

Integration of COVID-19 into the Sentinel Influenza and Other Acute Respiratory Infections Network

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Abstract: *Background:* In the COVID-19 pandemic period, surveillance relies on comprehensive testing and case-based reporting. In the post-pandemic phase, multi-layered surveillance, including sentinel surveillance, should be developed to provide information for policy-making. *Methods:* The existing sentinel network for surveillance of acute respiratory infections was upgraded in the 2020/2021 season with COVID-19 added to the list of reportable diagnoses. We have updated the instructions for the sentinel sites. The virological sampling protocol was adapted to the pandemic and sentinel samples were tested for SARS-CoV-2. To assess the reliability and usability of the upgraded system, we compared the weekly sentinel COVID-19 incidence rates with national incidence rates. *Results:* Weekly sentinel COVID-19 incidence rates were comparable to nationally reported rates with some deviations. The largest differences were in the age group ≥ 65 years, with lower incidence rates in the sentinel compared to the national data in the second wave of the pandemic. In adults (20–64 years), the discrepancy was less pronounced. Virological data showed the complete absence of influenza circulation in the 2020/21 season, the unusual course of the RSV season and the absence of hMPV in the first year of the pandemic. The proportion of positive sentinel samples for SARS-CoV-2 was comparable to national data. *Conclusions:* The process of integrating COVID-19 into the sentinel surveillance is ongoing. We closely monitor the data in order to contextually understand the factors that may affect the results and identify the limitations of the sentinel surveillance for the COVID-19 pandemic.

Keywords: COVID-19, Sentinel Surveillance, Influenza-Like Illness, Acute Respiratory Infections, Pandemic

1. Introduction

The COVID-19 pandemic has drastically changed the landscape of acute respiratory infections (ARI) globally. In the pre-pandemic era, each winter season sees a surge in the incidence of ARI and thus a substantial increase in the primary care consultation rates, hospitalizations and excess mortality. The burden of acute respiratory diseases was mainly driven by the influenza virus in the pre-pandemic period, with other viruses e.g. RSV (predominantly infecting neonates and toddlers) adding importantly to the overall increase in pressure on health services. In the pre-pandemic era, assessments of the seasonal intensity of respiratory virus activity were based on rates of influenza-like illness (ILI) and ARI. Virological indicators were used for geographical

spread and intensity assessment [1]. At the beginning of the COVID-19 pandemic, a correlation was found between the number of confirmed COVID-19 cases and an increase in the incidence rate of ILI notified in the French general practice-based *Sentinelles* network [2]. The authors concluded that the established sentinel system might prove useful for assessment of the rapidly evolving epidemiological situation [2]. The same was observed by Silverman et al. in the United States (US) [3]. The surge in excess ILI correlated with known patterns of SARS-CoV-2 spread across states within the US at a higher magnitude than the number of confirmed COVID-19 cases by the end of March 2020 suggested [3]. In the same period influenza positive tests decreased with an increase in ILI consultation rates, which suggested the utility of the system for COVID-19 sentinel surveillance [4]. Sentinel surveillance study that aimed to determine what

proportion of mild, outpatient influenza-like illnesses were caused by SARS-CoV-2 in first months of the pandemic found a surprisingly high 5% positivity rate in persons without known risk factors for infection [5]. The results suggested that containment efforts were unlikely to succeed and supported adoption of a more stringent mitigation strategy to reduce COVID-19 morbidity [5].

SARS-CoV-2 virus became an important cause of leveled-up ILI and ARI rates [6-10]. The World Health Organization (WHO) advised the adaptation of ILI and ARI sentinel surveillance to the COVID-19 pandemic situation with the integration of COVID-19 data derived from primary care sentinel sites and SARS-CoV-2 testing in respiratory specimens added to samples collected [11].

In Slovenia, the National Institute of Public Health (NIPH, epidemiology) and National Laboratory for Health, Environment and Food (NLHEF, virology) have collaborated with primary care physicians to provide sentinel ILI and ARI surveillance data for more than 20 years. The sentinel surveillance system was designed to detect the community transmission of influenza. According to WHO recommendations, NIPH and NLHEF implemented integrated sentinel surveillance of ILI, ARI and COVID-19 in autumn 2020 to gain the experience in the first waves of the pandemic.

We describe how the integrated sentinel surveillance functioned in the first pandemic season (2020/2021) and in first 20 weeks of the 2021/2022 season. Sentinel COVID-19 incidence rates were compared to national incidence rates in order to assess the reliability and usefulness of the adapted system as a source of information in the post-pandemic period.

2. Methodology

2.1. Pre-pandemic Sentinel Surveillance for Influenza-Like Illness and Acute Respiratory Infections

Sentinel surveillance for ILI and ARI is a network of 44-46 primary care physicians providing weekly, year-around numbers of consultations according to a list of International Classification of Diseases, 10th Revision (ICD-10) diagnoses including influenza and other ARI structured in predefined age groups from season 1999/2000 on. Primary care physicians are specialist in family medicine, pediatrics and school medicine (the latter taking care mainly for children and adolescents from 6 – 19 years of age). The appropriate geographical distribution of the rapporteurs has been warranted since the beginning of the sentinel surveillance.

Influenza-like illness was defined by sudden onset of malaise with fever ($\geq 37.5^{\circ}\text{C}$) and cough. The patients with ILI are coded with ICD-10 J11.0, J11.1 and J11.8 (influenza, virus not identified) or J10.0, J10.1 and J10.8 (influenza, virus identified). Acute respiratory illness was defined by any acute respiratory symptom (coryza, sore throat, cough or shortness of breath) with or without fever and clinical assessment of acute infection. Data were extracted from a

health care facility digital database and pre-defined tables are formed automatically and forwarded to NIPH.

In the pre-pandemic seasons, virological samples (throat and nose swabs) were taken by primary care physicians according to their assessment that the acute infection (i.e. ILI) was most probably caused by influenza virus. For every swabbed patient, a questionnaire is filled in. The questionnaire is used to collect demographic data, data on vaccination against influenza, clinical symptoms and risk factors for more severe course of the disease. According to the testing algorithm (step one) PCR for influenza A, influenza B, RSV, adenoviruses and enteroviruses were done. Influenza A and B positives were further characterized for subtypes (H1N1 and H2H3) and lineages (Yamagata and Victoria). Samples which were negative for all the above-mentioned viruses were tested for parainfluenza viruses 1, 2, 3, 4, human bocavirus (hBoV), human metapneumovirus (hMPV), rhinoviruses, human coronaviruses and parechovirus with PCR test.

2.2. Extending Epidemiological and Virological Sentinel Surveillance to COVID-19 in the 2020/2021 Season

2.2.1. Integrated ILI, ARI and COVID-19 Sentinel Surveillance

Updated instructions (renewed list of diagnoses, definitions, swabbing recommendations) were prepared and forwarded to the physicians participating in the network. To detect SARS-CoV-2 infection in sentinel population three new codes ICD-10 were added to the list of reportable diseases: B34.2 (coronavirus infection, nonspecified), U07.1 (SARS-CoV-2 identified) and U07.2 (SARS-CoV-2 not identified) in week 40, season 2020/2021. The National Insurance Institute of Slovenia instructed primary care physicians to code symptomatic patients with confirmed SARS-CoV-2 infection with B34.2 code at the beginning of pandemic before new, more specific ICD-10 codes became available.

By definition, a COVID-19 case was a person with positive PCR or rapid antigen test (RAT) for SARS-CoV-2, and coded B34.2 or U07.1. A probable COVID-19 case (coded U07.2) was a person with at least one of the following symptom: cough, fever, sudden onset of complete olfactory loss (anosmia), complete loss of taste (ageusia) or distortion of normal taste (dysgeusia), shortness of breath, or less typical symptoms such as headache, chills, muscle aches, fatigue, vomiting and/or diarrhea and epidemiological link to a confirmed COVID-19 case.

Definitions and ICD-10 codes for ILI and ARI remained the same as in the pre-pandemic period in order to ensure continuity of reporting. COVID-19, ILI and ARI data were extracted from the digital databases of healthcare facilities. Pre-defined tables are formed automatically and reported to NIPH.

2.2.2. Integrated Virological Sentinel Surveillance

Protocol for virological sampling has been adapted to the pandemic situation. Patients with ILI symptoms were not

sampled at sentinel sites as in pre-pandemic period but were referred to one of the dedicated sampling points for COVID-19. The sampling sites were located within healthcare facility or in community health center. The type of samples collected changed from combined throat-nose swabs to nasopharyngeal (NF) swabs. In adults, two NF were taken – one for SARS-CoV-2 and the second one for the other respiratory viruses. In children, one NF was collected for SARS-CoV-2 diagnostics, and a pharyngeal swab (PS) was collected for other respiratory viruses aiming to ensure better cooperation with children (and parents). The testing algorithm was simplified - all sentinel samples were tested for influenza A, B, RSV, enteroviruses, rhinoviruses, hBoV, hMPV, parainfluenza 1, 2, 3, 4 viruses, human coronaviruses, parechovirus and SARS-CoV-2 using the AUSdiagnostics Respiratory Viruses 16-well panel (ref. 20602). We compared the number of swabs taken in five pre-pandemic seasons with the number collected in the 2020/21 season and in w40-2021 to w7-2022 (first 20 weeks of the 2021/22 season). This was in order to identify the impact of the changed sampling practice.

In the 2021/2022 season the questionnaire was upgraded with questions regarding COVID-19 vaccination status and COVID-19 specific symptoms added (anosmia, ageusia and dysgeusia).

2.3. National COVID-19 Data

National COVID-19 data were extracted from the national COVID-19 notification system (source: NIPH), which includes cases with a positive PCR or RAT for SARS-CoV-2. National weekly incidence rates were calculated and compared to sentinel incidence rates in the 0–7, 8–19, 20–64 and ≥ 65 age groups for the 2020/21 season. National and sentinel standardized rates were calculated from age-specific rates using the direct standardization method, as the ≥ 19 age group is overrepresented in the sentinel population.

2.4. Ethics Approval

The study was based on an in-depth analysis of data collected for epidemiological purposes (to assess the epidemiological situation regarding acute respiratory infections). Commission ethical approval by a research ethics committee was not needed.

3. Results

The standardized weekly national and sentinel COVID-19 incidence rates in Slovenia in the 2020/21 season and in w40/2020-w7/2021 (20 weeks) in the 2021/22 season are shown in Figure 1.

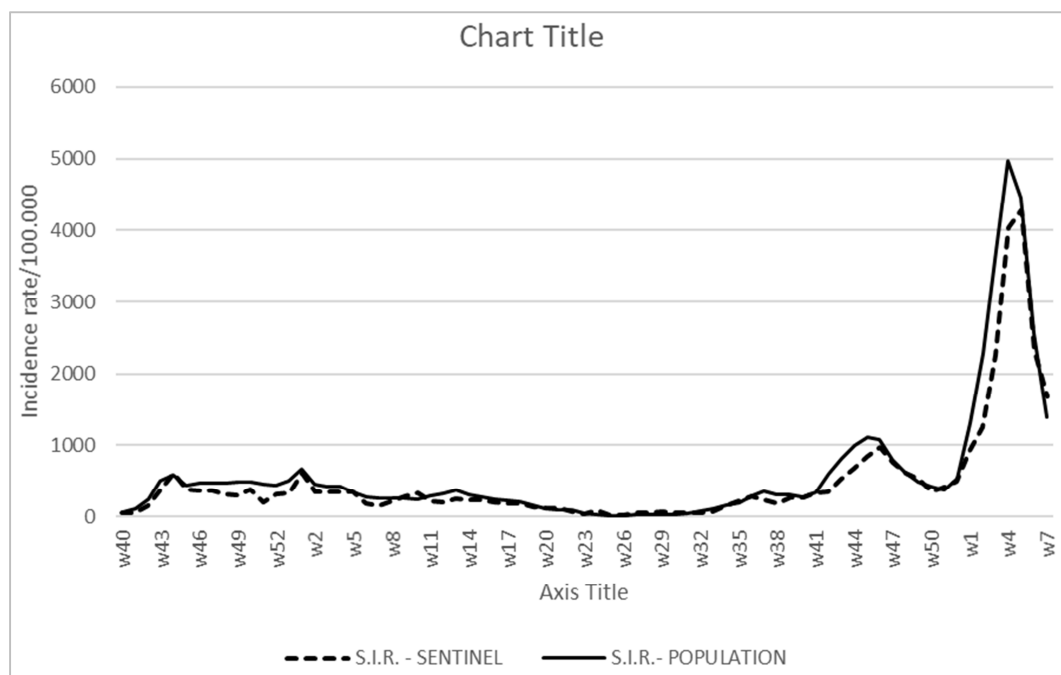


Figure 1. Weekly standardized national and sentinel COVID-19 incidence rates, 2020/21 and 2021/22 (w4-w7) seasons in Slovenia. (S.I.R = standardized incidence rate).

National weekly COVID-19 incidence rates and sentinel weekly incidence rates, stratified into four age groups in the 2020/21 season, are shown in Figure 2 and Figure 3. In the 0–7 age group, weekly sentinel incidence rates were higher in the second wave of the pandemic compared to the national

rates. The match between the two surveillance systems (national and sentinel) was better in students (8–19 years). Sentinel data indicated the comparative trends, with deviations being less extensive.

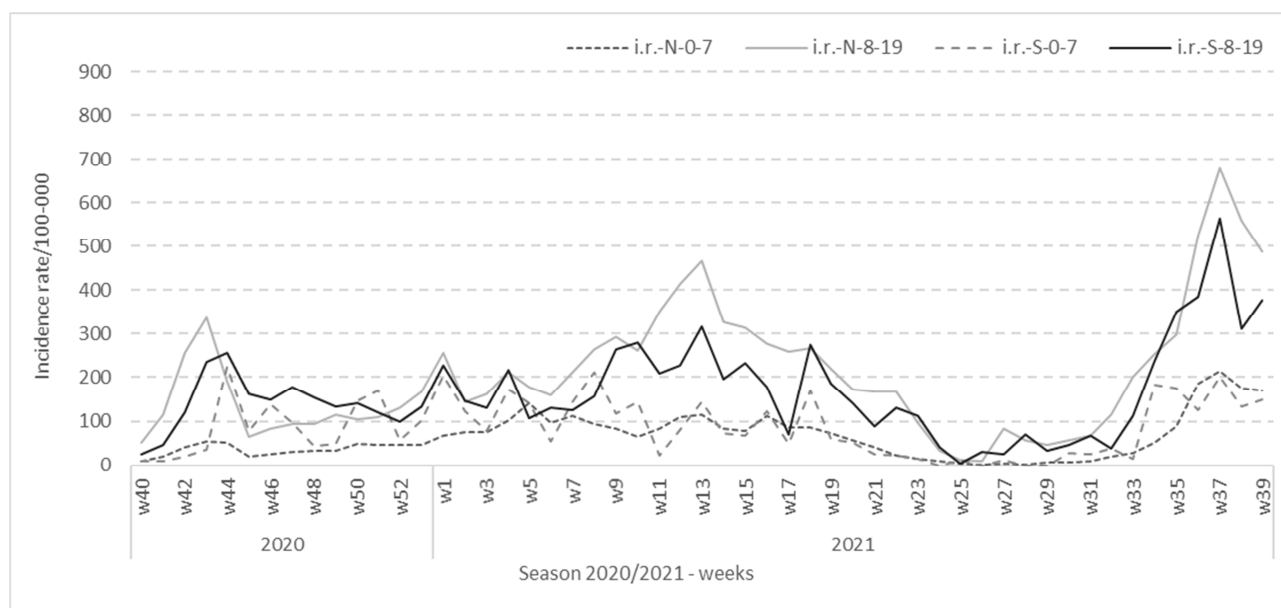


Figure 2. Weekly national and sentinel COVID-19 incidence rates in the 0–7 and 8–19 age groups in the 2020/21 season in Slovenia (i.r.-N = incidence rate – national, i.r.-S = incidence rate – sentinel).

In the elderly, weekly COVID-19 sentinel incidence rates were lower compared to the national data. Differences between weekly national and sentinel COVID-19 incidence rates were most pronounced in the second wave (autumn 2020) of the pandemic, with sentinel incidence rates being

much lower. In adults (20–64 years), the mismatch was less pronounced. While the sentinel system detected trends, a drop in the number of COVID-19 consultations in adults was clearly visible during the Christmas/New Year's and school holidays (second half of February).

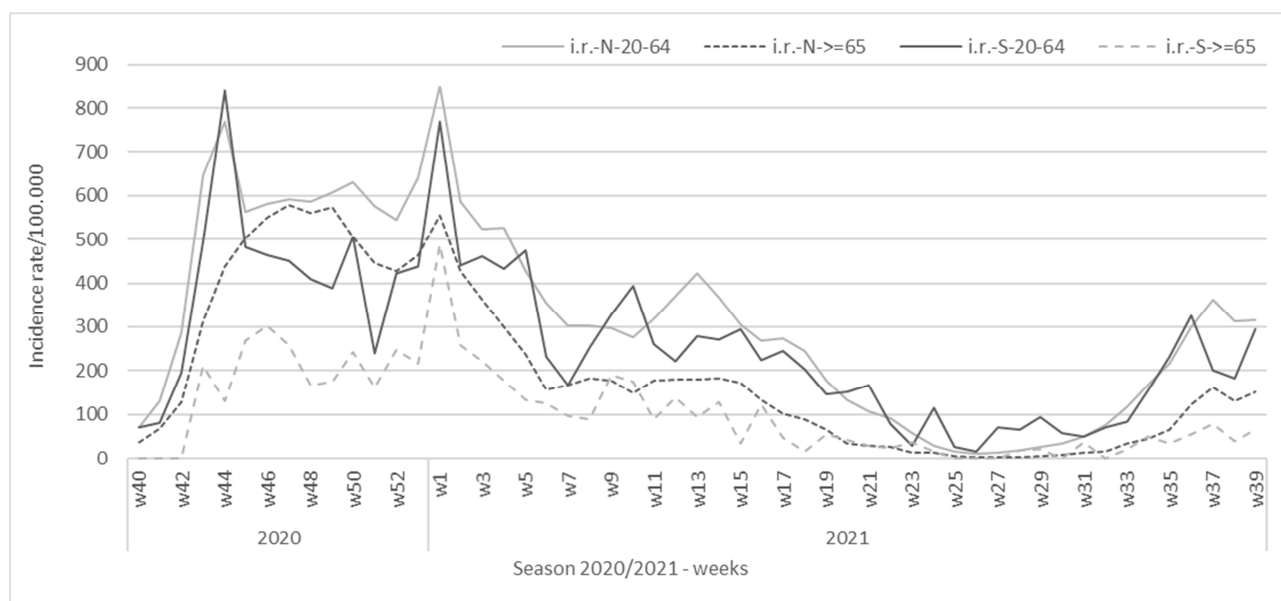


Figure 3. Weekly national and sentinel COVID-19 incidence rates in the 20–64 and ≥ 65 age groups in the 2020/21 season in Slovenia (i.r.-N = incidence rate – national, i.r.-S = incidence rate – sentinel).

The number of sentinel samples taken in the 2020/21 season decreased by 45% compared to the average number of sentinel samples in the five pre-pandemic seasons (data for pre-pandemic seasons not shown). The sampling frequency increased in the first 20 weeks of the 2021/22 season, reaching 71% of the five-year pre-pandemic average. There were 229 viruses detected by PCR test in 336 ILI patients

swabbed in the 2020/2021 season. Coinfections were rare, with SARS-CoV-2 being confirmed in one case alongside adenovirus, RV and hCoV (Table 1). In the 2021/22 season (w40–w7), there were 269 positive samples in 328 patients swabbed. There were few coinfections with SARS-CoV-2: two with adenovirus and one with RSV. Coinfections involving other viruses were much more common.

Table 1. Respiratory viruses in sentinel swabs of ILI patients in the 2020/21 and 2021/2022 (w40-w7) seasons in Slovenia.

Virus identified	No. of positive samples in 2020/21 (%)	No. of positive samples in w40/2021–w7/2022 (%)
Influenza virus	0 (0)	21 (7.8)
RSV	17 (7.4)	43 (16)
Adenovirus	41 (17.9)	29 (10.8)
Enterovirus	10 (4.4)	10 (3.7)
RV*	35 (15.3)	45 (16.7)
hMPV*	1 (0.4)	42 (15.6)
hBoV*	18 (7.9)	20 (7.4)
PIV*	30 (13.1)	13 (4.8)
hCoV*	41 (17.9)	10 (3.7)
SARS-CoV-2	36 (15.7)	36 (13.4)

*RV – rhinovirus, hBoV – human bocavirus, PIV – parainfluenza virus, hCoV – human coronavirus.

4. Discussion

We have described real-world experience with the integration of COVID-19 into ILI and ARI primary care sentinel surveillance in Slovenia from w40/2020 to w7/2022 done according to WHO recommendations [11–13]. The integrative process began during the rise of the second COVID-19 wave, when there were still pronounced changes in the organization of healthcare. Access to primary care physicians was reduced, and consultations were conducted by telephone or e-mail whenever possible to prevent the spread of infection in healthcare facilities.

The comparison between national COVID-19 notification system data and sentinel system data showed a greater mismatch in particular periods and age groups. The greatest differences were in the ≥ 65 age group, with lower incidence rates in the sentinel system compared to the national system in the second wave of the pandemic. In Slovenia, the second wave disproportionately affected the elderly in long-term care facilities (LTCF) – e.g. 12.4% of COVID-19 cases in November 2020 were LTCF residents (NIPH, available from <https://www.nijz.si/sl/dnevno-spremljanje-okuzb-s-sars-cov-2-covid-19>). LTCF residents were also extensively and systematically tested as part of the outbreak containment strategy. The sentinel network sample includes only seniors living in the community. The sentinel COVID-19 incidence rates in the ≥ 65 age group reflect the epidemiology in the community; and we recognize this as a limitation of the sentinel system.

The mismatch between weekly national and sentinel COVID-19 incidence rates in the 0–7 age group in the second wave of the pandemic might be due to the fact that the national notifiable system relies on PCR/RAT confirmed cases only, while the sentinel system also counts probable cases (symptoms and epidemiological link without confirmatory testing). After a sharp increase in cases in the second wave, the testing strategy was changed to primarily target high-risk groups and the elderly. Testing was not recommended for children and adolescents. Probable SARS-CoV-2 infections reported in the sentinel system (but not notified to the national system) were the most probable driver of the above-mentioned difference.

Sampling practices changed, and samples were taken at

dedicated sampling sites rather than sentinel outpatient clinics. The collection of two NF swabs further reduced patient cooperativity and contributed to the small number of sentinel samples taken. Nevertheless, sentinel virology in Slovenia reflected no influenza circulation in 2020/2021 and a low level of influenza virus activity in 2021/2022, the unusual timing of the RSV season, an absence of hMPV in the first year of the pandemic, and a SARS-CoV-2 positivity rate of more than 13% in ILI patients. The results are in good agreement with the findings of other sentinel systems [14].

Sentinel surveillance, system like syndromic surveillance, is a form of surveillance that generates information for public health action by collecting, analyzing and interpreting routine health-related data reported by clinicians [15, 16]. Sentinel surveillance system should enable prompt and flexible monitoring and investigation of public health problems and the ability to target public health interventions more effectively. Benefits include early warning and quantification of problem [6]. Sentinel surveillance complements traditional surveillance systems which rely on obligatory notification of communicable disease [6, 16]. Sentinel surveillance is the study of disease rates in a specific cohort to estimate trends in a larger population. The main question to be answered is if sentinel surveillance rates in a specific circumstance such as a pandemic reflect trends in the population [6, 17].

At the beginning of pandemic, non-adapted existing sentinel respiratory disease surveillance systems showed the capability to identify the signal of an evolving COVID-19 upsurge [2–4]. A study from Israel demonstrated that the morbidity patterns of the syndromic surveillance platforms were inconsistent with the progress of the pandemic, while the sentinel surveillance platform was found to reflect the national circulation of SARS-CoV-2 in the population [18]. According to Glatman et al., the robustness of the sentinel clinics platform in Israel during 2020 supports its use in locations with insufficient resources for widespread testing of respiratory viruses [18]. A study from California, USA, used sentinel sites to collect the samples for viral diagnostics and a set of variables to identify the risk factors for COVID-19. The sentinel data proved to be very useful and made it possible to understand the risk factors for disease and epidemiological parameters of the evolving epidemic in the first half of 2021 [7]. The advantage of an integrated COVID-19, ILI and ARI system is the readiness of real time

information not only on influenza and SARS-CoV-2 but also on other respiratory viruses circulating in the community [7, 19]. In depth analysis of adaptations in primary care sentinel surveillance from seven EU countries during and after first pandemic wave revealed substantial changes in patient pathways, consultation practices and testing policies, resulting in lower numbers of samples taken [20]. In some countries, the number of specimens collected within the sentinel surveillance system was too low to be meaningful [21]. Slovenian sentinel surveillance was also challenged by low numbers of NF swabs taken for respiratory viruses in the 2020/2021 season. The numbers increased in the 2021/2022 season and approached pre-pandemic level.

In the near future, SARS-CoV-2 will likely become endemic [12]. Sentinel COVID-19 surveillance will then be used to assess the level of community transmission in the post-pandemic (endemic) period to guide the selection and implementation of public health measures. We believe that sentinel surveillance will be increasingly useful as extensive nationwide testing will not be necessary anymore [5, 7-8].

5. Conclusion

Our study showed that the benefits of COVID-19 implementing sentinel surveillance were quantification of the size and scope of the ongoing pandemic with generally acceptable accuracy and functionality. Overall, the match between the national COVID-19 surveillance system and sentinel data was good enough to assess the developing situation. We recognized the challenge of insufficient sampling for the influenza virus due to the adaptation of the healthcare system to the pandemic which should be addressed in the following respiratory seasons.

Monitoring SARS-CoV-2 transmission through sentinel surveillance will allow custom public health measures in response to the prevalence and incidence trends of acute respiratory infections including COVID-19. Sentinel COVID-19 surveillance (integrated in ILI and ARI surveillance) in primary care together with hospital-based surveillance, mortality surveillance and serology surveys offers multi-layered information on COVID-19 epidemiology. The process of integrating COVID-19 into the sentinel system is evolving, and the information generated should be closely monitored to allow us to understand contextually those factors that may impact the outputs, and to recognize the limitations of the system.

Conflict of Interest

The authors declare that they have no competing interests.

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