]	Day 7[b] Absence of Infectivity n (Line %)	Day 7[b] Presence of Infectivity n (Line %)	Day 7[b] OR (95% CI)	Day 7[b] *P* Value[c]	Day 10[b] Absence of Infectivity n (Line %)	Day 10[b] Presence of Infectivity n (Line %)	Day 10[b] OR (95% CI)	Day 10[b] *P* Value[c]
Ct value: 20–<23	3 (7.9)	35 (92.1)	35.00 (4.79–255.47)	.001	2 (15.4)	11 (84.6)	16.84 (3.37–84.17)	<.001	2 (50.0)	2 (50.0)	10.63 (3.55–31.86)	<.001
Ct value: <20	1 (4.8)	20 (95.2)	60.00 (4.60–782.36)	.002	0 (0.0)	3 (100)	NE	.02	0 (0.0)	0 (0.0)	NE	NE
SARS-CoV-2 lineage												
BA.2	21 (28.8)	52 (71.2)	Ref		39 (53.4)	34 (46.6)	Ref		62 (84.9)	11 (15.1)	Ref	
BA.1	0 (0.0)	14 (100.0)	NE	.02	1 (7.1)	13 (92.9)	14.91 (1.85–199.99)	.01	8 (57.1)	6 (42.9)	4.23 (1.23–14.57)	.02
BA.4/5	3 (23.1)	10 (76.9)	1.35 (.34–5.38)	.67	8 (66.7)	4 (33.3)	0.57 (.16–2.07)	.40	10 (76.9)	3 (23.1)	1.69 (.40–7.14)	.48
Others (BQ.1, XBB.1, recombinant, unknown)	10 (47.6)	11 (52.4)	0.44 (.16–1.20)	.11	16 (76.2)	5 (23.8)	0.36 (.12–1.08)	.07	19 (90.5)	2 (9.5)	.59 (.12–2.91)	.52
Severity of symptoms												
Asymptomatic	3 (60.0)	2 (40.0)	Ref		11 (57.9)	8 (42.1)	Ref		38 (88.4)	5 (11.6)	Ref	
Very mild[d]	28 (26.7)	77 (73.3)	4.12 (.65–25.99)	.13	50 (54.3)	42 (45.7)	1.16 (.43–3.14)	.78	58 (79.5)	15 (20.5)	1.97 (.66–5.86)	.23
Mild[d]	3 (33.3)	6 (66.7)	3.00 (.31–28.84)	.34	1 (16.7)	5 (83.3)	6.87 (.67–70.81)	.11	1 (100)	0 (0.0)	NE	1.000
Evolution of symptoms												
Symptoms are better or entirely gone	30 (32.6)	62 (67.4)	Ref		61 (58.1)	44 (41.9)	Ref		92 (82.1)	20 (17.9)	Ref	
Symptoms are the same or worse than before	4 (14.8)	23 (85.2)	2.78 (.88–8.77)	.08	1 (8.3)	11 (91.7)	4.81 (1.90–122.49)	.01	5 (100)	0 (0.0)	NE	.59
Symptomatology												
Fever and antipyretics use (last 24 h)												
No fever, without antipyretics use	22 (40.0)	33 (60.0)	Ref		48 (60.8)	31 (39.2)	Ref		83 (87.4)	12 (12.6)	Ref	
No fever, with antipyretics use	9 (16.4)	46 (83.6)	3.41 (1.39–8.34)	.007	12 (34.3)	23 (65.7)	2.97 (1.29–6.82)	.01	13 (61.9)	8 (38.1)	4.26 (1.46–12.39)	.008
Fever	3 (33.3)	6 (66.7)	1.33 (.30–5.90)	.71	2 (66.7)	1 (33.3)	0.77 (.07–8.91)	.84	1 (100)	0 (0.0)	NE	1.000
Presence of any symptom (last 48 h)	22 (24.2)	69 (75.8)	2.35 (.97–5.72)	.06	38 (48.7)	40 (51.3)	1.68 (.77–3.69)	.19	52 (78.8)	14 (21.2)	2.02 (.72–5.69)	.18
Median number of symptoms (IQR)	3 (42.9)	4 (57.1)	NA	.14	2 (40)	3 (60)	NA	.07	1 (33.3)	2 (66.7)	NA	.41

BA.1 ↑ duration

Lack of improvement ↑ duration

Antipyretic use ↑ duration

Abbreviations: Ct, cycle threshold value; IQR, interquartile range; NA, not applicable; NE, no estimate could be calculated due to perfect correlation; RADT, rapid antigen detection test; Ref, reference category; RT-PCR, real-time polymerase chain reaction.

[a]Regardless of timing of last vaccine dose.

[b]Among 121 participants with data on infectivity on day 5, 2 had missing information for RADT result and symptoms and 1 had missing information on RT-PCR CT result; among 120 participants with data on infectivity on day 7, 3 had missing information for RADT result and symptoms; among 121 participants with data on infectivity on day 10, 4 had missing information for RADT result and symptoms, and 1 had missing information on RT-PCR Ct result.

[c]Means were compared using student's t-test, proportions were compared using χ^2 or Fisher exact test when appropriate.

[d]"Very mild" defined as able to carry out regular activities of daily living; "mild" defined as unable to carry out regular activities of daily living.

Table 2. Predictors of infectivity on day 5, 7 and 10 of COVID-19 among healthcare workers (bivariate analyses)

	Day 5			Day 7			Day 10		
Explanatory variable	N[b]	OR (95% CI)	P-value[c]	N[b]	OR (95% CI)	P-value[c]	N[b]	OR (95% CI)	P-value[c]
Antipyretic Use									
Fever and Tylenol use (last 24h)									
No fever, without Tylenol use	73	Ref		88	Ref		102	Ref	
No fever, with Tylenol use	36	1.52 (0.64-3.64)	0.34	26	2.67 (1.08-6.56)	0.03	14	1.36 (0.34-5.41)	0.66
Fever	9	1.17 (0.27-5.08)	0.83	3	0.83 (0.07-9.55)	0.84	1	NE	
Fever and NSAID use (last 24h)									
No fever, without NSAID use	78	Ref		95	Ref		106	Ref	
No fever, with NSAID use	31	2.75 (1.01-7.47)	0.047	19	1.60 (0.59-4.29)	0.36	10	9.86 (2.47-39.35)	0.001
Fever	9	1.32 (0.31-5.67)	0.71	3	0.72 (0.06-8.20)	0.79	1	NE	

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REVIEW ARTICLE OPEN

Check for updates

The use of non-steroidal anti-inflammatory drugs (NSAIDs) in COVID-19

Pamela Kushner[1,2]✉, Bill H. McCarberg[3], Laurent Grange[4,5], Anton Kolosov[6], Anela Lihic Haveric[7], Vincent Zucal[8], Richard Petruschke[9] and Stephane Bissonnette[9]

Early in the COVID-19 pandemic, anecdotal reports emerged suggesting non-steroidal anti-inflammatory drugs (NSAIDs) may increase susceptibility to infection and adversely impact clinical outcomes. This narrative literature review (March 2020–July 2021) attempted to clarify the relationship between NSAID use and COVID-19 outcomes related to disease susceptibility or severity. Twenty-four relevant publications (covering 25 studies) reporting original research data were identified; all were observational cohort studies, and eight were described as retrospective. Overall, these studies are consistent in showing that NSAIDs neither increase the likelihood of SARS-CoV-2 infection nor worsen outcomes in patients with COVID-19. This is reflected in current recommendations from major public health authorities across the world, which support NSAID use for analgesic or antipyretic treatment during COVID-19. Thus, there is no basis on which to restrict or prohibit use of these drugs by consumers or patients to manage their health conditions and symptoms during the pandemic.

npj Primary Care Respiratory Medicine (2022)32:35 ; https://doi.org/10.1038/s41533-022-00300-z

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Kushner P, et al. NPJ Prim Care Respir Med. 2022 Sep 21;32(1):35.

Predictors of loss of infectivity

- Multivariate analysis
  - Included variables
    - Age, sex
    - Immune status (vaccine-derived and natural)
    - Clinical characteristics (symptom severity, resolution, fever
    - Antipyretic use
    - RADT result
    - RT-PCR Ct value

Table 4. Predictors of Infectivity Among HCWs With COVID-19 (Multivariate Analysis)

	Day 5 (n = 121)			Day 7 (n = 117)			Day 10 (n = 117)		
	Adjusted OR	95% CI	*P* Value	Adjusted OR	95% CI	*P* Value	Adjusted OR	95% CI	*P* Value
Female sex	0.42	.09–2.06	.287	1.28	.31–5.34	.73	0.83	.16–4.18	.82
Age (y)									
20–39	Ref	…		Ref	…		Ref	…	
40–59	0.50	.15–1.68	.26	1.43	.47–4.34	.52	1.28	.36–4.63	.70
60–77	0.17	.02–1.63	.12	0.52	.06–4.71	.56	2.54	.25–26.31	.43
Immunity status stratified by timing of last vaccine and previous COVID-19									
No previous infection & last vaccine dose ≥6 m ago	Ref	…		Ref	…		Ref	…	
No previous infection & last vaccine dose <6 m ago	0.27	.03–2.33	.23	7.50	.89–62.83	.06	1.41	.14–14.15	.77
Previous infection, last vaccine dose> or <6 m ago[a]	0.005	.002–.16	.003	0.14	.003–6.61	.32	NE	…	
RADT result									
Negative	Ref	…		Ref	…		NE	…	
Positive	0.69	.11–4.43	.70	3.20	.74–13.91	.12	NE	…	
Uncertain	0.14	.1–1.48	.10	0.07	.002–1.82	.11	NE	…	
SARS-CoV-2 RT-PCR Ct									
≥27 (including negative)	Ref	…		Ref	…		Ref	…	
23–<27	1.30	.29–5.62	.73	4.81	1.52–15.25	.008	12.39	3.32–46.20	<.001
14–<23	22.75	3.89–133.05	<.001	182.30	8.83–3764.36	.001	24.71	1.53–398.50	.02
SARS-CoV-2 lineage[b]									
BA.1, BA.2 and subvariants	Ref	…		Ref	…		Ref	…	
BA.4, BA.5, BQ.1, XBB and subvariants	4.14	.50–33.97	.19	3.13	.46–21.43	.24	2.95	.52–16.70	.22
Evolution of symptoms									
Symptoms are better or entirely gone	Ref	…		Ref	…		NE	…	
Symptoms are the same or worse than before	0.52	.11–2.57	.42	18.67	.98–355.49	.05	NE	…	
Fever and antipyretic use[c]									
No fever, without antipyretics use	Ref	…		Ref	…		Ref	…	
No fever, with antipyretics use	4.83	1.30–17.98	.85	1.32	.40–4.35	.65	4.16	1.00–16.95	.047
Fever	1.21	.18–8.17	.85	NA	…		NA	…	

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; Ct, cycle threshold; HCW, healthcare workers; NA, not applicable; NE, not estimable; OR, odds ratio; RADT, rapid antigen detection test; Ref, reference category; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Regardless of timing of last vaccine dose.

[b]For 9 individuals with missing information, lineage BA.1/BA.2 or lineage BA.4/BA.5/BQ.1/XBB were assigned based on circulating variants at the date of testing.

[c]For the analyses of day 7 and day 10, "fever" and "no fever, with antipyretic use" were considered a single category.

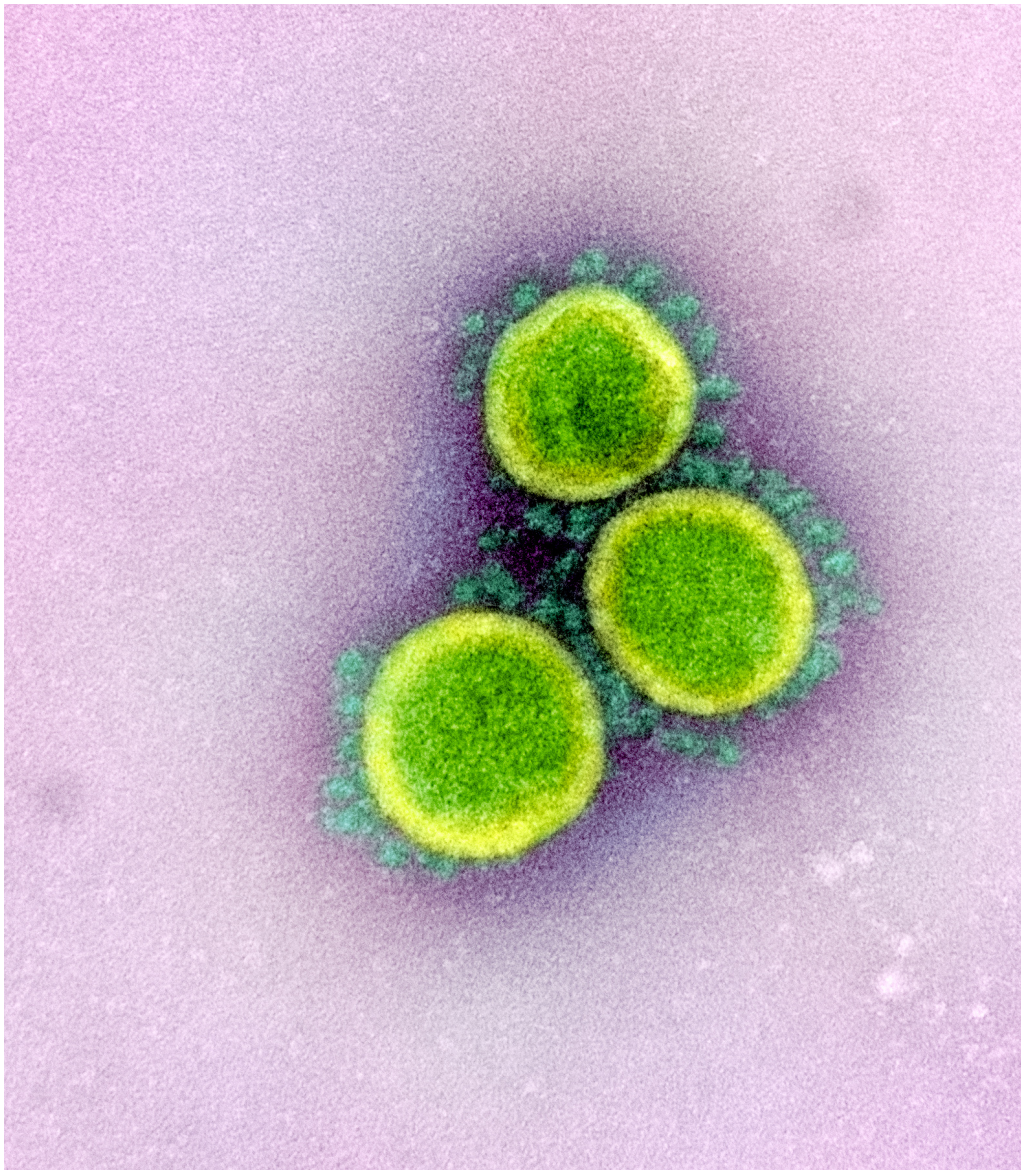
Previous infection

RADT
NOT predictive

RT-PCR Ct value

Symptomatology
Fever and antipyretic
NOT predictive

Evaluation of return-to-work algorithms



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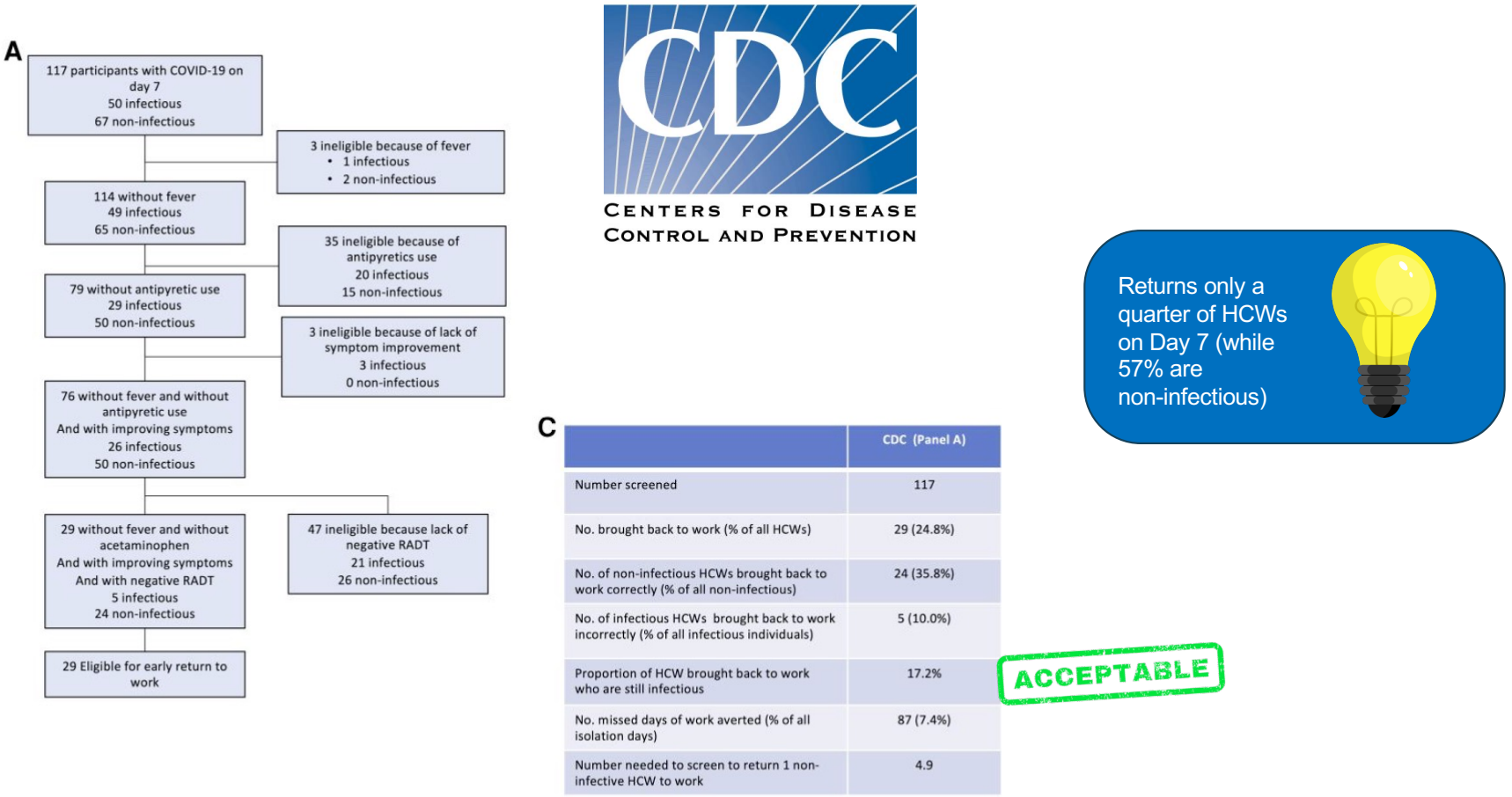
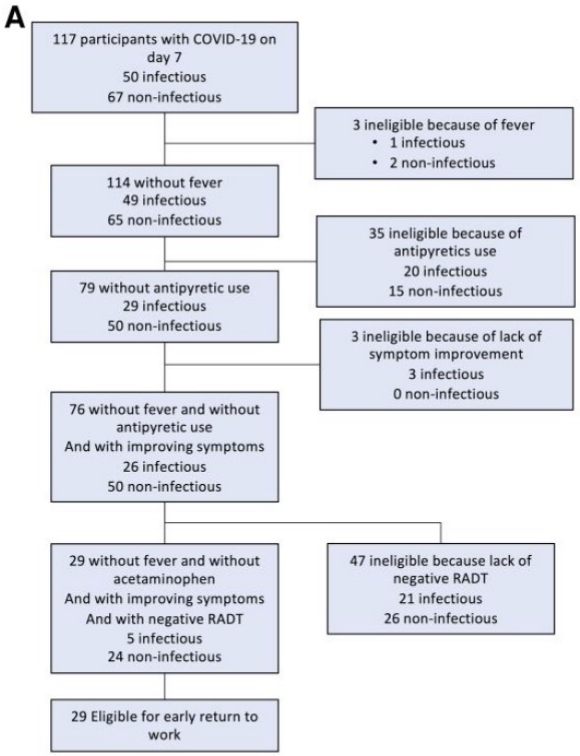
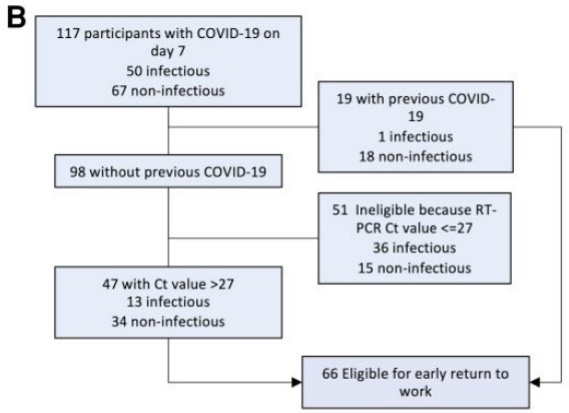


Figure 4. Performance of return-to-work criteria for healthcare workers with COVID-19. Panel *A* shows the performance of the US CDC Return to Work criteria on a cohort of healthcare workers with COVID-19. Panel *B* shows the performance of an alternative set of criteria derived from the current study. Panel *C* compares the CDC and alternative criteria. Abbreviations: CDC, Centers for Diseases Control and Prevention; COVID-19, coronavirus disease 2019; Ct, cycle threshold; HCW, healthcare workers; RADT, rapid antigen diagnostic test; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

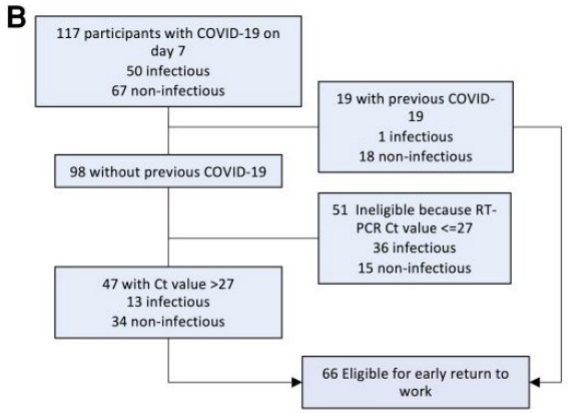




C

	CDC (Panel A)
Number screened	117
No. brought back to work (% of all HCWs)	29 (24.8%)
No. of non-infectious HCWs brought back to work correctly (% of all non-infectious)	24 (35.8%)
No. of infectious HCWs brought back to work incorrectly (% of all infectious individuals)	5 (10.0%)
Proportion of HCW brought back to work who are still infectious	17.2%
No. missed days of work averted (% of all isolation days)	87 (7.4%)
Number needed to screen to return 1 non-infective HCW to work	4.9

Figure 4. Performance of return-to-work criteria for healthcare workers with COVID-19. Panel *A* shows the performance of the US CDC Return to Work criteria on a cohort of healthcare workers with COVID-19. Panel *B* shows the performance of an alternative set of criteria derived from the current study. Panel *C* compares the CDC and alternative criteria. Abbreviations: CDC, Centers for Diseases Control and Prevention; COVID-19, coronavirus disease 2019; Ct, cycle threshold; HCW, healthcare workers; RADT, rapid antigen diagnostic test; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.



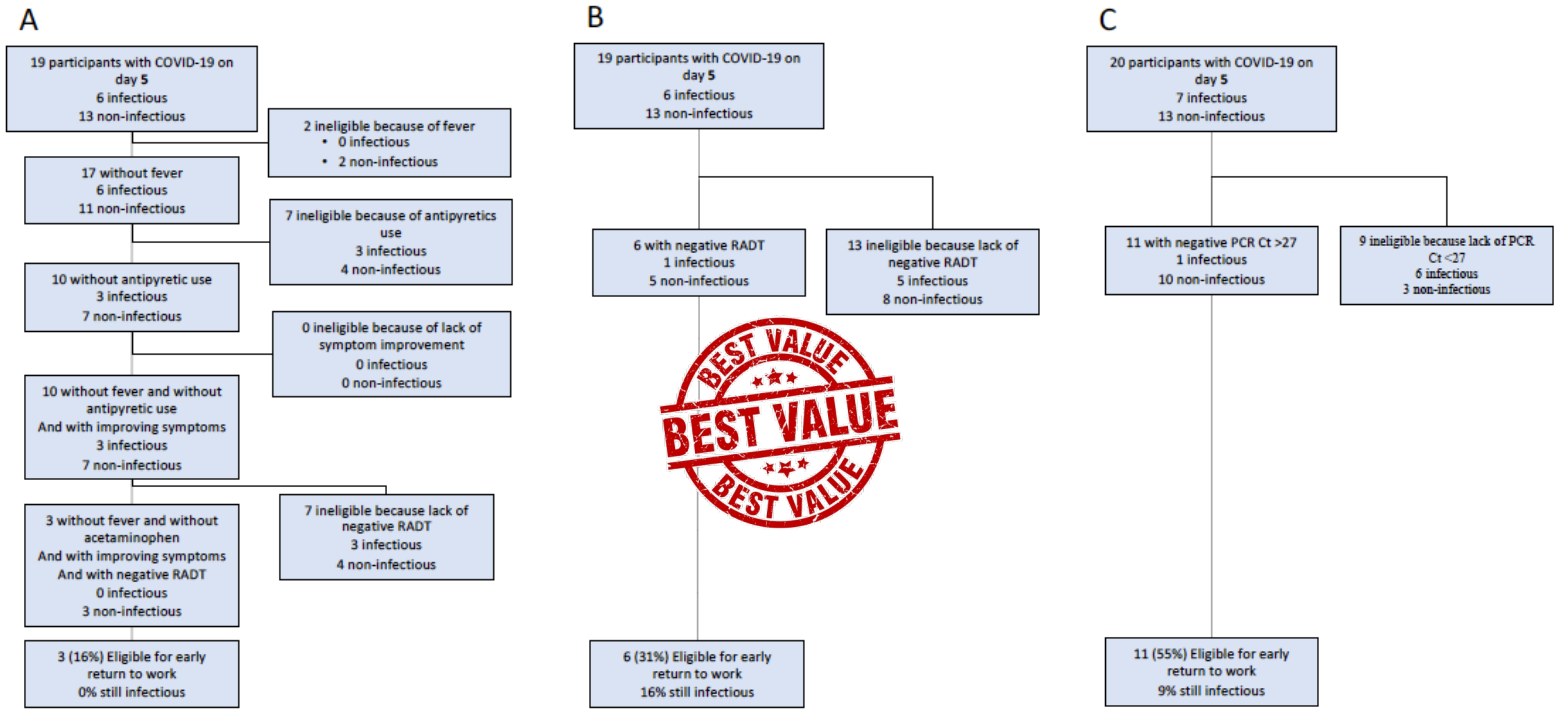
C

	CDC (Panel A)	Novel algorithm (Panel B)	*P* value
Number screened	117	117	--
No. brought back to work (% of all HCWs)	29 (24.8%)	66 (56.4%)	<.001 (χ^2)
No. of non-infectious HCWs brought back to work correctly (% of all non-infectious)	24 (35.8%)	52 (77.6%)	<.001 (χ^2)
No. of infectious HCWs brought back to work incorrectly (% of all infectious individuals)	5 (10.0%)	14 (28.0%)	<.02 (χ^2)
Proportion of HCW brought back to work who are still infectious	17.2%	21.2%	<.78 (χ^2)
No. missed days of work averted (% of all isolation days)	87 (7.4%)	198 (16.9%)	<.001 (χ^2)
Number needed to screen to return 1 non-infective HCW to work	4.9	1.8	

Figure 4. Performance of return-to-work criteria for healthcare workers with COVID-19. Panel *A* shows the performance of the US CDC Return to Work criteria on a cohort of healthcare workers with COVID-19. Panel *B* shows the performance of an alternative set of criteria derived from the current study. Panel *C* compares the CDC and alternative criteria. Abbreviations: CDC, Centers for Diseases Control and Prevention; COVID-19, coronavirus disease 2019; Ct, cycle threshold; HCW, healthcare workers; RADT, rapid antigen diagnostic test; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Earlier return-to-work of individuals with recurrent COVID-19?

DAY 5 Return-to-work algorithms



eFIGURE 3. Performance of return-to-work criteria for healthcare workers with recurrent COVID-19 on the fifth day of their infection. Panel A shows the performance of the Centers for Diseases Control and Prevention (US CDC) Return to Work criteria. **Panels B and C** shows the performance of alternate algorithms relying on rapid antigen detection tests (RADT) and RT-PCR cycle threshold (Ct) values.

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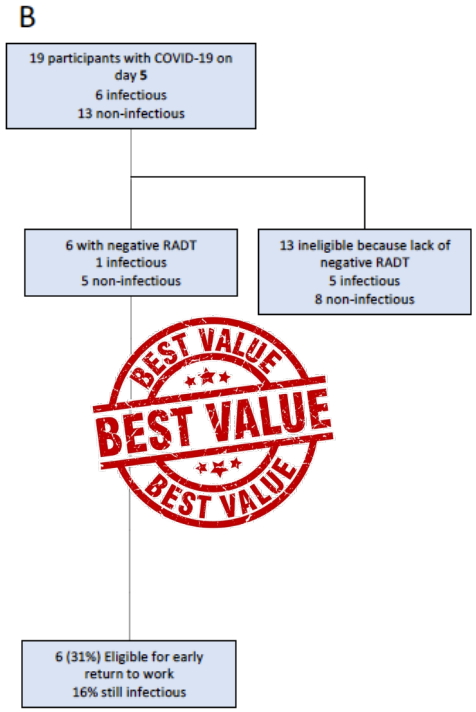
Earlier return-to-work of individuals with recurrent COVID-19?

B



C

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No. missed days of work averted (% of all isolation days)	87 (7.4%)	198 (16.9%)	<.001 (χ^2)
Number needed to screen to return 1 non-infective HCW to work	4.9	1.8	

16% back on Day 5
5% back on Day 7

421 (36%)

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Return to work criteria for HCWs with COVID-19

	CDC[1]	ECDC[2]	Quebec May 2023[3]
Without criteria	At least 10 days have past since onset of symptoms	At least 10 days	10 days
With criteria			
	At least 7 days	At least > 6 days	At least 7 days
	Symptom improvement	Symptom improvement	Symptom improvement
	No fever without antipyretic use x 24h	No fever	No fever without antipyretic use x 24h
	Negative viral test (NAAT or RADT)	Negative NAAT or RADT on Day 6	Negative RADT x 2

1. Last updated Sept 2022, for nonsevere COVID-19 not immunocompromised
2. 3rd update, Jan 2022. https://www.ecdc.europa.eu/en/publications-data/covid-19-guidance-discharge-and-ending-isolation
3. https://www.inspq.qc.ca/publications/3141-covid-19-gestion-travailleurs-sante-milieux-soins

Return to work criteria for HCWs with COVID-19

	CDC[1]	ECDC[2]	Quebec May 2023[3]	Quebec July 2023
Without criteria	At least 10 days have past since onset of symptoms	At least 10 days	10 days	6 days
With criteria				
	At least 7 days	At least > 6 days	At least 7 days	At least 4 days
	Symptom improvement	Symptom improvement	Symptom improvement	
	No fever without antipyretic use x 24h	No fever	No fever without antipyretic use x 24h	No fever
	Negative viral test (NAAT or RADT)	Negative NAAT or RADT on Day 6	Negative RADT x 2	Negative RADT

1. Last updated Sept 2022, for nonsevere COVID-19 not immunocompromised
2. 3rd update, Jan 2022. https://www.ecdc.europa.eu/en/publications-data/covid-19-guidance-discharge-and-ending-isolation
3. https://www.inspq.qc.ca/publications/3141-covid-19-gestion-travailleurs-sante-milieux-soins

Duration of infectivity of recurrent COVID-19

- The first study demonstrating that recurrent COVID-19 has a distinct virology:
  - Shorter period infectivity using viral culture as reference
  - Lower viral load
  - Faster negativization of RADT
- Impact on
  - Understanding of COVID-19
  - R0 and modelization of transmission
  - Return-to-Work algorithms

Duration of infectivity of recurrent COVID-19

- Could this be a spurious finding?
- No, it's indirectly supported by previous studies

Duration of infectivity of recurrent COVID-19

- NBA Occupational Health Cohort (players, staff)
  - 1241 first infections vs 159 reinfections
  - Reinfection associated with
    - Faster clearance by RT-PCR (4.9 days vs 7.2 days)
    - No impact of the lineage of the first infection

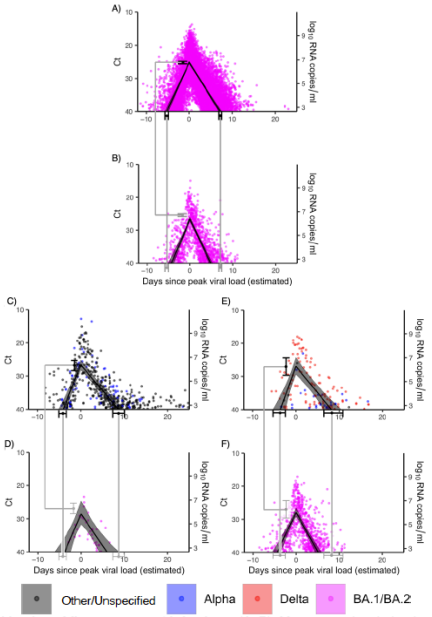

Figure 2. Viral kinetics of first *vs.* second infections. (A–B): Mean posterior viral trajectory (solid lines) with 95% credible interval (shaded region) for well-documented BA.1/BA.2 infections in individuals where the infection was (A) their first recorded SARS-CoV-2 infection (n = 1,241) or (B) their second recorded SARS-CoV-2 infection (n = 159; see **Supplementary Table 1, group 1**). (C–F): Mean posterior viral trajectory (solid lines) with 95% credible interval (shaded region) for well-documented infections in individuals who were infected twice during the study period. Panels (C, E) depict the viral kinetics of first Alpha/Delta/Other/Unspecified infections in unvaccinated (C, n = 42) and vaccinated (E, n = 15) individuals who later had a BA.1/BA.2 infection. Panels (D, F) depict the viral kinetics of second BA.1/BA.2 infections in individuals who did not have a vaccine dose between their first and second infection (D, n = 5) and in individuals who did have a vaccine dose between their first and second infection (F, n = 102) as well as a previous Alpha/Delta/Other/Unspecified infection (**Supplementary Table 1, group 2**, omitting any individuals with unknown vaccination status). In all panels, grey points depict the measured viral concentration for a single test. For each person, the points were shifted horizontally so that the individual's mean posterior peak viral concentration sits at day 0. Black points and whiskers (A, C, E) depict the mean and 95% credible interval for the proliferation time, peak viral concentration, and clearance time, from left to right, for first

Kissler SM, Hay JA, Fauver JR, et al. Viral kinetics of sequential SARS-CoV-2 infections. medRxiv 2023:2023.03.03.23286775

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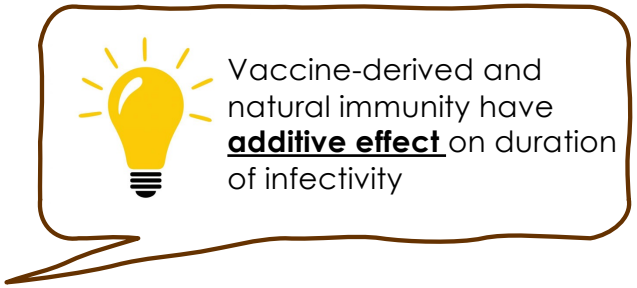
Morbidity and Mortality Weekly Report

Antigen Test Positivity After COVID-19 Isolation — Yukon-Kuskokwim Delta Region, Alaska, January–February 2022

Brian Lefferts, MPH[1]; Ian Blake, MS[2]; Dana Bruden, MS[2]; Melissa B. Hagen, MD[3,4]; Ellen Hodges, MD[1]; Hannah L. Kirking[3,4]; Elizabeth Bates, MD[1]; Amanda Hoeldt[1]; Brenda Lamont[1]; Sharon Saydah, PhD[3,4]; Adam MacNeil, PhD[3,4]; Michael G. Bruce, MD[2]; Ian D. Plumb, MBBS[3,4]

- COVID-19 infections in Yukon-Kuskokwim Health Corporation (YKHC)
- Jan-Feb 2022
- 729 COVID-19 with follow-up RADT (Binax NOW) at Day 5 to 9 of infection (to release from isolation
  - Global positivity: 54.3%
  - Decreased positivity :
    - Reinfections (aOR, 0.30 [0.19-0.46])
    - Complete primary vaccination (aOR, 0.60 [0.37-0.99])
    - Reinfection AND complete vaccination (aOR, 0.17 [0.09-0.33])



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Lefferts B et al. MMWR Morb Mortal Wkly Rep. 2022 Feb 25;71(8):293-298. doi: 10.15585/mmwr.mm7108a3.

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Article

https://doi.org/10.1038/s41591-022-02138-x

Infectiousness of SARS-CoV-2 breakthrough infections and reinfections during the Omicron wave

Received: 8 August 2022

Accepted: 18 November 2022

Sophia T. Tan[1], Ada T. Kwan[2,3], Isabel Rodríguez-Barraquer[1,3], Benjamin J. Singer[1], Hailey J. Park[1], Joseph A. Lewnard[4,5,6], David Sears[3,7] & Nathan C. Lo[1,3]

- Objective: understand the role of vaccination and natural immunity on infectiousness of individuals with COVID-19
- Setting: Surveillance data from 35 California state prisons
- n=22,334 individuals and 1,226 index infections
  - Index cases removed ASAP from cell
- Assessed risk of COVID-19 in cellmates of index case

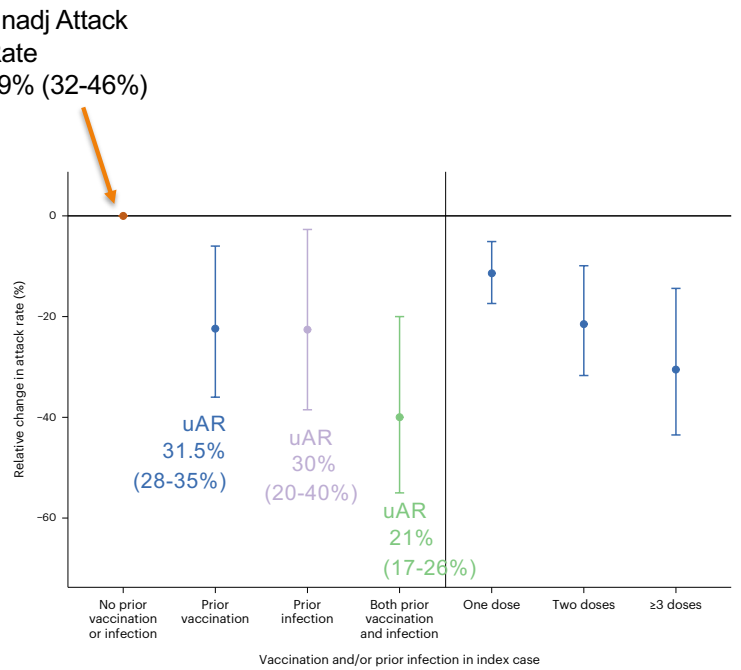

Fig. 4 | Relative change in Omicron SARS-CoV-2 attack rate in close contacts based on index cases' vaccine and prior natural infection status in an adjusted model. We applied a robust Poisson regression model to estimate the relationship between vaccination and natural immunity in index cases on their risk of SARS-CoV-2 transmission to close contacts. We plotted the adjusted relative reduction in infectiousness of index cases (represented as points), as measured via attack rate in close contacts, conferred by vaccination alone, prior infection alone and both vaccination and prior infection. The estimate for both vaccination and prior infection is based on a linear combination of regression coefficients, given lack of formal statistical interaction between vaccination and prior infection. We conducted a separate regression analysis (right side of graph) that was stratified based on the number of vaccine doses received by the index case. We plotted cluster-robust 95% CIs (represented by error bars).

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Tan ST, et al. Infectiousness of SARS-CoV-2 breakthrough infections and reinfections during the Omicron wave. Nat Med. 2023 Feb;29(2):358-365. doi: 10.1038/s41591-022-02138-x. Epub 2023 Jan 2. PMID: 36593393

nature medicine

Article

https://doi.org/10.1038/s41591-022-02138-x

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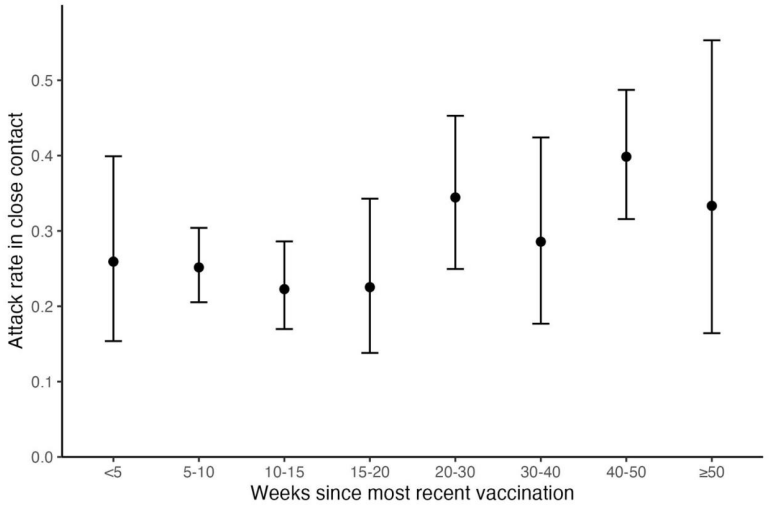

Supplementary Figure 9: Unadjusted estimates of the attack rate of Omicron SARS-CoV-2 infection of vaccinated index cases by time since the index cases' most recent vaccine dose. We plotted the unadjusted attack rate (represented by points) and 95% binomial confidence intervals (represented by error bars) for vaccinated index cases, stratified by time (in weeks) since the index cases' most recent vaccine dose prior to first positive SARS-CoV-2 test. The adjusted estimates from the regression model are available in Supplementary Table 5.

Infectiousness
Increases with increase time since vaccination
Does NOT increase with increase time since infection

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Tan ST, et al. Infectiousness of SARS-CoV-2 breakthrough infections and reinfections during the Omicron wave. Nat Med. 2023 Feb;29(2):358-365. doi: 10.1038/s41591-022-02138-x. Epub 2023 Jan 2. PMID: 36593393

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Supplementary Table 3: Primary analysis of the relationship of COVID-19 vaccination and prior SARS-CoV-2 infection on infectiousness of Omicron SARS-CoV-2 infections

		Relative % change in attack rate of infection in close contact (95% CI)
Index case	Prior vaccination only	-22.4 (-36, -6)
	Prior infection only	-22.6 (-38.5, -2.7)
Close contact	Duration of exposure (per day)	6.9 (-2.3, 16.9)
	Number of vaccine doses	
	1 dose	1.3 (-8.1, 11.8)
	2 doses	2.7 (-15.5, 24.9)
	≥3 doses	4.1 (-22.4, 39.6)
	Prior infection only	-19.1 (-34.9, 0.6)
Institution	SARS-CoV-2 incidence in the 7 days preceding the positive test in the index case (per natural log increase in incidence)	10.2 (-4.8, 27.6)

The primary analysis estimated the relationship of the index cases' vaccine status and prior natural infection history on attack risk of SARS-CoV-2 infection in the close contact. We adjusted for potential confounders, including the duration of exposure between index cases and close contacts, number of COVID-19 vaccine doses and prior natural infection history in close contacts as well as institution SARS-CoV-2 incidence.

Don't forgeet that exposed individuals are also likely to have previous infection and that this is protective!

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Tan ST, et al. Infectiousness of SARS-CoV-2 breakthrough infections and reinfections during the Omicron wave. Nat Med. 2023 Feb;29(2):358-365. doi: 10.1038/s41591-022-02138-x. Epub 2023 Jan 2. PMID: 36593393

Other coronaviridae

Epidemiol. Infect. (1990), **105**, 435–446
Printed in Great Britain

The time course of the immune response to experimental coronavirus infection of man

K. A. CALLOW[1]*, H. F. PARRY[2], M. SERGEANT[1] AND D. A. J. TYRRELL[1]
[1] *MRC Common Cold Unit, Harvard Hospital, Coombe Road, Salisbury, Wiltshire SP2 8BW, UK*
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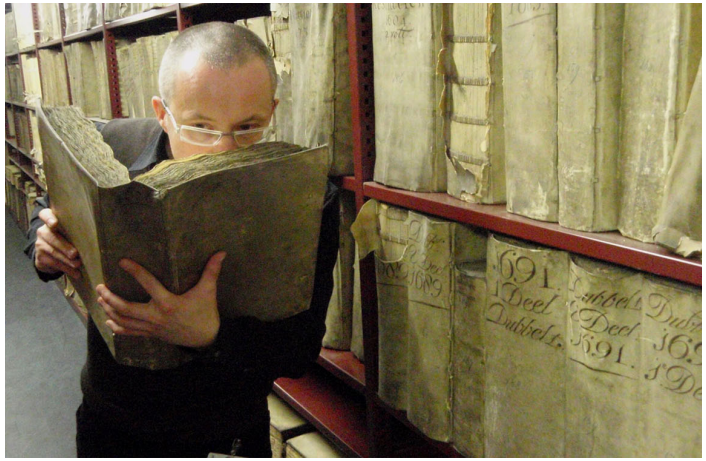
- Duration of viral shedding, coronavirus 229E, 15 healthy volunteers
  - Primary infections: 5.6 days
  - Reinfections (1 year later, same coronavirus): 2.0 days



Callow KA, et al. Epidemiol Infect. 1990 Oct;105(2):435-46.

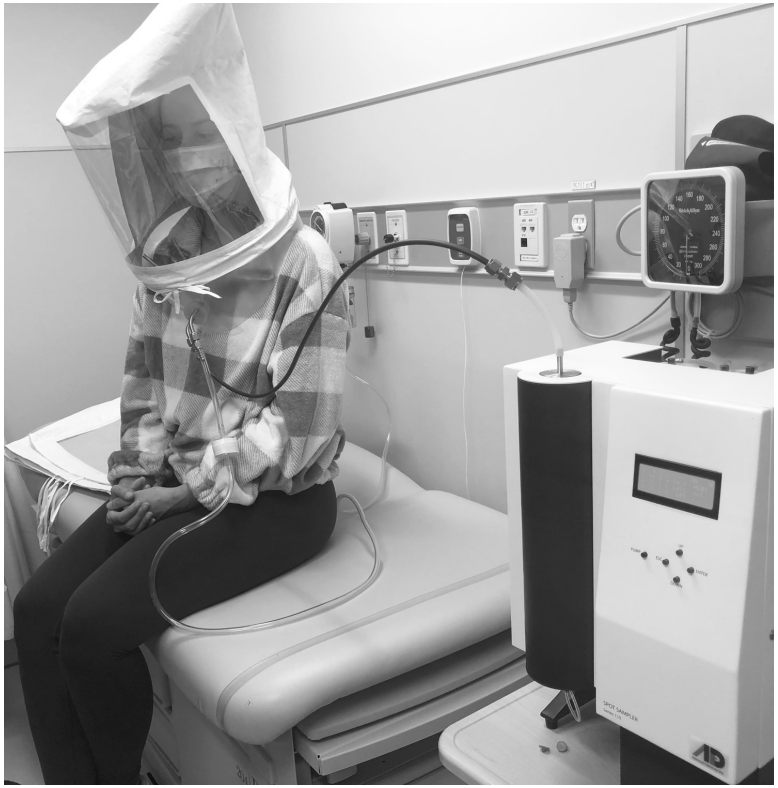

BACK
to the
DRAWING
BOARD
Knowledge from early pandemic has become OBSOLETE

Unknowns

- Correlation between viral culture positivity and transmissibility in healthcare setting unclear
  - Viral culture = the best available surrogate marker, but unclear correlation
- Applicability of these variables for return-to-work policies may be affected by desirability bias
  - E.g. Assessment of symptom improvement

Next steps

- Source control strategies to decrease infectivity of HCWs with COVID-19
  - Coll. Dr Caroline Duchaine, Ulaval
  - Sampling of exhaled air, Day 3 or 4 of COVID-19
    - Highly contagious; average Ct value NP swab: 18.9
  - 20 minutes per modality; including talking, coughing and moving head
  - Results
    - Without mask 3/6 (50%) RT-PCR positive
    - With procedure mask 1/6 (16%) RT-PCR positive
    - With N95 0/6 (0%) RT-PCR positive
  - Viral culture pending (Spot sampler)



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THANK YOU!

ANY QUESTIONS?

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www.webbertraining.com/schedulep1.php

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September 19, 2024	**THE PHYSICS OF FLYING FECES** Speaker: **James Gauthier**, Webber Training
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