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The Impact of Cocirculating Pathogens on Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)/Coronavirus Disease 2019 Surveillance: How Concurrent Epidemics May Introduce Bias and Decrease the Observed SARS-CoV-2 Percentage Positivity

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Background. Circulation of seasonal non–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) respiratory viruses with syndromic overlap during the coronavirus disease 2019 (COVID-19) pandemic may alter the quality of COVID-19 surveillance, with possible consequences for real-time analysis and delay in implementation of control measures.

Methods. Using a multipathogen susceptible-exposed-infectious-recovered (SEIR) transmission model formalizing cocirculation of SARS-CoV-2 and another respiratory virus, we assessed how an outbreak of secondary virus may affect 2 COVID-19 surveillance indicators: testing demand and positivity. Using simulation, we assessed to what extent the use of multiplex polymerase chain reaction tests on a subsample of symptomatic individuals can help correct the observed SARS-CoV-2 percentage positivity and improve surveillance quality.

Results. We find that a non–SARS-CoV-2 epidemic strongly increases SARS-CoV-2 daily testing demand and artificially reduces the observed SARS-CoV-2 percentage positivity for the duration of the outbreak. We estimate that performing 1 multiplex test for every 1000 COVID-19 tests on symptomatic individuals could be sufficient to maintain surveillance of other respiratory viruses in the population and correct the observed SARS-CoV-2 percentage positivity.

Conclusions. This study showed that cocirculating respiratory viruses can distort SARS-CoV-2 surveillance. Correction of the positivity rate can be achieved by using multiplex polymerase chain reaction tests, and a low number of samples is sufficient to avoid bias in SARS-CoV-2 surveillance.

Keywords. cocirculating respiratory viruses; COVID-19 surveillance; mathematical modeling; multiplex testing; SARS-CoV-2.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused a worldwide pandemic of coronavirus disease 2019 (COVID-19), prompting the need for global disease surveillance. Such global surveillance aims to monitor trends in COVID-19 to identify patterns of transmission and progression, estimate morbidity and mortality rates, and assess the impact of control measures [1]. Implementation of community control strategies (ie, mask wearing, lockdowns, social distancing, and school closures) to limit COVID-19 transmission also affected other common respiratory viruses, causing a drop in their detection. Indeed, national and international lockdowns and travel restrictions in March 2020 caused a sharp decline in seasonal influenza circulation in the United States, while the measures almost completely eliminated influenza in Southern Hemisphere countries such as Australia, Chile, and South Africa during their typical influenza season, June–August 2020 [2]. A similar drop in detection was observed for respiratory syncytial virus [3, 4], while rhinovirus activity appeared to be low during the lockdown period [5]. However, when these measures are relaxed, circulation of viruses can recur, mediated by the resumption of social interactions. For example, data from New South Wales, Australia, showed a surge in rhinovirus once schools reopened in mid-May 2020 [5]. Similarly, in Hong Kong, England, and

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France, school reopening in fall 2020 coincided with increased rhinovirus activity, particularly in school-aged children [6–8].

While the role of children in the transmission of SARS-CoV-2 is still debated and children are thought to be less efficient in transmitting the virus than adults, they are frequently the main drivers of transmission of other respiratory viruses, such as rhinovirus and influenza [9–13]. Indeed, the sharp increase in rhinovirus detection among adults admitted to hospitals observed in Southampton, United Kingdom, followed the reopening of schools in September 2020 [14]. As a consequence, circulation of other respiratory viruses during the pandemic may have an impact on COVID-19 surveillance. SARS-CoV-2 can cause a wide range of symptoms, varying in severity [15], and many of these resemble symptoms of other influenzalike illnesses and acute respiratory infections, including influenza viruses, respiratory syncytial virus, rhinovirus, and others. For example, the rise in symptomatic influenza-like illness cases observed in Canada in weeks 34–40 reflected rapidly rising enterovirus/rhinovirus disease activity rather than COVID-19 [16]. Delay in trend interpretation may lead to delayed decision making and control measure implementation, which may have substantial negative consequences on the public health system, owing to the exponential nature of the COVID-19 epidemic [17].

The World Health Organization recommends considering test positivity proportion over a 2-week period as a key epidemiological indicator to assess and classify the level of community transmission [18]; therefore, other respiratory viruses could generate misinterpretation of COVID-19 surveillance data. For instance, Public Health France reports showed a decrease in the SARS-CoV-2 symptomatic percentage positive in September 2020, which is when schools reopened in France, although the daily number of symptomatic COVID-19 cases did not decrease [19].

We hypothesized that this marked decrease in SARS-CoV-2 symptomatic percentage positive could be caused by increased cocirculation of another respiratory virus. In the current study, we used mathematical modeling to investigate the consequences of increased circulation of other respiratory viruses, in terms of both the number of SARS-CoV-2 tests performed and monitoring of the percentage positivity of SARS-CoV-2 tests and interpretation of surveillance data.

METHODS

SARS-CoV-2 Surveillance Data

We focus here on the surveillance of symptomatic individuals, as they are more likely to request SARS-CoV-2 tests. We used data on SARS-CoV-2 tests and positive cases in metropolitan France from Public Health France Screening Information System (SI-DEP) for the period from 24 August to 19 October 2020, when a decrease in symptomatic SARS-CoV-2 percentage positivity was observed (Figure 1). Symptomatic individuals who started presenting symptoms 0–4 days before polymerase chain reaction (PCR) test were classified (and are referred throughout) as symptomatic). Asymptomatic individuals, those who started presenting symptoms 5–14 days or more before the COVID-19 test, and those whose symptomatic status was not recorded, were classified as other. We separated the data in this way because individuals having recent symptoms relative to the time of testing were more likely to be infected with a non–SARS-CoV-2 respiratory virus with shorter symptom duration, with symptoms typically peaking at 1–3 days [20], as opposed to individuals who were presenting symptoms for a long time before requesting a COVID-19 test.

Hospitalization Data

Daily hospitalization data for COVID-19, from Public Health France, information system for monitoring victims of attacks and exceptional health situations (SI-VIC), were acquired from 24 August to 19 October 2020.

Neutral Transmission Model

We developed a multipathogen susceptible-exposed-infectious-recovered (SEIR) transmission model to explore and illustrate how cocirculation of another respiratory virus (called virus 2) with syndromic overlap during the ongoing COVID-19 pandemic may affect SARS-CoV-2 test percentage positivity. We build upon a model of 2 circulating pathogens [21] by adding an exposed compartment for both viruses, to more closely match the natural history of SARS-CoV-2 and other respiratory viruses (Figure 2). The model is neutral, assuming no interaction between 2 pathogens—that is, no change in infectiousness of coinfected classes and no change in the probability of acquisition of a second infection after the first infection (Supplementary Material [Appendix A1], Section S1, and downloadable code).

Testing Model

We modeled the total number of tests in symptomatic individuals by considering 4 reasons for testing symptomatic individuals: (1) symptomatic individuals infected with SARS-CoV-2 (T_{COV}); (2) contact tracing—we assumed that a positive SARS-CoV-2 test will trigger contact tracing investigation where contact tracing of a positive test on a day t would generate an increase in test demand after some contact tracing delay, d in days, where we considered only contacts presenting symptoms at the time of testing ($T_{Contacts}$); (3) symptomatic individuals infected with virus 2 (T_{V2}); and (4) a baseline number of symptomatic tests (T_b)—that is, symptomatic individuals tested for SARS-CoV-2 but truly negative for both SARS-CoV-2 and virus 2.

Thus, the total number of tests T for SARS-CoV-2 among symptomatic individuals on a given day t is given by the following:

$$T(t) = T_b + T_{COV}(t) + T_{CONTACTS}(t-d) + T_{V2}(t)$$

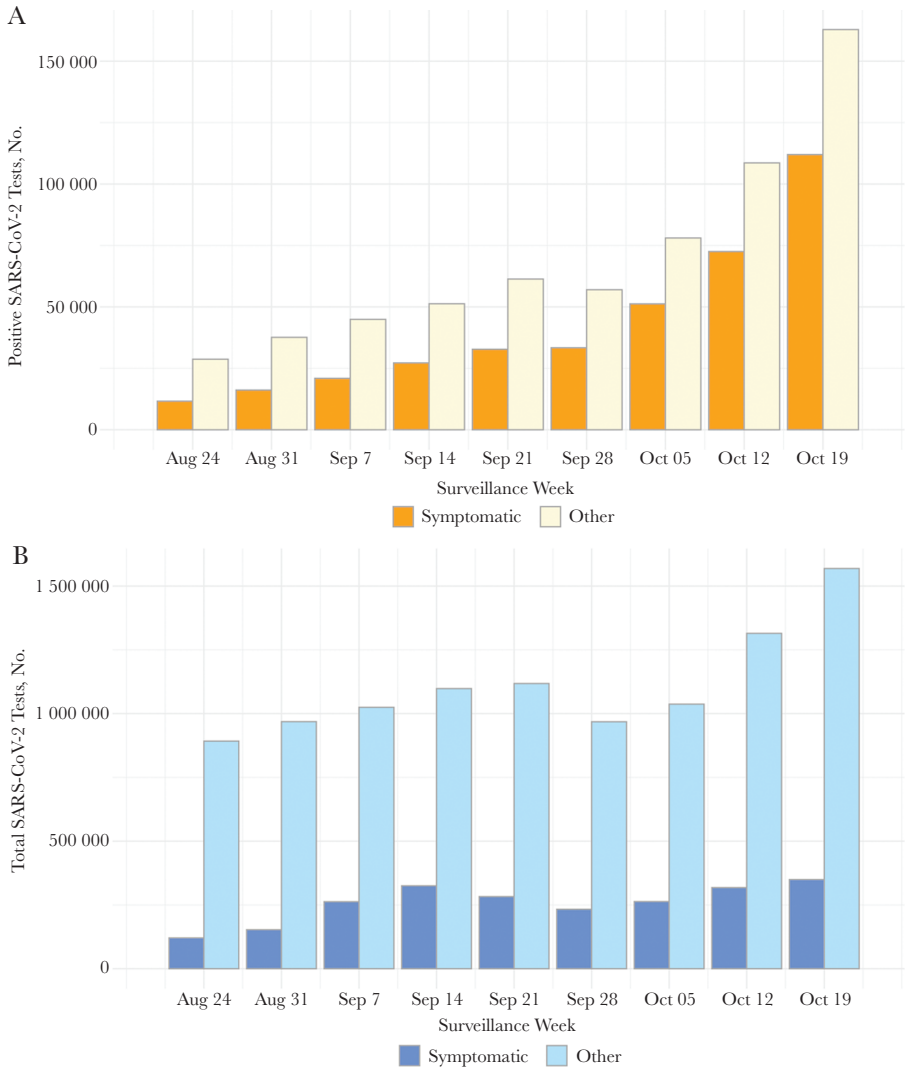

Figure 1. Weekly testing data for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in France, from 24 August to 19 October 2020 (Public Health France SI-DEP database). *A,* Number of positive SARS-CoV-2 tests. *B,* Total number of SARS-CoV-2 tests.

The total number of tests T are the sum of PCR SARS-CoV-2 tests (T_{pcr}) and multiplex tests (T_m) conducted on symptomatic individuals on a given day t:

$$T(t) = T_{pcr}(t) + T_m(t)$$

where $T_{pcr}(t)$ is given by

$$T_{pcr}(t) = T(t) * (1 - m)$$

and $T_m(t)$ by

$$T_m(t) = m * T(t)$$

with m being the proportion of the multiplex tests used on the symptomatic individuals.

The observed SARS-CoV-2 symptomatic percentage positive P_+ on a day t is given by the following:

$$P_+(t) = \left(\frac{T_+(t)}{T(t)}\right) * 100$$

where $T_+(t)$ corresponds to the number of SARS-CoV-2–positive tests among symptomatic individuals over time (see Supplementary Material [Appendix A1], Section 2.1, for details).

Testing Strategies

To investigate whether it was possible to correct the observed SARS-CoV-2 symptomatic positivity rate using the results of tests for virus 2 in a subsample of the population, we modeled the use of multiplex PCR tests along with standard PCR SARS-CoV-2 tests on a subsample of symptomatic individuals. We

tested whether results of multiplex tests could be used to maintain the surveillance of other viruses and determined what correction of the observed SARS-CoV-2 percentage positive was needed during other virus outbreaks.

Therefore, we introduced 2 different types of tests into the model: reverse-transcription PCR SARS-CoV-2 test with sensitivity s_{pcr} and a multiplex PCR test that simultaneously tests for multiple pathogens, with average sensitivity s_m to detect SARS-CoV-2 or virus 2. We assumed that the proportion of multiplex tests actually carried out across all tests on a given week was m.

We estimated the corrected SARS-CoV-2 symptomatic percentage positive (P_{C+}) on a day t as follows:

$$P_{C+}(t) = \left(\frac{T_+(t)}{T_C(t) + T_m(t) - T_{V2+}(t)} \right) * 100$$

where $T_C(t)$ represents the corrected total number of SARS-CoV-2 tests on a given day t, $T_m(t)$ the total number of multiplex tests conducted on symptomatic individuals on a given day t, and $T_{V2+}(t)$ the number of confirmed positive symptomatic virus 2 cases detected with multiplex tests on a given day t:

$$T_{V2+}(t) = m * T_{V2}(t)$$

The corrected total number of SARS-CoV-2 tests $T_C(t)$ among symptomatic individuals on a given day t is

$$T_C(t) = T_{pcr}(t) * (1 - prop_{V2+}(t))$$

where $prop_{V2+}(t)$ represents the proportion of symptomatic virus 2 confirmed positive cases among all multiplex tests conducted on symptomatic individuals (Supplementary Material [Appendix A1], Section S2.2).

To account for the impact of imperfect sensitivity of tests and multiplex test sample size on the uncertainty of indicators, we added a stochastic observation model. The observed numbers of positive tests for SARS-CoV-2 (T_{COV}) and virus 2 (T_{V2+}) were calculated assuming a binomial distribution (Supplementary Material [Appendix A1], Section S2.3).

We also evaluated unbiased or effective percentage positivity of SARS-CoV-2 based on a single-pathogen susceptible-exposed-infectious-recovered (SEIR) transmission model that describes transmission of SARS-CoV-2 in the population without presence of another respiratory virus. The effective percentage positive is given by the similar equation used for the observed percentage positive but without the presence of virus 2:

$$P_{E+}(t) = \left(\frac{T_+(t)}{T(t)} \right) * 100$$

(See Supplementary Material [Appendix A1], Section S2.1, for details.)

Simulation Study

We simulated the introduction of an outbreak of virus 2 in a population with circulating SARS-CoV-2 coinciding with a particular event that increases social interactions (eg, school reopening), giving the observed percentage positive. We assumed that 6% of the population had already been infected and became immune to SARS-CoV-2, which matches the situation of France in September 2020 at the time of school reopening [22]. We also assumed that 70% of the population is either immune to virus 2 or will not be exposed to the virus at all owing to generally never being in contact with schoolchildren, social distancing measures, and implemented community control strategies (Supplementary Material [Appendix A1], Section S1.5). We tracked 2 key epidemiological indicators: the number of tests requested and percentage positivity.

Sensitivity Analyses

Several sensitivity analyses were carried out. First, we varied the sensitivity of multiplex PCR test sensitivity (s_m), while maintaining the same sensitivity of SARS-CoV-2 PCR test (s_{pcr}) to investigate its impact on the corrected percentage positive of SARS-CoV-2. We also evaluated a range of proportion values of multiplex tests (m = 0.0005, 0.001, 0.002, or 0.005) to assess how sample size of multiplex tests affected the correction of the observed symptomatic SARS-CoV-2 percentage positive. Then, we conducted additional sensitivity analyses, varying s_{pcr} and the proportion of symptomatic individuals infected with virus 2 (s_2), while maintaining other parameters the same. Finally, we investigated the impact of the R_0 (basic reproduction number) of virus 2 and the initial proportion of the population immune to SARS-CoV-2 and to virus 2. Using an extended age-structured transmission model with assumptions that virus 2 has a 3 times higher acquisition rate in children than in adults, and that children (<15 years old) represent 20% of the total population, we finally analyzed the impact of heterogeneous virus 2 transmission across age groups on the proposed correction (Supplementary Material [Appendix A1], Section S4). R (version 4.0.3) and RStudio (version 1.3.1093) software and the deSolve package were used for modeling transmission, testing, and all statistical analyses [23–25].

RESULTS

Data from Public Health France show a decrease in symptomatic percentage positive for SARS-CoV-2 in France after 1 September 2020, synchronous with school reopening, while the hospitalization data show a steady increase in daily hospitalizations (Figure 3D). However, this decrease in positivity rate was not due to a decline in number of SARS-CoV-2–positive tests among symptomatic individuals (Figure 1A). Moreover, the number of tests for symptomatic individuals increased during September 2020, as did the number of other tests (Figure 1B).

In our simulation study, the outbreak of virus 2 lasted for 1.5 months, with a peak reached after 2 weeks (Figure 3A).

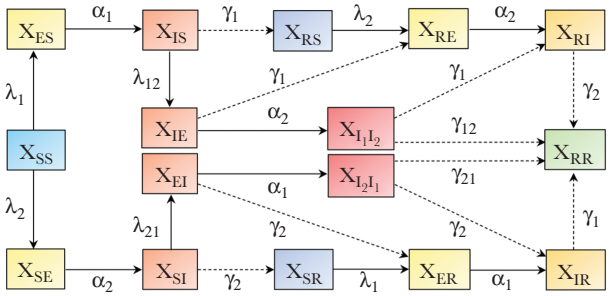

Figure 2. Model formalizing the transmission of 2 cocirculating viruses in a population. Individuals are split into compartments (X_{ij}) according to their status with respect to the 2 pathogens. In X_{ij}, *i* specifies the individual's status for virus 1 (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), and *j*, the individual's status for virus 2. The letters *S, E, I,* and *R* stand for susceptible, exposed, infected, and recovered, respectively with I_1I_2 and I_2I_1 representing dually infected compartments in the order of viral infection. The rates of transition between compartments are infectiousness onset rates (α_1 and α_2) and recovery rates (γ_1 and γ_2); λ_1 and λ_2 stand for the forces of infection for susceptible hosts by virus 1 (SARS-CoV-2) and virus 2, respectively; λ_{21} and λ_{12} are forces of infection by virus 1 (λ_{21}) and virus 2 (λ_{12}) for hosts already infected by the other pathogen (Supplementary Material [Appendix A1], Section 1.3).

These first weeks of virus 2 circulation led to up to a 23% increase in the number of daily tests performed on symptomatic individuals (Figure 3B). The observed SARS-CoV-2 percentage positive among symptomatic tests decreased sharply in the first 2 weeks, underestimating the effective percentage positivity by up to 3% (23% relative decrease), and then progressively increased to converge to the effective percentage positivity when the outbreak was nearly extinct (Figure 3C). We determined that a testing frequency *m* of 0.1% ($m = 0.001$; ie, performing 1 multiplex tests for every 1000 symptomatic individuals), which most closely represents the realistic proportion of multiplex tests currently used in France to test for non–SARS-CoV-2 respiratory viruses [7], was sufficient to provide a correction that closely follows the effective percentage positive for SARS-CoV-2 (Figure 3C).

Sensitivity analyses showed that changing the sensitivity of the multiplex assays (s_m) affected the corrected percentage positive of SARS-CoV-2, with higher values of s_m providing better estimates of the effective percentage positive (Supplementary Figure 1 and Supplementary Material [Appendix A1]). Similarly, the correction of the observed SARS-CoV-2 percentage positive was negatively affected by the lower proportion of the multiplex PCR testing (*m*) used in the model, and vice versa. A larger proportion of multiplex PCR tests used improved the correction of the observed SARS-CoV-2 percentage positive (Supplementary Figure 2 and Supplementary Material [Appendix A1]). The correction quality was not affected by varying s_{pcr}, s_2, R_0, or the initial proportion of the population immune to SARS-CoV-2 and to virus 2 (Supplementary Figures 3–7 and Supplementary Material [Appendix A1]). When an age-structured transmission model was considered, assuming acquisition rate 3 times higher in children than in adults, our analyses showed that testing demand increase was greater in children than in adults, as expected, and the observed percentage positive decreased by 37.5% (from 12.8% positivity to 8%) in that group (Supplementary Figure 8 and Supplementary Material [Appendix A1]). Despite this strong impact, correction quality in children was poorer when the previously proposed testing frequency of 0.1% ($m = 0.001$) was used, owing to the smaller size of the population. Increasing testing frequency to 0.5% ($m = 0.005$; ie, performing 1 multiplex tests for every 200 symptomatic children) improved the correction quality in this age group (Supplementary Figure 9 and Supplementary Material [Appendix A1]).

DISCUSSION

The implementation of the community control strategies to limit transmission of SARS-CoV-2 also decreased the circulation of other respiratory viruses. However, once control measures are relaxed and when social interactions are resumed, we are likely to observe increased activity of other respiratory viruses [6–8]. Using model simulations of 2 cocirculating pathogens, we showed that an outbreak of a secondary respiratory virus during COVID-19 pandemic may increase SARS-CoV-2 testing demand and, as a consequence, may hinder the detection of the initial increase of SARS-CoV-2 infections and lead to the overall underestimation of the SARS-CoV-2 epidemic. We proposed to correct the observed positivity rate of SARS-CoV-2 by using multiplex PCR testing in a subsample of the symptomatic population. We estimate that performing 1 multiplex test for every 1000 COVID-19 tests could be enough to significantly improve real-time epidemiological interpretation.

Underreporting of infection is a challenge in all pandemics and epidemics, including this one [26, 27], and we show here that short-term alterations in surveillance due to other epidemics may affect interpretation of COVID-19 trends. Indeed, after schools reopened, multiplex testing detected circulation of rhinovirus in France (Supplementary Figure 10 and Supplementary Material [Appendix A1]), which supports our hypothesis that secondary virus might have been responsible for decreased COVID-19 epidemic indicators. Percentage positivity, a key indicator monitored for epidemic control and public health decision making [18] appears particularly sensitive to this effect. Moreover, maintaining surveillance of other respiratory viruses should help public health officials better anticipate increases in SARS-CoV-2 testing demand.

The use of multiplex PCR assays for SARS-CoV-2 detection in a sample of symptomatic cases has already proved effective in detecting other respiratory viruses: a study in Northern California in March 2020 found that 26.7% of symptomatic patients who tested negative for SARS-CoV-2 were positive for ≥1 additional pathogens, most often rhinovirus or enterovirus [28]. Another study found that 13.1% of patients who tested negative for SARS-CoV-2 were positive for ≥1 non–SARS-CoV-2

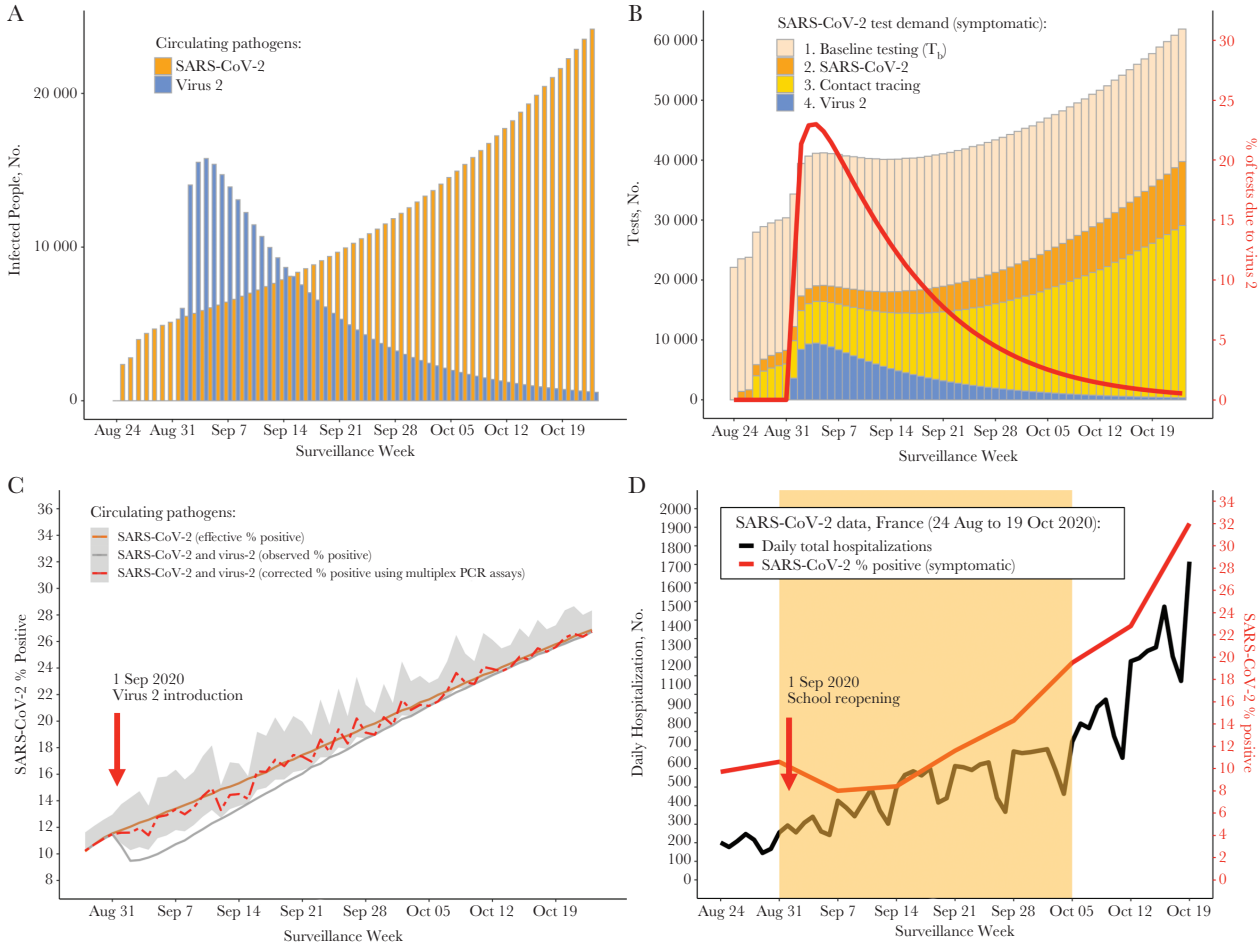

Figure 3. Impact on surveillance indicators, as shown by model simulations of virus 2 introduction in a population with the ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic and coronavirus disease 2019 (COVID-19) hospitalization and testing data in France, from 24 August to 19 October 2020. *A,* Simulations of daily incidence of SARS-CoV-2 and virus 2 in symptomatic individuals. *B,* Simulations of SARS-CoV-2 test demand among symptomatic individuals, including tests requested by individuals infected with both viruses, contacts of previously identified case patients, and a constant testing baseline. Red line represents the percentage increase in SARS-CoV-2 test demand. *C,* Simulated SARS-CoV-2 percentage positive among all tests for symptomatic individuals. 1 September 2020 marks the introduction time of virus 2 in the population (eg, after school reopening). The outbreak of virus 2 decreases the observed SARS-CoV-2 percentage positive (*solid gray line*) relative to the effective percentage positive (*solid orange line*) where we assumed no presence of a secondary respiratory virus and, therefore, SARS-CoV-2 testing demand and surveillance are not affected by virus 2. Observed percentage positive can be corrected by testing a proportion (m) of symptomatic individuals with multiplex polymerase chain reaction (PCR) assays. Corrected percentage positive is conducted with testing frequency of 1 multiplex per 1000 daily tests (red dashed line with 95% confidence intervals). All simulations are run assuming $s_{pcr} = 95\%$ and $s_{m} = 90\%$ (Supplementary Material [Appendix A1], Section S1.5). *D,* SARS-CoV-2 hospitalizations (Public Health France SI-VIC database) and symptomatic percentage positivity (Public Health France SI-DEP database) in France from 24 August to 19 October 2020. Orange shaded area represents observed underestimation of SARS-CoV-2 symptomatic percentage positivity.

respiratory viral pathogen [29]. These studies show not only that the non–SARS-CoV-2 respiratory viruses are circulating in our communities, but also that symptomatic cases due to other respiratory pathogens contribute to the overall number of negative SARS-CoV-2 tests. Increase in the hospitalization data and the number of SARS-CoV-2–positive tests in symptomatic individuals during an observed decrease in symptomatic percentage positive suggest that decrease in COVID-19 cases was not responsible for the decrease in test positivity rate. Considering that rhinovirus can cause fever and severe sore throat in children, and that epidemics of rhinovirus are common on school reopening [30, 31], it is likely that symptomatic children and parents requested testing for SARS-CoV-2, thus increasing the number of negative tests and inadvertently reducing the test positivity rate during this time.

Incorporating age structure in the transmission model suggested that heterogenous transmission of virus across ages could lead to even more pronounced increased testing demand and decreased percentage positivity in one age group, but achieving good quality correction of the observed percentage positivity can be more challenging and may require higher frequency of multiplex tests if the targeted population is small.

To keep our model simple, the mechanisms are a simplification of the real processes, and therefore, there are limitations. We did not incorporate testing capacity within this model, and we assumed that all symptomatic individuals requesting testing on

a given day will be able to be tested. In addition, we assumed no interaction between viruses, meaning that the presence of one of the viruses did not affect (promote or protect against) infection with the other virus. Recent studies have suggested some possible protection from COVID-19 infection conferred by rhinovirus interference with SARS-CoV-2 replication kinetics, and this may warrant further exploration at the population level [32].

Other causes, such as seasonal allergies and other circulating respiratory pathogens with symptoms overlap, could lead to increase in testing demand. In case of allergies, using additional data on allergy causes—such as pollen data to first identify allergy seasons throughout the year that cause similar respiratory symptoms, or data on antiallergic drug consumption (antihistamine prescriptions/steroids/sales of allergy medication)—could provide opportunities for corrections. When it comes to viruses and other respiratory pathogens, while there is some variation among panels, most multiplex PCR-based respiratory viral panels test for the common respiratory viruses and can detect most viruses that can increase the number of negative SARS-CoV-2 tests. If the multiplex assay tests for 2 viruses only—for example influenza and SARS-CoV-2, as recommended by the Centers for Disease Control and Prevention—knowing the epidemic patterns of respiratory viruses and real-time adapting multiplex tests for their identification are imperative for viral detection and continued surveillance to make the correction.

We proposed a method to correct the observed positivity rate of SARS-CoV-2 during an outbreak of another respiratory virus, to help reduce the overall underestimation of SARS-CoV-2 in the population. Clinical sensitivities between tests can differ markedly depending on the test manufacturer, and, with multiplex PCR testing, sensitivity also depends on the pathogen being detected [29, 33]. With the overall high sensitivity of both SARS-CoV-2 and multiplex PCR tests, correcting the observed positivity rate could be a very effective way to minimize underestimation of the true COVID-19 burden in the community. Furthermore, multiplex testing—which in France is generally performed by Sentinelles physicians on patients seen in the consultation, to test for various respiratory viruses—could be incorporated into laboratory testing for SARS-CoV-2 to improve surveillance and detection of other respiratory viruses, which in turn may improve identification of SARS-CoV-2–positive individuals in the population.

Using modeling simulations, we highlight the fact that cocirculating respiratory viruses affect COVID-19 surveillance. Our results demonstrate that systematic use of multiplex PCR tests on a subsample of symptomatic individuals is key to maintaining unbiased surveillance.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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