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Research

Mortality from pandemic A/H1N1 2009 influenza in England: public health surveillance study

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Abstract

Objective To establish mortality from pandemic A/H1N1 2009 influenza up to 8 November 2009.

Design Investigation of all reported deaths related to pandemic A/H1N1 in England.

Setting Mandatory reporting systems established in acute hospitals and primary care.

Participants Physicians responsible for the patient.

Main outcome measures Numbers of deaths from influenza combined with mid-range estimates of numbers of cases of influenza to calculate age specific case fatality rates. Underlying conditions, time course of illness, and antiviral treatment.

Results With the official mid-range estimate for incidence of pandemic A/H1N1, the overall estimated case fatality rate was 26 (range 11-66) per 100 000. It was lowest for children aged 5-14 (11 (range 3-36) per 100 000) and highest for those aged >65 (66 (range 30-200) per 100 000). In the 400 people in whom the confirmed

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minority of deaths occur in previously healthy people, there is a case for extending the vaccination programme and for continuing to make early antiviral treatment widely available.

Introduction

On 11 June 2009 the World Health Organization formally confirmed the first pandemic of influenza for 40 years.¹ The novel pandemic A/H1N1 virus, which contains swine, avian, and human elements,² began to cause illness in the United Kingdom about a month³ after it first emerged in Mexico⁴ in March 2009.

In the UK, influenza related mortality is traditionally calculated with the national system of vital statistics. This is achieved by analysing death certificates or by deriving a statistical estimate of influenza related mortality based on all cause “excess mortality.”⁵ When numbers are small, measures of excess mortality are of limited use in estimating deaths from influenza in adults. Estimates based on death certificates might be subject to a delay of weeks and depend on the accuracy and completeness of death certificates, which are known to be unreliable.⁶ So far, mortality associated with pandemic A/H1N1 2009 influenza (here after referred to as pandemic A/H1N1) has been reported with variable completeness worldwide⁷ and in particular subgroups, including inpatients,⁸ patients in critical care,^{9 10 11} pregnant women,¹² and children.¹³

To obtain timely and accurate information on all deaths, the chief medical officer for England instigated an investigation of every death in England considered to be related to pandemic A/H1N1. We analysed these data, describing all reported deaths related to pandemic A/H1N1 infection in England by 8 November 2009.

Methods

All acute hospitals in England’s National Health Service (NHS) report their daily bed capacity to the Department of Health during winter months. With the onset of the pandemic, from the 7 July 2009 acute hospitals were asked to use this system to report suspected and confirmed deaths from pandemic A/H1N1. On 14 August 2009, a separate reporting system was established for deaths occurring outside acute hospitals. This required staff in each of the primary care trusts in England to contact every general practice in their region to ascertain any such cases. The first such report captured community deaths retrospectively from the start of the pandemic. The reporting cycle was subsequently repeated every week. Reports from acute hospitals and from primary care trusts were mandatory. If no deaths had occurred, a nil report was made. Deaths in acute hospitals before 7 July 2009 were ascertained through the Health Protection Agency’s flu reference centres and cross checked with records held by the directors of public health in each English health region.

Six physicians working for the chief medical officer received the reports of deaths suspected to be related to pandemic A/H1N1. They made direct contact with the responsible senior physician in the organisation reporting a death. They collected a standard information set from this physician (box). The American Society of Anesthesiologists (ASA) scale was used to describe the patient’s general health before the onset of influenza.¹⁴

Data collected for every reported death

Unique patient identifier (NHS number or hospital number)

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Pre-morbid health status (ASA grade)

Underlying medical conditions listed by organ system

Malignancy, immunosuppression, and pregnancy (directly sought risk factors)

A confirmed death was defined as related to pandemic A/H1N1 if either or both of the following criteria were met: pandemic A/H1N1 infection recorded on any part of a patient's death certificate (or synonym, such as "swine flu," "H1N1 pneumonia," "H1N1 virus," or other phrase clearly referring to pandemic A/H1N1 in the clinical circumstances) or pandemic A/H1N1 infection confirmed by laboratory testing, either before or after death.

While the number of cases of pandemic A/H1N1 in England was small, the Health Protection Agency ascertained numbers from laboratory testing of all known suspected cases. On 15 July, the agency started weekly estimation of incident case numbers using two primary care surveillance networks.¹⁵ Estimates date back to 2 June 2009. Before this there were 225 confirmed cases in England.¹⁶ Consultation rates for influenza-like illness were recorded by the QSurveillance National Surveillance System. This captures electronic clinical record data for about 20 million patients in England registered with a general practitioner.¹⁷ The Royal College of General Practitioners and Health Protection Agency's regional microbiology network sentinel surveillance scheme estimated positivity rates of pandemic A/H1N1 based on laboratory testing of a sample of patients with influenza-like illness, by region and by age group. To estimate case numbers for the whole of England, rates were multiplied by consultation rates for influenza-like illness and scaled up with the most recent population estimates from the Office for National Statistics. The estimate was further scaled up to account for the proportion of individuals with symptomatic pandemic A/H1N1 who did not consult their general practitioner. This proportion was taken to be 50-80%.

On 23 July 2009, the National Pandemic Flu Service (NPFS) was activated in England. This is a telephone and internet based service. It provides treatment advice with a standardised algorithm, and, when appropriate, authorises individuals to obtain antiviral drugs from a local collection point. The Health Protection Agency's method of estimation therefore changed from this date. The number of individuals authorised by the flu service to collect antiviral drugs was multiplied by positivity rates of pandemic A/H1N1 derived from a sample of these individuals. This provided an estimated number of true positive cases. This weekly estimate was added to the weekly estimate derived from primary care surveillance. The two were scaled up to account for those individuals with symptomatic infection who neither consulted their general practitioner nor used the flu service. This proportion was estimated at 30-70%. Hence, age specific estimates of the total number of incident symptomatic cases in the population were made on a weekly basis.

We used the estimates of case numbers and the demographic information gathered about deaths to calculate age specific case fatality rates. To account for the lag between onset of symptoms and death,¹⁸ we used the cumulative number of cases until the date two weeks before 8 November 2009. Two weeks is the approximate time period observed between onset of symptoms and death. Sensitivity analyses were performed to test the impact of censoring at one week and four weeks.

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We determined whether the dead patient would have been eligible for the current (phase 1) vaccination programme in England based on their age and underlying conditions.^{21 22} The Department of Health has estimated that 9.31 million people in England are eligible. We estimated the length of stay in hospital and intensive care units by subtracting the date of admission to hospital or intensive care from the date of death.

In England all deaths are recorded on a standard death certificate, which distinguishes between direct causality and contributory factors. Part I of the certificate records diseases or conditions directly leading to death in a causal chain with up to three elements, where 1a is the disease or condition directly leading to death, 1b is a disease or condition leading to 1a, and 1c is a disease or condition leading to 1b. Part II records other relevant conditions contributing to the death but not related to the disease or condition causing it. Death certificates were also analysed according to the methods of ICD-10 (international classification of diseases, 10th revision),²³ used nationally and internationally to produce national mortality statistics.²⁴ This determines an “underlying cause of death” from the causal chain and contributing conditions reported on the death certificate.

Results

Initial reports of 208 deaths between 1 June and 8 November 2009 were received. Of these, 138 met the case definition as being related to pandemic A/H1N1. The others were excluded from analysis because the initial clinical suspicion was not borne out by investigation and hence the case definition was not met (n=56) or because they did not yet fulfil the case definition but death certification or results of postmortem tests were outstanding (n=14).

An estimated 540 000 people (range 240 000-1 100 000) in England had symptomatic pandemic A/H1N1 infection in the study period. With this denominator, the case fatality rate was 26 (11-66) deaths per 100 000 cases. On a general population basis over the same period, there were 1100 (400-2200) cases per 100 000 people and 2.7 (95% confidence interval 2.2 to 3.2) deaths per million (table 1).²⁵ Fig 1²⁶ shows the number of deaths occurring in each week and the mid-point estimate of case numbers. The time distribution of cases follows a classic epidemic curve, with a peak in July, and a second wave in October and November. The time distribution of deaths is similar, with deaths in the first wave peaking two to three weeks after the peak of cases.

 Figure 1

Fig 1 Weekly estimated incidence of pandemic A/H1N1 cases (mid-range estimates) and confirmed deaths in England (source: Health Protection Agency)

Age group (years)	Population* (1000s)	Cases (estimated)		No of deaths			Case fatality rate per 100 cases (range)
		No (range) (1000s)	Cumulative incidence per 100 000 population	Total	Male	Female	

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Age group (years)	Population* (1000s)	Cases (estimated)		No of deaths			Case fatality rate per 100 000 cases (range)
		No (range) (1000s)	Cumulative incidence per 100 000 population	Total	Male	Female	
5-14	5961	187 (86-381)	3100	20	7	13	11 (3-36)
15-24	6812	144 (67-297)	2100	17	8	9	12 (4-40)
25-44	14 460	125 (58-297)	850	37	21	16	30 (8-88)
45-64	12 661	45 (21-92)	350	29	21	8	65 (20-200)
≥65	8159	3 (1-5)	30	26	14	12	98 (30-320)
All ages	51 092	536 (247-1097)	1100	138	75	63	26 (6-80)

*From Office for National Statistics mid-population estimates 2007.

Table 1

Age specific indices of incidence of and mortality from pandemic A/H1N1 in 2009. All population and case estimates rounded to nearest 1000

A sensitivity analysis censoring cases one week before death yielded a similar case fatality rate of 22 (range 9-56) deaths per 100 000 cases. Censoring at four weeks yielded a case fatality rate of 34 (14-90) deaths per 100 000. If we included all the 14 deaths currently under investigation, censoring at two weeks, the case fatality

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Before contracting pandemic A/H1N1, over a third of those who died were either previously healthy (ASA grade one, 19%, 26/138) or had mild systemic disease that did not limit their activity (ASA grade two, 17%, 24/138). Two thirds had severe (ASA grade three, 33%, 46/138) or incapacitating (ASA grade four, 30%, 42/138) underlying systemic disease. Patients at the extremes of age (<5 and ≥65) had poorer pre-morbid health as assessed by ASA grade (fig 2)↓.

 Figure2

Fig 2 Age and pre-morbid health of patients who died from causes related to pandemic A/H1N1

Patients who died had a median of two long term conditions or risk factors (26 had no risk factors or long term conditions, 32 had one, 34 had two, 31 had three, 7 had four, 4 had five, 2 had six, and 2 had seven). Chronic respiratory disease and neurodevelopmental disorders were the most commonly reported long term conditions (table 2)↓. The median age of patients was 8 (interquartile range 2-19, n=25) in those with a neurodevelopmental disorder, 30.5 (20-47, n=15) in those with asthma, and 64 (48-74, n=13) in those with COPD (chronic obstructive pulmonary disease). Of all those who died, 67% (92/138) fell into one of the risk categories eligible for the first phase of vaccination in England. The population risk of death for those falling into a vaccination group (9.9 per million people) was nine times that for those not in an at risk group (1.1 per million people, Pearson $\chi^2=217$, df=1, $P<0.001$). Those who were aged ≥65 were more likely to fall into a priority group for vaccination than those outside this age group (24/26 v 68/112, $P=0.002$, Fisher's exact test).

	No of patients
Respiratory:	
Asthma	15 (3)
COPD	13 (1)
Scoliosis	6 (0)
Restrictive disease	5 (0)
Bronchiectasis	4 (0)
Tracheostomy	2 (0)
Other	6 (0)

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	No of patients
Other	6 (0)
Endocrine:	
Diabetes mellitus	9 (0)
Obesity	11 (2)
Hypothyroidism	5 (0)
Haematological:	
Leukaemia	6 (3)
Other haematological malignancy	9 (2)
Anaemia	6 (1)
Other	2 (0)
Non-haematological malignancy	5 (1)
Pregnancy	5 (3)
Neurological:	
Cerebral palsy	8 (4)
Other neurodevelopmental disorder	17 (2)
Epilepsy	4 (0)

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	No of patients
Other	4 (0)
Gastrointestinal:	
Chronic liver disease	8 (4)
Percutaneous endoscopic gastrostomy	8 (1)
Malnutrition	3 (0)
Ulcerative colitis	1 (0)
Other	8 (0)
Renal:	
Chronic kidney disease	13 (0)
Other	3 (0)
Rheumatological:	
Inflammatory disorders	7 (0)
Metabolic bone disease	2 (0)
Immunosuppression:	
Drugs	19 (2)
HIV/AIDS	1 (0)

COPD=chronic obstructive pulmonary disease

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ambulance or on arrival at hospital. The remainder (n=9) died in the community, having been solely cared for in the community.

In those admitted to hospital with pandemic A/H1N1, symptoms started a median of three days before admission (1-5 days, n=111). Two patients developed influenza-like symptoms while already in hospital. The date of onset of symptoms was missing or unclear for 12 patients admitted to hospital. After the exclusion of four patients (two with hospital acquired influenza, one discharged before death, and one with date of admission missing), patients spent a median of eight days in hospital (3-14 days, n=121). Most patients admitted to hospital (82%, 103/125), were treated in an intensive care unit at some stage, dying a median of six days (2-14 days, n=103) after admission to the unit.

Use of antiviral drugs

Of those who died, 78% (108/138) were prescribed antiviral drugs. In the 94 for whom a date of symptoms was reported, patients started taking the drugs a median of five days after symptoms began (interquartile range 2-8 days). Of those admitted to hospital, 9% (11/125) had started taking antiviral drugs before admission. Of those treated with antiviral drugs, 24% (26/108) received them within the recommended 48 hours after onset of symptoms. Greater use of antiviral drugs was observed in patients who died in acute hospitals than in those who died in the community (101/125 v 7/13, P=0.04, Fisher's exact test,).

Death certification

In 11 cases the death certificate had not yet been issued because a coroner's investigation was ongoing (8%, 11/138). Table 3 reports the position of pandemic A/H1N1 on the 127 death certificates issued. When we analysed all available death certificates using the ICD-10 methods used to produce mortality data, the underlying cause of 39% of deaths (49/127) would be classified as influenza.

Record of "pandemic A/H1N1" or synonym on death certificate	Confirmation of pandemic A/H1N1 by microbiological test		
	Positive result	No test conducted	Total
Recorded in part I (led directly to death)	70	4	74
Recorded in part II (contributed to death)	21	2	23
Not recorded on death certificate	30	NA	30
Death certificate not yet issued (coroner's investigation awaited)	11	NA	11

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43% of these cases (32/74). In 11% of cases (8/74) pandemic A/H1N1 was the sole condition recorded on the death certificate. In most cases, the direct cause of death was a respiratory condition (76%, 56/74).

Certified direct cause of death	No of cases (%)
Influenza	32 (43)
Pneumonia	14 (19)
Acute respiratory distress syndrome (ARDS)	4 (5)
Pneumonia and ARDS	1 (1)
Other respiratory complications	5 (7)
Multi-organ failure	13 (18)
Intracranial haemorrhage (secondary to anticoagulation for ECMO)	2 (3)
Myocardial infarction	1 (1)
Pulmonary embolism	1 (1)
Myocarditis	1 (1)
Total	74 (100)

ECMO=extracorporeal membrane oxygenation.

Table 4

Certification of direct cause of death in cases in which pandemic A/H1N1 infection was recorded within causal chain leading to death

Discussion

By 8 November, about 1% of England's population had had symptomatic pandemic A/H1N1 2009 infection (estimated range 0.5-2.2%). We estimate that 0.026% (range 0.011-0.066%) of these individuals died from

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the method did not capture deaths in independent sector hospitals, nearly all acute care in England is provided by the NHS.²⁵ Under-reporting of deaths is possible because cases are either not recognised or not reported. Mandatory reporting systems, requiring a “nil report” in the absence of a positive daily or weekly report, were instigated to minimise this risk. Similarly, under-reporting of comorbidities is a possibility, particularly among older people, because they might have been undiagnosed or not known to the physicians caring for the patient in their terminal illness. The presence of obesity was not specifically asked for and might therefore be under-reported. Inevitable delay in confirming or refuting the causation of some deaths might hamper the estimate of case fatality rate. There were, however, only 14 deaths in this category and so the effect on the estimate is not substantial.

These national reporting systems were established early in the pandemic. They were designed to be manageable for clinicians potentially faced with far greater numbers of deaths. Gathering more detailed clinical information would have been useful. Placing a high burden of reporting detailed data on busy clinicians, however, limits the accuracy of responses and the sustainability of data collection. Had we anticipated so few deaths, we might also have asked clinicians to provide information on surviving patients as controls. Our method focused on capturing key public health information. Comparisons with groups of patients who survived will be important in gaining full benefit from the data presented here.

Case fatality rates in influenza pandemics

The case fatality rate of 0.026% (range 0.011-0.066%) computed by this analysis is lower than most estimates made so far in this pandemic but is also based on a different denominator. Most estimates have used laboratory confirmed cases in their denominator, resulting in rates of 0.1-0.9%.^{7 26 27 28} Confining the denominator to laboratory confirmed cases will provide a gross underestimate of the incidence of true symptomatic cases and therefore a substantial overestimate of the fatality rate for symptomatic cases. One Mexican study calculated a case fatality rate of 0.1%, but the denominator was restricted to patients presenting to primary care.²⁸ The validity of this denominator is questionable. Not all of these presentations would have been caused by pandemic A/H1N1, not all people with symptoms seek medical attention, and access to care might be limited in poorer areas. A much lower estimate of 0.005% (95% confidence interval 0.003% to 0.01%) was made in New Zealand, based on an estimate of symptomatic case numbers in the population.²⁹ Given the move away from laboratory testing of large numbers of cases, it seems sensible that estimation of the case fatality rate should reflect this. The estimates of case fatality rates in our study have wide ranges, which reflect uncertainty about the proportion of people with symptoms who do not seek medical attention. If this proportion is higher than thought, our case fatality rates might be an overestimate. This proportion might have changed over time as public attitudes to the pandemic have evolved. The approach of using an estimate of total case numbers is subject to greater uncertainty than solely counting laboratory confirmed cases. As a measure, however, it should provide a more meaningful estimate of the case fatality rate among the symptomatic population as a whole.

Our estimate of case fatality rate compares favourably with those in the three 20th century influenza pandemics. The rate in the 1918-9 H1N1 pandemic was 2-3%. Rates in the subsequent pandemics (1957-8 and 1967-8) were in the order of 0.2%.³⁰ Estimates of numbers of deaths from previous pandemics are probably less reliable than current estimates, being based only on statistical methods and death certification. Laboratory confirmation of influenza viruses was not widely available. Deaths from other circulating viruses might also have been counted

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Our data suggest a particularly high case fatality rate among those aged ≥ 65 . Our age specific case fatality rates follow a pattern similar to the J shaped distribution described in the previous two pandemics³¹ and in a Mexican study of the current pandemic.²⁸ The low absolute numbers of deaths and cases, however, particularly in the very young, prevent us drawing conclusions. The 1918-9 pandemic was characterised by high case fatality additionally occurring among young healthy adults.³² There is no evidence of this from our analysis of the current pandemic.

Risk groups and vaccination

So far there have been an estimated 3000 cases of pandemic A/H1N1 among the eight million people aged ≥ 65 in England, with a case fatality rate of 1.0%. This group therefore has the lowest incidence rate and the highest case fatality rate. This finding is consistent with other analyses of confirmed cases and deaths during this pandemic.^{7 10} The population risk of death for this age group is not significantly different from that of any other age group. We note that almost all (24/26) of the deaths in this age group were in people in a risk group now eligible for vaccination. The low incidence rate in this age group—seen consistently in the southern hemisphere³³—might in part be because of previous exposure to strains similar to pandemic A/H1N1.³⁴ Without this previous exposure, the pandemic might have caused many more deaths in this age group. If the attack rate in the older population rises over the winter, as it did in the 1957 pandemic,^{35 36} a larger number of deaths might be anticipated. This has not, however, been observed in the southern hemisphere.³³

Our series shows that a high proportion of patients (67%) fell into one of the risk groups identified for phase one of the vaccination programme that is currently running in England. This finding supports the importance of achieving high vaccination uptake for these groups. This is consistent with the findings of a Californian study, in which 75% of patients who died had risk factors for complications of seasonal influenza.³⁷ Other studies^{8 10 13} have identified similar risk conditions, particularly asthma and other respiratory conditions and neurodevelopmental conditions.¹³ Obesity seems under-represented in comparison with other studies^{8 10} and might reflect under-reporting in our study because it was not recorded as a diagnosis within the patient's hospital record. Comparisons with surviving infected patients or patients in hospital will be important in allowing the risks associated with particular underlying conditions to be further quantified.

Delayed use of antiviral drugs

While most patients received antiviral drugs, only a minority received them within the recommended 48 hour window. Similar evidence of delays in the prescription of antiviral drugs, and of less than universal use, has emerged from recent studies of hospital patients in the United States.^{8 13} An analysis of 272 inpatients with pandemic A/H1N1 in the US suggests that use of antiviral drugs confers a survival benefit, particularly when they are started within two days of onset of illness.⁸ Although minimal, the risk of side effects associated with use of antiviral drugs and vaccination does become more important because the risk associated with the disease is also low, particularly for previously healthy people. End points other than death (such as illness requiring time off work, admission to hospital, admission to critical care) are also important. Further cost benefit analyses would be valuable although difficult, given the uncertainties of an evolving pandemic.

Unreliability of death certification

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categorising deaths by underlying cause. The approach we used complements these statistical approaches. Their use in combination could be considered in monitoring future disease outbreaks.

Conclusions

The first influenza pandemic of the 21st century is considerably less lethal than was feared in advance. Case fatality rates vary by age in a similar pattern to the two previous pandemics but are currently much lower. This is fortunate. The challenges of risk communication and of policy making remain.

Our findings lend support to a vaccination strategy that prioritises high risk groups. They also show that a substantial minority of deaths are occurring outside these groups. Wider population vaccination therefore merits consideration. Cost benefit analyses could further assist these decisions. These are difficult to conduct and to interpret in the uncertain context of an evolving pandemic.

We observed delayed antiviral use in most fatal cases. The value of this observation is limited by the absence of a control group, but it might be important. It suggests value in making antiviral drugs readily available to previously healthy people as well as to those at high risk. This reinforces that where countermeasures (antivirals, vaccines) are available, they should be actively deployed. A lower population impact than previous pandemics is not a justification for public health inaction when death, serious illness, and admission to hospital can be prevented.

What is already known on this topic

Past pandemics of influenza have produced assessments of mortality based on calculations of “excess death”; these estimates depend on death certification, which is known to be unreliable

Early reports of case fatality rates for the present A/H1N1 pandemic have used laboratory confirmed cases as the denominator, likely to be a gross underestimate of incidence

What this paper adds

The current estimated case fatality rate, using an estimate of symptomatic cases in the community as the denominator, is lower than previous estimates

In the current pandemic children have experienced the highest attack rate and the lowest case fatality rates, while older people are much less susceptible but are more likely to die when affected

Notes

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Footnotes

- We are grateful to the many clinicians in England who supplied the clinical information on their patients,

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- Funding: This work was conducted as part of the public health response to pandemic influenza in England. No additional funding was sought.
- Competing interests: LJD is the chief medical officer for England. In this role he advises the government on public health policy, including the management of the pandemic. PDR, BME, FECG, IEY, and OTM support him in this task. All authors have completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) (URL) and declare (1) no financial support for the submitted work from anyone other than their employer; (2) no financial relationships with commercial entities that might have an interest in the submitted work; (3) no spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; and (4) no non-financial interests that may be relevant to the submitted work.
- Ethical approval: This exercise was undertaken as part of a public health surveillance programme for the pandemic. As such no explicit ethical approval was necessary or sought. This exercise was undertaken under the Health Service (Control of Patient Information) Regulations SI1438/2002, which provide a basis for collecting and processing data without patient consent for the purposes of communicable disease control in England.
- Data sharing: No additional data available.

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