ACTaccelerator
ACCESS TO COVID-19 TOOLS

Developing a collaborative research agenda for

SARS-CoV-2 antigen rapid diagnostic tests

REPORT FROM THE VIRTUAL FORUM HELD
ON 29 OCTOBER 2020

CONTENTS

EXECUTIVE SUMMARY

BACKGROUND

Antigen-detecting rapid diagnostic tests (Ag-RDTs) for SARS-CoV-2 hold enormous potential in the COVID-19 testing response, but recommendations for their use are currently restricted by available data. This virtual forum brought together a broad range of partners from the diagnostic pillar of the Access to COVID-19 Tools (ACT) Accelerator, as well as representatives from academia, implementing partners and country programmes to develop a collaborative research agenda for SARS-CoV-2 Ag-RDTs. The virtual forum considered key research questions for SARS-CoV-2 Ag-RDTs across topics that would support optimal access to and use of Ag-RDTs, particularly in real-world settings. Breakout groups were convened to develop prioritized research questions and insights to inform planned operational initiatives. This process aimed to guide research efforts and maximize available resources to inform global normative policy and change, and improve outcomes for people affected by SARS-CoV-2.

FINDINGS

The breakout groups identified a number of key questions that, when answered, can contribute to expanding the uptake of and use cases for Ag RDTs. **Key questions revolved around better understanding the performance of Ag-RDTs when implemented in their intended settings of use and across specific populations.** Participants agreed that it would be important to determine the accuracy of Ag RDTs (sensitivity, specificity, predictive value) across settings and by patient-level factors, such as disease severity, age, and presence or absence of symptoms. These data are needed to better define the situations where Ag-RDTs have adequate performance for use as a diagnostic when PCR is unavailable. This is of particular importance in certain settings, for example, remote locations, where confirmatory PCR testing may not be possible. Furthermore, understanding Ag-RDT accuracy and feasibility when used at ports of entry was highlighted as a priority topic across all groups. Generation of evidence in these areas could then be used to develop guidance that can be provided to countries, including island nations, on the use of Ag-RDTs.

Participants noted that if performance is understood in a given intended setting, it will be important to **assess the harms, benefits and health impact of Ag-RDTs for various populations,** for example, among those in high-risk occupations or vulnerable groups. The value of Ag-RDTs for diagnosis, screening and/or surveillance needs to be carefully evaluated in terms of the benefits of testing versus the harms of false-negative or false-positive results (for example, the consequences of releasing false-negative cases at points of entry or unnecessarily quarantining a front-line healthcare worker who tests falsely positive).

Determining the role of Ag-RDTs in diagnostic algorithms will rely on the above mentioned research on the performance of Ag-RDTs and their value in different use settings. It was noted that modelling can help to evaluate specific use cases (e.g.,

through cost-effectiveness analyses) and scope out opportunities for additional use cases, for example, by determining which factors are needed for screening at-risk population groups and the value of collecting different types of data.

As most existing SARS-CoV-2 Ag-RDTs require nasopharyngeal samples, **research is needed to determine the accuracy of different sample types** (such as nasal swabs, saliva), as well as **the feasibility and ease of use of different sample collection methods.** At the programme level, the acceptability of different sample types to healthcare workers and patients also needs to be better understood in order to ensure that rapid tests are acceptable to those who will be using them. **In terms of quality control, implementation research should guide best practices to reinforce the validity of test results, along with post-marketing surveillance of Ag-RDTs,** across different end-user cadres and across different use settings.

Determining delivery models for Ag-RDTs was also noted as a priority research topic across groups in terms of which healthcare worker cadres can safely, accurately and feasibly perform Ag-RDT testing. It was noted that as task-shifting may be used to meet COVID-19 testing demands, it will be important to acknowledge that those performing sample collection and reading tests may not be professionally trained. Therefore, the training needs for different healthcare worker cadres will need to be determined.

NEXT STEPS

As an immediate next step to advance the research agenda for Ag-RDTs, the World Health Organization (WHO) has launched an expression of interest call for monitored implementation projects to assess the field performance, feasibility, acceptability and impact of SARS-CoV-2 Ag-RDTs in variable use settings in low- and middle-income countries. Proposals are invited from a broad range of stakeholders, including ministries of health, technical partners, academic partners and nongovernmental organizations, with funding available for up to five sites.

In terms of progressing the research agenda put forward here, there is a need for continued coordination and regular engagement. Given the potential value of Ag-RDTs in the COVID-19 response, it will be important to ensure that the funds and resources to address the questions in the research agenda are deployed in a timely manner. It is hoped that the framework provided can guide the allocation of resources and funding to high-priority Ag-RDT research questions. It was recommended that the outputs of the research agenda be linked to policy and shared, so that countries can align their national guidance with the evidence generated through this agenda. Momentum and continued investments are necessary to secure future advances in research on COVID-19 diagnostics and to meet the needs of people affected by this virus.

PRIORITIZED RESEARCH QUESTIONS

The following are the prioritized research questions for Ag-RDTs selected by the virtual forum participants

Focal area	Refined / specific research question
Performance	• **What is the performance of Ag-RDTs in different intended use settings,** particularly expanded use cases, which may include general screening (e.g., ports of entry)? • **How does test performance vary by patient-level factors** (e.g., asymptomatic vs. symptomatic patients, disease severity, level of infectiousness, age, etc.)? • **What is the impact of different serial testing algorithms on performance (i.e., NPV, PPV),** e.g., two different Ag-RDTs in series, repeat testing using the same Ag-RDT, Ag-RDT confirmed by PCR, etc.? • **Do Ag-RDTs have adequate performance for use as a diagnostic when PCR is unavailable** (e.g., in remote settings, overwhelmed laboratories)?
Use cases	• **What is the potential health/public health/economic impact of correctly diagnosing someone, and what are the potential risks of misdiagnosing someone across settings or among different populations,** e.g., high-risk occupations/vulnerable populations, settings outside of healthcare posts (e.g., schools, borders), etc.? • **What are the observed rates of onward transmission of COVID-19 for individuals who are detectable by Ag-RDTs versus those who are Ag-RDT negative and PCR positive?** • **When Ag-RDTs are included as part of a sequential algorithm, what timing should be considered?** If they are part of routine screening (e.g., of front-line healthcare workers), what is the most impactful frequency of testing? • **What are the harms/benefits of false positives/negatives with current Ag RDTs** with low specificity/ sensitivity across use cases (e.g., at ports of entry vs. in health facilities)? • **What are the observed rates of compliance/observance of public health measures** (e.g., self-quarantine) across settings/populations (e.g., universities, care homes, healthcare, etc.)? • **What is the acceptability, feasibility, sustainability and cost-effectiveness of implementing Ag-RDT screening in various settings** (e.g., schools, ports of entry, workplaces, etc.)?
Samples	• **What is the accuracy of different sample types** (e.g., NP, AN, saliva)? • **Which sample types are feasible/acceptable to healthcare workers and patients?** • **Can PCR be run off the same Ag-RDT sample?**
Biosafety	• **Do Ag-RDT buffers inactivate the virus?** If so, to what degree (e.g., pfu/ml) and over what time period? • **What biosafety measures are required for different sample types?**
Quality control	• **What are the observed invalid rates,** particularly between different Ag RDT products, across different end-user cadres, and across different use settings?
Training/delivery	• **Which healthcare worker cadres can safely, accurately and feasibly perform Ag-RDT testing?** Can task-shifting to lay providers be leveraged to support testing and contact tracing? • **What are safe, acceptable and effective strategies/interventions to improve uptake of testing services** (considering different strategies for different population groups)? • **Is self-testing a safe, acceptable and feasible testing approach for COVID-19? Is it effective in increasing uptake of COVID-19 testing?** • **What is the role of community-based groups and services in uptake and awareness during COVID-19 pandemic?**
Economics/cost	• **What is the most relevant way to articulate the costs and benefits of different testing strategies** (avoiding periods of self-isolation, economic disruption, costs and opportunity costs of the tests being used in a particular way, etc.)? • **What is the cost-effectiveness of various algorithms involving Ag-RDTs and NAAT?** How might this vary by use case (e.g., diagnosis vs. screening vs. surveillance)?

Ag-RDT: antigen-detecting rapid diagnostic test; **AN:** anterior nares; **NAAT:** nucleic acid amplification testing; **NP:** nasopharyngeal; **PCR:** polymerase chain reaction; **PPV:** positive predictive value.
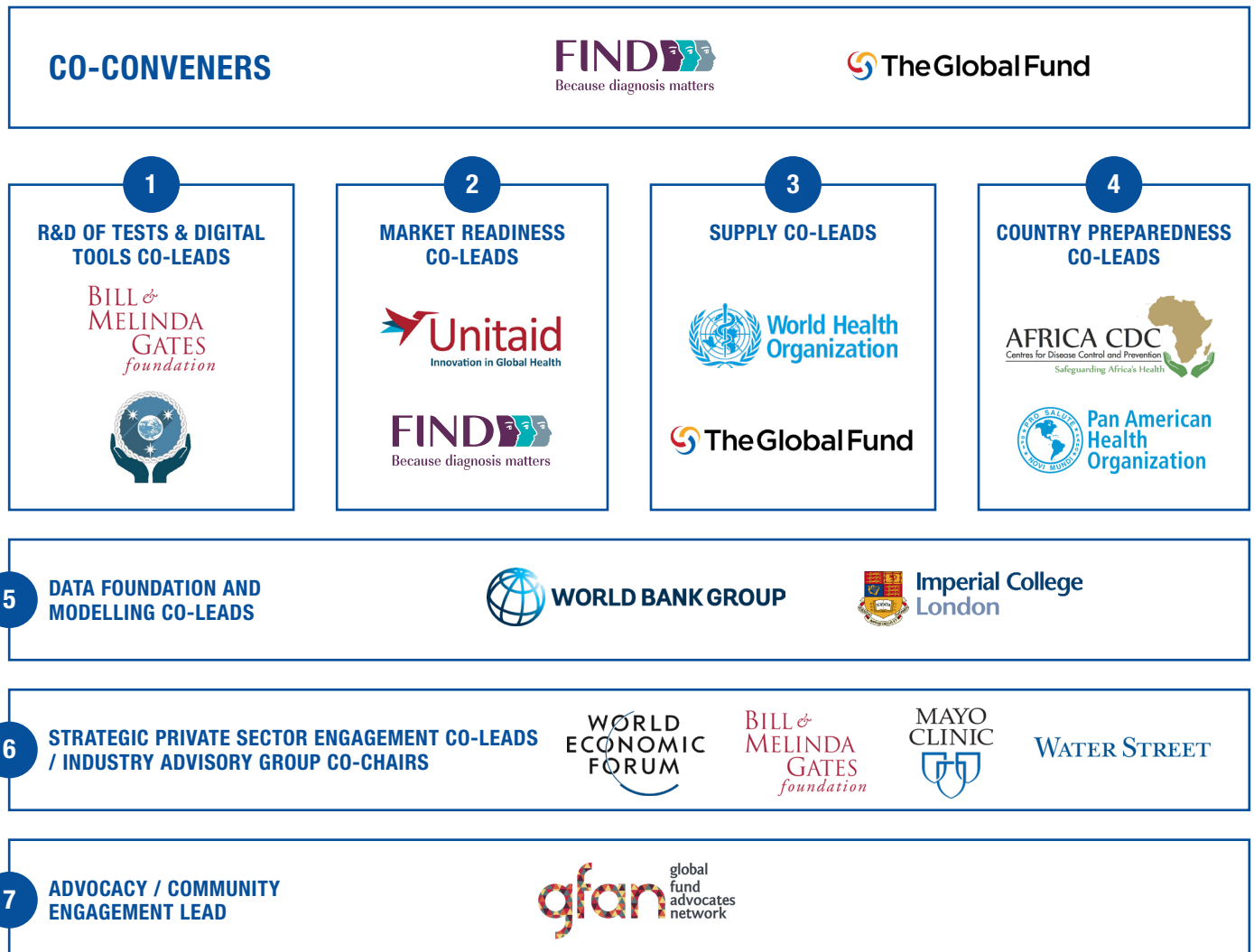
MAIN MEETING REPORT

SECTION 1. INTRODUCTION

ACT-ACCELERATOR DIAGNOSTICS PILLAR

In April 2020, the World Health Organization (WHO) convened the Access to COVID-19 Tools (ACT) Accelerator to accelerate development, production and equitable access to tools, products and services that will be critical to overcoming the COVID-19 pandemic. ACT Accelerator is a groundbreaking global collaboration with a shared agenda to accelerate the response to the COVID-19 pandemic. The ACT-Accelerator is made up of a vast partnership network working across vaccines, therapeutics, diagnostics and health systems to advance this agenda. The diagnostics pillar of the ACT-Accelerator is co-convened by the Foundation for Innovative New Diagnostics (FIND) and the Global Fund to Fight AIDS, Tuberculosis and Malaria with the aim to drive equitable access to affordable and accurate testing for an effective COVID-19 response. Specifically, the diagnostics pillar aims to bring to market two to three high-quality rapid tests, train 10 000 healthcare professionals across 50 countries and establish testing for 500 million people in low- and middle-income countries (LMICs) by mid 2021. FIND and the Global Fund are supported by over 30 partner organizations across the public and private sector, who are engaged in work to meet the objectives of the pillar (Fig. 1).

Fig. 1. The Access to COVID-19 Tools Accelerator diagnostic pillar partners

CO-CONVENERS — FIND (Because diagnosis matters), The Global Fund

1 R&D OF TESTS & DIGITAL TOOLS CO-LEADS — Bill & Melinda Gates foundation

2 MARKET READINESS CO-LEADS — Unitaid (Innovation in Global Health), FIND (Because diagnosis matters)

3 SUPPLY CO-LEADS — World Health Organization, The Global Fund

4 COUNTRY PREPAREDNESS CO-LEADS — AFRICA CDC (Centres for Disease Control and Prevention, Safeguarding Africa's Health), Pan American Health Organization

5 DATA FOUNDATION AND MODELLING CO-LEADS — WORLD BANK GROUP, Imperial College London

6 STRATEGIC PRIVATE SECTOR ENGAGEMENT CO-LEADS / INDUSTRY ADVISORY GROUP CO-CHAIRS — WORLD ECONOMIC FORUM, Bill & Melinda Gates foundation, MAYO CLINIC, WATER STREET

7 ADVOCACY / COMMUNITY ENGAGEMENT LEAD — gfan (global fund advocates network)

SARS-COV-2 ANTIGEN-DETECTING RAPID TESTING IN THE COVID-19 RESPONSE

Testing is a cornerstone of the response to COVID-19, enabling the early identification and isolation of cases in order to slow transmission, provide care to those affected, and protect health systems. SARS-CoV-2 antigen-detecting rapid diagnostic tests (Ag-RDTs) can complement molecular testing where capacity is limited, thereby alleviating pressure on laboratories and decreasing delays in diagnosis. Several countries have already started implementing testing using Ag-RDTs.

WHO recently issued interim guidance for the use of Ag-RDTs in the COVID-19 response based on the currently limited evidence. Given the urgent need to expand testing for COVID-19 and interest in using Ag-RDTs, the generation of additional high-quality evidence to address gaps in guidance would help to strengthen and expand use cases. To meet this need, timely evidence on the analytical and clinical performance of Ag-RDTs is required alongside operational research in order to address evidence gaps in a coordinated manner and generate solid data to inform policy.

SARS-CoV-2 Ag-RDT key facts

SARS-CoV-2 Ag-RDTs use **a simple lateral flow immunoassay** to detect viral antigens from clinical specimens.

Ag-RDTs have **a rapid turnaround time** and can produce results in around 10 to 30 minutes.

As of October 2020, **over 130 Ag-RDT products** were in development.

However, to date, **only two products have met the criteria** for WHO Emergency Use Listing (EUL).

Published data on the sensitivity of Ag-RDTs for SARS-CoV-2 have been **highly variable.**

Current data on the performance of Ag-RDTs have **limited recommendations for their use** to five specific epidemiological scenarios.

Four epidemiological scenarios recommended for Ag-RDTs by WHO based on current evidence[1]
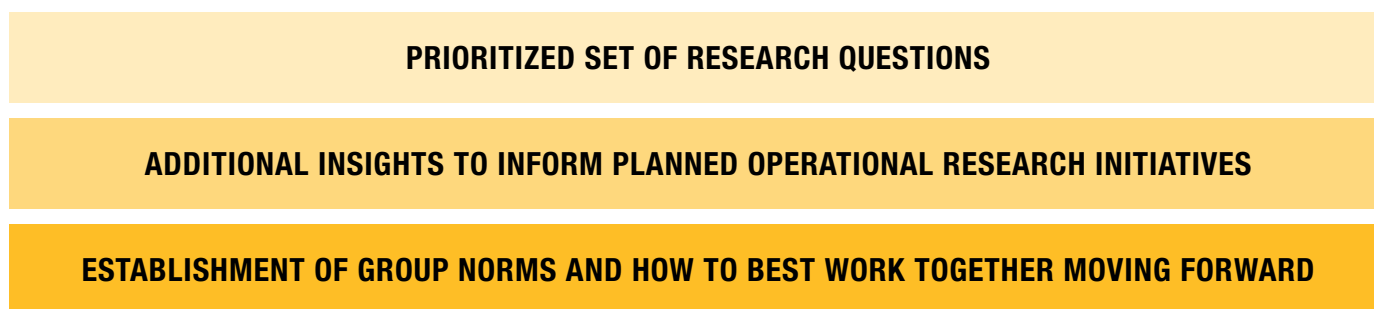
Outbreak response	Population recommended for screening
Outbreak investigation/ contact tracing	To respond to suspected outbreaks of COVID-19 in remote settings, institutions and semi-closed communities where NAAT is not immediately available
Monitoring trends in disease incidence	To support outbreak investigations (e.g., in closed or semi-closed groups including schools, care homes, cruise ships, prisons, workplaces and dormitories, etc.) and to screen at-risk individuals
Community transmission screening	Where there is widespread community transmission, RDTs may be used for early detection and isolation of positive cases in health facilities, COVID-19 testing centres/sites, care homes, prisons, schools, front-line and healthcare workers and for contact tracing
Testing of asymptomatic contacts of cases	Testing of asymptomatic contacts of cases may be considered even if the Ag-RDT is not specifically authorized for this use, as asymptomatic cases have been demonstrated to have similar viral loads to symptomatic cases, although, in this situation, a negative Ag-RDT should not remove a contact from quarantine requirements

1. Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays. Interim guidance. 11 September 2020. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays, accessed 5 November 2020).

SECTION 2. OBJECTIVES AND APPROACH

This virtual forum brought together ACT-Accelerator diagnostic pillar partners to discuss the development of a collaborative operational research agenda for SARS-CoV-2 Ag-RDTs. Fig. 2 shows the expected outcomes of the virtual forum.

Fig. 2. Target outcomes of the virtual forum

PRIORITIZED SET OF RESEARCH QUESTIONS

ADDITIONAL INSIGHTS TO INFORM PLANNED OPERATIONAL RESEARCH INITIATIVES

ESTABLISHMENT OF GROUP NORMS AND HOW TO BEST WORK TOGETHER MOVING FORWARD

The forum was organized around three breakout groups according to the following thematic areas for SARS-CoV-2 Ag-RDTs:
- technical research
- programmatic research
- modelling.

The breakout groups were responsible for developing prioritized research questions and insights to inform planned operational research initiatives for the thematic area in question. Participants were asked to review a set of initial questions, brainstorm any additional questions for consideration, and select the questions of the highest priority. Each question was then refined so that it was specific and measurable enough to translate into a clear research project/priority. The groups were also asked to identify the data inputs required to answer the questions.

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SECTION 3. FINDINGS: PRIORITY RESEARCH FOR Ag-RDTs

This section reports the findings from the breakout groups in terms of priority research questions for each thematic area, insights into operational considerations and the data needed to answer the questions.

A. TECHNICAL RESEARCH

Technical research will provide answers to fundamental questions about Ag-RDTs in terms of their accuracy and expected performance across end-users, intended use settings and/or types of specimens. In combination with information gathered through programmatic studies, data on the technical characteristics of Ag-RDTs can then be used to inform models and provide the foundation to strengthen and expand the use cases for Ag RDTs.

PERFORMANCE

It is essential to understand the performance of Ag-RDTs in different intended use settings, for example, at ports of entry and in health facilities. The suitability of Ag-RDTs for use at ports of entry was a topic of interest, particularly for island nations. Evaluating Ag-RDT performance in different patient populations, notably asymptomatic versus symptomatic patients, will also be valuable given the role asymptomatic cases play in the transmission of COVID-19 and the importance of early detection. Factors relating to the interpretation of Ag RDT results also need to be elucidated, such as whether readers improve performance, the value of visual aids and the interpretation of faint bands. Finally, although not a technical question, it was discussed that establishing systems to support appropriate training and quality control for conducting Ag-RDTs will be vital for ensuring their accuracy. The need for empirical data in different settings was emphasized, and countries that have started to generate this information are encouraged to share data with WHO, so that the evidence can be considered to support policy decisions.

SAMPLE TYPES

Most existing SARS-CoV-2 Ag-RDTs require nasopharyngeal samples, but there are a growing number of tests (none that are WHO EUL approved) that are recommended for use with nasal swabs. Further data are required to determine the accuracy and feasibility of expanded, easier to collect sample types, such as nasal swabs and saliva. At the community level, it will also be important to characterize which sample types are acceptable to healthcare workers and patients in terms of the perceived safety of sample collection and willingness of patients to provide the type of sample. Work may be required to understand how to reassure healthcare workers and patients about the safety of nasopharyngeal swabs, as misinformation about their safety has been noted.

DIAGNOSTIC ALGORITHMS

Findings from the previous two research topics can help to inform the placement of Ag RDTs in diagnostic algorithms, along with programmatic considerations. Specific questions are whether a positive Ag-RDT is sufficient for diagnosis of COVID-19 or whether confirmation using molecular testing (PCR) is required. Understanding the predictive value of Ag-RDTs is critical for interpreting Ag-RDT results. Research is required to ascertain whether the positive predictive value (PPV) of Ag-RDTs can be improved by testing two Ag-RDTs in series and how much the PPV can be improved when Ag-RDT positive results are confirmed by PCR. A practical question is whether molecular testing using PCR can be run off the same Ag-RDT sample, which may make reflex testing more feasible. Connected to programmatic considerations are questions related to the tolerance and consequences of false-positive or false-negative results in different settings (e.g., at ports of entry), which can then be modelled.

BIOSAFETY

Delivery of COVID-19 testing services may require task-shifting, with less specialized healthcare workers taking on Ag-RDT testing, particularly in low-resource settings. Training needs should be established for healthcare workers who may not previously have encountered the biosafety requirements needed for SARS-CoV-2 testing. A key question in determining Ag-RDT biosafety requirements is whether the test buffer inactivates virus in the specimen, and if so, to what degree and over what time period. The biosafety requirements for different specimen types will also need to be established if different sample types will be used with Ag-RDTs.

TRAINING

Which healthcare worker cadres can safely, accurately and feasibly perform Ag-RDT testing will need to be determined; training will be essential to maximize the accuracy of Ag-RDTs. As task-shifting may be used to meet COVID-19 testing demands, it will be important to acknowledge that testers may not be professionally trained. Therefore, the training needs for different healthcare worker cadres will need to be determined. Inputs from those with experience of implementing other RDTs would be valuable, especially insights into factors that may otherwise be overlooked. The creation of a community of practice could help to promote rapid knowledge sharing and following of best practice for testing with Ag-RDTs.

QUALITY CONTROL

Quality control is of particular importance for Ag-RDTs, especially for the current-generation tests that have lower accuracy than molecular testing. Research is required to determine the invalid rates between different brands of Ag-RDTs, across different end-user cadres and across different use settings. Well-organized training on quality control and supervision will be essential to ensure the quality of Ag-RDT testing upon implementation. Questions were also noted about external quality assurance for Ag-RDTs and the impact of storage conditions and exposure to sunlight on performance.

TRANSMISSION

Related to performance is whether Ag-RDTs are accurate enough to detect those individuals most likely to transmit. It may therefore be important to compare transmission rates of individuals who test Ag-RDT positive (and PCR positive) versus those who test Ag-RDT negative, but PCR positive. It was noted that modelling might be useful for this research question once the viral load thresholds for Ag-RDT positivity are more clearly understood and the correlation between viral load and transmissibility is better established.

The full list of prioritized technical research questions can be found in Appendix 1.

B. PROGRAMMATIC RESEARCH

Programmatic research on Ag-RDTs is essential to guide recommendations on the optimal use of Ag-RDTs across use cases and in the context of overall healthcare services. It helps to guide approaches in real-world settings to support the uptake of Ag-RDTs, and to develop strategies to establish the community and structural supports needed to mitigate the effects of the COVID-19 pandemic. Note that the research questions described relate to the current Ag-RDTs; next-generation Ag-RDTs with higher sensitivity and specificity may have discrete research requirements.

HARMS/BENEFITS OF FALSE NEGATIVES AND FALSE POSITIVES

Current Ag-RDTs have a sensitivity of around 80%; therefore, the risk of false-negative results is a concern. Early studies have suggested that false-negative results are commonly associated with people with low SARS-CoV-2 viral loads who are less likely to transmit disease; however, confirmatory studies are needed to fully assess this risk. Additionally, research is recommended to assess viral load distributions and the timing of peak viral load in asymptomatic children, as it is possible that these may differ from the distribution/ timing in asymptomatic adults.

Although the specificity of the current Ag-RDTs is reasonably high, the potential impact of false positives should also be evaluated to determine whether confirmatory testing should be recommended for positive Ag-RDT results across different use cases. Analyses of the impact of both false negatives and false positives should take into account potential social harms and benefits to patients, and address clinical concerns.

IMPACT OF TURNAROUND TIMES ON OVERALL CASE DETECTION RATES

Current evidence suggests that test sensitivity may be secondary to turnaround time for effective COVID-19 surveillance.[2] Further research on the trade-off between fast turnaround time with lower performance versus slow turnaround time with higher performance across different use cases will be critical to informing the optimal use of Ag-RDTs. Additionally, evidence to demonstrate whether the convenience of Ag-RDT tests leads to an overall increase in case detection rates would be informative.

2. Larremore DB, Wilder B, Lester E, Shehata S, Burke JM, Hay JA, et al. Test sensitivity is secondary to frequency and turnaround time for COVID-19 surveillance. medRxiv. 2020:20136309. doi: 10.1101/2020.06.22.20136309. https://www.medrxiv.org/content/10.1101/2020.06.22.20136309v3

USE CASES

Triage of symptomatic people

Although the sensitivity of PCR testing is high, false negatives can still occur, with subsequent impact on disease control and management. Research is needed to determine the value of using Ag-RDTs as confirmatory tests in people with negative PCR test results who exhibit other clinical symptoms (e.g., chest radiography results consistent with COVID 19 infection). The value of Ag-RDTs in this setting may depend on whether the test can detect infection for a longer period of time than PCR (as has been shown in the case of malaria RDTs). Further research on the accuracy of Ag-RDTs across the course of disease is therefore recommended.

Settings in which PCR testing is not available

Achieving acceptable turnaround times for COVID-19 PCR tests has proved challenging in both high-income countries and LMICs. The value of Ag-RDTs in settings with limited or no molecular testing should be investigated, particularly in the context of outbreak detection.

Contact tracing, vulnerable populations and common transmission settings

Contact tracing will be an important use for Ag-RDTs in LMICs. Therefore, research on the risks and benefits of using Ag-RDTs for this purpose will be critical for the effective use of these tests. Ag RDTs may also be of value for priority testing of high-risk and vulnerable people (and their carers) in communities, and in areas of gathering such as workplaces, schools and border crossings. Evidence on the efficacy of Ag-RDTs in these settings will be fundamental to developing recommendations on Ag-RDTs. In particular, the specific public health actions to accompany positive results in each use case should be defined, given the potential for false positives.

Current WHO recommendations state that Ag-RDTs are not appropriate for use in areas with low disease prevalence. However, due to low overall testing rates, the prevalence of COVID 19 in many LMICs is unknown. Data to inform guidance on the use of Ag-RDTs in settings with unknown prevalence are required.

Diagnostic algorithms

It is highly likely that Ag-RDTs will be used as part of diagnostic algorithms incorporating multiple tests. Research is needed to determine where Ag-RDTs might best sit within these diagnostic algorithms. In particular, the value of repeat testing with Ag-RDTs in people with an initial negative result (e.g., next-day testing) should be determined. Additionally, the impact of any multiple-test algorithm on positive and negative predictive values should be assessed in order to allow flexibility in adaptation to setting and disease prevalence.

IMPLEMENTATION AND USER FACTORS

Implementation of Ag-RDTs

Care must be taken to ensure that the implementation of Ag-RDTs is carried out effectively and leverages the platforms for delivery that exist within healthcare systems. It will be important to determine which cadres of healthcare workers can perform Ag-RDTs, including at the community level. Investigation of the conditions that may facilitate the continuity of differential diagnostics for respiratory diseases is recommended. Furthermore, the benefits of integrating COVID-19 testing with other services, such as tuberculosis services or platforms for HIV testing services (HTS), should be explored.

Ag-RDTs that can utilize alternative sample types, such as oral fluids, may have the potential to relieve the burden on healthcare workers by reducing the complexity of specimen collection and possibly enabling community health workers and non-healthcare personnel to perform tests outside of healthcare facilities. This represents a key area for further research and development. Evidence on the feasibility of self-collection and self-testing approaches with Ag-RDTs will also be key to understanding how best to address healthcare burden. Approaches to address considerations related to training and biosafety for community-level users and self-testing will be essential to the success of such strategies. The impact of diagnostic illiteracy and educational/communication strategies on the interpretation of results should also be considered, given that positive and negative predictive values may change with fluctuations in prevalence in a setting or population.

End-user preferences and healthcare-seeking behaviour

There is the potential for Ag-RDTs to have a positive impact on the healthcare-seeking behaviour of end-users. This should be taken into account when assessing the overall risk–benefit profile of these tests. For example, the availability of Ag-RDTs may help to create safe spaces within healthcare facilities, providing reassurance to people presenting to care with other conditions such as tuberculosis and HIV. Availability of Ag-RDTs in schools could enable teachers and parents to feel comfortable re-opening schools. These and other uses of Ag-RDTs to improve healthcare-seeking behaviour should be explored.

Engaging the community in seeking and using COVID-19 testing services will be important to ensure equitable access. Investigations into the role of community-based organizations in increasing the demand for Ag-RDTs and acceptability of these tests among both patients and healthcare workers will be required in order to establish the optimal approaches to engagement.

The full list of programmatic research questions that arose from the discussion can be found in .

C. MODELLING

Modelling has an important role in research agendas for SARS-CoV-2 Ag-RDTs. Modelling can help to evaluate specific use cases (e.g., through cost-effectiveness analyses) and scope out opportunities for additional use cases, for example, by determining which factors are needed to screen at-risk population groups and the value of collecting different types of data. As there is no "one-size-fits-all" approach for Ag-RDTs, more needs to be known about the exact use cases for Ag-RDTs in terms of their settings, the population to be tested and the consequences of not using Ag-RDTs in those settings.

As there is profound heterogeneity between settings, understanding the local context is particularly important for modelling. For example, the use of Ag-RDTs at ports of entry for island nations represents a substantially different use scenario compared to the use of Ag-RDTs in healthcare facilities. A key question is how likely the population is to comply with public health measures (e.g., self-quarantine) and how compliance varies by sub-population (e.g., universities, care homes, healthcare workers). It will also be important to know the phase of the epidemic and strategies employed against COVID-19 to determine whether the intended use of Ag-RDTs will make a difference in that setting.

PERFORMANCE

Information about the performance of the test is essential for accurate modelling in terms of how performance varies by time, viral load, age and severity of disease. Key questions also include the total sample size needed to ensure acceptable accuracy, how this varies with prevalence or point in the epidemic, and the relationship between viral load and onward transmission. The outputs of technical research on the types of specimens suitable for use with Ag-RDTs will be important to determine the cadres of staff that can implement testing. This knowledge will feed into modelling work on feasibility and demand.

HEALTH IMPACT

To understand the health impact of Ag-RDTs, research questions will need to address the potential health impact or risk of Ag-RDT use in various use cases (e.g., diagnosis, screening or surveillance), sub-populations (e.g., universities, care homes, healthcare workers) and demographic groups (e.g., children, young adults and the elderly). The necessary frequency of screening to ensure a positive health impact in select populations (e.g., high-risk, healthcare workers) was also raised. Additionally, further research is required to understand the role of Ag-RDTs within a larger testing algorithm involving molecular/PCR testing.

ECONOMICS/COST

A priority question is the cost-effectiveness of various algorithms involving Ag-RDTs and molecular testing, and whether this varies by use case (e.g., diagnosis, screening or surveillance).

DEMAND

In terms of the demand for Ag-RDTs, research is needed to understand how the availability and location of tests affect demand and uptake. Location and distribution were also cited as important for understanding the potential impact on local healthcare facilities (i.e., impact on patient volumes). Finally, the impact of introducing Ag-RDTs on the use and demand for molecular testing will also need to be characterized.

It was noted that partial information is available to provide initial guidance on answers to most of the questions identified in this group, but further information is required to fully address the topics in question.

The full list of prioritized modelling research questions can be found in Appendix 3.

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SECTION 4. NEXT STEPS TO ADVANCE THE Ag-RDT RESEARCH AGENDA

WHO FUNDING FOR MONITORED IMPLEMENTATION OF Ag-RDTs

WHO has launched a monitored implementation project to assess the field performance, feasibility, acceptability and impact of SARS-CoV-2 Ag-RDTs in variable use settings in LMICs. The team is looking to engage sites or countries that meet the implementation scenarios described below.

Scenarios for implementation

- Case management in settings with access to confirmatory NAAT testing

- Case management in settings with no access to confirmatory NAAT testing

- Surveillance or primary investigation of outbreaks or clusters

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The project aims to collect information about the sensitivity of Ag-RDTs and operational characteristics, including how well the tests perform in real-world settings, and data on user experience, competency and knowledge retention. Studies on the cost-effectiveness of Ag RDTs in different use settings are also welcome. Proposals are invited from a broad range of stakeholders including ministries of health, technical partners, academic partners and nongovernmental organizations, with funding available for up to five sites. Chosen sites will receive

technical support, up to US$ 200 000 and 200 000 Ag-RDTs. An expression of interest and request for proposals has been shared, with the intention of dispersing funds to sites by the end of 2020. The project is anticipated to last for six to nine months.

PLANS FOR WORKING TOGETHER IN THE FUTURE

It was acknowledged by the group that this forum should be the first of multiple discussions surrounding the research agenda for Ag-RDTs, as there is a need for coordination and continued engagement in order to efficiently and expediently enhance the existing evidence base.

In terms of future engagement and discussions, it was suggested that separate groups could also be formed per research topic and allowed to decide their own internal structures.

It was noted that evidence from the group needs to be linked to policy in order to ensure that information is used to form evidence-based policy recommendations. Sharing research with countries was recommended in order to provide countries with an opportunity to provide feedback and align their national guidance with the evidence produced by this group.

A priority for the group will be to determine whether any other groups are undertaking the research covered in this agenda. If not, plans should be made to deploy funds and resources to ensure that the research agenda is actioned in a timely manner.

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APPENDICES

Appendix 1. Priority technical research discussion and knowledge gaps identified

Focal area	Refined / specific research question	Data inputs required	Notes and considerations
Performance	• What is the performance of Ag-RDTs in different intended use settings (e.g., ports of entry) and patient populations (e.g., asymptomatic vs. symptomatic patients)? • Specific questions: Do readers improve performance? Value of visual aids? Interpretation of faint bands?	• Paired PCR and Ag-RDT results from different settings and in symptomatic and asymptomatic individuals • Positivity rate in the population	• **Countries that have started to generate this information for different settings are encouraged to share data with WHO so that this evidence can be considered to support policy.** • Need for empirical data in different settings was emphasized. • Understanding performance in asymptomatic patients is particularly important, as early detection is critical.
Sample types	• What is the accuracy of different sample types (e.g., NP, AN, saliva)?	• Paired PCR and Ag-RDT results for different sample types • Survey of healthcare worker and patient concerns about COVID-19 testing	• Which sample types are feasible/acceptable to healthcare workers and patients? (Link to programmatic)
Diagnostic algorithms	• How should Ag-RDTs be included in diagnostic algorithms, e.g., is a positive test sufficient or is confirmation using PCR required? (How does this vary by setting?) • Does testing two Ag-RDTs in series improve the PPV? Does testing Ag-RDT then PCR improve the PPV? • Can PCR be run off the same Ag-RDT sample (may make reflex testing more feasible)?	• Data from previous two questions can inform use cases	• Will form part of programmatic considerations as well • Link to programmatic/modelling question – What is the tolerance/consequence of false positives or false negatives in given settings?
Biosafety	• Do Ag-RDT buffers inactivate the virus? If so, to what degree (e.g., pfu/ml) and over what time period? • How does sample type affect biosafety measures?	• Data from Ag-RDT use with different sample viral levels • Risk of aerosolization with different sample types	• Some data on the inactivation of virus by Ag-RDT buffer noted on call • Communication around safety of NP swabs is part of communication and community engagement as well as training.
Training	• Which healthcare worker cadres can safely, accurately and feasibly perform Ag-RDT testing?	• Minimum requirements for healthcare workers conducting SARS-CoV-2 Ag-RDT testing • Recommended training materials	• What are the training needs for different cadres? • Inputs from those with experience of implementing other RDTs would be valuable. For example, it was noted that healthcare worker eyesight can be an issue in reading RDTs. • Suggested creation of community of practice

Focal area	Refined / specific research question	Data inputs required	Notes and considerations
Quality control	• What are the observed invalid rates, particularly between different brands of Ag-RDTs? Across different end-user cadres? Across different use settings?	• Quality control data from different brands of Ag-RDTs available for procurement	
Transmission	• What are the observed rates of onward transmission of NAAT+/RDT- vs. NAAT+/RDT+?	• Contact tracing with testing of contacts with NAAT and Ag-RDT	• Can this be modelled? If sufficient descriptive data on population-level viral load/cycle threshold are available and the accuracy of tests is known according to viral load/cycle threshold, does transmission need to be studied?

Appendix 2. Priority programmatic research discussion and knowledge gaps identified

Focal area	Refined / specific research question	Data inputs required
Risk–benefit analyses	• **What are the harms/benefits of false positives/negatives with current Ag-RDTs with low specificity/sensitivity?** • Can the use of Ag-RDTs increase overall case detection rates, testing rates and turnaround times across different settings and populations?	• Social and clinical harms • Optimal public health actions to follow a positive or negative result in each use case • Importance of turnaround time versus performance
Use cases	• **How should Ag-RDTs be used to triage patients who are symptomatic?** • **Do Ag-RDTs have adequate performance to be used as a diagnostic when PCR is unavailable (e.g., remote settings, overwhelmed laboratories)?** • **What is the value of Ag-RDTs for a) contact tracing; b) high-risk occupations/vulnerable populations; c) settings outside of healthcare posts (e.g., schools)?** • Should we consider multiple-test algorithms or the use of additional tools for asymptomatic populations, and how might this change the positive and negative predictive value? • How does local policy and communication impact update/demand?	• Data on the use of Ag-RDTs for symptomatic patients with a negative PCR test result • Data on extended use of Ag-RDTs, e.g., up to 10 days after symptom onset • Data on retesting with Ag-RDTs after initial negative result (e.g., next day) • Further evidence on correlation between viral load, Ag-RDT result and infectiousness • Data to inform guidance on the use of Ag-RDTs when prevalence of COVID-19 in a population is unknown
Users	• Which healthcare worker cadres will perform Ag-RDT tests? • What are the optimal approaches to implementing Ag-RDT testing without increasing the burden on health facilities? • How can end-user values and preferences be taken into account to create safe spaces for patients to present for care? • Can self-collection and self-testing contribute to the well-being of healthcare workers and their families?	• Effect of unavailability of definitive treatment on health-seeking behaviour and testing procedures • Impact of community health workers or self-testing on access • Potential impact of alternative sample types, e.g., saliva, on access • Potential for integration with other services, e.g., tuberculosis • Qualitative data on healthcare worker and community engagement with Ag RDTs • Impact of diagnostic illiteracy / educational strategies on result interpretation in light of changing prevalence within a population

Note: priority questions are noted in bold

Appendix 3. Priority modelling research discussion and knowledge gaps identified

Focal area	Refined / specific research question
Epidemiological context	• What sub-populations or settings (e.g., universities, care homes, healthcare, etc.) have the highest risk of transmission?
Performance	• **What is the total sample size (N) needed to ensure acceptable accuracy (e.g., sensitivity and specificity) and how does this vary with underlying prevalence or "point in the epidemic curve"?** • What is the optimal use of Ag-RDTs as a tool to reduce transmission in an algorithm including NAAT?
Health impact	• What is the potential health/public health/economic impact of correctly diagnosing someone, and what are the potential risks of misdiagnosing someone across settings or among different populations, e.g., high-risk occupations/vulnerable populations, settings outside of healthcare posts (e.g., schools, borders), etc.? • What is the necessary frequency of screening to ensure health impact for high-risk groups (e.g., healthcare workers)? • What is the optimal use or algorithm of Ag-RDTs in differential diagnosis?
Economics/cost	• **What is the cost-effectiveness of various algorithms involving Ag-RDTs and NAAT? Does this vary by use case (e.g., diagnosis vs. screening vs. surveillance)?**
Demand	• How does availability of tests impact hospital capacity/flow of patients? • How does testing site setting (e.g., hospitals, clinic, pharmacy, home) impact expected demand? • How does introduction of Ag-RDTs impact the use of/demand for NAAT?

Note: priority questions are noted in bold