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Oseltamivir Resistance in Influenza A (H1N1) Viruses

Preliminary results from the National Virus Reference Laboratory (NVRL) on antiviral drug susceptibility among seasonal influenza viruses circulating in Ireland this winter have revealed that some of the A/H1N1 viruses are resistant to the antiviral drug, oseltamivir (Tamiflu). These oseltamivir-resistant viruses are known as influenza A/H1N1 (H274Y) and are fully sensitive to other influenza antivirals.

The NVRL conducted nucleotide sequencing on specimens taken by sentinel GPs between December 2007 and January 2008. As of 27 February 2008, five of 46 specimens (10.9%) tested by the NVRL have shown resistance to oseltamivir. The NVRL is currently arranging for further Irish samples to be tested. To date this season, oseltamivir-resistant viruses have been detected in 15 European countries (including Ireland), the USA, Canada, Australia, Hong Kong and Japan. Testing has been conducted in 41 countries worldwide (22 of which are in Europe).[1]

The proportion of A/H1N1 viruses that are resistant varies across Europe. The highest proportion of resistant viruses to date has been in Norway where 63 (66%) of the 95 samples tested were resistant to oseltamivir (figure 1). High levels of resistance to oseltamivir were first detected at the end of January in Norway. The Norwegian authorities immediately notified their EU partners and WHO of this situation. The European surveillance network for vigilance against viral resistance (VIRGIL) has been undertaking routine surveillance of antiviral resistance since 2004/2005. Surveillance in previous years found only minimal numbers of resistant viruses.[1]

This year, the predominant influenza strain circulating in Europe is the A/Solomon Island/3/2006 (H1N1)-like virus, which is included in the 2007/2008 influenza vaccine.[2] Hence this season's vaccine is expected to give protection against the resistant and non-resistant viruses. A/H1N1 viruses usually cause milder disease than other seasonal human influenza A viruses. From the experience in Norway it seems that people who become ill with A/H1N1 (H274Y) do not appear to have more severe illness than those infected with non-resistant seasonal influenza strains. It should however, be remembered that any influenza A can cause severe disease or death in vulnerable people (older people, those with debilitating illnesses and the very young).[1]

A/H1N1 (H274Y) viruses are the first human influenza viruses resistant to oseltamivir found transmitting in the community anywhere in the world. Similar viruses have been observed before but usually following treatment and those viruses have not been able to transmit and infect and have rapidly disappeared. There is no evidence that the appearance of these new viruses is related to the use of oseltamivir which is currently thought not to be widely prescribed in Europe.

Antiviral resistance is a relative not absolute term. Patients ill with viruses that are deemed resistant in the laboratory often benefit when they receive oseltamivir. Equally A/H1N1 (H247Y) is a human seasonal virus and must not be confused with avian influenza viruses notably, the similarly named A/H5N1 which causes bird flu in poultry.

Experts from the European Centre for Disease Prevention and Control (ECDC), the European Commission, the European Influenza Surveillance Scheme (EISS) and WHO are currently assessing the significance of this development and examining the data from the EISS VIRGIL network. An interim European risk assessment has been published by ECDC. At this stage it is difficult to comment on the significance of these findings or to predict whether these viruses will become more or less common as the season progresses. Current Irish national guidance on the use of antivirals for treatment and prophylaxis of influenza remain in place though they are being kept under review.

Further information is available on the ECDC website at http://ecdc.europa .eu/index.html.

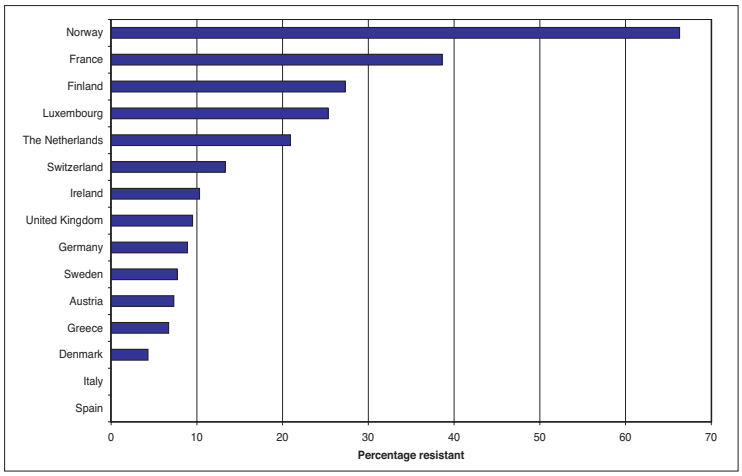

Figure 1: Percentage oseltamivir resistance in human seasonal influenza type A/H1N1 isolates detected in Europe (EU, EEA, EFTA countries). Data as of 20 February 2008.
Source: ECDC. It should be noted that for a number of countries the numbers tested are low and therefore the proportions are likely to change as more testing is undertaken.

Acknowledgements
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Surveillance of Respiratory Syncytial Virus in Ireland

Introduction

Respiratory syncytial virus (RSV) is the single most important cause of hospitalisation for viral respiratory tract disease in infants and young children. It is a significant cause of infection and outbreaks in hospitals, neonatal units, day units and nursing homes. RSV has a clear seasonality with outbreaks typically occurring during the winter months with peak numbers of cases usually reported in December and January. However, the size of the peak varies from winter to winter. RSV spreads efficiently among children during the annual outbreaks and most children will have serologic evidence of RSV infection by two years of age. Since its first isolation in 1956, RSV quickly became recognised as the most important viral agent of serious respiratory disease in the paediatric population worldwide. The impact of RSV in healthy adults and the elderly is less well quantified than it is for infants, but it is certainly under-diagnosed.[1 2]

Clinical Features

RSV can infect all age groups. It causes upper and lower respiratory tract infections ranging in severity from subclinical infections to pneumonia. For the majority of persons, symptoms are mild, similar to the common cold. The incubation period is short, ranging from three to five days with lower respiratory tract symptoms appearing one to three days after the onset of rhinorrhoea. The risk of serious disease is increased by prematurity, young age, chronic cardiac or lung disease, immunodeficiency or immunosuppression and a family history of allergic disease. However, approximately three-quarters of hospitalisations for RSV occur in children who were previously healthy. RSV infection is rarely fatal in children unless there is a severe underlying illness. [1 2 3]

RSV is the major cause of bronchiolitis and one of the major causes of pneumonia during the first years of life. Bronchiolitis or pneumonia occur most frequently between the ages of six weeks and nine months, with the peak incidence of lower respiratory tract disease occurring between the ages of two and seven months, corresponding with diminishing titres of maternal antibodies. Immunity to RSV is incomplete and short-lived. Repeated respiratory infections can occur, although these are usually mild and become less common with increasing age.[1 2]

Transmission

Infection is spread via respiratory secretions, through close contact with infected persons or contact with contaminated surfaces or objects. Spread can also occur when infectious material comes in contact with the mucous membranes of the mouth, nose or eyes and through inhalation of droplets generated by a sneeze or cough. [1 2]

Treatment and Prevention

There is currently no effective antiviral therapy or approved vaccine for RSV. Development of an RSV vaccine is a high research priority. Palivizumab, a monclonal antibody therapy, is licensed in Ireland for the prevention of serious lower respiratory tract infection caused by RSV in infants at high risk of infection. Antibiotics are not effective against RSV and it is important that unnecessary antibiotics are discontinued once a diagnosis of RSV infection is confirmed, to avoid adverse drug reactions and promotion of antibiotic resistance. Prevention of nosocomial transmission is the mainstay of RSV management in hospitals, with particular emphasis on frequent hand washing. Transmission can be prevented in the hospital setting by managing children with RSV together in the same ward, paying strict attention to hand washing recommendations, using barrier precautions (such as gowns and gloves), avoiding overcrowding and restricting visiting if necessary. Persons ill with RSV should be excluded from crèches, work, hospitals, school and non-residential institutions until well.[1 2 3]

Epidemiology in Ireland

The National Virus Reference Laboratory (NVRL) has been collecting data on RSV positive specimens since September 1988. The NVRL tests respiratory specimens (mainly from hospitalised paediatric cases) for a panel of respiratory viruses including: influenza A and B, RSV, adenovirus and parainfluenza viruses type 1, 2 and 3.

During the 2007/2008 season to date (October - January), the number of RSV positive detections reported by the NVRL reached the highest levels on record since surveillance began. RSV detections peaked in November (week 47 2007), earlier than in previous seasons (figure 1). Four hundred and thirty-two (33.5%, n=1,288) RSV positive specimens were detected during October–January of the 2007/2008 season, a 30% increase on the number of positive specimens detected during the same period in the 2006/2007 season. Prior to the 2007/2008 season, the largest seasonal outbreak of RSV occurred during the 2003/2004 season (figure 2).[4]

The number of positive RSV specimens by age group (in months) for the 2007/2008 season, are detailed in figure 3. Of the 432 RSV specimens detected this season, 364 (84.3%) were from patients aged less than one year of age, 48 (11.1%) were aged 1-4 years, seven (1.6%) were aged 5-14 years, 11 (2.5%) were aged 15-64 years, one (0.2%) was aged 65 years or older and age was unknown for one case. Between October 2007 and January 2008, 366 (84.7%) of the 432 RSV positive specimens tested by the NVRL were from hospitals in HSE East, 63 (14.6%) were from HSE Midland and three (0.7%) from HSE Mid-West.

The number of respiratory specimens tested by the NVRL has been gradually increasing since surveillance began (figure 4). During the 2007/2008 season, 1,288 respiratory specimens were tested by the NVRL (between October and January), the highest number on record. Prior to the 2007/2008 season, the largest number of specimens tested occurred during the 2003/2004 season, when 1,273 specimens were tested between October and January.

RSV Pilot Study

During the 2002/2003 season, the NVRL, HPSC and Irish College of General Practitioners (ICGP) carried out a pilot study to assess the incidence of RSV in specimens taken from patients with influenza-like illness (ILI) by sentinel general practitioners.* Of the 77 sentinel swabs

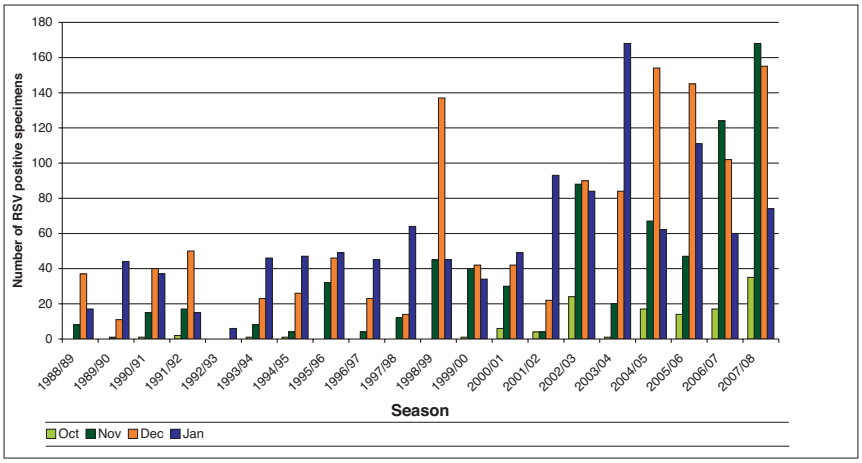

Figure 1: Number of RSV positive specimens detected by NVRL by season and month (1988/89-2007/08)

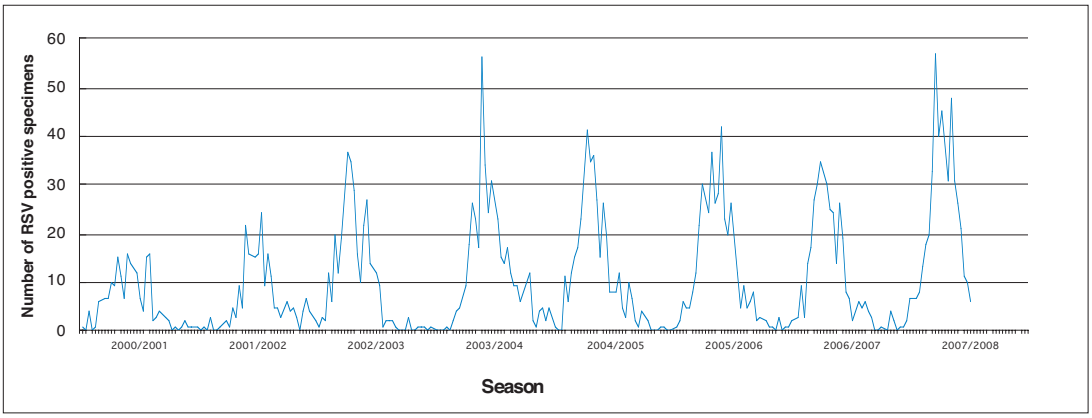

Figure 2. Number of RSV positive specimens detected by NVRL by week from the 2000/01 to 2007/08 season.
Please note that the 2007/08 season only includes data from week 40 2007 to week 5 2008. Weekly data are only available from 2000/01 on.

tested, seven (9.1%) were positive for RSV.[5] The pilot was expanded during the 2003/2004 season and all ILI specimens taken by sentinel GPs were tested for RSV and influenza using real-time PCR. Of the 370 sentinel specimens tested during the 2003/2004 season, six (1.6%) were positive for RSV. Five of the six positive specimens were from patients aged between 0 and 9 years and one was aged over 65 years.[6]

Discussion

RSV data from the NVRL provide a good indicator of seasonal patterns in Ireland.[4] During the 2007/2008 season, RSV peaked earlier and with a greater number of positive specimens than previously recorded for the period October to January. An early peak in RSV activity and an increased number of positive specimens was also reported in the United Kingdom.[7] For Europe as a whole, detections of RSV peaked in week 49 2007.[8] The number of respiratory specimens tested by the NVRL has gradually increased in recent seasons. The reasons for the increase in respiratory specimens tested are multifactorial. They may partly be due to increased awareness among health professionals of the importance of confirming respiratory viruses, particularly in light of avian and pandemic influenza. A number of factors contributed to the peak in 2003/2004 including the emergence of SARS, the early detection of the influenza A/Fujian-like strain in Ireland in September 2003 and the avian influenza outbreaks in Asia.

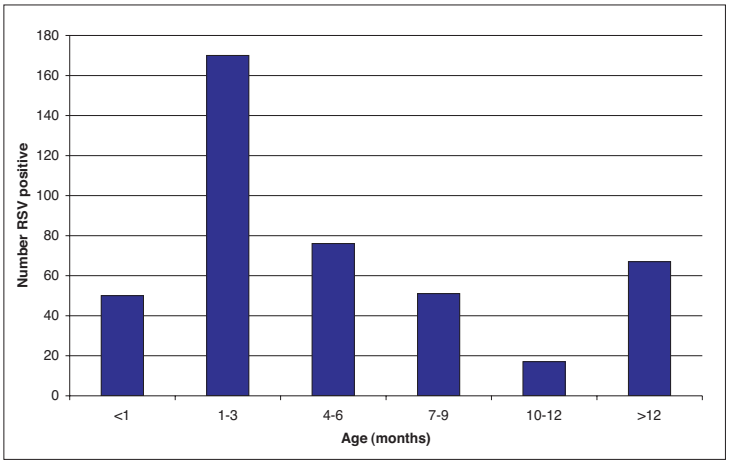

Figure 3. Number of RSV positive cases by age group (months) during the 2007/08 season (n=431). Age group was unknown for one case.

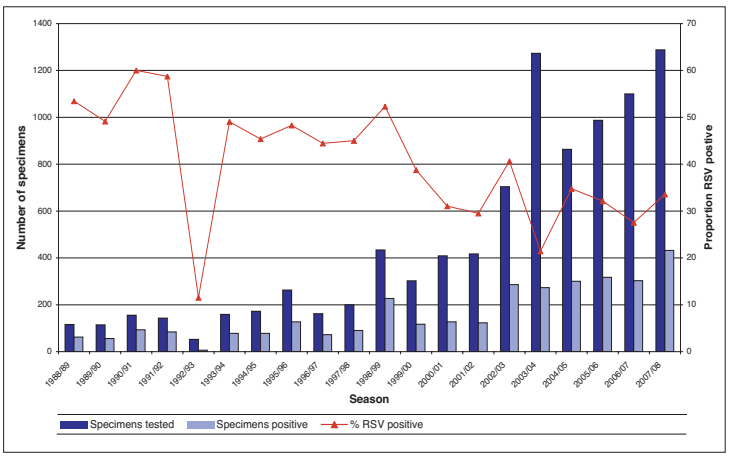

Figure 4: Number of non-sentinel specimens tested by the NVRL, number RSV positive and the proportion of positive specimens detected between October and January by season from 1988/89 to 2007/08

Due to the low number of positive RSV specimens detected in the adult population during the 2003/2004 pilot (only one RSV positive case was aged over 15 years of age), it was decided not to continue testing sentinel specimens for RSV. Non-sentinel RSV data from the NVRL provide comprehensive surveillance of RSV infection in the paediatric population. The decision to test sentinel specimens for RSV is reviewed on an annual basis and in the future will be informed from recommendations made by the European Centre for Disease Prevention and Control (ECDC) and the RSV task group of the European Influenza Surveillance Scheme (EISS). Currently, work is in progress with EISS to establish standardised methods to collect more detailed RSV data in all age groups across Europe. This should lead to improved RSV surveillance and a better knowledge of the role RSV plays in causing respiratory infections in Europe.

Further information on RSV can be found on the HPSC website at: http://www.ndsc.ie/hpsc/A-Z/Respiratory/RespiratorySyncytialVirus/.

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*Further information on the GP sentinel surveillance scheme is available on the HPSC website at http://www.ndsc.ie/hpsc/A-Z/Respiratory/Influenza/SeasonalInfluenza/InfluenzaSurveillanceReports/.

Emerging Problem with High-level Mupirocin Resistance Among MRSA in Ireland

The antimicrobial mupirocin (an isoleucine analogue) is a protein synthesis inhibitor that acts by binding irreversibly to isoleucyl t-RNA synthetase (IleS).[1] It is mainly used as an ointment (2% in paraffin base) and is very effective in eliminating MRSA carriage from nasal passages. Guidelines warn that the dosage (three times a day for five days) should not be repeated more than once to avoid emergence of resistance.[2] Two forms of resistance are reported:

- Low-level resistance with minimum inhibitory concentrations (MIC) of 8 to 256 mg/L due to a mutation in IleS
- High-level resistance (MIC ≥512 mg/L) due to acquisition of the plasmid-mediated *mupA* gene which encodes a second isoleucocyl t-RNA synthetase.[1]

The National Meticillin-Resistant *Staphylococcus aureus* (MRSA) Reference Laboratory (NMRSARL) monitors rates of resistance to clinically useful antibiotics among MRSA isolates recovered from blood of patients in Irish hospitals.[3] High-level mupirocin resistance (MpR) was detected among 37 of 2,586 (1.4%) MRSA blood-stream isolates sent to NMRSARL between 01 January 1999 and 31 December 2005 (Period 1) compared with 29 of 997 isolates (2.9%) sent between 01 January 2006 and 31 December 2007 (Period 2) (p = 0.005). In addition to this significant change in the proportion of high-level mupirocin-resistant isolates, NMRSARL also noted a change in the epidemiological types associated with mupirocin-resistant MRSA [the antibiogram-resistogram-pulsed field group (AR-PFG) typing method used in NMRSARL is outlined below*].

Prior to 2005, the majority of MpR blood-stream isolates (97%; 29/30) exhibited AR-PFG types 13-00 or 14-00. In contrast, during Period 2, only seven MpR isolates (24%, 7/29) exhibited these AR-PFG types but 55% (16/29) exhibited an unfamiliar AR pattern which included resistance to the aminoglycosides gentamicin, kanamycin and tobramycin but with PFG 01 patterns which are associated with the AR06 AR type. Fourteen percent of MpR isolates (4/29) exhibited AR-PFG 06-01. For the purposes of the present communication, MpR isolates exhibiting the unfamiliar AR pattern with aminoglycoside resistance and PFG 01 are designated MpR Strain 1 and MpR isolates with AR-PFG type 06-01 are designated MpR Strain 2.

During Period 2, 86 MpR MRSA from sources other than blood were submitted to NMRSARL from 12 institutions; 16% (14/86) exhibited AR-PFG 13-00 or 14-00, 7% (6/86) exhibited a variety of patterns but 66 isolates (77%, 66/86) from 11 institutions exhibited MpR Strains 1 or 2. The earliest recognised isolates of both strains were recovered from patients in Institution 1 (MpR Strain 1, June 2004; MpR Strain 2 October 2005). The table details the source of all MpR Strains 1 or 2 isolates investigated (22 from blood and 68 from other sites). The majority of isolates (93%; 84/90) were recovered from patients in institutions in or around Dublin.

Table. Numbers of patients from whom high-level mupirocin-resistant MRSA Strains 1 or 2 were submitted for investigation

Institution	MpR Strain 1		MpR Strain 2a	
	Blood	Various sites	Blood	Various sites
1	6	18	2	NR
2	4	7	NR	NR
3	3	6	NR	2
4	1	NR	1	NR
5	NR	NR	1	NR
6[b]	NR	8	NR	9
7[b]	NR	7	NR	3
8	NR	2	NR	NR
9	3	NR	NR	NR
Other (n = 4)	NR	5[c]	1	1
Total	**17**	**53**	**5**	**15**

a The AR pattern of this strain may vary with regard to fusidic acid and/or trimepthoprim.
b The laboratories in these institutions serve long-stay care institutions.
c Two isolates were recovered from veterinary sources; 4 isolates were susceptible to gentamicin.
NR, no isolates received

All isolates were investigated by PFGE and all showed closely related PFG 01 patterns including PFGE pattern 01018 which is exhibited by >50% of AR06 isolates investigated in NMRSARL in any one year. Additional molecular work is required to further characterise these isolates because the combination of aminoglycoside resistance with PFG 01 seen in MpR Strain 1 is unusual among MRSA recovered from patients in Ireland and suggests that AR-06 isolates may be acquiring *mupA* perhaps in conjunction with other resistance determinants.

The *mupA* gene is usually plasmid-mediated, is frequently carried on a large conjugative plasmid capable of mediating the co-transfer of other resistance determinants but isolates carrying a chromosomally-located *mupA* gene with resistance to gentamicin and kanamycin have also been reported.[4,5] If this has occurred with AR-PFG 06-01, it may give rise to a significant infection control problem. AR-PFG 06-01 accounts for more than 85% of MRSA blood-stream isolates in Ireland, indicating its propensity for spread and difficulty in control. If high-level mupirocin resistance were to become widespread in this strain, a highly effective means of decolonisation of MRSA would be lost.

The centres from which Institutions 6 and 7 received MpR Strains 1 and 2 were long-stay care centres and anecdotal evidence from Institution I suggests that the earliest isolates in that institution were also recovered from patients in long-stay care. **Prolonged use and multiple courses of mupirocin are associated with the development of mupirocin resistance**. Long-term use of mupirocin leading to the development of irreversible resistance in staphylococci has been reported worldwide.[2] **It would be prudent that institutions monitor the use of mupirocin to ensure that misuse, including inappropriate, prolonged or repeated use be avoided, especially among long-stay patients so that this most valuable antimicrobial is not lost to therapeutic practice**.

Angela Rossney, Brian O'Connell, NMRSARL.

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***Note on MRSA epidemiological typing**: NMRSARL types MRSA isolates by antibiogram-resistogram (AR) typing and by pulsed field gel electrophoresis (PFGE). AR types are assigned two-digit numbers (for example: AR06, AR07, AR13 etc.) and PFGE patterns are assigned 5-digit PFGE type (PFT) numbers abbreviated to 2-digit PFGE type groups (PFG).[3] Since 2001, the predominant AR-PFG type has been 06-01 (similar to UK EMRSA-15; genotype ST22-MRSA-IV).[3] AR-PFG 06-01 isolates exhibit non-multi-antibiotic resistant phenotypes, are susceptible to aminoglycosides and, in any one year, approximately 50% of isolates exhibit one PFGE pattern (PFT 01018).[3]