

## Surveillance and outbreak reports

# PROGRESS IN THE SURVEILLANCE OF RESPIRATORY SYNCYTIAL VIRUS (RSV) IN EUROPE: 2001-2008

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Respiratory syncytial virus (RSV) surveillance is important to get insight into the burden of disease and epidemic pattern of RSV infection. This information is useful for healthcare resource allocation as well as the timing of preventive messages and palivizumab prophylaxis. For influenza surveillance the European Influenza Surveillance Scheme (EISS) was established in 1996, but no surveillance platform is available for RSV. To improve surveillance an RSV Task Group was established in 2003 and recommendations for RSV surveillance were developed. By 2008, progress was made for four out of six recommendations: the number of European countries testing specimens for RSV increased from six to fourteen; nose and/or throat swabs were generally used for detection of influenza and RSV; a total of 25 laboratories performed molecular testing for diagnosis and participated in a quality control assessment for RSV with an overall good performance; four of the ten countries that joined EISS in 2004 started reporting RSV detections in addition to influenza in the period 2004-8. Limited progress was achieved for standardising methods and the development of a sentinel surveillance system of representative hospitals. Improving RSV surveillance is possible by further harmonising the data collection and increased reporting of RSV.

### Introduction

Respiratory syncytial virus (RSV) is the most important viral agent causing severe respiratory disease in young children [1-3]. RSV is also being recognised as a significant pathogen in adults [2,4] causing moderately severe respiratory disease especially in the elderly [5,6]. Influenza is widely recognised as a major cause of morbidity and mortality in humans [7,8]. Since RSV and influenza virus infections are associated with similar clinical symptoms [9] and frequently co-circulate around the same time of the year, there is substantial potential for confusion regarding the cause of influenza-like illness [10].

Influenza and RSV account for similar numbers of deaths in children and their impact varies by winter and age group. RSV is associated with more deaths than influenza in children aged 1-12 months [11]. Excess deaths due to RSV and influenza virus infection have also been reported for the elderly population [5,8]. When comparing cause-specific mortality due to influenza virus and RSV infection in all ages, it has been estimated that most deaths

were associated with influenza A(H3N2) viruses, followed by RSV, influenza B, and influenza A(H1N1) [8].

While influenza is on the list of communicable diseases that must be covered by the European Community network for surveillance, RSV is not on this list [12]. Nonetheless, RSV causes considerable burden of disease and RSV surveillance is important for determining the burden of illness in all age groups and in defining seasonality and epidemic pattern. This facilitates the preparation of hospital settings to receive more children and to define the timing of the start of palivizumab prophylaxis [13]. Palivizumab can be administered as passive immunoprophylaxis and is the only strategy that has been demonstrated to reduce RSV hospitalisations in high-risk children [14]. For real-time influenza surveillance the European Influenza Surveillance Scheme (EISS), a collaborative multinational project, was established in 1996 [15], but no such scheme was available for other respiratory viruses including RSV. Since RSV and influenza infections typically occur in the winter, EISS made it possible to report RSV detections into the EISS database, on a voluntary basis, from 1996 until September 2008.

In 2003 an RSV Task Group was established within EISS to explore the possibility to design a comprehensive RSV surveillance scheme within the EISS framework. This Task Group was composed of four epidemiologists and two virologists. Three meetings were organised between July 2003 and January 2006 and updates on the activities were presented to the EISS group during the EISS Annual Meetings. A retrospective analysis was carried out. Additionally, RSV surveillance recommendations were published in 2006 [16], and are presented below:

1. Specimens collected as part of an influenza surveillance programme should also be tested for RSV.
2. Both combined nose/throat swabs and nasal pharyngeal aspirates are acceptable for RSV diagnosis.
3. The application of molecular techniques such as real time PCR in the diagnosis of respiratory disease has been demonstrated and we advocate this technique for RSV detection.
4. Further developments are encouraged on the use of standardised methods and laboratory techniques.

5. The development of a sentinel approach of representative hospitals should be considered.
6. New countries joining EISS are encouraged to integrate RSV surveillance alongside influenza surveillance.

Our objective was to assess whether the RSV reporting within EISS in the period 2004-2008 complied with these surveillance recommendations, and to describe the detection and reporting of seasonal influenza and RSV infections in six selected countries in Europe.

## Methods

### Data collection in EISS

EISS was based on an integrated clinical and virological surveillance model. Sentinel primary care physicians reported weekly the number of new cases of influenza-like illness and/or acute respiratory infections and obtained respiratory specimens from a sample of patients for laboratory testing. The specimens were tested for influenza and in several countries for RSV as well. Weekly consultation rates and laboratory test results were entered

by the national surveillance networks into the EISS database via an internet-based system [17]. Non-sentinel, mainly hospital-based data for influenza and RSV were also collected, but will not be presented in this paper.

Since September 2008, European influenza surveillance has been carried out by the European Centre for Disease Prevention and Control (ECDC) and involves all 27 European Union Member States and Norway. Three other countries Serbia, Switzerland and Ukraine are reporting data to World Health Organization (WHO) Regional Office for Europe.

This paper presents a descriptive study. Surveillance data for seven winter seasons (2001-2 to 2007-8; week 40-20) in the EISS database were screened for RSV detections by country. The database containing virological detections of RSV and influenza was downloaded by September 2008. An RSV reporting country was defined as a country that reported at least 10 sentinel specimens positive for RSV from 2001-2008. With this method the progress for recommendation 1 and 6 could be assessed. For the other

TABLE 1

### Reporting of respiratory syncytial virus (RSV) and influenza data to the European Influenza Surveillance Scheme (EISS) in the period 2001-2008

Season	Number of countries reporting RSV*	Number of countries reporting influenza	Number of RSV detections	Number of influenza detections
2001-2	6	18	203	2276
2002-3	8	19	335	3787
2003-4	12	22	143	2732
2004-5	12	23	557	5483
2005-6	14	28	803	3171
2006-7	14	30	888	5077
2007-8	13	31	929	5076

\*Countries reporting RSV:

2001-2: CZ, FR, DE, SI, CH, UK-E, UK-S.  
 2002-3: CZ, FR, DE, NL, SK, SI, CH, UK-E, UK-S.  
 2003-4: CZ, FR, DE, NL, SK, SI, CH, UK-E, UK-S.  
 2004-5: AT, CZ, DK, FR, DE, IT, LU, PL, RO, SI, CH, UK-E, UK-S.  
 2005-6: AT, CZ, DK, EE, FI, FR, DE, IT, LU, NL, PL, RO, SI, UK-E, UK-S.  
 2006-7: AT, CZ, DK, EE, FI, FR, DE, IT, LU, NL, PL, RO, SI, UK-E, UK-S.  
 2007-8: AT, HR, CZ, DM, EE, FI, FR, DE, LU, NL, PL, SI, UK-E, UK-S.

Abbreviations: Austria (AT), Croatia (HR), Czech Republic (CZ), Denmark (DK), Estonia (EE), Finland (FI), France (FR), Germany (DE), Italy (IT), Luxembourg (LU), the Netherlands (NL), Poland (PL), Romania (RO), Slovenia (SI), Slovakia (SK), Switzerland (CH), UK-England (UK-E), UK-Scotland (UK-S).

TABLE 2

### Number of sentinel influenza and respiratory syncytial virus (RSV) detections by country in the period 2001-2008

Country	Number of RSV detections per season mean (range)	Number of influenza detections per season mean (range)	Total number of RSV and influenza detections mean (range)	Percentage of RSV cases (%)* (range)
Czech Republic	18 (5-30)	206 (83-311)	223 (102-327)	8 (3-19)
France	145 (47-227)	1053 (824-1374)	1198 (947-1601)	12 (4-18)
Germany	43 (12-138)	1129 (553-2145)	1172 (568-2172)	4 (1-10)
The Netherlands**	12 (1-19)	121 (15-142)	133 (16-153)	4 (0-16)
Slovenia	6 (1-12)	101 (69-132)	106 (77-135)	5 (1-12)
UK-England	44 (14-125)	231 (82-432)	275 (107-477)	16 (8-56)
UK-Scotland	23 (14-35)	101 (31-193)	123 (50-220)	18 (11-38)

\* The percentage of RSV cases in relation to the total number of samples that tested positive for either influenza or RSV.

\*\* No RSV detections were reported for the Netherlands in the winters of 2001-2 and 2004-5.

recommendations the progress was summarised by collecting relevant data from inventories and a quality control assessment.

### **RSV detections: six countries**

#### *Country selection*

Data from the Czech Republic, France, Germany, Netherlands, Slovenia and the United Kingdom (UK) (represented by England and Scotland) were assessed to describe the RSV surveillance in these countries. All had reported data for at least five winter seasons. Sentinel primary care physicians included general practitioners (GPs) in the United Kingdom and the Netherlands, and GPs and paediatricians in the Czech Republic, France, and Germany, and GPs, paediatricians and specialists in Slovenia. The sentinel doctors represented 1-5% of all physicians working in the country.

#### *Case definition*

Data on new cases were based on reporting of consultations for influenza-like illness (ILI) in the Netherlands, Slovenia and United Kingdom. Consultations for acute respiratory infections (ARI) were collected in France and Germany. From 2001-2 to 2004-5 the Czech Republic reported the number of new cases of ARI, and from 2005-6 onwards they reported cases of ILI in addition to ARI [18]. Case definitions for ARI and ILI differed slightly between countries [19]. The type of specimen that was collected (nose and/or throat swab) as well as transport conditions were similar [20]. Samples were generally collected within five days after onset of symptoms and systematically tested for both influenza virus and RSV in all countries. In Germany, only specimens of children aged 0-3 years were tested for RSV. Cases were defined positive for RSV or influenza when at least one laboratory test yielded a positive result. Between-country comparisons will not be made due to methodological differences.

## **Results**

### **Recommendation 1**

Specimens collected as part of an influenza surveillance programme should also be tested for RSV.

Seventeen countries had reported RSV detections in the period 2001-2008: Austria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Italy, Luxembourg, Netherlands, Poland, Romania, Slovenia, Slovakia, Switzerland, UK- England and Scotland. Since England and Scotland have their own sentinel surveillance systems, these are presented separately in this paper. The number of countries reporting influenza data increased from 18 in 2001-2 to 31 in the winter of 2007-8 (Table 1).

In 2001-2 only six countries reported RSV detections in addition to influenza, but their number gradually increased, particularly around 2003-4, among both countries that had participated since 2001 and new members (see also results for recommendation 6). From 2005-6 no further increase in the number of countries reporting RSV was observed (Table 1).

### **Recommendation 2**

Both combined nose/throat swabs and nasal pharyngeal aspirates are acceptable for RSV diagnosis.

Different types of specimens are used for detection of influenza and RSV [21]. Generally the nasopharyngeal aspirates have a high sensitivity, and are often used in a hospital setting. Easier to use

and less painful are nasal/nasopharyngeal swabs [22]. An inventory carried out in 2002 indicated that in sentinel surveillance systems in Europe nose and/or throat swabs were taken [20]. Twelve out of 20 national networks collected combined nose/throat swabs. The remaining networks collected either nasopharyngeal, nasal, or throat swabs. In addition, three networks took blood samples and one network obtained nasal aspirates [20]. Since all countries had already used the recommended type of respiratory sample and fulfilled the recommendation, no progress was assessed after 2002.

### **Recommendation 3**

The application of molecular techniques such as real time polymerase chain reaction (PCR) in the diagnosis of respiratory disease has been demonstrated and this technique is advocated for RSV detection.

In 2006, laboratories were invited to participate in a quality control study for molecular methods. Of the 33 laboratories participating in EISS, 25 performed this technique with an overall performance of 88% correct results [23]. The majority (22 out of 25) of laboratories used an in-house molecular assay. In particular, real time PCR and nested PCR assays provided the highest performance scores (93% correct score; range 70-100) and were used in 19 laboratories. Three laboratories used commercial assays and the percentage of correct results ranged from 50% to 80% [23].

### **Recommendation 4**

Further developments in the use of standardised methods and laboratory techniques are encouraged.

Limited progress was made in standardising methods. Only for influenza, not RSV, laboratory protocols were shared and standardised reagents were made available via the EISS website. However, with the application of molecular methods, as indicated in recommendation 3, and quality control assessment of this method, the quality of laboratory testing of RSV is ascertained.

### **Recommendation 5**

The development of a sentinel system of representative hospitals should be considered.

No efforts were made to develop a European sentinel surveillance system consisting of representative hospitals, though national initiatives may have been undertaken. For example, a laboratory-based surveillance for RSV involving different hospital laboratories in Slovenia was implemented in 2006 [24].

### **Recommendation 6**

We recommend the new networks joining EISS to integrate RSV surveillance alongside influenza.

Ten new countries became members of EISS between 2004 and 2008: Austria, Bulgaria, Croatia, Estonia, Finland, Cyprus, Greece, Hungary, Ukraine and Serbia [25]. Of these, four countries followed the recommendation and started reporting RSV data (Table 1).

### **RSV detections: six countries**

To illustrate the data that were collected by EISS, we present the results of RSV detections for six countries. All countries reported at least five seasons of data, which provided insight in the occurrence of RSV in these countries. RSV and influenza detections are

presented in Table 2. The percentage of RSV-positive specimens largely differed by season, e.g. from 3% to 19% in the Czech Republic (Table 2). For all seasons and countries together the percentage of RSV-positive specimens varied from 4% in Germany and the Netherlands to 16-18% in the United Kingdom. RSV activity usually started a few weeks before the onset of influenza activity (data not shown). The data collected are useful to describe the seasonality of RSV and show that RSV is detected in patients with ILI and/or ARI.

### Discussion and conclusion

Progress in RSV surveillance was made in the period 2001-2008, with the most obvious increase in the number of reporting countries during the time the RSV Task Group was active, between 2003-2006. Progress was made particularly in terms of the number of countries testing specimens for RSV and the use of molecular techniques. The results for the six countries that had reported at least five years of data showed that RSV surveillance and reporting is feasible in Europe. The overall percentage of RSV-positive specimens for the Czech Republic, France, Germany, Netherlands, Slovenia and the UK amounted to 4-18% indicating that a substantial number of patients who consulted their sentinel physician with influenza-like illness or acute respiratory infection actually had an RSV infection. The EISS surveillance is real time and therefore can be relevant for timing of the influenza and RSV peak and providing insight into the morbidity and seasonality of these respiratory illnesses.

Limited progress was made for recommendation 4 on the use of standardised laboratory methods. With the use of mainly in-house developed methods that perform well [23], the standardising of methods was not further explored. The rationale was that standardising methods is important and is encouraged by sharing protocols, but more important is the ability of the laboratory test to correctly identify RSV. Furthermore, limited progress was made for recommendation 5 on the development of a sentinel approach of hospitals. This recommendation was ranked as a lower priority because non-sentinel data from hospitals are currently being collected. The non-sentinel data could be used for the future establishment of a sentinel laboratory monitoring system and would then need to be assessed for representativeness and quality of data collection.

In this paper we presented data on sentinel RSV and influenza detections. Relatively low numbers of positive RSV tests were reported and this is therefore a limitation. In addition to sentinel data, RSV reports from non-sentinel sources, mainly derived from hospitalised infants are also available and these can provide insight into the epidemic peak of RSV during wintertime. We think that both sources of data are important and complement each other. Sentinel data highlights the occurrence of RSV in the community, where it is an important confounder in influenza surveillance. And hospital-based data present the circulation of RSV in more severe cases and high-risk groups.

The limitations of the sentinel influenza surveillance carried out by EISS are related to differences in case definitions [19], sampling guidelines and laboratory techniques among the different countries [20]. Some difficulty in obtaining swabs from all age groups has been reported, especially for young children in the Netherlands and the elderly in the Netherlands and France [16]. Another limitation is that we could not further investigate other possible causes of respiratory infections such as rhinovirus,

adenovirus and coronavirus [26,27] and human metapneumovirus [28]. Country resources however may limit the extension of testing for other viruses in addition to influenza and RSV. Furthermore, no comparison regarding the occurrence of RSV and influenza between the different countries could be made because of differences in data collection procedures and laboratory methods. Additionally, differences in healthcare seeking behaviour may influence the findings between countries.

Currently diagnostic specimens are collected from patients presenting with ILI or ARI. Although ILI and/or ARI case definitions have been used for the detection of influenza for many years, this may not be the optimal clinical indicator for RSV. To investigate the clinical impact and determine the burden of illness of RSV one should extend the diagnostic categories to include acute bronchitis and otitis media [29]. This may become feasible with the movement towards sentinel networks based on electronic data.

We presented the progress in RSV surveillance based on an influenza surveillance network and data collected for six countries. This illustrated the feasibility of reporting RSV data and showed that a proportion of about 4-18% of the patients were infected with RSV. Sentinel monitoring of RSV and influenza virus is important and may even be extended to other respiratory viruses as the development of multiplex PCR [30] facilitates the detection of other causative agents of respiratory illness. All countries are encouraged to test their specimens for RSV and improvements can be made as less than half of the countries participating in EISS had reported these data. Furthermore, swabbing procedures should be further harmonised and regular quality control of laboratory methods should be performed. When these criteria are met, surveillance of RSV and influenza virus will contribute to a better insight into the burden of respiratory diseases and may be used by healthcare organisations to decide on the timing of palivizumab prophylaxis for RSV in Europe. Overall, this paper illustrated that an existing influenza surveillance system can be relatively easily broadened to include the surveillance of RSV and may be extended to other viruses in the future.

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