How could rapid tests for influenza increase the (cost-)effectiveness of the National Pandemic Flu Service (NPFS)?
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BACKGROUND

In response to the 2009–2010 influenza A/H1N1 pandemic, England implemented an innovative internet and telephone-based service, the National Pandemic Flu Service (NPFS), to provide access to treatment to the general population and relieve pressure from traditional healthcare services. This was an unprecedented approach to rapid, targeted, mass treatment used in the 2009-10 pandemic, which identified 1.8M cases of influenza-like illness (ILI) vs 740k by general practitioners (GPs). The UK Influenza Pandemic Preparedness Strategy [Department of Health 2011] envisages its use in the future.

As GPs and NPFS used clinical diagnosis, some patients treated for influenza will not have the infection. A rapid test could reduce this over-use of antivirals – if the negative predictive value (NPV) is high enough to justify not providing treatment to those who test negative. However, average GP prescribing rates of antivirals for ILI are low (only ~30% of GP-diagnosed ILI cases in the pandemic), so a key benefit of a rapid test could be *increasing* influenza treatment by GPs (even with a low NPV) – if the positive predictive value were high enough. A rapid test could also alter patient behaviour in ways that could be beneficial to health, encouraging care-seeking and promoting uptake and completion of treatment.

The goal of this study was to contribute to the development of a target product profile for rapid tests for influenza, by determining the maximum cost per test at which it would be considered cost effective for use by the NHS in pandemic response under a range of scenarios of use by GPs and NPFS, including its effect on patient behaviour.

We also examined use of a rapid test to enhance real-time surveillance. In 2009-10, whilst data on numbers of ILI cases attending GPs and assessed by NPFS were available the day after they occurred, the swab positivity data typically took around 2 weeks to become complete, due to logistical requirements and limitations of laboratory testing capacity. A rapid test would avoid this delay.

DATA SOURCES

Flu Watch

Flu Watch is a household-based community cohort study of acute respiratory disease and influenza infection in England that has been previously described [Fragaszy et al. 2016, Hayward et al. 2014]. In brief, the study followed up cohorts during six influenza seasons which included 3 consecutive periods of seasonal influenza circulation (winters 2006-07, 2007-08 and 2008-09) and the first three waves of the 2009 influenza pandemic (spring-summer 2009, autumn and winter 2009/10, and winter 2010/11). In total there were 5484 participants followed up for 118,158 person weeks. Individuals were randomly recruited through GP registration lists and their entire household was invited to participate. Participants gave written informed consent and parents/guardians gave proxy consent for children. The Flu Watch study was approved by the Oxford MultiCentre Research Ethics committee (06/Q1604/103).

Upon entry into the cohort, participants completed a baseline survey that collected basic demographic, health and socio-economic data as well as self-reported vaccination status. Participants aged 16 and over also provided pre- and post- season blood samples for serological analysis of the currently circulating influenza strains. Blood samples were optional for children aged 5-15 years.

Throughout the follow-up period, participants were contacted weekly and asked to record if they had a "cough, cold, sore throat, or flu-like illness". During periods of acute respiratory illness, participants were asked to prospectively complete illness diaries in which they reported daily symptoms and temperature measurements. Participants were also asked to submit, by mail, a self-administered nasal swab on day two of any illness. These swabs were transported in viral transport medium and tested by RT-PCR for the presence of currently circulating influenza A viruses (H1N1, H3N2 and from 2009 onwards H1N1pdm09), influenza B, respiratory syncytial virus and human metapneumovirus. All swabs until October 2009 and a subset of swabs after that point were additionally tested for respiratory syncytial virus, human metapneumovirus, rhinovirus, coronavirus, adenovirus and parainfluenza virus). Participants' care-seeking behaviour and treatment was also monitored throughout periods of respiratory illness.

CALIBER

The CALIBER research platform has been described previously [Denaxas et al. 2012]. In brief it is a data resource which has linked primary care data from the Clinical Practice Research Datalink (CPRD), to secondary care data from the Hospital Episode Statistics (HES), Myocardial Ischaemia National Audit Project (MINAP), the Office of National Statistics (ONS) and the Index of Multiple Deprivation data.

Clinical Practice Research Datalink (CPRD)

The CPRD consists of longitudinal healthcare records for over 5 million patients, who form a representative sample of around 8% of the UK population. Data are available on lifestyle and demographic factors, consultations and prescriptions.

GP influenza-like illness swabbing scheme

As described in [Evans et al. 2011], "To obtain an estimate of the proportion of patients consulting with ILI whose illness was caused by pandemic influenza infection, data from two virological surveillance schemes in general practice were used. In the Royal College of General Practitioners (RCGP) sentinel surveillance scheme [Fleming & Elliot 2008], approximately 100 GPs report the number of cases of ILI consulting each week. A subset of 50% of these GPs obtain respiratory samples from a sample of patients presenting with ILI and submit them for investigation to the Respiratory Virus Unit of the HPA's Centre for Infections [Zambon et al. 2001]. In a complementary scheme in England, approximately 60 GPs submit respiratory specimens from patients presenting with ILI to one of the laboratories in the HPA's Regional Microbiology Network (RMN) [Joseph 1995]."

Hospital Episode Statistics (HES)
HES contains data collected for administrative purposes from all inpatient, outpatient, emergency critical care admissions at NHS hospitals in England [Denaxas et al. 2012].

National Pandemic Flu Service (NPFS)
The NPFS system routinely collected numbers of persons who (i) contacted the service, (ii) reported symptoms matching the definition of ILI and were authorised to obtain antiviral treatment; and (iii) collected antiviral treatment, as well as the time from authorisation to collection, and the demographic characteristics of these persons. NPFS was not able to collect detailed patient data, including tracking use of other healthcare services, date of symptom onset, or whether people who obtained antivirals took them or whether they were adherent or not.

National Pandemic Flu Service swabbing scheme
To determine the proportion of patients with ILI who used NPFS who has pandemic influenza, a sample of users of NPFS who were authorised to obtain antivirals was sent to Health Protection Agency (HPA), and a sample of those patients was posted a self-swab kit, with an equal number of kits being sent each time to each of the 10 Strategic Health Authority (SHA) regions (which meant that the probability of a person being sampled varied by region and time because the number of patients in each region varied over time).

National Pandemic Flu Service user survey
A survey of NPFS users who were authorised to obtain treatment was implemented, to investigate in detail patients' symptoms, care-seeking behaviour, and uptake of, and adherence to, treatment. The NPFS user survey was sent to a sample of patients who had been authorised by NPFS to obtain antiviral treatment and who had ticked a box on the swabbing-scheme form consenting to being contacted again for research. User survey questionnaires were sent to all persons with a positive swab test who consented to further contact, plus 3 persons who tested negative in the same week who consented to further contact (where possible: in a few weeks positivity was >25% so there were not enough negatives to sample 3 per positive). The response rate (as a percentage of those sent the user survey questionnaire) was 57%. The youngest patients included in the study were 5 years old. Those aged 5–12 years old received a slightly different version of the user survey questionnaire designed to be completed by their parent or guardian (see Appendix for questionnaires). Questions included the number of days between the start of symptoms and use of NPFS, and, where relevant, collection of treatment, and starting treatment; the duration and severity of illness; the number of days taken off work; contacts made with other health services; and reasons for using NPFS, and, where relevant, reasons for using other health services, not collecting treatment, not starting treatment, and not completing treatment.

QSurveillance
QSurveillance is a GP-based syndromic surveillance system with ~40% population coverage, which supplied rates of diagnosed ILI during the pandemic period. It is described in [Smith et al. 2007].

ANALYSES

Self-swabbing PCR sensitivity – analysis of Flu Watch

Influenza infections have a wide clinical spectrum of outcomes ranging from asymptomatic infection to severe disease and death. Among the symptomatic infections, not all illnesses will render PCR positive nasal swabs. This may in part be due to low levels of viral shedding in mild illnesses, non-optimal timing of nasal swabs in relation to viral shedding as well as the sensitivity of the PCR assay itself. This analysis aimed to estimate the minimum sensitivity of PCR assays of self-administered nasal swabs taken in the community. During the first three waves of activity of A(H1N1)pdm09 (summer 2009 – winter 2010/11) we identified Flu Watch participants who seroconverted to A(H1N1)pdm09, experienced a respiratory illness between the relevant blood samples and submitted a nasal swab for that episode of illness. We limited analysis to participants whose illnesses were most likely due to A(H1N1)pdm09 infection by only including illnesses which either tested swab positive for A(H1N1)pdm09 or negative to all respiratory viruses tested. If a participant had multiple swabbed illnesses then only one illness was kept (either the A(H1N1)pdm09 positive illness if there was one, or else the earliest illness). We also excluded participants who were vaccinated between their paired seroconversion blood sample dates as well as those vaccinated 3 weeks or less prior to this first blood sample. We calculated the overall proportion of illnesses which tested positive for A(H1N1)pdm09 and its 95% confidence interval and investigated whether this proportion varied by age or season using fishers exact test. In sensitivity analysis, we investigated whether limiting illnesses to time periods of known viral circulation in the Flu Watch cohort affected results.

There were 61 people whose illnesses met the case definition. The overall proportion of these illnesses testing positive for H1N1pdm09 was 47.5% (95% CI: 34.6%–60.7%). There were no H1N1pdm09 positive swabs in the summer wave of the pandemic and after excluding the summer wave there was no evidence that the proportion of positives changed between the two winter waves (p=0.431). There was no evidence that the overall proportion of positive illnesses varied by age group (p=0.897). The proportion of positive swabs by age group appeared to change over the two winter seasons with younger age groups more likely to have positive swabs in the first season and the older age group more likely to have positive swabs in the subsequent season but this was based on small numbers and the confidence intervals overlapped. In sensitivity analysis we identified 54 swabs meeting our case definition and found a slightly larger percentage of swabs were positive (53.7%, 95% CI: 39.6%–67.4%).

Minimum estimates of PCR sensitivity were around 50%. It is probable that some of our seroconverting patients had asymptomatic infection and their included illnesses were due to non-influenza infections. This would lead to an underestimate of sensitivity. It is also plausible that some influenza illnesses were PCR negative because they were not shedding enough virus to be detected by PCR or the sample was taken too late and missed the period of viral shedding. This would lead to an overestimation of PCR sensitivity.

Serology sensitivity – analysis of Flu Watch

Prospective identification of influenza infection (asymptomatic and symptomatic) is typically based comparison of pre- and post-season antibody titres measured through serological assays. Generally a four-fold rise in titre or higher between the first and second blood sample in an unvaccinated person is considered evidence of infection. There are however cases of influenza infection which do not lead to a four-fold rise in titre or higher but do lead to illness and viral shedding. This indicates that the serological case definition requiring a 4-fold rise in titre does not have perfect sensitivity. We estimated the maximum sensitivity of a serological case definition requiring a 4-fold rise in titre using data from the Flu Watch study.

We identified all participants with A(H1N1)pdm09 positive swabs who additionally had paired blood samples regardless of whether they seroconverted (had a 4-fold rise in titre or greater) or not. We excluded participants who were vaccinated between their paired seroconversion blood sample dates as well as those vaccinated 3 weeks or less prior to this first blood sample in order to ensure any titre rise was due to natural infection and not vaccination.

We calculated the proportion of positive swabs which seroconverted and 95% confidence intervals using a binomial distribution. We also calculated the changes in titres between the first and second blood samples for all participants.

There were 35 participants with (H1N1)pdm09 positive swabs which met our criteria of which 29 seroconverted (had a 4-fold titre rise or greater) to that same strain (82.9%, 95%CI: 66.4%–93.4%). Of the 6 participants that did not seroconvert, five of them had no change in titre and one of them had a two-fold decline.

We found that about one sixth of PCR-identified influenza illnesses came from non-seroconverters but most of these non-seroconverters had a two-fold rise in titre. We are unable to identify all influenza infections through swabbing and PCR analysis as many infections are asymptomatic and some milder illnesses may not shed virus at levels detectable by PCR. If asymptomatic and mild infections are less likely to have a 4-fold rise in titre compared to more moderate or severe infections, then our upper estimate of sensitivity of a 4-fold rise serological case definition would be an over-estimate.

Attitudes to antivirals, consultation behaviour for influenza-like-illness and use of antivirals in England during the 2009 influenza Pandemic – analysis of Flu Watch and CPRD

Flu Watch participants prospectively reported respiratory illnesses, submitted nasal swabs for PCR diagnosis of influenza and reported care-seeking behaviour and treatment over the course of the winter wave of the 2009 influenza pandemic. In spring 2010 participants completed an attitudinal survey. 21% (138/644) of ILI episodes led to a consultation with a health provider. The proportion consulting was similar in those with and without chronic illness (24% vs 21%). Antivirals were taken by 3% (19/664) of people experiencing ILI and 6% (3/50) of PCR-confirmed influenza cases. The GP was involved in 62% of illnesses that led to a consultation. The NPFS was involved in 16% of illnesses that consulted but half of these also involved the GP. Almost all of the antivirals prescribed were to those who had consulted the NPFS. Most respondents agreed that antivirals could reduce influenza symptoms and reduce severe complications but only a minority agreed that antivirals were safe.

Clinical Practice Research Datalink (CPRD) data from May 2009-March 2010 were analysed to show trends in consultation for ILI and GP prescribing of antivirals and identify those most likely to receive a prescription when consulting with ILI. GP consultation and oseltamivir prescription rates decreased with age and were highest during the summer wave of the pandemic (27 and 16 per 100,000 person weeks respectively) compared to the winter wave (18 and 3 per 100,000 person weeks respectively). Of those consulting their GP with ILI the elderly were least likely to be prescribed antivirals and those with chronic cardiovascular disease, liver disease, renal disease, immunosuppression or obesity were no more likely than others to receive antivirals. Those with chronic respiratory disease and those with neurological disease were more likely than others to receive antivirals.

Only around 20% of those with ILI sought any medical advice during the winter wave of the pandemic and only 3% took antivirals. NPFS were involved in only 16% of these consultations. Those with ILI and chronic illness (who are at higher risk of hospitalisation and death) also had low consultation rates and, with the exception of chronic respiratory disease and neurological disease were no more likely to receive antivirals from their GP than others. Elderly people consulting with ILI were least likely to be prescribed antivirals. Taken together these results suggest that the NPFS will have had minimal impact on patient outcomes at a population level. GPs showed minimal evidence of targeting antivirals at those most likely to benefit. The results suggest a need to rethink the strategies for achieving high antiviral coverage particularly in the most vulnerable groups in future pandemics.

Effects of seasonal and pandemic influenza on health-related quality of life, work and school absence in English households: results from the Flu Watch cohort study

Estimates of health-related quality of life (HRQoL) and work and school absences for influenza are typically based on consulting cases or those meeting ILI case definitions and thus biased towards medically attended or severe disease. Community influenza cases often do not meet ILI definitions or consult healthcare services and are generally milder but estimates of HRQoL and absences in this group are limited.

To measure HRQoL using EQ-5D and work and school absences for community cases of acute respiratory infections (ARI), ILI and influenza A and B cases, Flu Watch participants prospectively recorded symptoms, work/school absences and EQ-5D data on daily basis during all respiratory illnesses. Participants submitted a self-sampled nasal swab on day 2 of illness for RT-PCR influenza A and B testing.

Quality-Adjusted Life Days (QALDs) lost were 0.26, 0.93, 1.61 and 1.84 for ARI, ILI, H1N1pdm09 and influenza B respectively. A third of working participants with influenza A or B took time off. Among students this was 74% and 40% respectively. Almost 30% of influenza cases reported someone else taking time off to care for them. These estimates of QALDs lost and work and school absences were lower than previous estimates because we focused on community cases, most of which are mild and do not consult. Community cases represent the majority of cases and are likely contribute a substantial loss of HRQoL on a population level.

Use of GPs and the National Pandemic Flu Service: decision-tree model

A decision tree model (Figure 1) for the diagnosis and treatment of H1N1 ILI was designed to represent care pathways and was implemented in the statistical programming language R. We considered the population of England in 2009, stratified by age groups used in GP surveillance data.

We consider health benefits (from averted morbidity and mortality), measured in quality-adjusted life-years (QALYs), and cost-savings (e.g. from fewer antivirals given to patients who do not have influenza, averted hospitalisations from appropriate rapid use of antivirals) to calculate the value of the rapid test, from which a cost-effective price per test can be deduced, from the perspective of the NHS. A QALY was valued at £20,000.Future costs and health utilities were discounted at 3.5% per year.

In 2009-10, individuals with ILI could seek care with either the NPFS or GP, or not seek care. Those using NPFS were authorised to obtain treatment, and a proportion of them did so, with a proportion of those starting treatment and a proportion of those completing treatment. Individuals with ILI who attended their GP were diagnosed with ILI and a proportion prescribed treatment, a proportion of whom obtained treatment, with a proportion of those starting treatment and a proportion of those completing treatment. Treatment of individuals whose ILI was due to H1N1 pandemic influenza reduces the risk of hospitalisation and death. Some individuals with ILI were hospitalised and a proportion of them died.

We modelled the impact of using a rapid test by GPs or NPFS in a range of scenarios, described below.

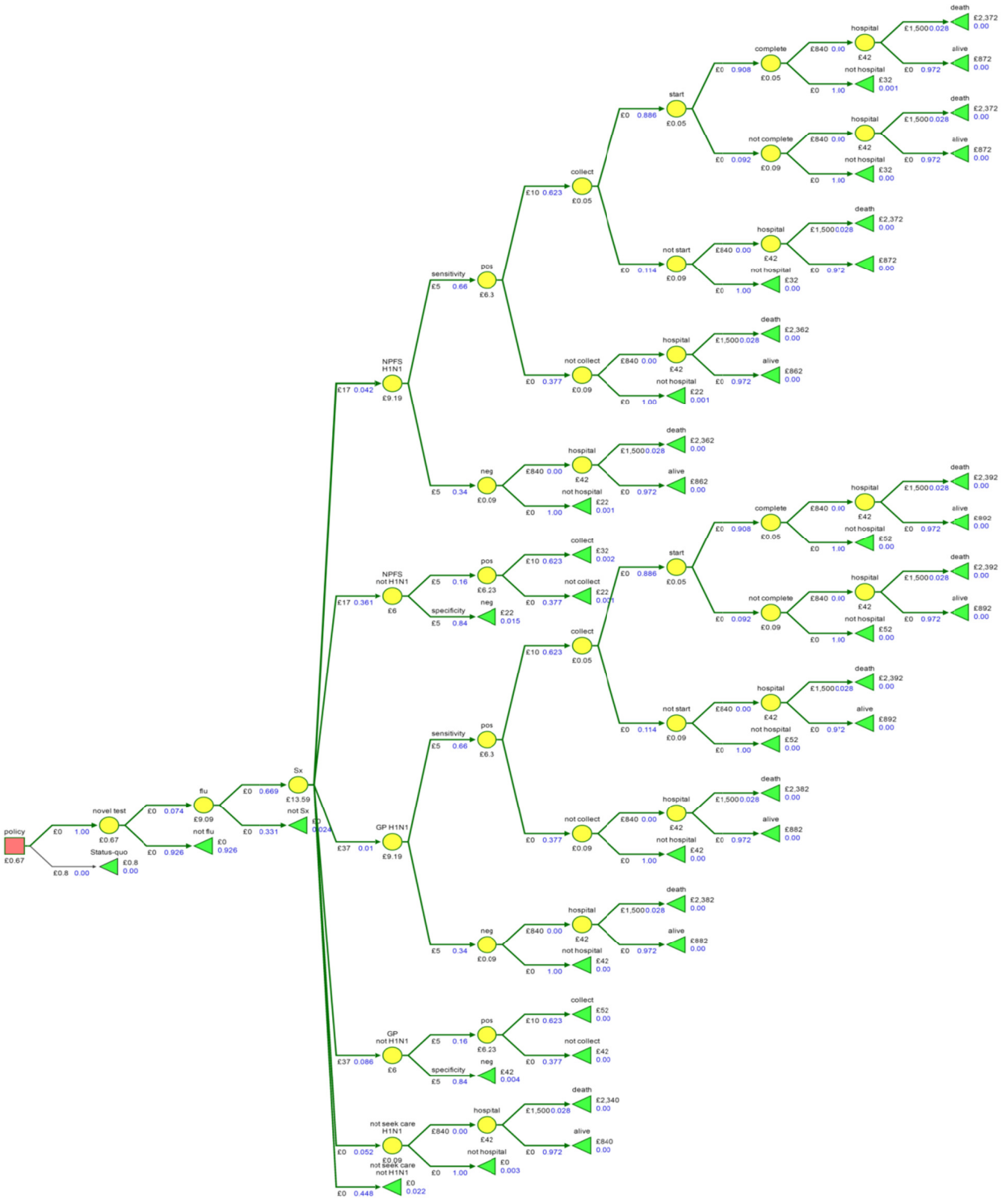

Figure 1. Decision-tree model describing care pathways for ILI

Scenarios for use of rapid test

GP-based testing

- **Scenario 1a**: GP patients with ILI are tested and those who test positive are prescribed antiviral treatment.
- **Scenario 1b**: GP patients with ILI are tested and those who test positive are prescribed antiviral treatment. GP patients with ILI who test positive and are therefore authorised to obtain antiviral treatment have a higher collection rate than observed in 2009-10 due to the test having indicated that they have influenza and therefore treatment is likely to be beneficial. The proportion of authorised patients not collecting treatment is halved in this scenario.

NPFS-based testing

- **Scenario 2a**: NPFS patients with ILI (who would otherwise have been authorised to obtain treatment based on symptoms) are tested and those who test positive are authorised to obtain antiviral treatment.
- **Scenario 2b**: NPFS patients with ILI who test positive and are therefore authorised to obtain antiviral treatment have a higher collection rate than observed in 2009-10 due to the test having indicated that they have influenza and therefore treatment is likely to be beneficial. The proportion of authorised patients not collecting treatment is halved in this scenario.
- **Scenario 2c**: in 2009-10 some patients expressed concern that their illness might be due to something more serious than influenza and wanted the reassurance of seeing a GP [Teasdale & Yardley 2011; Rubinstein et al. 2015]. Providing a rapid test through NPFS would provide reassurance that in the event of a positive test result then a GP visit is unlikely to be necessary. In this scenario 50% of individuals who initially sought care with their GP instead use NPFS.
- **Scenario 2d**: the availability of a rapid test via NPFS enabling determination of whether illness is due to influenza and therefore whether treatment is likely to be beneficial may increase use of NPFS. In this scenario we assume that half of individuals with ILI who did not seek care in 2009-10 do seek care with NPFS, in addition to those who sought care with NPFS in 2009-10; rates of care-seeking with GPs are unchanged.
- **Scenario 2e**: all of the effects of using the rapid test represented by scenarios 2b, 2c, 2d occur: collection of treatment is increased as in 2b, some patients use NPFS instead of the GP as in 2c, and some individuals with ILI who would otherwise have not have sought care use NPFS as in scenario 2d.

GP- and NPFS-based testing

- **Scenario 3**: all of the effects of using the rapid test represented by scenarios 1b, 2b, 2c, 2d occur: GPs test patients with ILI and prescribe treatment to those who test positive, collection of treatment is increased as in scenarios 1b and 2b, some patients use NPFS instead of the GP as in scenario 2c, and some individuals with ILI who would otherwise have not have sought care use NPFS as in 2d.

Use of GPs and the National Pandemic Flu Service: parameter estimation

We analysed multiple data sets relating to incidence of influenza infection and ILI, patients' use of health services, and treatment provision by those services. Surveillance data from GPs and NPFS (with rates of antiviral provision) were complemented by swabbing schemes to estimate the proportion of ILI patients who were infected with the pandemic influenza strain (including multiplex testing for other pathogens). A survey of NPFS patients provided detailed information on patient behaviour. A complex weighting scheme was developed to account for the sampling processes of the NPFS swabbing scheme and user survey.

QSurveillance [Smith et al. 2007] provided the daily number of ILI diagnoses, ILI diagnoses with prescription of antivirals and number of patients covered by the system, in age groups (0-4, 5-14, 15-24, 25-44, 45-64, 65+ years. NPFS provided corresponding information for that service.

Data from two GP virological surveillance schemes: the Royal College of General Practitioners (RCGP) and the Regional Microbiological Network (RMN) schemes provided virological positivity to A/H1N1 pandemic influenza

[Zhao et al. 2014]. Positivity data from NPFS self-swabbing and from GP swabbing (RCGP and RMN schemes) were pooled and modelled using a mixed-effects generalised linear model. Positivity estimates by time, region and age, and considering that the delay between symptom onset and swabbing and the number of antivirals taken are null were derived from this model and multiplied by the total number of ILI diagnoses made by NPFS or GP to obtain the number of ILI diagnoses positive for A/H1N1 pandemic flu.

The probabilities of collecting, starting and completing treatment in those authorised to obtain it were estimated from the NPFS data. Other parameter values, including probabilities of hospitalisation and death, and quality-of-life weights by age, were obtained from the literature [Baguelin et al. 2010; Carrat et al. 2008; Hayward et al. 2014; Kind et al. 1998; Muthuri et al, 2015; Presanis et al. 2011].

Maximum cost per test that would be considered cost-effective

We plot the maximum cost per test at which testing would be considered cost-effective by the NHS if a QALY were valued at £20,000 (Figure 2). Note that this is the total cost incurred by the NHS, which includes the cost of the staff time required to perform the test, the cost of any device required to 'read' the test (if applicable), the cost of disposal of test kits, etc.

As expected, there is a minimum performance in terms of sensitivity and specificity below which the test has no value. Higher sensitivity and higher specificity increase the value of the test. The greatest value per test was found in the scenario in which it is used by GPs. This is because the low prescribing rate of GPs means that a test can greatly increase the proportion of influenza infections that are treated provided its performance is high enough, as well as reducing the proportions of ILI patients whose illness is not due to influenza who receive (ineffective) treatment. If a positive test result increases treatment uptake compared with a clinical diagnosis of ILI then the value of the test is increased (scenario 1b). The value of a perfected test (100% sensitivity, 100% specificity) is £21 in scenario 1a and £29 in scenario 1b.

With regard to the use of the test by NPFS, the value of a perfect test is £7 in scenario 2a, and is greater in the scenarios where it affects patient behaviour, increasing collection of treatment (scenario 2b: £15), encouraging use of NPFS instead of GPs (scenario 2c: £11), and encouraging a greater proportion of patients with ILI to seek care (scenario 2d: £9). If all of these effects occur (scenario 2e) then the value of a perfect test is much greater, at £19, and under those circumstances if a perfect test were also used by GPs (scenario 3) then its value would be £20.

The sensitivity of the test is a critical determinant of its value: in the scenarios for use in NPFS it has to be at least 60%-80% for the test to have any value at all. In the GP scenario the threshold sensitivity is much lower, but this is because GP prescribing rates based on ILI diagnoses are low, meaning that effectively GPs had low 'sensitivity' for *diagnosing and treating* influenza, because typically they diagnosed ILI and did not prescribe treatment.

Specificity is also an important determinant of the test's value, although a relatively low specificity can be compensated-for to some extent by high sensitivity. However, it is likely that achieving high sensitivity will be more challenging than achieving high specificity, at least for tests that detect influenza virus RNA.

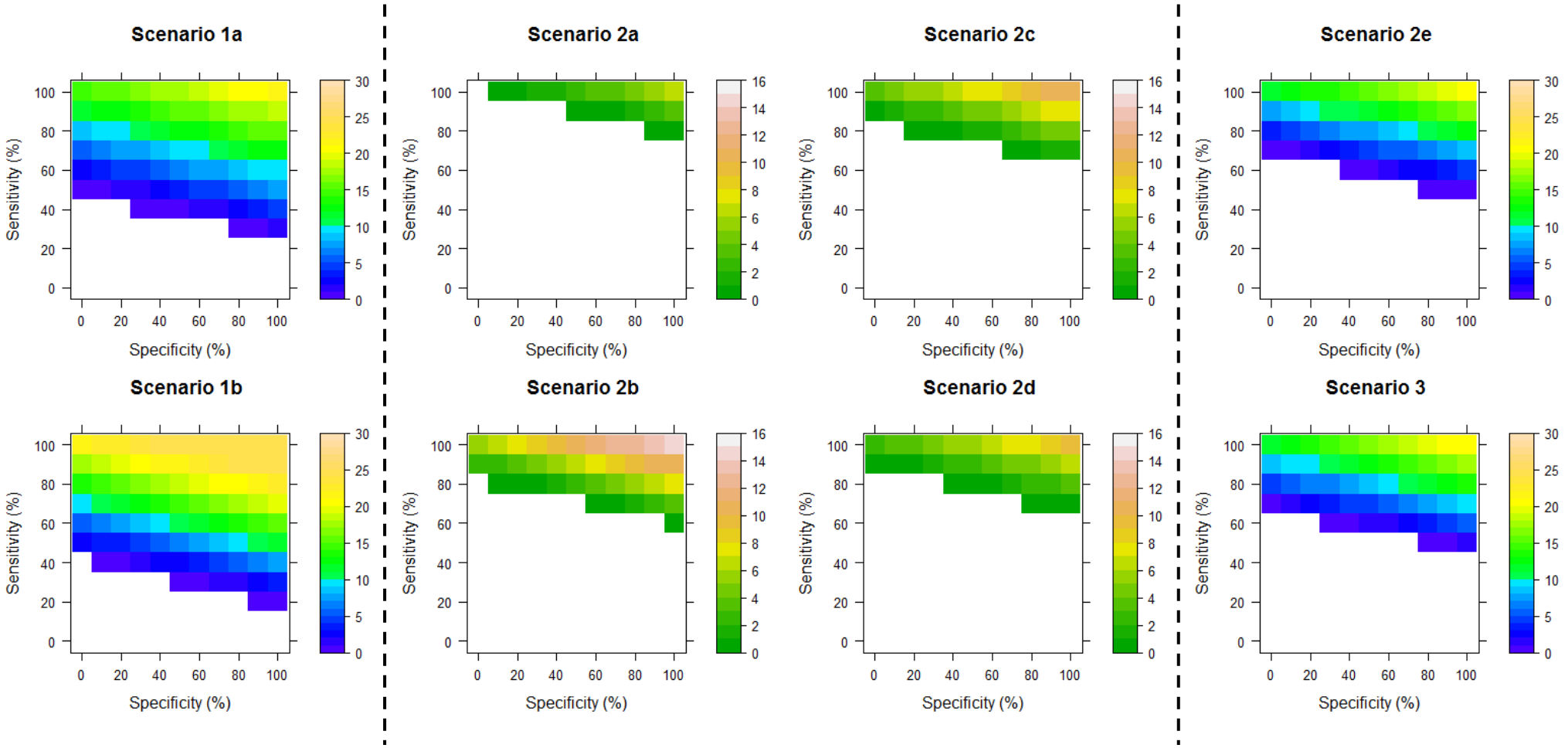

Figure 2. **Plots showing how sensitivity and specificity affect the maximum cost per test (£) which would be considered cost-effective under different scenarios**. Scenario 1 considers GP-based testing, scenario 2 considers NPFS-based testing, and scenario 3 considers both GP- and NPFS-based testing. Note that the colour scales are different for scenarios 2a-2d vs scenarios 1a,1b,2e,3, reflecting different maximum values per test.

Surveillance benefits of a rapid test

A rapid test could be used to enhance surveillance by providing results more rapidly than laboratory-based testing. In the 2009-10 pandemic it took approximately 2 weeks for laboratory test results for a particular week to become complete, due to limited laboratory capacity. With a rapid test reporting electronically these results could be available immediately. In Figure 3 we present visual representations of the information that was available in real time at four time-points in 2009-10 compared with the data that would have been available in real-time if a rapid test had been available in place of laboratory swab-testing.

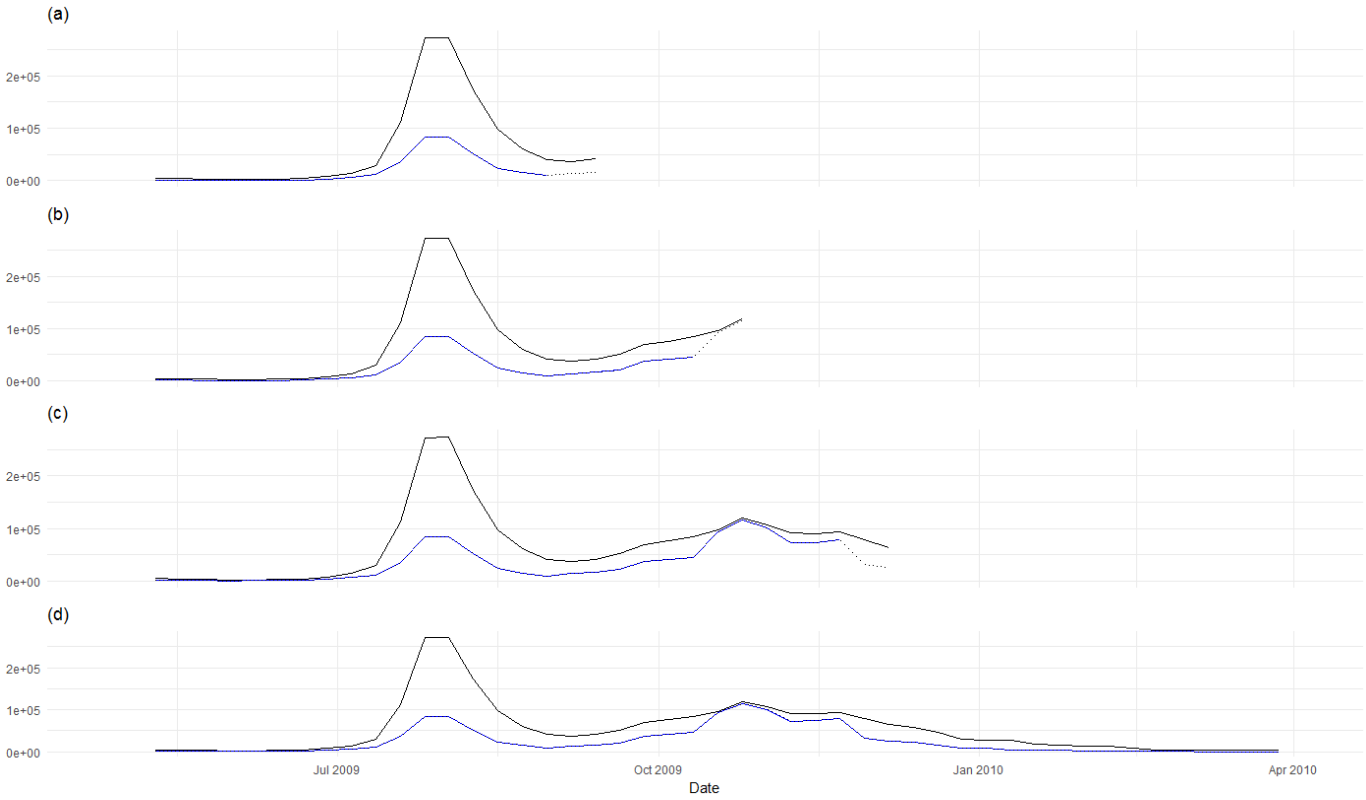

Figure 3. Real-time surveillance data time series of ILI diagnoses in England in 2009-10 comparing actual data with those that would have been available from a rapid test. The four graphs show the information available at a series of time-points. The black line shows the number of recorded cases of ILI; the solid blue line shows the estimated number of those that are due to H1N1 pandemic influenza based on laboratory testing of swabs, which lags 2 weeks behind. The dashed line shows the information that would have been available in real time if a rapid test had been used.

CONCLUSIONS

NPFS was intended to relieve pressure on GPs. NPFS assessed 2.7 million people and authorised 1.8 million courses of antiviral treatment, of which 1.2 million were collected. The number of ILI cases recorded by NPFS was 2.5 times the number recorded by GPs. However, half of NPFS patients also had contact with their GP or other healthcare provider, mostly prior to using NPFS, suggesting a need to increase public awareness of NPFS. Contacting a GP before using NPFS delays obtaining treatment from NFPS, which reduces treatment's effectiveness.

Patient behaviour is clearly an important determinant of the effectiveness and cost-effectiveness of services for pandemic influenza response, and the value of a rapid test depends on its impact on behaviour. With qualitative research having found that some patients had concerns that their illness might not be due to influenza and hence preferring to see a GP [Rubinstein et al. 2015; Teasdale & Yardley 2011], a rapid test provided by NPFS could provide the reassurance necessary to encourage use of NPFS instead of GP. Furthermore, many individuals with ILI did not seek care and the availability of a rapid test could encourage care-seeking. Finally, a third of NPFS patients did not obtain treatment that was authorised and some who obtained it did not take it, mostly due to feeling it was unnecessary and/or concern about side-effects: a positive rapid-test result might increase treatment uptake (by infected patients) by making the perceived risk of side effects 'worth it' by assuring that they did have influenza. However, false-negative test results would be likely to deter treatment of patients who would benefit from it.

Our analysis shows that unless use of a rapid test promotes patient behaviour change – encouraging care-seeking and uptake of treatment – then the value of the test to the NHS (i.e. the maximum cost per test at which its use would be considered cost-effective) for individual-level diagnosis is relatively low, even if its sensitivity and specific match that of the current laboratory test. Even a test with 100% sensitivity and 100% specificity had a maximum threshold cost of £29 in the scenarios we examined. Importantly, the cost is not merely the unit price of a test kit but all costs to the NHS, including staff time, any 'reading' device required, disposal of test kits, etc. To be commercially viable such a test would have to be cheap to manufacture, quick to use (to minimise the staff-time cost), cheap to read, and cheap to dispose of.

Currently, influenza tests suffer from low sensitivity. The swab-positivity data from GP and NPFS swabbing schemes indicate that laboratory testing of swabs by nucleic acid amplification tests (NAATs) has a sensitivity of around 60% or lower and analysis of the Flu Watch data produced a compatible estimate of around 50%. A rapid test with similar performance would have a low negative predictive value (NPV), which would make clinicians who are minded to offer treatment reluctant to withhold treatment from patients in high-risk groups who present with ILI and test negative. Furthermore, the likely cost of testing compared with the cost of treatment means that the cost saving of not providing treatment to patients who test negative would be largely negated by the testing cost – although it would preserve the treatment stockpile, which could be important in a moderate or severe pandemic. However, GP prescribing rates for oseltamivir are typically low, and GPs who do not prescribe oseltamivir because they suspect that ILI is unlikely to be due to influenza might be willing to prescribe if a rapid test indicated that the patient did indeed have influenza. In this case, a test with low sensitivity could actually increase rates of treatment of influenza, provided its specificity were high enough to have a high positive predictive value (PPV). In contrast, GPs who do not prescribe oseltamivir because they lack confidence in its efficacy would be unlikely to use a rapid test for clinical management. Having a better understanding of the reasons for GP prescribing behaviour is necessary for assessing the potential impact of rapid testing for influenza.

With regard to using a rapid test in NPFS, consideration needs to be given to how it would fit in to the process, since symptoms were assessed by phone or internet, and treatment was supposed to be obtained not by the patient themselves (who was supposed to remain at home to avoid spreading infection) but by a 'flu friend'. The characteristics of the test – for example, whether it is self-contained or requires a 'reader' device, and what type of specimen is required – are important considerations.

A potential alternative use of a rapid test is for surveillance to inform prescribing: i.e. testing a sample of patients with ILI each week to determine the proportion who have influenza in order that if this proportion exceeds a threshold then the PPV of ILI for predicting influenza is deemed high enough for treatment to be prescribed to all patients with ILI. A rapid test would make feasible testing of greater volumes of patients, due to not being limited by laboratory capacity. This would offer greater precision of estimates, the possibility of stratifying estimates by age and perhaps clinical subgroups, and accounting for geographic heterogeneity so that prescribing guidance could be regionally- or even locally-tailored. There could be different prescribing thresholds for different age groups or clinical risk groups, depending upon their risks of severe outcomes if infected with influenza. Substantial further work would be required to determine optimal algorithms; this would inform calculation of the maximum cost per test that would be considered cost-effective by the NHS, as well as the required testing volumes, which would determine budget impact.

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