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Visions for the next five years: ECDC as a sustainable and service-oriented organisation

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The European Centre for Disease Prevention and Control (ECDC) is celebrating its fifth anniversary on 20 May 2010. At the beginning of May I started as the new Director of ECDC: it is both a pleasure and a challenge for me to take up my post and to continue the dedicated work of my predecessor, Zsuzsanna Jakab. Long before the Centre was established, I supported the idea of a European Union (EU)-wide institution concerned with the prevention and control of communicable diseases, coordinating the efforts of the Member States and protecting the health of European citizens. As the first Chair of the ECDC Management Board, I was proud to be among those closely involved in the work of establishing ECDC from the outset.

Since 2005 I have seen recognition of the value of ECDC grow and the Centre has gradually become staffed to a level where it can achieve its full potential. Today, it has around 300 expert staff from 29 countries in the EU and European Economic Area, representing a unique intellectual capital. One of my aims is to continually demonstrate the added value of ECDC to our stakeholders, and to European citizens. With the necessary infrastructure now in place at ECDC, it is my goal to build on the excellent work done so far and strive for clear priorities in our work and a high quality of our scientific outputs. Prioritisation is the key to making the best use of the resources available to us, both human and financial, and to guarantee quality.

ECDC has on numerous instances supported the Member States and the European Commission in addressing old and new challenges and facilitating the exchange of experiences and good practices. The guidance document on the implementation of the new human papilloma virus vaccine [1], the EU-wide electronic surveillance system TESSy [2], rapid risk assessments and daily updates of epidemiological data during the 2009 influenza A(H1N1) pandemic [3] and the support, provided on request of Italian authorities, during the emergence of a Chikungunya fever outbreak in northern Italy in 2007 [4] are but a few examples.

The meetings organised by the Centre provide an opportunity for Member States to come together and exchange experiences on specific challenges on a national level and on the broader implications for the EU. In today's world, countries support each other with regard to communicable diseases and the impact of measures they take at regional or national level. Personal contacts among experts from various disciplines have facilitated the flow of information and fostered the transfer of knowledge in the EU. Because of the expertise of the Centre and of the Member States, ECDC is fulfilling one of the key tasks set out in its founding Regulation – to provide scientific advice.

A crucial element of the scientific advice produced by the Centre is transparency in concerning the contributors and how evidence and facts were weighted to support the scientific assessment and final conclusions. I will personally ensure that ECDC works closely with its political and technical partners to identify priorities specifically concerning our scientific advice that will be reflected in our annual work programmes and our future long-term visions, and that also serve our partners' needs. Service orientation is a core value of ECDC. I acknowledge the diversity of the public health situation across Europe and it is one of my goals to ensure an appropriate response to the different needs from the Member States.

Communicating scientific findings and providing a platform to exchange good practices is one of the core tasks of ECDC. The scientific journal *Eurosurveillance* serves as such a platform and, building on years of networking experience, has gained a considerable reputation in the past years. The journal has recently been accepted for an impact factor and the first figure will be assigned for 2011. *Eurosurveillance* is known worldwide for its capacity to disseminate scientific information rapidly so as to enable public health action where needed – a strength that has attracted many readers and contributors not just from Europe but from all continents, especially during the 2009 pandemic [5]. As publisher of the journal, ECDC grants full editorial freedom to *Eurosurveillance*, and as ECDC's Director I am personally committed to support *Eurosurveillance* and to guarantee the editorial independence of the journal.

Looking to the future, I see ECDC continuing to play a central role in providing EU and Member State policy-makers with the evidence base needed to respond to some of the key public health challenges Europe faces: how to respond to antimicrobial resistance, how to drive down the incidence of human immunodeficiency virus (HIV) infection and tuberculosis, assessing the impact of environmental change on the spreading of diseases, and further improving surveillance, preparedness and prevention of infectious diseases. The key to achieve this lies in collaboration, and it is with confidence that I look forward to continuing the excellent work with all ECDC's partners and to take the Centre into the future.

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Experiences of giving oseltamivir to school children during the 2009 influenza A(H1N1) pandemic

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In this week's issue, *Eurosurveillance* publishes an article on experiences of giving oseltamivir to school children during the 2009 influenza A(H1N1) pandemic in the United Kingdom (UK) [1]. Already in 2009 the journal published two other studies on the same subject. [2,3]. All three studies were carried out in late spring 2009, when the UK still upheld its strategy of containment against the new influenza and together they report on a total of 638 children.

There are at least three reasons to give antivirals against influenza to children. The first is obviously to prevent or mitigate a disease that can be quite severe even in healthy children. The second is the mounting evidence that school children play a major role in the spread of an influenza epidemic [4,5]. The third is somewhat similar to the second, but rather a family than a society matter: to provide indirect protection for infant siblings that are too young to receive drugs or vaccine.

In the UK one year ago, the reason for offering oseltamivir to school children seems to have been a combination of the first two points mentioned above [6].

All three studies include rather young children, aged from 4 to 14 years. They were prompted by the laboratory confirmed diagnosis of one or more cases of 2009 pandemic influenza in the school and in addition each school was closed for at least one week. None of the studies had as a primary aim to assess the effectiveness of the intervention, but rather to measure frequency of adverse events and compliance with medication. Most of the children were given oseltamivir in prophylactic dosage, but those who matched the clinical criteria for influenza were given the drug as therapy.

The common finding from these studies is that the frequency of self-reported adverse events was considerably higher than previously reported for oseltamivir [7]. Around half the children in all the schools reported at least one symptom that could be associated with the drug. Nausea was most common, reported by almost one third of the children, followed by stomach pain in

around one fifth. Other commonly reported symptoms (>10%) were headache, sleeping problems and tiredness. One pupil and one adult staff reported mood changes that could have been of the type that has led to increased alertness [8].

Compliance varied across the studies: only 48% of the primary school children (aged 4-11 years) in one school finished the full course versus 85% of the slightly older children (aged 7-12 years) reported in this week's study. There was little difference in compliance between those children who reported influenza-like symptoms during the course and those who did not. The authors of this week's study performed a multivariate analysis of reasons for non-compliance and found that nausea, vomiting and rash were significantly associated with stopping the medication.

The studies presented add to our knowledge of the spectrum of adverse events when oseltamivir is used for treatment and/or prophylaxis in large groups of children. They indicate that expected benefits must be weighed carefully against side effects when this drug is considered for outbreak situations. In such situations, it may be worth to try to develop a simple instrument to decide who in the group would be at the highest risk of exposure and infection. One should also observe that even if antivirals are given to school children in order to diminish spread in society, the studies cited here indicate that this effect is limited – influenza is spreading also outside the school yards.

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Highly divergent neurovirulent vaccine-derived polioviruses of all three serotypes are recurrently detected in Finnish sewage

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In Finland, surveillance of potential re-emergence of poliovirus transmission is mainly based on environmental surveillance, i.e. search for infectious poliovirus in sewage samples. Since December 2008, 21 genetically highly divergent, neurovirulent vaccine-derived polioviruses (VDPV) have been isolated from sewage in Tampere, Finland. While the source of the VDPV is unknown, characteristics of the viruses resemble those of strains isolated from immunodeficient, persistently infected persons. No cases of suspected poliomyelitis have been reported in Finland since 1985.

Introduction

Polioviruses are causative agents of acute paralytic disease, poliomyelitis (polio). Because of the work of the Global Polio Eradication Initiative and intensive polio immunisation programmes, wild polio virus is currently endemic only in four countries worldwide: Afghanistan, Pakistan, India, Nigeria. While the eradication of wild poliovirus gets closer, genetically drifted vaccine-derived polioviruses (VDPV) with regained neurovirulence, have become a new challenge for the eradication of polio [1-3]. In an individual vaccinated with oral poliovirus vaccine (OPV), the three vaccine strains (Sabin strains) infect the intestinal epithelium and replicate in the gut for a period ranging between several weeks and a couple of months. During this time, polioviruses undergo rapid genetic changes, which can result in the reversion of attenuating mutations. Very rarely, this may result in paralytic disease, the vaccine-associated paralytic poliomyelitis (VAPP), in vaccinees or in their immediate contacts. In suboptimally immunised populations the emergence of transmission of neurovirulent circulating vaccine-derived polioviruses (cVDPV) may occur. Several outbreaks caused by cVDPV have been documented [3-4]. In most cases, cVDPV have been detected soon after the onset of the first case of paralysis, but genetic analyses of isolated poliovirus strains have confirmed their silent circulation for at least one year before detecting the symptomatic case.

Since decades, polio surveillance in Finland has been carried out mainly through environmental surveillance. Between 1985, when a nationwide OPV campaign was launched to stop a polio epidemic which started in late 1984, and 2006 when an OPV-like poliovirus strain was isolated from sewage in Helsinki, no polioviruses were found in Finnish sewage. Since 2006, at least one Sabin-like poliovirus has been isolated from sewage almost every year. In Finland, only the inactivated poliovirus vaccine (IPV) has been used in vaccination campaigns, both before and after the 1985 OPV campaign. In spite of this Sabin-like poliovirus is occasionally detected in sewage. However, this is not surprising as a great number of people from OPV-using countries visit Finland every year. In this study we describe a more unexpected finding, namely the recurrent detection of neurovirulent and highly divergent VDPV strains of all three poliovirus serotypes, in Finnish sewage.

Methods

Sewage specimens were collected and analysed according to the recommendations made by the World Health Organization (WHO) [5-6]. Isolated poliovirus strains were characterised for serotype, intratype (ITD) and genetic properties as previously described [7].

Results

The first two highly divergent VDPV strains were isolated from a sewage specimen collected on 15 December 2008, in Tampere. The subsequent, intensified, weekly sampling revealed an additional 20 poliovirus strains (serotypes 1-3) in Tampere up to late March 2010 (Table).

Five of seven poliovirus-positive sewage samples contained more than one serotype and one specimen even contained several parallel strains from all three

serotypes. A poliovirus type 1 strain isolated from a sample collected on 14 April 2009 was shown to be Sabin-like in ITD assays and was not characterised further. All other poliovirus strains gave aberrant results in ITD assays and were therefore subjected to partial genomic sequencing.

Genetic relationships of vaccine-derived polioviruses

The nucleotide sequences encoding the complete viral capsid protein 1 were determined from 21 Finnish poliovirus strains. The strains shared only 85.4–87.7% nucleotide and 92.7–95.7% amino acid identities with the parental Sabin strains of corresponding serotypes, indicating that poliovirus strains had evolved from OPV, but were highly divergent VDPV. The extent of sequence divergence suggests that the viruses have been replicated in humans for more than 10 years. When the viral capsid protein 1 sequences were compared with all sequences available in the GenBank and in the other laboratories of the Global Polio Laboratory Network, no close genetic relatives were found, indicating unique evolution pathways of these strains. The comparison with past and still existing wild poliovirus genotypes definitely excluded the wild-type origin of the strains (Figure).

Analysis of the reciprocal genetic relationships of VDPV showed that distinct strains of poliovirus type 1 and 3, some isolated from separate sewage samples, were closely related to each other, but none of the strains were completely identical (Figure). Six poliovirus type 2-VDPV strains segregated into two discrete genetic lineages and representatives of both lineages were isolated from the same sewage sample collected on 6 July 2009. Analyses of partial 3D polymerase coding sequences showed that all VDPV have the closest similarity to poliovirus type 1 Sabin strain in this genomic region indicating that type 2 and 3 VDPV had recombinant genomes. Intertypic recombination of the Sabin strains is a common phenomenon in recipients of OPV.

Loss of attenuation in Finnish vaccine-derived polioviruses

The representative VDPV strains of each of the three serotypes were tested for attenuation or neurovirulence in transgenic mice expressing the human poliovirus receptor (PVR-Tg 21 mice) [8]. PVR Tg-21 mice were inoculated intraperitoneally and/or intracerebrally with either VDPV isolates or Sabin strains. In contrast to Sabin strains, all tested VDPV induced paralysis or death in at least some of the inoculated animals. These results indicate that all tested VDPV have lost the attenuated phenotype that characterises the vaccine strains.

Discussion and conclusion

Highly divergent VDPV of all three serotypes were recurrently isolated from Tampere sewage. The molecular analysis of the viral capsid protein 1 coding regions revealed that all strains had originated from an OPV dose given more than 10 years ago.

The source of the VDPV remains unknown, but both epidemiological and genetic data suggest that they might be originally derived from (a) chronically infected still unidentified immunodeficient individual(s). It is well recognised that sometimes, when patients with hypogammaglobulinaemia are infected either by direct administration of OPV or as a consequence of contact with someone who received a dose of OPV, the virus excretion may continue for years or even for the rest of their lives [1-2,4]. Until now approximately 40 chronically poliovirus-infected individuals have been confirmed worldwide [1,4,9]. Two of them have prolonged infection with two poliovirus serotypes, while the others are excreting only one serotype [4,9]. While the VDPV strains of all three serotypes detected in Tampere most likely were originally established in one person, we cannot exclude the possibility that some of the viruses have spread to close contacts.

The identification of chronic excretors is of high importance, since patients with primary immunodeficiencies (i.e. having defects in antibody production) have increased risk of developing VAPP (estimated as a 3,000-fold risk) [10]. Since hypogammaglobulinemia has been reported to occur most often in Caucasians, the problem of chronic excretors of VDPV is highlighted in Europe and North America [1]. Furthermore, patients with hypogammaglobulinemia only have a

Table

Strains of poliovirus isolated during environmental surveillance in Tampere, Finland, December 2008 to March 2010

| Specimen code	Collection date	Poliovirus serotype
2849	15.12.2008	PV1
2849	15.12.2008	PV2
2963	14.4.2009	PV1
3001	15.6.2009	PV3
3008	6.7.2009	PV1
3008	6.7.2009	PV1
3008	6.7.2009	PV1
3008	6.7.2009	PV2
3008	6.7.2009	PV2
3008	6.7.2009	PV2
3008	6.7.2009	PV3
3077	14.9.2009	PV1
3077	14.9.2009	PV1
3077	14.9.2009	PV1
3077	14.9.2009	PV3
3077	14.9.2009	PV3
3253	1.2.2010	PV1
3253	1.2.2010	PV3
3311	22.3.2010	PV1
3311	22.3.2010	PV1
3311	22.3.2010	PV2
3311	22.3.2010	PV2

longer life-expectancy in better resourced countries with a well developed health system. Persistent excretion of neurovirulent polioviruses poses a risk for transmission of the virus to susceptible contacts in the community, in spite of the lack of reports of paralytic cases among contacts of VDPV excreting immunodeficient individuals. While there is no medical treatment capable of interrupting poliovirus excretion, the risk of VAPP in an immunodeficient patient and his close contacts can be lowered by booster vaccinations with inactivated polio vaccine (IPV).

Although the loss of attenuation and regaining of neurovirulence were evident in all VDPV serotypes in transgenic mice, no poliovirus-induced paralyses have been found in Tampere or elsewhere in Finland since

FIGURE

A phylogenetic tree depicting the reciprocal genetic relationships of Finnish vaccine-derived poliovirus strains supplemented with sequences of wild-type polioviruses of each poliovirus serotype.
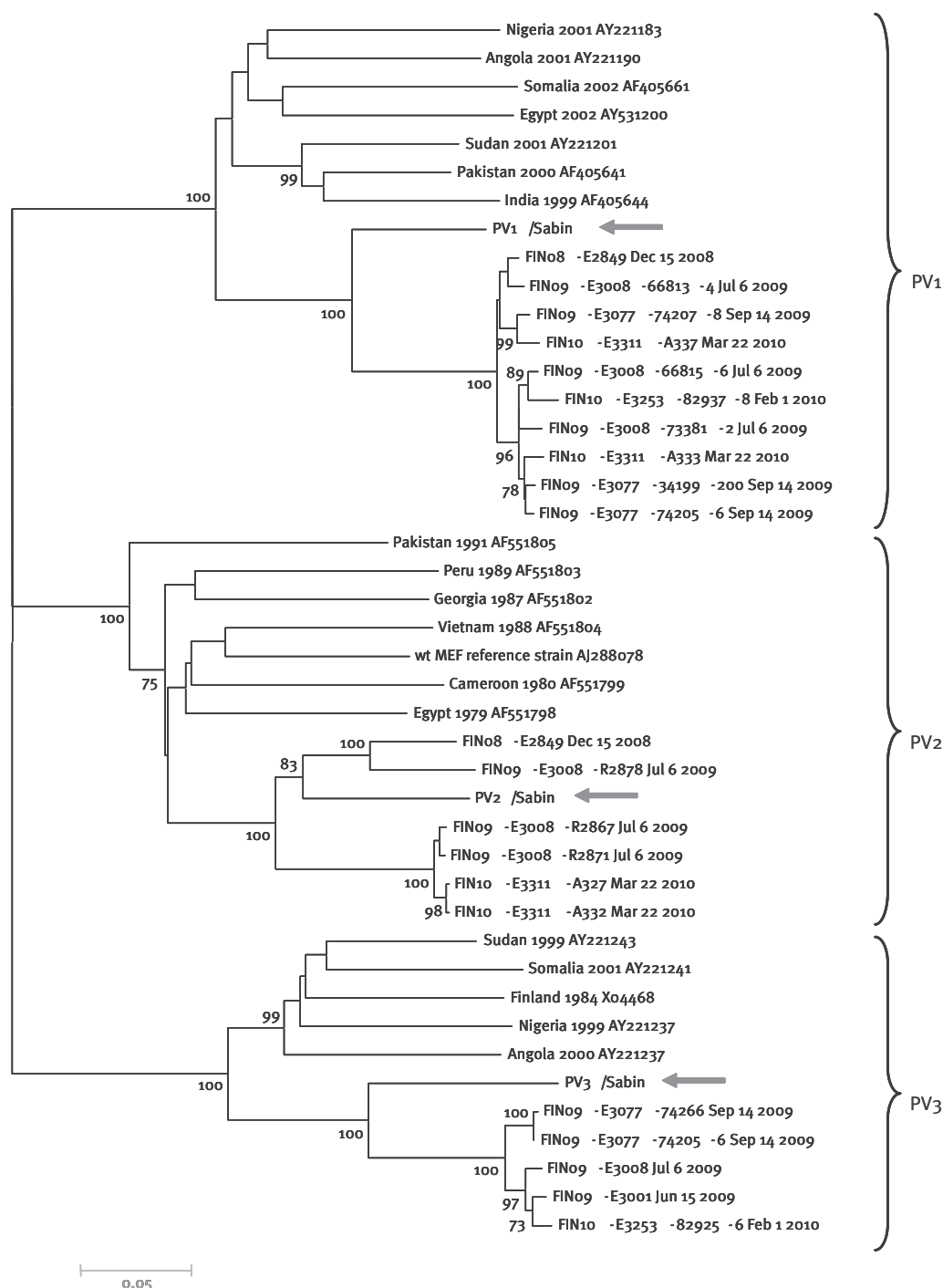
The tree was constructed from nucleotide sequences using neighbour-joining algorithm with Kimura 2-parameter substitution model. The consensus tree from 1000 replicate analyses is shown. The Finnish vaccine-derived poliovirus strains are in bold. The arrows indicate the parental OPV strains. The GenBank accession numbers and the country and year of isolation are shown for wild-type poliovirus strains.

1985. The recurrent isolation of neurovirulent, highly divergent VDPV from Tampere sewage emphasises the importance of maintaining high polio vaccination coverage, but also highlights the usefulness and importance of environmental surveillance in poliovirus control.

*Erratum: The name of the fifth author in this article had been misspelled. The mistake was corrected on 22 June 2010 and we apologise to the author.

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Management of health risks associated with oysters harvested from a norovirus contaminated area, Ireland, February–March 2010

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Oysters from a harvesting area responsible for outbreaks of gastroenteritis were relaid at a clean seawater site and subsequently depurated in tanks of purified seawater at elevated temperatures. This combined treatment reduced norovirus levels to those detected prior to the outbreak. On the basis of norovirus monitoring the sale of treated oysters was permitted although the harvest area remained closed for direct sale of oysters. No reports of illness have been associated with the consumption of treated oysters.

Oysters are filter-feeding bivalve molluscs which may become contaminated with human pathogens when grown in sewage-contaminated waters, which can lead to illness as the oysters are often consumed raw. In Europe, regulations are in place to prevent this risk [1]. Shellfish harvesting areas are classified into three categories (A, B or C) depending on the extent of faecal contamination of the area as judged by levels of *Escherichia coli*. Shellfish treatments are prescribed depending on the classification. Despite these controls outbreaks of illness associated with oyster consumption continue, in particular outbreaks of gastroenteritis associated with norovirus (NoV)-contaminated oysters. Until recently, suitable methods for the quantitative detection of NoV in shellfish have not been available.

A high prevalence of NoV in oysters from a range of harvesting areas throughout Europe has been shown by PCR [5-7]. Quantitative real-time PCR procedures are currently undergoing standardisation at the European level (CEN WG6 TAG4). Where quantitative data exists, NoV levels detected in shellfish harvest areas are often low and near the detection limit [8,9]. The public health significance of oysters containing low levels of NoV is unclear.

Various intervention steps are available to reduce the microbiological load in sewage-contaminated shellfish. These include relaying shellfish in clean seawater areas to allow them to purge contaminants. A similar, more controlled process is performed in tanks of seawater purified by disinfection. This process is called depuration and is used extensively throughout Europe. Depuration is commonly carried out for 24 to 48 hours at ambient temperatures. It has been demonstrated to eliminate bacteria from shellfish but has little impact on virus levels in oysters [10,11]. However, depuration carried out at elevated temperatures (17-20 °C) for extended periods of three to five days reduces virus levels in oysters significantly [12,13].

NoV generally causes a relatively mild gastroenteritis in most people that is significantly under-reported and often recognised only in outbreak situations. In recent months an unusually high number of NoV gastroenteritis outbreaks associated with the consumption of shellfish have been reported in Europe [14]. It is likely that the recent high incidence of oyster-associated outbreaks with is connected the unusually cold weather in 2010.

Norovirus outbreaks

Over a five week period in January and February 2010, more than 70 cases of gastroenteritis in Ireland and the United Kingdom (UK) were due to the consumption of oysters originating from an Irish harvesting area. The infections in England have been recorded as part of a wider report on European-wide outbreaks [14]. Oysters connected to two illness incidents in Ireland were available for testing and contained 2,040 and 2,350 NoV genome copies per g, respectively.

Table

Norovirus GII levels in oysters from the harvest area, Ireland, 2009

Date 2009	20/01	25/02	26/04	19/05	05/07	11/08	09/11	13/12
Genome copies per g	219	‹LOQ	‹LOQ	ND	ND	ND	1,280	278

LOQ: limit of quantitation (100 virus genome copies per g); ND not detected.

Following reports of illness two companies producing oysters from the affected harvest area voluntarily ceased production on 10 February and implemented a recall of product already on the market. On 12 February a formal compliance notice was issued by the competent authority in Ireland the harvest area was closed for direct sale of oysters. Prior to the outbreak limited data was available regarding NoV levels in oysters from this harvest area which to our knowledge was not associated with any reports of illness in 2009.

We report the use of relaying combined with extended depuration at elevated temperatures to reduce NoV in oysters of the harvesting area and highlight the potential of quantitative real-time PCR for monitoring treatment processes for oysters and more accurately assess the risk to consumers.

Methods
Treatment and sampling
On 26 February oysters from the harvest area were relaid in an area believed to be free from sewage contamination. Relaid shellfish were monitored for NoV levels at least once a week. On 15 March oysters from the relay site were further treated by depuration at elevated temperature (15-17°C) for a period of at least four days. Subsequent batches of relaid shellfish were depurated using the same treatment regime.

Samples of 24 whole oysters were transported to the laboratory within 24 hours of sampling under chilled conditions and analysed for NoV genogroup I (GI) and genogroup II (GII) within 24 hours of receipt in the laboratory.

Detection and quantification of norovirus by real-time PCR
Virus extraction was undertaken as described previously [15] followed by RNA extraction based on the Boom method [16] using NucliSens Magnetic Extraction reagents (Biomerieux). NoV RNA was then detected by reverse transcription (RT) quantitative real-time PCR employing primers and probes specific for NoV GI [17,18] and GII [19,20]. Real-time PCR controls were used to evaluate extraction efficiency [21] and amplification efficiency [17,18].

Results
During 2009, eight samples of oysters from the area had been analysed for NoV. These data had been collected retrospectively as part of a wider survey to determine background levels of NoV in shellfish harvest areas and results were not intended for regulatory control. Levels ranged from not detectable to 1,280 viral genome copies per g (Table).

Throughout the period of NoV monitoring following the outbreak in February and March 2010, NoV GI was detected in two samples from the harvest area. On both occasions levels were below the limit of quantitation of the assay (100 viral genome copies per g). NoV

GI was not detected in any samples from the relay site or in samples taken during the depuration period.

NoV GII levels in nine samples of oysters from the harvest area between 9 February and 15 March 2010 are shown in Figure 1. During this period in the norovirus load in the oysters did not decrease and ranged from 1,100 to 2,900 viral genome copies per g.

In oysters relaid from the harvest area to clean seawater, NoV GII levels decreased from 2,900 to 492 viral genome copies in a 17-day period from 26 February to 15 March (Figure 2). Subsequent depuration of the relaid shellfish at 17 °C reduced NoV GII levels to 136 viral genome copies per g after four days and to below the limit of quantitation of the assay (100 viral genome copies per g) after six days.

Subsequently, during the period from 29 March to 12 April, a further four batches of oysters which had been relaid since the 26 February have been depurated. Each depuration cycle was performed for between four and eight days at temperatures between 15 and 17 °C and reduced the levels of NoV GII to below 200 viral genome copies per g.

Norovirus levels in oysters from the main harvest area, Ireland, 9 February–15 March 2010

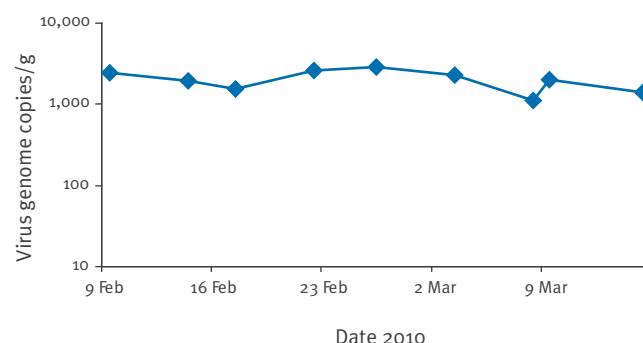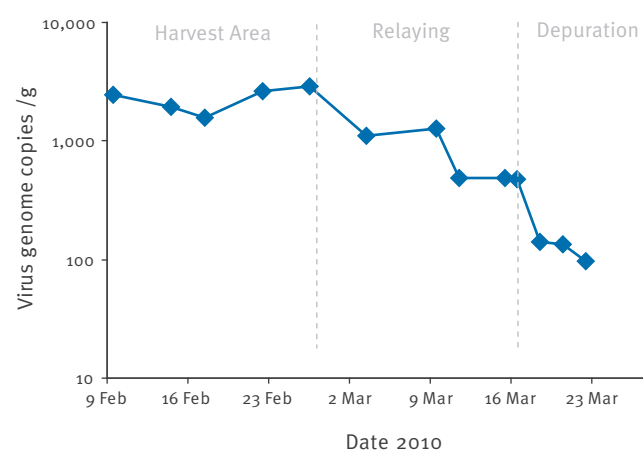Norovirus levels in oysters from the main harvest area during treatment by relaying and depuration, Ireland, 9 February–15 March 2010

Discussion

The oysters responsible for the outbreak described here originated from a category A classified water with *E. coli* levels consistently below 230 MPN (most probable number) per 100 g. Oysters from category A areas are approved for consumption without treatment. In practice, oysters from this harvest area were depurated at ambient temperature before sale. However it is well documented that depuration at low temperatures has little impact on reducing virus levels in shellfish [10,22]. The recent outbreaks of NoV infection associated with consumption of oysters from this harvesting site confirm the inadequacy of the current control measures and treatment processes to fully protect consumers in Europe.

Low levels of NoV are commonly detected in oysters, particularly during the winter months. A limited data set from 2009 suggests that NoV levels in oysters from the harvest area in question are also generally low. No reports of illness associated with this area were recorded during this period. In January and February 2010 however, the levels of NoV increased significantly, probably due to the seasonally high level of the virus in the human population and the particularly cold temperatures. This increase in NoV levels was clearly associated with outbreaks of NoV gastroenteritis in consumers. In response the competent authorities in Ireland closed the harvest area for direct sale of oysters and it remains closed at the time of publication of this report.

To facilitate the sale of oysters from the harvest area, treatment options were considered and validated by real-time PCR monitoring. Previous studies have demonstrated that NoV may persist following treatment such as relaying and depuration [10,22]. The data presented here demonstrate that relaying of oysters for 17 days in a clean seawater site followed by a minimum of four days purification at temperatures of 15-17°C reduced the NoV load to background levels detected in the harvest area before the gastroenteritis incidents. On this basis the risk to consumers was considered negligible, and while the main harvest area remained closed for direct sale, oysters treated in the described way since 26 February have been allowed on the market. Since 19 March 2010 more than 50,000 oysters have been placed on the market and no reports of illness have been received. NoV levels in these batches were less than 200 viral genome copies per g.

Limited data are available on the levels of NoV in oysters that have caused outbreaks. Recently two reports of large outbreaks have demonstrated high NoV levels (possibly >8,000 viral genome copies per g) in oysters from the harvest areas involved [9,23]. Although the NoV dose required to cause infection may be as low as 10 to 100 infectious particles [24] and sporadic cases may be caused by oysters with low NoV levels, the two reports and our results would suggest that relatively high levels of NoV (possibly >1000 viral genome copies per g) are required to cause significant outbreaks of illness. This may be consistent with a dose response pattern described in human volunteer studies investigating Norwalk virus (GGI.I) that indicated that 3.24×10^3 genome copies of NoV GGI.I were required before illness was observed [25]. In addition it has been suggested that PCR may overestimate the level of viable virus particles in shellfish and this should be taken into account when considering the risk associated with oyster consumption. There is growing evidence that it is possible to distinguish the relative risk of illness based on the level of NoV in the oysters. Given the current inadequacy of controls based on *E. coli* standards we believe that the introduction of an appropriate virus standard would have a positive public health benefit.

We believe that NoV monitoring of at-risk oyster harvesting areas and the introduction of an upper limit for NoV in oysters could prevent a significant number of outbreaks associated with oyster consumption in Europe. Validated treatment processes such as relaying and depuration at elevated temperatures can be used to produce oysters which are safe to consume despite the fact that low levels of NoV, as detected by real-time PCR, remain in the treated oysters.

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Adverse drug effects following oseltamivir mass treatment and prophylaxis in a school outbreak of 2009 pandemic influenza A(H1N1) in June 2009, Sheffield, United Kingdom

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During the containment phase of the 2009 influenza A(H1N1) pandemic, mass treatment and prophylaxis with oseltamivir was used to control an outbreak of pandemic influenza in a primary school in Sheffield, United Kingdom, where ten cases of pandemic influenza had been laboratory confirmed over a three day period in June 2009. A subsequent cross-sectional survey showed that 51 of 297 (17%) pupils and 10 of 58 (17%) reported an influenza-like illness. The most common symptoms were headache, cough, fever, tiredness, sore throat and nausea. Fifty-three staff and 273 pupils took oseltamivir for treatment or prophylaxis. Of this group, 41% (113/273) of pupils and 47% (25/53) of staff reported adverse effects. Overall, 14% (37/273) of pupils and 20% (11/53) of staff did not complete the course of oseltamivir, primarily due to adverse effects. Nausea, vomiting and rash were statistically significantly associated with failing to complete the course of oseltamivir. Given the potential for side effects from oseltamivir, particularly among those without influenza who receive the drug for prophylaxis, our findings have two important implications. Firstly, the benefits of mass treatment in an outbreak setting must clearly be greater than the benefits of targeted treatment. Secondly, any large scale regional or state level system for distribution of antiviral drugs for treatment should ideally include a robust quantification of an individual's probability of infection with influenza virus in order to avoid unnecessary treatment.

Introduction

An outbreak of 2009 pandemic influenza A(H1N1) occurred in a Sheffield junior school in June 2009, during the United Kingdom pandemic influenza containment phase. Over a three day period a seasonally unusual number of pupils and staff became unwell with influenza-like illness. Ten cases were laboratory confirmed as pandemic influenza and a decision was taken to close the school for one week and offer oseltamivir (unless contraindicated) to pupils and staff regardless of their being symptomatic or not.

As with any drug, oseltamivir is associated with adverse effects. In clinical trials including adults and adolescents with influenza, nausea and vomiting were statistically significantly more common in those who took the treatment dose of oseltamivir compared with those who took placebo (11% versus 7% for nausea alone, and 8% versus 3% for vomiting) [1]. Anecdotal evidence at the time of the outbreak described, suggested that the prevalence of adverse gastrointestinal effects could be somewhat higher than this, and subsequent studies in other outbreaks with pandemic influenza in England have confirmed this [2,3].

The prevalence and severity of adverse drug reactions, whether perceived or experienced, are important factors in patients' adherence to medication, and adherence is improved if the benefit of a drug is perceived to outweigh potential harm [4]. The balance between benefit and potential harm is particularly important where a drug is taken prophylactically for a disease that is considered to be mild. In such situations harm may easily outweigh benefit and lead to poor compliance. Poor compliance with prophylaxis in the context of a communicable disease outbreak is of public health concern if the drug is being used not only to protect the individual from disease, but also to reduce person-to-person transmission.

Our study aimed to determine the prevalence of adverse effects from treatment and from prophylaxis with oseltamivir, and whether these were associated with failure to complete the course of oseltamivir.

Methods

The school was closed at the end of the school day on Friday, 12 June and reopened on the morning of Monday, 22 June. Oseltamivir was offered to all staff and pupils at the school by local NHS Sheffield and Health Protection Agency staff. The medication was distributed at the school on the evening of 12 June, and the morning of 13 June. Those reporting fever plus two other influenza associated symptoms were considered clinical cases of influenza, and were prescribed an age appropriate treatment dose (60 mg for school pupils and 75 mg for adults) twice daily for five days. Laboratory confirmation was not routinely undertaken on the clinical cases reported during the mass treatment phase of the outbreak. Those who did not fit this case definition were prescribed the same dose as for treatment, but once daily for 10 days.

Questionnaire

We conducted a cross-sectional survey and approximately two weeks after the end of the outbreak, a questionnaire was distributed via the school to all pupils and staff to be filled in anonymously. The questionnaire asked for the following information: whether or not the respondents had been 'poorly with flu symptoms', which symptoms they had experienced, any past medical history, whether they had taken oseltamivir and how long they had taken it for, any adverse effects they had experienced, and if they had stopped taking oseltamivir, why had they done so. Finally, respondents were asked if there was anything else they would like to tell us (Figure 1).

Figure 1. Questionnaire on influenza-like illness and oseltamivir use, school outbreak of 2009 pandemic influenza A(H1N1), Sheffield, June 2009 (se attached questionnaire).

Statistical analysis

Data were analysed in R 2.9.1 [5]. For proportions we calculated 95% confidence intervals (CI) using the exact binomial method. Association between failure to complete the course of oseltamivir and the presence or absence of adverse effects was explored using multivariate logistic regression. We retained in the model

FIGURE 2

Epidemic curve of cases of influenza-like illness by onset date, school outbreak of 2009 pandemic influenza A(H1N1), Sheffield, June 2009
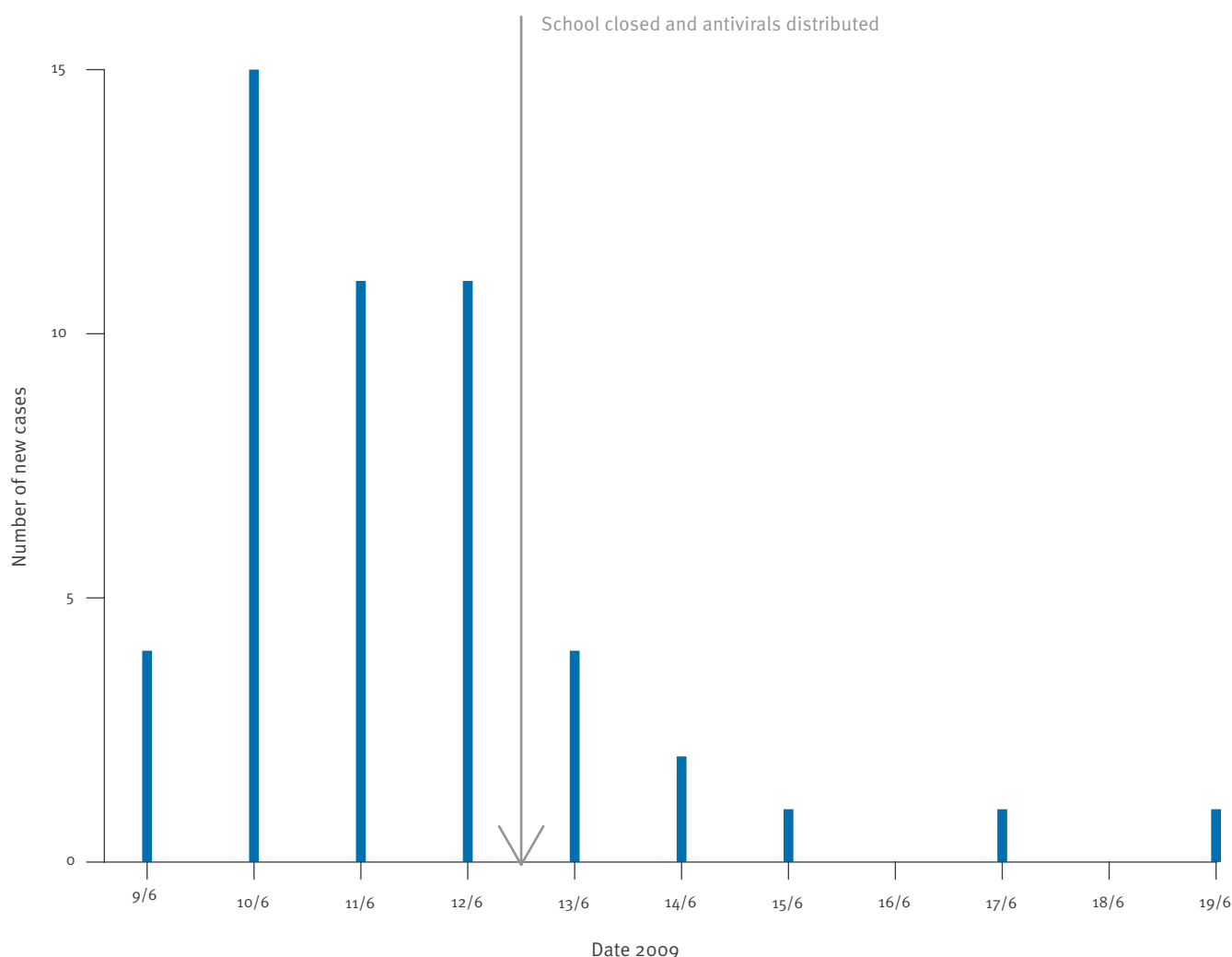
Symptomsa,b in people reporting influenza-like illness, school outbreak of 2009 pandemic influenza A(H1N1), Sheffield, June 2009 (n=61)

Symptom	n	%	95% CI
Headache	51	84	72–92
Cough	49	80	68–89
Tiredness	42	69	56–80
Fever	42	69	56–80
Sore throat	32	52	39–65
Nausea	31	51	38–64
Shivery	29	47	35–60
Runny nose	28	46	33–59
Aching	27	44	32–58
Abdominal pain	26	43	30–56
Dizziness	22	36	24–49
Leg ache	18	29	18–43
Vomiting	12	20	11–32
Breathing problems	8	13	6–24
Diarrhoea	8	13	6–24

CI: confidence interval.

a Symptoms reported in more than 10% of people are listed.

b More than one symptom may be listed per person.

Table 2

Adverse effects reported by >1% of people taking oseltamivir, school outbreak of 2009 pandemic influenza A(H1N1), Sheffield, June 2009 (n=326)

Adverse effect	n	%	95% CI
Nausea	86	26	22–32
Abdominal pain	64	20	15–24
Headache	38	12	8–16
Dizziness	28	9	6–12
Diarrhoea	25	8	5–11
Vomiting	22	7	4–10
Insomnia	19	6	3–9
Sore eyes	6	2	1–4

Table 3

Adverse effects reported by <1% of people taking oseltamivir, school outbreak of 2009 pandemic influenza A(H1N1), Sheffield, June 2009 (n=326)

Adverse effect	n
Rash	3
Nose bleed	2
Back ache	1
Itch	1
Blurred vision	1
Irritability	1
Mood swings	1
"Spaced out"	1
Anxiety	1
Frustration	1
Tearful	1

those adverse effect covariates that were significantly associated, at p<0.05 level, with failure to complete the course. For the included adverse effect covariates we present odds ratios (OR) as the measure of association, along with 95% CI.

We tested for a difference in the proportions of respondents with and without influenza-like illness reporting adverse effects using a chi-square test for homogeneity with a null hypothesis of no difference and a significance level of p<0.05. We tested for a difference in the proportions of respondents with and without influenza-like-illness who failed to complete the course of oseltamivir in the same way.

Results

The epidemic curve shows the number of new cases of influenza-like illness by day over the period of the outbreak from June 9 to June 19, 2009; fewer cases occurred with a reported onset date after the school closure compared with the time before (Figure 2).

The response rate to the questionnaire was 84% (58/69) among staff and 62% (297/476) among pupils. Pupils who responded were between seven and twelve years old with a mean age of 9.5 years. Staff were asked to indicate which 10-year age band they fell in and 64% (37/58) staff were aged between 40 and 59. Of the 341 respondents who indicated their sex, 45% (129/288) of pupils and 91% (48/53) of staff were female.

Influenza-like illness

Influenza-like illness was reported by 51 pupils (17%; 95% CI: 13-22%) and 10 staff (17%; 95% CI: 9-29%). Pupils who indicated that they were 'generally fit and well' in terms of their overall health were less likely to report that they had had influenza (OR=0.45; 95% CI: 0.22-0.98; p=0.038). In staff, no such association was seen.

Table 4

Reasons for not taking oseltamivir, school outbreak of 2009 pandemic influenza A(H1N1), Sheffield, June 2009 (n=29)

Reason	n
I didn't think it was needed	13
Contraindicated	3
I thought it would make me sick	2
I was worried about taking it	1
Worried about side effects	1
I don't like taking medicines	1
GP advised me not to take it	1
Already take other medication	1
Would take it only if sick with flu	1
In a different year to those affected	1
Doesn't stop flu, only reduces length of symptoms	1

GP: general practioner.

The most common symptoms reported by the 61 persons with influenza-like illness, were headache (84%; 95% CI: 72-92), cough (80%; 95% CI: 68-89), fever (69%; 95% CI: 56-80), tiredness (69%; 95% CI: 56-80), sore throat (52%; 95% CI: 39-65) and nausea (51%; 95% CI: 38-64) (Table 1).

Uptake, adverse effects and adherence to oseltamivir

Fifty-three staff (91%; 95% CI: 81-97) and 273 pupils (92%; 95% CI: 88-95) took up the offer of taking oseltamivir.

Adverse effects were reported by 113 pupils (41%; 95% CI: 35-47) and 25 staff (47%; 95% CI: 33-61). The most commonly reported adverse effects, mentioned by over 10% of the sample were nausea (26%; 95% CI: 22-32), abdominal pain (20%; 95% CI: 15-24), and headache (12%; 95% CI: 8-16) (Table 2). While the majority of adverse effects were physical in nature, two respondents, one staff and one pupil, reported a number of symptoms related to disturbed mood and 19 reported insomnia. There were no life-threatening adverse effects reported (Table 3).

Among those with influenza-like illness, 46% (95% CI: 31-61) of pupils and 56% (95% CI: 21-86) of staff reported adverse effects. In those who were well, 40% (95% CI: 34-47) of pupils and 45% (95% CI: 30-61) of staff reported adverse effects. There was no significant difference in the proportion reporting adverse effects between those with influenza-like illness and those without (chi-square=0.26, df=1, p=0.6), or between pupils and staff (chi-square=0.33, df=1, p=0.57).

Thirty-seven pupils (14%; 95% CI: 10-18) and 11 staff (20%; 95% CI: 11-34) did not complete the full course of oseltamivir. The most common reasons given were 'it made me feel ill' (50%; 95% CI: 35-65), 'I didn't think it would help' (17%; 95% CI: 7-30) and 'I forgot to take it' (15%; 95% CI: 6-28). In a logistic regression model, stopping oseltamivir was significantly associated with the presence of nausea (OR=2.4; 95% CI: 1.2-4.9; p=0.013), vomiting (OR=3.5; 95% CI: 1.3-9.3; p=0.014) and rash (OR=13.0; 95% CI: 1.1-299.3; p=0.046). There was no significant difference in the proportion between those with influenza-like illness and those without (chi-square=0.062; df=1; p=0.8), or between pupils and staff (chi-square=0.58; df=1; p=0.45).

Among those with influenza symptoms who did not complete a full course of oseltamivir the median number of days taking the drug was three (interquartile range (IQR) 3-4.5). Among those without influenza-like illness who did not complete a full course of oseltamivir the median number of days taking the drug was seven (IQR 5-8).

Reasons for choosing not to take oseltamivir

Twenty-four pupils (8%; 95% CI: 5-12) and five staff (9%; 95% CI: 3-19) chose not to take any oseltamivir. The most common reason given was 'I didn't think it was needed' (45%; 95% CI: 26-64%) (Table 4).

Discussion and conclusion

In a primary school outbreak of 2009 pandemic influenza A(H1N1), 41% of pupils and 47% of staff who took oseltamivir for either treatment or prophylaxis reported adverse effects. Overall, 48 of 355 (15%) pupils and staff stopped taking oseltamivir, primarily due to adverse effects. Nausea, vomiting and rash

TABLE 5

Prevalence of adverse effects in people taking oseltamivir prophylactically

People affected	Adverse effect	Prevalence (%)				
		Product characteristics[a]		South West England school study[b,c] n=247	London schools study[d,e] n=85	Sheffield study[f,g] n=326
		Oseltamivir	Placebo	Oseltamivir	Oseltamivir	Oseltamivir
Children aged up to 12 years	Nausea	14	–	33	29	23
	Abdominal pain	1	–	21	16	20
	Diarrhoea	1	–	7	0	6
	Vomiting	10	–	11	13	7
Adults and adolescents	Nausea	10	4	–	30	31
	Abdominal pain	2	2	–	22	8
	Vomiting	2	1	–	4	6
	Insomnia	1	1	–	15	6

[a] Source: [1].
[b] Source [2].
[c] Pupils were aged 11–12 years (school year 7).
[d] Source [3].
[e] Prevalence among pupils from both secondary schools included under Adults and adolescents.
[f] Source: this study (school outbreak of 2009 pandemic influenza A(H1N1), Sheffield, June 2009).
[g] Prevalence among staff included under Adults and adolescents.

were statistically significantly associated with failing to complete the course of oseltamivir.

We were able to distribute our questionnaire to an entire school population who had been offered oseltamivir irrespective of symptoms, and our response rate was high among staff (84%), and moderately high among pupils (62%). We received a considerable number of positive comments regarding the handling of the outbreak in response to the open question 'anything else you would like to tell us'. This suggests that there was general support for our intervention in the school. However, as with any study that does not have a 100% response rate, we cannot fully exclude that those who did not respond may have been systematically different from those who did. In particular, we might expect those who had experienced drug-associated adverse effects to be more likely to participate than those who had not, introducing a bias in our findings. Moreover, one difficulty with our questionnaire (and with this type of observational study in general) is in determining whether symptoms in those who reported influenza-like illness were a result of the oseltamivir used to treat the illness, or the disease itself. Furthermore, we did not ask about the severity of any influenza-like symptoms or adverse effects experienced, and to some extent this is a limitation of our study as we are unable to test for a relationship between oseltamivir dose (expressed, ideally, as dose per unit of child's weight) and the severity of the adverse effect. We were, however, able to determine through our contact with local paediatric services that there had been no reports of any life threatening or serious adverse effects associated with oseltamivir use in our cohort.

Due to the difficulties of obtaining accurate retrospective information from junior school aged children we do not know the degree to which our results may have been biased. We tried to reduce any such bias by asking parents to assist their children in filling the questionnaire, but we are aware that obtaining accurate information can be a problem in retrospective questionnaire studies, irrespective of the age of the respondents. In order to maximise the accuracy of the recall of symptoms and adverse effects we conducted our study as soon as possible following the reopening of the school.

Our study in the context of previous studies
Two studies similar to ours have been published recently in the United Kingdom, one following an outbreak of 2009 pandemic influenza in a school in South West England [2], and the other following outbreaks in three London schools [3]. The South West study reported adverse effects associated with oseltamivir and compliance with prophylaxis in 11-12 year old pupils in a single school year, whereas the London study involved pupils from one primary school (4- to 11-year-olds), and two secondary schools (11- to 14-year-olds).

The findings of our study are broadly consistent with those found in the two studies. Adverse effects were reported by 51% of 247 pupils in the South West, and 53% of 85 pupils in London, compared with 41% in our study. The majority of children in the previous studies were of secondary school age, and therefore older than our cohort. It is possible that older children are more likely to either experience, or report experiencing adverse effects following the use of oseltamivir. Interestingly, a trend in our study showed that a greater proportion of adults reported adverse effects than children, although this difference was not statistically significant.

The prevalence of adverse effects associated with a drug is reported in its Summary of Product Characteristics (SPC). The SPC for oseltamivir draws on adverse event data from treatment and prophylaxis trials and from post marketing surveillance [1]. Table 5 shows the comparative prevalence of adverse reactions (for those reactions reported in all studies) between the SPC and the school based studies amongst those taking oseltamivir for prophylaxis.

The school based studies fairly consistently report a higher prevalence of adverse effects than the trials that informed the SPC. This may be due to the inevitable differences in methods for eliciting adverse event information between highly structured and regulated clinical trials and more informal questionnaire surveys. It is possible that the presence of 'tick box' options for reporting a number of specific adverse reactions may have encouraged over reporting in our survey and also could have favoured symptoms and adverse effects listed over those not listed. Moreover, the anxiety generated by the arrival of a pandemic may have led to a greater attention towards adverse effects.

Reported adherence to oseltamivir for prophylaxis varied between the three school studies, with 66% of pupils in the London schools completing the full ten day course compared with 80% in the South West. Of the 271 asymptomatic pupils in our study 230 (85%) completed the full ten day course. It could be that older children are less likely to complete a course of medication, although we did not find this age effect within our data.

Conclusion
In our study, conducted in the context of a school outbreak of 2009 pandemic influenza, mass treatment and prophylaxis with oseltamivir was associated with adverse effects in a considerable proportion of pupils and staff. Despite this, adherence to the antiviral medication regime was generally good. Given the potential for side effects from oseltamivir, particularly among those without influenza who receive the drug for prophylaxis, our findings have two important implications. Firstly, the benefits of mass treatment in an outbreak setting must clearly be greater than the benefits of targeted treatment. Secondly, any large scale regional or state level system for distribution of antiviral drugs for treatment should ideally include a robust quantification of an individual's probability of infection with influenza virus in order to avoid unnecessary treatment.

Acknowledgements

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Spectinomycin in the treatment of gonorrhoea

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To the editor: We have read with interest the recent paper by Kubanova *et al.* in which they recommend the use of spectinomycin in case of difficulty to access ceftriaxone or in the presence of severe beta-lactam antimicrobial allergy [1]. Although we agree with most of the conclusions we would like to warn about the potential risks in cases of pharyngeal gonorrhoea. Spectinomycin is an aminoglycoside with poor saliva excretion. Probably due to changes in sexual behaviours the number of pharyngeal carriers of Neisseria gonorrhoeae is not anecdotal - papers report figures between 6% to 14% [2]. Moreover oral sex as only risk factor for urethral gonorrhoea is high ranging from 10% to 58% [2]. Lack of effective eradication of Neisseria gonorrhoeae from the pharynx with spectinomycin has been previously reported [3]. The Centers for Disease Control and Prevention (CDC) recommendations state that spectinomycin is useful for the treatment of patients who cannot tolerate cephalosporins and quinolones [4]. However, in the same guideline they recommended the use of a single dose of cefriaxone, 125 mg intramuscularly, or 500 mg of oral ciprofloxacin (except for cases where high quinolone resistance is suspected) for pharynx eradication since spectinomycin is unreliable against pharyngeal infections. When spectinomycin is used, a pharyngeal negative culture three to five days after treatment should be the result [4]. In contrast, a single dose of two grammes of oral azithromycin would be considered an effective choice to cure non-complicated gonorrhoea from cervix, urethra and rectum and to eradicate the bacteria from the pharynx [5].

In conclusion we would point out that the use of a single dose of spectinomycin, though effective in the treatment of uncomplicated gonococcal infections from the cervix, urethra, and rectum, is less effective in the eradication of gonococci from the pharynx, thus allowing an important route for transmission of disease.

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Authors' Reply: The Russian gonococcal antimicrobial susceptibility programme (RU-GASP)--national resistance prevalence in 2007 and 2008, and trends during 2005-2008

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To the editor: We are grateful to Gil-Setas *et al.* for their comments on our paper [1]. In their letter "Spectinomycin in the treatment of gonorrhoea", they further clarify and emphasise the importance of, if possible, avoiding spectinomycin in the treatment of pharyngeal gonorrhoea, which is an important comment. Spectinomycin is an effective injectable antimicrobial [2] and is useful for treatment of patients with uncomplicated anogenital gonorrhoea who, for example, cannot tolerate extended-spectrum cephalosporins or if extended-spectrum cephalosporins are not available. Fluoroquinolones have also been used in the past, but currently these are of limited importance for empirical treatment in most settings worldwide due to a high level of resistance [3]. However, it has been known for decades that spectinomycin is suboptimal (with sometimes as low as approximately 50% effectiveness) for treatment of pharyngeal infections, due to the pharmacokinetic properties of spectinomycin [2,4–7]. This lower efficacy in eradicating Neisseria gonorrhoeae from the pharynx, compared with eradication of the bacteria in anogenital infection, is also a problem for several other antimicrobials [2,3,7], and it would be valuable to assess this issue in additional studies. In fact, among the antimicrobials available for treatment of uncomplicated gonococcal, including pharyngeal, infections, extended-spectrum cephalosporins and fluoroquinolones seem to have the best balance of proven efficacy and safety for wild-type, susceptible gonococci. However, as mentioned above fluoroquinolones are not recommended for use in most settings due to the high level of resistance [2,7].

It is important to note that pharyngeal gonococcal infection, solely or combined with anogenital infection, is not extremely rare and prevalence may have increased over time, perhaps due to changes in sexual behaviours [8]. Accordingly, some patients treated for anogenital gonorrhoea may also have a coincident pharyngeal infection, which must also be treated. If spectinomycin is the only option for empirical treatment – due to unavailability of ceftriaxone and a high level of resistance to fluoroquinolones, or severe allergy to beta-lactam antimicrobials [rare cases] and in vitro resistance to all other treatment options – it is recommended that all patients with suspected (after a risk assessment has been performed) or confirmed pharyngeal infection have a pharyngeal culture taken approximately 3–5 days after treatment, i.e., as a test-of-cure to verify effective eradication of the gonococci.

Obviously, we totally agree with the warning of Gil-Setas *et al.* about the potential risks of using spectinomycin for treatment of pharyngeal gonorrhoea. Nevertheless, the recommendations for first-line empirical treatment described in our paper [1] are mainly for uncomplicated gonococcal infections of the urethra, cervix, and rectum (anogenital gonorrhoea) in adults and adolescents. In this type of paper, due to the limit in word count, it is not possible to separate all indications for treatment and discuss the pros and cons of each treatment (including the pharmacokinetic properties of the drugs) as described in different treatment guidelines. In addition to pharyngeal gonorrhoea, the indications also include other extra-genital gonococcal infections, different types of complications and sequelae, disseminated gonococcal infection (DGI), etc. All treatment indications related to gonorrhoea and their treatment options are thoroughly described in the Russian treatment guidelines. As in other guidelines, such as those published by the United States Centers for Disease Control and Prevention (CDC) [5,6] and the International Union against Sexually Transmitted Infections (IUSTI) [9], the Russian treatment guidelines do not recommend spectinomycin for treatment of pharyngeal gonorrhoea if other effective antimicrobials are available.

Regarding the use of azithromycin (single oral dose of 2 g) for treatment of anogenital as well as pharyngeal gonorrhoea, this is effective for wild-type, susceptible gonococci. However, using the azithromycin formula presently available in most countries, substantial gastrointestinal side effects may occur and this treatment option can rapidly select for resistance. Increasing resistance to azithromycin, including high-level resistance, has been identified in many countries [3]. Accordingly, this treatment option should not be widely recommended, i.e. if it is not used in a strictly controlled manner and the in vitro susceptibility to azithromycin has been determined before treatment.

One additional important comment is that although resistance to spectinomycin has remained rare in most countries, rapid selection of resistance was reported as early as the 1980s [10]. Accordingly, if spectinomycin is used for treatment of gonorrhoea, it has to be used in a strictly controlled manner and effective monitoring of its quality, use, as well as emergence and spread of resistance is essential.

In conclusion, the gonococci have developed resistance to almost all antimicrobials used in the treatment of gonorrhoea. At present, the first-line treatment in most countries is extended-spectrum cephalosporins such as cefixime (oral) and ceftriaxone (injectable). However, the susceptibility to all extended-spectrum cephalosporins is decreasing and treatment failures using oral ones have been identified in several settings [3]. If clinical resistance emerges also to ceftriaxone, gonorrhoea may become untreatable in certain circumstances. Accordingly, treatment options have to be available for these emergent situations, and having access to antimicrobials such as spectinomycin, which at present is not available in many countries, would be extremely valuable.

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