

# Monitoring SARS-CoV-2 Activity with Sentinel Surveillance: Lessons Learned from the First Wave in Israel

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## ABSTRACT

**Background:** Guidelines for pandemic preparedness emphasize the role of sentinel and syndromic surveillance in monitoring pandemic spread.

**Objectives:** To examine advantages and obstacles of utilizing a sentinel influenza surveillance system to monitor community severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) activity based on Israel's experience from mid-March to mid-May 2020.

**Methods:** Several modifications were applied to the influenza surveillance system. The clinical component relied mainly on pneumonia and upper respiratory infection (URI) consultations with primary care physicians as well as visits to emergency departments (ED) due to pneumonia. The virological data were based on nasopharyngeal swabs obtained from symptomatic patients who visited outpatient clinics.

**Results:** By epidemiological week 12 of 2020, the crude and age-specific primary physician consultation rates due to URI and pneumonia declined below the expected level, reaching nadir that lasted from week 15 until week 20. Similarly, ED visits due to pneumonia were significantly lower than expected from weeks 14 and 15 to week 20. The virological surveillance started on week 13 with 6/253 of the swabs (2.3%) positive for SARS-CoV-2. There was a peak of 13/225 positive swabs on week 14 (5.8%). During weeks 17–20, none of the swabs (47–97 per week) were positive for SARS-CoV-2. This trend was similar to national data.

**Conclusions:** The virological component of the surveillance system showed the SARS-CoV-2 community spread, but had low sensitivity when virus activity was low. The clinical component, however, had no yield. Sentinel surveillance can assist in monitoring future novel pandemics and should be augmented in revised preparedness plans.

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**KEY WORDS:** coronavirus disease 2019 (COVID-19), sentinel surveillance, pandemic preparedness, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), syndromic surveillance

The first case of coronavirus disease 2019 (COVID-19) was detected in Israel on 21 February 2020 (week 8). After that, the national weekly percentages of positive swabs increased to a peak of 8.1% on week 13 (22–28 March 2020) and then gradually declined, reaching a minimum of 0.4% on week 20. By 16 May 2020, there were 16,566 laboratory-confirmed COVID-19 cases in Israel (3.3% of 500,103 tests) [1]. The clinical manifestations of these cases ranged from asymptomatic or mild respiratory infection to severe respiratory infection, leading to hospitalization and even death [2,3]. Of note, during this first pandemic wave, in accordance with the Israel Ministry of Health (MOH) guidelines [4], patients at community clinics who had no epidemiological link (i.e., returned from abroad or had a close contact with a confirmed COVID-19 case in the previous 14 days) were not eligible for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing.

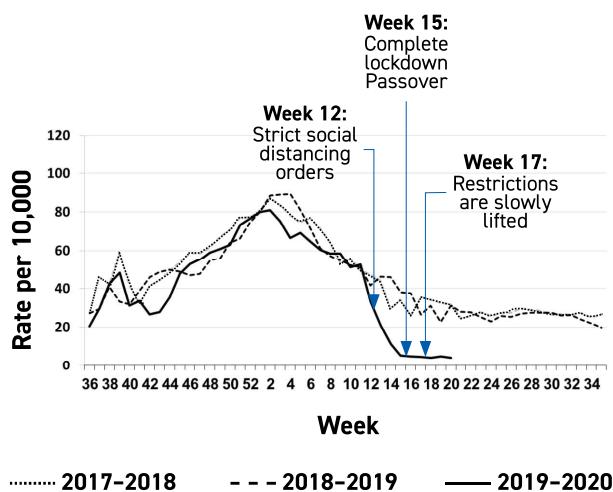
In the early stages of the pandemic, the World Health Organization (WHO) recommended adapting existing influenza surveillance systems to detect and monitor SARS-CoV-2 activity in the community [5]. The Israel Center for Disease Control (ICDC) at the MOH operates a seasonal influenza surveillance system. This system also has a designated role in the national pandemic preparedness guidelines [6] and was used as a surveillance tool during the 2009 influenza A/H1N1 pandemic [7,8].

The aim of this study was to examine the advantages and the challenges of utilizing an influenza surveillance system to monitor community SARS-CoV-2 activity during the pandemic first wave. Lessons learned from such adaptation are of utmost importance for the preparedness for future respiratory epidemics and pandemics.

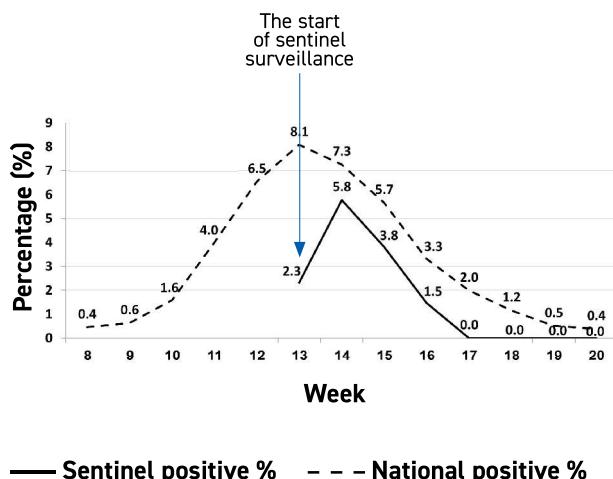
## PATIENTS AND METHODS

Israel's influenza surveillance system has clinical and virological components [7]. The clinical component relies mainly on consultations with primary physicians due to influenza-like illness (ILI), upper respiratory infection (URI), and pneumonia,

**Figure 1.** Weekly consultations with primary physicians due to upper respiratory infection, Maccabi Health Services, Israel, 2017–2020



**Figure 2.** Sentinel and national weekly percentages of positive nasopharyngeal swabs for severe acute respiratory syndrome coronavirus 2, Israel, February to May 2020



with coverage of approximately 25% of the Israeli population [9]. An additional clinical data source includes visits to internal medicine and pediatric emergency departments (EDs) due to pneumonia in eight representing hospitals across Israel. The virological data is based on results of real-time reverse transcriptase polymerase chain reaction (rRT-PCR) for influenza and other respiratory viruses performed by the Israel Central Virology Laboratory on nasopharyngeal swabs from patients with ILI who visit sentinel clinics [10].

Several modifications were applied to adapt the influenza surveillance for COVID-19 surveillance. First, the case definition was modified. For the virological surveillance, the national suspected COVID-19 clinical case definition (fever  $\geq 38.0^{\circ}\text{C}$  or cough or dyspnea or any other acute respiratory symptom) [4] was applied but the epidemiological link was omitted. For the clinical component, physicians' consultations due to URI rather than ILI were used [11,12].

Second, the sentinel clinics were provided with full personal protective gear (including surgical masks, gloves, disposable robes and visors) in accordance with the MOH COVID-19 guidelines [4]. Third, to raise the surveillance sensitivity and to improve population coverage, the number of weekly swabs per clinic was not limited and new clinics were gradually added, reaching 42 clinics by week 16. The clinics covered approximately 5% of the total population with representation from all geographical areas, all age groups, and sub-populations (including Arabs, Bedouin, Druze, and ultra-Orthodox Jews). Last, patients who met the case definition but contacted the clinic via telemedicine were swabbed at their homes by a representative from the Israeli National Emergency Medical Services Organization. Sentinel specimens were tested only for SARS-CoV-2.

Crude and age-specific weekly consultations (including by telemedicine) with primary physicians due to URI and pneumonia per number of the HMO's members were computed. Sequential consultations with the same diagnoses within 28 days were omitted. In addition, weekly percentages of visits to the EDs due to pneumonia and of positive swabs for SARS-CoV-2 from sentinel clinics were calculated. Statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA) and Microsoft Excel version 2010 (Redmond, WA, USA).

The ICDC surveillance system is conducted in accordance with the Public Health Ordinance in Israel and is not considered medical research. Verbal consent was given by participants before being tested for respiratory viruses by nasopharyngeal swabs.

## RESULTS

From week 8 until week 11 (16 February 2020–14 March 2020), consultation rates due to URI steadily declined, as anticipated. However, from week 12, the rates declined below the expected level, reaching nadir that lasted from week 15 until week 20 (5 April 2020–16 May 2020) [Figure 1]. This steep decline was prevalent in all age groups. A similar pattern was observed for consultations due to pneumonia (data not shown). Similarly, both weekly numbers and percentages of visits to the EDs due to pneumonia were significantly lower than expected from the first half of April to week 20 (data not shown).

The virological surveillance started on week 13 (22 March 2020–28 March 2020). During the first week, 259 swabs were collected and 2.3% (6) tested positive for SARS-CoV-2. This percentage rose to a peak of 5.8% (13/225) on week 14 and

then declined. From week 17 until week 20 (19 April 2020–16 May 2020), none of the swabs (47–97 per week) were positive for SARS-CoV-2 [Figure 2]. Altogether, during the 8-week period, 24 of 947 swabs (2.5%) were positive for SARS-CoV-2. The median age of the positive cases was 52 years (range 13–79); from all the positive cases 13 (54.2%) were male, and 15 (62.5%) presented with fever.

## DISCUSSION

From our experience during first wave of the pandemic, it is clear that utilizing a sentinel surveillance system to monitor community SARS-CoV-2 activity is both feasible and valuable. Most importantly, it appears that the sentinel SARS-CoV-2 activity has a trend similar to the national data, despite the small sample of swabs (47–253 swabs per week vs. an average of almost 40,000 per week), the low population coverage (5%), and the different criteria for SARS-CoV-2 testing. During the first wave of the pandemic in Israel, SARS-CoV-2 was tested only in well-defined cases, which did not include community clinics patients with no epidemiological link [4], in contrast to the sentinel clinics case definition. Therefore, the sentinel clinics network was the only systematic source for knowledge of SARS-CoV-2 community spread. This knowledge is crucial for policy makers in managing the COVID-19 pandemic [13–15].

Nonetheless, when the national percentages were 2% or lower, the sentinel surveillance was not sensitive enough to detect SARS-CoV-2 activity. Additional clinics nationwide were recruited and the number of swabs were not limited, and indeed in all weeks but one (week 18, n=47) above 50 swabs were collected [5]. Still, a low sensitivity is to be expected when the transmission in the community is low.

We encountered several obstacles. The most critical was the significant decline in consultations with primary physicians and visits to the EDs due to URI and pneumonia. The major decline in consultations started on week 12, when the public was instructed to maintain strict social distancing behaviors, including refraining from non-emergency face-to-face medical consultations [16]. The rates reached a nadir at week 15, when a complete lockdown was enforced [16]. Even though from week 17 onward some of the restrictions were gradually lifted [16], the consultation rates continued to remain extremely low. As the HMOs provided their members with increasing availability of telemedicine communication options and all consultations with primary physicians were monitored, including by telemedicine, it appears that the decline was not due to either option. Of note, other researchers from Israel also demonstrated a decrease in health services utilization due to non-infectious diseases during the pandemic first wave [17,18], suggesting that patients were generally hesitant about medical encoun-

ters at that time. Overall, the decline in URI and pneumonia visits made the clinical component of the surveillance system almost obsolete and challenged the virological surveillance that depends on it, highlighting the value of in-house swabs collection.

Other countries (e.g., Greece, Poland) demonstrated below expected rates of consultations with primary physicians due to ILI/URI during their first wave of the COVID-19 pandemic [19]. Nevertheless, some countries (e.g., France, United Kingdom, Belgium, Germany, Netherlands) were able to detect an increase in ILI and/or URI consultation rates [19–21], while others showed rates similar to those reported in previous years (e.g., Italy, Spain) [19].

Other challenges included encouraging the clinics to participate in SARS-CoV-2 surveillance (as fear from contagion and work overload was often expressed) and the worldwide shortage of equipment, including protective gear, swabs, and reagents. Both delayed the start of the virological surveillance and hampered participation of additional clinics.

## CONCLUSIONS

Adapting a routine sentinel influenza surveillance system to monitor novel respiratory virus activity allows researchers to define its transmission in the community and, therefore, when initiated promptly, can provide crucial knowledge to policy makers of the need to shift from containment to mitigation strategies. It can also assist in monitoring a pandemic when testing capacities are scarce and monitor potential future seasonal epidemics after the pandemic subsides. Nevertheless, it might not be sensitive enough when the total activity is very low or when there are only distinct pockets of transmissions in the population. Hence, testing should not be limited to sentinel clinics. Clinical syndromic surveillance, however, could be severely challenged by a decline in health services utilization.

The lessons learned from this retrospective analysis of the respiratory surveillance system performance during the COVID-19 pandemic are of utmost importance for the preparedness for future respiratory epidemics and pandemics, as they imply that sentinel virological surveillance should be included in all pandemic preparedness guidelines with strategic plans to rapidly initiate the system and to expand its coverage and capacity. Moreover, new clinical surveillance means (e.g., telephone helplines, Google search queries, and surveys) [21] should be vigorously sought. National pandemic guidelines should be revised based on this valuable experience.

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**Capsule****Impact of cytokine inhibitor therapy on the prevalence, seroconversion rate, and longevity of the humoral immune response against SARS-CoV-2 in an unvaccinated cohort**

**Simon** and co-authors investigated the impact of biologic disease-modifying antirheumatic drug (bDMARD) treatment on the prevalence, seroconversion rate, and longevity of the humoral immune response against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients with immune-mediated inflammatory diseases (IMIDs). In this study, 4508 participants (2869 IMID patients and 1639 controls) were analyzed. The unadjusted relative risk (RR) (0.44, 95% confidence interval [95%CI] 0.31–0.62) and adjusted RR (0.50, 95%CI 0.34–0.73) for SARS-CoV-2 IgG antibodies were significantly lower in IMID patients treated with bDMARDs compared to non-health care controls ( $P < 0.001$ ), primarily driven by treatment with tumor necrosis factor inhibitors, interleukin-17 (IL-17) inhibitors, and IL-23 inhibitors. Adjusted RRs for untreated IMID patients (1.12,

95%CI 0.75–1.67) and IMID patients receiving conventional synthetic DMARDs (0.70, 95%CI 0.45–1.08) were not significantly different from non-health care controls. Lack of seroconversion in PCR-positive participants was more common among bDMARD-treated patients (38.7%) than in non-health care controls (16%). Overall, 44% of positive participants lost SARS-CoV-2 antibodies by follow-up, with higher rates in IMID patients treated with bDMARDs (RR 2.86, 95%CI 1.43–5.74). The authors concluded that IMID patients treated with bDMARDs have a lower prevalence of SARS-CoV-2 antibodies, seroconvert less frequently after SARS-CoV-2 infection, and may exhibit a reduced longevity of their humoral immune response.

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