An Evidence-Based Approach to Testing

Dr. Annette Plüddemann
Centre for Evidence-Based Medicine

Nuffield Department of Primary Care Health Sciences
University of Oxford

Kellogg College
University of Oxford

The Pandemic
EVIDENCE Collaboration

CEBM

UNIVERSITY OF
OXFORD

Diagnostic Studies
Dr. Annette Plüddemann

What is the Question?

Patient/Population

Index Test

Reference Test

Target Disorder

What questions should we ask when assessing the evidence?

- Appropriate patient spectrum?
- What is the setting?
- Was the Reference Test appropriate?
- Clinically relevant outcome?

Patient/Population

Symptomatic? Asymptomatic?

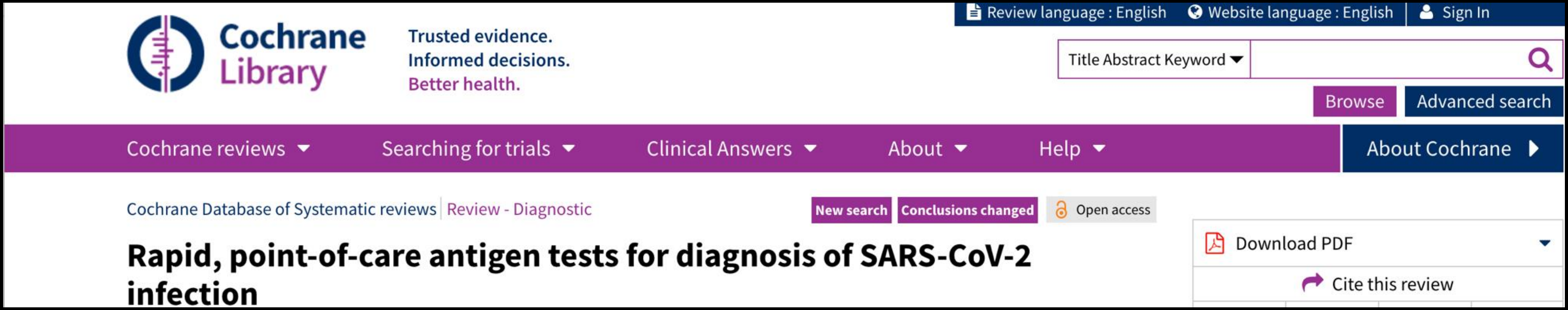
Setting?

Index Test   PCR or Lateral Flow?

Reference Test

Target Disorder

Population and Setting



August 2020

- 22 studies included
- No studies at low risk of bias; concerns about applicability
- *"The findings currently have limited applicability, as we are uncertain whether tests will perform in the same way in clinical practice, and according to symptoms of COVID-19, duration of symptoms, or in asymptomatic people"*

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.

Review language : English | Website language : English | Sign In

Title Abstract Keyword

Browse | Advanced search

Cochrane reviews | Searching for trials | Clinical Answers | About | Help | About Cochrane

Cochrane Database of Systematic reviews | Review - Diagnostic

New search | Conclusions changed | Open access

Download PDF

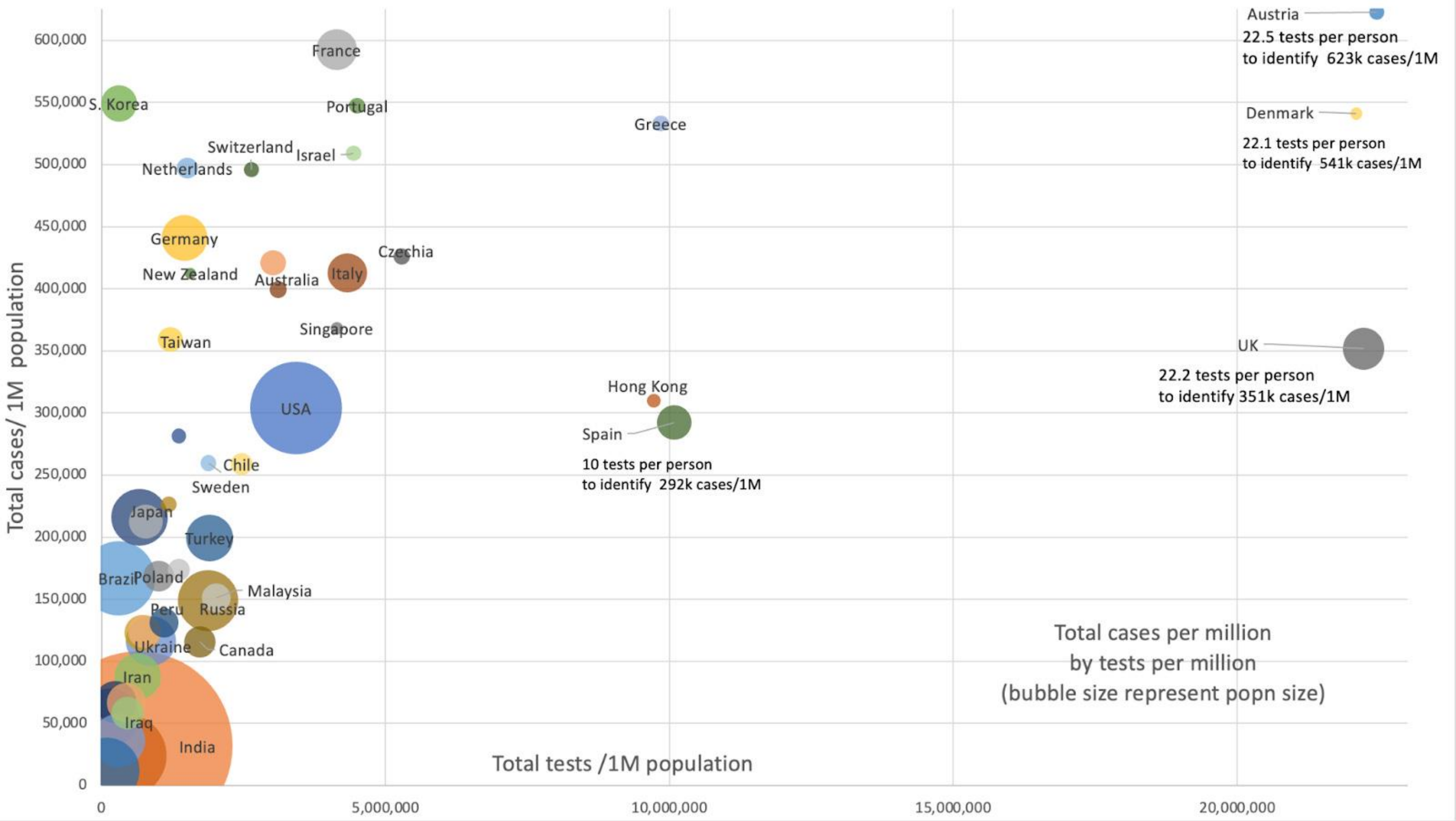
Cite this review

Rapid, point-of-care antigen tests for diagnosis of SARS-CoV-2 infection

July 2022

- 152 studies included
- Evidence for the clinical performance of many test brands scarce or lacking
- Lack of well-designed prospective and comparative evaluations of different test brands in clinically relevant settings - symptomatic and asymptomatic testing
- Lack of reporting of symptoms or symptom duration
- All used nucleic acid amplification as the reference test

The UK, therefore, did, on average, 22 tests per person, similar to Denmark and Austria. However, the UK identified fewer reported cases, meaning the number needed to detect one case is far higher, NND= 62.



Compare the total cases per million population to the tests used for the same population

Bubble size – Country size

NND: number of tests per million population/numbers detected per the same population

Patient/Population

Index Test

Reference Test PCR or ???

Target Disorder

Viral Cultures for Coronavirus Disease 2019 Infectivity Assessment: A Systematic Review FREE

Tom Jefferson ✉, Elisabeth A Spencer, Jon Brassey, Carl Heneghan

Clinical Infectious Diseases, Volume 73, Issue 11, 1 December 2021, Pages e3884–e3899,
https://doi.org/10.1093/cid/ciaa1764

Published: 03 December 2020 **Article history** ▾

PDF Split View Cite Permissions Share ▾

Abstract

Background

We aimed to review the evidence from studies relating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) culture with the results of reverse-transcription polymerase chain reaction (RT-PCR) and other variables that may influence the interpretation of the test, such as time from symptom onset.

The data suggest a relationship between the time from onset of symptom to the timing of the specimen test, cycle threshold (Ct), and symptom severity.

Twelve studies reported that Ct values were significantly lower and log copies higher in specimens producing live virus culture.

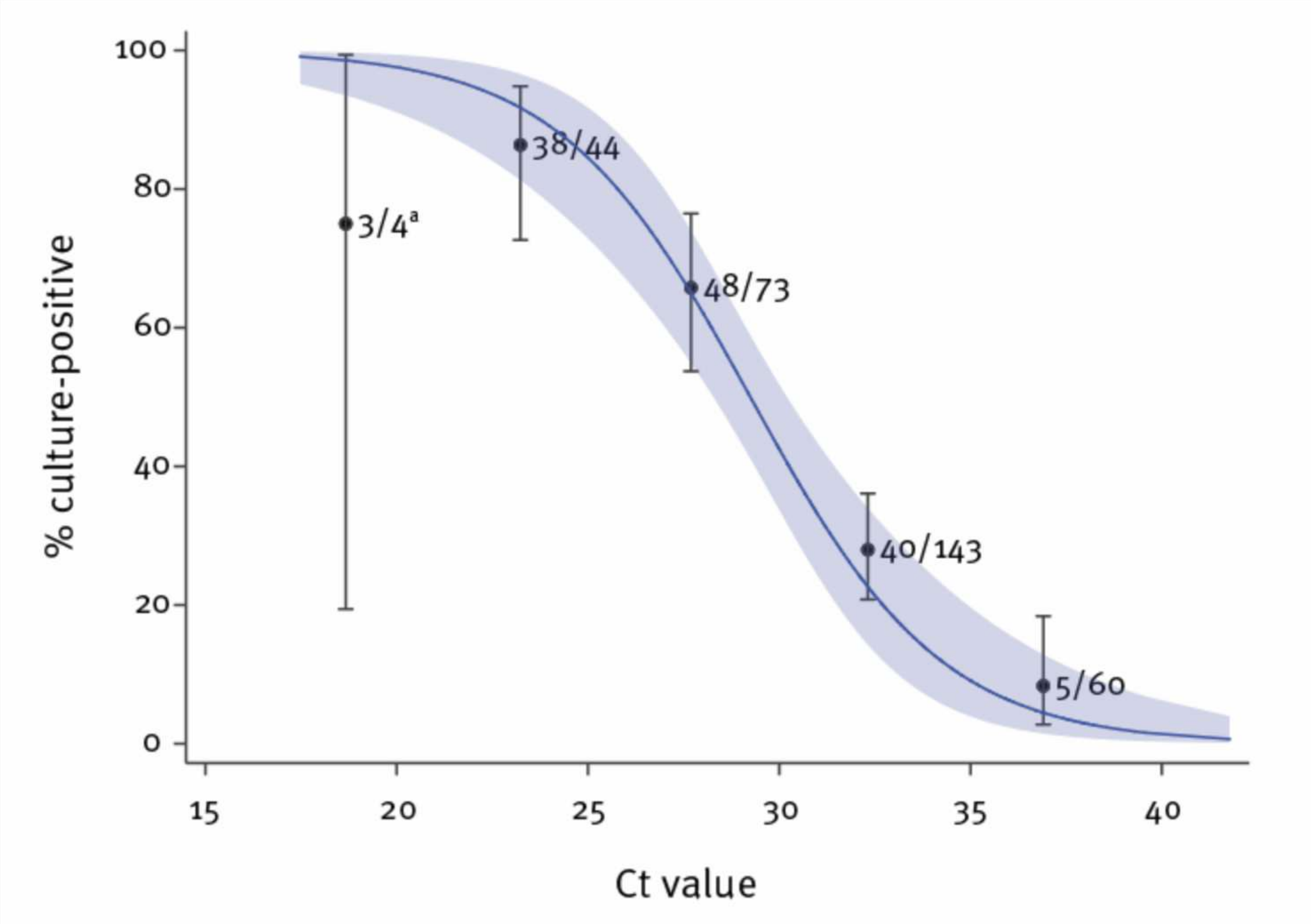
Two studies reported that the odds of live virus culture were reduced by approximately 33% for every 1-unit increase in Ct.

Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020

Like 0
Download
Check for updates

Anika Singanayagam[1,2], Monika Patel[1,2], Andre Charlett[3], Jamie Lopez Bernal[4], Vanessa Saliba[4], Joanna Ellis[1], Shamez Ladhani[4], Maria Zambon[1], Robin Gopal[1]

Figure 2. Relationship between RT-PCR Ct value and culture positivity in mixed effects logistic regression analysis, SARS-CoV-2, England, January–May 2020 (n = 324)



Bullard J, Dust K, Funk D, et al. Predicting infectious SARS-CoV-2 from diagnostic samples Clin Infect Dis. 2020;ciaa638. doi:10.1093/cid/ciaa638

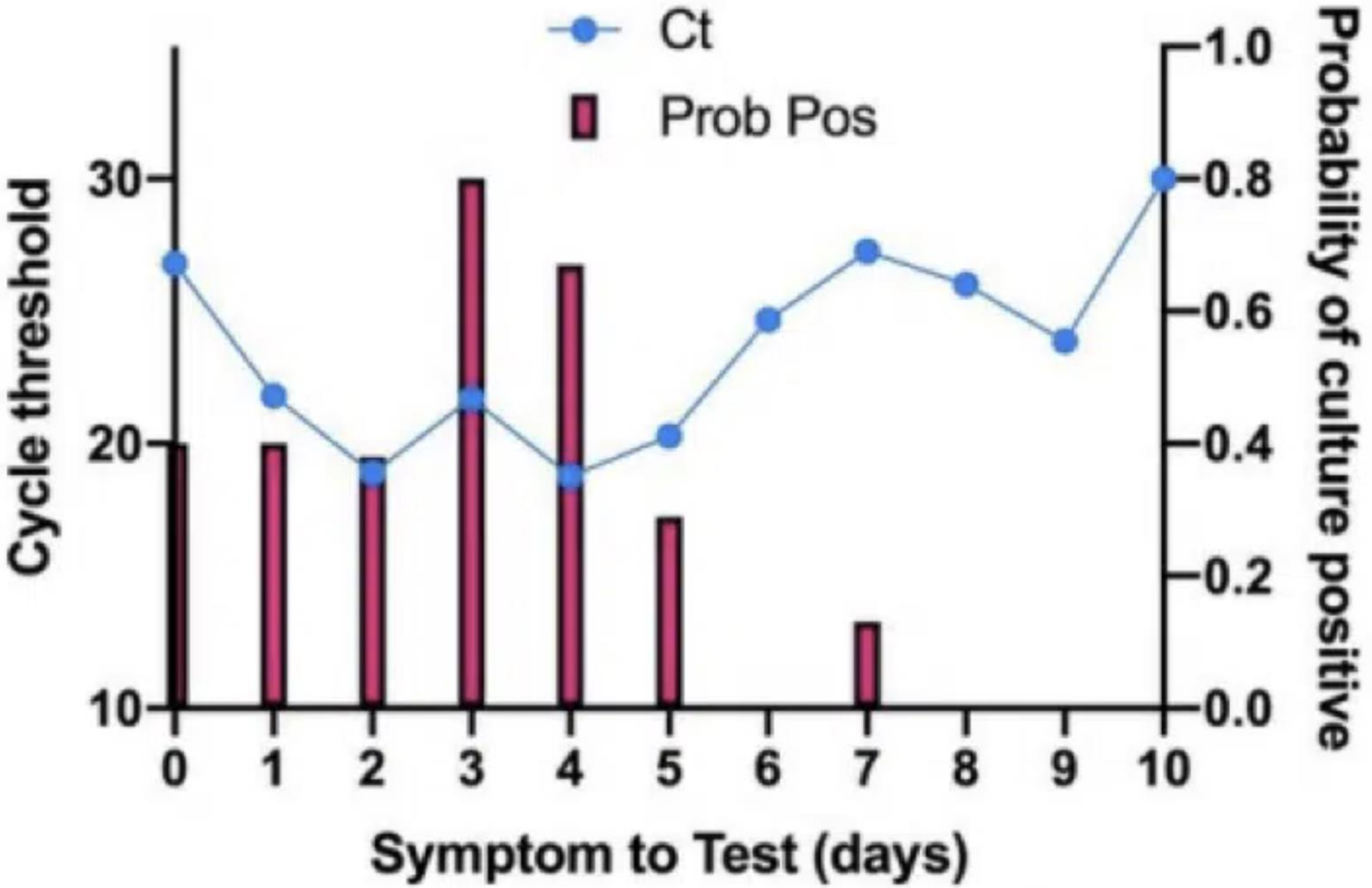
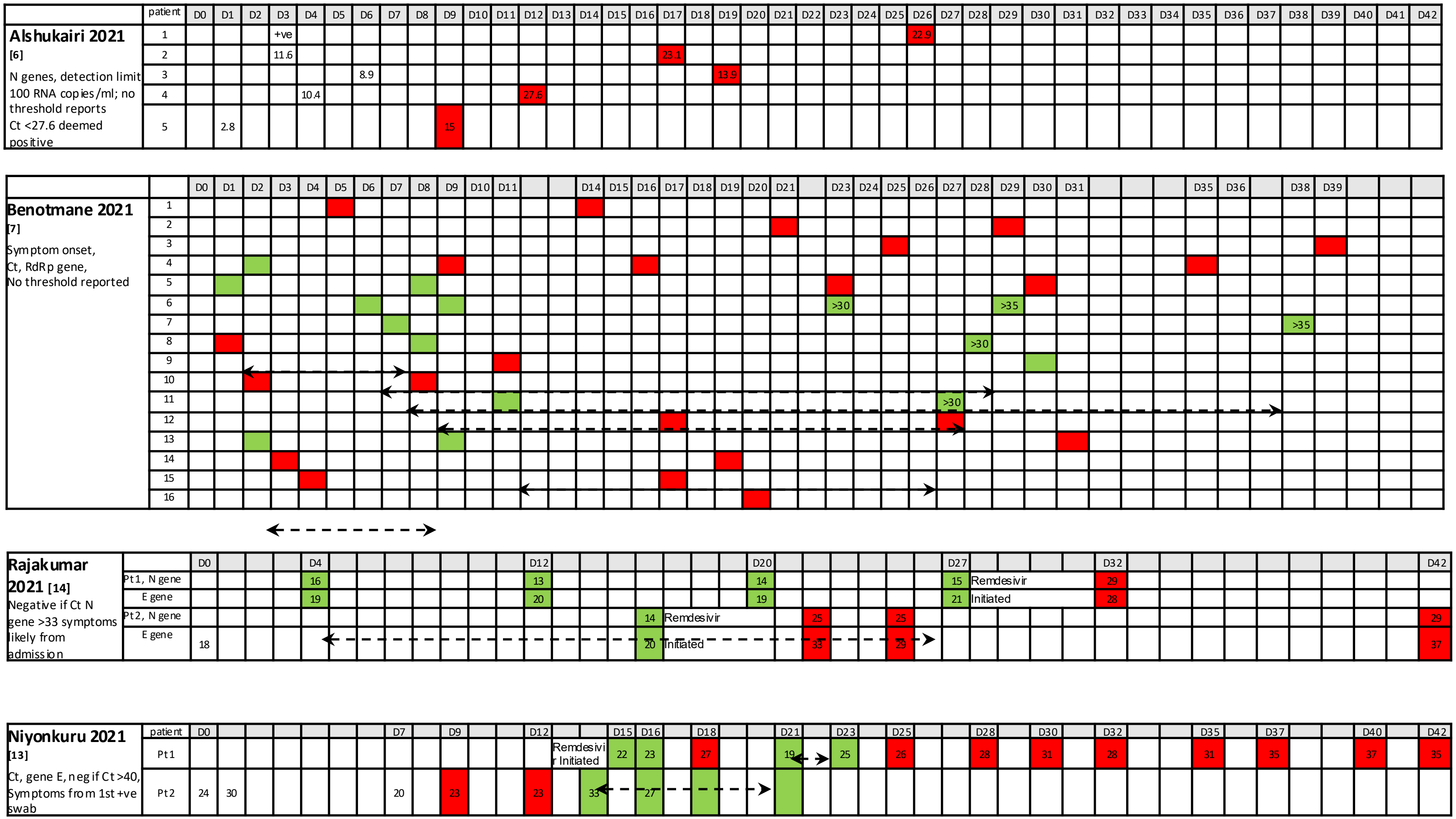


Figure 3a. Timings of positive culture results in Transplant Patients by duration of symptoms and Ct results

Negative Culture
Positive Culture
Number equals RT-PCR Cycle Threshold



Viral cultures, cycle threshold values and viral load estimation for assessing SARS-CoV-2 infectiousness in haematopoietic stem cell and solid organ transplant patients: a systematic review

T. Jefferson · E.A. Spencer · J.M. Conly · E.C. Rosc · S. Maltoni · J. Brassey · I.J. Onakpoyaa · D.H. Evans · C.J. Heneghan · A. Plüddemann. J.Hosp.Inf. (2023) 132: 62-72

Public Health England

Protecting and improving the nation's health

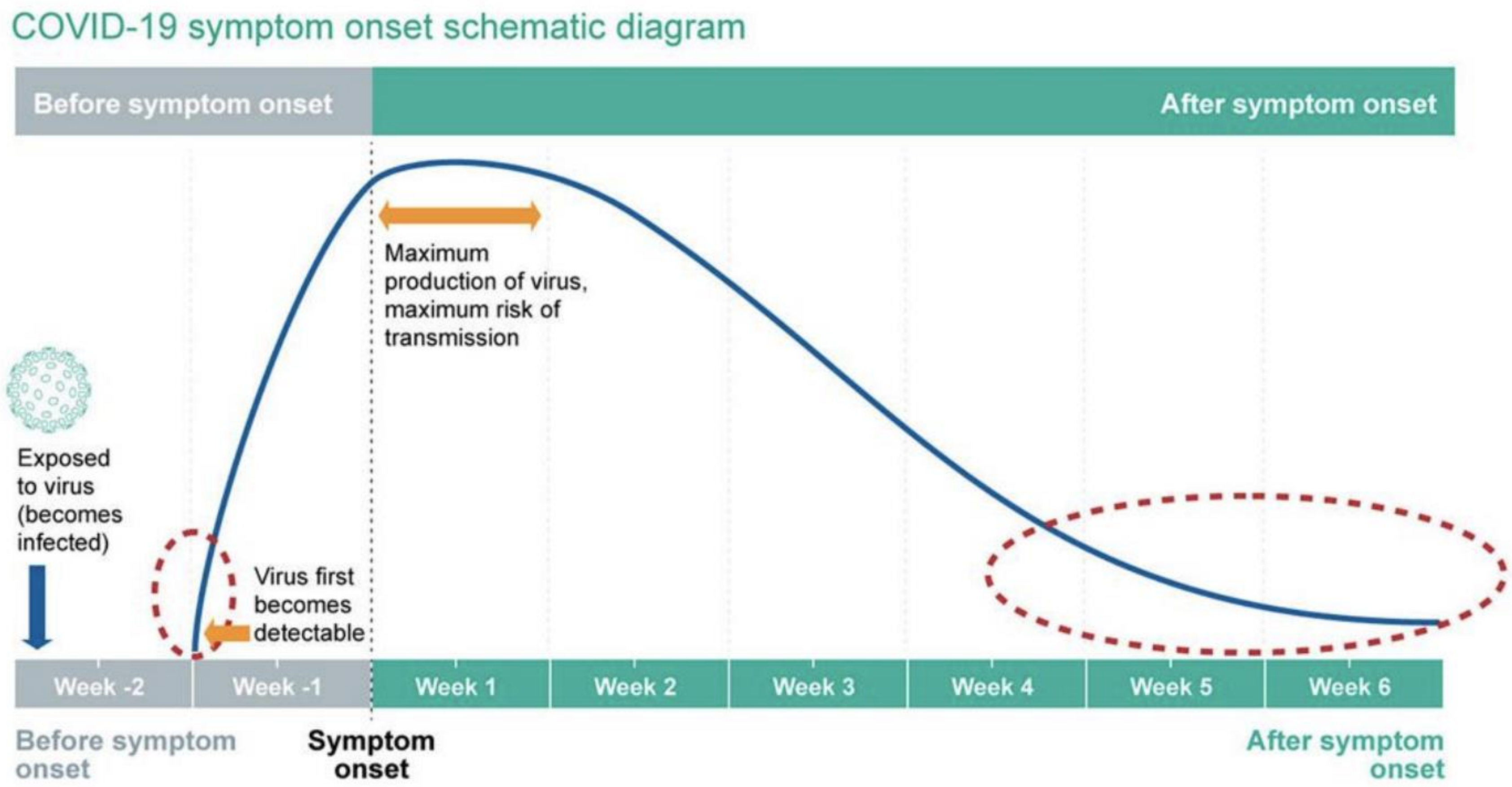
Understanding cycle threshold (Ct) in SARS-CoV-2 RT-PCR

A guide for health protection teams

October 2020

representation.

Figure 3. Timeline of detection of SARS-CoV-2 RNA in infection



COLLATERAL GLOBAL

CG Report 7:

PCR Testing in the UK During the SARS-CoV-2 Pandemic – Evidence From FOI Requests

Jefferson T,[1] Dietrich M,[2] Brassey J,[3] Heneghan C,[1]

(Version 1, 2 February 2022)

The number of validated tests in use in the UK is currently not clear:

Public Health England (PHE) report it may be “80” or “85”.

European regulations suggest there could be over 400 different CE marked tests available.

Only two FOI responses provided answers on Ct values, indicating that in a set time span, 24–38% of the Ct values were over 30.

The most common FOI asked if there was a cycle threshold for positivity. In those that responded, the Ct for a positive result varied from 30 to 45.

Conclusion: The current system requires significant changes to ensure it offers accurate diagnostic data to enable effective clinical management of SARS-CoV-2.

PCR is an important and powerful tool, but its systematic misuse and misreporting risk undermining its usefulness and credibility.

Jefferson T,[1] Dietrich M,[2] Brassey J,[3] Heneghan C,[1]
(Version 1, 2 February 2022)

viruses

MDPI

Review

A Hierarchical Framework for Assessing Transmission Causality of Respiratory Viruses

Tom Jefferson [1,*], Carl J. Heneghan [2], Elizabeth Spencer [2], Jon Brassey [3], Annette Plüddemann [2], Igho Onakpoya [1], David Evans [4] and John Conly [5]

Systematic reviews of 591 primary studies of the modes of transmission for SARS-CoV-2 show significant methodological shortcomings and heterogeneity in the design, conduct, testing, and reporting of SARS-CoV-2 transmission

We attempted to address the translational gap between the current research evidence and the assessment of causality in the transmission of respiratory viruses with a focus on SARS-CoV-2.

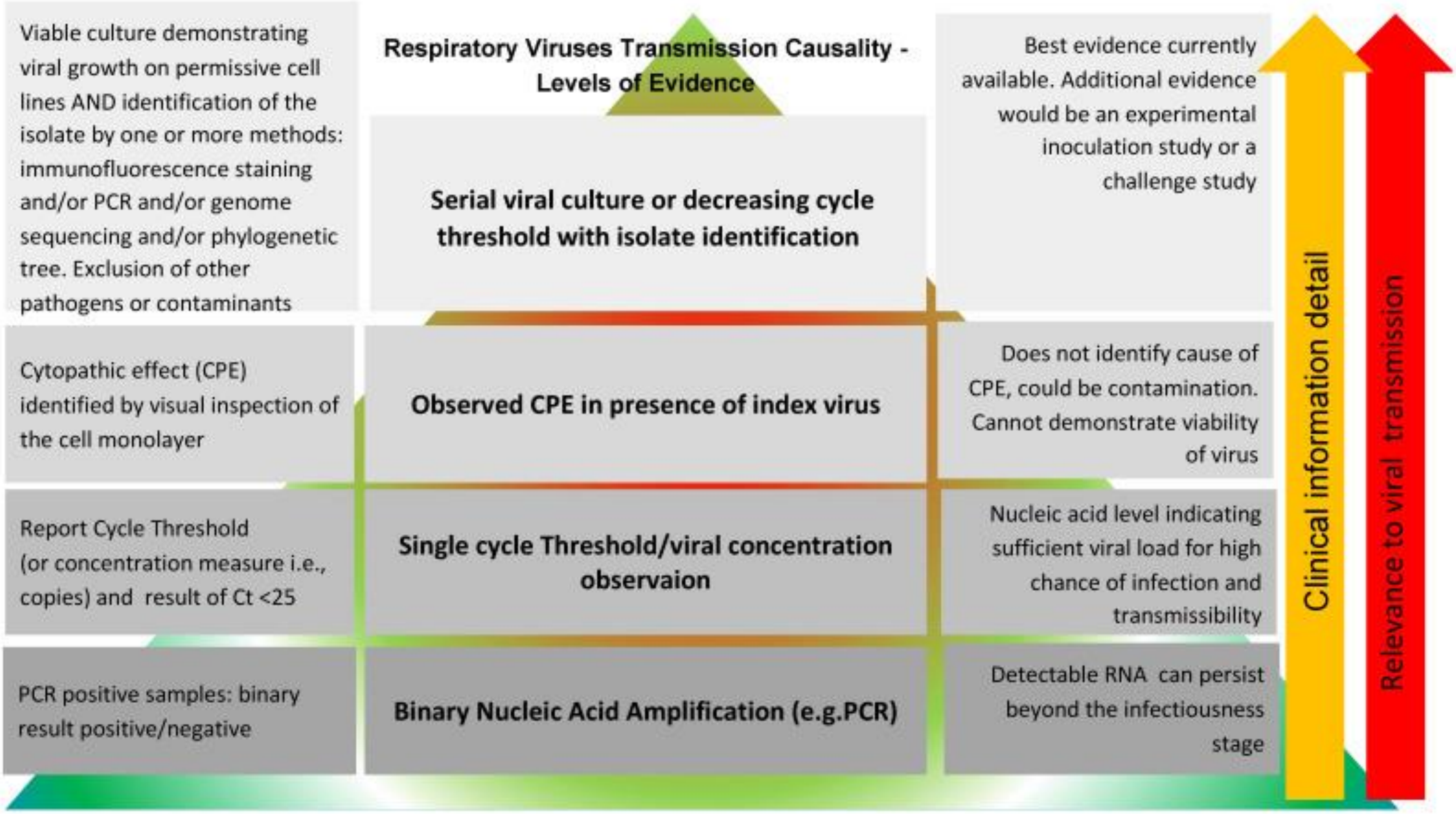
Table 6

Virological and genomic evidence reported in 591 studies included in five systematic reviews of transmission of SARS-CoV-2. Key: Ct = cycle threshold; CPE = cytopathic effect.

Review	Primary Studies	PCR Result (% of Studies)	Ct (% of Studies)	Ct < 25 (% of Studies)	Attempted Viral Culture (% of Studies)	CPE (% of Studies)	Genome Sequencing (% of Studies)	Serial Viral Culture Positive (% of Studies)
Airborne Transmission [10]	127	53 (79.1%)	51 (40.2%)	5 (3.9%)	26 (20.4%)	5 (3.7%) [1]	6 (4.7%)	3 (2.3%) [2]
Fomite Transmission [11]	63	51 (81.0%)	13 (20.6%)	3 (4.8%)	11 (17.5%)	0	0	0
Orofecal Transmission [9]	77	46 (59.7%)	22 (28.6%)	7 (9.1%)	6 (7.8%)	1 (1.3%) [3]	1 (1.3%)	0 [3]
Close Contact Transmission [12]	258	163 (73.7%)	26 (10.1%)	6 (2.3%)	4 (1.6%)	2 (0.6%)	18 (5.8%)	2 (1.2%)
Vertical Transmission [13]	66	66 (100%)	9 (13.6%)	2 (3.0%)	0	0	1 (1.5%)	0
(% of primary studies)	591	379 (64.1%)	121 (20.5%)	23 (3.9%)	48 (8.1%)	9 (1.5%)	26 (4.4%)	5 (0.85%)

[1] Some studies observed presumed virus-induced CPE. [2] Two studies detected other viruses, all studies had methodological limitations. [3] CPE did not show plaques and is not immunostained.

Levels of evidence for proof of the microbiological and clinical aspects of transmission of a viral respiratory pathogen



Viruses. 2022 Jul 22;14(8):1605. doi: 10.3390/v14081605.

Evidence-based approach to testing?

- Evidence for testing as important as evidence for treatment
- Repository of tests / strategy to evaluate tests
- Evidence in the setting
- Appropriate outcome of interest

Understanding the problem from a range of perspectives, with a particular emphasis on evidence, and using and interpreting data

- Most importantly, go back to the source of the evidence surrounding a claim.
- Critically appraise the evidence, considering the outcomes, the level of evidence, and the biases.
- Understand the limitations in the evidence in relation to the importance of the outcome to patients.
- Integrate the evidence with experience, expertise and the available resources

If the evidence isn’t high-quality, then ask why we are not improving the quality of the research.

Acknowledgements

Carl Heneghan
Tom Jefferson
Igho Onakpoya
Cecilia Rosca
Jon Brassey
John Conly
Susanna Maltoni
Sara Gandini
David Evans
Elizabeth Spencer

Grant funding from the UK National Institute for Health and Care Research (NIHR) School for Primary Care Research

Project funding: World Health Organization