EUnetHTA Joint Action 3 2016-2020

Rapid Collaborative Review on the role of antibody tests for novel coronavirus SARS-CoV-2 in the management of the current pandemic

Project ID: ***RCR 01***

Project description and planning

Regione Emilia-Romagna

Institute for Quality and Efficiency in Health Care

This report is part of the project / joint action '724130 / EUnetHTA JA3' which has received funding from the European Union's Health Programme (2014-2020)

Version Log

Version number	Date	Modification	Reason for the modification
V1	17/04/2020	Preliminary draft of Project Plan submitted to EUnetHTA Task Force on SARS-CoV-2	
V2	27/04/2020	Draft to be discussed between authors and co-author	
V3	05/05/2020	Draft for kick-off meeting	
V4	11/05/2020	Final draft	
V5	12/05/2020	Project Plan published	

CONTENTS

List of tables

List of abbreviations

CE	Conformité Européenne
CLIA	Chemiluminescenceimmunoassay
COVID-19	Coronavirus disease 2019
ECDC	European Centre for Disease Prevention and Control
ELISA	enzyme-linked immunosorbent assay
EUnetHTA	European Network for Health Technology Assessment
FIA	Fluoroimmnoassay
HAS	Haute Autorité de Santé (France)
HCW	health care worker
HIQA	Health Information and Quality Authority (Ireland)
HTA	health technology assessment
ICTRP	International Clinical Trials Registry Platform
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, Insitute for Quality and Efficiency in Health Care
IgA	Immunglobulin A
IgG	Immunglobulin G
IgM	Immunglobulin M
IVD	In-Vitro Diagnostic
JA	Joint Action
JRC	Joint Research Centre
LFA	lateral flow assay
MERS	Middle East respiratory syndrome
N/A	not applicable
NAAT	nucleic acid amplification test
NIPH	Norwegian Institute of Public Health
nr	not reported
OECD	Organisation for Economic Co-operation and Development
PCR	Polymerase chain reaction
PoC	point of care
PROSPERO	International Prospective Register of Systematic Reviews
qPCR	quantitative polymerase chain reaction
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
RDT	rapid diagnostic test
REA	Relative Effectiveness Assessment
RER	Regione Emilia-Romagna
ROC	Receiver Operating Characteristics Curve
RODT	Rapid Diagnostic Orientation Test
RT-PCR	reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SR	Systematic review
THL	Institute for Health and Welfare (Finland)
UK	United Kingdom
WHO	World Health Organization
WP	Working Package

1 Project organisation

1.1 Participants

Table 1-1: Project participants

	Agency	Role in the project	Country	Distribution of work
Assessment team				
1.	Regione Emilia-Romagna - RER	Authors	Italy	All process steps of assessment and writing draft of report
2.	Institute for Quality and Efficiency in Health Care - IQWiG	Co-Author	Germany	All process steps of assessment and review and comment on all parts of the report
3.	Institute for Quality and Efficiency in Health Care – IQWiG Regione Emilia-Romagna - RER	Information Specialist	Germany Italy	Review of information retrieval; reporting information retrieval check in the assessment report
4.	Institute for Quality and Efficiency in Health Care – IQWiG	Statisticians	Germany	Expert statistical support for authors
5.	Health Information and Quality Authority- HIQA	Dedicated Reviewer	Ireland	Review and comment on all drafts
6.	Austrian Institute for Health Technology Assessment - AIHTA	Project Manager	Austria	Coordination between involved parties throughout the assessment period

1.2 Milestones and Deliverables

Because the topic of this report is of utmost urgent importance for public health, the usual steps and timelines are reduced to an acceptable minimum. Importantly, the project will not include any formal exchange with patient representatives, clinical experts, or manufacturers.

Table 1-2: Milestone and Deliverables

Milestones/Deliverables	Start date	End date	Time*
Project duration	**20-Apr-2020**	**18-June-2020**	**41 days**
Scoping phase	20-Apr-2020	05-May-2020	8 days
Milestone 1: Kick-off meeting		**05-May-2020**	
Finalizing project plan	05-May-2020	12-May-2020	2 days
Quality checks & editing of project plan	06-May-	11-May-	4 days

Milestones/Deliverables	Start date	End date	Time*
	2020	2020	
Milestone 2: Publication of project plan		**12-May-2020**	
Literature searches	06-May-2020	22-May-2020	4 + 1 days
Literature screening	11-May-2020	26-May-2020	4 + 2 days
Data extraction: Study results	14-May-2020	27-May-2020	9 days
Data extraction: Risk of bias	14-May-2020	27-May-2020	9 days
Milestone 3: Data extraction complete		**27-May-2020**	
Statistical analyses & meta-analyses	26-May-2020	28-May-2020	3 days
Update table on national reports	26-May-2020	28-May-2020	3 days
Writing first draft rapid assessment	29-May-2020	05-June-2020	4 days
Milestone 4: First version complete		**05-June-2020**	
Internal review of report	08-June-2020	09-June-2020	2 days
Finalizing report	10-June -2020	17-June -2020	2 day
Quality checks & editing	12-June -2020	17-June-2020	4 days
Milestone 5: Publication of report		**18-June-2020**	

* Time is given in working days

The quickly evolving evidence on the topic may require one or more short-term updates of the assessment. If required, an update should be prepared within about 10 working days (6 for assessment and writing, 3 for reviewing, 1 for finalizing the report).

2 Project Outline

2.1 Project Background

Diagnostic tests for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), are currently divided into two main categories: those that detect the presence of SARS-CoV-2 and are primarily used to diagnose an active COVID-19 infection, and those that detect the presence of antibodies against SARS-CoV-2. Antibody tests could be used to support the diagnosis of COVID-19 infection and/or to identify past exposure to SARS-CoV-2.

In a document published on the 16th of April (1), the Organisation for Economic Co-operation and Development (OECD) identifies three main goals that testing strategies could achieve: 1) suppressing

the resurgence of local outbreaks; 2) identifying people who have developed some form of immunity and can safely return to work; and 3) gaining knowledge on the evolution of the epidemic, including on when a threshold for herd immunity has been reached. The deployment of validated antibody tests with demonstrated clinical performance is identified as a potential strategy for addressing the second and third goal.

This rapid review will address the research questions related to the role of antibody tests in the management of the current COVID-19 pandemic and will ultimately lead to a EUnetHTA Relative Effectiveness Assessment (REA) of antibody tests for SARS-CoV-2. The work is part of the project undertaken by the EUnetHTA task force on SARS-CoV-2, which has identified the following health policy priority questions:

- how to best screen asymptomatic subjects and monitor close contacts in order to promptly detect infections among the general population and health care workers;

- how to best test patients with clinical manifestations of SARS-CoV-2 in order to confirm a diagnosis of COVID-19;

- which tests should be used to monitor the course of disease and inform decisions on treatment, hospitalisation etc. and to determine viral clearance of recovered patients in order to allow re-entry into the community.

Data on confirmed cases of COVID-19 are systematically collected and communicated in daily updated reports. The data on confirmed cases are based on all subjects diagnosed with COVID-19 via real-time reverse-transcription polymerase chain reaction (RT-PCR) swab testing. Testing policies have varied during the outbreak of the pandemic. Following the recommendations by the World Health Organisation (WHO) (2) the initial approach has been to test those presenting with signs and symptoms for the disease and history of travelling or personal contact to persons with known or suspected SARS-CoV-2 infection, followed by more extensive testing also on asymptomatic or pauci-symptomatic subjects. As currently recommended by the WHO, routine confirmation of cases of COVID-19 in suspected subjects is based on detection of unique sequences of virus RNA by nucleic acid amplification tests (NAAT), such as RT-PCR, with confirmation by nucleic acid sequencing when necessary or feasible. Preliminary reports on sensitivity have ranged from 27% to 98%, while specificity is claimed to be very high (3). The laboratory process is quite complex and results are generally available within 24 hours, although testing large numbers of subjects is posing a great strain on facilities. Rapid molecular tests using different processes (i.e. reverse transcription-loop mediated isothermal amplification), as well as commercial kits are being developed and marketed in order to increase capacity and speed up processing and the delivery of results.

A large proportion of the general population is currently not undergoing any kind of testing, potentially meaning a serious underestimation of cases and thus compromising the potential effects of lockdown policies. The fast spread of COVID-19 in areas with high rates of hospitalisation has also raised the issue of how health workers are contributing to the spread of the disease within hospitals and in the community. Early detection of infected health workers could lead to their prompt isolation and counteract transmission, while evidence of full recovery could allow safe return to work.

A testing strategy capable of reliably identifying subjects who have been (knowingly or unknowingly) infected and successfully recovered from the infection would allow to obtain a more accurate estimate of the prevalence of the disease and increase knowledge on how widely the virus has spread and circulated among the population.

It is hypothesized that antibody tests could identify subjects with previous SARS-CoV-2 infections as well as - if the antibody test is used at the right time (e.g. after seroconversion) - detect current infections irrespective of symptoms. Should this be confirmed, antibody testing could prove valuable in providing more accurate estimates of prevalence, in detecting symptomatic and asymptomatic subjects with SARS-CoV-2 infections and in investigating immunity.

2.2 What we know so far on antibody testing for SARS-Cov-2/COVID-19

Antibody tests for COVID-19 targeting immunoglobulins (IgM, IgG and IgA) are currently in development, although many devices (mainly enzyme-linked immunosorbent assays [ELISAs] and immunochromatographic lateral flow assays [LFAs]) are already being marketed. LFAs do not require sophisticated laboratory procedures or equipment and claim to provide results in a very short time; however, due to their lack of reliability, the WHO currently recommends the use of such rapid point of care tests only in research settings (4). Preliminary research has been carried out to investigate the role of IgA, IgM and IgG to identify false negatives from molecular testing. Initial data on the time of detection of antibodies are still exploratory, with some studies reporting detection after 5 to 8 days from onset of disease and others reporting seroconversion after a median time of 10 to 14 days. The presence of antibodies has been found to increase sharply over time, while the viral load in the respiratory tract decreases (5). More results from primary studies are being reported as experiences with the use of antibody tests are increasing.

To date, a number of rapid reviews on the stage of development of antibody testing for SARS-Cov-2/COVID-19 have been carried out by research centres and national health technology assessment (HTA) bodies. After searching the literature and checking official websites of institutions and HTA bodies, five rapid reviews were retrieved, providing both descriptive and quantitative results. The first is a working document published on the 16th of April by the expert group from the Joint Research Centre (JRC) set up by the European Commission (6). Following a review of the publicly available information from manufacturers and performance assessment studies on test methods and commercially available devices, the document summarises results on the performance of available tests and proposes performance criteria for the different type of SARS-CoV-2 test methods and devices. It was out of the scope of the working document to identify the intended use of the different test methods and to assess their diagnostic accuracy and efficacy. The Norwegian Institute of Public Health has published a rapid review on immunity after SARS-CoV-2 infection, focusing on the role of antibodies and sero-conversion (7), while on the 22nd of April the Irish Health Information and Quality Authority provided a rapid HTA of diagnostic approaches for the detection of SARS-CoV-2 infection (8). On the 23rd of April, the Welsh HTA body released its report on the clinical effectiveness of tests for SARS-Cov-2 (3). The French Haute Autorité de Santé published a report on the 1st of May evaluating the indications for serological tests (9). This includes a non-systematic review of studies on seroconversion, while the other four reports include a systematic review of studies or documents reporting on the diagnostic performance and effectiveness of antibody tests. All five reports conclude that the available research on diagnostic performance, diagnostic accuracy and diagnostic role of antibody tests is still at a premature stage and that evidence from larger and well-conducted validation and accuracy studies is required to make informed decisions.

Table 2-1 below provides a summary of the outputs from the five reports, based on the extraction of the information related solely to antibody tests.

Table 2-1: Overview of available reviews – extraction of information on antibody tests for SARS-CoV-2/COVID-19

Publisher / date	European Commission (6) 16/04/2020	NIPHNO (Norway) (7) April 2020	HIQA (EIRE) (8) 17/04/2020	Health Technology Wales (3) 23/04/2020	HAS (9)
Title	Current performance of COVID-19 test methods and devices and proposed performance criteria	COVID-19 EPIDEMIC: Immunity after SARS-COV-2 infection – a rapid review	Rapid HTA of alternative diagnos-tic testing for coronavirus 2 (SARS-CoV-2)	The clinical effectiveness of tests to detect the presence of SARS-CoV-2 virus, and antibodies to SARS-CoV-2, to inform COVID-19 diagnosis	Place de tests sérologiques dans la stratégie de prise en charge de la maladie COVID-19
Objective	To collect and review publicly available information from manufacturers and performance assessment studies	To provide a rapid summary of the available research on immunity after SARS-CoV-2 infection	To investigate the potential usefulness of alternative diagnostic tests for the detection of SARS-Cov-2	To identify and summaries evidence addressing the question on clinical effectiveness and/or economic impact of tests that detect the presence of antibodies to the SARS-CoV-2 virus to inform diagnosis of COVID-19	Assessment of the indications for serological tests detecting antibodies to SARS-CoV-2
N. of included studies **Date of search**	27 primary studies 06/04/2020	17 primary studies Not reported	Information from 13 manufacturers 27/03/2020	9 primary studies 14/04/2020	9 primary studies on sero-conversion Not reported
Target population **Target condition**	Not specified	Subjects recovered after infection with SARS-COV-2 - Immunity after SARS-COV-2 infection - Seroconversion rate after SARS-COV-2 infection - Severity of disease and seroconversion - Transmission of antibodies from mothers to foetus	Not specified	People with suspected on-going or recent SARS-CoV-2 infection	Not specified
Antibody tests	Antibody tests for detection of immunological status: 54 DM targeting IgM, IgG; 1 DM targeting IgA	Serologic tests that identify antibodies (IgA, IgM and IgG) to SARS-COV-2	Antibody-based methods to detect the presence of IgG and IgM antibodies specific to SARS-CoV-2 in clinical samples	Any test designed to detect antibodies to SARS-CoV-2	Antibody tests (IgM, IgG)
Summary of results	Very limited information on **technical performance** (limit of detection, analytical specificity, cross reactivity) Efficiency, robustness, precision and turn-	No data on **immunity** found **Seroconversion rate and timing**: large variation across studies 1 to 7 days: IgM 11.1% - 60%; IgG:3.6% - 50% 8 to 14 days: IgM	Data from 8 manufacturers report values for **sensitivity** Range 85% to 100% and **specificity** Range 96% to 100% *NB: lack of confirmation with reference standard*	All studies tested hospitalised, symptomatic patients with strong clinical suspicion of COVID-19 **Sensitivity** ranged from 18.4% to 96.1% **Specificity** ranged from 90.9% to 100%	Seroconversion is accompanied by steady decline in viral load, but not removal of virus. Detection of IgM and/or IgG is optimal in all patients from day 15. About 50% of

Publisher / date	European Commission (6) 16/04/2020	NIPHNO (Norway) (7) April 2020	HIQA (EIRE) (8) 17/04/2020	Health Technology Wales (3) 23/04/2020	HAS (9)
	around time not reported for majority of devices. Tests do not require complex laboratory equipment	53.8%-86.7%; IgG 57.1%-76.9% >14 days: IgM 74.2%-96.7%; IgG 93.3% - 100% *N.B. non symptomatic patients not included in any of the studies* **severity of disease and seroconversion** : very limited data suggesting no influence seroconversion **Transmission during pregnancy**: insufficient data	*in majority of reports* Scarce information on diagnostic performance Turnaround time claimed to be from 2 to 20 minutes	*N.B: use of RT-PCR tests as reference standard challenging due to validation issues*. Timing of testing relative to symptom onset appears to influence test results	patients have a seroconversion between day 7 and 11 after onset of symptoms. Less severe/ asymptomatic patients seem to reach a peak at day 14, while more severe patients appear to develop antibodies between 5-6 days from onset of symptoms. No sufficient data to assess immune response of infected patients.
Authors' conclusions	Almost complete lack of proper validation and standardisation among antibody targeting methods. Data on false negatives, false positives and cross-reactivity are practically never reported	Answering the question regarding immunity after primary infection must await well-conducted studies with larger sample sizes, using validated methods.	Contingent on the availability of accurate, validated tests, antibody tests could be used later in the clinical course of infection or following recovery to identify those who have been exposed to SARS-COV-2	At present, key gaps exist in the available evidence on antibody tests as method of informing COVID-19 diagnosis. No evidence found on patients with milder symptoms or from community/home settings. No evidence found on time taken to obtain test results, economic impact, influence on subsequent patient management	Serological tests can only be used to determine whether a person has produced antibodies in response to an infection with the virus, They are not recommended as part of the early diagnosis of infection and shall not be used to determine whether a person is contagious or not

2.3 International and national guidance/policies

Due to the lack of available knowledge on the validation and accuracy of antibody testing, these tests are currently not recommended for clinical use (10). The European Centre for Disease Prevention and Control (ECDC) recommends that serum samples are collected from patients and stored during the different phases of the disease so as to carry out studies on the validation of antibody tests and on seroconversion (11).

While antibody routine testing is not recommended, serum collection is also being recommended in Germany (12), while guidance to developers is being provided by France (13) and the UK (14) on the standards of diagnostic accuracy to be achieved for clinical use.
Should a shortage of molecular tests occur, the Spanish Ministry of Health's guidance on testing, issued on the 7th of April, considers antibody testing for symptomatic patients in order to enhance the diagnostic capacity of the health system. Due to the uncertainty surrounding the sensitivity of these tests, molecular testing is recommended in patients with symptoms of COVID-19 but with negative antibody results (15).

Some countries have undertaken research programmes that introduce antibody testing in a controlled manner in order to gain better insight on their role. In Finland, the Finnish Institute for Health and Welfare (THL) has launched a seroprevalence study in a random population sample covering all age groups, and it is inviting Finnish citizens to participate in a study assessing the spread of the new coronavirus in the population. The study will cover all age groups and will be implemented in cooperation with university hospitals (16). In Germany, a large-scale antibody test programme will be run in three types of samples: from blood donations, from areas with large outbreaks of the virus, and from the general population. The objective is to estimate how many asymptomatic cases have occurred and how many people have become immune to the infection (17). Through a call for tender (18) Italy has just announced, the imminent start of a cross-sectional study in a representative population sample of 150,000 citizens aimed at estimating population seroprevalence of IgG for SARS-CoV-2.

Preliminary data from these research programmes are expected towards the end of May / beginning of June 2020, and the overview of national policies will be updated during this rapid review.

2.4 Ongoing clinical research

Up to now, the diagnostic performance of antibody tests has mostly been evaluated in diagnostic case-control studies (19) where the selection of participants is based on the disease status. While diagnostic case-control studies offer the advantage of a more reliable reference test as control samples often come from healthy blood donors (with samples obtained before November 2019, i.e. before the SARS-CoV-2 outbreak), these studies are prone to bias (in particular spectrum bias) and often overestimate the diagnostic accuracy. Thus, evidence from cohort and cross-sectional studies, where the study population should be representative of the target population (e.g. general population or health workers), is required to evaluate the clinical performance of antibody tests in practice.
Table 2-2 lists ongoing studies (status: April 27th 2020). Out of these 16 potentially relevant ongoing studies, 14 are cohort and cross-sectional studies and only two are diagnostic case-control studies. This may indicate a change in the focus of clinical research towards investigating the role and reliability of antibody tests in clinical practice. It is expected that new studies will appear at an increasing rate of about 2 to 5 per week. Therefore, it is very likely that new insights can be gained by updating the current review regularly.

Table 2-2: Ongoing clinical studies investigating antibody tests in clinical practice

Study ID	Country	Study design	Population	Number of participants	Index test (ELISA, CLIA/ FIA, LFA, PoC, other)	Index test target	Reference test	Estimated study completion date
NCT04348864	US	cohort	Adults, with symptoms and PCR test result	100	PoC, immuno-diagnostic rapid (5-20 minute) test	IgM/IgG	PCR	Apr 21
NCT04360954	US	case-control	Adults: hospitalized patients, recovered patients, healthy humans	1000	PoC	nr	RT-PCR, ELISA	Oct 20
NCT04341142	France	cohort	Adults	400	serological tests	nr	PCR	Sep 20
NCT04351646	UK	cohort	Adults: hospitalized patients, HCW, lab staff	500	ELISA	IgM/IgG	RT-PCR	Apr 22
NCT04362267	France	cohort	HCW	150	serological test	nr	RT-PCR	Sep 20
NCT04326387	UK	cohort	16+, hospitalized symptomatic	200	serological test (PoC)	IgM/IgG	RT-PCR	Oct 21
NCT04318431	France	cohort	Children, asymptomatic	600	rapid serology	IgM/IgG	PCR	Jun 20

Study ID	Country	Study design	Population	Number of participants	Index test (ELISA, CLIA/ FIA, LFA, PoC, other)	Index test target	Reference test	Estimated study completion date
NCT04345315	Italy	cohort	Healthy individuals at high risk of infection (HCW & patients)	500	serological test	nr	rapid molecular test	Mar 22
NCT04356560	Denmark	cohort	Children/ Adults: HCW, symptomatic patients, patients undergoing surgery involving mucosa/upper airway	300	antibody tests	IgM/IgG	oro/nasopharyngeal swab test; PCR during follow-up	Dec 20
NCT04337996	France	cohort	Adults: patients suspected SARS-CoV-2	176	serological RODT	nr	Antigenic RODT, PCR	Okt 20
NCT04348214	Egypt	cohort	HCW	3000	serological tests	nr	RT-PCR	Dez 20
ChiCTR2000029870	China	cohort	Confirmed and suspected cases	nr	rapid diagnostic kit	IgM/IgG	Nucleic acid detection method	nr
Drks00021270	Germany	Cohort	HCW	800	Antibody test	NR	PCR	nr
NCT04355533	France	cohort	Children, adults	1920	RDT	Neutralisation test: S1	qPCR, neutralisation test	Jul 21
NCT04346186	Denmark	cohort	HCW, healthy blood donors	30000	PoC	IgM/IgG	ELISA	Aug 21
NCT04329546[a]	Switzerland	Cohort	Patients with COVID-19, household contacts	250	ELISA	IgG	RT-PCR	Mar 22

a: only subpopulation meets inclusion criteria (household contacts)
ELISA: as enzyme-linked immunosorbent assays; HCW: health care worker; IgG: immunglobulin G; IgM; Immunoglobulin M; nr: not reported; qPCR: Quantitative polymerase chain reaction; (RT-)PCR: (Reverse transcription) polymerase chain reaction; PoC: point of care; RDT: rapid diagnostic test; RODT: rapid diagnostic orientation test

2.5 Objectives

The objective is to collaboratively produce a structured and systematic rapid review of the available primary research on the diagnostic accuracy of antibody tests and on their use in different scenarios. This rapid review will address the following questions:

Whether and with which testing strategies antibodies tests can be reliably used for:

1. surveillance for early detection of new cases of SARS-CoV-2 infection in the general population and/or specific subpopulations;
2. measuring seroprevalence in communities;
3. diagnosis of SARS-CoV-2 infection in patients presenting symptoms suggestive of SARS-CoV-2 infection;
4. ruling out risk of transmission in patients who recovered from SARS-CoV-2 infection;
5. assessing protective immunity in subjects with past SARS-CoV-2 infection.

As highlighted in the previous sections of this Project Plan, a substantial body of evidence on the role of antibody tests is expected to develop and be available in the near future. This review will therefore be continuously updated as more evidence becomes available and it will ultimately lead to a Relative Effectiveness Assessment (REA) to inform decisions on the effective and safe use of antibody testing.

2.6 Project Method and Scope

2.6.1 Approach and Method

Table 2-3: Project approach and method

Project approach and method
The following studies will be searched for and included: Retrospective and prospective cohort and cross-sectional studies evaluating the diagnostic accuracy of antibody tests for the detection of COVID-19. In order to provide a comprehensive overview of the state of development of antibody testing, studies reporting on diagnostic performance and diagnostic case-control studies will also be searched for and presented. Only studies providing sufficient data to construct the '2×2' diagnostic table (true positive, false positive, true negative, and false negative) will be included. Studies investigating the use of antibody tests at different points in time after onset of symptoms will be eligible, provided separate data can be extracted for different times of onset of symptoms. Published peer-reviewed journal articles and non-peer-reviewed manuscript preprints will be included as well as assessment reports by national/international regulatory agencies. Studies on previous SARS coronavirus types and on Middle East respiratory syndrome (MERS) will be excluded. The quality of studies will be assessed following guidance from the Cochrane Screening and Diagnostic Test Methods Group, which is adapted from the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (Whiting 2011). The following four domains will be assessed for risk of bias: patient selection, index test, reference standard, and flow and timing. Applicability concerns will also be assessed for the first three domains. Primary analysis of diagnostic accuracy will be based on bivariate meta-analysis of sensitivity and specificity. If sufficient data for a bivariate meta-analysis are not available, univariate meta-analysis of sensitivity and specificity will be applied, The summary results will be interpreted with respect to the role in a diagnostic pathway, to differences in patient characteristics, and to characteristics of the respective index and reference tests. Diagnostic accuracy results will be put into the context of current testing approaches in Europe. If suitable, subgroup analyses will be used to assess variables that potentially affect test accuracy, such as overall study quality, sample selection, type of antibody test, time interval between infection/occurrence of symptoms and the diagnostic tests, time interval between index and reference test, or handling of uncertain reference test results (e.g. probable cases according to the WHO case definition).

Table 2-4: Plan for information retrieval

Information retrieval
A systematic information retrieval for relevant studies or documents is carried out to obtain comprehensive information. The following sources of information as well as search techniques are considered: **Main information sources** Bibliographic databases • PubMed A preliminary search indicated that there is limited additional literature available on COVID-19 in Embase and Central. Therefore, a search in these standard sources is omitted. Study registries • U.S. National Institutes of Health. ClinicalTrials.gov • World Health Organization. International Clinical Trials Registry Platform Search Portal **Further information sources and search techniques** To identify further relevant studies or documents, depending on the research question, further information sources are used and further search techniques are applied. • Checking reference lists of relevant systematic reviews (SRs) / HTAs • Searching preprint servers: Europe PMC • Queries to authors **Selection of relevant studies and documents** EndNote X9.2 is used for citation management. Study selection is performed in Covidence. All selection steps are performed by 2 persons independently of each other. Discrepancies are resolved by discussion.

Table 2-5: Plan for data extraction

Planned data extraction (see Data Extraction Tables)
Based on the guidance provided by Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (2020) (20), the following data will be extracted • Author and year of publication. • Study design, type of recruitment (prospective or retrospective). • Study population characteristics, including sample size and the clinical context in which the test was evaluated. • Definition of the reference standard. • IgA, IgM and IgG thresholds used and technical performance data, when available. • Information regarding quality assessment items of the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (assessment of methodological quality) (21). • Data to enable derivation of 2×2 tables of the number of true positives, false positives, false negatives, and true negatives.

2.6.2 Project Scope

The EUnetHTA Guidelines, notably the Methodology Guideline "Meta-analysis of diagnostic test accuracy studies", available at https://www.eunethta.eu/methodology-guidelines/ will be consulted throughout the assessment process.

Table 2-6: Project Scope: PICO (please see HTA Core Model® for rapid REA)

Description	Project Scope
Population	Depending on the research questions 1) to 5) defined in section 2.5), the population may include 1) individuals without known active or previous SARS-CoV-2 infection 2) general population 3) patients presenting symptoms suggestive of SARS-CoV-2 infection 4) patients who recovered from SARS-CoV-2 infection 5) individuals with known past SARS-CoV-2 infection
Target condition	• active or previous infection with SARS-CoV-2
Index tests	Antibody tests (IgM, IgG, IgA, combined or not combined) such as enzyme-linked immunosorbent assays (ELISAs) and immunochromatographic lateral flow assays (LFAs)
Reference Standard	Any appropriate testing strategy (including nucleic acid amplification tests (NAAT) or NAAT in combination with clinical findings or clinical follow up *N.B. limitations on the validation of NAAT current tests will be taken into account*
Outcomes	Sensitivity (95%CI) Specificity (95%CI) Area under the curve (AUC) from a receiver operating characteristics curve (ROC curve), Proportion of true-positive participants Proportion of false-positive participants Proportion of true–negative participants Proportion of false-negative participants Positive and negative predictive value (95%CI) Proportion of inconclusive test results
Study design	Retrospective and prospective cohort and cross-sectional studies Case-control studies are included for reporting

Table 2-7: Data extraction form – Characteristics of studies

Study ID, Author, year	
Characteristics of study	
Design	Study design Inclusion criteria Exclusion criteria
Stated objective	Quote from publication
Participants characteristics and setting	Number of participants Proportion of participants with unknown status of COVID-19 Proportion of participants with no symptoms or signs for COVID-19 Proportion of participants with symptoms and signs for COVID- 19 Proportion of participants with confirmed diagnosis of COVID-19 infection Mean (SD)/median (quartile range) time from infection/occurrence of symptoms to time of diagnosis/test Proportion of males and females Age (mean, SD) List of countries Comorbidities Symptoms related to COVID-19 Date of the sample Setting
Target condition	
Reference standard	
Index test	(Commercial) name of index test Name of manufacturer Regulatory status (e.g. CE-IVD) Test format (e.g. ELISA) Target (e.g. IgG)

	Sample type (e.g. fingerprick, plasma) Reported cut-off values Reported analytical sensitivity/limit of detection Reported analytical specificity/cross-reactivity
Flow and timing	
Publication details	Language of publication Funding Publication status
Notes	

Table 2-8: Data extraction form - Results

Study ID, Author, year	
Results	
Diagnostic accuracy	Sensitivity (95% CI) Specificity (95% CI) Area under the curve (AUC) from a receiver operating characteristics curve (ROC curve) Absolute and relative number of true-positive participants Absolute and relative number of false-positive participants Absolute and relative number of true-negative participants Absolute and relative number of false-negative participants Positive and negative predictive values (95% CI)
Authors' conclusions	

Risk of bias

The results are checked for risk of bias for each measure and for each study. The QUADAS-2 tool for the quality assessment of diagnostic accuracy studies will be used. The results are described, merged and analysed. If possible, a summarising evaluation of the information is performed.

Statistical Analysis

The statistical analysis will follow the recommendations in the EUnetHTA Methodology Guideline "Meta-analysis of diagnostic test accuracy studies", available at https://www.eunethta.eu/methodology-guidelines/. For each study, 95% confidence intervals will be calculated for the measures of accuracy (sensitivity, specificity, positive and negative predictive values). The predictive values are highly dependent on the prevalence. Thus, predictive values will interpreted with caution in the case that representative prevalences cannot be estimated. Univariate meta-analysis will be performed for the AUC. The following strategy will be used to derive summary estimates for sensitivity and specificity: The primary meta-analysis will be the bivariate meta-analysis with random effects. If sufficient data for a bivariate meta-analysis are not available, separate univariate meta-analysis will be performed. Narrative summaries will be provided in the case that meta-analysis cannot be applied in a meaningful way due to pronounced heterogeneity.

3 Communication and collaboration

Table 3-1: Communication

Communication Type	Description	Date	Format	Participants/ Distribution
Scoping	To internally discuss and reach consensus on the scoping and first draft of project plan.	05/05/2020	E-meeting	Author(s), co-author(s), dedicated reviewers, project manager
Final draft of the rapid assessment	*To discuss comments of dedicated reviewers*	*[DD/MM/YYYY]*	*E-meetings may be planned*	*Author(s), co-author(s), dedicated reviewers*

3.3 Dissemination plan

The final rapid review will be published on the EUnetHTA website: http://eunethta.eu/xxxx/ .

All partners and contributors are informed about the publication of the final assessment by the project manager.

This project will be registered on PROSPERO and the authors hope to publish findings in a peer reviewed journal.

3.4 Conflict of interest and confidentiality management

Conflicts of interest will be handled according to the EUnetHTA Conflict of Interest Policy. All individuals participating in this project will sign the standardised “Declaration of Interest and Confidentiality Undertaking” (DOICU) statement.

Author, co-author(s) and dedicated reviewers who declare a specific conflict of interest will be excluded from the whole work under this specific topic. However, they still may be included in other assessments.

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5 Appendix A

5.1 Selected Assessment Elements

The table shows the research questions that will be addressed in this rapid review. They are based on the assessment elements contained in the 'Model for Rapid Relative Effectiveness Assessment'. Additionally, assessment elements from other diagnostic technologies and screening HTA Core Model Applications have been screened and included/ merged with the existing questions if deemed relevant. Due to the time constraints, only very few, most basic elements have been included, even if more elements are considered mandatory under routine circumstances. The questions listed in the table will be used as checklist for the retrieval and reporting of information.

Table 5-1: Selected Assessment Elements

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
Description and technical characteristics of technology					
A0020	Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?		M	
B0018	Features of the technology	Are reference values or cut-off points clearly established?	Are conflicting/varying definitions of an abnormal finding likely to affect the interpretation of the results? (If so, please describe them.)	M	
B0009	Investments and tools required to use the technology	What equipment and supplies are needed to use the technology and the comparator(s)?		NM	
Health problem and current use of technology					
A0007	Target Population	What is the target population in this assessment?		M	
A0002	Target Condition	What is the disease or health condition in the scope of this assessment?		M	
A0004	Target Condition	What is the natural course of the disease or health condition?		M	
A0006	Target Condition	What are the consequences of the disease or health condition for the society?		M	
Clinical effectiveness					
D0001	Mortality	What is the expected beneficial effect of the intervention on mortality?		M	
D0005	Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health		M	

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
		condition?			
D0006	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?		M	
D1001	Test accuracy	What is the accuracy of the test against reference standard?		M	
D1002	Test accuracy	How does the test compare to other optional tests in terms of accuracy measures?		M	
D1003	Test accuracy	What is the reference standard and how likely does it classify the target condition correctly?		M	
D1004	Test accuracy	What are the requirements for accuracy in the context the technology will be used?		M	
D1005	Test accuracy	What is the optimal threshold value in this context?		M	
D1006	Test accuracy	Does the test reliably rule in or rule out the target condition?		M	
D0014	Function	What is the effect of the technology on work ability?		M	
D0015	Function	What is the effect of the technology on return to previous living conditions?		M	
Safety					
C0006	Patient Safety	What are the consequences of false positive, false negative and incidental findings generated by using the technology from the viewpoint of patient safety?		M	
C0020	Occupational safety	What kind of occupational harms can occur when using the technology?		NM	
C0008	Patient safety	How safe is the technology in relation to the comparator(s)?		M	
B0010	Safety risk management	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator(s)?		NM	