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Rapid increase of carbapenemase-producing Klebsiella pneumoniae strains in a large Italian hospital: surveillance period 1 March – 30 September 2010

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The first case of carbapenemase-producing *Enterobacteriaceae* in Italy was reported in 2009. We performed a study over a period of seven months in 2010 to survey the circulation of *Klebsiella pneumoniae* carbapenemases (KPC) in a 1,500-bed university hospital in northern Italy and report the presence and rapid increase of these multidrug-resistant bacteria. The results raise a major concern about these pathogens and demonstrate the urgent need for infection control and antibiotic stewardship programmes.

Introduction

The spread of multidrug-resistant (MDR) gram-negative pathogens is one of the major hazards for patients requiring long-term hospitalisation or hospitalisation in intensive care units (ICU) [1]. In particular, given the use of carbapenems as second- or third-line drugs against MDR gram-negative germs, the resistance to this class of molecules poses a serious problem in the management of healthcare-associated infections. *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, among the most common aetiologic agents of hospital-acquired infections worldwide, frequently show an MDR phenotype including resistance to carbapenem drugs. In the last few years, *Klebsiella pneumoniae*, often isolated from patients with pneumonia, bloodstream and urinary tract infections, has emerged worldwide as a carbapenem-resistant microbe [2]. A resistance to carbapenems in *Enterobacteriaceae* can be mediated by three different mechanisms, namely: production of extended-spectrum beta-lactamase (ESBL) associated with loss of porins, production of metallo-beta-lactamase (MBL) and production of *K. pneumoniae* carbapenemases (KPC)-type carbapenemases [3]. The first KPC-producing *K. pneumoniae* strain was isolated in 2001 in North Carolina [4] and until 2005 these MDR organisms were only identified along the eastern coast of the United States, where they rapidly became a frequent cause of hospital-acquired infections [4]. Since 2005, KPC-producing strains have been described worldwide [2]. As recently described [5], almost all European countries are affected by the expansion of carbapenem-resistant *Enterobacteriaceae*, even if the epidemiological scale of the diffusion is widely variable, from endemic presence, in particular in Greece, to sporadic occurrence. In Italy the first isolation of a KPC-positive *K. pneumoniae* was reported in 2009 [6,7].

The aim of this study was to evaluate the incidence of *K. pneumoniae* strains showing a reduced susceptibility to carbapenems among patients hospitalised at the St.Orsola-Malpighi University Hospital in Bologna. The molecular mechanism of this phenotypic resistance was also investigated.

Identification and characterisation of carbapenem-resistant *Klebsiella pneumoniae* strains

The strain identification and antimicrobial susceptibility testing were performed using a Vitek2 automated system (Biomerieux, France). From 1 March to 30 September 2010, 431 consecutively isolated *K. pneumoniae* strains were included in this study. All the isolates showing a minimum inhibitory concentration (MIC) of ≥1 mg/L for meropenem (for this phenotype the Vitek2 system predicts probable production of KPC or MBL) were collected (86 isolates in total) and further evaluated in order to investigate the mechanism of resistance. During the seven-month surveillance period, at least one *K. pneumoniae* strain with suspected resistance to carbapenems was isolated from each of 69 patients for a total number of 86 strains. Additional antimicrobial testing was performed by E-test with Imipenem and Imipenem/EDTA (IPM-IPM/EDTA) to detect the production of MBL, while the modified Hodge test was used as phenotypic confirmatory method for KPC-production [4]. This last method confirmed the production of carbapenemases in 52 strains isolated from 41 patients. Antimicrobial resistance associated with the production of MBL was excluded in all the collected isolates with a MIC of ≥1 mg/L. The isolates were further analysed by PCR for the presence

of genes controlling other resistance mechanisms [8]. The bla_{KPC} gene was detected in 56 of the 57 isolates positive in the modified Hodge test. Among those, 45 resistance genes were bla_{KPC-3} gene and seven were bla_{KPC-2} gene as determined by sequence analysis of the amplicons. Complete molecular genotyping is scheduled in order to better characterise and correlate all the KPC-positive strains.

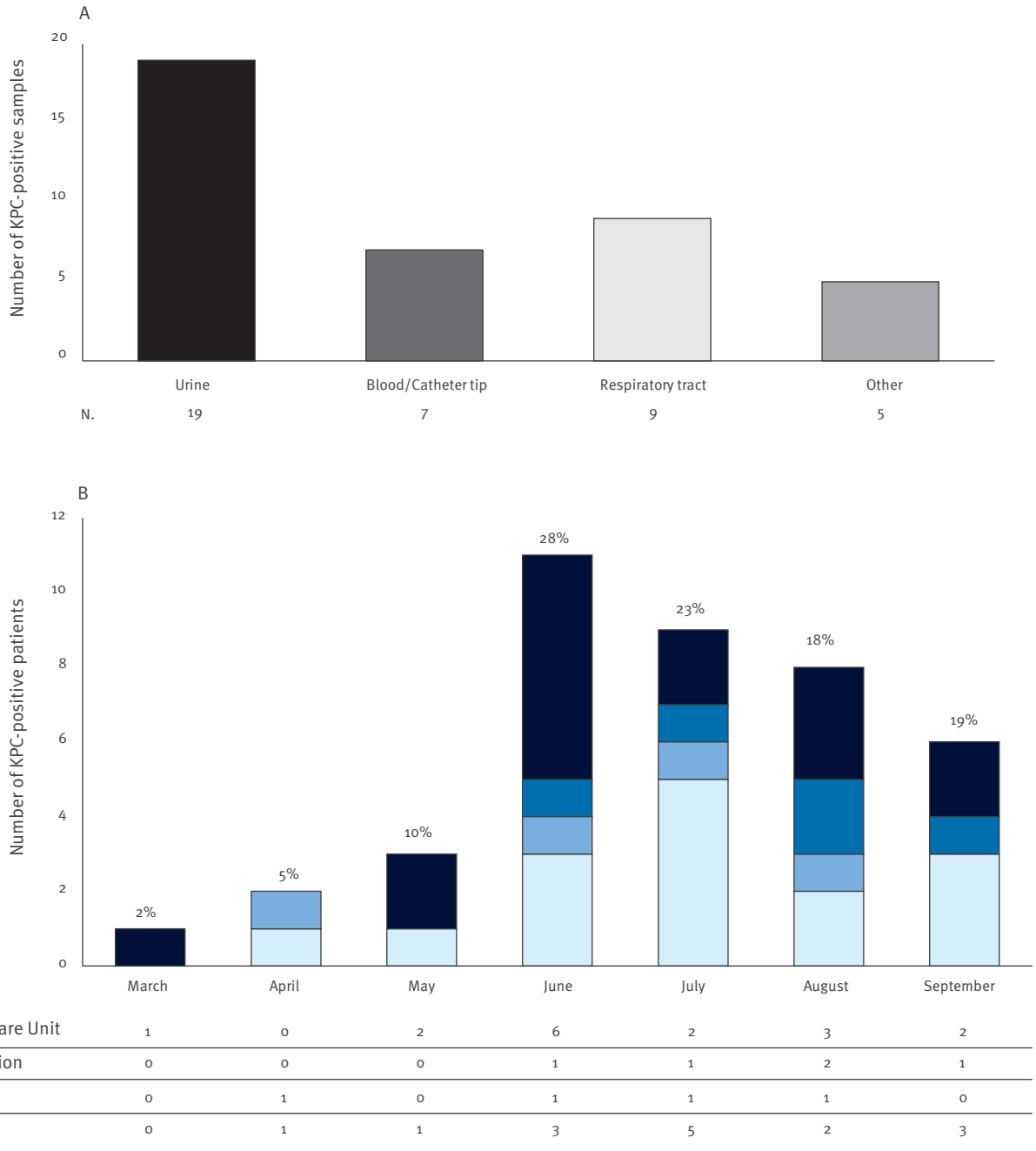
Clinical and epidemiological data

All 52 KPC-positive strains were also resistant to all others beta-lactams (including the 3rd and 4th generation cephalosporines and piperacillin-tazobactam), to fluoroquinolones, and to sulfonamides. The susceptibility to gentamicin, tigecycline and colistin was retained in 47 of these KPC strains.

As shown in the Figure, most of the KPC-positive strains were isolated from urine (19 strains) and respiratory tract samples (nine isolates). Sixteen of the 40 patients bearing KPCs were hospitalised in an ICU (Figure, panel B). During the study period, the monthly number of new cases with KPCs and the rate of meropenem resistance increased from March to September,

Figure

Isolations of KPC-positive *K. pneumoniae* by anatomical site of isolation (A) and monthly cases by type of hospital ward (B), St.Orsola-Malpighi University Hospital, Bologna, 1 March – 30 September 2010 (n=40)



KPC: *Klebsiella pneumoniae* carbapenemase.
The monthly rates (%) of meropenem resistance in *K. pneumoniae* isolates are shown above each bar (B).

with a peak in June due to a cluster of colonisations and infections in an ICU (Figure, panel B).

Discussion

These data clearly demonstrate a consistent increase in carbapenem-resistant *K. pneumoniae* isolations during the study period. In addition our findings suggest that this phenomenon is linked to different KPC genotypes. It is noteworthy that in 2009 a similar surveillance protocol gave different results. In fact no KPC- or MBL- producing isolates were found at the time, suggesting that the phenotype with reduced susceptibility to carbapenems was mainly due to the production of ESBL associated with a loss in porins. In 2010 this phenomenon was largely replaced by KPC production that is nowadays the most prevalent cause of carbapenem-resistance in *K. pneumoniae* isolates. These data clearly indicate an increase of this phenomenon over a short period of time. It is interesting to note that KPCs in patients hospitalised in non-intensive or surgical wards were generally isolated only from urine whereas for ICU patients the main and first isolation site was the respiratory tract followed by other anatomical sites. We can speculate that this clinical feature is related to the different use of invasive devices during the hospitalisation: urinary catheters for medical and surgical patients, many other devices (intubation tubes, surgical drains, intravascular devices) for ICU patients.

From the microbiological point of view it is important to consider that more than 60% of KPC strains had MIC values of 2 mg/L for meropenem when evaluated by Vitek2: these isolates would be categorised as having intermediate susceptibility to meropenem using interpretation criteria from the Clinical and Laboratory Standards Institute (CLSI) after the revision of breakpoints in June 2010 [8]. If the breakpoints of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are applied [9], these isolates would be considered susceptible to meropenem. Our data suggest that a second level of investigation is required to evaluate the mechanism of reduced susceptibility, which could predict the clinical efficiency of carpapenem drugs. All the KPC-producing strains were still susceptible to antimicrobials that are not commonly used as alternative therapy for the treatment of nosocomial infections caused by to MDR gram-negative organisms [10]. In conclusion, the spread of carbapenem-non-suceptible *Enterobacteriaceae* in European countries a reason for great concern for public health services and calls for global diagnostic and management strategies. In our hospital in particular, KPC-producing *K. pneumoniae* strains spread fast and the isolation rate of these MDR bacteria is increasing. Appropriate surveillance and infection control measures are therefore urgently needed. We believe that it is also essential to apply strict antimicrobial stewardship policies to reduce the selective pressure that inevitably favours the emergence of carbapenem-resistant strains, so that these antibiotics remain therapeutically useful.

Acknowledgements

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Ongoing outbreak of mumps infection in Oban, Scotland, November 2010 to January 2011

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We report on an ongoing outbreak of 119 cases of mumps virus infection in the Oban area of Scotland, from 29 November 2010 to 31 January 2011. The median age of cases was 20 years, with the highest incidence in the 13-19-year-olds. A total of 53 cases had received two doses of measles-mumps-rubella (MMR) vaccine, in accordance with the United Kingdom vaccination schedule, while 33 had received only one dose and 30 had not been vaccinated.

Outbreak description

NHS Highland Health Protection Team in Scotland was notified on 29 November 2010 of one case of mumps in Oban, a rural coastal town, with a population of around 8,000, on the west coast of Scotland. There were no further cases for a two-week period, but by 20 December an outbreak in Oban was obvious, with 23 cases. Many of the cases were notified around the Christmas holiday period when young people returned from work and university in urban areas.

Following the identification of the ongoing outbreak, all the general practitioner (GP) practices in the Oban area were subsequently contacted by telephone and requested to notify all cases of mumps virus infection promptly to Health Protection.

By 31 January 2011, a total of 119 cases had been notified in the Oban area (Figure 1). These represented more notifications than for the rest of Scotland for the same period (90 cases in a population of 5,168,500 individuals). Of the 119 cases notified in Oban, 18 were laboratory confirmed and 101 were clinically diagnosed, by local GPs (based on those presenting with typical clinical features, including parotitis after 29 November).

Background

Mumps, an infection caused by a paramyxovirus, is characterised by parotitis. It may also cause orchitis, pancreatitis and meningitis, among other clinical features. In Scotland, mumps is a notifiable disease and is reported electronically to health boards by clinicians, in particular by general practitioners.

Mumps immunisation was introduced in the United Kingdom (UK) in 1988 as a single dose of measles-mumps-rubella (MMR) vaccine, for those aged 12–15 months. Before 1988, mumps virus caused outbreaks among 5–9-year-olds every three years. They would now be aged 23 years and over. In 1996 a two-dose schedule was introduced: the first dose is given to children aged 13 months and the second dose is given from the age of 3 years and 4 months onwards [1].

Current vaccination uptake rates for the first dose of MMR vaccine at 24 months (for the year ending 31 March 2010) were 93.7% for Scotland and 91.5% for the Argyll area (in which Oban is located). However, in the years post 1998, following vaccine controversy, which surrounded an alleged link between autism and the MMR vaccine, the uptake rates fell, reaching a low level in Scotland of 88.5% and in Argyll of 85.6% in 2003 [2]. This cohort, who would have been due vaccination in 1998–2003, would now be 8–14 years old.

Following a large outbreak of mumps which affected the whole of the UK in 2005, the number of cases fell until 2009, when an increase was seen again (personal communication, Katy Sinka, January 2011). In Scotland this increase has been characterised by periodic, localised occurrences of mumps cases: the outbreak reported here is the latest. Recently, there have been reports of outbreaks of mumps in other parts of the UK and other countries [3-5].

Procedures following notification

Once a mumps case is notified, oral fluid testing kits are routinely sent to GP practices for laboratory confirmation of the clinical diagnosis and epidemiological surveillance. The primary care team then contact the patient and recall them for testing. Samples are then sent to the Centre for Infections, Health Protection Agency, London. For the first notified cases in the Oban outbreak, laboratory kits were sent out. Once laboratory confirmation had been received on the first 12 of these cases, we suspended testing and recorded cases that had been notified on the basis of clinical diagnosis alone. The clinicians involved were confident

Figure 1

Mumps cases by date of symptom onset, Oban outbreak, Scotland, November 2010–January 2011 (n=119)

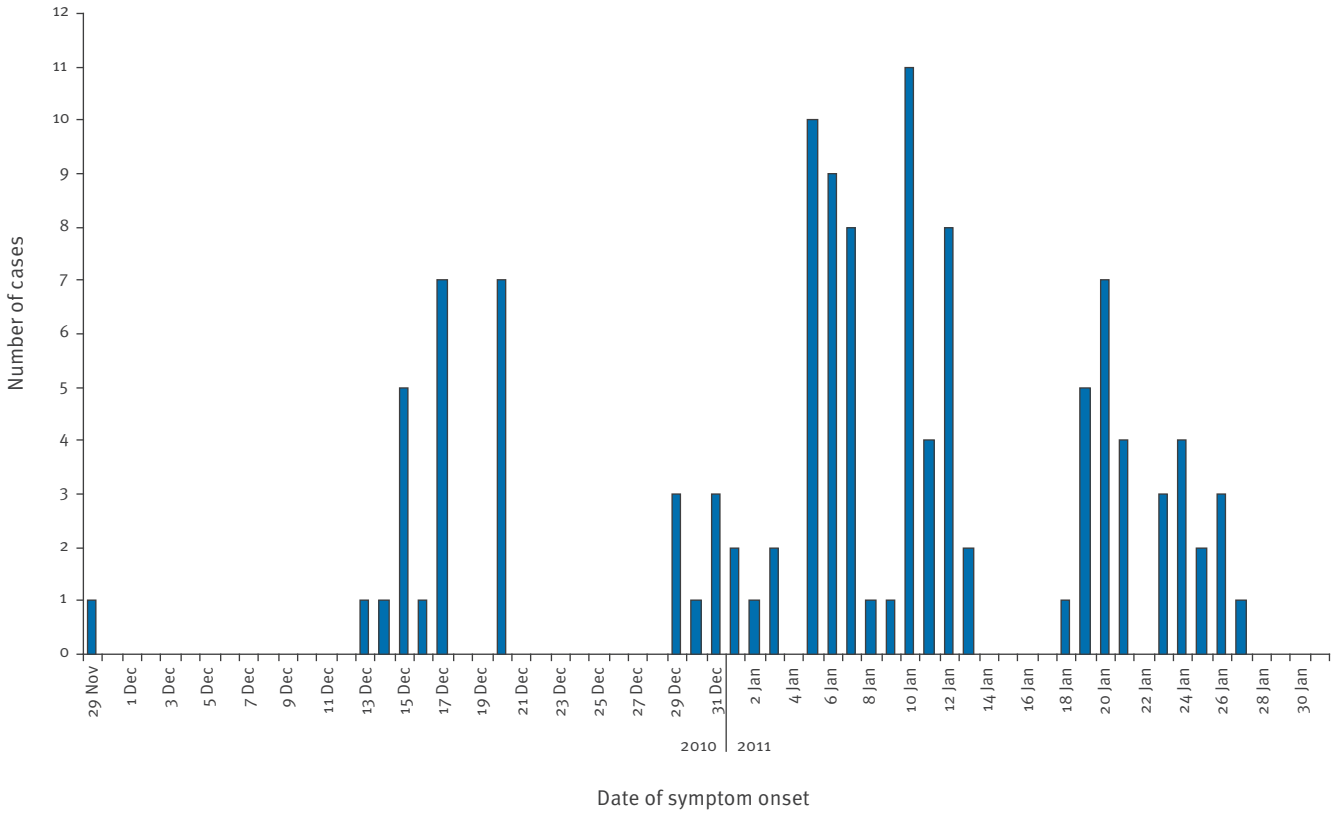
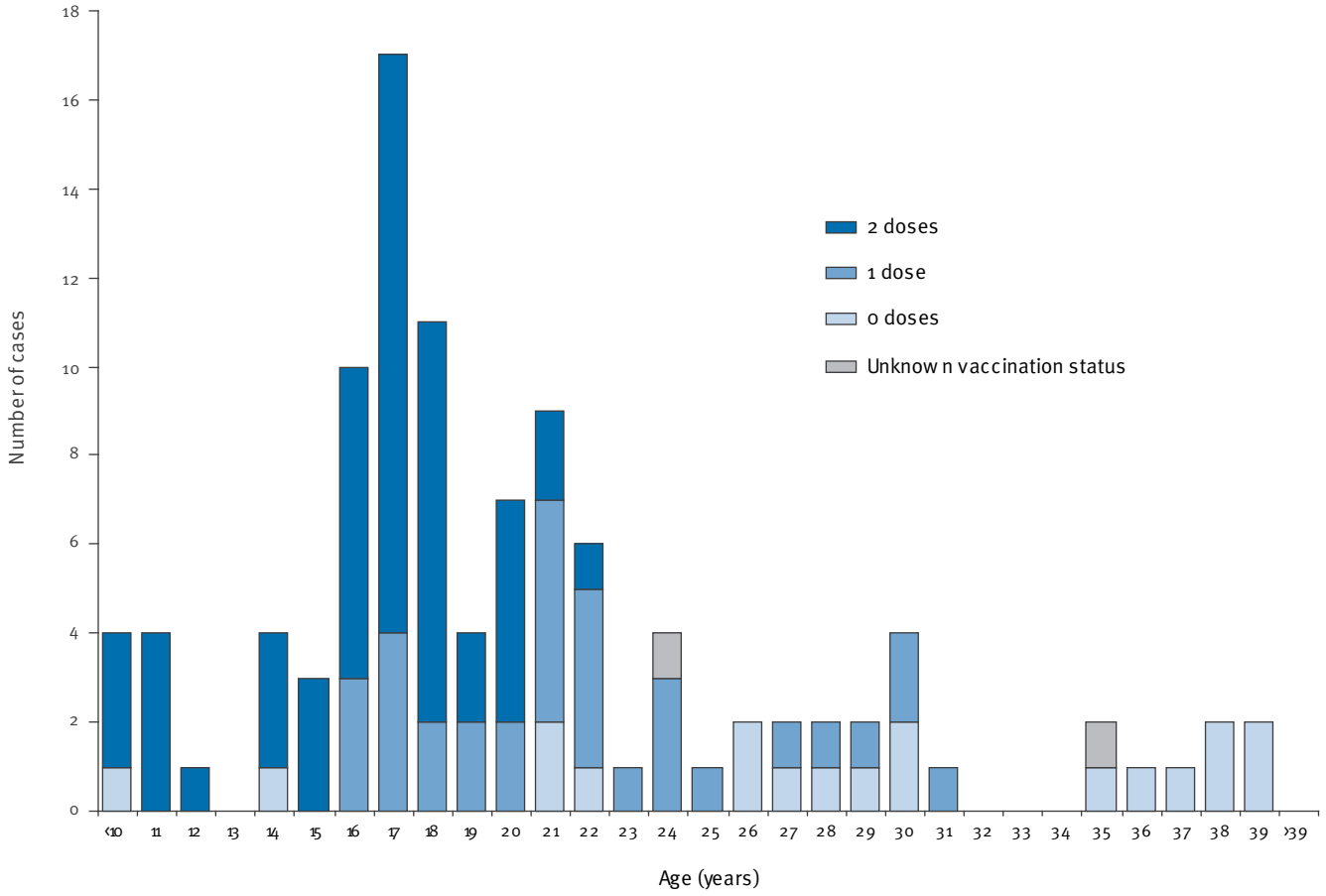


Figure 2

Mumps cases by age and measles-mumps-rubella vaccination status, Oban outbreak, Scotland, November 2010–January 2011 (n=119)



of their diagnosis and for small practices, extra testing seemed unduly burdensome.

Vaccination status is not routinely recorded when mumps cases are notified. However, given the excess number of cases from 13 to 17 December 2010 (when 15 cases were notified), the Health Protection Team contacted the relevant practices and enquired about the vaccination status of each individual and the date of vaccination. The team also enquired initially about the batch numbers of each vaccine, but it became apparent that the cases were not linked to any particular vaccine batch and that vaccinations had been given over several years by a range of primary care staff.

Towards the end of January 2011, as cases continued to be notified, it was agreed following discussion with primary care colleagues, that parents of children aged 5 to 18 years would be contacted by a letter from each GP practice involved and reminded of the offer for children to be vaccinated with two doses of MMR vaccine. At this moment in time we do not have information on vaccine uptake following the letter sent.

Case information

Of the 119 cases, 63 were females and 56 males. The age range of cases was 4 to 71 years: 85 of the cases were in the 13–29 age group and 12 were aged over 40 years. Anecdotal information revealed three cases with complications (orchitis, pancreatitis). However more detailed information on complications overall is currently being evaluated.

By 31 January 2011, vaccination status was known for 116 of the 119 cases: 53 had received two doses of MMR vaccine, 33 had received only one dose and 30 received no doses (Figure 2). For those who had one dose, the date of vaccination ranged from 5 December 1988 to 23 February 2009. For those who had received two doses, the vaccinations dates ranged from 28 September 1989 for the first dose to 13 May 2008 for the second dose.

The majority of the cases aged under 22 years had received two doses of MMR vaccine (53 of 80). Among the nine cases aged 12 years or under, eight had received two doses; among the 49 cases aged between 13 and 19 years, 37 had received two doses and 11 one dose.

Anecdotally, it appears that the index case may have been a student at one of Scotland's main universities who had returned home for the holidays. Many of the initial cases had subsequently attended a school dance and a large party in Oban. There was no common link with place of residence.

Cases continue to be notified but the rate of notifications has decreased. The peak date of symptom onset for cases was 10 January, when 11 cases were notified. By 31 January 2011, there were 18 laboratory-confirmed cases, the rest were clinically diagnosed.

Discussion

Some GPs reported that not all those affected presented to GP practices and our numbers may therefore be an underestimate. On the other hand, we applied a non-specific case definition which led to wide inclusion of cases.

Initial concerns regarding a historical problem with a vaccine batch were soon discarded as the date ranges for the first and second vaccinations were wide and vaccinations were given in different practices by different individuals and there was no link with any particular vaccine batch numbers.

The main limitation in our study is the low number of laboratory-confirmed cases. We felt that after the initial tranche of cases, clinical diagnosis was adequate and this was undertaken by several different primary care teams (101 of the 119 were clinically diagnosed). The laboratory has confirmed that the strain involved is genotype G5 in common with all strains currently seen in the UK (personal communication, Kevin Brown, 10 February 2011).

MMR vaccination coverage was affected by adverse publicity some years ago and uptake rates fell to a low of 85.6% in 2003 in the Oban area. Unvaccinated individuals, plus those who were immunised but in whom protection had subsequently waned, combined to provide a cohort of vulnerable individuals who were infected in this outbreak. The 45% (n=53) of notified cases who had received two doses of MMR vaccine is higher than the 29% of cases reported in England and Wales in 2010 [3] and the 31% reported in England in 2004–05 [7] but lower than the 61% noted in the Netherlands in 2010 [8] and the 75% reported in New Jersey, United States in 2009–10 [4]. If we look at the 13–19 years age group in our study – the most affected age group – 76% (n=37) had received two doses of MMR.

Published estimates of MMR vaccine efficacy to protect against mumps vary. It has been reported as 88% (95% confidence intervals (CI): 83% to 91%) for one dose and 95% (95% CI: 93% to 96%) for two doses [7]. In addition, two doses of vaccine were reported as being more effective (88% (95% CI: 62% to 96%)) than a single dose (64% (95% CI: 40% to 78%)) [9]. Furthermore, Cohen *et al*. report waning immunity in older vaccinated individuals [9].

Although the numbers in our cohort are small, they add to the growing body of evidence which suggests that immunity to mumps virus may wane over time [4,7-9].

These cases highlight the importance of ensuring high uptake of the recommended two doses of MMR. They also imply a need for further research into long-term mumps immunity among those partially or fully vaccinated in order to inform future immunisation programmes.

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Ongoing outbreak of measles in Oslo, Norway, January–February 2011

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Between 19 January and 17 February 2011, 10 cases of measles (eight laboratory-confirmed and two probable) were reported in Oslo with the majority of cases in a mainly unvaccinated immigrant community. Of these, two cases were identified outside the immigrant community, in Norwegian children.

Outbreak description

The measles outbreak described here started on 19 January 2011 in Oslo and the index case was an unvaccinated two-year-old child from the Somali immigrant population (Figure). The child developed classical symptoms of measles 12 days after a family visit from Ethiopia, and the source case was probably one of the visiting relatives, according to the symptoms described by the parents.

By 17 February, eight confirmed and two probable cases were reported in Oslo. The case definition used was based on the World Health Organization (WHO) classification of measles cases [1] and included clinical and laboratory aspects: any person in whom a clinician suspects measles infection, or any person with fever and maculopapular rash (i.e. non-vesicular) and cough, coryza (i.e. runny nose) or conjunctivitis (i.e. red eyes) and presence of measles-specific IgM antibodies. A confirmed case was defined when both clinical case definition and laboratory criteria were fulfilled. A probable case was defined as fulfilling the clinical picture; two cases were classified as probable after a weak positive IgM result.

Epidemiology of measles in Norway

Nowadays, measles is a rare disease in Norway due to high coverage of the measles-mumps-rubella (MMR) vaccine. MMR vaccine was introduced in the national vaccination programme in 1983 as a two-dose schedule (at 15 months and at 11-12 years of age). In 2009, the vaccination coverage in two-year-olds (birth cohort 2007) [2] with the first dose was 93% in Norway, 92% in Oslo and 88% in the district of old Oslo. The MMR vaccine coverage in Oslo for children born in 2008 and 2009 was 91% and 72%, respectively. The MMR vaccine coverage data for the second dose are available for 16-year-olds (birth cohort 1993) and is 94% in Oslo and 90% in the district of old Oslo.

All measles cases identified in the last ten years in Norway have been linked to importation from endemic areas or linked to other outbreaks in Europe [3-4]. The last outbreak in Norway occurred in 2008 in an anthroposophical community, where the index case fell ill immediately after returning from Austria [5]. In 2007, there was an outbreak among Irish travellers who were working in Norway at the time, but no cases occurred in the local population [3].

Clinical and laboratory data

Of the 10 cases, nine were children (one female and eight males) and one was an adult female healthcare worker (Table). All cases had typical symptoms of measles including a generalised maculopapular erythematous rash, fever, cough, runny nose and red eyes. Seven cases were admitted to hospital due to dehydration and impaired general condition, although none developed serious illness. In Norway, threshold to hospitalise measles cases is low for isolation purposes.

For all the 10 cases described above, samples were tested for measles and in eight cases measles IgM antibodies were detected in serum and/or saliva by Anti-Measles Virus IgM test (Enzygnost; Simens Healthcare Diagnostics Products, Marburg, Germany) and/or Measles IgM Capture EIA (Microimmune Ltd, Middlesex, United Kingdom) performed at the Norwegian Institute of Public Health (NIPH). In two cases the laboratory results were weak positive IgM and the cases were classified as probable. Additionally, five of the ten cases were confirmed by measles PCR [6]. Data from sequencing are not yet available.

Epidemiological investigation and public health measures

Of the 10 patients, eight were unvaccinated, one was vaccinated with one dose of MMR containing vaccine and for one the vaccination status was not known. All

cases live in districts of Oslo with low vaccination coverage [2]. The first six cases in the outbreak, cases 1 to 6, (Table) were among the immigrants living in the same area of Oslo. Case 7, vaccinated with one dose, was suspected of having acquired measles by exposure to case 5 in an emergency center. There is no known other contact with other measles patients.

The adult case (case 8) is from another immigrant group and is working in the health service in Oslo. We have no information on any possible linkage to the other cases in this outbreak and the vaccination status is unknown.

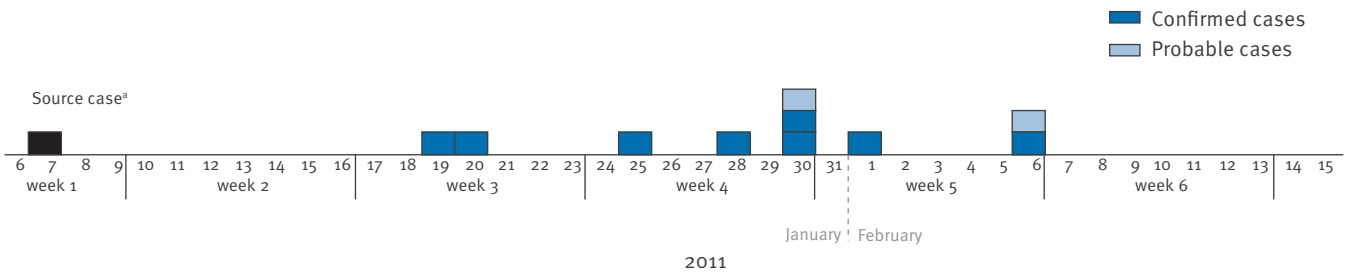
The last two cases (cases 9 and 10) are Norwegians and they were exposed to the first measles patients in an emergency center in Oslo. None of the two last cases have had any known contact with measles other than the waiting room at the emergency center. Both were around the recommended age for the first MMR containing vaccine dose.

Local health authorities have conducted contact tracing around the affected children immediately after the first case was notified. For the children attending nursery schools, the local health authorities provided information to parents, and checked the immunisation status of the other children enrolled in the same school. The adult hospitalised case attended a meeting during the time she was infectious and therefore was not in contact with patients. The other participants at the meeting were informed about the measles case and asked to check their vaccination status and be aware of development of symptoms.

The municipal and local health authorities also conducted a door-to-door campaign to inform and check immunisation status in the families living in the area. Many Somali parents in Oslo are sceptical about MMR vaccination and fear of autism seems to be the main reason. Information meetings and discussions were held with the community, in cooperation with Somali healthcare workers and the local Muslim society. Statements

Figure

Confirmed and probable outbreak measles cases by IgM result and epidemiological link, Oslo, January–February 2011 (n=10)



[a] Probable source case, not included in the outbreak.

Table

Confirmed and probable measles cases, Oslo, Norway, January–February 2011 (n=10)

Case	Age groups (years)	Onset of symptoms	Laboratory results	Epidemiological information	Vaccination status
1	< 2	19 January	IgM+ PCR+	Contact with the source case	Unvaccinated
2	2-10	20 January	IgM+	Contact with the source case	Unvaccinated
3	2-10	25 January	IgM+	Sibling of case 2	Unvaccinated
4	2-10	28 January	IgM+ PCR+	Sibling of case 2	Unvaccinated
5	2-10	30 January	IgM+ PCR+	Contact with cases 2,3 and 4	Unvaccinated
6	2-10	1 February	IgM+ PCR+	Contact with cases 2,3 and 4	Unvaccinated
7	2-10	30 January	IgM+ (weak positive)	Contact with case 5 in an emergency center	Vaccinated in 2008[a]
8	> 40	30 January	IgM+ Seroconversion IgG PCR+	No known contact to any other case	Unknown
9	< 2	6 February	IgM+ PCR+	Contact with confirmed cases in the emergency center	Unvaccinated
10	< 2	6 February	IgM+ (weak positive) PCR-	Contact with confirmed cases in the emergency center	Unvaccinated

[a] One dose of measles-mumps-rubella containing vaccine.

from parents in the immigrant group pointed to belief that MMR vaccine was associated with autism and this was the reason why they chose not to have their children vaccinated. After the outbreak and the associated information campaign, around 25 children from the immigrant community have been vaccinated against MMR.

Conclusions

This outbreak shows that also in settings with high vaccination coverage, there may still be pockets of unvaccinated individuals that can transmit measles to susceptible children under the recommended age of MMR vaccination and that measles can spread outside communities with low vaccination coverage. It also demonstrates that transmission of measles can occur in healthcare settings if children suspected of having a highly contagious disease are not isolated when arriving. Moreover, the case in a healthcare worker (HCW) provides more evidence for the need to improve the immunisation coverage among the HCWs in Europe.

This outbreak also shows the importance of reaching communities with low vaccination coverage as the Somali immigrant community mentioned above. It also shows the importance of continuous efforts despite high vaccination coverage. Although the vaccination coverage is very high in Norway it is still below the WHO recommended threshold of 95% and the NIPH are now planning to perform a catch-up vaccination campaign. We also demonstrated the benefit of organising information campaigns on vaccination for targeted groups or in general.

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First reported cases of human adenovirus serotype 14p1 infection, Ireland, October 2009 to July 2010

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We report the first nine confirmed cases of human adenovirus 14p1 infection (HAdV-14p1), identified at different locations in Ireland between October 2009 and July 2010. These were the first notifications in Ireland and all were sporadic cases. Following these notifications, the Health Protection Surveillance Centre set up an enhanced surveillance system for HAdV-14p1infection. Seven cases were male and five were aged less than one year. Three patients died, giving a case fatality rate of 33%. It should be noted that cases presented here were diagnosed on presentation to hospital and may represent the severe end of the spectrum of HAdV 14 disease in Ireland.

Introduction

Between October 2009 and July 2010, nine cases of human adenovirus 14p1 (HAdV-14p1) infections were identified at different locations in Ireland. Human adenoviruses (HAdVs) are a common cause of infection and are associated with sporadic infection and community and institutional outbreaks, particularly among military recruits. Infection with HAdV occurs all year round but may be more common in temperate regions from late winter to early summer. The viruses are predominantly transmitted by the respiratory and faecal-oral routes [1]. They rarely cause serious or fatal illness in otherwise healthy individuals, but can cause severe disease in newborn or elderly patients and immunocompromised persons, particularly transplant recipients. The clinical spectrum of disease in humans can vary substantially depending on the infecting serotype and can include asymptomatic infection, fever, colds, pharyngitis (sore throat), conjunctivitis, gastroenteritis, bronchitis, pneumonia, acute haemorrhagic cystitis, meningoencephalitis, hepatitis, myocarditis and life-threatening disseminated disease [1]. There are 51 recognised HAdV serotypes, which are assigned to six subgroups (A–F) on the basis of biophysical, biochemical and genetic characteristics [1].

The epidemiological characteristics of HAdV infection vary by viral serotype. Compared with other adenoviruses, infection with HAdV-14p1 serotype appears to result in a higher rate of severe illness [2]. However, in general, information on severe adenovirus disease in healthy individuals is limited and severe manifestations (including sepsis and pneumonia) are typically limited to newborns, immunocompromised persons and persons with underlying respiratory or cardiac disease [3]. This serotype was first discovered in 1955 during an outbreak of acute respiratory disease (ARD) at a military recruit training facility in the Netherlands [4]. It was subsequently identified during similar outbreaks of ARD among young adults in Great Britain in 1955 [5], Uzbekistan in 1962 [6] and the former Czechoslovakia in 1963 [6]. Reports of clusters of cases of HAdV-14 infection are unusual, with most reported infections being sporadic cases.

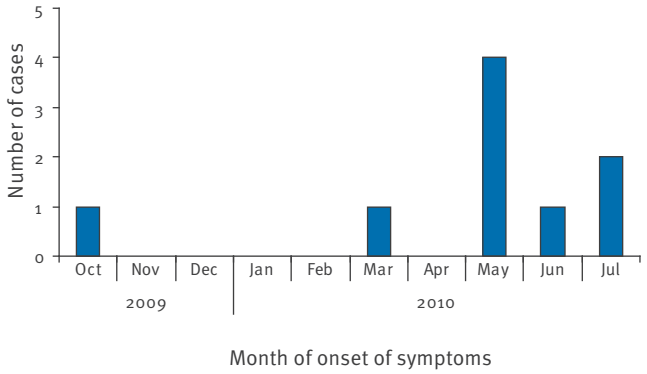
In 2008, Louie *et al*. described a severe pneumonia in the United States (US) associated with a newly emergent HAdV-14 strain, designated HAdV-14a, now called HAdV-14p1, which displayed some genetic differences from the strain detected in the 1950s [7]. Outbreaks of HAdV-14-associated ARD of variable severity were subsequently detected in US military bases [8,9] and in civilian populations in Washington [10], Oregon [11], Alaska [2], Wisconsin and Pennsylvania [6]. The community outbreak in Oregon resulted in 29 hospitalisations and seven deaths [11], while an outbreak in a military base in the US described by Tate *et al*. involved high rates of transmission of HAdV-14 infection sustained over five months and was associated with 23 hospitalisations and one death [9]. The Alaskan outbreak in 2008 involved 46 confirmed and probable cases of HAdV-14 infection, of whom 11 were hospitalised and one died [2]. In 2010, an article by Kajon *et al*. described how retrospectively molecular analysis was undertaken on 99 isolates (between 2003 and 2009) in the US, from military and civilian populations from different geographic locations and circulation periods. Civilian populations included those from Alaska, Oregon, Pennsylvania and Wisconsin. All examined viruses were identical and belonged to the new genome type designated HAdV-14p1 [6].

Cases of HAdV-14p1 infection are statutorily notifiable in Ireland under the Infectious Disease Regulations

2004 (S.I. 865) which came into effect on 1 January 2005. These regulations require that clinicians and directors of laboratories report any unusual clusters or changing pattern of any illness or individual cases thereof that may be of public health concern to the Medical Officer of Health. In August 2010, the National Virus Reference Laboratory (NVRL) in Ireland notified the Health Protection Surveillance Centre of HAdV-14p1 infection in nine patients whose specimens were sent to the NVRL between November 2009 and July 2010. These were the first notifications of HAdV-14p1 infection in Ireland and all were sporadic cases. Following these notifications, the Health Protection Surveillance Centre set up an enhanced surveillance system for HAdV-14p1 infection in Ireland. In this article, we report the characteristics of these initial Irish cases of HAdV-14p1 infection.

Figure 1

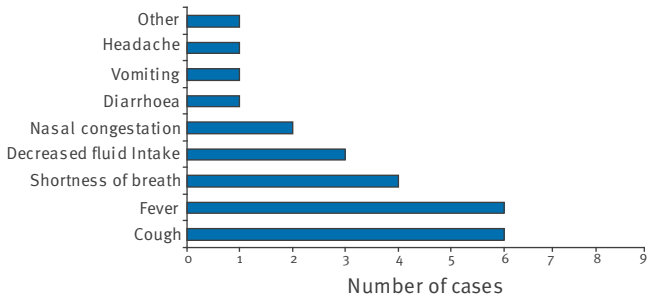
Cases of HAdV-14p1 infection by month of symptom onset, Ireland, October 2009–July 2010 (n=9)



HAdV-14p1: human adenovirus 14p1.

Figure 2

Symptoms reported for cases of HAdV-14p1 infection, Ireland, October 2009–July 2010 (n=9)[a]



HAdV-14p1: human adenovirus 14p1.

[a] Some cases may have had more than one symptom.

Table 1

Signs reported for cases of HAdV-14p1 infection, Ireland, October 2009–July 2010 (n=9)[a]

Sign	Number of cases
Fever (≥38 °C)	7
Tachypnoea[b]	7
Decreased systolic blood pressure[b]	2
Hypoxaemia documented[c]	7

HAdV-14p1: human adenovirus 14p1.

[a] Some cases may have had more than one sign of clinical infection.

[b] Tachypnoea (elevated respiratory rate) is defined as › 60, › 40, › 30, › 25 and › 20 breaths per minute for individuals aged under 6 weeks, 6 weeks to ‹6 months, 6 months to ‹3 years, 3 years to 6 years, and ›6 years, respectively.

[c] Decreased systolic blood pressure is defined as ‹50, ‹70, ‹80 and ‹90 mmHg for individuals aged under 6 weeks, 6 weeks to ‹6months, 6 months to ‹3 years, 3 years to 6 years, and ›6 years, respectively.

[d] Hypoxaemia (decreased oxygen saturation) is defined as less than 93%, for all age groups.

Microbiological investigation

Specimens from the nine patients with HAdV-14p1 infection [12] were analysed at the molecular level by

Table 2

Laboratory and radiological investigations for cases of HAdV-14p1 infection, Ireland, October 2009–July 2010 (n=9)

Investigation	Result	Number of cases
White blood cell count	Low	1
	Normal	6
	Elevated	2
Lymphocyte count	Low	4
	Normal	4
	Elevated	1
Neutrophil count	Low	1
	Normal	6
	Elevated	3
Creatinine levels	Elevated	2
Lung infiltrates	Single-lobe	1
	Multi-lobe	4
	Interstitial	0
Normal chest X-ray	Yes	2
	No	7

HAdV-14p1: human adenovirus 14p1.

Table 3

Treatment given to patients with HAdV-14p1 infection, Ireland, October 2009–July 2010 (n=9)

Treatment	Number
Antiviral treatment	3
Antibiotic therapy	9
Mechanical ventilation	6
Renal replacement therapy	2
Bronchodilator therapy	5
Supplemental oxygen	6
Corticosteroid therapy	2
Vasopressor therapy	4
Extra corporeal membrane oxygenation (ECMO)	2

HAdV-14p1: human adenovirus 14p1.

the NVRL. The HAdV-14 infections were detected by immunofluorescence (IF) and/or a generic HAdV hexon real-time polymerase chain reaction (PCR) for detection of all serotypes. HAdV positives were then typed by HAdV-14-specific real-time PCR, HAdV-14-specific end-point PCRs and DNA sequencing from a range of clinical specimens (serum, plasma, urine, nasopharyngeal aspirates, bronchoalveolar lavages and a lung biopsy). The molecular characterisation of these cases as HAdV-14p1 will be published elsewhere (Carr *et al.*, submitted). A virology screen for influenza A, influenza B, respiratory syncytial virus and parainfluenza 1, 2 and 3 viruses was also undertaken on patients' specimens.

Epidemiological investigation

A case definition for HAdV-14p1 infection was developed. A confirmed case was defined as a person hospitalised with HAdV-14p1 who meets the clinical description of one or more of the following: respiratory infection, pneumonia, pharyngitis, gastroenteritis, conjunctivitis, cystitis, meningoencephalitis and disseminated disease.

The Health Protection Surveillance Centre wrote to all consultant microbiologists, infectious disease consultants, intensive care unit (ICU) directors, respiratory physicians and consultant paediatricians in August 2010 to alert them to the situation. They were requested to report all cases of HAdV-14p1 infection, including unusual clusters of severe adenoviral respiratory disease or clusters of pneumonia of unknown aetiology to the local Director of Public Health, who would subsequently notify the Surveillance Centre.

As previously stated, an enhanced surveillance system was initiated. The objectives of the system were to describe: (i) the incidence of the disease (based on the number of cases meeting the case definition); (ii) the symptoms and signs on hospital admission and results of initial investigations; (iii) the treatment provided; (iv) the complications associated with the infection; (v) the outcome at 30 days after the start of treatment; and (vi) the presence of known predisposing risk factors.

Enhanced surveillance data were collected on the nine reported cases and included demographic details, clinical details, medical complications, risk factors (e.g. immunosuppression, chronic respiratory disease, post solid-organ transplant and smoking status), investigations on admission, treatment and outcome at 30 days.

Details of the cases of HAdV-14p1 infection

Of the nine cases, two were female and seven were male. Five cases were less than one year of age, of whom two were less than one month old, and the remaining three were aged between two and seven months. One case was in the 5–9-year age group, one in the 30–39-year age group and the remaining two were in the 40–49-year age group. All nine cases were Irish. The majority of the cases (n=8) lived in eastern Ireland. No cases resided in institutional settings. Two of the three adults were smokers.

Clinical details

The date of onset of symptoms ranged from October 2009 to July 2010. For seven cases, symptom onset occurred between May and July 2010 (Figure 1). All nine cases were hospitalised. The length of stay in hospital was known for six cases, ranging from four to 36 days, with a median of 10 days. Five cases were admitted to an intensive care unit. The most commonly reported symptoms were cough (n=6), fever (n=6) and shortness of breath (n=4) (Figure 2). The signs are detailed in Table 1.

All patients aged over one year had underlying medical conditions, which included developmental delay, immunosuppression, chronic pulmonary disease, hypertension and congenital genetic disorder. Of those aged less than one year of age, one was premature and one had intrauterine growth retardation. Three of the nine patients died, giving a case fatality rate of 33%.

Of the nine cases, six developed pneumonia, two had disseminated infection, one had acute respiratory distress syndrome, one had hepatitis and one had meningoencephalitis. Other reported complications included bronchiolitis and seizures. Complications were not mutually exclusive. Table 2 outlines the results of laboratory and radiological investigations. Seven patients had abnormal chest X-ray findings, with four having multi-lobe infiltrations and one having single-lobe infiltrates and right mid-zone consolidation. A sixth case had mild pulmonary oedema. Chest X-ray findings were not provided for the seventh case. Of those with multi-lobe infiltrations, two had pleural effusions and one had bilateral pneumonia.

A summary of treatment interventions is provided in Table 3. Three of the nine patients had received antiviral therapy with cidofovir (n=1) and acyclovir (n=2). All patients received antibiotic therapy. Two thirds of patients were mechanically ventilated and two, both aged less than one year, were on extracorporeal membrane oxygenation (ECMO).

Discussion

Of the nine cases of newly emergent HAdV-14p1 infection described in this report, the majority were male and more than half of cases were aged less than one year. This compares with the Alaskan and Oregon outbreaks, where 70% (32 of 46) and 66% (25 of 38) of cases, respectively, were male. In our series, five cases were neonates or infants, which contrasts with the Alaskan outbreak, where 91% (29 of 32) cases were older than 19 years, and the Oregon outbreak, where 61% (23 of 38) patients were aged over 40 years [2,11]. Six of the nine (67%) Irish cases had underlying medical conditions including immunosuppression, developmental delay, chronic lung disease, hypertension, intrauterine growth restriction and prematurity.

Previous publications suggest that underlying chronic illness may predispose individuals with HAdV-14p1 infection to severe illness [10,11]. However, other respiratory adenoviruses are also known to be associated with higher fatality rates among immunocompromised individuals [13]. In the Oregon outbreak, 47% (18 of 38) of cases had one or more underlying medical condition while the Alaskan outbreak reported 61% of cases (28 of 46) had an underlying medical conditions including chronic heart and lung disease, diabetes mellitus and asthma [2,11].

An outbreak investigation in Alaska in 2008 identified that smoking may have facilitated transmission of the virus [14]. Smoking was also observed in a high proportion of patients in the Oregon outbreak, with 60% (18 of 30) adult cases reporting having smoked in the previous 30 days. The Alaskan outbreak investigation also suggested that the spread of the HAdV-14p1 virus was more likely to occur in situations leading to close person-to-person contact such as sustained household contact or contact among members of a tight social network. It also indicated that spread is less likely to occur during most normal social contact situations in the community. This is also supported by the reporting of outbreaks of HAdV-14p1 infections in military bases in the US, where recruits live in close proximity [9].
Adenoviruses spread from person to person via coughing or sneezing. People may also become infected by touching something with adenovirus on it and then touching their mouth, nose or eyes [15]. In order to prevent spread of the infection, it is important to advise patients to follow respiratory precautions [16].

Healthcare professionals should follow standard contact and droplet precautions when caring for people hospitalised with adenoviral infections. Environmental decontamination should also be implemented in the rooms occupied by such patients. Patients with symptoms of severe viral respiratory infections and those diagnosed with adenovirus infection should be placed in a single room or share a room with other patients with the same infection, to help control the spread of infections [17].

Management of adenoviral infections is largely supportive using antibiotics, steroids, bronchodilators, mechanical ventilation and ECMO. A number of antiviral drugs including ribavirin, vidarabine and cidofovir have been used to treat adenoviral infections such as those caused by HAdV-14p1 and may be beneficial [10]. A retrospective review of a community outbreak of HAdV-14p1 infection in Oregon did not provide any conclusions about the efficacy of cidofovir, the antiviral drug used by clinicians for critically ill patients, except that its use was associated with worsening renal function [11]. In our study, six of the nine patients required mechanical ventilation and two patients aged less than one year required ECMO, highlighting the severity of illness and also the intensity of interventions required. Cases presented here were diagnosed on presentation to hospital and may represent the severe end of the spectrum of HAdV 14 disease in Ireland. Information on asymptomatic or mild cases of HAdV-14 disease in the community is lacking at this time.

Currently no licensed vaccine for HAdV-14p1 virus exists. Safety and efficacy trials are currently in progress in the US for HAdV-4 and HAdV-7 vaccines and vaccines for these adenovirus serotypes may provide cross immunity to HAdV-14 [4,18]. Rapid diagnosis and improved surveillance, with serotyping and molecular characterisation to identify emerging adenovirus variants, may assist with the targeted development of antiviral agents or type-specific vaccines.

Infections with HAdV-14p1 are not commonly reported and most are not thought to be serious. However, clinicians should consider this infection in the differential diagnosis of severe acute respiratory disease or pneumonia and of clusters of respiratory disease. This especially relates to patients who are immunosuppressed (including transplant recipients), those who have underlying respiratory or cardiac disease as well as children aged one year and under (particularly neonates) and those aged 65 years or older. Clinicians should liaise with a virus reference laboratory for guidance on testing patients with a possible diagnosis of HAdV-14p1 infection. It is recommended that clinicians and laboratories should endeavour to report all cases of HAdV-14p1, including unusual clusters of severe adenoviral respiratory disease, to their local Public Health Authority. Public health surveillance of this re-emerging pathogen is also recommended in order to improve our knowledge of the pathogenesis associated with species B adenovirus infections.

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