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Evaluation of the national laboratory-based surveillance system for respiratory syncytial virus in Sweden, 2015–2016

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ABSTRACT

Background: Most laboratories use RSV PCR but near-patient tests (NPT) performed at paediatric clinics are believed to be increasingly used. Anonymised data on RSV infections has been collected since 1990 in Sweden. No evaluation of Swedish RSV surveillance or use of laboratory testing had previously been performed.
Objectives: Swedish RSV data and methods used for RSV laboratory testing and reporting were evaluated in order to improve RSV surveillance in a forthcoming vaccine era.
Study design: RSV data obtained in Sweden 2015–2016 were reviewed. Data on methods used for the RSV laboratory detection and reporting were collected via on-line questionnaires submitted to laboratories (n = 26) and clinics (n = 4) known to perform virological testing. Swedish Quality Control Program reports from 2013 to 2015 on the performance of RSV testing were also evaluated.
Results: Over 60% of RSV infections were diagnosed in children under 5 years (1917/2925), but infections were also common in those 65 years and older (n = 607). Two laboratories limited RSV testing to children only. RSV NPT was utilised in eight clinics; four participated in RSV surveillance. RSV NPTs evaluated could only detect 50% of RSV positive samples. Reporting was complete and timely, but took too much time (18 min/week/laboratory).
Conclusions: Although most common in children, RSV infections are also common in the elderly, and testing should not be limited to children only. The poor performance of RSV NPT and importance of confirming results should be communicated to all relevant laboratories and clinics. All clinics should be encouraged to participate in surveillance. Automated case-based reporting should be considered.

1. Background

Respiratory syncytial virus (RSV) is a common cause of severe lower respiratory tract infections, including bronchiolitis and pneumonia, in infants [1], as well as in the elderly and immunocompromised patients. RSV infections in these risk groups are associated with significant morbidity and mortality [2]. In temperate climates, RSV infections usually occur in seasonal outbreaks during late autumn, winter and early spring months [3]. In Sweden and other Nordic countries, RSV epidemics occur in a biennial pattern, with larger epidemics every other winter and milder epidemics during the interceding winters [4]. Palivizumab (Synagis), an RSV monoclonal antibody, is licenced as an immunoprohylaxis and approved for use for infants and children under 2 years of age who are at high risk for severe RSV disease [5]. Repeated monthly dosing is required due to the short lasting protection of palivizumab. Due to its high cost, palivizumab immunoprophylaxis is restricted to the RSV season. A preventative, vaccine-based approach for RSV is in active development with several candidates entering clinical trials. It has been estimated that an RSV vaccine will be available within the next 5–10 years [6].

Laboratory diagnostics for RSV have to be rapid and accurate to facilitate appropriate clinical management, including supportive care and hospital admission, as well as isolation or cohorting within hospital wards; to decrease nosocomial transmission of virus; and to avoid unnecessary antibiotic usage [7,8]. RSV infection can be detected using immunofluorecence (IF) for detection of antigen, molecular methods (i.e. reverse transcriptase polymerase chain reaction [RT-PCR]) or chromatographic rapid antigen detection (referred as near-patient test, NPT) [9]. Most laboratories in Sweden use multiplexed RT-PCR methods, often combining the detection of RSV with influenza virus [10].

The Public Health Agency of Sweden collects case-based anonymised data on RSV infections diagnosed in Sweden through a surveillance system established in late 1990's. It is based on voluntary

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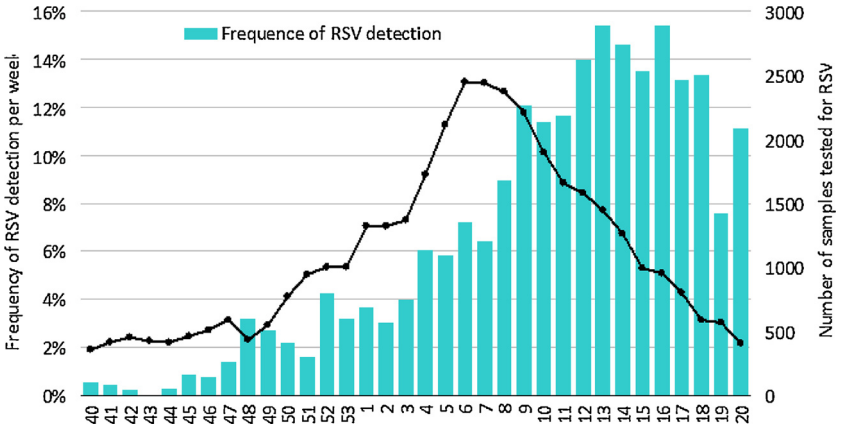

Fig. 1. Frequency of reported RSV infections in comparison to the total number of samples tested, Sweden, from 28 September (week 40) 2015–22 May (week 20) 2016.

reporting by microbiology laboratories and clinics performing RSV testing. These data are submitted and analysed weekly, with results published in the form of an online RSV report. In addition, data on severe RSV infections are periodically collected via the Swedish Intensive Care Registry (SICR, http://portal.icuregswe.org/). SICR is a national health registry to which 78 of Sweden's 84 intensive care units (ICU) voluntarily report data on all cases admitted to intensive care. Surveillance aims to guide clinicians through the RSV season and help them, for example, optimize the timing of RSV immunopropylaxis, in order to prevent severe cases among vulnerable infants in a cost-effective manner. However, there has been some concern that current surveillance may not cover all RSV infections diagnosed in Sweden, as clinics and in-patient wards may have started to perform their own testing outside the main laboratories. Furthermore, there have also been concerns relating to the quality of methods used for RSV NPT. Finally, no evaluation of RSV surveillance in Sweden had previously been completed.

2. Objectives

The main aim of this study was to collect data on the laboratory methods currently used for RSV testing in Sweden and to review the RSV surveillance in terms of completeness, timeliness, and methodological quality data obtained. These study results can help determine if current RSV surveillance would be useful in a forthcoming vaccine era, and how it could be potentially improved.

3. Study design

Weekly RSV surveillance data were used to describe the main characteristics of the 2015–2016 RSV season, including the number of specimens tested, the number of positive results for RSV, and the age of RSV-positive individuals, per county. The completeness of RSV surveillance was evaluated based on how often each laboratory and clinic reported these parameters to the Public Health Agency of Sweden (% of laboratory reports received per laboratory on time, and in total). RSV infection was defined as severe if the individual was admitted to ICU with diagnosis code J121, RSV-pneumonia, as a diagnosis. Aggregated data on patients in intensive care with RSV-diagnosis by age were obtained from the SICR after the end of the season. Calculations use population data for 2015 from Statistics Sweden, when relevant.

Two on-line questionnaires on laboratory methods used for detection of RSV and reporting of RSV results were prepared. The first was sent to all 26 microbiological laboratories known to perform virological testing, and the second to the four clinics known to perform RSV NPT. The responses were used to summarise where RSV testing is performed (*i.e.* microbiology or clinical chemistry laboratory, or at a paediatric clinic), laboratory methods used, and workload of RSV surveillance on laboratories and clinics, as well as to evaluate the usefulness of the weekly RSV report provided by the Public Health Agency of Sweden. Data collected included testing criteria (*i.e.* whether all patients with respiratory symptoms/bronchiolitis are tested, or only children), types of samples collected, methods used, and, if NPTs were used, how often NPT results were confirmed and/or reported to the Public Health Agency of Sweden. The workload of RSV surveillance was estimated in terms of time used per week for reporting (in minutes), as well as qualitatively, in terms of whether the respondent felt the time required was appropriate. Both questionnaires aimed to identify other clinics performing RSV testing but not currently participating in national RSV surveillance. The questionnaires were sent on 17 March 2016, with responses expected by 6 April 2016.

The Swedish Quality Control Program (EQUALIS) reports on the performance of laboratory detection of RSV by PCR, IF and NPT were obtained for 2013, 2014 and 2015.

4. Results

4.1. RSV surveillance

Based on the data reported to the Public Health Agency of Sweden, 37,827 respiratory samples were tested for RSV in Sweden between 28 September 2015 (week 40) and 22 May 2016 (week 20) (Fig. 1). The largest number of samples was tested in week 5, coinciding with influenza peak. A total of 2935 individuals tested positive for RSV, with the peak number of RSV detections observed in week 9 (n = 267). The overall detection frequency of RSV was 7.8%, and the highest frequency, 15.5%, was observed in week 13. Most RSV infections were diagnosed in children under 5 years of age (n = 1917; 66%) with a reported incidence of 327 infections per 100,000 children (Table 1). However, 21% of infections were identified in individuals 65 years of age and older (n = 607), with an incidence of 31 infections per 100,000 individuals. Although 10-fold lower than that observed in children under 5 years of age, this incidence is higher than remaining age groups. A total of 90 individuals with RSV infection were admitted to the ICU during the study period, most of them being children under the age of 5 years (n = 55), with an incidence of 9.4 ICU admissions per 100,000 children (Table 1).

The number of samples tested for RSV per 100,000 individuals varied significantly among Swedish counties (Fig. 2a). More individuals were tested in counties where RT-PCR was used, in comparison to counties where molecular methods were not used (456/100,000 versus 35/100,000, $p < 0.0001$ by chi-square test of association; two counties excluded from the analysis due to lack of data). Similarly, the incidence of RSV per 100,000 individuals varied significantly between counties