



Pandemic (H1N1) 2009 in England: an overview of initial epidemiological findings and implications for the second wave

v4 2 December 2009

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Executive summary

The Health Protection Agency (HPA), working with key partners including the Devolved Administrations, the Department of Health and the National Health Service (NHS), has undertaken a vigorous response to pandemic (H1N1) 2009. This report describes the HPA's response to the first wave of pandemic (H1N1) 2009 in England from April to the end of September 2009, summarises key findings about the pandemic and assesses the implications of this information for the second wave.

The initial response in England centered on a containment strategy: individual cases were investigated and treated with antivirals and their contacts were traced and offered antiviral prophylaxis. In addition, schools were typically closed if confirmed case(s) were identified and close contacts offered prophylaxis. In mid-May, Flu Response Centres were established in each of the 10 Strategic Health Authority regions of England to support these intensive efforts initially undertaken by the HPA's 26 Health Protection Units. Nonetheless, case numbers continued to rise and the occurrence of large outbreaks in parts of the country indicated the spread of the pandemic virus. On 2 July a 'treatment-only' phase was initiated to manage the pandemic: oseltamivir was offered to anyone who had an appropriate clinical illness, without the need for testing. Shortly thereafter the telephone- and internet-based National Pandemic Flu Service (NDFS) was launched to authorise access to antivirals.

During the first wave of pandemic (H1N1) 2009 in England it is estimated that between 144,000 and 670,000 people (mid-estimate of 320,000) fell ill. However, this varied considerably by age group and region. People aged 24 years and younger were many more times likely to become infected than adults >65 years. Using modelled estimates, London and the West Midlands accounted for 30% and 12%, respectively, of clinical cases in England to the end of September. Most people experienced a mild, typical influenza-like illness and the number of deaths in the first wave has been far fewer, compared with a typical influenza season. However, severe cases have occurred and the overall rate of hospitalisation ranged from 1.3% to 2.5%. The likelihood of hospitalisation increased in the presence of one or more risk conditions, particularly chronic renal disease, immunosuppression and chronic neurological disease, and was considerably higher for infants <1 year and adults >65 years, compared with all other age groups.

Intensive epidemiological and laboratory investigation of the 'first few hundred' cases and their household contacts during the containment phase estimated that the secondary household virologically confirmed attack rate was 7%; however, the rate was approximately four times higher in children (<16 years) than adults and >90% lower among household contacts who received antiviral prophylaxis.

Pandemic (H1N1) 2009 is the dominant influenza strain in England with only a small proportion of influenza activity attributable to other strains. Over 1000 pandemic A (H1N1) 2009 viruses from patients in the United Kingdom were analysed for the genetic marker commonly associated with resistance to oseltamivir; only three patients have been identified as having isolates resistant to oseltamivir, as of September 2009.

Information from initial serological studies suggests that a sizeable proportion of people, especially those in younger age groups, were infected with the pandemic virus. Preliminary results of seroepidemiology studies indicate that, overall, about 15% of

children in England were infected during the first wave. In London and the West Midlands the estimated cumulative incidence of infection in children <15 years of age and young adults aged 15-24 years was about 25% and 21%, respectively.

The HPA's investment in pandemic preparedness and planning was critical in responding to the first wave of pandemic (H1N1) 2009 in England. Synthesis, review and reflection of the initial epidemiological findings can help inform planning and delivery of essential clinical and public health services for a second wave of cases.

Pandemic (H1N1) 2009 in England: an overview of initial epidemiological findings and implications for the second wave

Introduction

This report describes the Health Protection Agency's (HPA's) response to the first wave of pandemic (H1N1) 2009 in England from April to the end of September 2009, summarises key findings about the pandemic and assesses the implications of this information for the second wave.

The HPA, working with key partners including the Devolved Administrations, the Department of Health and the National Health Service (NHS), has undertaken a vigorous and multi-faceted response to pandemic (H1N1) 2009. A particular focus, essential to preparing for further pandemic impact, has been an assessment of the epidemiological and clinical characteristics of the first wave cases. This has been accomplished through traditional and enhanced surveillance schemes, virological monitoring and individual case, household and outbreak investigations (see Annexes for a description of data sources and methods). Such information is critical for policy-makers and for those responsible for planning and delivering clinical and public health services.

Detection of the pandemic and the early response

Following the identification of the first cases of pandemic (H1N1) 2009 in Mexico and the United States, England embarked on a strategy of enhanced surveillance for respiratory illness amongst travellers and close contacts of confirmed cases (see Box 1 for surveillance case definitions) (1). The first cases of pandemic (H1N1) 2009 infection in the United Kingdom were reported on 27 April 2009 in a couple who returned home to Scotland after a trip to Mexico. Two days later, the first case in England was reported in a person who had travelled on the same flight from Mexico.

Box 1. Early case definitions for pandemic (H1N1) 2009, England (April 2009)

- **Possible case:** a person with a history of acute respiratory illness and recent travel to an affected area or contact with a confirmed or probable case
- **Probable case:** a person who was a possible case and tested positive for influenza A which was non-subtypeable
- **Confirmed case:** a person who tested positive for the pandemic H1N1 2009 influenza virus by specific real time reverse transcriptase- polymerase chain reaction (RT-PCR) confirmed by sequence analysis

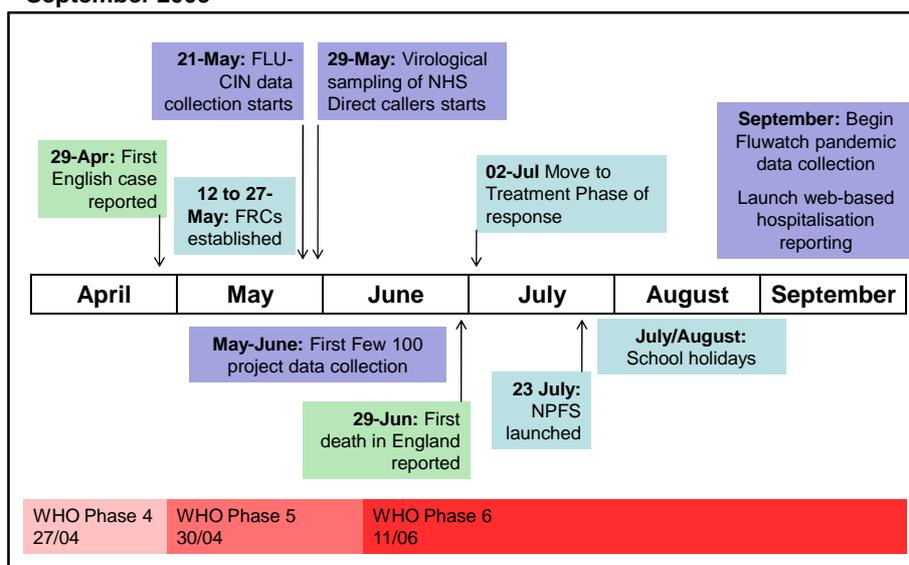
In an effort to minimise secondary spread as much as possible, England initiated a containment strategy (see Box 2 overleaf). During May and June when the containment phase was operative, individual cases were investigated, their contacts traced and antiviral drugs were recommended for early treatment of all confirmed cases and prophylaxis of close contacts.

Box 2. Key actions during containment and treatment-only phases for pandemic (H1N1) 2009 in England

- Containment phase**
- Diagnosis by laboratory confirmatory testing
 - Suspect cases treated with antivirals and requested to self-isolate at home
 - Household / close contacts of suspect cases traced
 - Contacts offered antiviral prophylaxis if index case laboratory confirmed; contacts advised to self-isolate only if they became clinically ill
 - Closure of schools for 7 days if confirmed case(s) identified; treatment of clinically ill persons with antivirals
 - Close contacts of confirmed / suspect cases in confirmed school outbreaks offered prophylaxis
- Treatment-only phase**
- Diagnosis by clinical illness; laboratory testing not required
 - Clinical cases offered antiviral treatment through consultation with health care professional or National Pandemic Flu Service (NPFS); emphasis on treatment for persons in higher risk groups
 - Contacts of cases not offered prophylaxis apart from special circumstances (e.g. household member with serious underlying health problem)

The initial response (see Figure 1 for timeline of key events) was provided by the HPA working, where appropriate, with local NHS authorities and trusts and school authorities. Algorithms were developed and published for the identification of potential cases based on recent travel to affected parts of the world or contact with known or suspected cases within the UK (1, 2). Suspect cases were interviewed, advised to isolate themselves at home (unless their clinical condition warranted hospital admission), tested for infection and offered treatment with oseltamivir. Close household or equivalent contacts were identified and, if the index case was confirmed on laboratory testing, offered prophylaxis with oseltamivir. Contacts were not quarantined but were advised to self-isolate if they became unwell. The 'First Few Hundred' (FF100) surveillance project was quickly launched to collect detailed demographic, exposure, clinical, treatment, outcome and virological data for laboratory confirmed cases of pandemic influenza and their close contacts during the early part of the first pandemic wave (see Annexe).

Figure 1: Timeline of pandemic-related key events in England, April to September 2009



FRC = Flu response centre; NPFS = National Pandemic Flu Service

Outbreaks in schools occurred, following the introduction of infection by school-age children who had acquired infection through travel and subsequently through contact with other cases in the household or elsewhere. The response during most of the

containment phase to the confirmation of cases in a school was to advise closure of the school for seven days (based on the usual maximum incubation period for the infection). Those in the school with clinical illness were offered treatment with oseltamivir and allowed to return to school only when symptom-free. Close contacts of confirmed cases (and of suspected cases in confirmed outbreaks) were offered prophylaxis, but no restriction was placed on their activities unless they became unwell. In many instances, with large numbers of cases in schools, contacts could not be individually identified and the relevant school year or whole school were offered prophylaxis.

In response to a direct request from the Civil Contingencies Committee, during the period 12-27 May 2009 Flu Response Centres (FRCs) were established in each of the 10 Strategic Health Authority regions of England to take on much of the frontline response work initially undertaken by the HPA's 26 Health Protection Units. The FRCs were set up at very short notice by the HPA, in collaboration with the NHS at national, regional and local levels. Their aim was to extend the intensive public health response and maintain public confidence during the containment phase, when the first few thousand confirmed cases of pandemic influenza were identified. To facilitate the work of the FRCs a new case-based decision support system, Fluzone, was developed and implemented in all FRCs within a very short timescale.

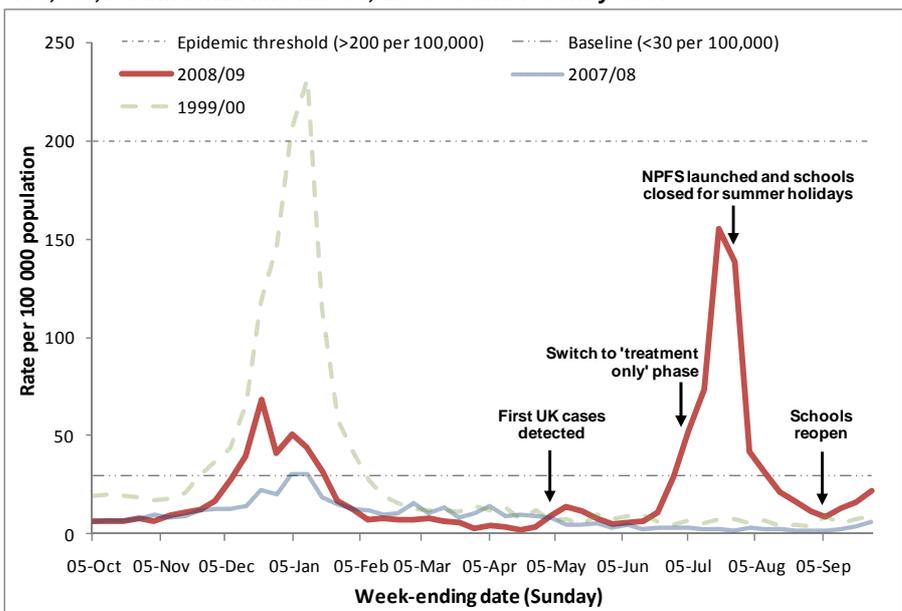
Subsequent spread of the pandemic and impact on the public health and primary care services

Despite these intensive efforts, sentinel surveillance schemes and the occurrence of large outbreaks in parts of the country indicated spread of the pandemic virus. The number of cases began to rise very sharply in June. Sporadic cases, with no links to known cases or outbreaks, were increasingly identified. By 22 June, the Royal College of General Practitioners (RCGP) weekly consultation rate for influenza-like illness increased above baseline for the first time since the start of the pandemic (Figure 2).

However, it was difficult to ascertain if these elevated rates mirrored transmission in the wider community. First, general practitioner consultation trends likely reflected a more severely ill subset of people with pandemic influenza and second, laboratory testing was limited to ill people with epidemiological linkages to affected countries or other confirmed cases.

To help gauge the occurrence of community transmission, a scheme was implemented in collaboration with NHS Direct, a nurse-led telephone advice line. A subset of callers >16 years of age with cold/flu symptoms and no history of epidemiological links to other cases of pandemic influenza

Figure 2: Royal College of General Practitioners weekly consultation rate, per 100,000, for influenza-like illness, 2008/09 and recent years.



* NPFS = National Pandemic Flu Service

were mailed a self-sampling kit to obtain nasal swabs for testing. Overall, between 28 May and 30 June 2009, 91 (7%) of 1,385 callers were positive for the pandemic virus (3). Further, rising positivity rates among self-samplers correlated temporally and geographically with rising rates among specimens obtained from patients attending general practitioner surgeries and tested at HPA regional laboratories. Data from both systems indicated that sustained community transmission of the pandemic virus was occurring in England, principally in London and the West Midlands where multiple school-related outbreaks were under way at the time.

As the number of schools affected by outbreaks increased, so did the pressure on local health protection staff who were overseeing all the containment measures, including distribution of antiviral treatment and prophylaxis. In some areas, such as London and the West Midlands where there was growing evidence of sustained community transmission, this response became unsustainable and disproportionate to the epidemiological picture. Accordingly, more limited measures in school outbreaks were adopted in heavily affected areas where prophylaxis was restricted to close contacts only. In addition, testing of all cases became impractical and treatment on the basis of clinical illness began to be instituted.

As case numbers continued to rise (by the end of June nearly 7,000 confirmed cases were reported), pressure on local health protection staff and the staff of the FRCs escalated. During the containment phase the FRCs took over 5,000 calls per day over the period of peak activity, provided antivirals to over 6,000 cases and 10,000 contacts and dealt with outbreaks in over 400 schools.

On 2 July, in view of the accumulating evidence for widespread community transmission in different areas across the country, the government announced that England would move to a treatment-only phase to manage the pandemic (http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_102027.pdf). Treatment with oseltamivir was offered to anyone who had an appropriate clinical illness, without the need for testing. Prophylaxis was no longer offered other than in limited circumstances involving high-risk close contacts. Shortly after the start of the treatment phase, the National Pandemic Flu Service (NPFS) was launched. This national telephone- and internet-based service authorises patients who are not in a specified risk group access to antivirals without the need to see a general practitioner. FRCs closed within a few weeks of the change to the treatment-only strategy.

Sentinel clinical surveillance schemes (Figure 2) and mathematical modelling suggest that the first wave of the pandemic peaked around mid- to late July. At the peak of pandemic activity, it was initially estimated that more than 100,000 new symptomatic cases a week occurred (http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1248940851283). However, subsequent refinements of these estimates suggest that the figure was closer to 80,000 new symptomatic cases per week (HPA, unpublished data). Two events occurred roughly coincident with the decline in cases. First, the decline in the number of cases began just before the closure of schools for the summer holidays; cases decreased by approximately 30% to 50% each week after schools closed (HPA, unpublished data). Second, the activation of the NPFS on 23 July occurred just after the peak. The NPFS reduced general practitioner consultations for influenza-like illness, but it is unclear by how much (http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1250150839845).

After the move to the treatment-only phase, the HPA ceased reporting counts of laboratory-confirmed and clinically-presumed cases. It became clear that reporting of individual cases significantly underestimated the actual magnitude and spread of the pandemic in England. Further, local and regional efforts to detect and report cases were very resource-intensive and were needed for critical prevention and control measures. Mathematical modelling was used to estimate the number of new pandemic (H1N1) 2009 influenza cases each week, beginning the week 21 to 27 July.

During the summer, influenza activity continued, albeit at a low level. However, with the resumption of school in September, an upward trend in cases began. By 27 September 28, schools with virologically-confirmed pandemic influenza were reported from eight regions and a further 25 schools were under investigation because of increased absenteeism due to influenza-like illness. Primary, secondary and special, day and boarding schools were all affected.

(http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1253205561258).

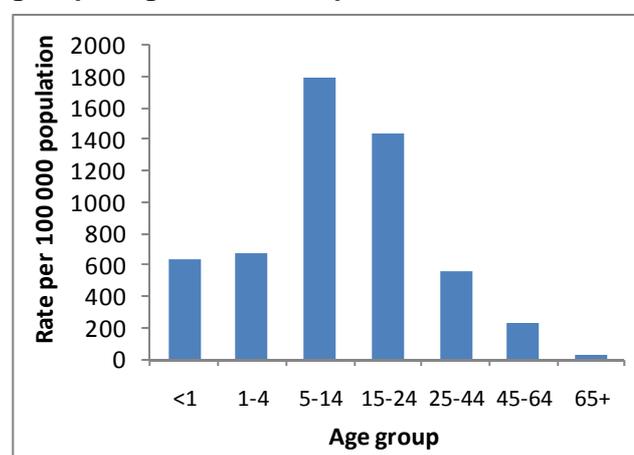
Demographic features

Age and sex

Cases occurred among males and females in about equal proportions. Among cases reported with clinical illness, younger rather than older age groups were most affected. During the peak period of the first wave in mid-July, Q Surveillance®¹ indicated that children in the under-1 year, 1-4 year and 5-14 year age groups had the highest daily general practitioner consultation rates for influenza-like illness (≥ 100 visits per 100,000) or approximately 4,500 total visits per day.

In contrast to seasonal influenza, people 65 years and older were least affected. Modelling estimates suggest that the cumulative rates of clinical illness among people aged 24 years and younger may be about 30 to 80 times higher than that of people aged 65 and older (Figure 3) (HPA, unpublished data). This age pattern likely reflects past exposure to other strains of (H1N1) and some level of cross-protecting antibodies among older age groups (4). In addition, younger age groups may have had more opportunities for exposure (for example, through attendance at school) compared with older age groups.

Figure 3: Estimated rate, per 100,000 population, of clinical cases of pandemic H1N1 2009, by age group, England to 27 September 2009*



* Estimated number of cases to 27 September using data reported on 28 October 2009

Geographic distribution

Cases of pandemic influenza were not dispersed homogeneously throughout England. London and the West Midlands Strategic Health Authorities experienced high numbers of cases, with rapid rates of increase in new cases from week to week early in the first wave (Table 1). Both of these areas experienced multiple school-related outbreaks which could account in part for the heterogeneous geographic distribution. In the West

¹Q Surveillance® includes general practices from England, Wales and Northern Ireland. The majority of the practices are from England.

Midlands region, most of the activity was seen in the Birmingham area rather than in the wider region (HPA, unpublished data). Using modelled estimates, London and the West Midlands accounted for 30% and 12%, respectively, of clinical cases in England to the end of September (HPA, unpublished data). Seroepidemiology studies also support that regional variations occurred during the first wave (see section on 'Estimating the magnitude of the first wave', p14).

Table 1: Estimated rate, per 100,000, of clinical cases of pandemic H1N1 2009, by Strategic Health Authority, England to 27 September*

Region	Estimated number of cases	Population	Rate per 100,000
East Midlands (EM)	23276	4,433,000	525.1
East of England (EE)	26226	5,728,700	457.8
London (LN)	102403	7,619,800	1343.9
North East (NE)	16676	2,575,500	647.5
North West (NW)	40109	6,875,700	583.3
South Central (SC)	18923	4,062,300	465.8
South East Coast (SE)	19608	4,317,800	454.1
South West (SW)	23232	5,209,200	446.0
West Midlands (WM)	41262	5,411,100	762.5
Yorks & Humber (YH)	25565	5,213,200	490.4

* Estimated number of cases to 27 September using data reported on 28 October 2009

Clinical spectrum of disease

Most cases appear to have experienced a typical influenza-like illness. Detailed investigation of a subset of 373 early cases, as part of the FF100 surveillance project (see Annex), found fever, malaise, dry cough, sore throat and headache to be among the most commonly-reported symptoms ($\geq 70\%$ of respondents) (HPA, unpublished data). The median duration of illness for these cases was seven days (range 1-29 days).

One feature of the clinical picture has been the occurrence of gastrointestinal symptoms at a higher frequency than is usually observed with seasonal influenza. In several case series, between 20% and 40% of people reported one or more gastrointestinal symptoms of diarrhoea, nausea and/or vomiting (1,2,5,6). However, this was not a consistent feature; for example, in a boarding school outbreak, approximately 5% of 63 confirmed cases reported diarrhoea/vomiting (7).

Asymptomatic infection is a well-recognised feature of seasonal influenza. However, the proportion of those infected with the pandemic (H1N1) virus who have a mild illness or are asymptomatic has not been well-characterised. Based on serological studies of the boarding school outbreak, subclinical infection occurred in about one third of those without symptoms (HPA, unpublished data). More studies in well-characterised populations are needed to further assess this important clinical parameter.

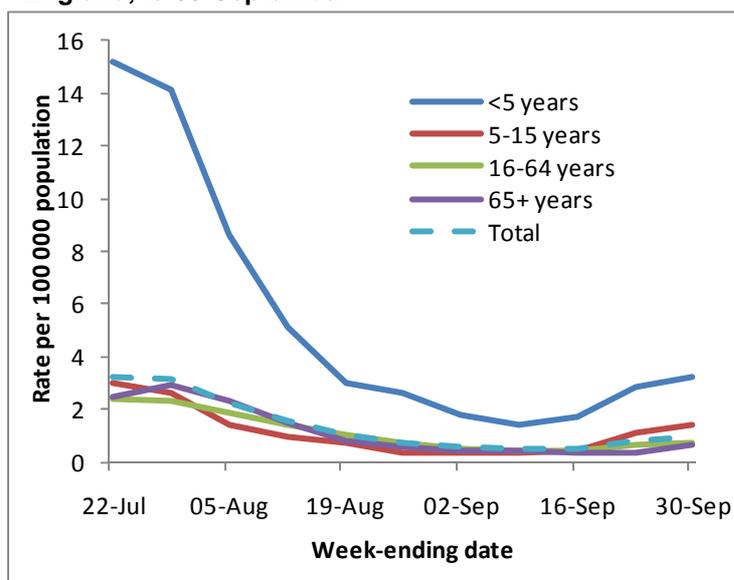
Hospitalised cases

During the containment period to the end of June, when all people with influenza-like illness were being identified and tested, 170 confirmed cases of pandemic (H1N1) 2009 were reported in England as hospitalised. The overall rate of hospitalisation ranged from 1.3% to 2.5%, depending on the methodology used to estimate the total number of

cases of pandemic influenza (HPA, unpublished data). Case hospitalisation ratios were considerably higher for infants <1 year and adults >65 years, compared with all other age groups.

Using data reported by primary care trusts to the Department of Health in England, the highest rates of hospitalisation for people with suspected pandemic influenza were observed in those aged less than five years (Figure 4). Hospitalisation rates declined in August but began to increase again in late September.

Figure 4: Weekly rate, per 100,000 population, of hospitalisations for suspected pandemic H1N1 2009, England, to 30 September



A preliminary analysis of 266 hospitalised cases available through the Flu Clinical Information Network (FluCIN) (see Annexe) found that the average length of stay in hospital was shorter in children (3.7 days) than adults (5 days) and longer in those with co-morbidities (4.7 days) compared with those without (4.1 days). Less than 20% of either children or adults, with illness severe enough to warrant hospitalisation, had received antivirals prior to admission. (J Van Tam, personal communication).

Risk factors for severe disease

Based on cases reported in the FF100 system, the likelihood of being identified as a case appeared not to differ according to whether an individual had underlying risk factors for severe disease (HPA, unpublished data). The likelihood, however, of being hospitalised with pandemic influenza was considerably increased by the presence of underlying risk factors. Using data from a case-control study of follow-up of laboratory confirmed cases and negative controls, the presence of one or more risk factors increased the likelihood of hospitalisation, overall to more than five times that of the general population (HPA, unpublished data). All the risk conditions used as the basis for recommending seasonal influenza immunisation, as well as pregnancy, were associated with increased risk of hospitalisation, particularly chronic renal disease, immunosuppression and chronic neurological disease.

Among those hospitalised, the likelihood of an underlying co-morbidity increased with age: less than 20% of the under-5 year group were reported to have a co-morbidity, compared with over 80% in the 65-year and over group (J Van Tam, personal communication, preliminary FluCIN data). Asthma, heart disease and diabetes were the most commonly reported co-morbidities.

The risk of dying was also considerably increased in cases with underlying risk conditions although, as the number of deaths is small, the confidence intervals around estimates of risk are wide. Based on the prevalence of reported risk factors in those patients dying and using HPA modelled estimates of the total numbers of cases, case fatality rates were calculated by risk group. Much higher case fatality rates were

observed among those with chronic liver and chronic neurological disease and people >65 years of age (HPA, unpublished data).

Deaths

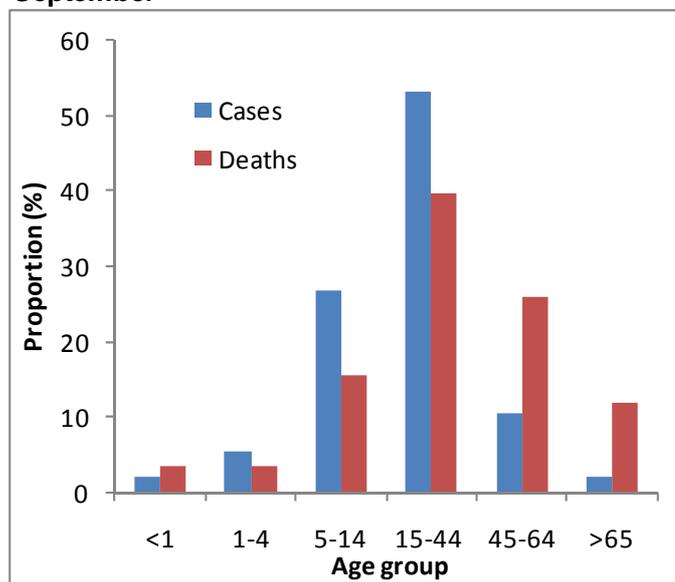
Compared with seasonal influenza, pandemic-associated mortality has been modest. No excess all-cause mortality (either overall or by age-group) has been observed in England through to the end of September http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1253205412438.

A total of 72 people with confirmed pandemic influenza were reported to have died in England to 27 September 2009.² Detailed information on 58 deaths was available to the HPA to the end of September. The proportional distribution of the estimated number of cumulative clinical cases and the number of deaths by age group differed in that deceased cases were skewed towards the older, rather than younger age groups (Figure 5).

Although only 13% of estimated clinical cases were in people older than 45 years, this age group

accounted for 38% of all deaths. Very few deaths were reported for adults >65 years.

Figure 5: Proportional distribution of cumulative estimated number of clinical cases of pandemic H1N1 2009 and reported deaths, England to 27 September*



* Estimated number of cases to 27 September using data reported on 28 October 2009; number of deaths based on data available to HPA on 58 deaths with confirmed pandemic H1N1 2009 infection.

Transmission characteristics of the pandemic virus

Information to assess transmission characteristics of the pandemic virus is available from field investigations conducted principally in household and school settings. Mathematical modelling has provided further insight into the transmission dynamics of the pandemic virus.

Findings from field investigations

Results of intensive epidemiological and laboratory investigation of the 'first few hundred cases' and their household contacts during the containment phase were used to estimate key transmission parameters for the pandemic virus. Overall, the preliminary secondary household virologically-confirmed attack rate was 7%. However, it was approximately four times higher in children (<16 years) than adults and >90% lower among household contacts who received antiviral prophylaxis (HPA, unpublished data).

During the early part of the first wave, in contrast to Scotland which experienced clusters of cases primarily amongst adults, cases in England were largely school-associated. Although some of the early individual cases identified in school-aged children were not associated with subsequent outbreaks in those schools, outbreaks in schools soon emerged and increased rapidly in number. Detailed investigation of three

² HPA receives data on hospitalisation and deaths due to pandemic influenza in England from the Department of Health.

school outbreaks found that clinical-based attack rates for influenza among all students ranged from 4% to 35%; lower rates were reported among adult members of staff (Table 1). Attack rates for influenza-like illness varied within schools across school year, boarding houses (4-7).

Table 2: Characteristics of three school outbreaks of pandemic H1N1 2009 in England, 2009

Location	School Type	Students			Staff*			Lab-confirmed cases			Days to intervention**	Ref. Number
		ILI	Total	%	ILI	Total	%	n	Total	ILI %		
SE England	Boarding	101	1307	8%	1	825	0.1%	63	102	62%	7	6
West Midlands	Primary	167	479	35%	8	84	10%	64	175	37%	9	4
London	Primary/Secondary	47	1177	4%	13	444	3%	23	60	38%	7	5

* Including non-teaching staff; ** Days from confirmation of first case to implementation of first intervention; ILI = Influenza-like illness

Among students, the different attack rates likely reflected varying opportunities for close and/or prolonged exposure to infectious individuals. In school-related investigations which included detailed contact tracing to determine probable chains of transmission, the highest rates of laboratory-confirmed influenza-like illness were found in those settings with prolonged exposure, such as the classroom of the index case (6,8). Other settings where enhanced transmission occurred included children's parties (6,8) and a choir. A symptomatic choir member transmitted to 4% of 107 other members of the choir who rehearsed and performed together over a two-day period (8). No transmission was detected among students who travelled on school bus journeys for 50 minutes or less with an infected student (8).

Understanding the transmission patterns observed in these outbreaks is limited by under-ascertainment of all infected people. In accordance with HPA guidance, at the time only people with symptomatic illness and links to a confirmed case were investigated (8). Also, some people with influenza-like illness who tested negative by PCR may represent false negatives (9). Finally, there are likely to be many non-ill people who have been infected with the pandemic virus. For example, based on serologic testing, the infection attack rate was estimated to be 39% at the boarding school where interventions (closure and antivirals) were implemented at three weeks and blood specimens taken five weeks after the first cases became ill. How infectious people with asymptomatic/sub-clinical infection are is uncertain.

Modelling studies

Mathematical modelling was used to estimate key epidemiological parameters to inform policy-making, using data from laboratory-confirmed cases and contacts in the UK during the first two months of the pandemic. These analyses indicate that, at the beginning of the first wave in England, transmission of the pandemic (H1N1) 2009 virus was sporadic and not sustained. However, within a few weeks, transmission in England increased as the estimated value of the reproduction number, R, exceeded the 'epidemic threshold' value of 1. Other key findings include estimates of the incubation period and the serial interval. The impact of treatment with antivirals, coupled with widespread prophylaxis during the containment phase, was assessed. These findings have been submitted for publication (Ghani et al, submitted for publication).

Virological surveillance

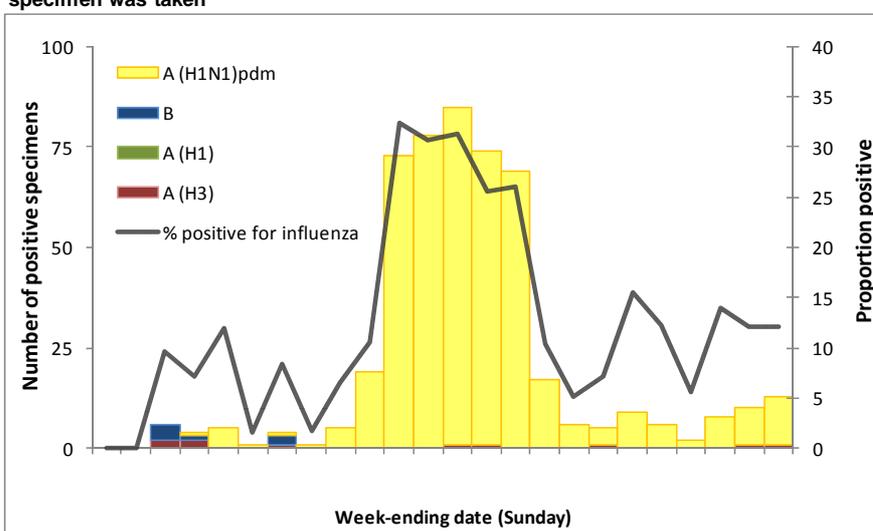
A total of 11,510 cases of pandemic (H1N1) 2009 were confirmed by laboratory testing in England from April 2009 to 29 September 2009. Following an initial rise in numbers of confirmed cases in May and June, the numbers of confirmed cases declined from the beginning of July, when routine testing of patients ceased with the introduction of the treatment-only phase. An increase in the number of laboratory-confirmed cases

occurred following the re-opening of schools at the beginning of September and subsequent outbreaks in schools and increased clinical activity in school-age children and young adults.

The pandemic (H1N1) 2009 virus has been the predominant influenza virus identified during this period. Small numbers of seasonal influenza A H3N2, A (H1N1) and B were identified in April and May. Since then, very few other influenza viruses have been detected. Compared with other years, a slight increase in the detection of other respiratory viruses, such as respiratory syncytial virus, rhinoviruses, adenoviruses and parainfluenza viruses has been observed. This is most likely due to increased testing in the context of the pandemic. In recent weeks, small numbers of respiratory syncytial virus have been identified, consistent with the annual rise in these infections which peaks over the Christmas/New Year period.

Among specimens examined in patients presenting with influenza-like illness to general practitioners in the RCGP/HPA and Regional Microbiology Network virological surveillance schemes (Figure 6), the proportion positive for pandemic (H1N1) 2009 varied from 5% to over 30% in late June through July; positivity rates varied considerably by age. Although the proportion

Figure 6: Number and proportion of viruses positive for influenza through two GP-based sentinel virological surveillance schemes in England (RCGP and RMN*) by week specimen was taken



* RCGP = Royal College of General Practitioners; RMN = Regional Microbiology Network.

positive among specimens submitted by patients in the NHS Direct and NPFS schemes was lower (range 5% to 10%) than that seen in the sentinel general practitioner surveillance schemes during this time period, the trend was similar. The differences in positivity between the schemes is likely to be influenced by the fact that the NHS Direct and NPFS schemes do not include under-16 year olds in their sampling – ages where both positivity rates and numbers of cases are at their highest. Also, people in the NPFS scheme who self-swabbed were taking antivirals for varying periods of time.

Virus isolates are characterised antigenically and by genetic sequencing by the Respiratory Virus Unit of the HPA Centre for Infections. All isolates of pandemic (H1N1) 2009 which have been analysed to date were similar to the prototype vaccine strain A/California/7/2009, and no variation of clinical or public health significance has been observed to date.

Drug susceptibility

By the end of September 2009, over 1,000 pandemic A (H1N1) 2009 viruses from patients in the UK had been analysed for the genetic marker commonly associated with resistance to oseltamivir in seasonal (H1N1) influenza and more than 250 specimens had been fully tested for susceptibility. Three patients have been identified as having isolates resistant to oseltamivir as of September 2009. The viruses had the genetic change, H275Y in the N1 gene. All three viruses carrying the H275Y mutation were

confirmed to be phenotypically resistant to oseltamivir, while retaining susceptibility to zanamivir. Two of the patients were immunocompromised and samples found to be resistant were taken during or after completion of the course of treatment with oseltamivir. In both cases, examination of pre-treatment specimens revealed that their influenza infection had been with a fully drug-sensitive strain. No evidence of transmission to contacts was identified.

Estimating the magnitude of the first wave

England's network of surveillance schemes provides good documentation of the overall temporal and geographic unfolding of the pandemic. However, these schemes cannot be relied upon to estimate the 'true' number of people in England who were infected during the first wave of the pandemic.

First, clinical schemes, by definition, capture people who attend general practitioner surgeries and so underestimate people with milder or uncomplicated illness. Findings from a national community cohort study (FluWatch) of approximately 600 to 850 individuals indicate that the rates of influenza-like illness with confirmed fever and rates of laboratory-confirmed influenza are up to 50 and 25 times higher, respectively, than those reported through general practice surveillance schemes. Preliminary analyses suggest that the extent of under-ascertainment of cases in primary care surveillance was lower during the first wave of the pandemic than during seasonal influenza. Nevertheless, the levels of influenza-like illness estimated through general practitioner surveillance data during the first wave are several times lower than those identified in FluWatch (A Hayward, personal communication). In addition, as noted previously, once the NPFS was activated and provided access to antiviral treatment, contact with general practitioner surgeries for uncomplicated illness was actively discouraged.

Second, because the symptoms of influenza are non-specific, they can mimic other respiratory infections. Information from general practitioner-based sentinel virological schemes as well as from the NPFS/NHS Direct scheme underscores that not all clinical influenza-like illness in the community is pandemic influenza. Also, some people with influenza-like illness who tested negative by PCR for influenza may represent false negatives.

Third, it is well recognised that influenza can result in an asymptomatic / sub-clinical infection. For seasonal influenza it has been estimated that 50% or more of all infections are asymptomatic (10). Information from seroepidemiological studies is needed to assess the level of asymptomatic infection that occurred during the first wave of the pandemic.

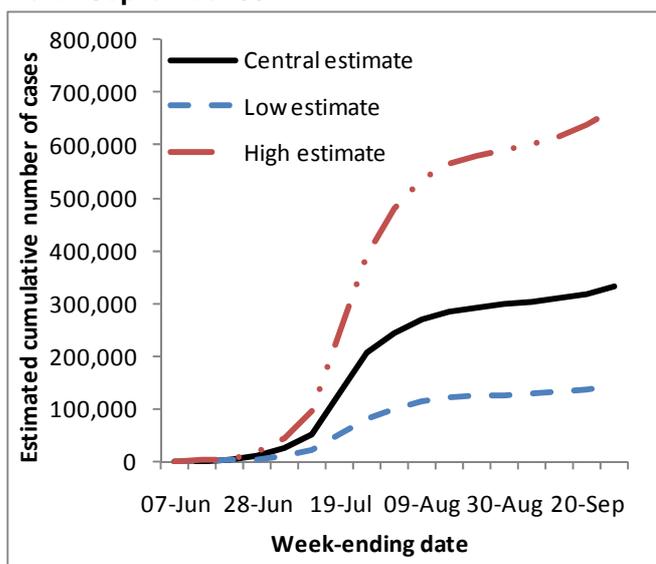
Estimates of the numbers of clinical infections

It is estimated that by 27 September, the cumulative number of people in England with symptomatic illness was between 144,000 and 670,000 people with a mid-estimate of 320,000 (Figure 7) (HPA, unpublished data).

However, these estimates are based on two main assumptions. First, the virological swabs are assumed to be taken from a representative sample of people diagnosed with influenza-like illness by their general practitioners or people who collected antivirals through the NPFS and the virological test has a high sensitivity. Second, it is assumed that a large proportion of clinical cases will consult their general practitioner or self-refer to the NPFS (HPA, unpublished data).

A detailed examination of viral swabbing data by age and region during the first wave suggests that the virological test has a reasonably high sensitivity of at least 70%. The proportion of clinical cases who either consult their general practitioner or self-refer to NPFS has been estimated to be 50% (range 30% to 70%). However, data from FluWatch and other sources indicate that this estimate is too high which, in turn, suggests an underestimate of the clinical case numbers, especially in the most recent weeks. It is unclear whether the estimated clinical cases are grossly underestimated or whether a large proportion of those infected have either a very mild illness or are asymptomatic (HPA, unpublished data). The boarding school outbreak showed that, based on serological studies, subclinical infection occurred in about one third of those without symptoms (HPA, unpublished data). However, it may not be possible to generalise broadly from these results, given the setting of a school outbreak and an over-representation of younger age groups, as well as the use of antivirals for prophylaxis. Additional studies in well-described cohorts are needed to provide more information on the proportion of asymptomatic/sub-clinical infection with the pandemic virus.

Figure 7: Estimated cumulative number of clinical cases of pandemic H1N1 2009, England to 27 September 09



NB Estimated number of cases to 27 September using data reported on 28 October 2009

Estimates of the incidence of infection through seroepidemiology studies

Information from initial serological studies suggests that a sizeable proportion of people, especially those in younger age groups, were infected with the pandemic virus (HPA, unpublished data). Overall, about 15% of children in England were estimated to be infected during the first wave. There was evidence of significant differences in the incidence of pandemic (H1N1) 2009 infection between regions, with the highest rates observed in London and the West Midlands. In these two areas the estimated cumulative incidence of infection in children <15 years of age and young adults aged 15-24 years was about 25% and 21%, respectively.

Assessment and implications for the second wave

The impact of the first wave of pandemic activity in England, coupled with the experiences of countries worldwide, reaffirm the value of the HPA's prior pandemic planning and the need to maintain a high level of readiness and response for the 2009/2010 influenza season. Review and reflection of the initial epidemiological findings (Box 3) can help inform planning and delivery of essential clinical and public health services for a second wave of cases. Four areas of particular relevance to the HPA are discussed in detail.

Box 3. Summary of key epidemiological findings for the first wave of pandemic (H1N1) 2009, England, April to September 2009

Demographic features

- Young adults 15-14 and 15-24 years of age had highest estimated rates of clinical illness; lowest rate in adults 65 years and older
- London and West Midlands estimated to account for 30% and 12%, respectively of all clinical cases

Clinical spectrum

- Mild influenza-like illness most common clinical manifestation
- 20% to 40% of cases had gastrointestinal symptoms
- Infants <1 year and adults >65 years had highest case hospitalisation ratios
- Increased risk of hospitalization in persons with medical conditions, especially chronic renal disease, immunosuppression and chronic neurological disease
- No excess mortality observed

Transmission characteristics

- Secondary virologically confirmed household attack rate about 7%; 90% lower in contacts who took antiviral prophylaxis
- Clinical attack rates in school pupils ranged from 4% to 35%

Estimated magnitude

- 320,000 persons estimated by mathematical modeling to have clinical illness (range 144,000 – 670,000)
- In London and the West Midlands, 25% of <15 year olds and 21% of 15-24 year olds estimated to have been infected based on serological surveys

Influenza activity

During the first wave of pandemic (H1N1) 2009 in England it is estimated that 0.66% of the population fell ill. However, this varied considerably by age group and region. In particular, people aged 24 years and younger were many more times likely to become infected than adults >65 years. In view of the evidence from serological studies showing widely varying incidence rates for infection with the pandemic virus between regions, it is considered likely that further regional differences in the magnitude, timing and age-specific incidence of infection will be observed in the second wave (HPA, unpublished data). Overall, the government has estimated that approximately 12% of the UK population may become clinically ill during this influenza season, although these forecasts are subject to uncertainty.

(http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_107413).

Pandemic (H1N1) 2009 is the dominant influenza strain in England, with only a small proportion of influenza activity attributable to other strains. This is similar to the experience of most countries in the northern and southern hemispheres

(<http://www.flu.gov/professional/global/southhemisphere.html> and http://www.who.int/csr/disease/swineflu/laboratory16_10_2009/en/index.html).

However, it is noteworthy that South Africa experienced two peaks of influenza activity during its winter season; a peak dominated by seasonal influenza A (H3N2) followed by the pandemic (H1N1) 2009 virus. Seasonal influenza A (H3N2) viruses also appeared prior to the pandemic (H1N1) 2009 virus in East Asia, particularly in China. Although influenza A (H3N2) has continued to co-circulate with the pandemic virus, over time the proportion of influenza cases in Asia which are related to seasonal influenza has declined as the proportion related to the pandemic (H1N1) 2009 virus increased (http://www.who.int/csr/don/2009_10_23/en/index.html). It is possible that England and other northern hemisphere countries could experience an early peak of influenza due to

pandemic (H1N1) 2009, followed by a second peak of activity due to seasonal strains, particularly influenza A (H3N2). Most of the H3N2 viruses circulating globally are a different strain from the A/Brisbane/10/2007 (H3N2)-like virus contained in the northern hemisphere 2009/10 vaccine.³

Worldwide, more than 10,000 clinical specimens (samples and isolates) of the pandemic (H1N1) virus have been tested and found to be sensitive to oseltamivir (http://www.who.int/csr/disease/swineflu/laboratory23_10_2009/en/index.html). Only a very small number of pandemic viruses in England and worldwide with resistance to oseltamivir have been detected to date ([http://www.who.int/csr/disease/swineflu/notes/\(H1N1\)_antiviral_use_20090925/en/index.html](http://www.who.int/csr/disease/swineflu/notes/(H1N1)_antiviral_use_20090925/en/index.html)). All of these viruses show the same H275Y mutation that confers resistance to the antiviral oseltamivir, but not to the antiviral zanamivir. It is likely that continued sporadic cases of resistance to oseltamivir will occur during the second wave. Continued vigilance is needed, not only to detect such cases, but to conduct epidemiological investigations to assess any evidence of person-to-person transmission of resistant strains.

Surveillance remains a fundamental cornerstone in the HPA's strategy during the second wave. Specific areas of focus include:

- Monitoring of observed national trends for both pandemic and seasonal influenza activity through a range of surveillance schemes
- Mathematical modelling to estimate numbers of cases and trends in influenza activity
- Microbiological characterisation and monitoring of the pandemic virus to detect changes in antiviral susceptibility and molecular markers of severity
- Investigations to assess potential changes of particular concern in the epidemiological, clinical or virological characteristics of the pandemic virus (for example, person-to-person transmission of a resistant strain; increased clinical severity)
- Serological surveys to assess the proportion of the population infected with the pandemic virus
- Monitoring the impact of the pandemic vaccination programme
- Intelligence gathering about the pandemic at the global level

Disease severity

Most people in England and elsewhere have experienced a mild, typical influenza-like illness associated with pandemic (H1N1) 2009 infection. In England, the number of deaths in the first wave has been far less than in a typical influenza season.

However, severe cases have occurred and the risk of hospitalisation was increased by the presence of underlying risk factors. During a recent WHO consultation, it was noted that the clinical picture in severe cases is 'strikingly different from the disease pattern seen during epidemics of seasonal influenza with a sizeable number of severe cases and deaths in previously healthy young people ([http://www.who.int/csr/disease/swineflu/notes/\(H1N1\)_clinical_features_20091016/en/index.html](http://www.who.int/csr/disease/swineflu/notes/(H1N1)_clinical_features_20091016/en/index.html)). Primary viral pneumonia has been the most common finding in severe cases and a frequent cause of death at the global level. It is of some concern that

³Between 01 September and 11 October 2009, seven seasonal influenza A (H3) viruses have been characterised at the HPA's Respiratory Virus Unit as A/Perth/16/2009-like.

preliminary FluCIN data suggest that a sizable proportion of hospitalised patients did not receive antivirals prior to admission.

Even if the proportion of severe illness remains unchanged, as the number of cases increases overall, the number of severe cases requiring hospitalisation, critical care and other specialised care will rise concomitantly. It has been estimated that during the upcoming pandemic wave up to a further 35,000 people may be admitted to hospital, with up to 5,300 requiring critical care

(http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_107413).

Reducing pandemic-related morbidity and mortality continues to be a key priority for the HPA, working in collaboration its partners and stakeholders. Key areas of focus include:

- Amplification of hospital-based surveillance to assess trends in hospitalised cases, disease severity, secondary bacterial infections, other complications and outcomes
- Surveillance of deaths reported to be due to pandemic influenza and estimates of total excess mortality during the period of pandemic influenza activity
- Regular review and updating of guidance in the areas of vaccination, case investigation, management and treatment, and laboratory testing
- Early treatment with antivirals for people at increased risk of severe disease or complications
- Provision of evidence-based advice on precautionary measures for people at increased risk of severe disease or complications to reduce their risk of infection
- Selective investigations to better understand the transmission dynamics of the pandemic virus, including the infectivity of asymptomatic/subclinical infections

Impact of interventions

Treatment of cases with antivirals, coupled with extensive tracing and prophylaxis of contacts, were the principal countermeasures used during the containment phase of the first wave in England. Preliminary analyses suggest that they were effective in reducing transmission at the individual level (for example, household contacts), but the impact at the population level is less clear (HPA, unpublished data).

In general, antivirals appeared to be well-tolerated. However, among children who were prescribed a course of oseltamivir prophylaxis in response to school-related outbreaks, compliance was variable (11,12). Secondary school students reported higher rates of compliance, compared with primary school students. About one half of all students who were surveyed reported 'feeling unwell' with one or more side effects. Gastrointestinal symptoms, headaches and neuropsychiatric symptoms (for example, trouble concentrating) were among the more commonly-reported adverse events.

During the second wave, vaccination will be an important pharmaceutical countermeasure to protect people at increased risk of severe illness, as well as frontline health and social care workers. However, the effectiveness of vaccination will depend on a number of factors, such as the timing of delivery, uptake and efficacy.

A limited number of non-pharmaceutical measures were utilised during the containment phase of the first wave of the pandemic. Some of these measures, such as hand hygiene, respiratory etiquette, self-isolation while ill and adherence to infection control measures in acute and primary health care settings, will continue in the second wave. Other measures, such as school closures, which were undertaken during the containment phase to slow transmission, are not expected to be routinely implemented.

Nonetheless, there are important opportunities to evaluate lessons learnt from all of these approaches.

Robust evaluation of pharmaceutical and non-pharmaceutical interventions is critical for HPA to provide sound guidance for their use and/or target efforts to improve their effectiveness in reducing pandemic-associated disease. Key areas of focus include:

- Monitoring and evaluation of vaccine uptake, effectiveness and safety
- Evaluation of the effectiveness and costs associated with school closures, contact tracing and other non-pharmaceutical interventions
- Evaluation of the impact of antiviral prophylaxis and treatment during the containment phase

Operational response

The implementation of an initial containment response was carried out primarily by the public health services in England, notably the Local and Regional Services and Regional Microbiology Network of the Health Protection Agency, and the local NHS. As case numbers increased, the pressure on the public health teams became intense. Collaboration with the NHS at the local level in the establishment and running of Flu Response Centres helped to reduce the workload. However, the pressure remained considerable and, in some areas, unsustainable, leading to modification of the containment response at the local level.

The move to the treatment-only phase from early July, and the introduction of the National Pandemic Flu Service later that month, changed the approach to management of patients and eased the pressure on the public health teams. Although consultations increased in primary care to levels seen during seasonal influenza epidemics, and increased numbers of cases were admitted to hospital, the health service coped without much difficulty with this extra load.

An assessment of the effectiveness of the containment strategy during the first wave is underway. Preliminary data indicate that prophylaxis of household contacts was effective in reducing the risk of infection in this setting, but the impact at the population level is less clear. As pandemic influenza A (H1N1) 2009, however, is now widely spread within the population of England, further attempts at a containment approach in subsequent waves would not be considered.

Experience in the southern hemisphere and from the northern hemisphere, up to the time of writing, suggest that a second wave will be associated with increased hospitalisation (particularly among children and young adults) and may lead to pressure on intensive care facilities because of the occurrence of severe illness in a small but significant minority of cases. It appears unlikely, however, that overall mortality will be substantially increased, due to the relative sparing of the elderly population. A later increase in activity of other influenza viruses, however, particularly seasonal influenza H3N2 virus, cannot be ruled out and would be likely to impact on the elderly population, with resultant increases in mortality. Vigilance, through surveillance, will need to be maintained to identify further developments of influenza activity as the season progresses.

Acknowledgements: This report was prepared by a Health Protection Agency drafting group, but represents the contributions of numerous colleagues from across the agency, particularly in the Local and Regional Services and Regional Microbiology Network Divisions and the Centre for Infections. Substantial contributions were provided by colleagues in academic institutions, the Department of Health, and the UK devolved

administrations. NHS colleagues provided information and support without which this report could not have been compiled.

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Annexe: Methods and data sources

Pandemic influenza is monitored in England through a range of surveillance systems, epidemiological studies and modelling analyses (http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1247728943615). In brief, these include:

Consultation rates for influenza-like illness with general practitioners

Rates of consultation for influenza-like illness (per 100,000 population covered) are reported by general practitioners in two sentinel surveillance schemes. The Royal College of General Practitioners (RCGP) Weekly Returns Service collects data from 60-100 general practices in England and Wales each week, covering a population of approximately 900,000. Q Surveillance® collects daily data on consultations for influenza-like illness from over 3,400 general practices in the UK. The scheme is based on data covering 43% of England's population, 10% of the population in Wales, and 17% in Northern Ireland.

Community syndromic surveillance

NHS Direct is a 24/7 nurse-led telephone health advice and information service in England, from which the proportion of callers reporting colds/flu and fever can be calculated. Beginning on 28 May 2009, symptomatic callers were asked to participate in a scheme to self-collect nasal swabs and post them for virological testing. On 23 July 2009 the National Pandemic Flu Service (NPFs) became operational and replaced NHS Direct as the source of community syndromic surveillance. The service issues antiviral drugs to people with influenza-like illness who do not fall into a specified risk group. Sampling from NHS Direct stopped after week 30 and started from NPFs in week 32. Implementation of NPFs affected general practitioner consultation rates from week 30 onwards.

First Few Hundred Surveillance System (FF100)

The FF100 system collected detailed demographic, exposure, clinical, treatment and outcome data for more than 300 cases of laboratory confirmed pandemic influenza and their close contacts, during the early part of the first pandemic wave. Information was obtained through interviews and record reviews. Virological swabbing was undertaken, when possible, for people with an influenza-like illness and blood samples for serological testing were sought from cases and their contacts.

FluZone

FluZone is a case-based decision support system based on an earlier system of data collection and risk assessment (HPZone). It was rapidly developed and rolled out to Health Protection Units and Flu Response Centres. This provided helpful data by Health Protection Unit area and was also used in case management and follow-up of contacts.

Hospitalisation data

During the initial part of the first wave, detailed information was collected for laboratory-confirmed cases in England as part of the in the FF100 project. Information collected included details of contact with the health service and, where appropriate, of hospitalisation. Subsequently more limited information was collected by Health Protection Units through the FluZone system.

Once it became impractical to test all suspected cases for influenza infection, primary care trusts reported to the Department of Health the number of confirmed or clinically-suspected cases of pandemic influenza admitted to local hospitals.

Contributions to the collection and collation of data on hospitalised cases of pandemic influenza have been provided by two further schemes. First, as part of an investigation of the potential protective effect of prior seasonal influenza immunisation, HPA regional microbiology laboratories have collected selected information from laboratory-confirmed cases (and from laboratory-negative cases). Second, a separate system has been developed by the University of Nottingham, on behalf of the Department of Health, to investigate clinical aspects of pandemic influenza through collection of detailed clinical and other information on hospitalised cases (the Flu Clinical Information Network or FluCIN). Cases have been recruited from a subset of major clinical centres in England.

In October 2009, a web-based reporting system was introduced across England to collect information on all laboratory-confirmed cases admitted to hospital. In addition to collecting information prospectively, this system has been used to collect information retrospectively on laboratory-confirmed cases admitted to hospital since the beginning of the pandemic.

Mortality monitoring

Death registrations collated by the Office for National Statistics and General Registry Office report total deaths from all causes and total respiratory deaths on a daily/weekly basis. This information is used to estimate any excess in all-cause death registrations as compared to previous years. This system has a reporting delay of 1-2 weeks. In addition to this, a more rapid assessment through provisional data from the General Registry Office has provided information on deaths by age and this has been used to more promptly examine for any excess deaths in specific age groups.

In addition, information on individual laboratory-confirmed pandemic influenza deaths is sought through various routes (for example, local Health Protection Units and, during the period they were open, Flu Response Centres). Based on available information, cause of death is determined in individuals who had laboratory-confirmed pandemic (H1N1) 2009 infection.

Field epidemiology studies

A number of ad hoc investigations were undertaken by local Health Protection Units. These investigations occurred in schools, households and other venues.

Virological surveillance

The National Laboratory Reporting Scheme comprises approximately 230 NHS, HPA and independent sector laboratories throughout England which report on laboratory-confirmed influenza infections, identified in patients from community and hospital settings, to the HPA Centre for Infections.

A subset of 40-50 general practices in the RCGP Weekly Returns Service submit respiratory samples for virological testing from patients presenting with influenza-like illness. Specimens, along with key information about the patient and illness, are submitted to the HPA Centre for Infections. A complementary scheme of sampling by general practitioners is carried out by the HPA, whereby specimens from patients with acute respiratory infections are submitted to the local regional laboratory of the HPA Regional Microbiology Network (RMN). Specimens are evaluated by PCR for influenza and other respiratory virus infections.

The HPA Centre for Infections Respiratory Virus Unit characterises isolates of influenza viruses and carries out molecular sequencing. The unit also monitors the occurrence of

antiviral resistance in influenza isolates using a molecular marker for oseltamivir resistance (H274Y) and subsequent full phenotypic susceptibility testing.

Serological testing

Serological analysis of serum samples was performed by the combined application of two assays – microneutralisation (MN) and haemagglutination inhibition (HI) - which were designed and validated at the HPA Centre for Infections Respiratory Virus Unit (RVU). Samples for field epidemiological studies were collected as serum pairs where possible (acute and convalescent, separated by at least 14 days), but in most cases a single convalescent sample was obtained. For a sero-incidence study (around 1,000 samples per month), chemical pathology laboratories represent the principal source of sera. Serological assays were performed according to procedures established at RVU using NIBRG122, a reverse genetics version of a virus isolated from a human case (confirmed and isolated end of April 2009; A/England/195/2009) and antigenically representative for the viruses currently circulating in the UK. Recent infection was confirmed on the basis of 4-fold titre increases between an acute and convalescent serum sample by HI or MN. For unpaired sera (single convalescent serum samples from field studies or samples for sero-incidence study) probability of recent infection was calculated based on the achievement of HI titres ≥ 32 (which correlates to a four-fold titre rise from a baseline titre of <8).

Mathematical modelling

The estimated number of cases of pandemic flu, by region and age group, is calculated each week using a statistical model. The model uses data from several sources including general practitioner consultations, NPFS and sentinel virological schemes. An estimate of the total number of new cases is given each week. The methodology has altered slightly each week to take into account changes in policy (for example, the introduction of NPFS) and improvements in data. Previous week estimates are recalculated with updated data. The methodology has been described in more detail in Health Protection Reports (<http://www.hpa.org.uk/hpr/>) or on the Surveillance and Epidemiology page of the swine flu section of the HPA website (<http://www.hpa.org.uk/swineflu/>).

Version control

v4 2 December 2009: Added text on West Midlands and local NHS

v3 24 November 2009: Minor text amendments

v2 23 November 2009: Minor text amendments

v1 20 November 2009: Original version