i-sense
EPSRC IRC in Early Warning Sensing Systems for Infectious Diseases

Imperial College London

How Could a Rapid Test Increase the (Cost-)Effectiveness of the Management of Pandemic Influenza?

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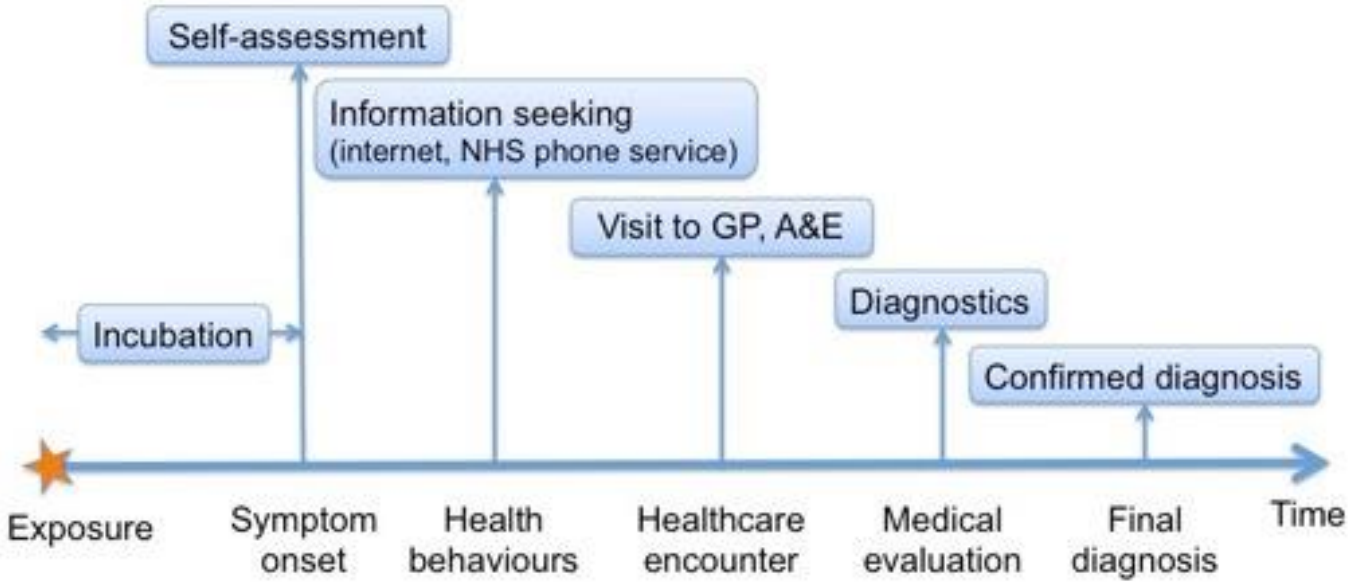
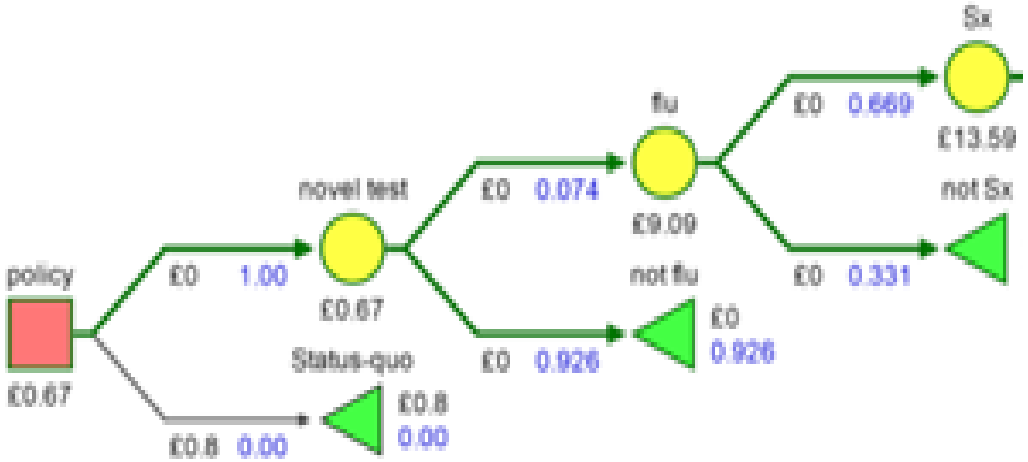
Introduction

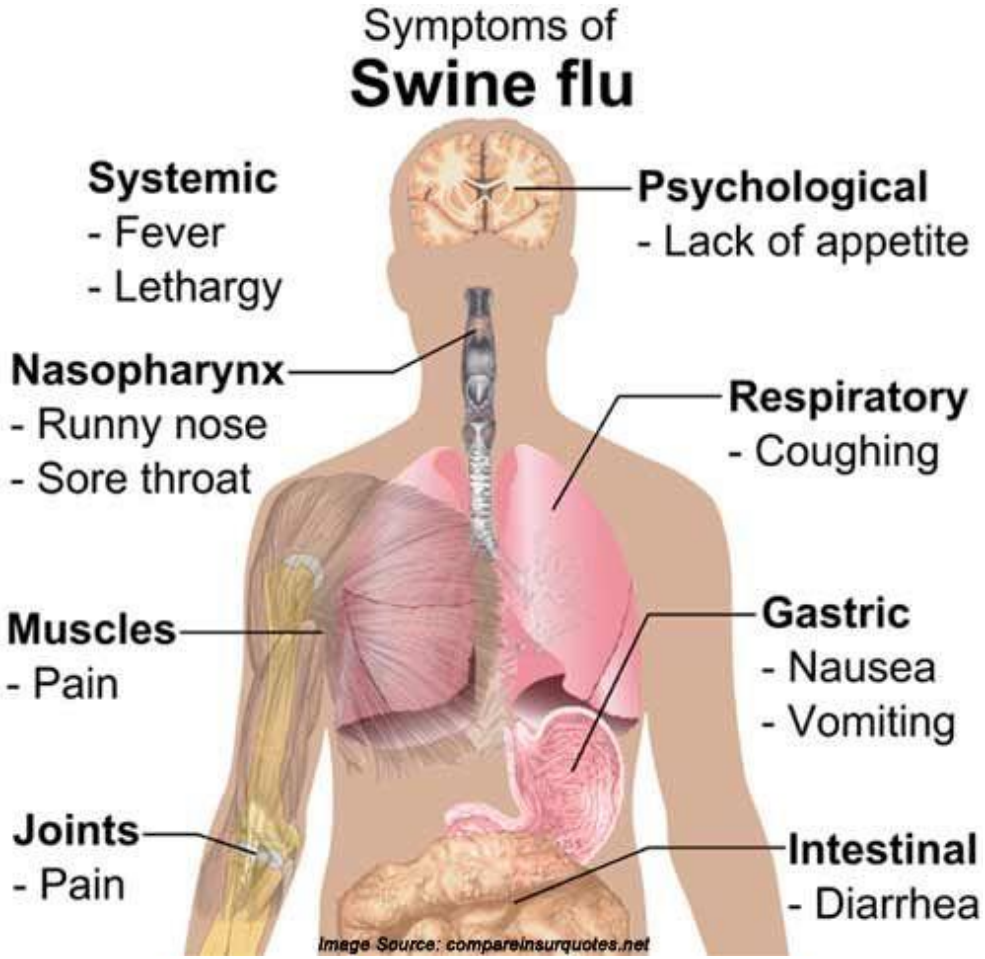
- In response to the 2009–2010 influenza A/H1N1 pandemic, England implemented an innovative internet and telephone-based service, the National Pandemic Flu Service (NPFS)
  - Access to treatment to general population & relieve pressure from traditional healthcare services.
- Unprecedented approach to rapid, targeted, mass treatment
  - identified **1.8M** cases of influenza-like illness (ILI) vs **740k** by general practitioners (GPs).
- UK Influenza Pandemic Preparedness Strategy 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
- Goal of this study was to contribute to the development of a *target product profile* for rapid tests for influenza
  - 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.
- Also examined use of a rapid test to *enhance real-time surveillance*
  - 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



https://www.i-sense.org.uk/


policy
£0.67
£0 1.00
novel test
£0.67
£0.8 0.00
Status-quo
£0.8
0.00
£0 0.074
flu
£9.09
£0 0.926
not flu
£0
0.926
£0 0.669
Sx
£13.59
£0 0.331
not Sx

Clinical diagnosis



Data

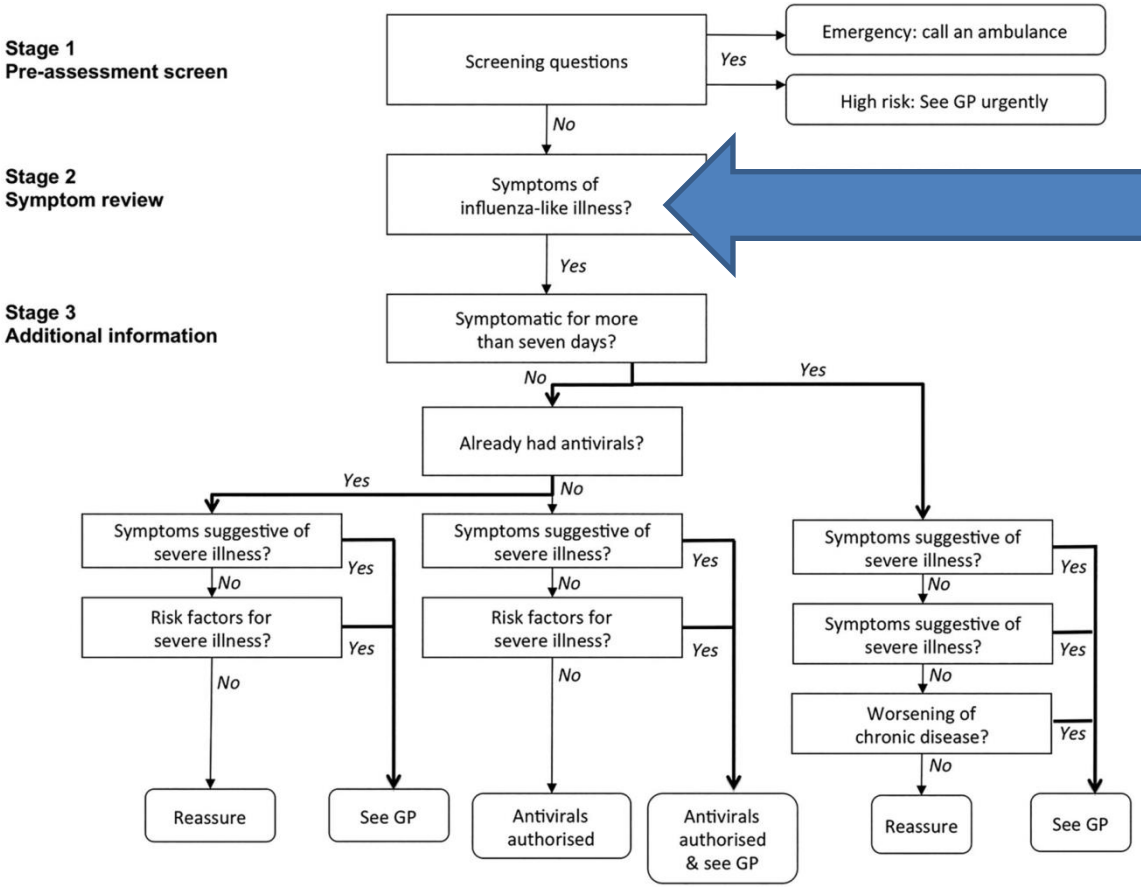
- **GP influenza-like illness swabbing scheme**
  - Royal College of General Practitioners (RCGP) sentinel surveillance scheme
    - 100 GPs report the number of cases of ILI consulting each week
  - HPA's Regional Microbiology Network (RMN)
    - ~60 GPs submit respiratory specimens from patients presenting with ILI
- **National Pandemic Flu Service (NPFS)**
- **NPFS swabbing scheme**
- **NPFS user survey**
- **Flu Watch**
  - pre- and post- season blood samples for serological analysis of the currently circulating influenza strains

RCGP Royal College of General Practitioners

Public Health England

Health Protection Agency

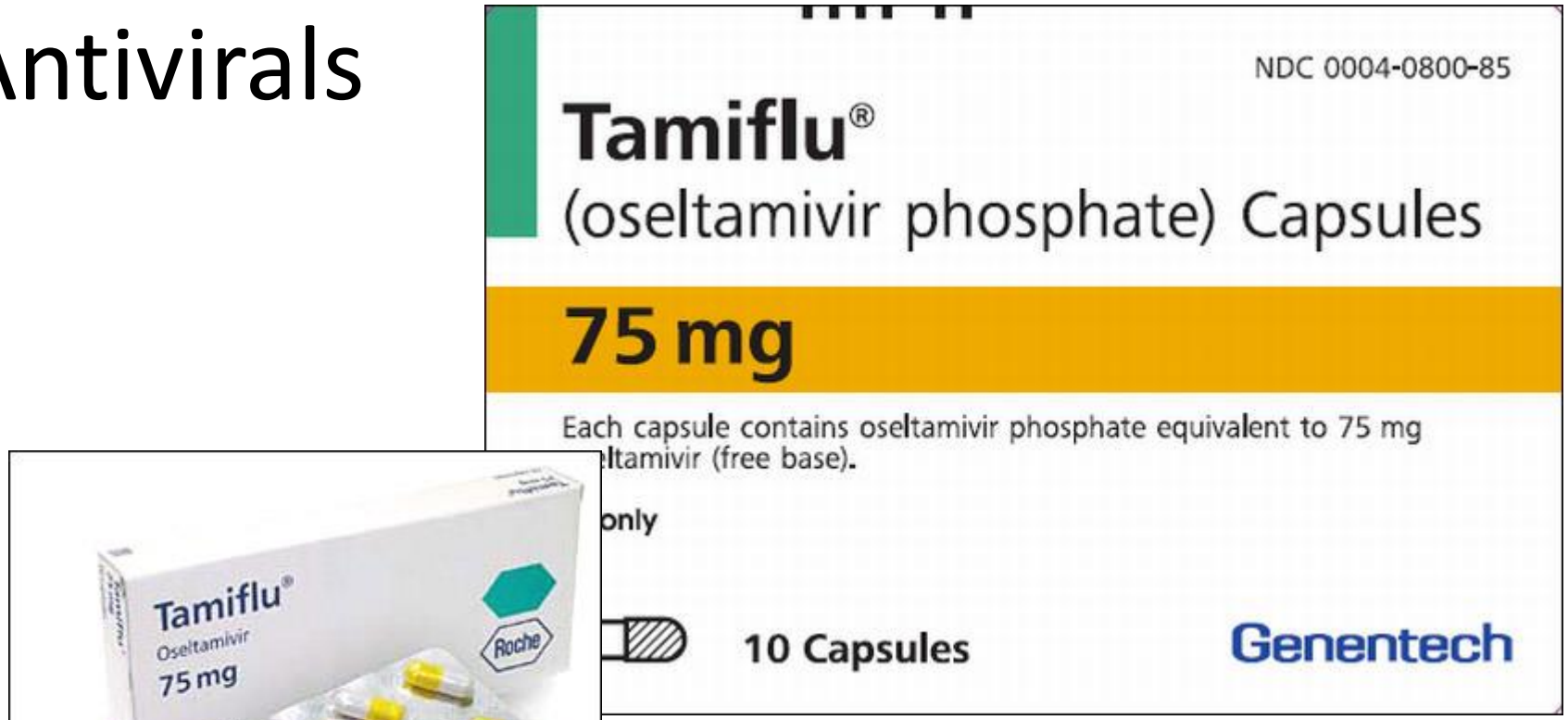
NATIONAL PANDEMIC FLU SERVICE



- Widespread muscle and joint aches
- Cough
- Headache
- blocked or runny nose
- sore throat
- Vomiting
- watery diarrhea
- cannot stop crying (only children)

Rutter P, Mytton O, Ellis B*, et al,* Access to the NHS by telephone and Internet during an influenza pandemic: an observational study, *BMJ Open* 2014;**4:**e004174. doi: 10.1136/bmjopen-2013-004174

Antivirals


NDC 0004-0800-85
Tamiflu®
(oseltamivir phosphate) Capsules
75 mg
Each capsule contains oseltamivir phosphate equivalent to 75 mg
ltamivir (free base).
only
10 Capsules
Genentech

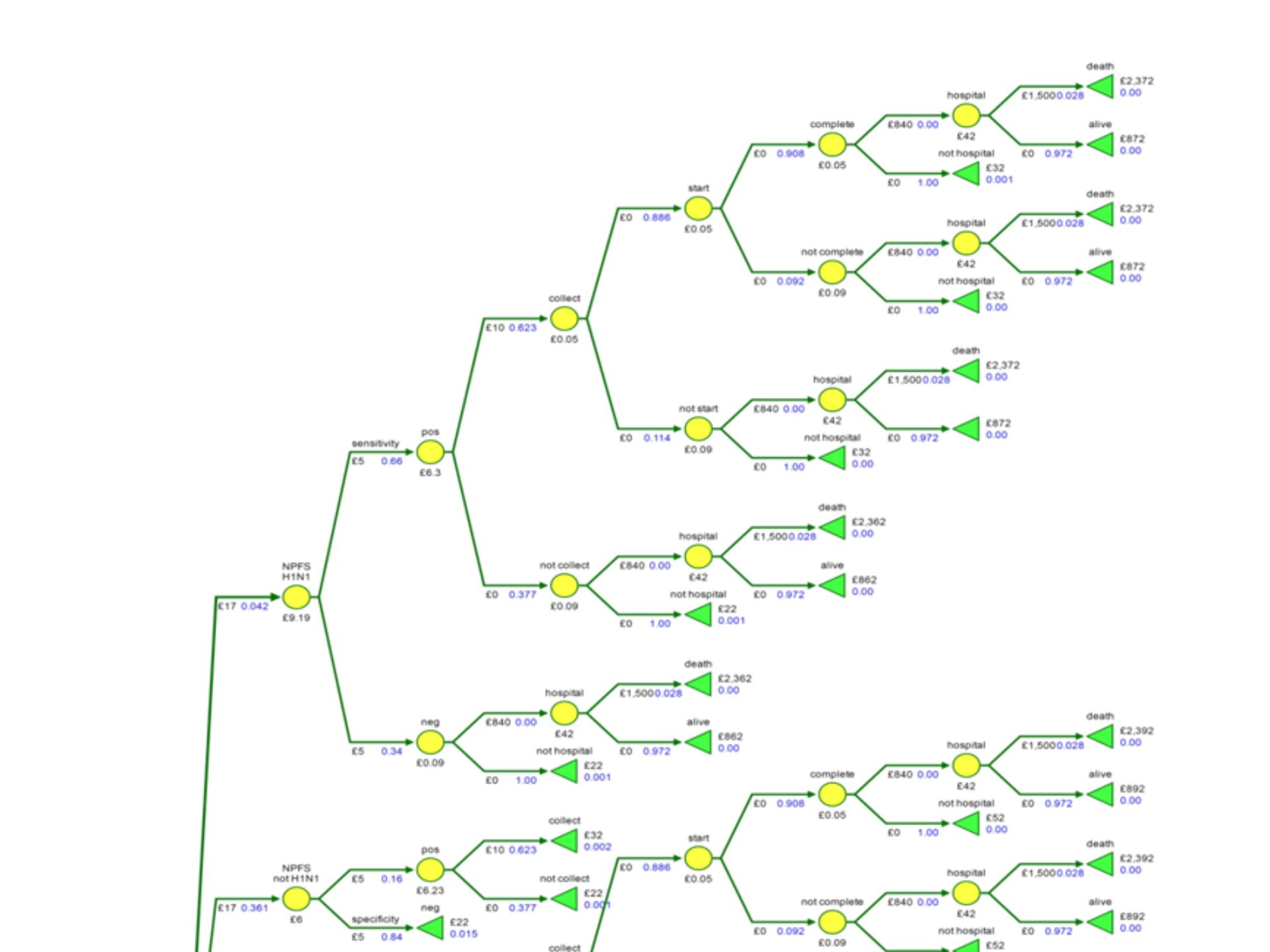
Tamiflu®
Oseltamivir
75 mg
Roche


Oseltamivir
Antiflu
75 mg
Antiflu

Rapid Tests


QUIDEL
QuickVue
Influenza A+B TEST
QUIDEL
QuickVue
25 Tests
Influenza A+B TEST


BD Directigen™ EZ Flu A+B
256050
30


NPFS H1N1
£17 0.042
£9.19
sensitivity
£5 0.66
pos
£6.3
£10 0.623
collect
£0.05
£0 0.886
start
£0.05
£0 0.908
complete
£0.05
£840 0.00
hospital
£42
£1,500 0.028
death
£2,372
0.00
£0 0.972
alive
£872
0.00
not hospital
£32
0.001
£0 1.00
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not complete
£0.09
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hospital
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not collect
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alive
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NPFS not H1N1
£17 0.361
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not collect
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hospital
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death
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alive
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not complete
£0.09
£840 0.00
hospital
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£1,500 0.028
death
£2,392
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£892
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not hospital
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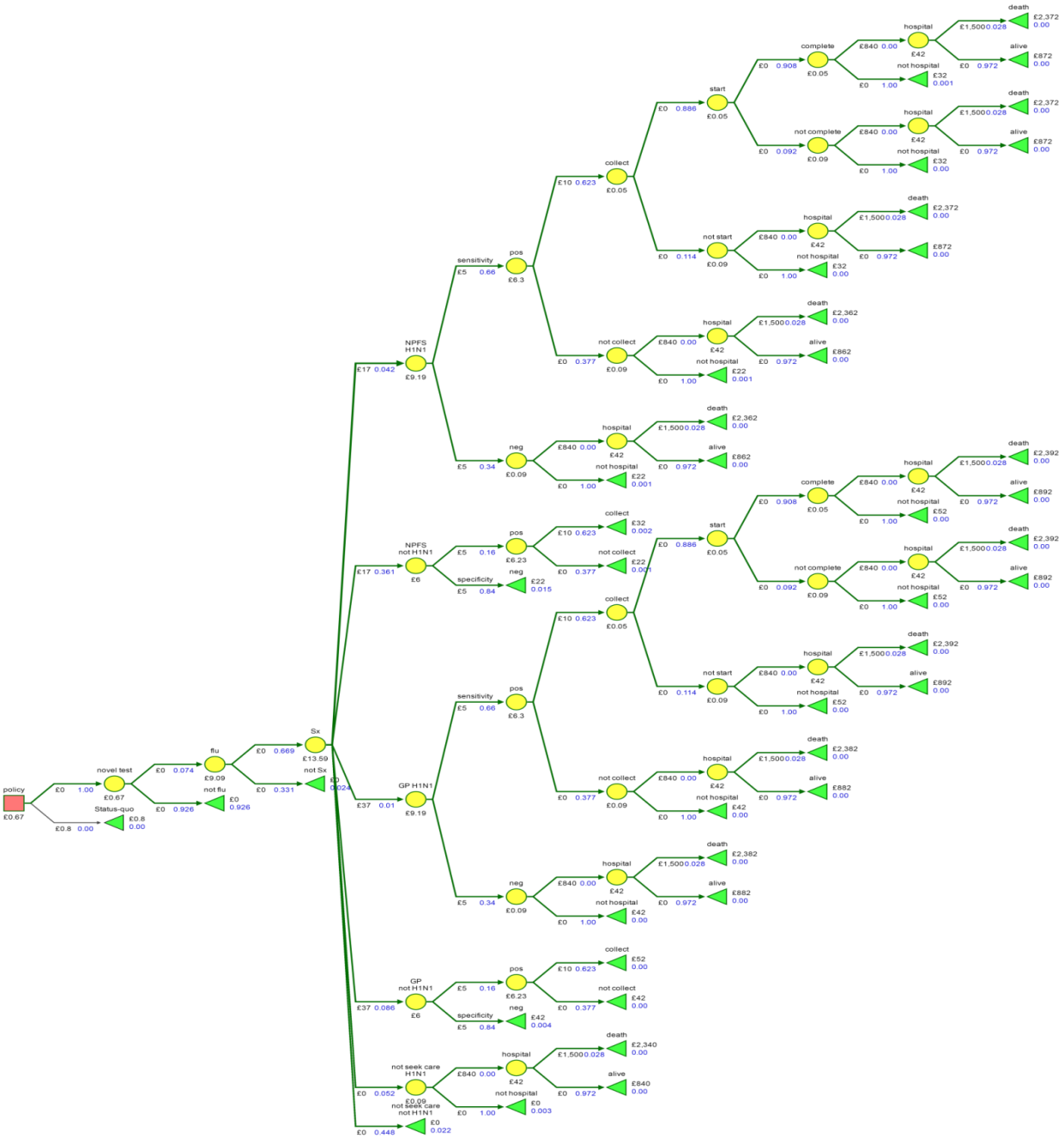
0.00
£0 1.00
collect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£0.67
£0 1.00
novel test
£0.67
£0.8 0.00
Status-quo
£0.8
0.00
£0 0.074
flu
£9.09
£0 0.926
not flu
£0
0.926
£0 0.669
Sx
£13.59
£0 0.331
not Sx
£0
0.074
£17 0.042
NPFS
H1N1
£9.19
£37 0.01
GP H1N1
£9.19
£17 0.361
NPFS
not H1N1
£6
£37 0.086
GP
not H1N1
£6
£0 0.052
not seek care
H1N1
£0.09
£0 0.448
not seek care
not H1N1
£0
0.022
£5 0.66
sensitivity
£5 0.66
pos
£6.3
£5 0.34
neg
£0.09
£5 0.16
pos
£6.23
£5 0.84
specificity
neg
£22
0.015
£10 0.623
collect
£0.05
£0 0.377
not collect
£0.09
£0 0.886
start
£0.05
£0 0.114
not start
£0.09
£0 0.908
complete
£0.05
£0 0.092
not complete
£0.09
£840 0.00
hospital
£42
£0 0.972
not hospital
£0 1.00
£1,500 0.028
death
£2,372
0.00
alive
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£2,382
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£42
0.004
£2,340
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£840
0.00
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0.003
£0
0.022

Scenarios for use of rapid test

GP-based testing: Scenario 1a & 1b

- GP patients with ILI are tested and those who test positive are prescribed antiviral treatment.

- 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.

```
16  trans_mat_1b <-
17    trans_mat %>%
18    mutate(prob = ifelse(from == "Rx_GP" & to == "coll",
19                         prob + (1 - prob)/2,
20                         prob))
21
```

NPFS-based testing: Scenario 2a & 2b

- 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.

- 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.

```
25  trans_mat_2b <-
26    trans_mat %>%
27    mutate(prob = ifelse(from == "auth_NPFS" & to == "coll",
28                         prob + (1 - prob)/2,
29                         prob))
30
```

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. 50% of individuals who initially sought care with their GP instead use NPFS.

```
trans_mat_2c <-
  trans_mat %>%
  dcast(from + age + NPFS_weeks_window ~ to,
        value.var = "prob") %>%
  mutate(NPFS_H1N1 = ifelse(NPFS_H1N1 == 0,
                            0,
                            ifelse(is.na(NPFS_H1N1),
                                   NA,
                                   NPFS_H1N1 + GP_H1N1/2)),
         NPFS_notH1N1 = ifelse(NPFS_notH1N1 == 0,
                               0,
                               ifelse(is.na(NPFS_notH1N1),
                                      NA,
                                      NPFS_notH1N1 + GP_notH1N1/2)),
         GP_H1N1 = ifelse(NPFS_H1N1 == 0,
                          GP_H1N1,
                          ifelse(is.na(GP_H1N1),
                                 NA,
                                 GP_H1N1/2)),
         GP_notH1N1 = ifelse(NPFS_notH1N1 == 0,
                             GP_notH1N1,
                             ifelse(is.na(GP_notH1N1),
                                    NA,
                                    GP_notH1N1/2))) %>%
  melt(id.vars = c("from", "age", "NPFS_weeks_window"),
       variable.name = "to",
       value.name = "prob") %>%
  select(from, to, everything()) %>%
  filter(complete.cases(.))
```

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. 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.

```
trans_mat_2d <-
  trans_mat %>%
  dcast(from + age + NPFS_weeks_window ~ to,
        value.var = "prob") %>%
  mutate(seekcare_H1N1 = NPFS_H1N1 + GP_H1N1,
         seekcare_notH1N1 = NPFS_notH1N1 + GP_notH1N1,

         NPFS_H1N1 = ifelse(NPFS_H1N1 == 0,
                            0,
                            ifelse(is.na(NPFS_H1N1),
                                   NA,
                                   NPFS_H1N1 + seekcare_H1N1)),
         NPFS_notH1N1 = ifelse(NPFS_notH1N1 == 0,
                               0,
                               ifelse(is.na(NPFS_notH1N1),
                                      NA,
                                      NPFS_notH1N1 + seekcare_notH1N1)),
         notseekcare_H1N1 = ifelse(NPFS_H1N1 == 0,
                                   notseekcare_H1N1,
                                   ifelse(is.na(notseekcare_H1N1),
                                          NA,
                                          notseekcare_H1N1 - seekcare_H1N1)),
         notseekcare_notH1N1 = ifelse(NPFS_notH1N1 == 0,
                                      notseekcare_notH1N1,
                                      ifelse(is.na(notseekcare_notH1N1),
                                             NA,
                                             notseekcare_notH1N1 - seekcare_notH1N1))) %>%
  select(-seekcare_H1N1, -seekcare_notH1N1) %>%
  melt(id.vars = c("from", "age", "NPFS_weeks_window"),
       variable.name = "to",
       value.name = "prob") %>%
  select(from, to, everything()) %>%
  filter(complete.cases(.))
```

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.

```
trans_mat_2e <-
  trans_mat_2d %>%
  mutate(prob = ifelse(from == "auth_NPFS" & to == "coll",
                       prob + (1 - prob)/2,
                       prob)) %>%
  dcast(from + age + NPFS_weeks_window ~ to,
        value.var = "prob") %>%
  mutate(NPFS_H1N1 = ifelse(NPFS_H1N1 == 0,
                            0,
                            ifelse(is.na(NPFS_H1N1),
                                   NA,
                                   NPFS_H1N1 + GP_H1N1/2)),
         NPFS_notH1N1 = ifelse(NPFS_notH1N1 == 0,
                               0,
                               ifelse(is.na(NPFS_notH1N1),
                                      NA,
                                      NPFS_notH1N1 + GP_notH1N1/2)),
         GP_H1N1 = ifelse(NPFS_H1N1 == 0,
                          GP_H1N1,
                          ifelse(is.na(GP_H1N1),
                                 NA,
                                 GP_H1N1/2)),
         GP_notH1N1 = ifelse(NPFS_notH1N1 == 0,
                             GP_notH1N1,
                             ifelse(is.na(GP_notH1N1),
                                    NA,
                                    GP_notH1N1/2))) %>%
  melt(id.vars = c("from", "age", "NPFS_weeks_window"),
       variable.name = "to",
       value.name = "prob") %>%
  select(from, to, everything()) %>%
  filter(complete.cases(.))
```

GP- and NPFS-based testing: Scenario 3

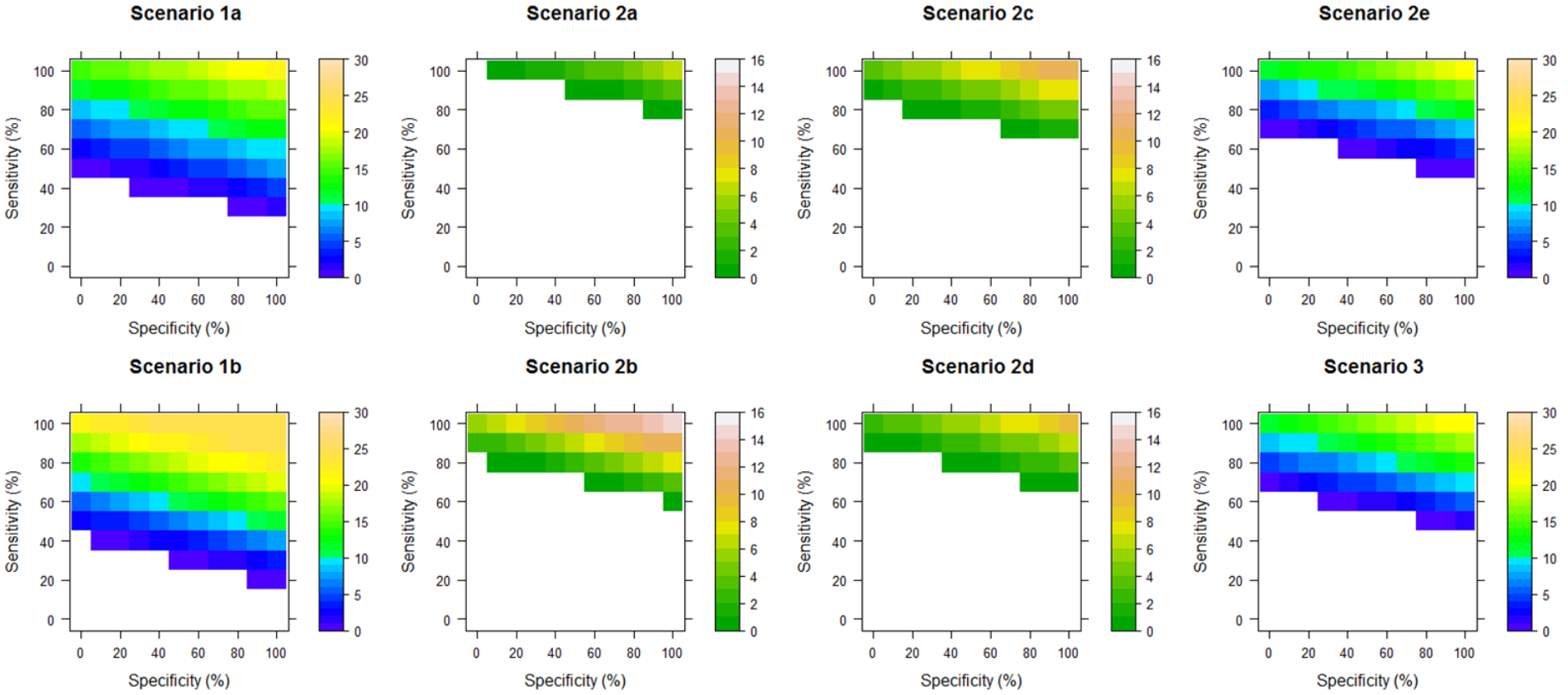
- All of the effects of using the rapid test represented by scenarios 1b, 2b, 2c, 2d occur
  - GPs test patients with ILI and prescribe treatment to those who test positive, collection of treatment is increased as in scenarios 1b and 2b, some patients use NPFS instead of the GP as in scenario 2c, and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

```
141 trans_mat_3 <-
142   trans_mat_2e %>%
143   mutate(prob = ifelse(from == "Rx_GP" & to == "coll",
144                        prob + (1 - prob)/2,
145                        prob))
146
```

	GP			NPFS			
Scenario	**Rapid test**	**⇧ collection**	**⇩ from prop already seek care**	**Rapid test**	**⇧ collection**	**⇧ from prop already seek care**	**⇧ from prop not already seek care**
1a	✓						
1b	✓	✓					
2a				✓			
2b				✓	✓		
2c			✓	✓		✓	
2d				✓			✓
2e			✓	✓	✓	✓	✓
3	✓	✓	✓	✓	✓	✓	✓

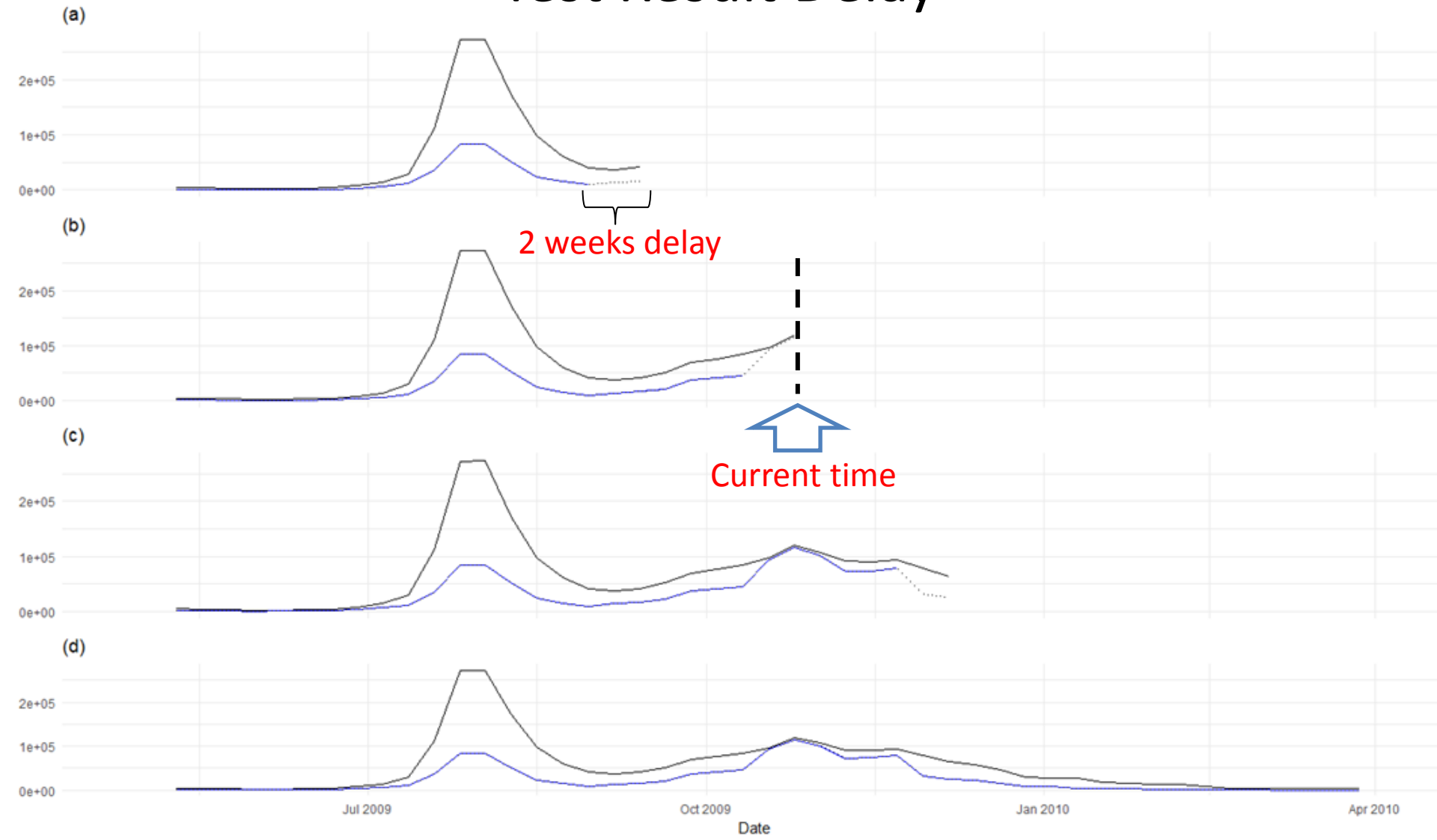
Maximum Unit Cost for Given Test Performance:

Cost-Effective using INMB



Real-Time Surveillance:

Test Result Delay



Conclusions

- Upper costs (100% performance) were
  - (GP) 1a & 1b: £21, £29
    - Effective sensitivity poor since low prescribing rate
  - (NPFS) 2a-e: £7, £15, £11, £9, £19
  - (All) 3: £20
- rapid test provided by NPFS could provide the reassurance necessary to encourage use of NPFS instead of GP
- rapid test could encourage care-seeking
- positive rapid-test result might increase treatment uptake
- 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.
- How would rapid test fit in NPFS process?
  - Treatment obtained by ‘flu friend’

Thanks

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2Institute of Health Informatics, University College London, London, UK
3Faculty of Epidemiology & Population Health, London School of Hygiene & Tropical Medicine, London, UK
4Modelling and Economics Unit, National Infection Service, Public Health England, London, UK
5Respiratory Diseases Department, National Infection Service, Public Health England, London, UK
6Institute of Epidemiology & Healthcare, University College London, London, UK