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Review Article

Antivirals in the 2009 pandemic – lessons and implications for future strategies

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The World Health Organization's declaration of an imminent swine-origin influenza A pandemic in April 2009 triggered the global launch of national pandemic preparedness plans. An integral component of pandemic preparedness in many countries was the targeted use of antiviral therapy for containment, disease mitigation, and treatment. The 2009 pandemic marked the first pandemic during which influenza antivirals were available for global use. Although most national pandemic plans included provisions for antiviral treatment, these pre-determined protocols required frequent updating as more information became available about the virus, and its susceptibility to antiviral agents, the epidemiology of infection, and the population groups that were most susceptible to severe disease. National public health agencies in countries with both plans for use of antivirals and pre-existing stockpiles, including those in Japan, the United Kingdom, and the United States, operated distinctly different antiviral distribution and treatment programs from one another. In the 3 years following the pandemic, there is still little comparison of the diversity of national antiviral treatment policies and drug distribution mechanisms that were implemented, whether they had any mitigating effects and which might be most efficient. The purpose of this study is to outline roles of antiviral medicines in a pandemic period, provide insights into the diversity of antiviral treatment and distribution policies applied by selected countries between April 2009–July 2010, and to stimulate discussion on whether these policies remain appropriate for implementation in future pandemics.

Keywords 2009 Pandemic, antivirals, influenza.

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Pre-pandemic preparedness

WHO guidance on antiviral policy

In 2005, the World Health Organization issued a checklist to guide the development of national influenza pandemic preparedness plans. With reference to antiviral prophylaxis and treatment protocols, the document called for modeling estimates to predict the effect of potential interventions with antiviral medication and/or pandemic strain influenza vaccine in various (risk) groups. The document also highlighted the need for surveillance systems that would monitor sales/uptake of antiviral drugs for influenza A viral infection.[1]

The WHO issued a further guidance document in 2007 outlining a "rapid containment strategy," to stop the development of pandemic influenza at the time when it is initially detected to prevent or slow the spread of the virus.

The plan was based largely on early mathematical modeling studies, which suggested the possibility of containing an initial pandemic if the initial outbreak was localized through the administration of antiviral prophylaxis, effective use of quarantine, and other non-pharmaceutical measures within the first 3 weeks. Although the plan was proposed in anticipation of a severe H5N1-like pandemic, the guidance cited clinical severity as an unimportant consideration for initiating a containment response, as early cases could be "mild" and later cases "severe." The WHO document acknowledged the "demanding" assumptions of the models, including the emergence of the virus in a geographically demarcated area, rapid detection of confirmed and potential cases, and notably, timely deployment and administration of antiviral drugs to eighty percent of the Containment Zone population within 3 weeks of initial cluster detection.[2]

National antiviral stockpiles

In early 2004, growing awareness of the potential for emergence of an H5N1 pandemic triggered a surge in pandemic preparedness activities. During this period, several guidance documents were published, primarily from the WHO, advising national governments to consider stockpiling antiviral medicines.[3] Oseltamivir became the primary choice

of stockpiled drug partly as a result of availability, concerns about antiviral resistance to the adamantanes, and lack of orally bioavailable alternatives. The subsequent purchasing agreements between national government agencies and pharmaceutical companies were calculated on the basis of modeling estimates of worst-case attack rates, desired population coverage, and affordability. By 2008, the United States, Japan, and the United Kingdom had each procured a national antiviral stockpile covering 25, 45, and 50 percent of each country's population, respectively. In April of 2009, uncertainty over the severity of the pandemic prompted the UK to augment its stockpile with 18 million additional antiviral courses. This additional investment diversified the stockpile to include more doses of zanamivir, brought the total stockpile coverage to 80 percent of the British population, and reinforced the role antivirals could play in reducing the impact of a potentially devastating pandemic.[4]

Pandemic response

The pandemic begins

When the WHO declared the imminent threat of a A(H1N1) pdm2009 pandemic on April 24, 2009, pandemic response plans across the globe were rapidly put into action. The majority of these plans had been drawn up using a severe pandemic scenario, characterized by high illness attack rates and case fatality ratios. In the absence of confirmed data describing the virulence of the new virus and in the presence of alarming reports emerging from Mexico, the initial phases of global pandemic response were marked by a succession of guidance documents, updated, and re-published with new details. Without a pandemic vaccine or other preventive measures, it was clear that antivirals were the first specific line of defense in combatting the novel virus.

The role of antivirals

The 2009 pandemic marked the first pandemic for which antivirals were globally available. The licensure and entry of neuraminidase inhibitors (NAIs) into the marketplace in 1999 were largely based on modest reductions in symptom severity and duration of uncomplicated seasonal influenza illness in healthy adults. In the decade between their introduction and the onset of the 2009 pandemic, a prominent role for NAIs in the prevention or mitigation of seasonal influenza had not been firmly established in global clinical practice and lacked uptake in diverse healthcare systems, although some countries relied heavily on antivirals as part of seasonal influenza control policies, for example, Japan. When the pandemic began, the paucity of frontline clinical experience and dearth of observational data about antiviral efficacy on important public health outcomes such as hospitalization and mortality led to controversy over their utility within segments of the medical community. Early during the pandemic, questions arose regarding the specific function of antivirals – did they prevent viral transmission? Were they for treatment purposes only? Was post-exposure prophylaxis more effective than early treatment? As the pandemic evolved, and its impact on susceptible segments of the population became more visible, widespread recognition of need for antiviral intervention prompted their use for three distinct purposes: pre-exposure prophylaxis, post-exposure prophylaxis, and treatment for confirmed and suspect cases. Unsurprisingly, categories of use were proportionately different between countries and in different settings.

National treatment policies and distribution mechanisms – Japan, England, and The United States

Significant scrutiny has been directed toward evaluating the clinical efficacy of antivirals in treating patients with confirmed influenza, but very little has been carried out to evaluate the systems or arrangements used to deliver antivirals in the community in different countries. It has been repeatedly established that the maximal efficacy of antiviral medicines is achieved when administered early (although benefit has also been established beyond the 48-hours period in severe illness); therefore, it is important to understand how selected countries fared in accomplishing the goal of delivering early treatment to gain insights and apply lessons learnt for future pandemics. Here, we describe key aspects and novel features of the antiviral use policies implemented in Japan, England, and the United States. These three countries have been chosen as case studies for several reasons (i) availability of antiviral surveillance and usage data, (ii) diverse antiviral use policies, and (iii) presence of pre-existing stockpiles.

Japan

Japan is the world's largest consumer of neuraminidase inhibitors and one of the few countries where antivirals have been routinely used for the treatment for seasonal influenza.[5] The implementation of a universal antiviral use policy in Japan dates back to 1999 when NAIs were first introduced onto the market. Japanese clinicians have routinely performed rapid diagnostic tests (RDTs) on patients with influenza-like illness and recommended NAIs for all positive results, including otherwise healthy individuals who are not in a risk group category. The costs associated with RDTs and NAI treatments are largely covered by public health insurance systems in Japan, leaving patients responsible for approximately 10–50% of NAI treatment cost.[6]

When the pandemic was declared in April 2009, clinical experience with an emphasis on early treatment with AVs for all persons was already well established in Japan. After pregnant women were placed into a higher risk category, the Japanese Society of Obstetrics and Gynecology (JSOG) launched an aggressive outreach campaign to minimize the

number and impact of A(H1N1)pdm2009 cases amongst pregnant women. The JSOG recommended (i) prompt use of antiviral drugs for treatment for pregnant women on May 8 via their website; (ii) an early visit to the general practitioner when pregnant women developed fever on June 16; (iii) active use of antiviral drugs for prophylaxis after close contact with an infected person on August 4; and (iv) vaccination against the pandemic A(H1N1)pdm2009 strain on September 7. Retrospective analysis of antiviral drug use amongst hospitalized pregnant women with confirmed cases of A(H1N1)pdm2009 virus in Japan shows that 96·6% (n = 118) were treated with either oseltamivir or zanamivir and 89% (n = 118) were treated early (within 48 hours after symptom onset).[7,8] 17 women (9·7%, n = 118) developed viral pneumonitis; however, all 118 cases fully recovered from the original infection, and no fatalities amongst pregnant women were reported. Successful treatment and recovery rates were also documented within Japan's pediatric population. Children 15 years of age and younger accounted for 59% (n = 128 million) of Japan's A(H1N1)pdm2009 cases, of which 38 deaths were reported. A study documenting 1000 hospitalized children reported the use of AVs to treat 98·4% (n = 1000) of patients and early receipt in 88·9% (n = 1000) of cases. Of this cohort, only one patient died of A(H1N1)pdm2009 infection.[9]

It has been suggested that Japan's universal implementation of antivirals since 2000 and the emphasis on early use of antivirals were primarily responsible for the lower mortality burden and the absence of mortality amongst A(H1N1)pdm2009-infected pregnant women in Japan.[6–8] Japan's pandemic response was an extension of an already well-established mechanism to administer antiviral treatment for seasonal influenza. An emphasis on early treatment and rapid delivery in the outpatient setting if replicated in other countries would help to facilitate distribution and uptake of antiviral drugs amongst those at highest risk of severe infection.

England

In contrast to the liberal Japanese policy, from the time of their first licensure, NAI antivirals were unavailable in the United Kingdom for use in the treatment of seasonal influenza, unless influenza activity exceeded a set level in the community. Over a decade later, these guidelines have now been revised to afford General Practitioners (GPs) more flexibility with antiviral prescribing, but as a result of these guidelines, there was relatively little experience of using antivirals in community practice over a 10-year period.[10] The pre-pandemic guidelines outlined by the National Institute for Clinical Excellence, authorized by the UK Department of Health, in conjunction with the Health Protection Agency (HPA) and Royal College of General Practitioners (RCGP), issued guidance to physicians regarding points at which they could begin prescribing antivirals to patients with "relevant illness." Initially, this trigger system was controlled by the RCGP sentinel surveillance system, which triggered an alert once a threshold of 30 GP consultations for influenza-like illness (ILI) per 100 000 population was observed within a 1-week period.[11]

When the first pandemic cases emerged in Scotland on April 27, 2009, NICE guidelines were replaced as a pandemic response was activated. England's initial response was a containment strategy, which attempted to delay the spread of the novel virus, to minimize the impact prior to availability of vaccine. Containment activities included identifying and treating all cases with antivirals and widespread tracing of all contacts (both household and community based) to offer antiviral chemoprophylaxis, as well as school closures and the provision of antivirals to student cases and their contacts. To facilitate distribution of antivirals and remove bottlenecks in access to treatment, by mid-May, geographically distributed Flu Response Centers (FRCs) were established in England to support the containment efforts which had initially been undertaken by the HPA's local Health Protection Units. Despite this added capacity for access to antivirals in the community, increasing case numbers led to the abandonment of containment policy and the initiation of a "treatment-only" phase on July 2. Also called the "mitigation" phase, the treatment-only period enforced the offering of antivirals to all suspected cases of influenza without the need for laboratory confirmation.[12]

On July 23, 2009, the FRC centers were closed, and a telephone and internet-based system, the National Pandemic Flu Service (NPFS), were launched to authorize access to antivirals without a medical consultation. Symptomatic individuals were instructed to access the NPFS website or phone the telephone line where they were then taken through a series of clinical questions to determine whether antiviral treatment was appropriate and assess whether a medical General Practitioner (GP) consultation was necessary as NPFS staff were not medically trained. Individuals who were authorized AVs were instructed to have a non-infected friend or family member (termed "flu friend") collect their medicines from an Antiviral Collection Point.[13] The major goals of the NPFS were to ensure universal availability and rapid delivery of antiviral medicines to suspected cases of A(H1N1)pdm2009 in the community and to alleviate pressure from GPs. The NPFS was the first mass antiviral distribution mechanism to have been implemented during the pandemic and one of the few instances since licensure of the NAI drugs where antivirals were available without a prescription, and without access to a healthcare worker assessment. Antiviral medicines were also available over the counter in New Zealand for a period from 2007 to 2011. Although this was not a long-term health system delivery mechanism in that country, no significant changes in antiviral resistance devel-

opment were reported during its employment. Additionally, consumer stockpiling (a commonly cited fear of Over-The-Counter antiviral availability) was not reported at any point during the 4-year period which included the A (H1N1)pdm2009 pandemic from 2009 to 2010.[14]

Despite the widespread availability of antiviral drugs in the UK, the early receipt of NAIs amongst high-risk groups was extremely low. A recent study examining the clinical course of pregnant women with laboratory-confirmed A(H1N1) pdm2009 infection in the UK indicated that while 84% received antiviral medication, only 9·8% (n = 82) received their medications prior to hospital admission.[15] A retrospective study describing the epidemiology of the UK's pandemic experience reports the overrepresentation of pregnant women amongst fatal cases when compared to the general population.[16] Additional insights can also be gained from retrospective analyses of England's significant A(H1N1) pdm2009 burden during the 2010–2011 winter season, which was largely attributed to a change in the age distribution of infection and a greater number of patients with underlying health conditions.[17] After the NPFS was dismantled on February 2010, antiviral prescribing policy returned to pre-pandemic protocols with some modifications, limiting accessibility to antiviral medications within the community. The historic trend of pandemic waves, notably the possibility of more severe subsequent waves, should be an important consideration when determining the duration of novel community treatment mechanisms and the time point at which reversion to pre-pandemic procedures is enacted.

Although the NPFS was not entirely effective in delivering antivirals amongst high-risk groups or ensuring delivery within 48 hours, the system's surveillance value was reported in a recent study analyzing antiviral susceptibility within the NPFS community cohort. With the launch of the NPFS, a virological self-sampling scheme was also deployed in which 200–400 patient recipients were enrolled on a daily basis. The sampling scheme was used to monitor the emergence of antiviral resistance and a means of documenting antiviral efficacy. Reported results found oseltamivir-resistant virus (containing the Tyrosine-275 substitution) in a total of 5 patients (n = 1312) and significantly lower virus isolation rates in samples taken post-AV treatment initiation compared with those taken prior to AV use.[18] This added surveillance value demonstrates the utility of a community treatment scheme during a pandemic period but does not reduce the need to enhance its efficacy in delivering antivirals to high-risk populations.

The United States

Since the licensure of the adamantanes (amantadine and rimantadine), oseltamivir, and zanamivir in the United States, these medicines were used sparingly to treat cases of influenza when compared to countries with more liberal policies, for example, Japan.[19] In 2005, the Advisory Committee on Immunization Practices (ACIP) issued detailed information on all four antiviral medicines as well as recommendations on their use. The recommendations emphasized the efficacy of antivirals when administered within 48 hours of symptom onset, using data from the registrational studies conducted in the outpatient setting. Clinicians consequently became focused on the concept of treatment within 48 hours and may have missed opportunities to provide treatment to those who would have benefitted beyond the 48-hours period, as indicated by recent studies in severely ill patients during the pandemic.[20] It was not until March 2009 that the Infectious Disease Society of America published guidelines recommending antiviral treatment for hospitalized patients with laboratory-confirmed influenza, including those who had passed the 48-hours time period as illness onset.[21]

A recent study examining population-based, outpatient usage rates of influenza antiviral medications from January 2000 through June 2010 revealed useful insights into how US clinicians modified their prescribing practices during the pandemic as treatment guidelines rapidly evolved. Results indicated that dispensing rates were consistent with changes in the national treatment guidelines published by the Centers for Disease Control and Prevention (CDC). CDC reports of adamantane resistance in 2006 led to the rapid rise of oseltamivir use until CDC reported resistance to oseltamivir amongst 98% of A(H1N1)pdm2009 virus strains in 2008, which in turn led to increased use of zanamivir and combination therapies using oseltamivir and an adamantane. With the emergence of the pandemic, antiviral use rapidly increased, specifically oseltamivir, after it was established as the primary agent of antiviral intervention.[22]

Although several guidelines were successfully translated into clinical practice during the pandemic, increased dispensing rates did not ensure early treatment in individuals at high-risk of severe illness. A study analyzing the receipt of antiviral medicines amongst pregnant women in the United States indicated 86·6% (n = 588) received antiviral treatment, but only 43% received treatment early (<48 hours after illness onset). Of the pregnant women who were admitted to the ICU, only 15·9% received treatment within 2 days of illness onset and 18·3% in 3–4 days after illness onset. There was a clear progression in median time between illness onset and antiviral receipt in hospitalized patients (2 days), patients in the ICU (5 days), and patients who died (6 days).[23]

Recent reports have cited a significant decline in antiviral use in hospitalized patients in the year following the pandemic. A recent study demonstrated a 27% decline in hospitalized children receiving antiviral treatment during the 2010–2011 influenza season when compared to the pandemic period. Approximately 25% of all children with severe illness

admitted to the ICU did not receive antiviral treatment. Of this cohort, children <2 years of age represented the age group with the largest decline in antiviral treatment during the 2010–2011 season. The authors attributed this decline to the lack of licensure for oseltamivir in children less than 1 year old, although dosing guidelines for this age group were available through the American Academy of Pediatrics (AAP) and the Advisory Committee on Immunization Practices (ACIP) at the time.[24] Subsequent safety and pharmacokinetic studies facilitated the FDA approval of oseltamivir treatment for infants aged two weeks and older.[25]

Containment

In 2005, Ferguson *et al.* used estimates based on an H5N1-type pandemic to suggest that the targeted, geographical use of antiviral prophylaxis at the source of a pandemic could contain the virus and inhibit its spread. It was also emphasized that if the pandemic were to become global, then a containment approach would be impractical.[26] Despite the global spread of the A(H1N1)pdm2009 virus, containment policies were still implemented by several national public health agencies. In England, containment was defined as measures taken in attempt to slow the spread of the pandemic.[12] Contact tracing and the distribution of antiviral drugs for treatment of cases and chemoprophylaxis of contacts were key components of the containment strategy. Local public health units in England and the United States were tasked with mobilizing the containment phase and became rapidly overwhelmed by the burden of implementation. A published report of a local Health Protection Unit's experience in England concluded that during the containment phase, the median estimate for the earliest point cases could have received antiviral treatment was 2 days (95% CI 2–3 days) and the earliest point contacts of cases could have received prophylaxis was 4 days (95% CI 4–5 days).[27] Because the success of containment is dependent upon the speed at which primary cases are identified and antiviral medications are delivered, the delays evidenced by this data further confirmed the difficulty of the containment attempt during the 2009 pandemic in a publically funded, centrally managed healthcare system.

In contrast to larger, population-dense areas, the targeted application of containment effectively controlled viral spread in smaller, closed communities where rapid contact tracing and antiviral administration were feasible. An analysis of a containment approach using oseltamivir for ring prophylaxis on a military base in Singapore reported a significant reduction in the overall reproductive number (the number of new cases attributable to the index case), from 1·91 (95% credible interval, 1·50–2·36) before the intervention to 0·11 (95% credible interval, 0·05–0·20) after the intervention.[28] It has also been clearly documented that the targeted use of antivirals for treatment and prophylaxis within households can reduce the rate of viral transmission.[29] Despite these limited scenarios of success, the population effect of containment has proven to be negligible. The health system burden of delivery of a containment policy in an already global pandemic, as was seen in 2009, rapidly overwhelmed local public health systems in the very early stages and could have potentially become a hindrance to response activities. In its most recent pandemic preparedness guidelines, published in 2011, The UK Department of Health clearly describes a containment approach as "not possible" and instills the expectation that any future pandemic virus will spread regardless of containment activities.[30] The experience of application of a containment strategy during the 2009 pandemic suggests that future planning for pandemic response capabilities will focus on delivering a more refined assessment of severity early during the pandemic course, with the intention of focusing antiviral resources and control measures on maximal mitigation for risk groups and vulnerable segments of the population.

Emerging AV Resistance

The role of antiviral resistance in shaping policy decisions was established early in the pandemic. The rapid identification of A(H1N1)pdm2009 resistance to the adamantanes excluded the M2-inhibitors from the antiviral arsenal. When NAIs became the standard treatment, concerns over AV resistance influenced policy decisions in some countries, specifically the choice to adopt a "treat all" or "treat high-risk only" approach. When reports of oseltamivir resistance began to emerge, primarily in immunocompromised patients, there was heightened scrutiny regarding the source of resistant virus and its fitness. In September 2009, the WHO issued a briefing note citing the risk of AV resistance as higher amongst persons receiving oseltamivir for post-exposure prophylaxis who then subsequently develop influenza. Based on this observation, WHO strongly advised against the use of antivirals for prophylactic purposes, even for patients in a high-risk category. Alternatively, the note recommended close monitoring post-exposure and prompt initiation of early treatment if influenza-like symptoms began to develop.[31] Clusters of oseltamivir-resistant virus in hematology-oncology units in the United States and intensive care units in the UK further emphasized the need for vigilant monitoring of antiviral treatment protocols, particularly regarding dosaging, in immunocompromised populations. The virus's ability to persist and replicate in immunocompromised hosts, even after higher dosage regimens, underlines the need for alternative therapy considerations in these populations, as well as the paucity of therapeutic options for these high-risk groups.[32,33] It should be emphasized, however, that post-exposure prophylaxis in specialized settings for individuals at high risk of developing severe influenza has proven its utility in several

studies, including one conducted in a pediatric ward in Japan.[34]

Post-pandemic assessment

Measuring the impact of policy on public health outcomes

Given the diverse national policies enacted by public health agencies, how can we measure the impact of these policies on serious public health outcomes such as reductions in hospitalization and overall mortality? With the data that is available from the pandemic, creating the linkage between national policy and epidemiological outcomes is difficult to achieve. Assumptions, however, can be drawn from published data evaluating antiviral receipt amongst those most severely affected by the novel virus. The percentage of hospitalized patients receiving antiviral treatment prior to hospital admission and the time period between illness onset and AV receipt provides a reliable reflection of implementation of policy, providing a surrogate measure of policy efficacy. It can be inferred that the most effective policies would ensure that those at greatest risk of severe disease would have rapid access to antiviral medicines in the outpatient setting, prior to hospital admission (Table 1).

Lessons learned

There were several key lessons learned from the course of this pandemic. Containment strategies, with pre-exposure antiviral prophylaxis consume extensive public health resources, and are unlikely to prevent spread significantly if applied beyond an isolated cluster, when there is clear evidence of international spread of infection and may use a disproportionate amount of healthcare resources. Focussing on analytical studies to provide a robust early assessment of severity with a new virus strain is important in guiding targeted use of pre- and post-exposure prophylaxis to groups in the population particularly at risk.

The utility of early treatment in severe cases was well established and is increasingly being described in studies being published from several different settings or meta-analyses.[36] Additional insights can also be drawn from the health systems that successfully facilitated early treatment, as was seen in Japan, or struggled to do so, as was seen in the United States and England. Surprisingly, even the advent of novel delivery systems such as the NPFS did not necessarily render more positive public health outcomes. Using the Japanese example, it is clear that an existing level of familiarity with diagnostic testing and antiviral prescribing amongst clinicians in management of seasonal influenza is an important enabler to ensure a robust response during a pandemic and provide early, targeted therapy to those most susceptible with an emerging novel virus. Increased attention to delivery mechanisms that enable early antiviral treatment is essential in the future pandemic preparedness so as to maximize the benefit from interventions that seek to reduce viral shedding, so preventing end-organ damage. The efficiency of early delivery in Japan was facilitated by many years of experience of management of seasonal influenza, emphasizing the importance of building responses to unusual situations on systems that are operational during seasonal influenza.

Retrospective observational data and meta-analyses that have been consolidated from the pandemic period unanimously support a significant effect rendered by antiviral medicines on mitigating severe illness amongst hospitalized patients. Such retrospective analyses of the pandemic have also demonstrated the importance of observational clinical data collection as an alternative, but often neglected source of evidence. Reports on clinical cases and epidemiological analysis of clinical outcomes have produced high-grade evidence for future policy decisions. The collection of observational data on antiviral receipt and utilization, particularly in hospitalized patients, should be embedded in existing surveillance systems to ensure accurate, consistent collection in an emerging pandemic to guide an assessment of the speed and utility of delivery. The creation of clinical research networks with standardized collection methods using simple, key indicators such as mortality, admission to critical care, and age is essential to share clinical data and

Table 1. Number of pregnant women with A(H1N1)pdm2009 infection treated with antivirals in selected countries

Country	No. of Cases Per Study	Total No. Treated with AVs	Total No. Treated early (<48 hours after symptom onset)	No. of Maternal Deaths
Japan[7]	118	114 (96·6%)	105 (89·0%)	0
France[35]	315	299 (94·9%)	237 (75·2%)	3 (0·9%)
England[15]	82	69 (84·1%)	8* (9·8%)	3 (3·7%)
USA[23]	788	509 (n = 588; 86·6%)	219 (n = 384; 43·0%)	30 (3·8%)

*Treated prior to hospital admission, data not available on treatment timing.

compare the differences in outcomes between countries so that valuable lessons can be learned from national public health response efforts.

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References

1 WHO Checklist for Influenza Pandemic Preparedness Planning. Geneva: WHO, 2005. Available at http://www.who.int/influenza/resources/documents/FluCheck6web.pdf (Accessed 10 December 2012).
2 WHO Interim Protocol: Rapid Operations to Control the Initial Emergence of Pandemic Influenza. Geneva: WHO, 2007. Available at http://www.who.int/influenza/resources/documents/RapidContProtOct15.pdf (Accessed 10 December 2012).
3 WHO Guidelines on the Use of Vaccines and Antivirals during Influenza Pandemics. Geneva: WHO, 2004. Available at http://whqlibdoc.who.int/hq/2004/WHO_CDS_CSR_RMD_2004.8_eng.pdf (Accessed 10 December 2012).
4 The UK Government signs influenza pandemic contract with GlaxoSmithKline for Relenza®. London: GlaxoSmithKline, 2009. Available at http://us.gsk.com/html/media-news/pressreleases/2009/2009_pressrelease_10015.htm (Accessed 10 December 2012).
5 Further Expansion of Tamiflu Manufacturing Capacity. Basel: F. Hoffmann-La Roche Ltd, 2005. Available at http://www.roche.com/med-cor-2005-10-18 (Accessed 10 December 2012).
6 Sugaya N. Widespread use of neuraminidase inhibitors in Japan. J Infect Chemother 2011; 17:595–601.
7 Nakai A, Saito S, Unno N *et al.* Review of pandemic (H1N1) 2009 among pregnant Japanese women. J Obstet Gynaecol 2012; 38:757–762.
8 Nakai A, Minakami H, Unno N *et al.* Characteristics of pregnant Japanese women who required hospitalization for treatment of pandemic (H1N1) 2009 - low mortality rate may be due to early antiviral use. J Infect 2011; 62:232–233.
9 Sugaya N, Shinjoh M, Mitamura K *et al.* Very low pandemic influenza A (H1N1) 2009 mortality associated with early neuraminidase inhibitor treatment in Japan: analysis of 1000 hospitalized children. J Infect 2011; 63:288–294.
10 Seasonal Flu Plan: Winter 2011/12. London: UK Department of Health, 2011. Available at http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_127088.pdf (Accessed December 20, 2012).
11 Antiviral Prescribing and NICE Guidelines. London: Health Protection Agency Centre for Infections, 2007. Available at http://www.nice.org.uk/nicemedia/live/11488/36610/36610.pdf (Accessed December 20, 2012).
12 The role of the Health Protection Agency in the 'containment' phase during the first wave of pandemic influenza in England in 2009. London: Health Protection Agency, 2010. Available at http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1274088320581 (Accessed 20 December 2012).
13 Davies L. National Pandemic Flu Service: Letter to Medical Practitioners. London, 2009. Available at http://www.google.com/url?sa=t&rct=j&q=national%20pandemic%20flu%20service%20algorithm&source=web&cd=6&ved=0CFIQFjAF&url=https%3A%2F%2Fwww.cas.dh.gov.uk%2FViewandAcknowledgment%2FViewAttachment.aspx%3FAttachment_id%3D100922&ei=YazKUJvsJ4j69QS1jYC4AQ&usg=AFQjCNHZQ15agJ7Tp2jjgxPwedy6HPPS6A&bvm=bv.1355325884,d.eWU (Accessed 20 December 2012).
14 Gauld N, Jennings L, Frampton C *et al.* Five years of non-prescription oseltamivir: effects on resistance, immunization and stockpiling. J Antimicrob Chemother 2012; 67:2949–2956.
15 Dolan GP, Myles PR, Brett SJ *et al.* The comparative clinical course of pregnant and non-pregnant women hospitalised with influenza A (H1N1)pdm09 infection. PLoS ONE 2012; 7:e41638.
16 Pebody RG, McLean E, Zhao H *et al.* Pandemic influenza A(H1N1) 2009 and mortality in the United Kingdom: risk factors for death, April 2009 – March 2010. Euro Surveill 2010; 15:pii: 19571.
17 Hoschler K, Thompson C, Andrews N *et al.* Seroprevalence of influenza A(H1N1)pdm09 virus antibody, England, 2010 and 2011. Emerg Infect Dis 2012; 18:1894–1897.
18 Lackenby A, Elliot A, Powers C *et al.* Virological self-sampling to monitor influenza antiviral susceptibility in a community cohort. J Antimicrob Chemother 2013. doi:10.1093/jac/dkt203.
19 Hayden F, Pavia A. Antivirals in the treatment of seasonal and pandemic influenza. J Infect Dis 2006; 194:119–126.
20 Fiore A, Fry A, Shay D *et al.* Antiviral agents for the treatment and chemoprophylaxis of influenza recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2011; 60:1–24.

21 Doshi S, Kamimoto L, Finelli L *et al.* Description of antiviral treatment among adults hospitalized with influenza before and during the 2009 pandemic: United States, 2005–2009. J Infect Dis 2011; 204:1848–1856.

22 Greene SK, Shay DK, Yin R *et al.* Patterns in influenza antiviral medication before and during the 2009 H1N1 pandemic, Vaccine Safety Datalink Project, 2000–2010. Infleunza Other Resp Viruses 2012; 6:e143–e151.

23 Siston A, Rasumussen SA, Honein MA *et al.* Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA 2010; 303:1517–1525.

24 Garg S, Chaves SC, Perez A. Reduced influenza antiviral treatment among children and adults hospitalized with laboratory-confirmed influenza infection in the year after the 2009 pandemic. Clin Infect Dis 2012; 55:18–21.

25 Kimberlin DW, Acosta EP, Prichard MN *et al.* Oseltamivir pharmacokinetics, dosing, and resistance among children aged years with influenza. J Infect Dis 2013; 207:709–720.

26 Ferguson NM, Cummings DAT, Cauchemez S *et al.* Strategies for containing an emerging influenza pandemic in Southeast Asia. Nature 2005; 437:209–214.

27 Padfield S, Kemp M, Saravanan A, Wensley A. A practical review of 'containment' during the influenza A (H1N1): an audit of the fluresponse centre in Yorkshire and the Humber. J Public Health (Oxf) 2012; 34:203–208.

28 Lee VJ, Yap J, Cook AR *et al.* Oseltamivir ring prophylaxis for containment of 2009 H1N1 influenza outbreaks. N Engl J Med 2010; 362:2166–2174.

29 Pebody RG, Harris R, Kafatos G *et al.* Use of antiviral drugs to reduce household transmission of pandemic (H1N1) 2009, United Kingdom. Emerg Infect Dis 2011; 17:990–999.

30 UK Influenza Pandemic Preparedness Strategy 2011: Strategy for Consultation. London: UK Department of Health, 2011. Available at http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_125346.pdf (Accessed 20 December 2012).

31 Recommended use of antivirals: Pandemic (H1N1) 2009 briefing note 8. Geneva: WHO, 2009. Available at http://www.who.int/csr/disease/swineflu/notes/h1n1_use_antivirals_20090820/en/index.html (Accessed 20 December 2012).

32 Chen L, Dailey N, Rao A *et al.* Cluster of oseltamivir-resistant 2009 pandemic influenza A(H1N1) virus infections on a hospital ward among immunocompromised patients-North Carolina, 2009. J Infect Dis 2011; 203:838–846.

33 Harvala H, Gunson R, Simmonds P *et al.* The emergence of oseltamivir-resistant pandemic influenza A (H1N1) 2009 virus amongst hospitalised immunocompromised patients in Scotland, November-December, 2009. Euro Surveill 2010; 15:pii: 19536.

34 Shinjoh M, Takano Y, Takahashi T *et al.* Post exposure prophylaxis for influenza in pediatric wards oseltamivir or zanamivir after rapid antigen detection. Pediatr Infect Dis J 2012; 31:1119–1123.

35 Dubar G, Azria E, Tesniere A *et al.* French experience of 2009 A/H1N1v influenza in pregnant women. PLoS ONE 2010; 5: e13112.

36 Muthuri S, Myles P, Venkatesan S *et al.* Impact of neuraminidase inhibitor treatment on outcomes of public health importance during the 2009–2010 influenza A(H1N1) pandemic: a systematic review and meta-analysis in hospitalized patients. J Infect Dis 2013; 207:553–563.