Rapid antigen tests for SARS-CoV-2: their sensitivity, benefits for epidemic control, and use in Austrian schools

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Abstract:
Rapid antigen tests detect proteins at the surface of virus particles, identifying the disease during its infectious phase. In contrast, PCR tests detect viral genomes: they can thus diagnose COVID-19 before the infectious phase but also react to remnants of the virus genome, even weeks after live virus ceases to be detectable in the respiratory tract. Furthermore, the logistics for administering the tests are different. In this article, we discuss the relative advantages of the different testing procedures and summarise evidence that shows that using antigen tests 2-3 times per week could become a powerful tool to suppress the COVID-19 pandemic. We also discuss the results of recent large-scale rapid antigen testing in Austrian schools.

Rapid SARS-CoV-2 antigen tests are now widely available and have been provided free of charge for home-testing in Austria since March 1, 2021. We focus specifically on their comparison to PCR tests, which are the gold standard for diagnosing COVID-19. Frequent testing can improve pandemic control by lowering the transmission rate and the effective reproduction number. This potential can only be fully realized if these tests are used effectively and if the public fully understands both their capabilities and their limitations. A particularly important factor is that even when used in a supervised manner, rapid antigen tests are less sensitive than PCR tests. The results and discussion presented below focus on the base SARS-CoV-2 strain, dominant in 2020. The main points are applicable to new variants as well, though some of their parameters differ. For example, preliminary evidence suggests that for the faster spreading variants Alpha (B.1.1.7) [1] and Delta (B.1.617.2), the infectious phase may be slightly longer, the viral load higher [2,3], and the pre-infectious window shorter [4]. Vaccinations, on the other hand, reduce the viral load in the realized infections [5–7].

In general, a virus can be detected by looking for its genetic material (DNA or RNA) or by detecting viral antigens which are present at the surface of the virus. As opposed to antibody tests, which detect antibodies from previous infection, antigen tests are used to detect people who are currently infected – and infectious. A few dozen to a hundred virus particles are sufficient for a rapid antigen test to detect SARS-CoV-2 [8]. Antigen tests are now readily available to the public and can provide results within 15 minutes. Therefore, they are a useful tool for rapidly identifying and isolating positive, infectious cases in order to reduce further transmissions. In contrast, a PCR test can detect the virus at even lower concentrations, as the PCR cycler multiplies the viral genetic material, but the execution of a PCR test, from sample collection to delivery of the results, is time consuming. The resulting delay in obtaining the result of a PCR-test may enable further transmissions.
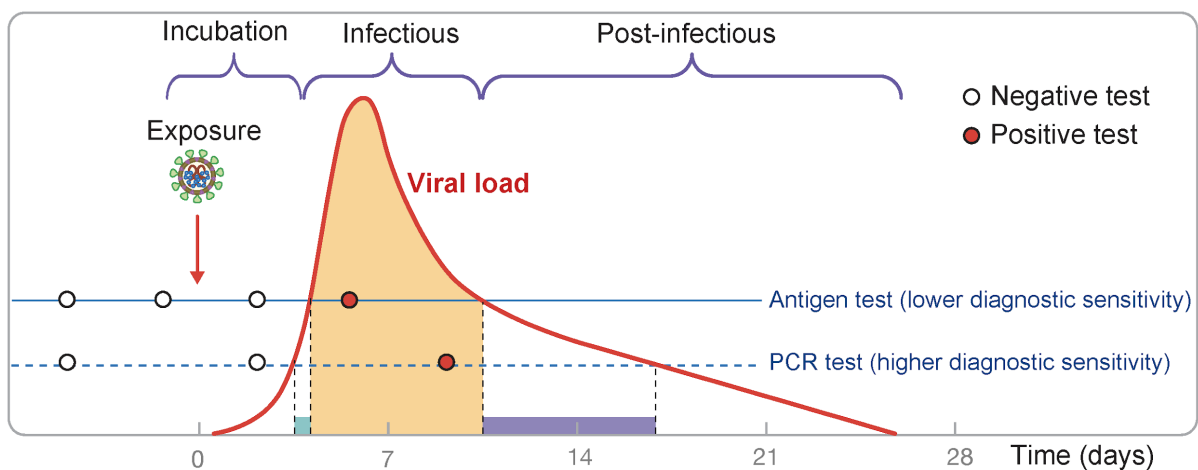

Figure 1. Despite having lower diagnostic sensitivity, rapid antigen tests identify the vast majority of infectious cases. Frequent testing is essential to identify these cases early and to efficiently limit the spread of the virus in the population. Figure, first published in [9], is modified from [10] with permission; viral load is shown on a logarithmic scale.

Within the first two to three days after infection with SARS-CoV-2, neither PCR nor rapid antigen tests can detect the virus (Figure 1), as its concentration is too low [11]. During the subsequent steep rise in virus concentration, a PCR test detects infection a little earlier than a rapid antigen test [12]. This period, however, is short, lasting around a day or even less

[13]. It is primarily within this 24-hour period that PCR tests provide additional benefit compared to antigen tests for the purpose of reducing further transmissions. While detecting infections early is key, the benefit of a PCR-test to detect cases at a lower viral load (earlier in the infection) is negated by the significantly longer turnaround time of the PCR-test result. In specialized settings such as hospitals, it is possible for an urgent PCR test to be returned in a few hours, but in general practice, it takes about a day or even longer.

As the viral load increases and the person becomes infectious, the rapid antigen test will start detecting the virus. This "infectious period" is shown in orange in Figure 1 and usually lasts 5 to 8 days. Typically, SARS-CoV-2 concentration in the upper respiratory tract peaks within a week after infection [14,15], which is when the vast majority of new infections occur [16,17]. This short period of infectivity explains why a high frequency of testing is essential for suppressing the spread of COVID-19: testing less frequently than once per week has little effect on new infections as most cases will be detected too late. In the last phase of disease progression (day 10 through 25), the load of live virus gradually diminishes and the concentration of viral RNA declines. Without any live virus, a person is no longer infectious and the antigen test will be negative. In contrast, PCR tests may produce positive results even when infectious particles are no longer present, because viral RNA remains in the respiratory tract at detectable levels. This post-infectious phase is shown in purple in Figure 1; the duration of the post-infectious phase is longer among those with severe infections and somewhat shorter among asymptomatic individuals [15,18,19].

The sensitivity of a test is defined as its ability to detect infection by a virus, and PCR remains the gold standard for diagnosing a COVID-19 infection. Importantly, the infectious phase (orange in Figure 1) is considerably shorter than the overall time during which a PCR test can detect viral RNA in an infected person. To suppress an epidemic the ability to detect and isolate an infectious person before they infect others is decisive: timing is paramount. Identifying a case in the post-infectious phase is important for diagnosis, but not from a public health perspective, i.e., for preventing secondary infections. This results in higher diagnostic sensitivity for PCR tests but does not directly translate to improved pandemic control: [13,20] demonstrate that the *frequency* of testing is more important than the modality of testing. Smith et al. [20] indicate that antigen tests and PCR tests have similar power to identify "individuals before or during the period when infectious virus was detectable in nasal samples" when the interval between tests is one day shorter for antigen tests than for PCR tests (Fig 3B); there was also no significant difference between antigen and PCR tests (nasal or saliva) when the same testing interval was used. In addition, they showed that when testing at least every 3 days, both PCR tests (nasal and saliva) and rapid antigen tests (Quidel SARS Sofia FIA) find over 98% of infected cases through the course of the infection. While antigen tests are effective in detecting an active infection, nasal PCR tests perform significantly better in the pre-infectious phase: the PCR test has a reported sensitivity of 70%, compared to 40% for an antigen test, to detect an infection within two days before virus could be cultivated from a nasal swab [20].

It is therefore important to prioritize systems which allow for more frequent testing or testing immediately before an event with high transmission risk. Larremore et al. [13] indicate that if half of the population would self-test every 3 days with a rapid antigen test and (immediately) isolate in the case of a positive result, we could achieve approximately a 40% reduction of the effective reproduction number R. For example, an R of 1.3 could be reduced to 0.8, and the epidemic would dissipate.

Furthermore, it has been reported that over 80% of new infections are caused by fewer than 20% of cases [21–23]. Such so-called 'superspreading' is caused by 'superspreaders' who have both a large number of contacts and often a higher viral load. These cases are more easily identified using rapid antigen tests, and identifying them early would yield a large reduction in further transmissions. As such, there is an additional benefit in testing people with many contacts even more frequently.

The mode of sampling may impact the sensitivity of both PCR and rapid antigen tests, e.g., nasopharyngeal sample collection versus gurgle tests or anterior nasal swabs. Evidence suggests that the effect of sampling on the detection of infectious individuals is minimal. A German study found that out of 30 individuals with high viral loads (more than 10 million of viral RNA per swab; $C_t < 25$) all were correctly identified through rapid antigen tests with professionally administered nasopharyngeal swab, and 29 were identified through rapid antigen tests with self-performed anterior nasal swab [24]. The authors also concluded that "supervised self-sampling from the anterior nose is a reliable alternative to professional nasopharyngeal sampling using a WHO-listed SARS-CoV-2 [rapid antigen test]".

In order to interpret the outcome of wide scale antigen testing, it is helpful to have a rough estimate for how many positive cases one expects to find. We consider testing a randomly selected person from the general population whose infection status is unknown but who is currently not in quarantine, i.e., a person who does not suspect to be infected at the time of testing. What is the approximate probability that their rapid antigen test will be positive? Bearing in mind that we only aim to understand the order of magnitude of antigen-detectable cases, multiple lines of reasoning suggest that it is very low. First, a detailed epidemiological model fitted to Austrian data on February 15, 2021 estimates that 0.09% of the population is infected but not in quarantine [25]. Second, a back-of-the-envelope calculation arrives at a similar conclusion. Assume that there are around 1,500 new cases reported per day (as observed for much of February in Austria) and that there is a case detection rate of 50% [26]. In this scenario, 1,500 people become infectious every day and do not quarantine. Assuming that they are infectious for a week (in line with Figure 1), this results in around 10,000 undetected infectious individuals in Austria – i.e., cases which can be detected via an antigen test. Since the population of Austria is 8.9 million, the probability that a person in Austria tests positive via an antigen test is therefore approximately 0.1% under the given scenario. (Note that this calculation has been simplified by ignoring errors that are hard to quantify and have countervailing effects. For example, many people will be infectious for some days before they learn of their status, and others might never be detected but still quarantine themselves because they are a close contact of somebody who has been detected or because they have symptoms.)

Upon reopening schools in February 2021 after a prolonged lockdown, Austria started mass rapid antigen testing of all school children twice a week. Tests were conducted every Monday and Wednesday using the Lepu Medical antigen test, which uses an anterior nasal swab. The first week of school antigen testing resulted in 198 positives among 470,000 tests conducted in Vienna and Lower Austria (in the week February 8 to 12, 2021), yielding a positivity rate of 0.04% [27]. Among these, more than 75% were subsequently confirmed positive using a PCR-test (suggesting a rather high specificity of 99.99%). In weeks two through six, the tests were conducted in all provinces, yielding weekly, Austria-wide positivity rates of 0.04%, 0.065%, 0.09%, 0.08%, 0.08% and 0.08% [28–32]. Across all provinces, the largest increase in positive tests between rounds – on average more than two-fold –

occurred between the first and second round of testing (see Supplementary Table 1). This may be due to increased quality of swab taking; an explanation also offered by Austria's Minister of Education Heinz Faßmann after the second week of testing. In addition, it is possible that COVID-19 incidence is lower in pupils than in the general population, especially right after a lockdown [33,34]. Furthermore, it is conceivable that school children stay infectious – and hence antigen-test positive – for a shorter period of time than adults. This would lower the estimate of the expected proportion of positive rapid antigen tests for this group compared to the calculation given above.

The recent average constant trend among pupils contrasts with the general population, where the effective reproduction number R (based on PCR-incidence) is approximately 1.1 [35]. Roughly, it seems to be possible to maintain around a 10% lower R in the tested cohort. Rapid antigen tests serve both to detect infectious cases among teachers and pupils, and to identify nascent clusters: in case of a suspected outbreak, a whole class is PCR-tested. This leads to a very high detection rate for the tested cohort: in the time of intense testing in schools (but limited testing at workplaces) 5-14 year olds became over-represented among population-wide PCR-incidence. While self-administered antigen tests enable the prevention of the majority of future infections [16], there is a small fraction of infectious adults which are not detected using self-administered tests [8,24,36], and this may occur more often for children. The 'Gurgelstudie' [gargling trial] in March 2021 indicated that the proportion of potentially infectious samples missed by antigen tests may be somewhat higher in children than in adults, although the small sample, coupled with 'relatively high' C_ts does not allow for a robust conclusion (5 out of 14 children with at least one PCR $C_t < 30$ were also detected by the antigen test) [37]. While the current capacity of PCR testing and sampling-to-result delay still limits the applicability of wide-spread PCR testing for controlling the pandemic, mixed strategies would be feasible. Note that in the absence of efficient testing, school closures have been ranked as a very effective measure in reducing spread of COVID-19 [38,39].

Michael Mina, a professor of epidemiology from Harvard School of Public Health, has been advocating the use of rapid antigen tests as a public-health tool since summer 2020 [9,13,18,40]. A recent analysis from Germany [41] estimates that rapid antigen tests reduced infections by approximately 40% between March and June 2021, despite being used by only about 10% of the population. This is comparable to the reduction caused by seasonality. The large effect is thought to come from the higher probability of taking an antigen test when cases increase in the social vicinity. The immediate availability and convenience of the rapid antigen tests means that one learns about an active infection promptly, which effectively limits further spread.

While a recent antigen test (self-administered or not), is a good indicator of infectiousness [24,36], it is inevitable that some people will swab incorrectly, leading to false negative results. Even professionally administered antigen tests can miss cases with low viral loads that are on the cusp of becoming infectious. As such, rapid antigen tests must not encourage reckless behavior, but rather enable people to lower their risk of infecting others by testing at least twice per week. Having longer gaps between tests decreases the potential benefit for reducing transmissions [13]. In conclusion, testing frequently, even with self-administered tests, can be a powerful tool to suppress the COVID-19 epidemic.

Although vaccination programs are progressing well, vaccine uptake varies greatly across socio-economic groups and is lower in the younger population, especially 18-25 year olds

[42–45]. Vaccination against COVID-19 is only slowly becoming approved and recommended for children; in the fall, schools will reopen with pupils largely unvaccinated. We expect that testing will stay exceptionally useful for many months to come: to increase safety in schools and at public events, as well as to help to suppress local outbreaks.

Ethics approval:
Ethics committee approval was not required as no new data was collected for this study.

Acknowledgements:

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Supplementary Table 1.
Weekly positive rapid antigen tests in Austrian schools, per province. Approximately 10% of the Austrian population is tested in this program. Primary schools (age 6-10) are open 5 days a week and pupils are tested twice per week. In secondary schools (age 10-15), half of the pupils go to school Monday and Tuesday and are tested on Monday; the other half attend Wednesday and Thursday, and are tested on Wednesday. (Exceptionally, schools use alternate weeks instead). Initially, only Lepu Medical tests were used; lately, some secondary schools started to use Flowflex (ACON) [46]. The frequency of school-testing has now been increased to 3-times a week. All staff wear FFP2 masks, secondary school pupils wear face masks in the classroom, primary school pupils wear masks when indoors outside of their class group. There is some variability to this general guideline for more specialized institutions.

Week starting	8.2.	15.2.	22.2.	1.3.	8.3.	15.3.	22.3
Wien	142*	250	258	429	345	606	599
Niederösterreich	56*	103	187	209	212	195	234
Oberösterreich		43	118	161	217	139	147
Steiermark		43	109	148	122	134	145
Salzburg		19	68	97	90	100	82
Kärnten		40	65	86	84	53	61
Tirol		13	42	54	66	43	60
Burgenland		10	34	44	41	49	61
Vorarlberg		15	23	19	11	6	16
Total Positive	198	536	904	1247	1188	1325	1405
Total Tests (appr.)	470 k	1.3mil	1.4mil	1.4mil	1.5mil	1.6mil	1.7mil
Percent Positive	**0.042**	**0.041**	**0.065**	**0.089**	**0.079**	**0.083**	**0.083**

* 75% and 80% of the cases, respectively, were confirmed by PCR in the first week; in later weeks, the % of false positives rose to about 40% [32].