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Living with COVID-19 endemic (of SARS-CoV-2 Omicron): self-test with RTK-Ag, antibody testing and antivirals against SARS-CoV-2

First published on 23rd December 2021 by Boon-How Chew, Beng-Kah Song, Hui-Yee Chee and Yit-Siew Chin for the Pandemic Scientific Response team

Caution: Summary is a preliminary report of work by Pandemic Scientific Response team. It will be continuously updated in accordance to the unfolding of events and emerging of scientific evidence.

In Brief

- Living with SARS-CoV-2 in the endemic COVID-19 will depend on the circulating variant's pathogenicity to humans (gentle or ferocious), this would decide the nature of the booster vaccine, and the level of appropriate SOPs in daily life.
- Armamentarium of the world living in the endemic COVID-19 would include accurate and rapid diagnostic testing for SARS-CoV-2, viral genomic surveillance, availability of and accessible to better vaccines, healthy lifestyle as the mean to good immune system, effective and safe oral antiviral drugs against SARS-CoV-2.
- Any dispute or doubt about COVID-19 vaccine effectiveness is unintelligible and irrational. Long-term safety and efficacy are yet ascertained.
- The vaccines are effective in preventing SARS-CoV-2 infection, transmission to others, preventing severe COVID-19, lesser hospitalisation, faster recovery and lower deaths even in the face of the SARS-CoV-2 Delta and Omicron variants (but reduced efficacy from laboratory findings).
- Breakthrough infections are more likely in older people with other comorbidity, immunocompromised people, related to vaccine type and concentrate, time after vaccination and community incidence rates.
- RTK-Ag tests performance has to be interpreted based on the study population from where the results came about. They were most accurate when used in the first week after onset of symptoms.
- Based on a recent review, in people with confirmed COVID-19, antigen tests correctly identified the infection in an average of **72% of people with symptoms**, compared to **58% of people without symptoms**; in people who did not have COVID-19, antigen tests correctly ruled out infection in **99.5% of people with symptoms** and **98.9% of people without symptoms**.
- COVID-19 antibody tests measure antibodies to SARS-CoV-2 which are produced 1-3 weeks after infection or vaccination.
- Not all antibodies neutralize the virus, the laboratory analysers are machine- and laboratory-dependant, concurrent memory B cells, CD8+ T cells and CD4+ T cells against SARS-CoV-2 are believed to be protective and can persist for more than 6 to 8 months.
- Antibody tests are not recommended for checking whether one has been truly vaccinated, or the immunity is working well, or whether it is time for a booster jab.
- Two most promising oral antivirals to date are the **molnupiravir** and **ritonavir**.
- Molnupiravir has an efficacy of **3.0%** absolute risk reduction or a **30%** relative risk reduction in reducing hospitalization and death in at risk adults with mild-to-moderate COVID-19 compared with a placebo.
- Ritonavir (PAXLOVID™) reduced risk of hospitalization or death by **89%** in Phase 2/3 EPIC-HR STUDY in an interim analysis.

Living with COVID-19 endemic (of SARS-CoV-2 Omicron): self-test with RTK-Ag, antibody testing and antivirals against SARS-CoV-2

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SARS-CoV-2 has caused much changes to the world socio-economic routines and many lives lost, more than 5 million recorded from more than 260 million cases till now [1]. From the past years of worldwide effort of combating the COVID-19 pandemic, the SARS-CoV-2 behaviours known to us has thus far produced some insightful viewpoints [2,3]. COVID-19 could be compared to influenza on possible scenarios of humans living with SARS-CoV-2 suggesting the life with repeat booster vaccination, repeated self-testing and a need for effective antivirals as the treatment for COVID-19 [3].

COVID-19 RTK-antigen and antibody tests are expected to be a new norm of life or even routine tests before travelling. These tests have their clinical indications and performance to be understood less they are misunderstood, misused or abused. Since the commencement of vaccination program in February 2021, the public's clamour for antibody testing is not waned, especially when the need for booster shot was recently raised, for "checking" whether one had been genuinely vaccinated, or whether one's antibody level is "high enough" to provide protection. While the antigen testing has gained a foothold in almost daily life of many school children, travellers and even larger meeting attendees as a compulsory screening testing.

Recent evidence has proven the effectiveness of the vaccines in preventing COVID-19 and to a larger extends in preventing severe COVID-19 and deaths even in the face of new SARS-CoV-2 variants namely the Delta and Omicron. Early reports showed that the vaccine efficacy against the Omicron is 40x lesser after the 2 doses and **75%** against symptomatic COVID-19 after the booster of the 3rd dose when compared to that against the Delta [4,5]. People who are vaccinated are less likely to develop symptoms, more likely to recover from their illness, and much less likely to require hospitalization compared with unvaccinated people [6-8]. The similar with Omicron is yet to be clear [9,10]. With more than 50 mutations [9] multiplies **70 times faster** in human bronchus [10], Omicron is very infectious with > **5 times** more than the Delta which was **2 times** more transmissible than the original Wuhan strain, and the viral loads **> 1000 times** higher than those in people infected with the original viral strain [11,12]. The reports so far have indicated that there were mostly mild diseases in the vaccinated but no milder than the Delta in the unvaccinated [12]. The protection afforded by past infection against reinfection with Omicron may be lower than 20% [12], lower than 40 times with Pfzer/Moderna vaccination, almost none with Sinovac vaccinations [13,14]. Omicron COVID-19 symptoms were mild flu-like include mainly myalgia (muscle ache), headache (could be very severe), sore throats, nausea, and slight temperatures.

> *A point-prevalence survey of almost 100 000 people conducted in England in June-July 2021 during the height of that country's spring Delta variant surge found that fully vaccinated people (n = 55 962) were two-thirds less likely to harbor SARS-CoV-2 compared with unvaccinated people (n = 15 135), with absolute rates of 0.40% vs 1.21%, respectively* [15]*. Likewise, in a randomized trial of the mRNA-1273 vaccine (Moderna) vs placebo, vaccinated participants (n = 14 287) were two-thirds less likely to be asymptomatic carriers than unvaccinated participants (n = 14 164), with absolute rates of 1.5% vs 3.5%, respectively (estimated vaccine effectiveness against asymptomatic infection, 63.0% [95% CI, 56.6%-68.5%])[6].*

Another study [16] among 1197 patients hospitalized with symptomatic COVID-19 observed that those vaccinated were less likely to require intensive care (25% vs 40%), less likely to require invasive mechanical ventilation (7.7% vs 23%), and less likely to die (6.3% vs 8.6%). These differences persisted after risk adjustment: the odds of invasive mechanical ventilation or death by day 28 among vaccinated patients was significantly lower than among unvaccinated patients (12.0% vs 24.7%; aOR, 0.33 [95% CI, 0.19-0.58]).

However, new evidence shows that fully vaccinated people can still infected with SARS-CoV-2 and down with COVID-19 but they are less likely to become infected and contagious for shorter periods than the unvaccinated people. Studies of viral dynamics suggest viral loads in vaccinated people with breakthrough infections may be as high in unvaccinated people, but the viral loads in the vaccinated decline more rapidly and less likely to be culture-positive compared to that in the unvaccinated people [17, 18].

In a study of 7771 household contacts of 4921 index cases in the Netherlands, the rate of transmission from fully vaccinated household members was 13% vs 22% from unvaccinated household members (estimated vaccine effectiveness against transmission, 63% [95% CI, 46%-75%]) [17]. Similarly, in an English study of 151 821 contacts of 99 567 index patients, the rate of transmission from people fully vaccinated with BNT162b2 (Pfizer-BioNTech) was 23% vs 49% for transmission from unvaccinated people (adjusted odds ratio [aOR], 0.35 [95% CI, 0.26-0.48] for transmission of Delta to unvaccinated contacts; aOR, 0.10 [95% CI, 0.08-0.13] for transmission of Delta to fully vaccinated contacts) [18].

Breakthrough infections are due to differences in the person's immune status, age, vaccine type/preparation, time since vaccination, and infection with the Alpha vs Delta variants. Breakthrough infections are more likely in the older people with other comorbidity, immunocompromised people, related to vaccine type and concentrate, time after vaccination and community incidence rates [6]. Yet, it is unknown why both humoral and cellular immunity wane over time and do not seem to protect against breakthrough infections when the same viruses are circulating.

*Among immunocompetent hospitalized patients for COVID-19, **11.2%** were vaccinated vs **53.5%** among controls (aOR for vaccination, 0.10 [95% CI. 0.09-0.13]). Whereas among the immunocompromised patients hospitalized with COVID-19, **40.1%** were vaccinated vs **58.8%** of immunocompromised controls (aOR for vaccination, 0.49 [95% CI, 0.35-0.69]). Protection against hospitalization was similar for the Alpha and Delta variants (aOR, **0.10** [95% CI, 0.06-0.16] for Alpha; aOR, **0.14** [95% CI, 0.10-0.21] for Delta). This similar observation was noted across different age groups.*

The Moderna vaccine (aOR, 0.11 [95% CI, 0.08-0.14]) was better than the BioNTech-Pfizer vaccine (aOR, 0.19 [95% CI, 0.16-0.23]) ($P < 0.001$) in overall protection again COVID-19, but they showed marked differences when taking into consideration time since vaccination. The protective association against hospitalization for the BioNTech-Pfizer vaccine more than 120 days following vaccination declined somewhat (aOR, 0.36 [95% CI, 0.27-0.49]; the median was 143 days from vaccine dose 2 to illness onset), whereas the effectiveness of the Moderna vaccine more than 120 days postvaccination was largely preserved (aOR, 0.15 [95% CI, 0.09-0.23]; the median was 141 days from vaccine dose 2 to illness onset) ($P < 0.001$).

COVID-19 antigen testing

In a recent Cochrane review [19] that included 64 studies with a total of 24087 nose or throat samples, and 7415 confirmed COVID-19 samples, investigated 16 different antigen tests and 5 different molecular tests, and studies were mainly in Europe and North America. Some of these assays were shown to meet appropriate criteria, such as the WHO's priority target product profiles for COVID-19 diagnostics as 'acceptable' when the **sensitivity is ≥ 80%** and **specificity ≥ 97%**.

The tests performance were reported that in people with confirmed COVID-19, antigen tests correctly identified COVID-19 infection in an average of **72% of people with symptoms**, compared to **58% of people without symptoms**. Tests were most accurate when used in the first week after symptoms first developed (an average of 78% of confirmed cases had positive antigen tests). This is because people have the most virus in the first few days after infection. In people who did not have COVID-19, antigen tests correctly ruled out infection in **99.5% of people with symptoms** and **98.9% of people without symptoms**. For molecular tests, although overall results for diagnosing and ruling out COVID-19 were good (95.1% of infections correctly diagnosed and 99% correctly ruled out), 69% of the studies used the tests in laboratories instead of at the point-of-care.

Understanding and Interpreting the Test Performance

Before reading the test performance results, do make sure you understand about the study designs. The meaningful results rely on whether the diagnostic test study was carried out

- using a test kit that was of high quality in its creation such as based on sound scientific basis (eg. best antigen and reagent) and good materials,
- in study samples who were experiencing the disease, in situations where the test was required or indicated (the study samples should not be all or mostly in the highly likely or unlikely to have the disease category),
- the test must be compared to a referent test of proven accuracy,
- the researcher or assessor who performance the test should be blinded from the referent test result, and vice versa, and
- all the test performance indicators are analysed and generated from the same study samples and not separate study samples for different indicators.

The **sensitivity** of a test indicates the proportion of the people with the disease who have a positive test for the disease. A sensitive test will rarely miss the people with the disease. This causes a highly sensitive test to have many **false-positive** test results. Since a highly sensitive test tends to give positive results, it gives very few negative results and naturally also very few false-negative results. Therefore, a highly sensitive test should be highly regarded when its test result is negative; it is useful to 'rule out' diseases. Therefore, a highly sensitive test has high **negative predictive value**, given the same setting. Without concurrent proven good specificity level, a test with high sensitivity is a 'strong' but poor in differential quality.

The **specificity** of a test signifies the proportion of people without the disease who have a negative test for the disease. A specific test will rarely misclassify the people without the disease as diseased. This causes a highly specific test to have many **false-negative** test results. In other words, a highly specific test has very few false-positive results. Thus, a highly specific test should be highly regarded when its test result is positive; it is useful to 'rule in' the disease. Therefore, a test with a higher specificity is also a test with higher **positive predictive value**, given the same setting. Without concurrent proven good sensitivity level, a test with high specificity is a 'weak' and poor quality test.

Conventionally, high **sensitivity** tests are desirable for dangerous but non-fatal and treatable conditions; and high **specificity** tests are used to confirm conditions that are serious, without efficacious treatment and traumatic physically, psychologically, socially and financially from the diagnosis or treatment.

In the context of COVID-19 pandemic and endemic, test kits that are high in sensitivity is preferred among the vaccinated for social activity related decisions. Whereas test kits that are high in specificity is preferred among the unvaccinated as they are more likely to contract the infection where 'ruling-in' quality is more important than unnecessarily 'strong' sensitive test.

Extracted and adapted from Chapter B: Classification of clinical research, Section: Diagnostic research, page 39. Chew Boon How. Understanding and Conducting Clinical Research- A Clinical Epidemiology Approach by a Clinician for Clinicians. 3rd Print, 2021. ISBN 978-967-960-449-8. UPM Serdang. Malaysia.

What: There are antigen and molecular-based tests for detection of current infection that are suitable for use at the point of care [19]. Both tests use the same respiratory-tract samples by swabbing, washing or aspiration as for laboratory-based RT-PCR, and newer tests accept saliva sample. Rapid antigen tests use lateral flow immunoassays in the form of disposable plastic cassettes akin to a pregnancy test. Antigen detection is captured and indicated by visible lines on the test strip (colloidal gold-based immunoassays, or CGIA), or through fluorescence, which can be detected using an immunofluorescence analyser (fluorescence immunoassays or FIA). While, the molecular-based tests detect viral ribonucleic acid (RNA). This has historically been the laboratory-based assays using RT-PCR technology. Recent technological advances have allowed molecular technologies to be suitable for use at the point-of-care. However, these are small portable machines and they take longer to produce results compared to antigen tests. The Foundation for Innovative Diagnostics (FIND) and Johns Hopkins Centre for Health Security have maintained online lists of available tests for SARS-CoV-2 (FIND 2020). Table 1 enlists the currently available self-test kits and their reported performance. Medical Device Authority (MDA) Malaysia is routinely updating the approved self-test kits on their website. However, beside administrative information about the test kits there are no clinical performance results being published even though these are believed to be submitted to MDA. It is also stated on the website that "*the use of COVID-19 self- test kit shall be limited for screening purpose only and all test results need further confirmation using RT-PCR*". This blanket statement is unjustified and every test kit should stand it its own pit of performance.

Why: Point-of-care tests could be a good replacement for RT-PCR if they are sufficiently accurate. This test can help in screening and rapid management such as for quarantine or treatment, contact tracing or for confirmatory RT-PCR testing for those with symptoms and a negative test result.

> If sufficiently accurate, **negative** rapid test results in **symptomatic** patients could allow faster return to work or school, therefore conferring important economic and educational implications; or prompts immediate consideration of other causes of the symptoms, for example bacterial pneumonia or thromboembolism. For **asymptomatic** individuals, accurate rapid tests may also be considered for screening at-risk (exposed) populations such as frontliners, in-hospital workers or in local outbreaks [19].
>
> *Rapid tests, particularly antigen tests which can be more easily delivered at scale, could also be used for mass screening purposes or used in a more targeted fashion such as single test application at airports or for border entry, to allow entry to large public gatherings, or screening students as a risk-reduction strategy. Preliminary data on the rollout of such a policy in the UK has highlighted the many challenges in such an approach, and the requirement for full and proper field trial evaluations. Frequent repeated use of antigen tests in asymptomatic individuals with no known exposure to identify COVID-19 cases has also been proposed, but field trial evaluations would be required to determine whether promising results from modelling studies can be borne out in practical settings [19].*

When: Patients may be tested for SARS-CoV-2 when they present with symptoms, have had known exposure to a confirmed case, or in a screening context asymptomatic and no known exposure to SARS-CoV-2. The standard approach to diagnosis of SARS-CoV-2 infection is through laboratory-based testing of swab samples taken from the upper respiratory (e.g. nasopharynx, oropharynx) or lower respiratory tract (e.g. bronchoalveolar lavage or sputum) with RT-PCR.

RT-PCR is considered the reference standard. However, ***RT-PCR continues to detect viral RNA days and weeks after the onset of infection****, and this will wrongly classify some people as infectious if clinical history is ignored. The use of the* ***cycle threshold*** *(**Ct** value) [also known as* ***quantification cycle*** *(**Cq**) or* ***crossing point*** *(**Cp**) values] from RT-PCR results to group individuals above or below a particular value (as a proxy for viral load) as more or less likely to be infectious is machine- and laboratory-dependant. Thus, Ct values are unlikely to be comparable across studies [19].*

Alternative reference standards that have been proposed for ***infectiousness*** *include assessing the viability of the virus using* ***viral culture****. However, viral culture is unsuitable as a reference standard because it is technically complex and often unreliable, and insensitive test because the failure to culture virus is often a result of the culture technique and not an indicator of non-infectiousness [19].*

COVID-19 antibody testing

Serology tests to measure antibodies to SARS-CoV-2 have been evaluated in people with active infection and in convalescent cases [20]. Antibodies are formed by the body's immune system in response to infections, and can be detected in whole blood, plasma or serum. Antibody tests are available for laboratory use including enzyme-linked immunosorbent assay (ELISA) methods, or more advanced chemiluminescence immunoassays (CLIA). There are also rapid lateral flow assays (LFA) for antibody testing that use a minimal amount of whole blood, plasma or serum on a testing strip as opposed to the respiratory specimens that are used for rapid antigen tests.

The "antibody testing" here refers to serology test looking for antibodies in the blood that are produced by our own immune system after being vaccinated or infected. The test must not be confused with the RT-PCR and RTK-Ag tests, which are respectively meant for assessing the viral RNA and antigen in the body. RTK-Ag serves as a screening test while RT-PCR is the gold standard to confirm the SARS-CoV-2 infection. This cannot be achieved by antibody testing. The reason is that the time needed for our body to produce antibodies after an infection is too long, ranging from 1 to 3 weeks or longer in some people.

So, since the antibody test could gauge the level of antibody after vaccination, and existence of these antibodies could implicate the body's preparedness to fight off the SARS-CoV-2 virus, why the "level of antibody" cannot be translated into the "strength of immunity"? To understand the rationale behind this, we need to know the basic immunology.

First of all, not all antibodies neutralize the virus. Only some antibodies can bind SARS-CoV-2 spike protein and prevent the virus from infecting cells, and almost all the clinical tests available on the market cannot differentiate between neutralizing antibodies from other non-neutralizing antibodies.

Second, even if there is, say, a company claims that the rapid test can be used to assess the level of neutralizing antibodies, it doesn't mean that low or high level of the neutralising antibodies translate into weak and strong immunity.

Although it is possible that higher titre (a technical term for "amount of antibody" in immunology) of antibodies does correlate with "increased protection", it merely means that a vaccinated person "might be" protected against COVID-19 [21]. In this case, the variants under study are B.1.177 and Alpha B.1.1.7, tested

using AstraZeneca vaccine. Such "no simple relationship" between the level of neutralizing antibodies and protection is made complicated by the fact that scientists still do not know the "minimum level" of the antibodies conferring protection. How high should the antibody level be to ensure an immunity protection, is dependent upon individual's immune system, which can be complicated. It is currently a question with no answer.

On the other hand, if a person has a lower level of neutralizing antibodies, it doesn't mean that the person has no protection. These circulating antibodies are only part of the COVID-19 immunological components. The more important responses upon vaccination are the production and retention of memory cells, which comprise memory T (including the killer T cells) and B cells. These memory cells serve as a strong and durable defence against SARS-CoV-2 when the real virus enters the body in the future. And this is the ultimate aim of having us vaccinated.

On top of the studies proving that the SARS-CoV-2 memory B cells, CD8+ T cells and CD4+ T cells persist for 6 to 8 months after the viral infection [22, 23], there are also recent studies supporting the notion that vaccination generates robust antigen-specific memory cells in humans. For instance, scientists from the University Of Pennsylvania Perelman School Of Medicine analysed the T-cell responses in 47 healthy individuals who were fully vaccinated by Moderna and BioNTech-Pfizer mRNA vaccines, and concluded that vaccine-induced T cells responses can be long-lasting [24].

Given the high standard research requirement of these assessments of memory cells, none of the currently available antibody tests on the market could relay the information of memory T or B cells. In line with the recommendation from the US CDC that "antibody testing is not currently recommended to assess for immunity to SARS-CoV-2 following COVID-19 vaccination", or to "assess the need for vaccination in an unvaccinated person" (CDC; https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html), the abovementioned research studies do not support the use of antibody tests for assessment of protection after COVID-19 vaccination. Worse still, different types of antigens are used in various antibody tests. The test used might not detect the antibodies induced by the specific vaccine type.

We do not intend to give the impression that the level of antibody does not spell out anything at all. It is just not a good idea to use it for checking whether one has been truly vaccinated, or the immunity is working well, or whether it is time for a booster jab.

Oral antivirals

Availability of effective oral antivirals against SARS-CoV-2 is perceived to be an important armamentarium of world living in the endemic COVID-19 [2]. This would come in as the widely accessible treatment for people with early or mild COVID-19. The other ends of the disease spectrum is taken care of by the vaccines and social SOP-measures as the preventive fortress, and the more invasive and restricted therapies such as monoclonal antibody infusion, intravenous steroids, supportive therapy of antimicrobials and extracorporeal or endotrachial oxygenation.

A frenzy exploration and testing of many possible and off-labels drugs of all kinds was seen in the past couple of years [25]. Two most promising oral antivirals to date are the **molnupiravir** by Merck and **ritonavir** by Pfizer.

Molnupiravir was recently reported to have an efficacy of **30%** relative risk in reducing hospitalization and death in at risk adults with mild-to-moderate COVID-19 compared with a placebo [26,27].

> The MOVe-OUT study of molnupiravir enrolled 1433 participants. The company shared data shows that the risk of hospitalization or death was 9.7% in the placebo group (68/699) and 6.8% (48/709) in the molnupiravir group; an absolute risk reduction of 3.0% (95% CI: 0.1, 5.9; nominal *p* value=0.0218) and a relative risk reduction of 30% (relative risk 0.70; 95% CI: 0.49, 0.99). Nine deaths were reported in the placebo group, and one in the molnupiravir group.
>
> *Molnupiravir (MK-4482, EIDD-2801) is an investigational, orally administered form of a potent ribonucleoside analog that inhibits the replication of SARS-CoV-2. Molnupiravir is being studied as a single medicine, without the use of concomitant medicines and without food intake restrictions or dose modifications based on renal or hepatic impairment [26].*

The FDA's antimicrobial drugs advisory committee came to a split 13–10 decision about molnupiravir [27] and some responsible clinical decision on prescribing it is cautioned. It might be used in highly selected patients who may be benefited more than its probable serious side effects:

1. Obesity and those high risk of hospitalisation and death from COVID-19 (elderly and multi-comorbid)
2. During or when there is high community infectivity rate of SARS-CoV-2
3. Not for people with diabetes mellitus, not kids, adolescents and not pregnant women as it may increase hospitalisation and inhibit bone growth, respectively
4. Those who are infected with earlier than Delta variant (uncertain on the Delta yet); also uncertain of efficacy among those vaccinated
5. To be used for a 5 day course, not less or more, or else the risk of
6. Severe probability of viral mutation to a bad variant
7. Serious probability of human DNA mutations

PAXLOVID™ (PF-07321332; ritonavir) is specifically designed SARS-CoV-2-3CL protease inhibitor to inhibit viral replication at a stage known as proteolysis, which occurs before viral RNA replication and the EPIC Development Program (see below) [28].

1. The Phase 2/3 **EPIC-HR** (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) randomized, double-blind study of non-hospitalized adult patients with COVID-19, who are at high risk of progressing to severe illness.
2. The Phase 2/3 **EPIC-SR** (Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients), to evaluate efficacy and safety in patients with a confirmed diagnosis of SARS-CoV-2 infection who are at standard risk (i.e., low risk of hospitalization or death).
3. The Phase 2/3 **EPIC-PEP** (Evaluation of Protease Inhibition for COVID-19 in Post-Exposure Prophylaxis) to evaluate efficacy and safety in adults exposed to SARS-CoV-2 by a household member.

The interim analysis showed that it reduced risk of hospitalization or death by **89%** in Phase 2/3 EPIC-HR STUDY. Should this treatment effect hold up in the end, PAXLOVID™ (ritonavir) would be the drug the world has been waiting for in the life of COVID-19 endemicity.

Conclusion

COVID-19 vaccine effectiveness should have no doubt from now onwards. Any dispute about it is unintelligible and irrational [2]. Similarly, the needs for and effectiveness of other protections have also been shown. These are:

1. Vaccination, complete the doses according to the type and get timely booster
2. Masking, use N95 or double masking of surgical and cloth masks, or antivirals-coated masks (coating with copper, silver, zinc, grapheme, etc.)
3. Avoid 3Cs, crowded and confined spaces, and closed conversation
4. Practise 3Ws, wear mask always as when needed, washing hands and body parts with soaps or appropriate sanitisers and on the alert about the warning symptoms
5. Improve air ventilation and indoor air quality,
6. Good mental health, good sleep, communicate nicely and frequently with all others and stay in good relationship
7. Healthy nutrition [29], consuming balance, moderate and variety of healthy foods, including 2-3 cups of coffee/day, 2-3 cups of tea/day, more vegetables, and avoid unhealthy diet such as processed meat (such as bacon, ham, sausages, meat pies, kebabs, burgers, chicken nuggets), and managing malnutrition problems (i.e. overweight and obesity, underweight, micronutrient deficiencies such as Vitamin D deficiency).
8. Exercise, both aerobic and muscle strengthening activities [30]

Some promising hopes in the near future are better vaccines (RBD-based vaccines that elicit high titres of S2X259-like neutralizing antibodies) [31] and oral antiviral drugs against SARS-CoV-2. These are to be affordable and equitable to all people to stop the pandemic of new mutated variants and as co-inhabitants of the 'new' world. Obviously, living with SARS-CoV-2 in the endemic COVID-19 will depend on the circulating variant's pathogenicity to humans ie. gentle or ferocious, this would decide the nature of the booster vaccine, and the level of appropriate SOPs in daily life. As viral fever, influenza and COVID-19 by the SARS-CoV-2's Omicron virus (hopefully so would be the future variants) are becoming more similar in clinical manifestation and symptomatology [32], the world should know better how to live with these viruses and diseases while always keeping the watchful eyes on them.

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Diagnostic Tests of SARS-CoV-2

Consisted of:

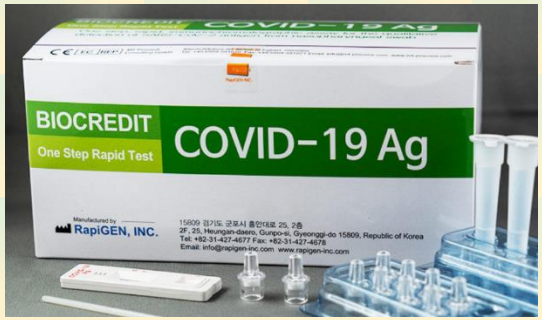
- 2 antibody detection tests
- 16 antigen detection tests
- 5 molecular tests
- 12 RT-PCR
- 2 based on taste & smell, and breaths.

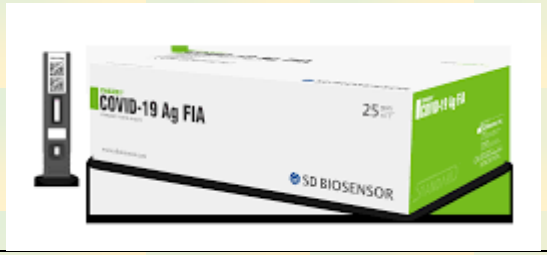
No.	Test / Brand / Picture	Mechanism	Sensitivity [a]	Specificity [b]	PPV [c]	NPV [d]	References / websites
1.	DKSH – Biolidics Rapid Test Kit for Covid-19 	IgG/IgM Antibody Detection (rapid test)	91.54% (86.87-94.65%)	97.02% (94.74 – 98.33%)			https://www.dksh.com/my-en/products/ins/biolidics-covid-19-test-kit
2.	Megna Health Rapid Covid-19 Combo test kit 	IgM/IgG Antibody Detection (rapid test)	100% (88.7 - 100%)	95.0% (87.8 - 98%)	51.3% (27.7–72.9%)	100% (99.3-100%)	https://www.fda.gov/media/140297/download

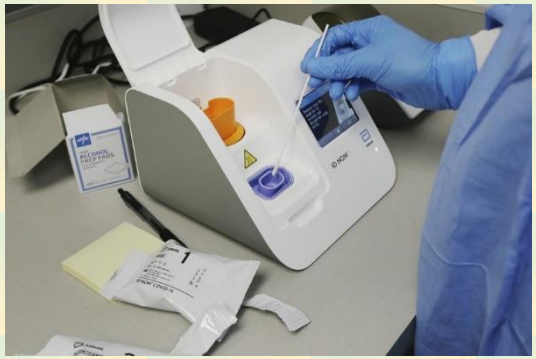
3.	AAZ - COVID-VIRO 	Antigen Detection (rapid test)	61.7 (55.9 to 67.3)	100 (98.9 to 100)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.
4.	Abbott - Panbio Covid-19 Ag 	Antigen Detection (rapid test)	72.0 (60.6 to 81.1)	99.3 (99.0 to 99.6)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.
5.	Becton Dickinson - BD Veritor 	Antigen Detection (rapid test)	82.3 (62.1 to 93.0)	99.5 (98.3 to 99.8)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.
6.	BIONOTE – NowCheck COVID-19 Ag 	Antigen Detection (rapid test)	89.2 (81.5 to 94.5)	97.3 (94.8 to 98.8			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.

7.	Biosynex - Biosynex COVID-19 Ag BSS 	Antigen Detection (rapid test)	59.6 (53.8 to 65.2)	100 (98.9 to 100)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.
8.	Coris Bioconcept - COVID-19 Ag Respi-Strip 	Antigen Detection (rapid test)	39.7 (31.3 to 48.7)	98.3 (97.4 to 98.9)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.
9.	E25Bio - DART (N-based) 	Antigen Detection (rapid test)	80.0 (70.8 to 87.3)	91.1 (83.2 to 96.1)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.

10.	Fujirebio - ESPLINE SARS-CoV-2 	Antigen Detection (rapid test)	80.6 (68.6 to 89.6)	100 (96.4 to 100)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.
11.	Innova Medical Group - Innova SARS-CoV-2 Ag 	Antigen Detection (rapid test)	47.9 (34.3 to 61.8)	99.8 (99.5 to 99.9)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.
12.	Liming Bio-Products - StrongStep® COVID-19 Ag 	Antigen Detection (rapid test)	0 (0 to 33.6)	90.0 (55.5 to 99.7)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.

13.	Quidel Corporation - SOFIA SARS Ag 	Antigen Detection (rapid test)	93.8 (79.2 to 99.2)	96.9 (83.8 to 99.9)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.
14.	RapiGEN - BIOCREDIT COVID-19 Ag 	Antigen Detection (rapid test)	63.3 (45.7 to 78.0)	99.5 (99.1 to 99.8)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.
15.	Roche - SARS-CoV-2 	Antigen Detection (rapid test)	88.1 (74.4 to 96.0	19.4 (7.5 to 37.5)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.
16.	Savant Biotech - Huaketai SARS-CoV-2 N Protein	Antigen Detection (rapid test)	16.7 (9.2 to 26.8)	100 (88.8 to 100)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.

17.	SD Biosensor - STANDARD F COVID-19 Ag 	Antigen Detection (rapid test)	72.6 (54.0 to 85.7)	97.5 (96.4 to 98.2)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.
18.	SD Biosensor - STANDARD Q COVID-19 Ag 	Antigen Detection (rapid test)	79.3 (69.6 to 86.6)	98.5 (97.9 to 98.9)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.
19.	Shenzhen Bioeasy Biotech - 2019-nCoV Ag 	Antigen Detection (rapid test)	86.2 (72.4 to 93.7)	93.8 (91.9 to 95.3)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.

20.	Abbott – ID NOW 	RT LAMP (Isothermal PCR) Molecular test (rapid test)	78.6 (73.7 to 82.8)	99.8 (99.2 to 99.9)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.
21.	Cepheid – Xpert Xpress 	Automated RT-PCR Molecular test (rapid test)	99.1 (97.7 to 99.7)	97.9 (94.6 to 99.2)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.
22.	DNANudge – COVID Nudge 	Automated RT-PCR Molecular test (rapid test)	94.4 (86.2 to 98.4)	100 (98.8 to 100)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.

23.	Diagnostics for the Real World – SAMBA II 	Automated RT-PCR Molecular test (rapid test)	96.0 (81.1 to 99.3)	97.0 (93.5 to 98.6)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.
24.	Mesa Biotech – Accula 	RT-PCR Molecular test (rapid test)	68.0 (53.3 to 80.5)	100 (92.9 to 100)			Dinnes et al. 2021 DOI: 10.1002/14651858.CD013705.pub2.
25.	Computed Topography	Chest CT	91.9% (89.8-93.7)	25.1 (21.0-29.5)	119.4 (93.6-152.5)	30.1 (4.3-212.4)	Böger et al. 2021 https://doi.org/10.1016/J.AJIC.2020.07.011

26.	Altona Diagnostics (821003) 	RT-PCR (RUO)	RUO	RUO	RUO	RUO	van Kasteren et al. 2020 https://doi.org/10.1016/j.jcv.2020.104412
27.	R-Biopharm AG (PG6815RUO) 	RT-PCR (RUO)	RUO	RUO	RUO	RUO	van Kasteren et al. 2020 https://doi.org/10.1016/j.jcv.2020.104412
28.	BGI Real-Time Fluorescent RT-PCR Kit for 2019-nCoV 	Target ORF1ab (open reading frame 1a and b 226 of SARS-CoV-2, includes the RdRp; RNA-dependent RNA polymerase of SARS-CoV-2, part of ORF1ab) RT-PCR (one step real time test kit)	100.0% (91.1%–100.0%)	100% (69.1%–100%)	100.0%	100.0 %	van Kasteren et al. 2020 https://doi.org/10.1016/j.jcv.2020.104412 doi: 10.1002/jmv.26691

29.	CerTest Biotec VIASURE SARS-COV-2 REAL TIME PCR DETECTION KIT  	Target ORF1ab, N (nucleocapsid protein of SARS-CoV-2) RT-PCR (one step real time test kit)	97% ORF1ab: 98% (90, 100) N: 100% (93, 100), 50	97% ORF1ab: 100% (96, 100), N: 100% (96, 100),			van Kasteren et al. 2020 https://doi.org/10.1016/j.jcv.2020.104412 https://www.finddx.org/product/viasure-sars-cov-2-real-time-pcr-detection-kit/
30.	KH Medical RADI COVID-19 Detection Kit and RADI COVID-19 Triple Detection Kit  	Target RdRp (RNA-225 dependent RNA polymerase of SARS-CoV-2), S (spike protein of SARS-228 CoV-2) RT-PCR (one step real time test kit)					van Kasteren et al. 2020 https://doi.org/10.1016/j.jcv.2020.104412
31.	PrimerDesign Coronavirus COVID-19 genesig® Real-Time PCR assay 	Target RdRp RT-PCR (one step real time test kit)					van Kasteren et al. 2020 https://doi.org/10.1016/j.jcv.2020.104412

32.	Seegene Allplex 2019-nCoV assay 	Target RdRp N, E (envelope protein of SARS-CoV-2) As does the in-house "Corman" E-gene PCR, these E-gene assays are specific for bat(-related) betacoronaviruses, i.e. they detect both SARS-CoV-1 and -2 RT-PCR (one step real time test kit)	100.0% (91.1%–100.0%)	100% (69.1%–100%)	100.0%	100.0 %	van Kasteren et al. 2020 https://doi.org/10.1016/j.jcv.2020.104412 Garg et al. 2020 doi: 10.1002/jmv.26691
33.	Mylab Patho Detect RT-PCR kit 	Target E, RdRP RT-PCR (one step real time test kit)	88.8% (75.9% – 96.2%)	100% (69.1%–100%)	100.0%	66.6% (46.6 %–82.0%)	Garg et al. 2020 doi: 10.1002/jmv.26691
34.	Fosun FOSUN COVID-19 RT- PCR Kit 	Target E, N, ORF1ab RT-PCR (one step real time test kit)	95.2% (83.8%–99.4%)	100% (69.1%–100%)	100.0%	83.3% (56.3 % - 95.0%)	Garg et al. 2020 doi: 10.1002/jmv.26691

35.	Black Biotech TRUPCR SARS-CoV-2 RT- qPCR kit 	Target E, N RdRP RT-PCR (one step real time test kit)	100.0% (91.1%–100.0%)	100% (69.1%–100%)	100.0%	100.0 %	Garg et al. 2020 doi: 10.1002/jmv.26691
36.	Thermo Fisher Scientific TaqPath COVID-19 Combo Kit 	Target S, N ORF1ab RT-PCR (one step real time test kit)	100.0% (91.1%–100.0%)	100% (69.1%–100%)	100.0%	100.0 %	Garg et al. 2020 doi: 10.1002/jmv.26691
37.	Lab Genomics Lab Gun Real-Time PCR Kit 	Target E, RdRP RT-PCR (one step real time test kit)	93.02% (80.9%–8.5%)	100% (69.1%–100%)	100.0%	76.9% (52.8 %–90.8%)	Garg et al. 2020 doi: 10.1002/jmv.26691
38.	Clinical symptoms as predictor	Smell and Taste Symptom-Based Predictive Model	70%	73%			Lauren et al. 2020 doi: 10.1002/alr.22602 Note: these are less relevant with new variants Delta and Omicron

39.	Breath-based rapid 	detection and monitoring of COVID-19 from exhaled breath by using sensors composed of different gold nanoparticles linked to organic ligands, creating a diverse sensing layer that can swell or shrink upon exposure to volatile organic compounds (VOCs), causing changes in the electric resistance	83-100%	61-100%	61-100%	71-100%	https://dx.doi.org/10.1021/acsnano.0c05657

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Explanatory footnotes:

[a] **Sensitivity: "Proportion of people with a disease in whom a diagnostic test correctly indicated a positive result"**

Sensitivity

$$= \frac{\text{Number of people with a disease who tested positive}}{\text{Total number of people with a disease}} \times 100\,(\%)$$

[b] **Specificity: "Proportion of people without a disease in whom a diagnostic test correctly indicated a negative result"**

Specificity

$$= \frac{\text{Number of people without a disease who tested negative}}{\text{Total number of people with a disease}} \times 100\,(\%)$$

[c] **Positive predictive value (PPV): "Proportion of people with positive test results who are correctly diagnosed (or who are turned out to be truly infected with the disease)"**

$$\text{PPV} = \frac{\text{Number of people with the disease who have positive test results}}{\text{Number of people with positive test results}} \times 100\,(\%)$$

[d] **Negative predictive value (NPV).: "Proportion of people with negative test results who are correctly diagnosed (or who are truly not infected with the disease)"**

$$\text{NPV} = \frac{\text{Number of people without the disease who have negative test results}}{\text{Number of people with negative test results}} \times 100\,(\%)$$

(Yerushalmy 1947, Public Health Rep. 1947 Oct 3; 62(40):1432-49; Asai 2020, J Anesth. 2020 Dec 11 : 1–5; doi: 10.1007/s00540-020-02875-8)

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