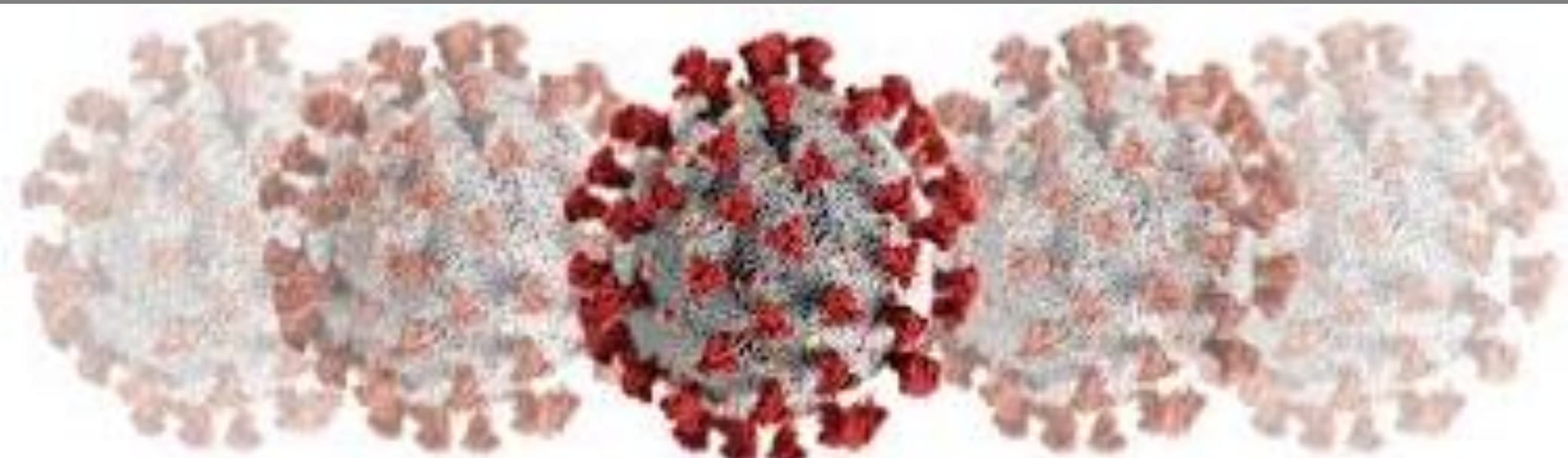
TONY BLAIR INSTITUTE FOR GLOBAL CHANGE

COVID-19: Antibody (Serological) Testing

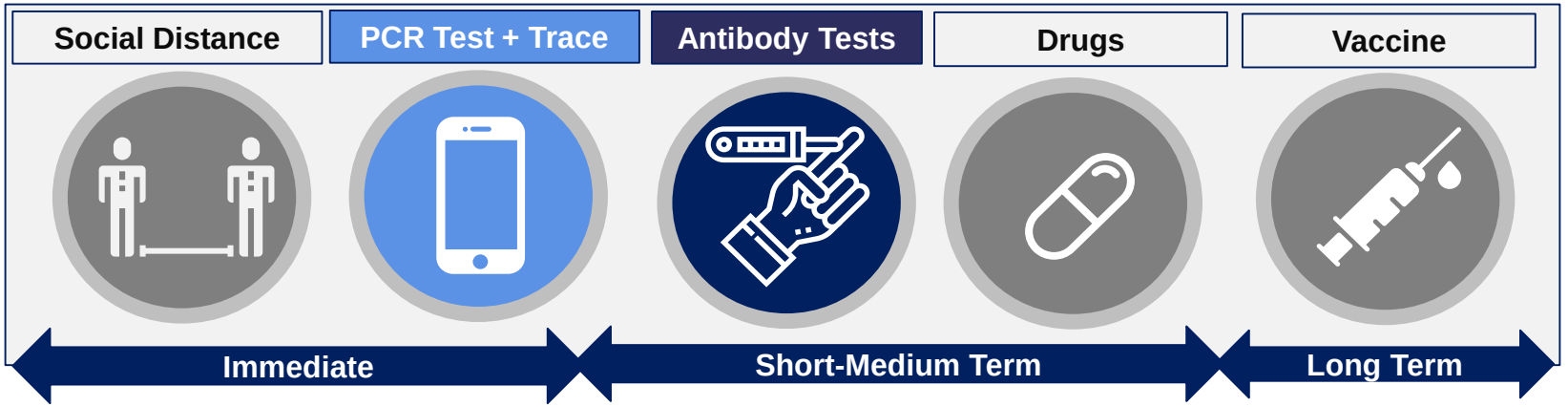
May 2020



Executive Summary

- Antibody testing can support surveillance by confirming who has previously been exposed to the virus. It has the potential to help track immunity, as the science develops, and may in turn help with prioritisation of vaccine roll-out.
- Antibody testing can improve data around true case numbers and patient recovery, supplementing modelling that ages rapidly and the disproportionate testing of only those with more severe symptoms. Antibody testing has challenges with accuracy such that they are at best a guide rather than definitive data for the purpose of policymaking.
- Antibody tests can supplement PCR and molecular testing for patients who are suspected to currently have the virus. Because of the risk of false negatives at the early-mid stage of the illness, antibody testing should not be used instead of PCR testing. In general, combining PCR and antibody tests are a “gold standard” of testing as they can mutually compensate for respective weaknesses, though this may not be feasible in low-resource environments.
- Using antibody testing to make public-policy decisions around easing restrictions, issuing immunity certificates or building up “herd immunity” rests on assumptions that are only partially evidenced and would likely be plausible only in cases of mass-testing capacity. Understanding the length of immunity requires longer-term studies and inferences based on other coronaviruses may be inaccurate. Though the World Health Organisation (WHO) does not currently recommend their use in patient care, a number of countries now consider antibody testing crucial for easing restrictions.
- Rapid antibody tests can be easily stored and administered with little training and provide an almost instant result. Availability is increasing and accuracy is improving. But more revealing antibody tests, which disclose the quantity of antibodies and their ability to neutralise the virus, still require laboratory analysis.
- Issuing immunity certificates entails risks and may not be practical, especially where there is weak social cohesion or high incidence of poverty. They should not be considered until scientific understanding of post-infection immunity improves and testing capacity increases.

An increasing number of countries consider antibody testing an essential part of their virus mitigations.



PCR: Detects presence of the virus	**Antibody:** Detects immune-system response
Detects viral ribonucleic acid (RNA), which clears as the patient recovers	Detects proteins called antibodies, which generally remain in the blood after recovery
Most useful during acute stage of infection, as RNA gradually increases and reaches a peak	Most useful during chronic stage (at least 7-10 days after infection), when antibodies have had time to develop
Indicates that a patient has the virus and is likely to be contagious	Indicates the patient may be in mid-to-late stages of illness or has previously had the virus
Requires use of nasal swabs to obtain sufficient amount of viral sample from the patient	Methodology varies, typically uses blood or plasma sample
Helps identify who should self-isolate to avoid transmitting the virus and tracing people they have had contact with	Knowing who has had the virus can underpin patient-care decisions, improve data and inform public policy
Test is highly sensitive but good specimens are hard to collect and can be easily spoiled	Varying accuracy but can be easily collected with minor phlebotomy and with antibodies uniformly distributed in blood

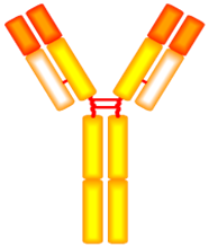
Sources: LineVector, Roundicons, Ecalyp, Darius Dan, Vitaly Gorbachev, Surang

The use of the appropriate test at the right time is essential to ensure accurate results.

Types of antibody

Immunoglobulin M (IgM)

These are the first antibodies to be produced by the immune system. They appear within 5-7 days of infection and peak at around 21 days. If detected without IgG, the person has or recently had the virus.



Immunoglobulin G (IgG)

More numerous than IgM, these antibodies appear around 10-14 days after infection. If detected alongside IgM, infection was within the last month. If detected without IgM, infection was more than a month ago.

Emerging evidence on antibody detection

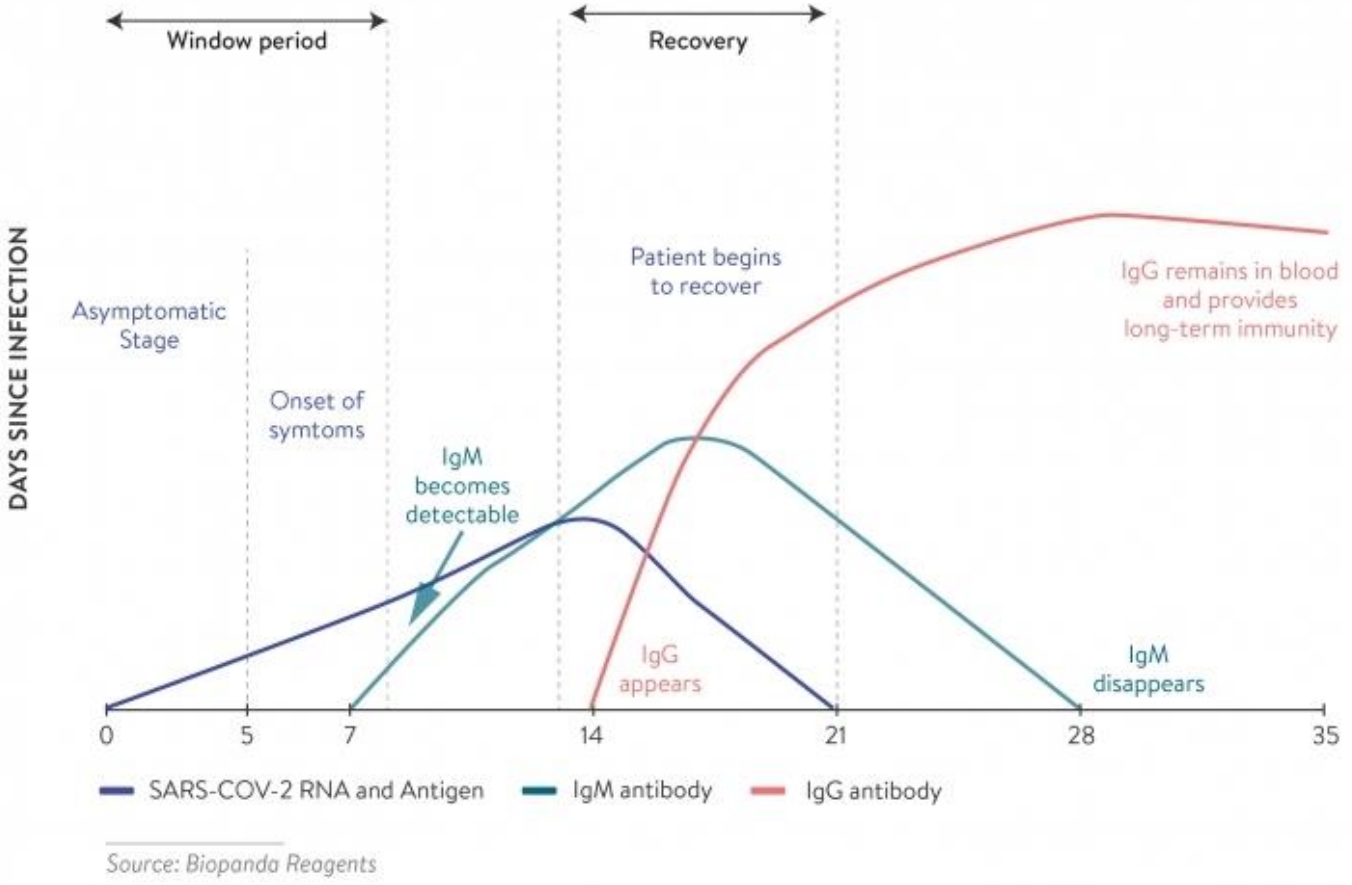
- First production and duration of detectability of different kinds of antibodies overlap to different extents in different patients.
- Emerging evidence suggests that viral elimination happens gradually, not abruptly, after production of antibodies. At the early stages of antibody detectability, patients may still be contagious.
- Detection rates are generally highest when IgG and IgM detection is combined in a single test to maximise the likelihood of identifying at least one of the types.

Sources: MedRxiv, Tony Blair Institute, Artur Jan Fijałkowski

Antibody tests can be used in combination with PCR tests to aid in the diagnosis of Covid-19.

How antibody tests can aid diagnosis

- Scientific knowledge of how antigens, IgM antibodies and IgG antibodies become detectable and correlate with time of infection, onset of symptoms and recovery is growing.
- Studies suggest **combining PCR and antibody testing can improve diagnosis** of the virus as one may detect indicators of infection that the other may miss. Disagreement between the two types of test can therefore help improve understanding of a patient's current stage of infection.
- Because of the risk of false negatives at the early-mid stage of the illness, **antibody testing should not be used instead of PCR testing.**



Sources: World Health Organization, British Medical Journal, COVID-19 Testing Project, Johns Hopkins University, Tony Blair Institute, Biopanda, Oxford University

Antibody tests can be used retrospectively to improve the accuracy of data on infection and understand risks.

Improve data on infections

- Retrospective antibody screening can **detect whether a person has already had the virus** and may therefore have immunity.
- Since most cases are mild or asymptomatic and are neither tested nor treated at the time, and testing capacities in most countries are heavily constrained, there is emerging scientific consensus that the **actual number of cases is likely to be much higher than official figures**.
- Through mass testing or representative samples, or gradually accumulating information from individual antibody tests, accuracy of **data about true case numbers ("seroprevalence") and recovery rate can be improved.**

WHO encourages more research

Help determine risk factor of individuals

- Quantitative tests may be used to determine if patients have **sufficient number and quality of antibodies to protect against reinfection**. Where they do not, in combination with other information on general patient risk and comorbidities, the patient may be considered a priority for vaccination.
- Tests for health-care workers can help establish who may have some immunity and can work around Covid-19 patients with less risk.
- Antibodies may be harvested from survivors for the treatment of live cases – but convalescent plasma treatment is still poorly understood.

Help determine risk factor of population as a whole and inform public policy

- **Accurate estimation of infection and immunity at population level are necessary to ease restrictions on movement**. If a very small proportion of the population has had the virus, there is a risk of a sudden peak in cases if restrictions are lifted too rapidly. Understanding geographic variations in infection and immunity may allow governments to ease restrictions at differing rates.
- **If a significant proportion of the population have had the virus, governments may consider "herd immunity" strategies**. Though the precise proportion of population who need to be immune is unknown and may vary across countries, it is estimated to be around 70%. Even in the worst affected areas of the US, France and Germany, the proportion tends to peak at 14%. WHO estimated in April that only 2-3% of people have antibodies, but this will vary at national level depending on stringency of national containment strategies and public adherence to them.

WHO does not currently recommend

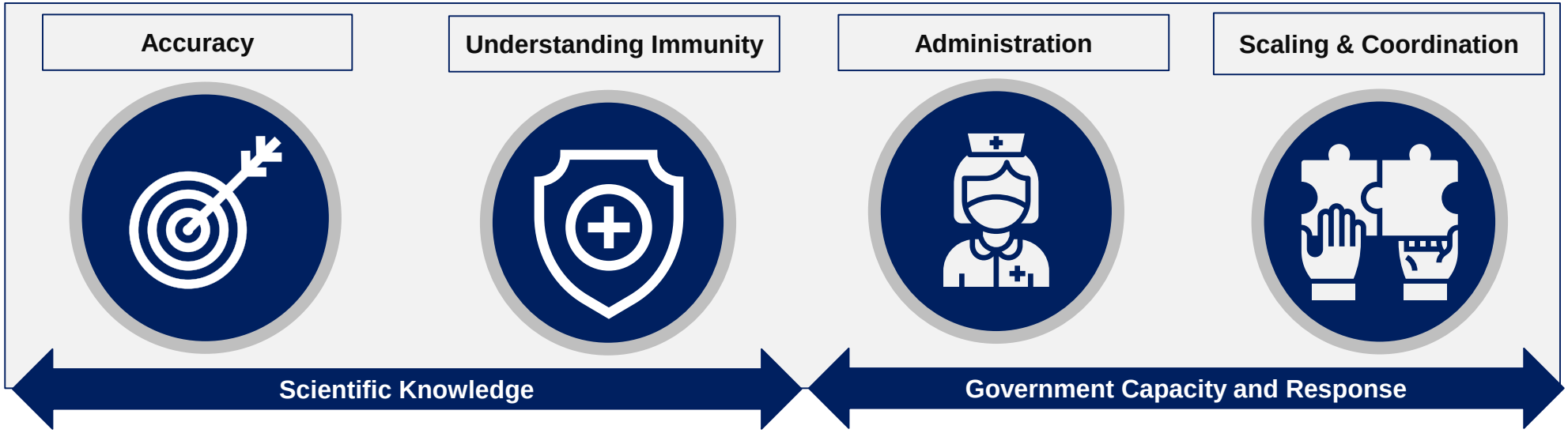
Sources: World Health Organization, British Medical Journal, COVID-19 Testing Project, Johns Hopkins University, Tony Blair Institute, Biopanda, Oxford University

Point-of-care and lab tests are available. More resource intensive tests tend to provide more detailed results.

	Results	Administration	Disadvantages
Lateral flow assay (LFA)	Qualitative – whether antibodies are present	• Results within 20 minutes • Ease of use at point of care • Small, portable, device; requires no additional equipment • Currently most widely available	• Result indicator may be open to interpretation • Difficult to distinguish recent infection from older one as some patients present IgG early and without detectable IgM
Enzyme-linked immunosorbent assay (ELISA)	Quantitative – how many, if any, antibodies are present	• Lab-based process • 2-5 hours	• Accuracy of quantitative result often relies on access to additional, often proprietary equipment (with limitations on throughput)
Neutralisation assay	Quantitative and Efficacy – how many antibodies are present and whether they are effective in neutralising the virus	• Lab-based process • 3-5 days	• Most human-, time- and equipment-resource intensive • Number of dilutions must be made by highly skilled technicians in a biosecure lab

Descriptions are schematic and process may vary across diagnostic devices.
Sources: Johns Hopkins University

There are barriers that must be overcome so that the full potential of antibody testing can be realised.



> “ Right now, it’s a wild west show our there. It really has created a mess that’s going to take a while to clear up…You’ve got a lot of companies marketing a lot of stuff and nobody has any idea of how good it is – **Eric Blank, Association for Public Health Laboratories**

> “ We will not allow [antibody tests] to proceed until we are confident that it is a good test, because no test is better than a bad test. – **Matt Hancock, UK Health Minister**

Sources: Time, The Independent, LineVector, Roundicons, Ecalyp, FreePk, Darius Dan, Vitaly Gorbachev, Surang

There are more antibody tests for Covid-19 now commercially available than for any other infectious disease, but the majority are insufficiently accurate for any use.

- There is **considerable variance in the accuracy of different commercially available tests**. There are also discrepancies between the claims of manufacturers and independent validations. Given the variance in antibodies present under real-world conditions, accuracy may be lower.
- **Appropriate thresholds for the different components of accuracy depend on the purpose for which the test is used.**
  - In general, for informing release from quarantine, very high specificity is essential as false positives may give assurance to vulnerable people.
  - For mass testing, false results will quickly accumulate. One simulation suggests low prevalence in the general population means a large number of false positives even for tests with high specificity are likely**.**
  - When used in combination with other data for diagnosis, lower levels of accuracy are tolerable.

	Purpose	Achieving high levels is critical to…	Desirable level[1]	Tolerable level[1]
Sensitivity	**How well the test detects what it is meant to detect,** that is IgM and IgG antibodies associated with Covid-19	Prevent **false negatives** (detecting a person hasn't had the virus when they have)	>98%	>95%
Specificity	**How focused the test is on the antibodies it is designed to test**, without being triggered by other similar ones	Prevent **false positives** (detecting a person has had the virus when they haven't)		

1.Thresholds used by UK Medicines and Healthcare Products Regulation Authority

Sources: World Health Organization, The Lancet, The Scientist, National COVID Testing Scientific Advisory Panel, COVID Testing Project, Arup, OCCRP, University of Liverpool

Understanding of the degree and duration of immunity conferred by antibodies is still developing but is likely to vary across patient groups.

Use of antibody testing beyond use in aiding diagnosis rests on the assumption that, as with other viruses, survivors are immune from reinfection after their initial recovery. This assumption is not yet conclusively proven for Covid-19.

Degree of Immunity	Duration of Immunity
• Early studies suggest **most people do retain antibodies** after infection and recovery. The transferal of antibodies from recovered patients to those with severe, active cases through convalescent plasma therapy led to rapidly improved symptoms in a small trial. • Some scientists believe that even without full immunity, a **second infection of the same strain is likely to cause milder illness**. • Isolated reports of reinfection or reactivation of the virus are believed to be caused by faulty tests. • There are **no reports of reinfections of SARS.**	• Data from SARS and MERS indicates **immunity may last between three and six years**. • **Reinfection with the same strain is highly unlikely** in the same or following outbreak season. • Immunity is likely to wane and not drop off suddenly.
• The WHO insists there is **no evidence that having the virus prevents a reinfection**. • The **degree of protection that antibodies provide is not known**. People with compromised immune systems, such as those undergoing chemotherapy or living with HIV, may be less able to produce antibodies. • Some studies, with data limitations, suggest **antibody production/retention may be higher in people who have had a more severe form of the virus**, and lower in children and young people. One early study found that only 70% of people developed high concentrations of antibodies in the blood, 25% low concentration and 5% no detectable antibodies.	• **Longitudinal studies will be required to better understand the duration** of immunity. Most survivors of the virus are still only now within two months of recovery. • People infected with this strain of the virus could be **plausibly re-infected in the event of a mutation** – though the likelihood of mutation and severity of the illness a new strain may cause is unknown.

Sources: The Lancet, European Centre for Disease Prevention and Control, Proceedings of the National Academy of Sciences of the United States of America, COVID-19 Testing Project. Science Focus, British Medical Journal, medRxiv

Global demand for antibody tests is significant and national supplies may be rapidly exhausted without a testing prioritisation strategy.

Considerations for policymakers

- **Being clear about use is critical:** A range of decisions rest on this, including accuracy, volume of equipment required, testing prioritisation.
- **Trade-offs and risks need to be considered:** Rapid tests are likely to be the least accurate antibody tests but governments must decide if they are likely to be good enough by weighing up the benefits and risks. Benefits of using antibody tests to enable resumption of economic and social activity must be considered against the cost of further infections.
- **Errors in administration are likely:** As labs are converted from other purposes and technicians are placed under pressure, and given variation in test collection quality, reagent quality and sample storage.
- **Nationwide standardisation is valuable:** The same testing kits and protocols should be used to ensure comparability. To build a national snapshot of transmission at any given point in time, local studies must be done as quickly as possible and at close regular intervals with minimal lags in reporting.

Prioritising use will depend on purpose and supply…

- For seroprevalence studies, samples should be representative of the population and participation voluntary, though self-selection biases associated with volunteers suspecting they have had Covid-19 must be avoided and elderly, immunocompromised individuals and children must not be excluded.
- For establishing immunity, health-care workers should be prioritised to understand who may be able to more safely care for Covid-19 patients, followed by essential public-facing jobs. Nonessential workers who cannot work from home may be prioritised over nonessential workers who can work from home.
- For use as a prerequisite for easing restrictions on movement, access must be equitable.
- For supporting diagnosis in patients with symptoms as a supplement to PCR testing, PCR testing prioritisation should be retained.
- Countries with significant access to antibody testing are allowing private purchase (e.g. United States).

Sources: University of Liverpool, Johns Hopkins University

Governments need to source tests from reputable suppliers to ensure quality.

FDA-approved tests with highest accuracy claims

Manufacturer	Type	Accuracy Claim	Availability	Capacity
Roche Switzerland	Tests for IgM and IgG antibodies, lab based (ELISA), requires COBAS immunoassay analyzer	100% sensitivity 99.8% specificity	$495m invested in production, producing 3 million tests in May, 5 million each subsequent month, anticipates 100 million tests per month by end of 2020.	Fully automated, 18 minutes per test, can process up to 300 tests/hour
Abbott Laboratories United States	Tests for IgG antibodies, lab based (ELISA), requires Abbott's ARCHITECT instrument	100% sensitivity 99.5% specificity	Distributed around 4 million tests in April and plans 20 million tests in June. Plans to extend use to Alinity instrument in future.	Between 100 and 200 tests/hour, 29 minutes to first result
Autobio Diagnostics China	Tests for IgG and IgM antibodies, rapid test	99% sensitivity 99% specificity	Unknown	15 minutes per test
Bio-Rad United States	Tests for IgM and IgG antibodies, lab based (neutralisation assay)	98% sensitivity 99% specificity	Unknown	Unknown

Considerations for policymakers

- **Pool demand for best prices:** Price points are likely to be lower for sub-Saharan African customers, especially when obtained through pooled procurement mechanisms.
- **Identify the original manufacturer:** Tests from little-known Chinese companies, including ones independent validation has shown are very inaccurate, are being imported and relabelled as originating in the EU, with European safety marks.
- **Query and cross-reference claims:** Distinguish products that have been granted, and are merely being submitted, for Emergency Use Authorisation. Information that may be omitted from marketing information or device leaflets, such as nature of clinical trials underpinning claims of accuracy, including ethical approvals, symptom severity of participants, and number of patients involved may be important in making purchasing decisions. A number of labs are now testing accuracy claims of manufacturers and findings are available in medical journals and through preprint servers online.

Further Information: US Food and Drug Administration for full list of approved diagnostic tools; 360Dx for fuller list of commercially available diagnostic tools

Sources: US Food and Drug Administration, Statens Serum Institut, Evalute Vantage, Hardy Diagnostics, Hardy Diagnostics, FiercePharma, Fierce BioTech, Forbes, Abbott

Case studies – sourcing, regulation and uses

United States

- 12 tests have Emergency Use Authorisation.
- The Food and Drug Administration originally permitted marketing without official review if developers validated accuracy. Now requires data be submitted for review after more than 200 kits flooded the market, including many fraudulent ones.
- Prevalence surveys have been conducted in California and New York though there are concerns over recruitment methods and representativeness of samples.
- National Institutes of Health recruiting 10k volunteers nationwide.

United Kingdom

- No tests yet approved by Public Health England.
- Antibody kits are one of the five components in testing plan but Scientific Advisory Group states concerns.
- Health Secretary indicates “very strong interest” in immunity certificate scheme as “science of immunity” develops.
- Government abandons 3.5m testing kits purchased from China after validation indicated they were accurate in <70% cases.

Kenya

- Intends to conduct seroprevalence survey in areas that recorded high number of cases in Mombasa County.
- Intends to use antibody testing to supplement PCR testing in light of shortage of kits.

India

- Governments tasks Zydus Cadila with domestic production of tests developed by National Institute of Virology after failure of inaccurate tests imported from China.
- Test is ELISA, 90 samples per 2.5 hours and to be used for surveillance at the district level.

Germany

- Carrying out Europe’s first large-scale antibody testing to monitor true infection rate using various sampling techniques.
- Procuring 5m tests a month but will consult ethics council before use in restricting movement.

Sources: National Institutes of Health, US Food and Drug Administration, US Food and Drug Administration, British Medical Journal, The Guardian, Tuko Kenya, Times of India, Reuters

There are practical and ethical considerations associated with immunity certificates.

- Immunity certificates may be used to exempt people from physical restrictions and aid return to daily life.
- Issuing immunity certificates is likely to incentivise certain behaviours in the population and cause unintended, knock-on consequences that may contribute to transmission. All options entail trade-offs and risks.
- Issuing certificates is likely to be ineffective, and possibly counterproductive, until reliable lab-based analysis of presence of sufficient antibodies can be conducted at scale based on scientific knowledge of how Covid-19 immunity functions.
- Lessons can be learned from the experience of issuing certificates in the wake of Ebola in West Africa.

Chile (Case Study)

- Will only be used to provide assurance that holders may help the vulnerable without risk of infecting them. Holders will still need to obey lockdown restrictions and follow provisions on mask-wearing.
- Does not require antibody testing – based on assumption that patients who recover after positive PCR testing have immunity.

Risks

- **Stigma and discrimination:** ICRC reported barriers to social reintegration of Ebola survivors with certification of clearance by medical authorities, including threats of violence. In case of widespread transmission, the reverse logic may apply: Those who have not had the virus may be shunned and employers may make certification a condition for work.
- **Decline in health-promoting behaviours:** Immune people may behave in ways that may contribute to further transmission to vulnerable people (e.g. stop hand-washing).
- **Deliberate virus acquisition:** Relatively young/healthy people may deliberately seek out infection in order to obtain certificates, on basis of own assessment of risk/benefits. During the 2014 Ebola outbreak in West Africa, WHO discovered the illicit sale of blood of Ebola survivors to obtain antibodies.
- **Inconsistency and technical obstacles:** Trust in testing may decline without consistent practices across public and private providers and mechanisms to prevent bribery of medical staff. In China, regional disintegration of the QR code system and technical failures are inhibiting access to basic services.
- **Inequitable testing access:** General testing capacity limitations may compound with access challenges for the poorest and most marginalised, damaging social cohesion. Permitting testing at home may promote access but entails accuracy and reporting considerations.
- **Fraud:** Emergence of fake certificates and black markets for sale.

Sources: The Lancet, Social Science in Humanitarian Action, CNN, Financial Times