WORKSHOP ON BURDEN OF RSV DISEASE IN EUROPE

ECDC Expert Consultation Meeting
Stockholm
23-24 November 2015

Background

Respiratory Syncytial Virus (RSV) is the leading viral cause of acute lower respiratory tract infections, including bronchiolitis and pneumonia, in infants and young children.

RSV vaccines for maternal or childhood immunisations are progressing past phase two trials and are expected to be available on the markets within the coming 7-10 years. However, the burden associated with RSV infection and epidemiological patterns of virus circulation globally, remain understudied and burden concentrates mainly in the younger age-groups.

The European influenza surveillance system captures RSV detection through the influenza like illness (ILI) or acute respiratory infection (ARI) surveillance system from 21 EU countries in 2014-2015 season. Furthermore, comprehensive data for RSV detection are available from a more limited number of EU countries and through specific research studies. However, case definitions in ILI surveillance systems are not ideal for RSV surveillance and biases need to be studied and understood to inform data interpretation. Routine health systems in many European countries gather data on deaths, hospitalisations, out-patient visits, general practitioner attendance and prescriptions related to bronchiolitis and in many countries these data can be linked by use of unique identifiers. In some settings these data can also be linked to viral (reference) laboratory data. This gives the potential to estimate burden of disease across all age groups and association of RSV infections with health service contacts for wheezing in long term.

WHO has recently embarked on a process to strengthen RSV surveillance globally and is consulting global stakeholders on the appropriate approach to such strengthening.

During the 2015 annual influenza meeting arranged by ECDC, RSV surveillance was also discussed and participants suggested that a working group for RSV surveillance be formed to draft a case definition, develop the objectives,

assess how to best meet the objectives, and develop an implementation plan. These data could help improve understanding of disease burden and yield estimates which could inform decision-making / priority setting by national immunisation policy bodies and could serve as baseline estimates for the assessment of the future RSV vaccine impact.

Scope and purpose

The purpose of this meeting was:

- To scope available RSV surveillance mechanisms and stakeholders in Europe for the evaluation of burden of RSV disease in Europe.
- To evaluate data gaps for burden of RSV disease analysis and how those should be addressed.
- To evaluate the need and feasibility of establishing a European network of RSV researchers and public health experts in order to stimulate activities improving the assessment of the burden of RSV disease in EU.
- To assess the need to develop a joint research protocol and seek funding to undertake research activities related to RSV disease burden in Europe.

Aim and outcomes of the meeting

The aim of this workshop was to elaborate how RSV surveillance is conducted in different Member States (MS) across EU and what data gaps exist to assess RSV-related burden of disease in anticipation of the introduction of maternal or childhood vaccination programmes.

Selection of experts

Twenty-two external experts were invited to participate in this consultation. They were selected based on their expertise in surveillance or research on RSV at national or international level or on their acknowledged expertise in public health surveillance systems. Some experts were ECDC operational contact points within the European Influenza Surveillance Network (EISN) which covers influenza and other respiratory viruses. To support the consultation, ECDC influenza and other respiratory viruses experts were present during the meeting to facilitate the discussion.

The annual and specific declarations of interest submitted by the experts were reviewed by ECDC. Drs. Philippe Beutels, Louis Bont, Harry Campbell, Bruno Lina, Harish Nair, Barbara Rath and Jonathan Van Tam declared in their annual or specific declaration interests that could potentially form a conflict of interest in the field of RSV. These interests, which were in a form of advisory roles or research funding, were reviewed according to ECDC policy and found to be outweighed by the expertise these participants had in the subject. No other conflicts of interest with the RSV topics discussed during the meeting were declared by the participants.

Harry Campbell and Harish Nair (University of Edinburgh) were acknowledged for their work in planning and organisation of the meeting.

Day 1, 23 November 2015

Introductions

Pasi Penttinen, head of Influenza and other Respiratory Viruses (IRV) Disease Programme (DP) from ECDC welcomed the participants to the expert consultation and gave an outline of the meeting with the expected outcomes.

Penttinen opened the meeting by giving an overview of the background for this RSV burden of disease surveillance expert consultation and by mentioning the expectation of future RSV vaccines and the need for EU to be prepared in terms of surveillance data and estimations of RSV disease burden. He stated the aims of the meeting as: 1) to identify the stakeholders; 2) to identify surveillance and any other available databases with RSV data; 3) to identify data gaps; 4) to evaluate the need for and feasibility of network of public health (PH) agencies and research groups to tackle these issues; and 5) to capitalise on the IMI opportunity to seek funding for burden of disease work. He raised also the questions, what is the role of the existing influenza surveillance networks and how we can use RSV data from these networks.

The declarations of interest of the experts were reviewed by ECDC and no conflicts of interest with RSV topics discussed during the meeting were found.

After the opening, each participant introduced him/herself.

Session 1: Global and European RSV surveillance – current status

Chair: Pasi Penttinen, ECDC

Global RSV surveillance

Sandra Jackson, WHO HQ, Geneva, acknowledged the 10 years anniversary of ECDC in 2015 and ECDC's work in influenza surveillance data collection from 53 Member States in the WHO European Region as part of Global Influenza Surveillance and Response Scheme (GISRS). She then presented the rationale for global RSV surveillance as part of the influenza surveillance scheme. More than fifty percent of RSV disease in young children presents as acute lower respiratory infection (ALRI) without fever and this may contribute towards an underestimation of global RSV burden if influenza case definitions are used. Furtermore, many of the patients do not seek care, or they present for care with RSV disease but a specimen is either not collected or not tested for RSV. The functions of the surveillance and surveillance networks are: to describe seasonality, estimate burden of disease, identify viral mutations, standardise global analysis and reporting, organise data sharing, contribute to vaccine development, support introduction of RSV vaccines, standardise availability of reagents, provide standard protocols, reference and research functions and report on the collected data. WHO is currently exploring the potential for global RSV surveillance to link with the GISRS platform and will host the next meeting in February 2016. Global reference laboratories have been agreed and those are based in the US CDC; Public Health England, UK; and the Centre for Respiratory Diseases, CID, Johannesburg, RSA. RSV national laboratories will be developed in pilot countries (2 -3 countries in each WHO region) which will report to the three global reference laboratories with standard operation protocols and external quality assessment programmes. ECDC's support is appreciated in defining the case definition, specimen collection, sampling strategy, clinical epidemiological core dataset and reporting to integrated GISRS platform.

Discussion included points on the cases not presenting with fever and the evidence behind this. The paper by Manoha C et al. from 2007 was mentioned as one such studies supporting this finding. WHO colleagues also clarified that it is not yet decided at the global level what respiratory case definition and/or modifications would be used as a basis for RSV global surveillance.

What RSV-related data does ECDC currently collect?

Eeva Broberg from ECDC presented the current status of the data collection on RSV at ECDC surveillance database TESSy (The European Surveillance System). Currently, there is no mandate for ECDC to collect RSV surveillance data

and there is no existing EU case definition for RSV disease. The European Influenza Surveillance Scheme (EISS) created an RSV task force (2003-2006) that recommended 1) influenza specimens to be tested for RSV, 2) combined nose/throat swabs and nasal pharyngeal aspirates to be used as specimens, 3) to use RT-PCR for RSV detection, 4) to standardise methods and laboratory techniques, 5) to use sentinel hospitals and 6) to ask any new networks joining EISS to integrate RSV surveillance. The recommendations 1-3 and 6 were followed well but for standardisation of methods and for sentinel hospitals there was very limited progress by 2009. The current data in TESSy show that last five seasons of RSV have occurred approximately with the same timing. For the past two seasons, 21 EU/EEA countries have provided data. The majority of the detections are reported from the non-sentinel sources. The challenges with RSV surveillance include that there is no RSV surveillance system in its own right and it is dependent on the influenza surveillance, no common case definition is available and the data are mostly from non-sentinel sources without a common sampling scheme and with hardly any denominator data. Age of cases and RSV type are not collected. Therefore, this meeting was organised to discuss the need and objectives for RSV surveillance, the public health benefits and expected outputs as well as actions based on the data collection.

Discussion included comments on the possibility to link epidemiological and virological data and the case definitions. In France, the switch from ARI to ILI surveillance had resulted in lower detections of RSV. The audience commented also on the laboratory methods and need for serology on top of PCR that distinguishes between group A and B of RSV but does not provide long-term sensitivity after acute phase.

Needs for RSV surveillance data from the vaccination programme point of view

Kari Johansen from ECDC reported on the needs for RSV surveillance data from a vaccination point of view. She noted the global estimates of RSV burden of 33.8 million lower respiratory tract infection (LRTI) yearly due to RSV, 3.4 million hospitalisations and a major burden of disease in developing countries. Up to 199 000 deaths worldwide have been estimated with few in developed countries but with significant disease burden due to bronchiolitis and pneumonia, including very severe disease requiring intensive care which can include mechanical ventilation and occasionally extracorporeal membrane oxygenation (ECMO). The known risk factors are prematurity, bronchopulmonary dysplasia, congenital heart conditions, male gender, age lower than 6 months, neuromuscular disorders, immunodeficiency, trisomy 21 and cystic fibrosis. The recommended treatment option is currently supportive care. Nebulised adrenaline has been shown to provide short-term clinical benefit. Therefore, there is a great interest in the development of new vaccines, prophylactics and therapeutics. Palivizumab, a humanized antibody against the F glycoprotein of RSV that reduces to half the number of hospitalized cases but does not reduce mortality is restricted to use in premature infants considered at high risk of severe RSV disease. Several experimental prophylactic and therapeutic agents are in development. The first RSV vaccine was developed in the 1960s but produced an enhanced RSV-associated disease resulting in death of two children. Current RSV vaccine candidate development strategies include live attenuated and recombinant viral vectors expressing RSV antigens. Several products are in phase 3 clinical trials. Target populations include pregnant women, young infants, older children (siblings of infants) and elderly (above 65 years of age). For introduction of a new vaccine in the vaccination programmes and for understanding the impact of a vaccine, surveillance, vaccination programme and coverage as well as monitoring platform experts need to collaborate.

Discussion: Disease burden in 6 weeks – 6 months olds comes from hospital data; peak incidence is greater in the 6-11 months olds. For policy makers, for a vaccine with high costs the severe disease burden is likely to be the key argument although societal costs based on wider incidence estimates are also important. Phase 3 RSV vaccine studies are already underway in elderly with large sample sizes (n=10 000) and maternal vaccine phase 2 data are available. Rotavirus studies have focused on hospitalisation studies and that could be used as a mode of study. RSV has a very high transmission rate, does not induce neutralising antibody protection and therefore high rates of coverage will be required (similar to pertussis). Adults are also transmitting RSV. High risk groups include children, especially the premature infants.

European data collection on RSV – challenges and opportunities

Jonathan Nguyen-Van-Tam, WHO CC Nottingham joined by teleconference and presented an epidemiological study of respiratory syncytial virus in Member States of the European region of WHO (RSV-EuroFlu Study). The aim of the study was to describe the epidemiology of RSV to investigate the burden of this infection using sentinel and non-sentinel surveillance data in WHO European Region Member States from 2006 to 2012. The study was to answer the following questions: 1) What is the overall and age-specific notification and incidence rate of laboratory confirmed RSV detections and clinical diagnoses of ARI and ILI? 2) What is the association between the incidence rate of ARI and ILI and laboratory confirmed RSV detections? The study design was based on a retrospective ecological study with weekly number of RSV tests and detections as well as ILI/ARI rates reported from the MS. Eight countries were included in the full analysis: Austria, France, Ireland, Israel, the Netherlands, Russian Federation, Spain and the UK (England and Scotland). Overall, poor correlation of ILI and ARI case definitions for RSV detections was shown. RSV testing had increased after 2009 influenza pandemic. The analysis showed also a lack of data for persons above 65 years of age.

Discussion included points about RSV clinical signs that the adult presentation is less characteristic with less fever and very often no specimen is collected. Viral shedding is also lower in adults. RT-PCR sensitivity might be only 75-82% (positive in early illness; but later negative), combining PCR with serology may have higher sensitivity (85-90%). Interpretation is that RSV is an important cause of burden of disease in adults but is often not detected. The conclusions related to this group were that ILI and ARI are not adequate to detect RSV in this age group, however no better solution was proposed for the case definition. Therefore, there is a need for repeated cohort studies with both PCR and serology to capture all RSV activity and to learn from those to design RSV surveillance.

Session 2: European RSV surveillance – current status

Chair: Denis Coulombier, Pasi Penttinen, ECDC

The aim of tsession 2 was to give an overview of the existing surveillance systems for RSV in the EU/EEA.

RSV surveillance in Sweden

AnnaSara Carnahan from Public Health Agency of Sweden, presented the RSV surveillance in Sweden. All clinical microbiology laboratories and clinics performing RSV diagnostics are invited to participate. They report weekly between weeks 40 and 20 to Public Health Agency of Sweden total number of positive RSV detections as well as age, sex, date of result and county. They also report the total number of specimen tested and diagnostic method used. In Sweden, an often low (later) seasonal pattern followed by high (often a little earlier) seasonal pattern has been observed on the national level. The cumulative incidence has been calculated as 52.56/100 000 population per season in 2014. The peaks for children occur earlier than for older adults, whose peak coincides with the influenza peak. In Sweden, no burden of disease data are available and the country has stopped doing ILI surveillance. The likely reason for the increasing number of RSV detections over time is better completeness of the surveillance in the recent years and an increase in multiplex analyses during the influenza season. The typing of RSV is done for 10% of the specimens and for the 2014-2015 season, 44% RSV-A and 55% RSV-B were found. Severe influenza seasons influence the number of specimens tested for RSV. For the ICU surveillance, 78/84 ICU units participate but the completeness of data reporting is not known. In 2012-2014, 135 patients were admitted to ICU for RSV and of those more than 80% were children. Approximately 3% of RSV-positive individuals were admitted to ICU. Laboratory-confirmed RSV is used as the national case definition. The data gaps include: representativeness of current surveillance is unknown (counties, age groups); data on testing criteria for RSV are unknown; data on the performance of diagnostic tests are available but not reviewed; age-specific data on denominators are not collected and mortality data are not collected.

RSV surveillance in Germany

Brunhilde Schweiger, from Robert Koch Institute, Germany, presented on RSV surveillance in Germany. There is no

RSV-specific surveillance system in Germany but it is a part of national influenza surveillance that has been established in 1992. ILI and ARI case definitions are used during autumn to capture the first cases of influenza and also RSV and other respiratory viruses. Data on number of consultations, hospitalisations, absenteeism from work and school and RSV associated need for care are available. RSV surveillance including ILI/ARI sentinel children ≤ 4 years old and the elderly is performed since 1999-2000 whereas all sentinel specimens are analysed for RSV since 2010-2011. RSV positivity rates varied between 7% and 10% when analysing all sentinel specimens. The positivity rate in children ≤ 4 years old was on average about 20%. High RSV activity was characterised by positivity rates between 31% and 53% but detected only in three out of 14 seasons. Further typing of RSV-positive samples revealed a co-circulation of RSV-A and RSV-B. RSV-A dominated in eight and RSV-B in two seasons, respectively, whereas both subgroups circulated to the same extent during three seasons. Further on, a co-circulation of different genotypes was observed for RSV-A and RSV-B.

Barbara Rath, Charité Universitätsmedizin Berlin, Germany presented on a hospital-based RSV surveillance system in Berlin. An independent quality management team in the hospital performed syndromic ILI surveillance from 2010-15 based on a simplified version of the new WHO ILI case definition in addition to physician requests/diagnoses of ILI. The specimens were tested at RKI for influenza A&B, RSV, human metapneumovirus, rhinovirus and adenovirus by PCR, viral culture, and in the clinic with second generation influenza and RSV rapid antigen testing. A standardised clinical assessment, done at point of care, and a disease severity score were used to indicate association between average disease severity and respiratory viruses. RSV gives the strongest association. Partnering for enhanced digital surveillance of influenza has been initiated via the PEDSIDEA consortium using mobile apps. The specimens used are rather nasopharyngeal swabs than nasopharyngeal aspirates but nasal swab also works well (with a little lower sensitivity and higher specificity for RSV rapid testing).

In **discussion**, the algorithm for when to test the patient was taken up. In German National Surveillance, every ILI patient is tested at the set point of time in the week.

RSV surveillance in the UK (England and Scotland)

Richard Pebody, Public Health England, the UK, presented on burden of disease studies and RSV surveillance in England. Several BoD studies on RSV have been conducted in children and adults. The national case definition for RSV is laboratory confirmed RSV as well as ICD-10 hospital codes. RSV surveillance is based on community and hospital based surveillance, with primary care consultation, hospital admission and mortality data being used for burden of disease estimations. The objectives of RSV surveillance are to detect when RSV circulation starts, to define the intensity of circulation and the main groups affected. Within the sentinel influenza GP surveillance system, both ILI and ambulatory cases are tested for influenza and RSV. The BoD of RSV in England has been estimated in various studies, e.g. Muller-Pebody et al. (Epidemiol. Infect. 2002) and Fleming et al. (BMC 2015). In children, mean annual incidence of hospital admissions attributable to RSV is 28.3/1000 in less than1 year olds and 1.3/1000 in 1-4 year olds. In adults, 18+ year olds, there were estimated to be 487 247 GP episodes, 17 799 hospitalisations, and 8482 deaths attributable to RSV per season. Of these, 36% of GP episodes, 79% of hospitalisations and 93% deaths were in 65+ year olds. Public Health England is involved in updating burden estimates through statistical modelling, linkage and economic burden studies, as well as estimating impact and calculating cost-effectiveness of alternate vaccination scenarios.

Jim McMenamin, Health Protection Scotland, the UK, presented the Scottish BoD and surveillance of RSV. Scottish Intercollegiate Guidelines Network (SIGN) 91 guideline (Bronchiolitis in children, A national clinical guideline, 2006, available at http://www.sign.ac.uk/pdf/sign91.pdf) contains BoD data for RSV as well as the regional case definition which includes laboratory-confirmation and ICD-10 hospital codes for bronchiolitis in children. The surveillance comprises of community and hospital surveillance and the severity is estimated through hospital and ICU activity. Pharmacy proxy data are used as well, e.g. palivizumab powder doses. SIGN 91 stated that around 75% of bronchiolitis in children is caused by RSV and therefore the burden is significant (around 15 000 children in Scotland annually). The peak prevalence is from November to March and re-infection during a single season is possible.

Around 70% of all infants will be infected with RSV in their first year of life and 22% develop symptomatic disease. About 3% of all infants <1 year of age are admitted to hospital with bronchiolitis and the rates have increased during 1996-2005 without obvious reasons. RSV-attributed death rate (1-12 months of age) was 8.4/100 000 population, with most deaths in those less than6 months of age and with underlying cardiac or pulmonary disease. 34-50% of bronchiolitis cases result in wheezing. Health Protection Scotland has planned to follow the mortality in season 2015/16 and annually thereafter. Until now, based on unspecific coding, approximately 1/1000 hospitalisations have had a death reported. During the peak of the season, hospitals experience 300-450 admissions per week and the demand outstrips capacity for ICU admissions. This can be overcome to some degree by considering data on specific medical treatment used in severe RSV infection (e.g. palivizumab) for which Scotland has access to such pharmacy data. Assessment of long-term sequelae is yet to be done.

RSV surveillance in Hungary

Enikő Bán, National Center for Epidemiology, Hungary, presented on RSV surveillance in Hungary. In Hungary, RSV surveillance is based on influenza surveillance with 167 GPs and 111 sentinel hospitals departments (until 2011) taking part during weeks 40-20. Multiple respiratory viruses are tested from the collected specimens and attention has been put on SOPs for sampling, transportation and testing. No burden of disease studies have been conducted yet. Case definitions in use are ILI and ARI (EC 2012). No clinical data on severity of infection are available to laboratories. In 2012-2013, 80 of 1155 specimens were RSV positive and age distributions were different between sentinel and non-sentinel samples with 0-4 years of age (54%) predominating in non-sentinel whereas in sentinel 30-64 years olds contributed with highest percentage (31%). In the 2013/14 season, only 16 of 1191 specimens were positive for RSV. In 2014/15 season, 99 specimens were positive and in that season, 30-64 years olds were in majority in both sentinel (32%) and non-sentinel surveillance (38%).

RSV surveillance in Slovenia

Maja Socan, Public Health Institute, Slovenia, presented on RSV surveillance in Slovenia. The objective of the system is to detect the start, peak and end, duration and magnitude of RSV season. Weekly numbers of patients tested for RSV are collected. The information is used for guiding diagnostic testing and timing of palivizumab prophylaxis for severe RSV infection. The national case definition is laboratory confirmed RSV infection by any laboratory method (direct immunofluorescence, PCR, isolation) reported from any of the eight public laboratories. The onset week is defined as the first of two consecutive weeks when the weekly percentage of all specimens testing positive for RSV antigen in all reporting laboratories in the area is ≥10% (US CDC The National Respiratory and Enteric Virus Surveillance System (NREVSS) definition). A more stable reporting was established after the 2009 influenza pandemic and the number of tested patients has increased during 2010-2015, however the number of positive RSV detections has decreased from 22% to 9% which reflects the change in testing practice to include 25% adults instead of testing only children with bronchiolitis. The impact of influenza and RSV on hospitalisations was studied in Slovenia in 2006-2011 (Ucakar et al. 2013) and shown that RSV alone causes 105.9/100 000 children less than5 years of age to be hospitalised due to ALRI and 54.5/100 000 due to acute bronchiolitis.

RSV surveillance in Finland

Niina Ikonen, National Institute for Health and Welfare, Finland, shared a PDF presentation and a summary of the presentation as she could not attend the meeting due to illness.

In Finland, there is no specific surveillance system or case definition for RSV. All respiratory specimens that are received through influenza surveillance system are tested for RSV along with influenza A and B viruses. Virological sentinel surveillance network for ILI consists of primary healthcare centres, healthcare centres of garrisons and private paediatric clinics (from season 2015-16 onward). Virological surveillance is closely linked to clinical surveillance. Primary healthcare centres send respiratory specimens and also report data on ILI visits. Besides ILI surveillance there is also surveillance of SARI in intensive care units. Limitations of sentinel surveillance network are: uneven distribution of patients by gender and age, specimens from children and elderly have been scarce and

specimens are mostly limited to influenza season (weeks 40 to 20). RSV surveillance is possible using the National Infectious Disease Register (NIDR; in Finnish TTR) where all national clinical microbiology diagnostic laboratories notify all positive microbe findings. Each notification also includes date and type of specimen, diagnostic methods, date of birth, gender, unique national identity code, and place of residence. Limitations of using NIDR are: total number of tested specimens is unknown and the register does not include clinical information. Based on the RSV findings reported to NIDR there is a bigger RSV epidemic every second year.

RSV surveillance in Denmark

Thea Kølsen Fischer, SSI, Denmark, presented on RSV surveillance in Denmark. Denmark does not have active RSV nor ALRI surveillance. During the influenza season, influenza surveillance specimens are tested for RSV from sentinel sources. Data from the national microbiology laboratory database (MiBa) on RSV testing are reported weekly to WHO. National hospital discharge register, national microbiology database and SSI laboratory database can be to obtain age information and other social data. Using linkage of civil unique identifier to national hospital discharge registry, MiBa, and the death registry attempts are undertaken to retrieve age incidence estimates for severe RSV disease and RSV deaths in Denmark during the period of 2010 to 2015. Most cases were found in 0-5 months olds and with 1-2 months olds being the largest group affected by RSV in Denmark over all seasons. Seasonality of hospital admissions follows RSV seasons. If only hospital discharge data are studied, 10-15% of cases will be lost and therefore it is important to study also laboratory databases. As case definition, hospital discharge code and RSV detection or RSV detection in laboratory report only. Length of stay was higher in 0-1 months olds than for 1-2 months olds. Data on prematurity or other risk factors has recently been published in another study.

Discussion

Timing of season can be captured from existing systems (most seasons are very similar within a country but can vary between countries). The value of the data is in indication of RSV season, awareness raising and in their use in reimbursement systems of prescription drugs. There is more variability across countries for BoD than for surveillance (clinical data on sample; hospital discharge data). Clinical phenotype varies by age group (prematures / infants / other children). Passive surveillance data are enough for seasonality across Europe and at country level data are available for age groups and gender which helps to interpret trends over time but is less useful for incidence estimation due to underreporting. The burden consists obviously also of community cases and therefore emphasis should not be only on hospitalisations but to capture also mild ALRI cases that do not seek health care and for that active surveillance would need to be established. The timing and seasonality will probably not be critical for vaccination programmes as the vaccination would not be annual as for influenza. A marker for likely severe illness would be useful for the administration of antiviral treatment as the hospitalisation occurs at later stage which might be too late for treatment. Overall the focus should still be to prevent severe outcomes of RSV infection and not to prevent transmission and therefore emphasis on hospitalised cases is important.

RSV surveillance in the Netherlands

Anne Teirlinck, RIVM, Netherlands, presented on surveillance systems for RSV in the Netherlands which are mainly based on NIVEL primary care GP sentinel practices. On top of that ILI incidence and swabbing in nursing homes, virological laboratory surveillance, Dutch hospital data, SARI surveillance and serological surveillance are available. Sentinel GPs cover 0.7% of Dutch population and ILI and ARI patients are swabbed all year round for influenza, RSV A/B, rhinoviruses and enteroviruses. A more in depth analysis for RSV is done to study genetic changes and antigenic sites. RSV positivity in ILI and ARI specimens has varied over the seasons from 5.2% (ILI epidemic period 2012/13 in ARI samples) to 22% (ILI epidemic period 2013/14 in ARI samples). Since the 2011/12 season, the number of positive diagnoses dropped due to changes in financial regulations concerning diagnostic requests in many hospitals. SARI surveillance is conducted as a pilot in two hospitals in the Netherlands and may be extended to RSV. For serological surveillance blood from 7900 Dutch persons is available and could be used for population exposure. As case definition ILI and ARI and RSV-laboratory confirmation has been used. For BoD, RSV-attributable mortality has been studied (Van der Wijngaard, 2012) and shown that elderly have higher mortality due to RSV than children. Also, the

Burden of Communicable Diseases in Europe (BCoDE) project can provide an interesting approach for calculating and ranking the BoD of RSV in comparison to other pathogens, if the right data become available to model the assumptions for the outcome tree. The data gaps include a lack of systematic sampling for RSV, denominator data for virological surveillance and clinical information, as well as established SARI surveillance and burden in target groups.

In **discussion**, a question in regard to the use of ICD codes was raised. Those were RSV specific and did not include the bronchiolitis code (could account for the low child estimates). In serology, no distinction of RSV-A and RSV-B due to high homology between A and B would be expected. In Belgium, within the public health system, it is free to test for all vaccine preventable pathogens.

RSV surveillance in France

Bruno Lina, University of Lyon, France, presented the RSV surveillance in France. ILI case definition is used in community-based surveillance of influenza for RSV detections. Hospital notifications are received for RSV infection. In France, 400 GPs and 100 paediatricians take part in ILI surveillance. Crude incidence rates vary between 145-485 / 100 000 population in all age groups. Clinical picture varies as adults are less prone to develop fever with RSV. RSV season (weeks 45-52 usually) in France, precedes influenza season. RSV season is preceded by human rhinoviruses. Based on seven seasons' data, RSV cases are picked up by hospital surveillance but not by ARI surveillance. ILI case definition is even less specific for RSV. No BoD studies have been conducted for RSV in France. SARI data may give some indication of severe disease. Case definition for RSV is "proven infection of RSV". The French National Public Health agency is willing to implement RSV surveillance from 2016 onward.

In discussion, it was reiterated that no clinical syndrome is specific enough for RSV and would probably need case definitions for young and elderly separately. ARI surveillance could be possibly used and ILI cases extracted from ARI surveillance to avoid double systems for RSV and influenza. The surveillance data from SARI and ILI are reliable and consistent over large number of sites and long periods and need to remain for influenza surveillance. ILI surveillance in the PAHO region works for detection of RSV seasonality. Overall, there is a need for a simple and reliable system which does not continually change.

RSV surveillance in Italy

Alessandra Pierangeli and Fabio Midulla, Sapienza University of Rome, Italy, presented RSV surveillance in Italy. No national surveillance for RSV exists but it could be conducted as part of influenza surveillance that exists since 1965. Several studies on infants with bronchiolitis and ARI with RSV have been conducted. Hospital-based surveillance has captured bronchiolitis cases since 2004 with approximately 2% of all admissions of infants across the years, with a slight increase over the past years. 67% of infants with bronchiolitis have RSV infection, 10% have co-infection of RSV with another pathogen. Higher outdoor air pollutants and environmental factors (NO and NO_2; low temperature and high humidity) have been associated with RSV seasonal peaks. RSV group A and B vary in predominance in different seasons with a nearly identical pattern in different large Italian hospitals. The epidemic peak of the novel RSV genotype ON1 in the 2012/13 season occurred earlier than the previous two seasons; ON1 has been shown to be less severe and to affect younger babies (median 2.5 months vs. 5.0 for non-ON1). RSV disease severity has been shown to depend on both viral load and host factors (e.g. expression of IFN lambda1).

Short- and long-term RSV burden in Spain

Xavier Carbonell-Estrany, Collegi Oficial de Metges de Barcelona, Spain, presented hospitalised cases with RSV in Spain. Acute RSV bronchiolitis is the single most common cause of hospitalisations of LRTI in Spain among children 0-14 years of age. The rate of hospitalisation has been estimated as 1-2% for healthy children under 1 year of age. In RSV in risk populations (premature babies, patients with coronary heart disease, Down syndrome, immunosuppression or chronic lung disease) the RSV admission rate is much higher. Data on burden of non-RSV and RSV hospitalisations have been published (Carbonell et al 2000, 2001 and Pedraz et al. 2003). For premature children ≤32 weeks of gestational age, hospitalisation rate is approximately 13% for RSV and for other respiratory infections

7% in two consecutive seasons in a large multicentre study. With palivizumab prophylaxis for RSV the hospitalization rates drop to 4% in this group of premature population of ≤ 32 weeks gestational age at birth. The burden on parents was studied and the majority (57%) of the burden on parents is not only directly associated with medical factors, but relates to family/social, personal and financial factors. RSV infection has been associated in the pathogenesis of recurrent wheezing in the first years of life. The multicentre, observational, nested, case-control study with independent cohorts (SPRING study, Carbonell, PlosONE, 2015) with multivariate analysis revealed that the most important factor for wheezing was RSV hospitalization. Healthcare resource utilization was significantly higher in cases than controls.

Session 3: Global Burden of RSV disease

Chair: Mike Catchpole, ECDC

Burden of disease studies' methodology

Alessandro Cassini, ECDC, presented the Burden of Communicable Diseases in Europe (BCoDE) project. Disease burden is defined as an impact of a health problem and can be measured by financial cost, mortality, morbidity or other indicators. The BCoDE study allows assessment of the comparative impact of infectious diseases with objectives to introduce an evidence-based approach to health description, foster an overview of surveillance data quality and availability, facilitate the communication of complex information to decision makers and to provide a tool for planning and prioritisation. For comparison of different notifiable diseases, BCoDE used disability-adjusted life years (DALYs) as the "common currency". DALYs are composed of years of life lost due to premature mortality (YLL) added to years of healthy life lost due to disability (YLD). The data needed for BCoDE comprise incidence data for (a) symptomatic infection, permanent disability, transitional sequelae and fatal cases. Influenza causes the highest burden of disease in Europe of all notifiable diseases (>70 DALYs per 100,000 population), according to the results of the BCoDE 2015 study. The ONBOIDS (2012) study from Ontario showed 96 deaths and >340 000 health care utilization episodes attributable to RSV / 12.2 million residents, which would compare to BCoDE with approximately 11 DALYs per 100,000 population. The BCoDE project was presented to give an example of how RSV burden of disease could be calculated and how the BCoDE tool could be later utilized.

Systematic review and meta-analysis: Global Burden of RSV disease

Harish Nair, University of Edinburgh, presented a review of global burden of RSV estimates and revised interim RSV-ALRI estimates. The Nair et al. 2010 review looked into ALRI due to RSV in children under 5 years of age and especially in developing countries, the interim estimates were that of 33.4 million cases of RSV-associated ALRI and 3.4 million RSV-associated hospitalisations with 53 250 in-hospital deaths and up to 199 000 deaths overall occurring annually. Approximately 80% of ALRI deaths in those less than 5 years of age occur outside hospitals. The RSV Global Epidemiology Network (RSV GEN) assembles unpublished data from more than 70 research groups, mainly from low and middle income countries. It estimates RSV ALRI and severe RSV ALRI incidence (from community-based active surveillance studies); hospitalisation rates (from systematic hospital studies with population denominator data); hospital case fatality ratios; and community RSV ALRI mortality from models of weekly ALRI deaths (verbal autopsy data) from community-bases studies together with data on RSV and influenza weekly activity. Data for a minimum of three years are collected. Limitations of the RSV-related ALRI mortality data in community include that there is a lack of national ALRI mortality estimates in children less than1 year of age and secondary bacterial infections subsequent to RSV-ALRI are underestimated. Updated global estimates from RSV GEN should be available later in 2016.

Data gaps for estimation of global RSV burden

Harry Campbell, University of Edinburgh, discussed data gaps for estimation of global RSV burden. The first question is which burden to measure as the risk groups for RSV range from young children to elderly, HIV positive, children with chronic conditions and special populations e.g. aboriginal populations. RSV has the highest odds ratio and attributable fraction exposed (AFE) among all respiratory viruses in children with ALRI (Shi et al. 2015). The second

question is which mortality is caused by RSV and how to measure that, as fatal cases in young children with very severe viral ALRI occur usually in the patients with co-morbidities. Mortality estimates also do not account for secondary bacterial pneumonia. Deaths from other RSV syndromes and from longer term sequelae are also not taken into account. Issues in making burden estimates further include issues with numerators (case definition validity, sampling scheme, diagnostic test used etc.) and denominators and how those are obtained. In high/middle income countries, RSV is identified only in a fraction of hospital deaths and typically not at all identified in community deaths. Globally, especially in low income countries, RSV transmission and seasonality is not well known. Data on children are not readily available and very little data in adults or other risk groups exist. Possible future approaches could include RSV transmission studies with globally assembled phylodynamic analysis. An expansion in the number of prospective hospital studies would improve the representativeness of hospitalisation estimates. The global influenza surveillance and reporting system (GISRS) SARI surveillance sites can be used as a platform to establish RSV surveillance (albeit with a revised case definition and greater attention to case recruitment in young children (0-2 years), especially in low and middle income countries. For measuring vaccine impact of RSV, baseline data for RSV burden are crucial. RSV vaccine development is currently ahead of global policy development and there is therefore a need for international leadership from agencies such as WHO and ECDC to define disease burden and raise awareness of this problem, partly through establishing RSV surveillance and reporting these data. Key national stakeholders, e.g. ministries of health, are not always aware of RSV burden as typically no surveillance is conducted at national level.

Discussion

Syndromic case definitions, such as ILI, ARI or SARI have low positive predictive value and sensitivity and their validity can vary substantially with different case definitions. RSV and pneumonia time series analysis would help to study the link with secondary bacterial infections. For BoD studies, there is a need to be clear about the specific age groups most at risk – with young infants and elderly affected mostly. BoD studies do not include asymptomatic cases unless there are longer term sequelae (could argue that asymptomatic cases by acting as transmitters can contribute to the burden). For age-specific estimates it isclear that the target group is young infants with severe disease as RSV infections occur at very young age. There is a need for key data on incidence of severe disease / hospitalisation in young infants. One needs to clarify also the key elements in the burden of disease decision trees as cost of hospitalisation is key factor for policy making but not included in burden of disease models. Indirect protection for RSV infection could occur through vaccination of older children as RSV is highly transmittable. Some countries are starting to vaccinate for pertussis in pregnant women to protect high risk young infants and that could be used as a model for RSV. Large linked registries could give information on what is the attributable risk of RSV for later life attributable effects.

Day 2, 24 November 2015

Introduction to the day and summary of the previous day's discussions

Pasi Penttinen, ECDC, summarised the discussions and presentations of day 1. The ILI and ARI case definitions may be sufficient for seasonality purposes but not for burden of disease studies. Expansion of hospital-based registries would be needed in Europe to cover for hospitalised cases of RSV. Serology was raised as one method to capture the true RSV burden but has technical challenges to separate the recent and previous infections and to differentiate between types of RSV. ECDC and WHO aim to synchronise the work and to benefit of the national and subnational activities already in place. The challenges are in agreeing which age groups and severity level to target and how. The global burden of disease work can be used as conceptual model for Europe where there is better understanding of burden in infants but less so in the elderly. Some time series models reviewed on day 1 showed significant mortality due to RSV in the elderly but this is not found in surveillance yet and needs further attention as well as the long-term impacts of RSV.

Brainstorming session on EU-wide data collection needs

Chair: Eeva Broberg, ECDC

The experts were split to surveillance and burden of disease working group. The surveillance group discussed the needs for RSV surveillance and formulated public health objectives for such. The burden of disease group discussed the focus areas for burden of disease studies in Europe.

Surveillance group listed many objectives and expected benefits of RSV surveillance (Table 1).

Table 1. Proposed public health objectives, expected benefits, potential implications and expected outputs of RSV surveillance.

Public health objectives	Expected benefit	Potential implications	Expected outputs
Estimation of impact of RSV in various age groups	Support disease prevention efforts Morbidity and mortality stratified by age / gender / country Definition of risk groups (stratification by month in first year; including also elderly)	Information for health care planners, e.g. for use of palivizumab Evidence for prevention including vaccines Evidence to inform priority setting and policy making Data for direct and indirect costs / societal planning / planning health care planning – data for public health action	Targeted announcements to policy makers / public health officials of any special events with recommendations Report to clinicians; health care professionals, PH bodies and policy makers
Understanding role of RSV in overall respiratory disease	Integrated surveillance of all respiratory pathogens Differentiation of RSV impact from other respiratory pathogen impacts, e.g. influenza;	Better understanding of RSV disease burden Targeting of specific populations for vaccination Resource planning for community vs hospital health care services	Seasonal alerts of unusual patterns leading to further investigations Information for public health organisations and health services

	Differentiation of community versus hospital burden	Inform PH authorities / hospitals about the surveillance system – to receive financial support (from the state) Information on secondary bacterial disease by differentiation diagnosis	
Epidemiology of RSV in the community and hospitals to define seasonality	Timing of epidemics by country and age groups Obtaining baseline data before vaccine introduction Continuous data collection on RSV infections	Real time data for public health authorities and health care planners to guide public health action, e.g. for use of palivizumab (timing and target groups) Support for future vaccine effectiveness studies	Real time surveillance reports – website; national and ECDC level; weekly reporting
Virologic surveillance to follow prevalence of types and drift of RSV	Agreement on standard methods for RSV diagnosis and sampling frame	Standardise lab procedures, criteria etc. so that data generated are comparable across borders; standard sampling frame Better understanding of clinical and laboratory diagnosis Tracking of RSV viral sequences to inform PCR composition and understand genetic diversity; support diagnostics Establishment of biobank of samples	Standardised protocols for laboratory methods Standardised sampling frame Sharing of sequencing / subtyping data in case of emergence of new strains; this pattern could be different across Europe (season "intensity")

Needs for surveillance system

To take a pragmatic approach the group looked into what could be available as RSV surveillance in the next 3 years. There is a need to define what can be built on the influenza surveillance but also how specific RSV surveillance can be built in a few countries. The ILI/ARI surveillance is not ideal for RSV and therefore RSV surveillance needs increased sampling from infants, in-patients and the elderly. The current passive laboratory surveillance is what is possible at present and is good for seasonality but not for prediction of burden without population denominators. Other surveillance systems, e.g. rotavirus surveillance in hospitals can act as a model for RSV surveillance to support e.g. estimation of disease burden for one year (once only) which could be done in one country only and is not necessary to perform in all countries in Europe.

Key needs in the area of surveillance are standardised data, epidemiology and laboratory methods as well as weekly data and reports. Even if the surveillance would be voluntary, it needs to have international recognition as this helps countries to find financial support. Outputs should include both virological and epidemiological reports including morbidity and mortality data from community and hospital-based surveillance. Active laboratory surveillance could be set up in a few countries to complement the passive surveillance.

Burden of disease group discussed the objectives and feasibility of burden of RSV disease studies (Table 2). Surveillance and burden of disease studies are both important, complement each other and have therefore similar objectives and expected benefits but some BoD outputs cannot be covered with routine surveillance and need special studies.

Table 2. Proposed objective, expected benefits, potential implications and expected outputs of burden of RSV disease studies.

Objective	Expected benefit	Potential implications	Expected outputs
Inform policy makers of RSV disease burden in the community	Support disease prevention efforts Definition of risk groups Creation of baseline data prior to vaccine introduction Understanding of RSV induced severity and long-term sequelae	Information for health care planners Evidence for prevention including vaccines Evidence to inform priority setting and policy making Data for direct and indirect costs / societal planning / planning health care planning – data for public health action Raising profile for national governments and public health institutes	Targeted announcements to policy makers / public health officials of any special events with recommendations Policy and guidance for clinical societies Advocacy with patient groups Global markets pricing in low-middle income countries

Feasibility and gaps were discussed with influenza surveillance as a basis. ILI case definition could be studied further together with adjustment for fever criteria in case definition. ARI case definition can be used to capture RSV data when including youngest children. SARI case definition should be looked at more carefully to analyse if the youngest infants are included and to use regression modelling to overcome data gaps. The most feasible route to capture most severe RSV cases would be to add RSV testing to ICU surveillance. Serological markers of RSV should be studied further as these may be important for BoD studies. Standardised study protocols should be prepared to assist in the interpretation of country-to-country specific surveillance.
Economic burden of RSV is currently captured and needs to be built in any framework for future outputs (there is a need for protocols to achieve this). Safety monitoring for vaccines and potential antivirals should be built in the system from the beginning. The immediate needs are to define the objectives and to agree on case definitions.

Session 5: Examples of usage of RSV disease burden data

Chair: Harry Campbell

Estimating the economic burden of RSV disease

Philippe Beutels, University of Antwerp, Belgium, described the methods to estimate economic burden distinguishing health care and personal direct costs, as well as indirect and intangible costs (pain or suffering). Different costs and outcomes are relevant from different viewpoints (e.g. health care payer versus society). Economists tend to agree that society represents the most relevant viewpoint for policy, but health policy makers tend to focus more on the narrower health care payer's perspective. Quality-adjusted life year (QALY) estimates for

children under 8 years of age are only obtainable by proxy (i.e., from caregivers, usually parents). The impact of a child's illness on parental quality of life has been explored previously and was shown to greatly impact the cost-effectiveness of childhood vaccines (e.g., rotavirus). Estimating costs that are specifically attributable to RSV is difficult given the generic nature of a clinical RSV diagnosis, especially for ambulatory care cases and cases not seeking health care (i.e. the majority of cases). Hospital databases allow using relevant ICD codes, but the RSV attributable fraction is better to be estimated separately, for instance by regressing RSV-coded numbers of hospitalised cases against concurrent lab confirmed pathogen circulation. Focusing on the cost per case, rather than the attributable caseload, different costing methods based on hospital records were discussed, with microcosting being the most accurate, but also the most time and money consuming costing approach and DRG based costing the easiest and most readily available approach. Examples were shown of ICD based hospital costs per case (e.g. for influenza, which can be expected to show similarities to RSV). These costs show a classic U shaped pattern by age, with high variability at older ages. When estimating such costs it is important to investigate the sensitivity of database selection options. Estimating costs in ambulatory care or for non-care seeking cases usually requires a specific study set-up. The pros and cons of retrospective / cross sectional studies, web-based surveillance or prospective data collection were briefly highlighted, showing examples of the costs per ILI case using a retrospective survey design, and the costs per pneumococcus case by linking laboratory diagnosis to an insurance claims database in a retrospective matched case-control design. Delphi panels, which offer a popular cheap way to estimate costs should be used only as a last resort as they are prone to bias. The attributable age-specific number of cases (and the proportion hospitalised) and deaths tend to be more influential for the cost effectiveness of vaccination than the estimated costs per average case by age. For RSV the costs of long term sequelae may be specifically challenging. Whether these are influential for the average costs per RSV infection depends on whether the proportion of infections with sequelae is high (e.g., wheezing accompanies 50% of RSV ALRI cases). An additional challenge at the European level is that health care systems (and health care costs per episode) differ by country, and different practices exist in database management (e.g. the existence of centralised (and the representativeness of) hospital databases differs between countries).

Burden of RSV disease in the USA

Mark Miller, Fogarty International Center, National Institutes of Health (NIH), Bethesda, Maryland, USA presented epidemiology and disease burden of RSV in the USA. CDC Atlanta is in charge of surveillance and policy but NIH have developed methodologies to apply influenza surveillance for RSV. Weekly respiratory deaths or hospitalisations are used as outcome in modelling where influenza and RSV activities are included as covariates. Laboratory-confirmed surveillance time series are available for influenza and RSV and RSV-coded hospitalisations or bronchiolitis-coded hospitalisations in less than2 years olds demonstrate excellent proxies for RSV viral activity. In the US, excess respiratory mortality in 65 years olds or older has been associated with influenza and RSV infection (Charu et al. 2013). Many countries do not have these data streams. Great diversity in timing of RSV epidemics has been shown globally with less of a peak in tropics (Bloom-Feshbach, PlosONE 2013). In the US, latitudinal gradient of RSV activity and strong association between RSV timing and fall temperature is seen (Pitzer et al., PLos Path 2015). Latitude gradient may be important also in Europe.

Biomarkers in RSV burden of disease studies

The presentation of **Louis Bont, University of Utrecht, the Netherlands** was not given in the interest of time but shared as PDF among the meeting participants. He summarised the presentation shortly stating that the virological marker studies are most important. RSV infection may prevent subsequent or concomitant infection with other viruses through the induction of antiviral proteins at the nasal level, including type 1 interferons. Pharmaceutical industry has not been keen to analyse unrelated pathogens as the treatment regimens are usually targeting only one. This is important for public health bodies and surveillance should not focus on one virus only.

Conclusions

Pasi Penttinen, ECDC, summarised the objectives and available data of RSV surveillance and BoD studies in Table 3.

Table 3. Possible indicators and available or required data for these.

Indicator	Surveillance	Burden of disease studies	Other studies
Start and end of season	All surveillance		
Incidence of symptomatic illness/GP consultations	ILI/ARI+laboratory surveillance	Incidence, burden	
Hospitalisations	SARI+laboratory surveillance	Burden	
ICU admissions	ICU + laboratory surveillance	Burden	
Deaths	All-cause mortality	Burden	
Safety signals			Adverse events registries and studies
Economic burden			Economic burden studies
Long-term sequealae		Burden	Long-term follow-up with cohorts

RSV vaccines are likely to come to market within the next 3-15 years in Europe. Results of large trials may become available in 2016. Currently, estimates of burden of RSV disease in Europe do not exist and the laboratory-based passive surveillance of RSV is not standardised and is without denominator in most countries. Baseline data for incidence/ burden of disease need to be established to document the potential impact of future vaccination. Surveillance objectives suggested by the experts of the meeting included estimation of RSV incidence across age groups and target populations such as very young infants and elderly, both in community and hospitals. Virological surveillance should focus on following the RSV types and strains and the impact of vaccination on those. The burden of disease estimates need to be calculated prior and after the vaccine implementation to inform policy makers of the impact of vaccination. The seasonality of RSV is detected through surveillance and that will inform the health professionals about the timing of palivizumab use. As there may be only a few years before the vaccines come to market, the need for establishment of standardised RSV surveillance is key at European and global level. Influenza surveillance systems can be used as basis for RSV surveillance but it is important to agree on the case definition to be used and how the influenza case definitions need to be modified to capture the RSV burden in the youngest and elderly populations. Hospital surveillance for influenza has been implemented only in eight EU/EEA countries and this would require expansion to understand better the influenza and RSV burden in Europe. As the surveillance systems, especially in hospitals, are costly, the international recognition of RSV surveillance is crucial for the countries to ensure funding through national and EU sources. Furthermore, special studies on burden of RSV disease, economic burden and long-term sequelae of RSV are warranted with research programmes.

Annex 1 – Meeting programme

Burden of RSV disease in Europe workshop

23-24 November 2015
Stockholm, Sweden
Room N315, ECDC
PROGRAMME

Monday, 23 November 2015 **Room: N315**	
10:00-10:30	**Registration, coffee**
10:30-10:45	**Welcome, introductions and scope of the meeting** *Pasi Penttinen, ECDC*
10:45-12:15	**Session 1: Global and European RSV surveillance – current status** *Chair: Pasi Penttinen, ECDC* *Aim: To understand the existing data collections on RSV surveillance and plans for future.*
	10:45- 11:00 Global RSV surveillance *Sandra Jackson, WHO HQ, Geneva* **11:00-11:15 What RSV-related data does ECDC currently collect?** *Eeva Broberg, ECDC* **11:15-11:30 Needs for RSV surveillance data from vaccination programme point of view** *Kari Johansen, ECDC* **11:30-11:45 European data collection on RSV – challenges and opportunities** *Jonathan Nguyen-Van-Tam, WHO CC Nottingham, via TC/VC* **11:45 – 12:15 Discussion: Needs for RSV surveillance**
12:15-13:15	**Lunch, Königs restaurant**

13:15-16:30	**Session 2: European RSV surveillance – current status** *Chair: Denis Coulombier, ECDC* *Aim: Country representatives to give an overview of the existing surveillance systems for RSV and to answer the following questions:* *What surveillance systems exist for RSV in your country?* *What BoD studies have been conducted and what do those tell?* *How do you estimate the BoD of RSV for severe outcomes?* *Do you have a national case definition for RSV?* *What data gaps exist for estimation of BoD for RSV in your country?*
	13:15-13:20 Opening of the session *Denis Coulombier, ECDC* **13:20-13:30 RSV surveillance in Sweden** *AnnaSara Carnahan, Public Health Institute, Sweden* **13:30-13:40 RSV surveillance in Germany** *Brunhilde Schweiger, RKI and Barbara Rath, Charité Universitätsmedizin Berlin, Germany* **13:40-13:50 RSV surveillance in the UK (England and Scotland)** *Richard Pebody, Public Health England, and Jim McMenamin, Health Protection Scotland, the UK* **13:50-14:00 RSV surveillance in Hungary** *Enikő Bán, National Center for Epidemiology Department of Respiratory Viruses, Hungary* **----------** ***14:00-14:15 Questions and answers*** **----------** **14:15-14:25 RSV surveillance in Slovenia** *Maja Socan, Public Health Institute, Slovenia* **14:25-14:35 RSV surveillance in Finland** *Niina Ikonen, National Institute for Health and Welfare, Finland* **14:35-14:45 RSV surveillance in Denmark** *Thea Kølsen-Fischer, SSI, Denmark* ***14:45-15:00 Questions and answers***

15:00-15:30	**Coffee**
	15:30-15:40 RSV surveillance in the Netherlands, *Anne Teirlinck, RIVM, Netherlands* **15:40-15:50 RSV surveillance in France** *Bruno Lina, University of Lyon, France* **15:50-16:00 RSV surveillance in Italy** *Allessandra Pierangeli and Fabio Midulla, Sapienza University of Rome, Italy* **16:00-16:10 Short and long term RSV burden in Spain** *Xavier Carbonell Estrany, Collegi Oficial de Metges de Barcelona, Spain* **16:10 – 16:30 Discussion: what surveillance systems and data gaps exist in RSV surveillance?**
16:30-18:00	**Session 3: Global Burden of RSV disease** *Chair: Mike Catchpole, ECDC* *Aim: To understand the current data on burden of disease of RSV at the global level.*
	16:30 – 16:45 Burden of disease studies' methodology *Alessandro Cassini, ECDC* **16:45-17:05 Systematic review and meta-analysis: Global Burden of RSV disease** *Harish Nair, University of Edinburgh* **17:05 – 17:25 Data gaps for estimation of global RSV burden** *Harry Campbell, University of Edinburgh* ***17:30 – 18:00 Discussion*** What do we mean by burden of disease studies? What data is needed for burden of RSV disease studies? What case definitions have been used? What populations have been targeted? What is available for elderly?
18:00-18:15	**House-keeping announcements** *Linnea Jannes, ECDC*
19:00-21:00	**ECDC organised dinner, bus transfer**

Tuesday, 24 November 2015 Room: Auditorium	
08:30-09:00	**Registration**
09:00-09:15	**Introduction to the day and summary of the previous day's discussions** *Pasi Penttinen, ECDC*
09:15-10:00	**Session 4: Brainstorming session on EU-wide data collection needs** *Chair: Eeva Broberg, ECDC* *Aim: To collect ideas on how RSV surveillance and burden of RSV studies should be developed at EU-level.*
	09:15-10:15 Group work on EU wide data collection needs ***Group 1: Surveillance, room N514*** *Facilitator Eeva Broberg* *Questions:* *Need for RSV surveillance and expected public health benefits?* *Surveillance systems for RSV surveillance? Including discussion on case definition and type of setting for surveillance.* ***Group 2: Burden of RSV disease, room N315*** *Facilitator Harish Nair* *Questions:* *Need for national disease burden estimates and feasibility* *Burden of medically attended RSV infection – GP clinics and hospitals* *How to capture burden of non-medically attended RSV infection* *Feasibility of using influenza disease burden framework for estimating RSV burden* *How to measure economic burden – direct costs/indirect costs/societal impact* **10:15 – 10:45 Plenary: Reports from groups 1 and 2** *Rapporteur group 1, rapporteur group 2* **10:45 – 11:00 Discussion**
11:00-11:30	**Coffee break**
11:30-13:00	**Session 5: Examples of usage of RSV disease burden data** *Chair: Harry Campbell* *Aim: To understand the benefits of RSV surveillance and burden of disease studies.*
	11:30-11:45 Estimating the economic burden of RSV disease *Philippe Beutels, University of Antwerp, Belgium* **11.45 – 12.00 Burden of RSV disease in the USA** *Mark Miller, Fogarty International Center, National Institutes of Health, Bethesda, Maryland, USA* **12.00 – 12.15 Biomarkers in RSV burden of disease studies** *Louis Bont, University of Utrecht, the Netherlands*

	12:15-12:45 Discussion
12:45-13:00	**Closing of the meeting** *Pasi Penttinen, ECDC*
13:00-14:00	**Lunch, next to meeting room**
14:00	**Departure**

Annex 2 – Meeting participants

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