

Rapid Antigen Tests For Safe School Opening in the COVID-19 Pandemic Era

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Background: Since the beginning of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic, school closure as a mitigating measure was at the center of a public and professional debate. While the negative effects of school closure cannot be ignored, accumulating data suggested that it is necessary for reducing community transmission. Our study presents an optional strategy for safe school opening during a pandemic, implemented in selected Israeli high schools by a special task force constructed by the Sheba Medical Center (SMC).

Methods: The study took place between November 2020 and April 2021. Three schools from different areas of Israel were enrolled. The participants were asked to undergo bi-weekly SARS-CoV-2 rapid diagnostic antigen tests (Ag-RDT). Those who tested positive were requested to self-isolate, whereas their school contacts were tested daily by Ag-RDT. Participants with a previously documented SARS-CoV-2 infection or who were found to be SARS-CoV-2 seropositive upon enrollment were exempted from screening.

Results: Of a total of 361 participants who enrolled in the study, 12.3% were found to be seropositive. Fourteen SARS-CoV-2 cases were detected (3.5%), 12 of them in one single school located in an endemic area for SARS-CoV-2. The 14 cases resulted in 84 days of COVID-19-related absence from school, comparing with 1775 potential days of COVID-19-related absence under a strategy implementing self-isolation instead of testing.

Conclusions: Safe continuation of academic routine during the pandemic is possible when using rapid Ag-RDT as a screening tool, while allowing swab collection by trained students and teachers.

Key Words: COVID-19, SARS-CoV-2, School opening, living safe, rapid

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Since the beginning of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic, one of the major debates is school closure as a key mitigating measure. Advocates of school closure based their position on the accumulating evidence which showed that school closure during pandemic surges reduced transmission,¹ and on the notion that given high levels of community transmission, school opening may put the students, school staff and their household members at risk. Evidence on the importance of school

closure in controlling transmission is also based on data on influenza transmission.^{2,3} However, school closure carries a financial toll, with a potentially extensive negative impact on the wellbeing of children and their parents.⁴⁻⁷ A task force of the Sheba Medical Center (SMC), led by the Infection Prevention & Control Unit developed a strategy for safe school reopening based on rapid antigen testing (Ag-RDT) as a substitute for postexposure quarantine, consisting of three stages: (1) serology testing to detect unidentified recovered students or staff who will not be required to quarantine, regardless of exposure, (2) Ag-RDT, performed twice weekly, as a screening tool to detect asymptomatic yet potentially infectious individuals who should isolate, and (3) daily Ag-RDT for exposed individuals, replacing mandatory quarantine of in-school contacts. To implement this policy, designated students and teachers who had undergone training by the SMCs task force implemented stages 2 and 3 of our strategy in each school. Here, we report a pilot study, testing this strategy in 3 schools of different socioeconomic backgrounds.

METHODS

Setting

The study took place between November 2020 and April 2021, in 3 large Israeli high schools located in 3 different geographical regions serving populations of different ethnical and socioeconomic characteristics: (1) Tel-Aviv Gymnasia Herzelia – a large high school with 1930 students, located in the city's center, with students from various parts of the city, with different socioeconomic backgrounds. (2) Bikurim youth village in Eshkol – a boarding school for 50 students in the Eshkol council, residing in proximity to the Gaza strip, an area which was frequently under missile attacks, during which the students stay in closed and unventilated bomb shelters from time to time. Students of this school reside there and go back home for weekends and holidays. (3) Taibe Amal High school – with 1100 students, located in an Arab local council, which was a SARS-CoV-2 endemic area during the study period.⁸

Study Population

In total there were 398 participants, including 225 students and 173 educational staff.

IRB

Students and parents who agreed to participate signed an informed consent form. The study protocol was approved by the SMC Institutional Review Board committee.

Funding

The study was self-funded by the SMC. No funding from any third party or a commercial company was received.

Study Design

Recruitment and Training

Upon enrollment, each school held a zoom conference in which the principal investigator explained the goals of the study to

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the students and their parents, followed by an open discussion. Each school designated ~10 students and/or teachers to undergo training to collect nasopharyngeal swabs for PCR and Ag-RDT. These individuals were trained through a zoom session, a video guidance tutorial and personal onsite 1-hour training. During the first 3 weeks of the project, SMC personnel visited each school to supervise and guide the sampling process and school personnel. Random visits for inspections were made as well by the members of the SMCs task force.

Inclusion and Exclusion Criteria's

Only classes in which all parents gave consent for their children to participate in the study were enrolled. Therefore, from each school only 2 to 3 classes were able to participate

Screening Strategy

We asked the students to disclose if they had a previous documented SARS-CoV-2 infection, such recovered students were

exempt from further testing or quarantine as per the Israeli Ministry of Health (MOH) policy at the time. For those who did not report a previous SARS-CoV-2 infection, we offered a serology test to detect antispikes SARS-CoV-2 IgG. Seropositive individuals (IgG>1 S/CO) were exempt from bi-weekly Ag-RDT tests. While all other participants were tested twice weekly for SARS-CoV-2 by Ag-RDT. Those with a negative result were allowed to attend class on the following days. In the case of a positive Ag-RDT result, the parents and student were notified, and a confirmatory Quantitative Real Time Polymerase Chain Reaction (qRT-PCR) RT-PCR swab was performed. SARS-CoV-2 positive students were isolated for 10 days as per the Israeli MOH policy at the time. In the case of a confirmed positive student, all of the student's classmates were obliged to undergo daily Ag-RDT screening for the following 10 days and were thus exempt from quarantine. Additionally, ~3% of tests performed were immediately followed by an RT-PCR test to assure acceptable sensitivity (Fig. 1).

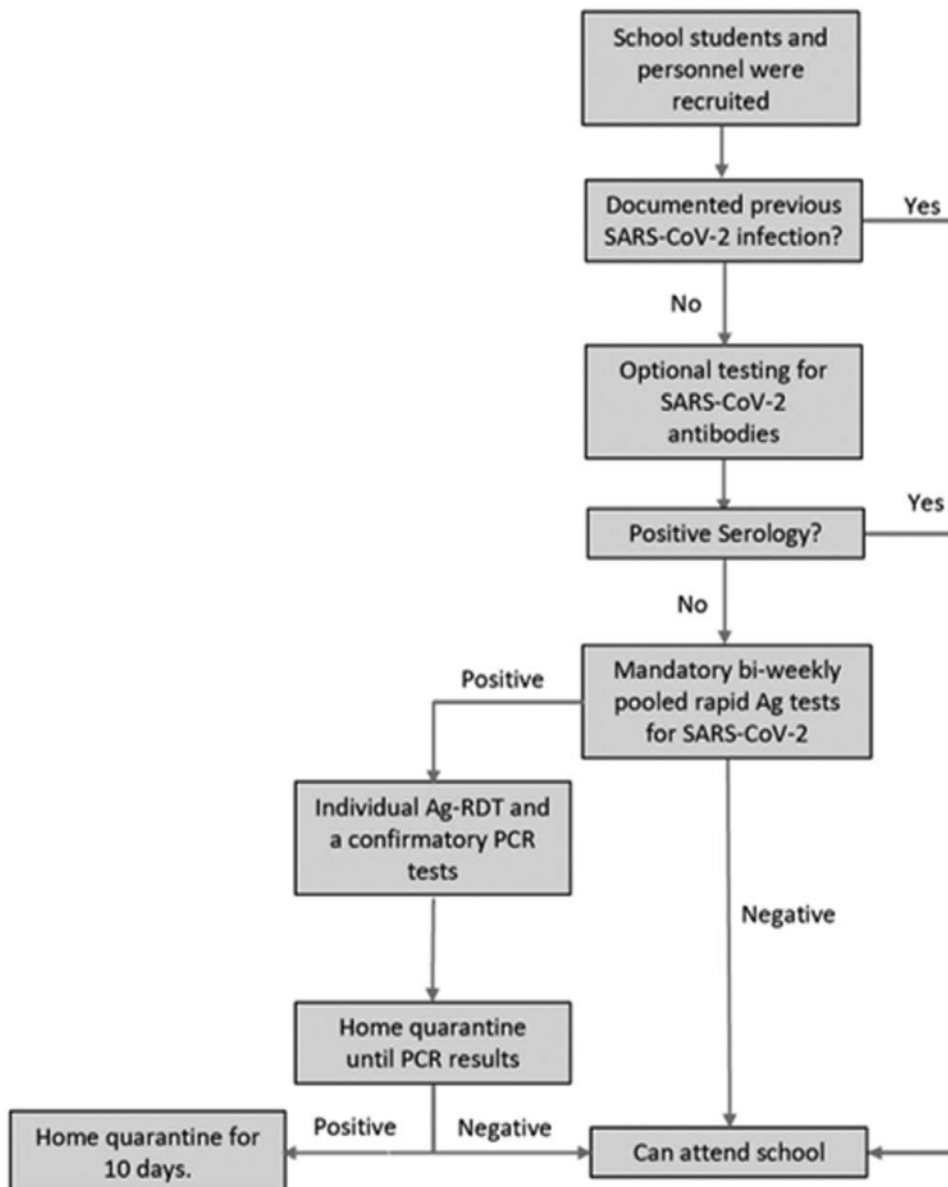


FIGURE 1. Decision making flow chart for pooled and individual Ag test results.

Serologic Testing

Serologic testing was optional and conducted on the first day of the study in each school. We tested for Anti-S1 IgG antibodies (Beckman Coulter, USA).

Antigen Test Pooling and PCR Tests

For the purpose of rapid antigen testing, we used the following kits: Nowcheck rapid antigen test (Bionote, South Korea),⁹ SD rapid antigen test (Roche, SSS Australia),¹⁰ Panbio rapid antigen test (Abbott Diagnostic, Jena, Germany).¹¹ All had an emergency authorization by the Food and Drug Administration/Conformite Europeenne and had undergone validation according to the Israeli MOH regulations. Kits were used depending on availability. Swabs were obtained according to the manufacturer's instruction,⁹⁻¹¹ but the kits were used with modification of the manufacturers' instructions which used pooling for efficiency and to reduce costs: 4 samples from 4 different students were tested together using 4 different cotton swabs, 1 Ag-RDT card and 1 reagent tube. Swabs were inserted into the reagent and then applied onto the Ag-RDT card (Fig. 1). In the case of a positive result for a pooled test, the relevant individuals were subsequently re-tested individually by new swabs for Ag-RDT and PCR. We validated the pooling technique of 4 swabs together as it was compared to individual Ag-RDT and qRT-PCR tests, with a sensitivity of 76.9% and specificity of 97.57% (Detailed explanation in Supplemental Digital Content 1; <http://links.lww.com/INF/E729>). Additionally, random PCR screening was per-

formed using the Allplex SARS-CoV-2 qRT-PCR assay following nucleic-acid extraction (Seegene Inc., S. Korea) according to the manufacturer's instructions, as requested by the Israeli MOH.

COVID-19-related Absence Days

The Israeli MOH policy at the time of the study was that any individual with a positive SARS-CoV-2 test was obligated to self-isolate and their contacts were obligated to be in quarantine for 10 days. Therefore, if a student or teacher were found to be SARS-CoV-2 positive, the entire class was requested to be in quarantine. For the purpose of this study, COVID-19-related absence days were defined as school days, excluding weekends and holidays, during which students were positive for SARS-CoV-2 and their contacts were missed due to isolation and quarantine. Potential COVID-19-related days were defined similarly, as days that would have been missed by contacts of a positive student, if not for our strategy that implemented daily testing instead of quarantining contacts.

Sociologic Assessment

To test the effect of our intervention on the wellbeing, sociologic aspects and mental health of students, participants from one of the high schools (Taibe Amal High School) were asked to respond to a questionnaire which consisted of 10 statements regarding their wellbeing and their thoughts on participating in the study. The students were asked to rate the statements on a scale of 1 (strongly disagree) to 5 (strongly agree). For more detail, see Supplemental Digital Content 1; <http://links.lww.com/INF/E729>.

RESULTS

A total of 193 students and 168 teachers and staff participated in the study (Table 1). Serologic screening was optional and included 162 participants. Of these, 20 (12.3%) were found to be seropositive for Anti-S SARS-CoV-2 IgG, and were exempt from bi-weekly testing; 19 (18.6%) in Taibe, a highly endemic city, vs. 0.5% and 0% in Tel-Aviv and Bikurim, respectively. Two additional students from Taibe had official documentation of prior SARS-CoV-2 infection. The students were exempt from the bi-weekly testing but were kept as part of the study cohort when school absences

TABLE 1. Study Population

	Tel-Aviv N = 184	Eshkol N = 75	Taibe N = 102	Total N = 361
9th grade	–	8	–	8
10th grade	25	15	22	62
11th grade	25	14	35	74
12th grade	26	8	–	34
Personnel	107	30	24	161
Positive serology	1	0	19	20
Known past infection	0	0	2	2

days were calculated. Thus, a total of 339 students participated in the screening strategy. During the course of the study, we used 813 kits to conduct a total of 3711 Ag-RDT, of them, 2997 were used to test students and 714 to test teachers and other educational staff. Of 339 participants who participated in the screening strategy, 14 were detected as SARS-CoV-2 positive, and of these, 12 were from a single school, Taibe Amal, located in an area endemic for SARS-CoV-2 during the study's period. All positive Ag-RDT participants underwent a confirmatory RT-PCR test and were all PCR-positive as well, thus suggesting a 100% specificity for the Ag-RDT kits used. Additional 111 random RT-PCR tests were performed for participants who had tested negative by Ag-RDT, to assess the sensitivity of Ag-RDT in this setting, and all were negative.

Prevention of In-School Transmission of SARS-CoV-2

In Tel-Aviv, 1 single student was detected as SARS-CoV-2 positive during the study period, their result was confirmed by a PCR test, no further transmission was reported and all Ag-RDT of their contacts following the detection were negative. Similarly, in Eshkol 1 student was found positive for SARS-CoV-2. She was tested at a health maintenance organization (HMO) while spending a long weekend at home: she came in contact with a SARS-CoV-2 positive person and tested positive before returning to school. Since this occurred during a long weekend spent at home, no other students or staff were exposed, and indeed all participants from that school tested negative on the following bi-weekly screenings tests. In Taibe, 10 students and 2 teachers were found to be SARS-CoV-2 positive via Ag-RDT and then confirmed by PCR. Upon epidemiologic investigation, the 12 SARS-CoV-2 positive cases were detected on 5 independent events, as demonstrated in Fig. 2A. The events were at least 14 days apart from one another, excluding a transmission event, in between events all tested contacts tested negative. Since only the students and teachers who tested positive for SARS-CoV-2 were requested to isolate, only 86 days of COVID-19-related absence occurred during the study's period, compared to 1476 days of COVID-19-related absence that would have occurred had all students who came in contact with positive cases had to quarantine (Fig. 2B).

Sociologic Aspects

Fifty-six of the 71 (79%) students that participated in the pilot in Taibe responded to the questionnaire that was sent to them. Most students reported that attending school did contribute to their academic achievements and social life and that they would cooperate with such a testing strategy if they are to be exempted from collective quarantine in the future. The full results are presented in Supplemental Digital Content 1; <http://links.lww.com/INF/E729>.

DISCUSSION

Here we present a strategy for safe school reopening which was implemented successfully during the SARS-CoV-2 pandemic in Israel, among high school students in 3 different locations in the country.

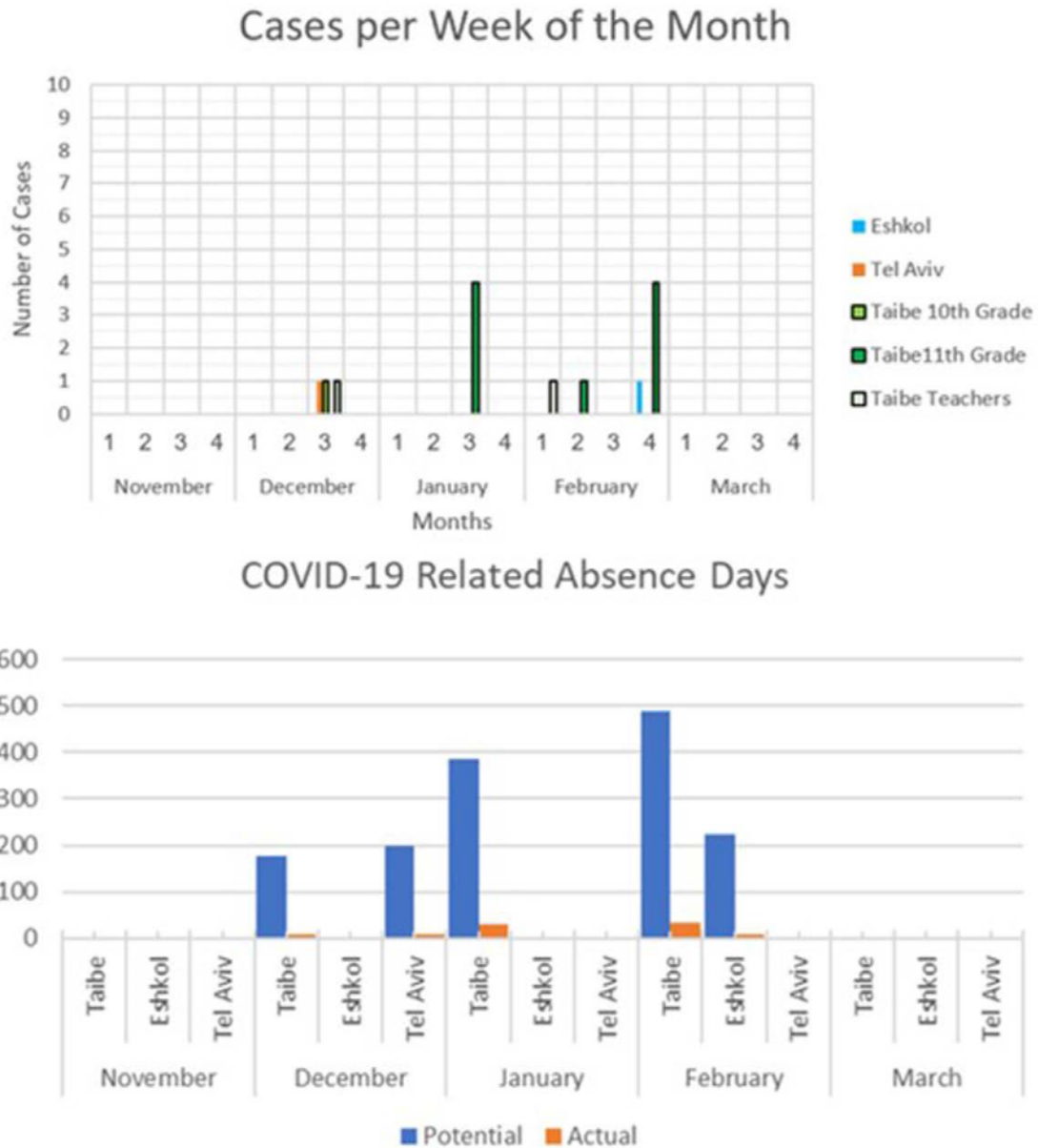


FIGURE 2. Chart A demonstrates SARS-CoV-2 Incidents for each high school during the study period. Chart B demonstrates potential vs. Actual COVID-19 related absence days during the study period.

Certain studies suggest that school closure can be beneficial for reducing the rate of transmission and hospitalization in intensive care units^{1,2} during the pandemic, while other studies suggest that schools are seldomly linked to SARS-CoV-2 outbreaks,^{13,14} and the ones that are linked to schools are mostly due to an asymptomatic index patient.¹⁵ Thus, different countries adopted varying approaches to school opening. While some did not implement a school closure policy at all,¹⁶ others took part in outdoors studying and hybrid programs which included in-school studying along with online studying via video conference applications.¹⁶ In Israel, schools were mostly closed during the 2020–2021 SARS-CoV-2 pandemic surges, and frequent events of large SARS-CoV-2 outbreaks in schools were reported.¹⁷ While schools were open, symptom-based screening tools were used as a main infection prevention tool, and were found to be insufficient in doing so.¹⁸ We believe that the main reason is due to

the high rates of asymptomatic SARS-CoV-2 carriage among teenagers and children, who may be contagious.

The strategy of bi-weekly Ag-RDT surveillance to detect SARS-CoV-2 positive individuals and isolating only those who test positive, allows all other students to continue and attend school while closely monitoring them on a daily basis. Our results suggest that by using this strategy we were able to detect asymptomatic or presymptomatic cases which could have been the cause of a potential school outbreak, while substantially lowering the amount of COVID-19-related school absences days. Vaccine rollout in the adult population in Israel which began during the study's period had little to no effect on the study results. Most teachers were eligible to receive a SARS-CoV-2 vaccine during February 2021 and students became eligible on mid-March 2021. Furthermore, a recent mathematical model and a real-life large-scale study in England were able

to demonstrate how bi-weekly Ag-RDT mass testing may reduce in-school transmission and COVID-19-related absence days.^{19,20}

To keep schools open, a potential strategy should not only be effective in preventing infection transmission but should also be easy to implement nationwide. Testing for SARS-CoV-2 via Ag-RDT by trained students and school staff allows receiving results quickly, yet, the gold standard procedure is a qRT-PCR test conducted by a health care professional. Throughout our study, each school was responsible for conducting Ag-RDT and allocated volunteers who underwent brief training to collect nasal swabs. During the first few weeks of the study, a delegate of the SMC task force supervised the testing process and later during the study period the task force conducted random qRT-PCR tests to verify Ag-RDT results, as was required by the Israeli MOH. We did not find any discrepancies between the results of Ag-RDT conducted by the schools and the qRT-PCR tests. We believe that with brief yet sufficient training it is possible to pass the testing responsibility on to the teachers and students and to recruit them to the continuous efforts in mitigating the pandemic. A potential alternative would be self-testing by students before arriving to school and reporting their results as was performed in England²⁰ and recently in Israel. Both demonstrate that the responsibility for testing can be passed on to the hands of the community rather than having health care professionals as the sole qualified sample collectors.

Furthermore, a feasible school-opening strategy needs to be inexpensive. Ag-RDT is a cheap method for SARS-CoV-2 testing, and using the pooling methods allows a decrease in costs.

Our strategy presented here had several indirect benefits. The teachers reported increased engagement of the students in class, higher compliance with homework and improvement in academic achievements. Furthermore, some of the participating classes were of lower attaining students, which according to UNESCO had increased dropout rates due to school closure.⁵ All students who participated in our study finished their school year. An additional indirect effect was in the social aspect, where teachers and students reported improved relationships with their peers, as well as better communication with the educational staff. Students and teachers also reported an increased sense of security while teaching face-to-face and knowing that they are all negative for SARS-CoV-2.

Our study has several limitations. First, it is a small study, which included only 3 schools. However, we intentionally chose schools of varying socioeconomic characteristics to test our strategy in different settings, trying to overcome the small scale of the study. Furthermore, the usage of Ag-RDT from 3 different manufacturers using pooling of 4 samples may impair the internal validation of the study. Therefore, we performed a validation process of all 3 Ag-RDT, as well as of the pooling results as detailed in Supplemental Digital Content 1; <http://links.lww.com/INF/E729>. All manufacturers reported a 95%–98% specificity, and we did not detect any false-negative results through the random qRT-PCR tests that were conducted. Moreover, the study was conducted during a time before SARS-CoV-2 variants of concern (either Alpha, Delta and Omicron) were detected. While for the current emerging Omicron surge, which is highly transmissible, the success of this policy needs to be shown, Ag-RDT have been shown to detect Omicron cases, and we believe that policies, such as the one we developed may even be of greater importance. Another potential limitation was that recovered patients were exempted from SARS-CoV-2 testing. Yet, at the time, before Omicron's emergence, reinfection within several months was rare. This policy nowadays should probably exempt only recently recovered students. Lastly, we had limited tools to assess the strategy's impact on the students' wellbeing and academic achievements; however, we did manage to show a subjective improvement in those aspects. We believe that more thorough sociologic studies should take place to assess those outcomes.

Following this study, the Israeli MOH and ministry of education decided to implement a similar policy based on our study

(“Green Class”) since October 2021. The strategy was implemented successfully on the younger age groups of 6 to 11 years who were not eligible to get the vaccine yet.

Summary

In conclusion, we present a strategy for keeping schools open during pandemic surges, which is based on SARS-CoV-2 screening using rapid antigen tests. The strategy provides a fast, low cost and effective screening tool, that does not require specifically trained personnel. When implemented it dramatically reduced COVID-19-related absences from school and had additional benefits such as a positive impact on the student's subjective well-being. This strategy is meant to enable a responsible and safe school opening while maintaining both safety and the continuity of education.

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