Rapid reviews on COVID-19: Challenges and Opportunities

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Acknowledgement of Traditional Land

The Knowledge Translation Program is located on land now known as Tkaronto (Toronto). Tkaronto is the traditional territory of many groups, including the Mississaugas of the Credit and the Chippewa/ Ojibwe of the Anishnaabe Nations; the Haudenosaunee, and the Wendat. It is now home to many diverse First Nations, Inuit and Métis peoples. We also acknowledge that Tkaronto is covered by Treaty 13 with the Mississaugas of the Credit and The Dish with One Spoon treaty between the Anishinaabe, Mississaugas and Haudenosaunee that connected them to share the territory and protect the land. All Indigenous Nations and peoples, Europeans and newcomers, have been invited into this treaty in the spirit of peace, friendship and respect.

We would like to honour the Elders and Knowledge Keepers, both past and present, and are committed to continuing to learn and respect the history and culture of the communities that have come before and presently reside here.

We acknowledge the harms of the past and present, and we dedicate ourselves to work with and listen to First Nations, Inuit and Métis communities in the spirit of reconciliation and partnership.

We recognize and are grateful to have this opportunity to work on this land, and commit to caring for this land and continuously and actively working towards reconciliation. We recognize that Indigenous practices of health and well-being have been in place in this territory for over 10,000 years and are maintained to this day.

Outline of presentation

- Define rapid reviews
- Describe methods for rapid reviews
- Present a case example on a rapid review
  - COVID-19 diagnostic test accuracy network meta-analysis
- Discuss challenges and opportunities related to rapid reviews

Rapid Reviews

What is a Rapid Review?

If an organization produces rapid reviews for decision-making, then this definition can be used: “A rapid review is a form of knowledge synthesis that accelerates the process of conducting a traditional systematic review through streamlining or omitting a variety of methods to produce evidence for stakeholders in a resource-efficient manner.”

- 5-12 weeks to complete
- Cost $25,000 CAD

THE COCHRANE COLLABORATION®

Hamel, J Clin Epi, 2021

How are Rapid Reviews Useful?

- Rapid review-informed decisions helped in savings of approximately $3 million per year in one hospital in Quebec, Canada
- Rapid HTA in Austria helped inform investment decisions on variety of new health technologies reducing costs in hospitals
- Useful for decision-makers during urgent situations (e.g., COVID-19)
- Moving away from rapid reviews as a method on its own, more of a framework to situate the knowledge synthesis in
- Can do systematic review, overviews of reviews, and scoping reviews rapidly

McGregor and Brophy. (2005) Int J Technol Assess Health Care; Zechmeister and Schumacher (2012) Int J Technol Assess Health Care.; Tricco JBI ES 2021

What are Rapid Evidence Products?

Category	Description
Inventories	Inventories only list the evidence that is available on a given topic. There is no attempt to appraise, summarize or synthesize the evidence for further use, nor is there an attempt to present conclusions or recommendations to the knowledge user.
Rapid response briefs	Rapid response briefs present a summary of the best available evidence in a synthesized and contextualized manner, in direct response to a decision-maker's question. They are knowledge translation products created through formal methods to synthesize and appraise the evidence. They do not generate new knowledge but use findings that are already available, especially from existing systematic reviews.
Rapid reviews	Rapid reviews represent a knowledge generation strategy. They synthesize findings and assess the validity of research evidence using "abbreviated" systematic review methods, modifying these methods to generate evidence in a short time.

Hartling et al. (2015) Agency for Healthcare Research and Quality

Rapid Review steps

- Develop research question using PICOST
- Determine eligibility criteria using the PICOST research question
- Plan a literature search
- Only register protocol

Protocol Development

Literature Search

- Limit literature search (e.g., # of databases, by date, grey lit)
- Use a layered search approach

Level 1 and Level 2 screening

- Level 1: Titles and abstracts
- Level 2: Full- text articles

Abstract Data

- Pilot the form
- Use two reviewers for *some* of the data points to be abstracted
- Limit to a single reviewer only or single reviewer and one verifier

Critical Appraisal and assessment

- Prioritize assessment of key sources of bias
- Streamline by limiting to a single reviewer and one verifier
- (Skip this step)

Summarize study and patient characteristics

- Limit the number of tables and text used to describe study and patient characteristics

Status	Patients, n (%)	
Disposition after evaluation in emergency department		
Hospitalized	377	(66)
Discharged from emergency department	140	(25)
Discharged after observation period in emergency department	44	(8)
Transferred to other health facility	6	(1)
Died in emergency department†	1	(0)
Hospitalization‡		
Discharged within the first 3 days	112	(30)
Hospitalized for 4–9 days	187	(50)
Stayed in the hospital ≥10 days	78	(20)
Treatment		
Nonoperative	288	(51)
Surgery	243	(43)
Transferred to other health facility	6	(1)
Died	31	(5)

Synthesize results

- Limit to basic descriptive summary of studies
- Prioritize type of analysis

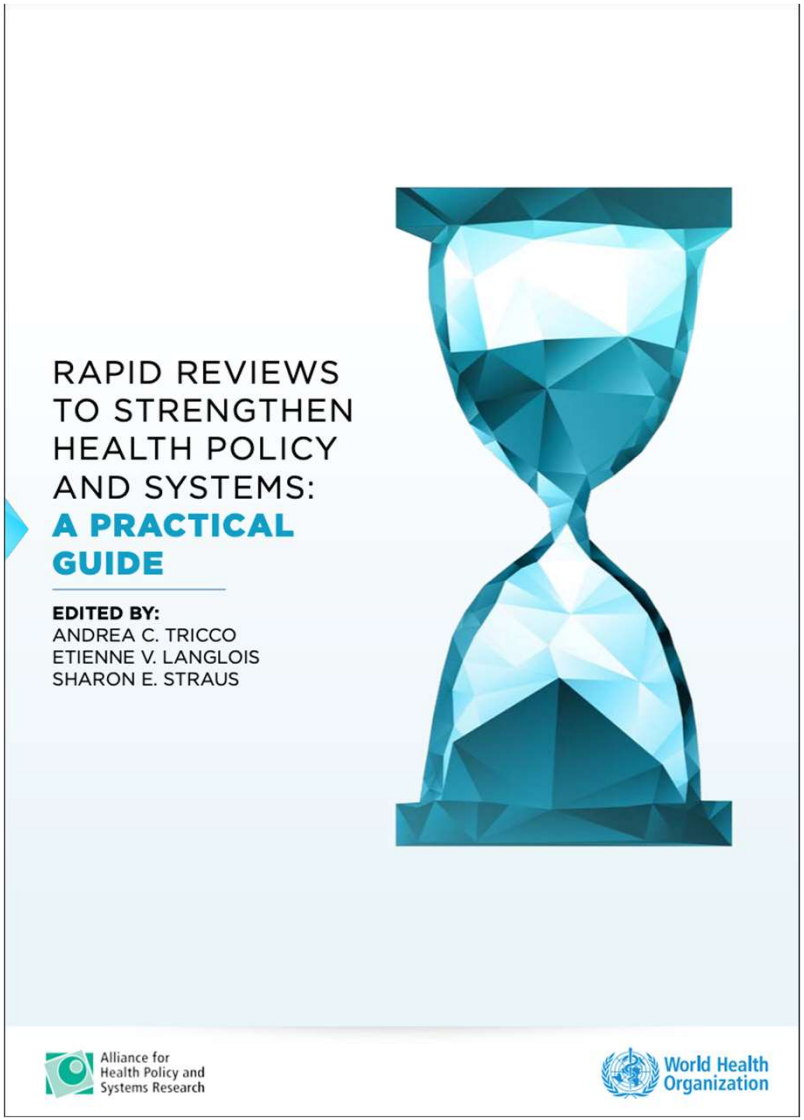
Present results

- Provide a more streamlined product (e.g., 1-page summaries)
- Discuss policy, practice, and clinical implications **with caution**

Rapid Review steps

Conduct guidance

- Guidance for conduct of rapid reviews for health policy and systems research developed in collaboration with WHO
- WHO guide recommends researchers tailor methods to needs of decision-makers
- Several ways that rapid reviews can be streamlined to accommodate decision-makers' needs related to both scope of review and timeliness across all steps of review process



Tricco, A. et al. (2017) WHO

Reporting guidance

Enhancing the QUAlity and Transparency Of health Research

Developing PRISMA-RR, a reporting guideline for rapid reviews of primary studies (Protocol)

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Rapid Reviews & COVID-19

Challenges identified:

- Involving all relevant knowledge users (patient partners, clinicians, policy-makers)
- Urgency of the request (5-10 days)
- Finding all relevant evidence (scattered across websites and pre-print servers)
- Interpreting results when clear and direct evidence does not exist
- Sharing the results widely
- Updating reviews on a continuous basis (e.g., living reviews)

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Journal of Clinical Epidemiology

COVID-19 ARTICLES

Rapid review methods more challenging during COVID-19: commentary with a focus on 8 knowledge synthesis steps

Andrea C. Tricco, Chantelle M. Garritty, Leah Boulos, Craig Lockwood, Michael Wilson, Jessie McGowan, Michael McCaul, Brian Hutton, Fiona Clement, Nicole Mittmann, Declan Devane, Etienne V. Langlois, Ahmed M. Abou-Setta, Catherine Houghton, Claire Glenton, Shannon E. Kelly, Vivian A. Welch, Annie LeBlanc, George A. Wells, Ba' Pham, Simon Lewin, Sharon E. Straus

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Conflict of interest: A.C.T., J.M., and G.W. are associate editors and S.E.S. is on the editorial board for the Journal of Clinical Epidemiology; none were involved with the peer review of this article or decision to publish. B.H. previously received honoraria from Evermos for provision of methodologic advice related to the conduct of systematic reviews. J.M. is a co-convener of the Cochrane Information Retrieval Methods Group. C.M.G. is the co-convener of the Cochrane Rapid Reviews Methods Group and provides consultancy to Cochrane Response. S.L. is the Joint Coordinating Editor of Cochrane Effective Practice and Organisation of Care (EPOC) and Chair of the Governance Group of the Global Evidence Synthesis Initiative (GESI). E.L.V., A.A.S., V.W., B.P., S.K., C.H., M.W., N.M., C.G., L.B., P.C., C.L., M.M., A.L., and D.D. have no competing interests to declare.

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Tricco, A. J Clin Epi, 2020

Case Example from the "Real World"

COVID-19 rapid antigen & molecular tests: A rapid review with diagnostic test accuracy network meta-analysis (DTA-NMA)

Rapid Review Example

Health Canada and the Public Health Agency of Canada contacted us to lead a review to determine the most sensitive and/or specific rapid test for the diagnosis of COVID-19

They needed the report **as soon as possible**

We set up our team considering to include the policy-makers who requested the evidence, at least one clinician/content expert, two patient partners, content experts, research methodologists, and statisticians

1. Research Question

- We developed a research question and determined eligibility criteria as follows:
  - *Population*: Adults and/or children screened/suspected for COVID-19
  - *Target condition*: COVID-19 infection
  - *Index tests*: We included studies evaluating one or more commercially available COVID-19 rapid lateral flow antigen test or rapid molecular test (providing a result in ≤1 hour) used for screening of asymptomatic individuals or the diagnosis of COVID-19 infection in symptomatic individuals
  - *Reference Standard*: polymerase chain reaction (PCR) test
  - *Study design*: We included RCTs and observational studies providing the 2x2 table data
  - *Outcome*: Sensitivity and specificity of rapid antigen and molecular tests suitable for screening and diagnosing COVID-19
- Registered our protocol with PROSPERO: CRD42021289712

2. Literature Search Strategy

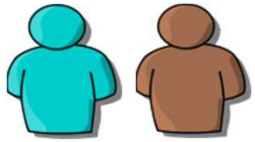
- We worked with an experienced librarian
- The search was peer-reviewed by another librarian using the Peer Review of Electronic Search Strategies (PRESS) Checklist
- Searched 3 databases:
  - Embase, MEDLINE, and EBM Reviews - Cochrane Central Register of Controlled Trials
  - Completed on September 12, 2021
- We included only primary studies from December 2019 up to September 2021
- Grey literature was not searched
- Limited to English publications with available data for analysis
- Did not contact authors for clarifications

3. Study Selection

- We used a standardized screening form for both levels of screening
  - Level 1: Titles and abstracts
  - Level 2: Full- text articles
- A pilot exercise was completed to calibrate and test the form at each level of screening with all reviewers (i.e., 50 citations at level 1 and 15 articles at level 2)
- We made decisions based on 1 reviewer

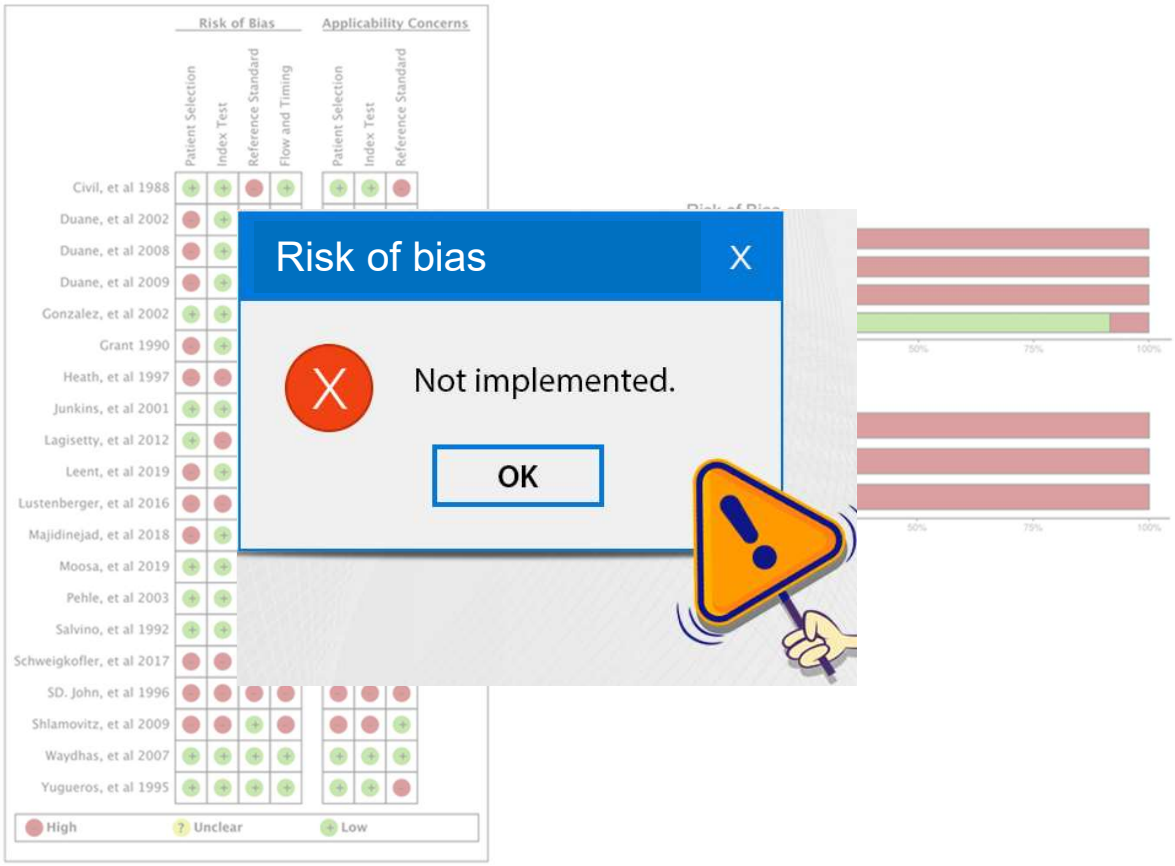
4. Data Extraction

- We used a standardized data extraction form
- Performed a pilot exercise to calibrate and test the form with all reviewers using 5 full-text articles
- We made decisions based on 1 reviewer and 1 verifier

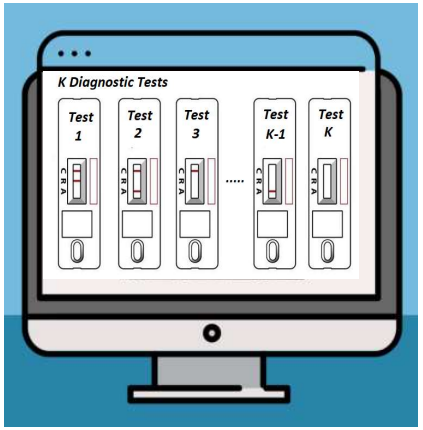


5. Risk of Bias Assessment

- This step was not performed
- We plan to assess risk of bias using the QUADAS-2 and QUADAS-C tools for the included studies



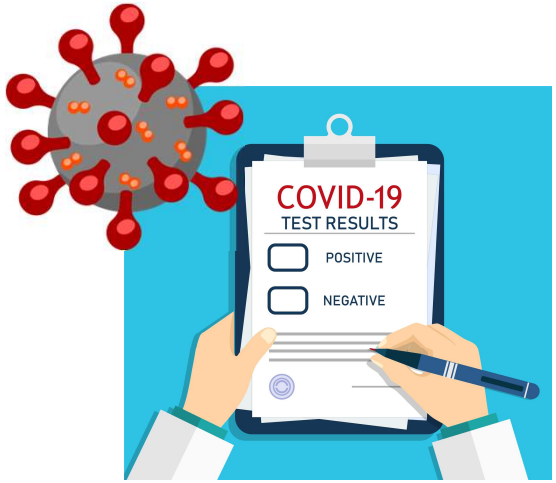
6. Data analysis



- Limited to basic descriptive summary of studies
  - Country of conduct and type of rapid test
- Kept the analysis high-level:
  - Random-effects DTA meta-analysis (bivariate model)
  - Random-effects DTA-NMA (Nyaga ANOVA model)
- Estimated sensitivity and specificity for each test along with their 95% credible intervals
- Investigated potential sources of heterogeneity that may influence diagnostic accuracy using:
  - **Subgroup analysis**: symptom status (asymptomatic vs symptomatic), sample type (e.g., saliva, nasal swab), participant type (e.g., general public, healthcare worker), and rapid molecular test category (i.e., rRT-PCR, PT-Isothermal, RT-Lamp)
  - **Meta-regression**: age
- Assessed transitivity based on the distribution of the above potential effect modifiers across test comparisons

7. Summary and Display of Data

- Sent preliminary results and asked for a deep-dive on any key issues from our knowledge users:
  - Health Canada, Public Health Agency of Canada, Ministry of Public Health in Thailand, and Irish Department of Health
- Discussed implications of results with caution
- Provided our knowledge users with a 1-page summary



Appendix 2: Preliminary results of the rapid review

How was the rapid review conducted?

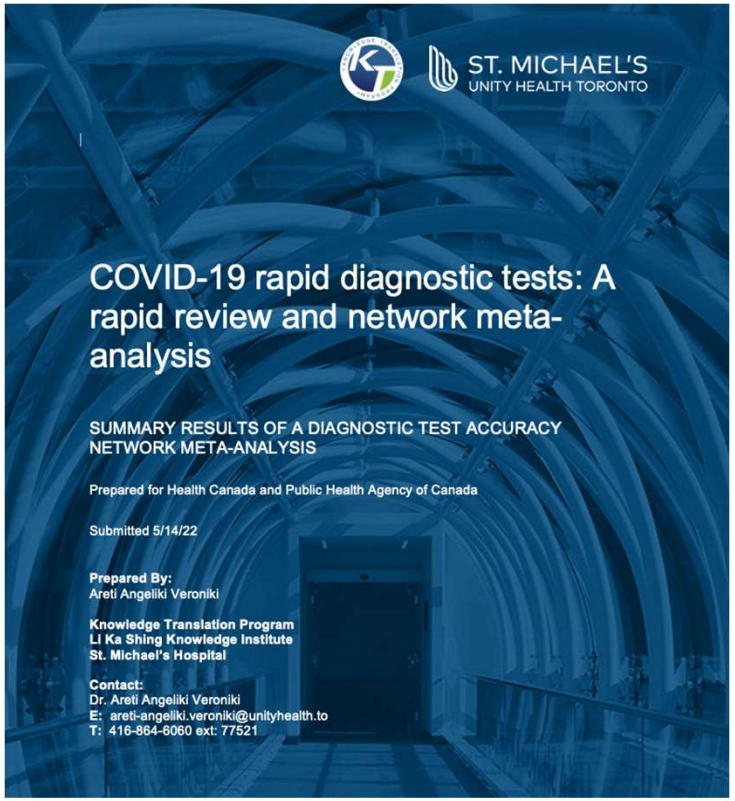
- The protocol for the review was developed and revised with input from researchers, clinicians, methodologists, statisticians, and knowledge users (KUs) from: Health Canada, Public Health Agency of Canada (PHAC), Alberta Health Services, the Irish Department of Health, and the Ministry of Public Health in Thailand. PROSPERO registration: CRD42021289712
- We searched Embase, MEDLINE, and EBM Reviews - Cochrane Central Register of Controlled Trials up to September 2021 for randomized controlled trials (RCTs) and observational studies (e.g., cohort studies) assessing any rapid antigen and any rapid molecular test to detect COVID-19.
- The outcomes of interest were the sensitivity and specificity of rapid antigen and molecular tests suitable for the detecting COVID-19.
- Screening of literature search results was conducted by one reviewer, data abstraction was completed by one reviewer and independently verified by a second reviewer.
- We conducted random-effects meta-analysis and DTA-NMA.

What did the rapid review find?

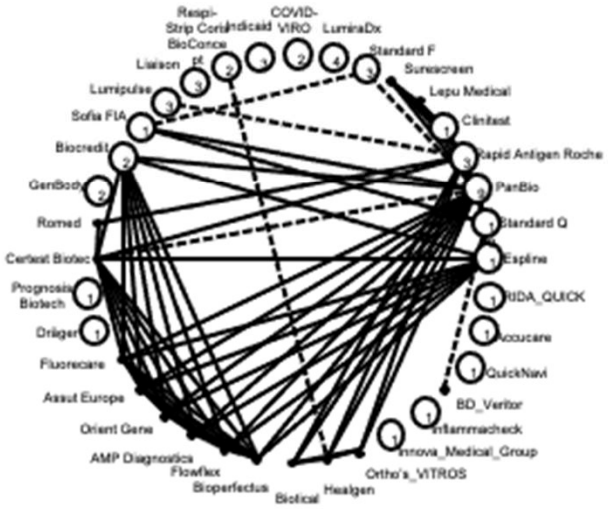
- We identified 312 citations evaluating rapid antigen and rapid molecular tests to detect COVID-19. Of these, we prioritized RCTs and cohort studies, and studies with available 2x2 data for analysis.
- Our analysis included 93 studies (reported in 88 articles): 68 studies assessed rapid antigen tests (composed of 55 single-test studies, 8 paired-test studies, and 5 multi-test studies), and 27 studies assessed rapid molecular tests (composed of 23 single-test studies, 3 paired-test studies, and 1 multi-test study). Two studies assessed both types of rapid tests.
- We included 35 rapid antigen tests and 23 rapid molecular tests, and 115,410 participants (104,961 participants in antigen tests; 10,449 participants in molecular tests). The included studies were conducted in 28 countries (16 [17%] North America; 56 [60%] Europe; 18 [19%] Asia).
- Rapid molecular tests were more accurate and more precise than rapid antigen tests in identifying TP and TN participants (general public, antigen: sensitivity 0.79 with 95% confidence interval (CI) [0.73, 0.84], specificity 0.99 [0.98, 0.99], molecular: sensitivity 0.92 [0.83, 0.97], specificity 0.98 [0.97, 0.99]).
- The Xpert Xpress rapid molecular test by Cepheid was associated with the highest sensitivity (0.94, [0.77, 0.99]) and specificity (0.93 [0.83, 0.97]), followed by Cobas Liat SARS-CoV-2 and influenza A/B nucleic acid test by Roche (sensitivity: 0.87 [0.67, 0.96]; specificity 0.82 [0.50, 0.99]). RR-LAMP tests (0.84 [0.67, 0.93]) were less sensitive than rRT-PCR tests (0.97 [0.95, 0.99])
- Among the rapid antigen tests, the following four tests ranked highest with regards to both sensitivity and specificity: COVID-VIRO test (AAZ-LMB; sensitivity: 0.90 [0.72, 0.97]; specificity 0.90 [0.78, 0.99]), Sofia SARS Antigen FIA test (Quidel; sensitivity: 0.89 [0.79, 0.95]; specificity 0.83 [0.62, 0.94]), Dräger Antigen Test SARS-CoV-2 test (Dräger; sensitivity: 0.81 [0.53, 0.95]; specificity 0.83 [0.50, 0.96]), and GenBody COVID-19 Ag test (Meridian Bioscience; sensitivity: 0.81 [0.70, 0.94]; specificity 0.92 [0.80, 0.99]).
- Our subgroup analyses of rapid antigen tests showed that sensitivity may decrease when: saliva is used as a sample type (saliva 0.71 [0.66, 0.76]; nasopharyngeal 0.82 [0.71, 0.90]), and when asymptomatic individuals are tested (symptomatic 0.77 [0.58, 0.88]; asymptomatic 0.55 [0.32, 0.76]). Data on symptomatic vs asymptomatic individuals were not available for rapid molecular tests, but sensitivity for nasopharyngeal was 0.91 (0.84, 0.96). Our meta-regression suggested that the relative change in sensitivity increased by 0.50 (0.49, 0.50) with a unit increase in age.

8. Report Findings

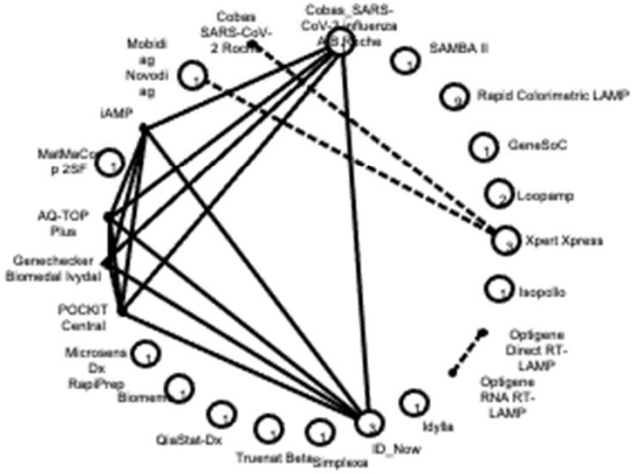
- Used reporting guidelines to ensure transparent and complete reporting of our research approach and findings (e.g., PRISMA-DTA and PRISMA-NMA Checklist)

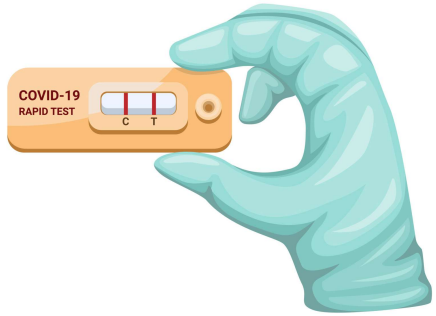


Network plot for rapid antigen tests
68 studies, 104,961participants, 36 tests



Network plot for rapid molecular tests
27 studies, 10,449 participants, 23 tests

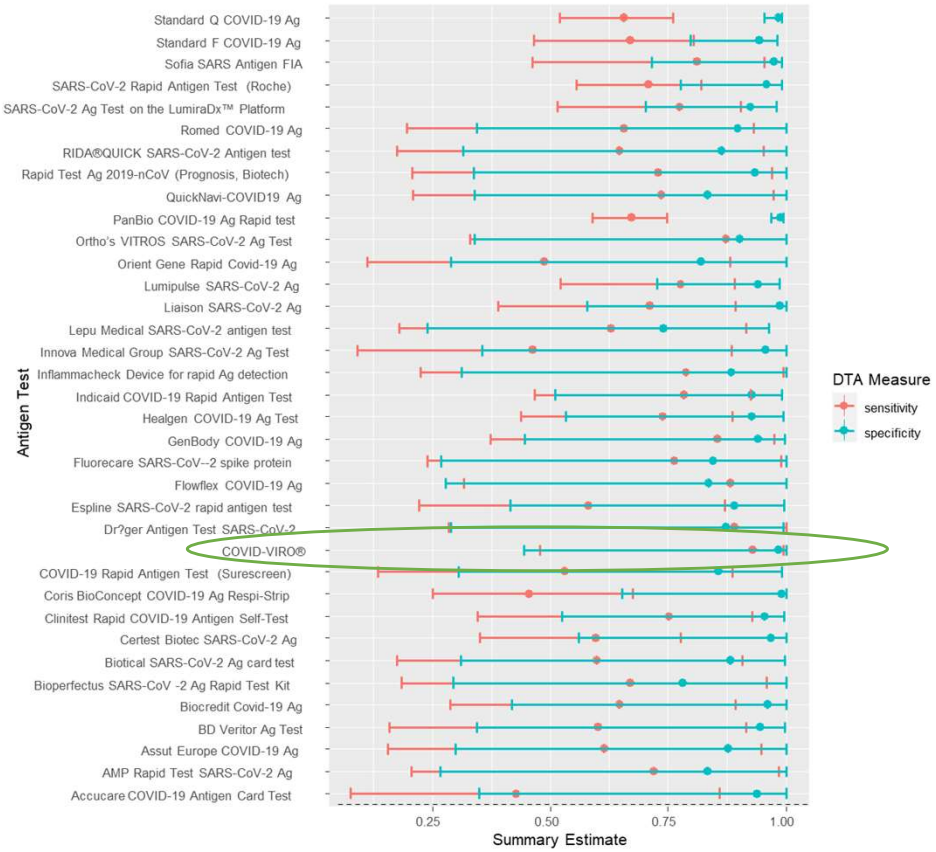




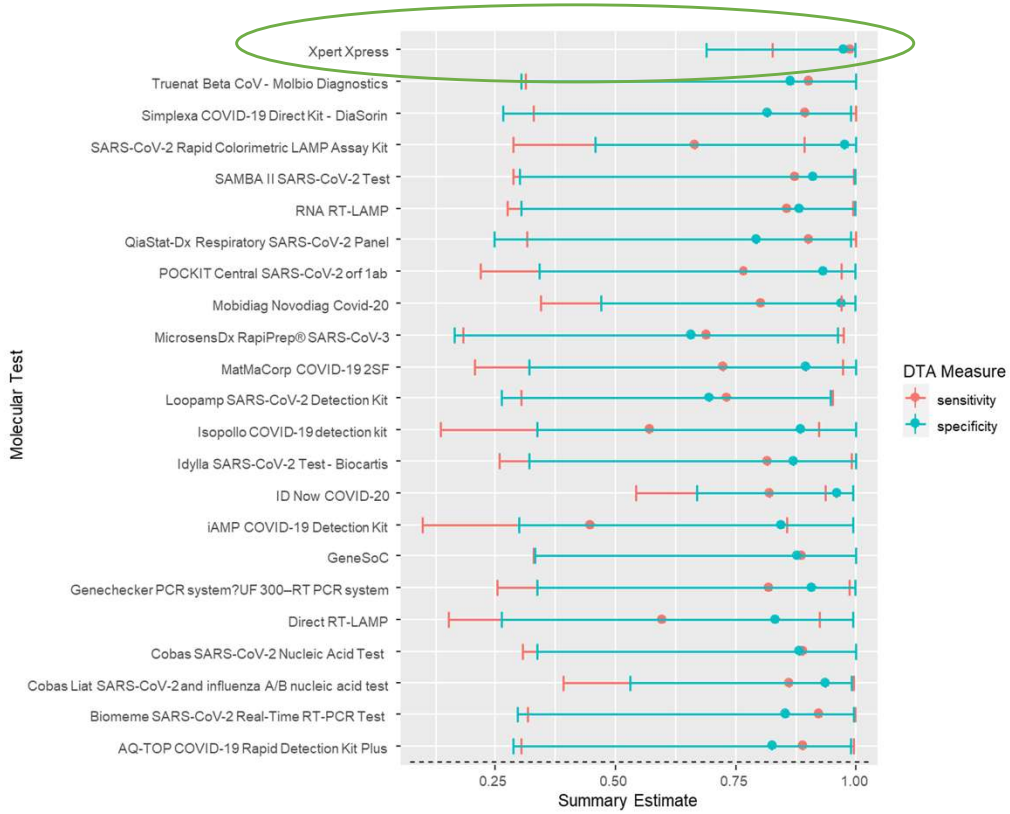
8. Summarized results

DTA-NMA results

Rapid antigen tests



Rapid molecular tests



Challenges of rapid reviews for COVID-19 during the pandemic

- Challenges and study limitations:
  - Literature searches are 7 months old and this is a rapidly-moving area
  - Staff shortages due to covid-19
  - We might have missed studies to contribute to the evidence-base (e.g. 1 reviewer)
  - Findings have not been assessed regarding the study risk of bias
  - Unclear what variants of SARS-CoV-2 the participants had during these studies
  - Transitivity could not be assessed appropriately, since reporting was inadequate in the original studies
- A more comprehensive (systematic) review should be completed
  - To conduct a full systematic review that will be updated on a continuous basis (i.e., living review)
  - To assess methodological quality using the QUADAS-2 and QUADAS-C tools
  - To consider the inclusion of both preprints and publications in any language, and to contact the authors for potentially missing or unclear data
  - To evaluate the impact of circulating variants, vaccination status, test operator (e.g., nurse, self-testing), who interpreted the results (e.g., nurse, self-testing), and participant age on the accuracy of the individual rapid tests

Opportunities of rapid reviews for COVID-19 during the pandemic

- Opportunities:
  - Initiated project and submitted results for COVID-19 rapid tests within 8 months
  - Registered with PROSPERO to help avoid duplication and increase transparency
  - Not fundamentally different from a standard systematic review – but faster
  - Matched to decision-making timeframes; provided input to decision-making
  - Performed formal comparison of all identified rapid antigen tests and rapid molecular tests using a DTA-NMA
  - This work involved two patient partners to ensure patient perspectives are integrated in our research question.
  - Will publish these results for transparency and accountability, as well as for knowledge transfer and translation within the fast-moving field of COVID-19

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Thank you!
Questions?

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