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EDITORIAL
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New perspectives on respiratory syncytial virus surveillance at the national level: lessons from the COVID-19 pandemic

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Shareable abstract (@ERSpublications)
Learning from the COVID-19 pandemic and considering the effects of this pandemic, we provide recommendations that can guide towards sustainable RSV surveillance with the potential to be integrated into the broader perspective of respiratory surveillance. https://bit.ly/40TsO0G

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The emergence of SARS-CoV-2 and the resulting coronavirus disease 2019 (COVID-19) pandemic has led to the reconsideration of surveillance strategies for respiratory syncytial virus (RSV) and other respiratory viruses. The COVID-19 pandemic and the non-pharmaceutical interventions for COVID-19 had a substantial impact on RSV transmission in many countries, with close to no transmission detected during parts of the usual season of 2020–2021. Subsequent relaxation of social restrictions has resulted in unusual out-of-season resurgences of RSV in several countries, causing a higher healthcare burden and often a higher proportion of hospitalisations than usual among children older than 1 year in age [1]. In case of an emerging infectious disease with pandemic potential, preparedness to scale up surveillance for the emerging disease while continuing the maintenance of surveillance activities of pre-existing seasonal diseases is necessary. The COVID-19 pandemic demonstrated, however, a lack of surge capacity in respiratory surveillance [2]. Many of the existing respiratory surveillance systems across Europe were affected by the COVID-19 pandemic. Usual healthcare seeking routes, that are often the source of the sentinel surveillance, were altered for patients with respiratory symptoms to be diagnosed elsewhere for SARS-CoV-2 in many countries. Additionally, there were initially major reductions in testing availability, workforce numbers and access to test consumables due to repurposing of human and material resources to SARS-CoV-2 diagnostics and surveillance in the first half of 2020 [3, 4]. To help countries prioritise efforts towards construction of resilient and sustainable surveillance systems, the World Health Organization (WHO) European region and European Centre for Disease Prevention and Control (ECDC) convened Member State consultations to develop a strategic surveillance framework for a broader respiratory pathogen surveillance in the post-acute phase of the COVID-19 pandemic [5, 6]. It is important for RSV surveillance to be aligned and integrated within this broad respiratory surveillance framework for increased efficiency and sustainability of RSV surveillance. We here address the specific needs of RSV surveillance, based on the set of recommendations we proposed in 2019 [7], which we revised during a virtual workshop in October 2021, with 40 participants from 16 EU/EEA countries, representing expertise within RSV epidemiology, virology and public health. We take into consideration the need for robust surveillance of RSV to inform healthcare planning and appropriate timing of RSV prophylaxis and other preventive measures, and the lessons learned from the COVID-19 pandemic (table 1).

The COVID-19 pandemic measures and/or the extensive circulation of SARS-CoV-2 itself changed the seasonal pattern of circulation of RSV in the short term. As it is unclear whether and how fast a seasonal pattern will be restored [1, 8], and since this has shown the ability of RSV to surge out-of-season under

TABLE 1 Lessons learned from COVID-19 pandemic on respiratory surveillance, and updated recommendations for respiratory syncytial virus (RSV) surveillance in the EU/EEA

Lessons learned	New/updated recommendations
Surveillance systems are vulnerable to changed circumstances	• Increase adaptability of surveillance; enable ongoing surveillance during a pandemic and rapid upscaling • Use multiple, parallel systems, *e.g.* community-, hospital- and register-based • Invest in digitalisation and make use of electronic patient records • Encourage participatory surveillance systems, such as InfluenzaNet [34] • Explore other surveillance systems that proved useful during the pandemic, *e.g.* sewage screening and serosurveys
Typical seasonal patterns of circulation can be disrupted	• Implement year round surveillance[#]
COVID-19 necessitates moving to a broader respiratory pathogen framework for surveillance	• Use the broad WHO/ECDC ARI and extended SARI case definition [35], with collection of symptoms to allow separation of ILI cases[#] • Implement case-based surveillance including information on age (group) or collect aggregated age-stratified data to be able to focus on specific age groups[#] (very young and elderly) for RSV and other pathogens • Sample both the nasopharynx and oropharynx; this can be done with site-specific swabs separately or with an adapted procedure limiting the number of swabs and tubes with virus transport medium • Test broadly with multi-pathogen NAAT and use of additional assays for virus characterisation (at specialised laboratories) • Include positive and negative test results for register-based surveillance • Include pandemic preparedness for emergence of new pathogens in surveillance plans
Importance of data for effectiveness studies for vaccines and monoclonals	• Consider adding (P)ICU surveillance for RSV • Investigate data sources necessary for studies of effectiveness, including options for different immunisation strategies and target groups (maternal, paediatric and elderly)
Standardised RSV detection and sequencing protocols and read analysis pipelines are not readily available	• Create a virtual library of protocols for NGS and NAAT for sharing and concerted development on different platforms • Take part in detection and virus characterisation external quality assessments and training[#]
High throughput rapid WGS could become feasible for RSV	• Sequence a more representative and higher number of RSV-positive specimens than our previous recommendation [7]
Nomenclatures for genotypes are still very divergent	• Use the harmonised nomenclature for naming RSV strains published by the WHO initiative [27]
Data-sharing can be challenging	• Develop (legal) guidelines for case-based data sharing and data linkage • Include key data elements in all respiratory surveillance, where available, including symptoms and patient information (age and sex)

WHO: World Health Organization; ECDC: European Centre for Disease Prevention and Control; ARI: acute respiratory infection; SARI: severe acute respiratory infection; ILI: influenza-like illness; NAAT: nucleic acid amplification tests; (P)ICU: (paediatric) intensive care units; NGS: next-generation sequencing; WGS: whole genome sequencing. #: these recommendations were already in the previous set of recommendations [7], and are added here to emphasise that the importance of these recommendations were confirmed during the COVID-19 pandemic.

certain conditions, we reinforce our earlier recommendation for year-round surveillance in all countries. This is important as data on the onset of RSV transmission are used to guide prophylaxis with the monoclonal antibody palivizumab and probably also with the recently approved nirsevimab [9], and are likely to be used in future for RSV immunisation if a seasonal immunisation strategy is adopted. Multi-pathogen testing of patients with the broad WHO/ECDC acute respiratory infection (ARI) and the extended severe acute respiratory infection (SARI) case definition, as previously recommended [7], among all age groups, would facilitate surveillance of many respiratory pathogens of concern. Consideration needs to be given regarding how to integrate these more sensitive and less specific case definitions into existing systems, bearing in mind available resources and the need for historical comparability. We therefore propose that data should be collected on symptoms, so that other case definitions, such as the influenza-like illness case definition, could be recreated to allow monitoring trends with past data. If not sampling all (S)ARI patients, the sampling strategy should be as representative as possible for age groups, geographical distribution, disease severity (for SARI), use of antivirals and/or monoclonal antibodies, and once applicable, vaccination status (of mother).

As sentinel primary care surveillance systems can get disrupted in a pandemic, alternative community surveillance systems need to be considered as parallel year-round routine sentinel surveillance systems. Linking community surveillance systems to data that are gathered for other (*e.g.* clinical) purposes and expanding the network of general practitioners and paediatricians to compensate for loss of capacity could be considered. Alternatively, a more resilient community surveillance approach such as participatory surveillance could be used. To track RSV, this would require the incorporation of self-sampling. Reporting of results through participatory surveillance would need to be discussed and defined in the future. Such a system could be scaled up in case of an epidemic situation.

Sentinel SARI surveillance through testing of hospitalised patients is most useful if data are collected in a timely fashion to improve its early warning function. Unlike SARS-CoV-2, RSV disproportionately affects children younger than 2 years of age, especially in terms of severe illness. Therefore, guidelines on systematic sampling within the <2-year age group should be provided. Furthermore, to evaluate vaccine effectiveness against severe disease, surveillance needs to include tertiary hospitals [10]. As the unusual out-of-season epidemic of RSV included an increase in the number of older children that were severely affected by RSV [1], and immunisation could potentially cause a similar change in age distribution, paediatric surveillance should not be restricted to children <2 years old only. Furthermore, SARI surveillance in elderly and immunocompromised patients (*e.g.* in the haematology department [11]) is important to cover the other side of the age spectrum. In community dwelling elderly people in Europe, RSV is prevalent, mostly with a mild course of disease [12] and with generally a good recovery of health-related quality of life [13], but also with high variability between seasons. A meta-analysis [14] reported a hospitalisation attack rate of 1.0 (95% CI 0.5–2.1) per 1000 population in adults ⩾65 years of age in industrialised countries, with underlying conditions as a major risk factor. In addition to community-acquired infections, nosocomial infections and outbreaks of RSV in long-term care facilities [15] and hospitals [16] are frequently reported. Nosocomial infections typically reflect the infection prevention control (IPC) measures in a specific health facility and are not reflective of community transmission of RSV. Nosocomial infections are effectively monitored with IPC surveillance protocols. Inclusion of nosocomial infections in RSV surveillance may serve as a signal for outbreak investigation but may potentially bias RSV disease/hospitalisation burden estimates. Data to distinguish nosocomial infections from community-acquired infections may not be available for all countries. Recruitment within, for example, 24 h of hospitalisation would be a potential proxy for this.

The COVID-19 pandemic initiated an increase in demand for data on respiratory infections. In some countries, new laboratory registries were created, SARS-CoV-2 became notifiable, and data linkage between registries rapidly became possible [17, 18]. The pandemic has highlighted that passive RSV surveillance needs to be taken in the context of the circulation of other respiratory pathogens and the population being tested. Changes in testing practices for respiratory pathogens other than RSV due to public health assessment needs, in a pandemic situation, need to be considered when contextualising the results of passive RSV surveillance. We therefore recommend including data on the major respiratory pathogens (at minimum for influenza virus, SARS-CoV-2 and RSV) and including both positive and negative test results. In addition to our previous recommendations on optimal core data elements [7], we recommend extracting the most detailed level of RSV typing and subtyping data that is available in the registers.

A large number of children with RSV do not get admitted to hospital but are cared for in emergency departments. A system for syndromic surveillance of RSV, assessing bronchiolitis cases at emergency departments, has been in use in France for many years [19], using readily available electronic hospital data, and has been initiated in the UK [20]. Such a surveillance system would be low-cost and highly sensitive [20], but with some loss of specificity, as other respiratory viruses also cause a proportion, although small, of viral bronchiolitis [21].

New data streams and other surveillance systems that became available during the pandemic should be evaluated for their potential future use in RSV surveillance. For instance, wastewater surveillance has been useful in SARS-CoV-2 monitoring [22] and could also be considered for RSV [23]. Population serosurveys could tell us more about prevalence and, if the right contemporary strains are used, simultaneously about the immune status of the population [24].

From a virological perspective, progress has been made on a number of the published recommendations [7, 25–27]. Implementing multi-pathogen testing for all specimens or a representative subset of specimens increases efficiency of testing and generates additional information for public health needs. All sampled sentinel patients fulfilling the (S)ARI case definitions should be tested at minimum for influenza virus, SARS-CoV-2 and RSV in a multi-pathogen test approach and the positive specimens further analysed (or sent to specialised reference laboratories) for type and subtype/lineage depending on the available resources, laboratory capabilities and needs for the pathogen under investigation. Ideally, at minimum a representative subset of specimens from non-sentinel sources should be tested for the same pathogens in parallel, although sampling and testing strategy of non-sentinel sources can usually not be guided from the surveillance perspective. For RSV, multi-pathogen testing will be highly important when vaccination is introduced to understand the potential influence of vaccination on shifts in circulation of other pathogens [28] and to increase insight into the patterns of cocirculation. With broadened testing for more pathogens of concern, the anatomical site of sampling of patients becomes also more important. Sampling both the nasopharynx and oropharynx of patients with acute respiratory complaints seems to work well for most respiratory viruses in the acute phase of the infection [29].

The COVID-19 pandemic has increased the number of laboratories with capacity for next-generation sequencing (NGS) suitable for whole genome sequencing (WGS). Standardised RSV WGS protocols and read analysis pipelines are an essential next step. Creating a virtual library of protocols for key laboratory methods, such as nucleic acid amplification tests and sequencing, for sharing and concerted development on different platforms, is therefore recommended, as now initiated as RSVLabNet [30]. Potential amino acid changes with a proven or possible negative effect on the performance of existing and future monoclonal antibody therapies and potential vaccines [25–27] should be closely followed. Sequencing the whole F and G genes using Sanger or NGS is still sufficient for clade designation and profiling of these amino acid changes. Rapid upscaling of SARS-CoV-2 WGS in several countries proved that high-throughput, rapid WGS is feasible and can be considered on an increased number of RSV-positive specimens than recommended previously [7]. The magnitude of upscaling depends on the evolving needs after the introduction of vaccination and expanded use of existing and new antiviral treatments [31]. As we recommend a representative sampling strategy, a similar representative selection should be made for samples to be sequenced. In the future, the move from F and G genes alone to whole genome will likely also be driven by knowledge about the effects of mutations elsewhere in the genome on antibody-based and antiviral-based treatment and prevention strategies [31]. With respect to molecular RSV surveillance, we recommend using the harmonised nomenclature for naming RSV strains published by the WHO initiative [27]. To harmonise nomenclature for genotypes, other groups have also made valuable proposals, but further harmonisation is needed [25, 26]. We also recommend that diagnostic and reference laboratories take part in internationally and nationally organised external quality assessments for RSV and take part in training for more complex sequencing, and sequence analysis and interpretation.

Ideally, case-based data should be collected and reported so that more detailed analyses can be performed. At the ECDC, integrated surveillance of respiratory infection for COVID-19, influenza and RSV and case-based reporting for those pathogens has been implemented. An important issue is the data confidentiality of shared data, depending on national interpretations of the General Data Protection Regulation. Development of guidelines on this issue would be beneficial. The advances in open data sharing, achieved through the support of the European Commission [32] during the COVID-19 pandemic, should be built upon. In addition, pandemic preparedness will be considered in surveillance plans and links between outbreak investigation and surveillance planning should be strengthened. Given the expectation that novel RSV immunisations may be available in the near future, planning how surveillance data could contribute to vaccine effectiveness studies would be important. The suggested surveillance changes require adequate financing and investment in human resources, both at national and European level. This would be facilitated by the adoption of RSV by the European Commission as a disease under

EU/EEA epidemiological surveillance with a case definition mentioned in the Commission's case definition list [33], by strengthened ECDC leadership on the issue, and by maintaining consistency with evolving Global Influenza Surveillance and Response System (GISRS+) guidelines for integrated respiratory surveillance [2].

The COVID-19 pandemic has highlighted the importance of robust, flexible, multi-respiratory pathogen surveillance. In table 1 we summarise the lessons learned from the COVID-19 pandemic period and what this changed from our previous recommendations.

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