Impact of neuraminidase inhibitor treatment on hospitalisation in patients with pandemic influenza: a multi-method modelling approach

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Abstract

Background: Influenza pandemics are public health emergencies that can have potentially serious consequences. The 2009-10 influenza A(H1N1) pandemic was the first pandemic of the 21st century, and neuraminidase inhibitor (NAI) treatment was an important component of pandemic influenza mitigation plans around the world. While NAIs were licensed on the basis of reducing duration of illness in infected patients, their effectiveness in reducing complications, particularly in patients with pandemic influenza is less clear. Evaluating the impact of NAI treatment on outcomes of public health interest in patients with pandemic influenza is, therefore, crucial to informing future pandemic influenza preparedness plans. The main aim of this thesis was to evaluate the impact of NAI treatment on hospitalisation in patients with pandemic influenza.

Methods: This thesis used an interdisciplinary approach to address the thesis aim. The first part of the thesis used an Individual Participant Data (IPD) meta-analysis of clinical data to derive NAI effectiveness estimates, and the second part used computational and health economic modelling methods to extrapolate the NAI effectiveness estimates to assess public health impact.

A total of five studies were performed to address the thesis aim. In the first two studies, IPD meta-analyses were performed using a mixed-effects logistic regression, and mixed-effects negative binomial regression models, respectively, to estimate the effectiveness of community-based NAI treatment on the risk of subsequent hospital admission (Study 1) the effectiveness of in-hospital NAI treatment on the risk of subsequent length of hospital stay (LoS) (Study 2). In the third study, a novel behavioural model was developed (based on the COM-B model of behaviour change) and integrated with an agent-based

epidemic model (ABM) to explore the impact of potential public health interventions on improving NAI treatment collection rates in patients (not at high-risk) during a pandemic. In the fourth study, this coupled behavioural-epidemic model was extended to include a discrete event simulation (DES) to assess the impact of community-based NAI treatment on hospital admissions, and NAI treatment given on hospital admission on hospital bed occupancy during a pandemic scenario. In the final study, a health economic decision tree model was used to evaluate the cost-effectiveness of community-based NAI treatment in a range of pandemic influenza scenarios.

Results: Using a global pooled dataset with clinical data on patients with laboratory-confirmed and clinically suspected A(H1N1)pdm09, the first study found that in a population of patients with severe influenza, community-based NAI treatment was associated with a reduction in the likelihood of hospital admission, compared to no NAI treatment [odds ratio: 0.24; 95% confidence interval (95% CI): 0.20-0.30). The second study found that an NAI 'treatment-at-admission' policy would reduce the subsequent LoS by 19% (incidence rate ratio: 0.81; 95% CI: 0.78-0.85), when compared to later/no NAI treatment. Using an empirically validated behavioural model, in the third study, a coupled behavioural-epidemic ABM indicated that public health interventions geared towards improving people's 'Capability' and 'Opportunity' are likely to improve NAI collection rates during an influenza pandemic. Study 4 found that public health interventions that seek to improve people's 'Capability' to collect NAIs could in turn result in a reduction in peak hospitalisation during a pandemic by 37.5% (through improved NAI collection rate). Further, when improved community-based NAI treatment collection was combined with a

‘treat-at-admission’ (with NAI) policy for hospitalised patients, peak hospital bed occupancy could be reduced by up to 41%, when compared to no NAI treatment. Finally, the decision tree model suggested that, across pandemic scenarios, community-based NAI treatment would be cost-saving for patients at high-risk of complications from pandemic influenza. Community-based NAI treatment was only found to be cost-saving for the whole population in higher severity influenza pandemics.

Conclusions: When interpreted in the context of the limited previous evidence on this topic, the findings across studies indicate that NAI treatment, both community-based and in-hospital, are beneficial to high-risk patients with severe influenza, and also tend to be cost-saving in this group of patients. A combination NAI treatment strategy that combines improved NAI treatment compliance and a ‘treat-at-admission’ strategy could result in significantly reduced hospital bed occupancy, particularly during severe influenza pandemics. The findings of this thesis support current advice on pandemic influenza treatment and shed valuable insight for future pandemic preparedness planning.

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Abbreviations

ABM	Agent-based Model
ABM&S	Agent-based Modelling and Simulation
BMI	Body Mass Index
CAR	Clinical Attack Rate
CDC	Centers for Disease Control and Prevention
CFR	Case Fatality Ratio
CHR	Case Hospitalisation Ratio
CI	Confidence Interval
COM-B	Capability Opportunity Motivation- Behaviour
DES	Discrete Event Simulation
FDA	Food and Drug Administration
GISRS	Global Influenza Surveillance and Response System
HA	Haemagglutinin
HBM	Health Belief Model
ICU	Intensive Care Unit
IIV	Inactivated Influenza Vaccines
ILI	Influenza-like Illness
IPD	Individual Participant Data
IQR	Interquartile Range
IRP	Influenza-related Pneumonia
IRR	Incidence Rate Ratios
LAIV	Live Attenuated Influenza Vaccines
LoS	Length of Stay
MDV	Master Donor Viruses
NA	Neuraminidase
NAI	Neuraminidase Inhibitors
NHS	National Health Service
NIC	National Influenza Centres
NPFS	National Pandemic Flu Service
OR	Odds Ratio
p(b)	Probability of behaviour
POC	Point-of-care
PRIDE	Post-pandemic Review of anti-Influenza Drug Effectiveness
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
R_0	Basic reproductive number
RCT	Randomised Controlled Trial
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SARI	Severe Acute Respiratory Infection
SD	System Dynamics
SEIR	Susceptible-Exposed-Infected-Recovered
SIR	Susceptible-Infected-Recovered
UK	United Kingdom
UML	Unified Modeling Language
USA	United States of America
WHO	World Health Organization
α	Capability threshold
η	Opportunity threshold

θ	Motivation threshold
δ	Weighted discount rate

1 Background and literature review

1.1 Influenza

1.1.1 Virology

Influenza viruses are members of the *Orthomyxoviridae* family and are negative sense single stranded RNA viruses with a segmented genome. They are divided into three different types: A, B and C by antigenic differences in their core proteins. Type A and B viruses cause significant illness in humans resulting in regular outbreaks or epidemics, whilst influenza C causes a mild respiratory illness. The influenza A viruses can be further subdivided into subtypes based on the two major viral surface glycoproteins, haemagglutinin (HA) and neuraminidase (NA). So far, 18 variants of HA (H1-H18) and 11 variants of NA (N1-N11) have been identified in influenza A viruses, and most of the resulting subtypes (H/N combinations) are found in aquatic birds (H1-H16 and N1-N9).

The 1889 'Russian flu' pandemic, one of the earliest known pandemics, is believed to have been caused by a H3 subtype virus.[1] The 1919 'Spanish flu' pandemic, which was the first pandemic of the 20th century and the most destructive influenza pandemic to date, was caused by an avian origin A/H1N1 virus.[1] The influenza pandemic of 1957 was a lineal descendent of the 1918 A/H1N1 virus, but the two surface proteins had been replaced by the H1 and N2 subtypes respectively.[1] In 1968 the influenza A/H3N2 subtype caused a pandemic, replacing the previously circulating A/H2N2 virus. A/H3N2 viruses have continued to circulate since this time, undergoing progressive and stepwise antigenic changes with at least 14 antigenically distinct viruses found which were often associated with higher mortality levels.[2] In 1977, the A/H1N1

subtype re-appeared after a 20-year period without circulation, causing illness in children and young adults. This A/H1N1 continued to co-circulate with the A/H3N2 subtype. Then, in 2009 a novel triple reassortment influenza virus derived from the North American and Eurasian swine lineages caused the first pandemic of 21st century.[3] This virus replaced the previously circulating seasonal A/H1N1 virus and has subsequently continued to circulate as a seasonal strain.

Antigenic drift: In a process called antigenic drift, influenza viruses in humans continually undergo antigenic changes in surface glycoproteins (HA and NA) resulting in escape of the host's acquired humoral immunity. Antigenic drift occurs because of the lack of accurate proof-reading ability of the RNA-dependent RNA polymerase resulting in point mutations in the viral genome and particularly mutations in the outer head of the HA protein, which give the novel virus a selective advantage. Once high levels of strain specific antibodies are present in the population, the novel drifted virus exerts its selective advantage to become the predominant circulating strain. Antigenic drift is responsible for the annual interpandemic outbreaks of influenza; consequentially the influenza strains in the seasonal vaccine require annual review, and frequently one or more of the components requires updating.

Antigenic Shift: When a host cell is simultaneously infected by two different influenza A viruses, an exchange of gene segments can occur creating a novel virus to which there is little or no immunity in the human population, potentially producing a pandemic.[4] Reassortant events, amounting to 'antigenic shift' have been described during interpandemic periods. For example, in late 2001, a seasonal A/New Caledonia/20/99 (H1N1)-like virus reassorted with a seasonal

A/Moscow/10/99 (H3N2)-like virus to produce a novel H1N2 virus, A/Saudi Arabia/2231/01, which became established in humans.[5] This virus did not produce a pandemic, because it was derived from two pre-existing human viruses and did not incorporate any novel genetic material of avian or animal origin.

1.1.2 Clinical manifestations

Influenza typically presents as an acute respiratory infection with fever (>37.8 °C), cough, sore throat and malaise,[6] commonly defined as Influenza-like Illness (ILI). However, because the rate of asymptomatic influenza infection is so high and the spectrum of possible illness severity so broad, influenza cannot be reliably distinguished from other respiratory viruses based on clinical symptoms.[7] Notwithstanding, during a known influenza epidemic, (defined by high quality surveillance data) the likelihood of ILI indicating influenza infection is quite high, with cough and fever having positive predictive values of 79% for laboratory-confirmed influenza in some studies.[8] The clinical presentation of influenza related illness in hospitalised patients tends to be more complicated. In hospitalised patients, the positive predictive value of ILI drops significantly to 23-50%.[9]

Pulmonary complications: Of the many respiratory tract-related complications associated with influenza A and B, acute bronchitis is the most commonly seen complication in adults (seen in about 20% of patients) and otitis media with lower respiratory tract infection in children (seen in more than 25% of patients).[7] Pneumonia is a significant complication of influenza, with influenza related pneumonia (IRP) accounting for about 18% of all community-acquired viral

pneumonia identified in adults.[10] Although the available data are difficult to interpret, about one quarter of all influenza infections seem to be complicated by secondary bacterial respiratory infection,[11,12] some of which presents as pneumonia.

Systemic complications: Influenza has been known to be associated with a number of systemic, or extra-pulmonary, complications including those related to the central nervous system (febrile seizures, Guillan-Barrè syndrome, meningoencephalitis), cardiovascular system (myocardial ischaemia, congestive cardiac failure), renal system (renal failure from myoglobinuria, exacerbations of nephrotic syndrome), gastrointestinal system (Reye's syndrome, gastritis, parotitis), musculoskeletal complications, haematological complications and complications related to childbirth.[13] Musculoskeletal and nervous system-related complications are seen more commonly in children.[7] Damage to the respiratory mucosa and disruptions to bacterial flora, as a consequence of influenza, could result in invasive meningococcal infections which are observed after some influenza outbreaks.[14]

1.1.3 Diagnosis and Surveillance

Whilst the clinical features of respiratory viruses are easily recognisable, influenza virus aetiology can be ascertained through laboratory diagnosis or point-of-care (POC) tests. Nasopharyngeal swabs are the most appropriate sample for detection of influenza. A number of diagnostic tests are available including virus isolation, direct antigen or genome detection or measuring influenza specific antibodies in serological assays. The sensitivity and specificity of these different tests varies according to the type of test used, the time from onset of illness to specimen collection, the type of specimen tested,

specimen quality, and the laboratory performing the test. Viral culture is being replaced in routine diagnostic practice by the more cost effective and highly specific method of detecting the influenza genome in respiratory samples using Reverse Transcriptase Polymerase Chain Reaction (RT-PCR).[15] Until recently, POC tests have largely been antigen-based tests that provide rapid influenza diagnosis in 15-30 minutes at the point of care. These antigen-based POC tests have reduced sensitivities (50-70%) compared with RT-PCR or viral culture, leading to false negative results, but high specificities (>90%).[16,17] During a suspected influenza outbreak, the WHO recommends confirmation of negative POCs by RT-PCR, immunofluorescence or viral culture alongside current influenza surveillance. Thus, a positive POC result is useful to confirm a decision to start antiviral treatment for influenza, but a negative POC result does not justify withholding antiviral treatment if influenza is clinically suspected. More recently, however, rapid molecular-based tests have been developed for influenza detection and some of these rapid molecular tests can be deployed as POC tests.[18,19] The diagnostic performance of molecular POC tests is broadly comparable with laboratory-based PCR.[18] Improvements in the sensitivity and specificity of molecular-POC tests are likely to influence guidance in influenza diagnosis significantly.

In human beings, surveillance of influenza broadly comprises two components: 1) clinical surveillance, necessary to track temporal and geographical patterns of illness and identify any new clinical symptoms, is commonly maintained through electronic medical records from outpatient practices and hospitals linked to laboratory confirmation of influenza, as well as through internet surveys; and 2) virological surveillance, performed to determine the exact virus

type and antigenic changes over time, assess vaccine effectiveness for circulating strains, identify antiviral resistance and potentially signal detection of a novel virus with pandemic potential. Effective surveillance systems are central to epidemic and pandemic mitigation plans. The World Health Organization (WHO) has established a global network, called the Global Influenza Surveillance and Response System (GISRS), comprising of over 140 National Influenza Centres (NIC) to test clinical specimens from around the world in order to monitor viral antigenicity, help identify strains and subsequently provide viral samples for vaccine development.[20] But the principal goal of global influenza surveillance is to aid in advanced detection of the disease so that public health impact can be minimised.[20] The 2009 A(H1N1) pandemic exposed a number of gaps in worldwide influenza surveillance systems. Lack of data on severe disease in relation to past outbreaks in most countries, the absence of a global data sharing mechanism and the lack of standardisation of data collection procedures were identified as the key shortcomings in existing surveillance systems.[20] Among the recommendations made by WHO to address these shortcomings are, adopting a global standard for minimal respiratory disease surveillance, and integrating routine surveillance of severe acute respiratory infection (SARI) into existing public health systems.[20]

1.1.4 Overview of interpandemic (seasonal) and pandemic influenza

Based on the nature of the circulating virus, an influenza outbreak can be classified as being either interpandemic influenza (or 'seasonal influenza' in everyday parlance), or pandemic influenza. Interpandemic influenza is generally caused by circulating influenza A or B viruses that evolve slowly,

through antigenic drift, to partially escape host immunity.[7] When an influenza A virus undergoes a reassortant event and a new gene segment has been introduced (antigenic shift), the novel virus can lead to pandemic influenza.[7] Pandemic and interpandemic influenza are not entirely separate diseases; rather, they can be described as representing "a continuum of disease", from the appearance of a novel pandemic strain, to the subsequent circulation of related virus subtypes for many years.[21] Nevertheless, important differences exist in patterns of disease occurrence between interpandemic and pandemic influenza– they are briefly discussed in the chapters below.

1.1.4.1 Interpandemic (seasonal) influenza

Interpandemic influenza is distinctly seasonal in the temperate regions of the Northern and Southern hemispheres with outbreaks typically occurring during winter.[22,23] While one subtype of influenza A or influenza B usually predominates in any given season, A(H1N1), A(H3N2) and two lineages of influenza B co-circulate to some extent, and mixed epidemics are periodically observed. In temperate zones of the Northern Hemisphere, influenza transmission generally occurs between November and early spring[24] and at much lower level during the summer months.[24] The reciprocity of summer and winter seasons in the Northern and Southern Hemispheres corresponds with an oscillation of influenza activity in the temperate regions across the equator.[25]

The close correlation between winter and increased influenza transmission in temperate zones strongly suggests that seasonality may be related to environmental factors during winter including lower temperatures and a decrease in solar radiation.[23,26] It has also been argued that human behaviour

and lifestyle changes during colder seasons, such as increased indoor crowding in small spaces with little ventilation, may be responsible for increased influenza activity during winter.[25,27,28] Another proposed mechanism for the seasonality of influenza relates to seasonal variations in viral survival. Variations in host immunity may also play a role in the observed seasonality of influenza. In temperate regions, the low levels of solar radiation observed during winters could consequently contribute to lower levels of Vitamin D in the body,[29,30] thereby resulting in reduced host immunity and increased susceptibility to the influenza virus. Although it is possible that all the above factors contribute to the seasonality of influenza, the precise reasons and mechanisms for this remain unclear.[31,32]

In comparison to temperate regions, the epidemiology of influenza in tropical and equatorial regions has not been as extensively studied. However, the seasonality of influenza in tropical regions is not as marked[33] and there is generally background activity throughout the year.[34] In addition to year-round background activity, data from some tropical countries suggest two periods of increased influenza activity. Seasonal influenza patterns in some countries like Brazil propagate in the form of a wave originating in the equatorial north of the country around March which then sweeps southwards over approximately the next three months.[35]

1.1.4.2 Pandemic influenza

For an influenza outbreak to be considered a pandemic, a number of conditions must be met; they can be summarised as follows:

a) It must be caused by a novel influenza A virus, the HA of which is significantly different to the HA of circulating influenza strains immediately prior to the outbreak
b) There must be little or no pre-existing immunity to the novel influenza virus across most of the population
c) Efficient human-to-human spread of the novel virus must occur across the world, resulting in significant morbidity and mortality.[36,37]

Influenza pandemics are rare events that have occurred throughout history. Not surprisingly, recent pandemic events are better documented than earlier ones. Notwithstanding, there are records of pandemic-like events occurring over the past 500 years at least (Figure 1).[1] Previous pandemics are briefly discussed below.

Pre-20th century pandemics: Most pandemic influenza-like events prior to the 20th century are affected by significant uncertainty in relation to their virology. The implication of the uncertainty is that these pandemic influenza-like events may well have been caused by other (non-influenza) pathogens.[1,36] However, based on assessments of the epidemiological and clinical characteristics of records of pandemic-like events, Taubenberger and Morens (2009) have identified 9 'influenza pandemics' from the year 1500 to 1899 CE as follows:[1]

The first documented pandemic in this time period was the pandemic of 1510 that came into Europe from Africa during the summer. About 47 years later, the pandemic of 1557-58 occurred which spread west from Asia. A similar west-ward spreading pandemic from Asia occurred in 1580. Between 1729-30 and 1732-1733, two waves of a pandemic emerged from Russia and spread west and

south. The second wave was characterised by extensive geographical spread including the Americas. Following this, pandemics were recorded in 1761-62, 1780-82 and 1788-90, with the first one having originated in the Americas, and the other two in Southeast Asia. In 1830-31, 1832-33 and 1836-37 three pandemic waves were recorded occurring within a short period between them, originating in Southeast Asia. The pandemic of 1889-93, or the 'Russian flu pandemic', originated in Russia and then spread west and south. This is the earliest influenza pandemic (and the only pre-20th century influenza pandemic) to have serological confirmation of the virus.[1,36]

20th and 21st century pandemics: The 1918 'Spanish flu' pandemic, the first pandemic of the 20th century, inflicted an estimated 50 million deaths and remains the deadliest pandemic ever recorded. Caused by an avian-origin A(H1N1) virus, the 'Spanish flu' pandemic, despite its name, is believed to have originated in either the USA or China. A lineal descendent of the 1918 virus acquired novel gene segments and emerged as an A(H2N2) virus in 1957 causing the second pandemic of the 20th century. Also known as the 'Asian flu' pandemic, the 1957 influenza pandemic originated in Yunnan, China. Eleven years later, in 1968 an A(H3N2) virus originating in China caused the third pandemic of the 20th century. Although the virus originated in China, the 1968 pandemic is often referred to as the 'Hong Kong flu' pandemic as most of the global spread of the infection occurred from Hong Kong. In 1977, a descendent of the A(H1N1) virus from 1918 re-emerged affecting almost exclusively people under 25 years of age. While some have called this a pseudo-pandemic, other have argued that this should be considered a true pandemic.[1,36]

The most recent pandemic is the 2009 A(H1N1) influenza pandemic, more commonly known as the 'Swine flu pandemic'. The novel virus was first identified in March 2009 in Mexico and the USA (California) and spread through the rest of North America and then across the globe.[38,39] Instead of the avian-origin influenza virus that was widely expected to cause the first pandemic of the 21st century, it was a swine-origin virus that was responsible for the 2009 influenza pandemic[40]. Since much of this thesis will focus on the 2009 A(H1N1) influenza pandemic, it is described in more detail in subsequent sections.

	Year	*Virus*
Pandemic 1	1510	Virological uncertainty
Pandemic 2	1557-58	
Pandemic 3	1580	
Pandemic 4	1729-30 1732-33	
Pandemic 5	1761-62	
Pandemic 6	1780-82	
Pandemic 7	1788-90	
Pandemic 8	1830-31 1832-33 1836-37	
Pandemic 9	1889-93	H3?
Spanish flu pandemic	1918	H1N1
Asian flu pandemic	1957	H2N2
Hong Kong flu pandemic	1968	H3N2
Debatably a pandemic	1977	H1N1
Swine flu pandemic	2009	H1N1

Figure 1: Influenza pandemics since 1500 CE, based on data from[1,41]

1.1.5 Epidemiology of the 2009 A(H1N1) influenza pandemic

Public health responses to future pandemics are often based on assessments of previous influenza pandemics. Evaluation of the epidemiology of previous pandemics can help understand the burden of illness associated with pandemics of varying levels of transmissibility and severity, and can thereby help mount effective public health responses to an unfolding outbreak. Given that much of the work described in this thesis relates to the 2009 A(H1N1) pandemic, particularly the United Kingdom's (UK) experience of the pandemic, it will be the focus of this section. However, important epidemiological characteristics of previous influenza pandemics are summarised in Table 1 for comparison.

On the 23rd of April 2009, the first human cases of the novel A(H1N1) virus were confirmed in Mexico and in the United States of America (USA).[41] Within a week, on 27th April 2009, the WHO raised its pandemic alert level to Phase 4, confirming human-to-human transmission of the infection leading to sustained outbreaks in communities.[42] On 29th April 2009, the alert had been raised further to Phase 5, at which point the infection had spread to at least two other countries and the probability of a pandemic occurring was very high.[41] Soon after, the WHO raised the pandemic alert to its highest possible level– Phase 6, declaring the 21st century's first pandemic on 11th June 2009 by which time, the outbreak had spread to several countries.[41]

Year	Viral subtype	Clinical Attack Rate (CAR)	Case Fatality Rate (CFR)	Average age of case fatality
1918	H1N1	25%	2.5%	27 years
1957	H2N2	30%	0.4%	65 years
1968	H3N2	35%	0.4%	62 years
2009	H1N1	7%	0.05%	45 years

Table 1: Epidemiological characteristics of influenza pandemics since the 20th century, based on data from [43]

In the UK, the 2009 A(H1N1) influenza pandemic caused two distinct waves of pandemic influenza activity (within the declared WHO pandemic period) which were seen to be separated by school closures over the summer (Figure 2).[44] The first wave peaked in July 2009 (summer wave) and the second wave peaked in October 2009 (autumn wave).[27] The WHO had declared that the pandemic had ended in July 2010;[45] however, the winter of 2010-11 experienced intense influenza activity with both, A(H1N1)pdm09 and influenza B circulating at the same time.[46] The A(H1N1)pdm09 was the main strain that circulated during the winter, and this has now been identified as the third wave of the 2009-10 A(H1N1) influenza pandemic in the UK, which was marked by higher rates of illness in young adults when compared to previous seasons.[46,47]

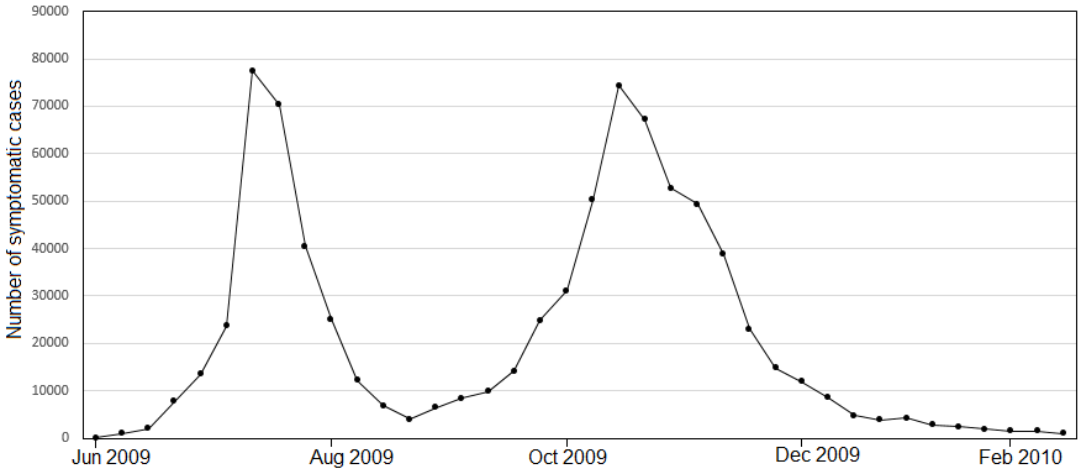


Figure 2: Epidemic curve of the 2009 A(H1N1) influenza pandemic in the UK based on real-time estimates[44,48]

The overall burden of illness of a particular influenza pandemic can largely be attributed to its transmissibility and clinical severity.[49] The 2009 A(H1N1) influenza pandemic caused a relatively mild illness in most infected people. Its transmissibility and severity are described below.

1.1.5.1 Transmissibility

There are several measures that shed insight into the level of transmissibility of an infectious disease outbreak, each with its own set of strengths and limitations. The basic reproductive number (R_0), attack rate (clinical, community, household, school/workplace), genetic markers of transmissibility with the virus, and animal transmission experiments are some measures that can be used to describe transmissibility.[49] Of these, the R_0 and attack rates are the two most commonly used measures of transmissibility.

The basic reproductive number is defined as the average number of secondary cases (infections) per typical case in an otherwise susceptible population.[49] The advantage of using the R_0 to describe transmissibility is that it is fairly intuitive and, when combined with the serial interval (which is the time duration between symptom onset in an infected person and symptom onset in a person they infect), can help provide an estimate of the speed of spread of the outbreak in a population.[49] Moreover, the R_0 is particularly well-suited to inform public health counter-measures even in relatively small populations.[49] However, R_0 tends to be specific to the populations that have informed its estimation, and therefore, tends not to be generalisable across populations.[49]

Attack rates can be calculated by dividing the number of new cases of the disease by the total population. Epidemiological investigations of outbreaks

often describe transmissibility in terms of 'clinical attack rates' (CAR) which can be defined as the proportion of the population who develop clinical symptoms during the course of an epidemic or a pandemic.[43] Attack rates are most useful for estimations of the overall morbidity over the course of an infectious disease outbreak, including societal disruptions due to workplace absenteeism, and possible economic impacts of an outbreak.[49] The main disadvantage of using attack rates to describe transmissibility is that they often require larger populations that have had sufficient levels of transmission to be estimated accurately.[38] Another potential limitation of using attack rates, especially for influenza outbreaks, is that case ascertainment can be a significant challenge as a considerable proportion of influenza infections tend to be mild or asymptomatic; this can cause missed 'true influenza' infections.[49]

A systematic review based on published evidence from several countries reported that, for the 2009 A(H1N1) pandemic, the median R_0 value was 1.6 (range: 1.1-3.3) and the mean serial interval was 3 days [(95% confidence interval (95% CI): 2.4-3.6)].[50] The WHO estimated that the R_0 for most countries varied between 1.3 and 1.7.[51] Lower R_0 values were observed during the first wave of the 2009 pandemic in the UK, when compared to the second wave.[44] It was found that children were associated with an increase in risk of infection by two to four times; the highest rates of infection were seen in children, and the lowest in adults above the age of 50 years.[51] In the UK the CAR was estimated to have been 7%; although, because over half the infections were asymptomatic, precise estimation of the CAR was difficult.[43] Overall, the 2009 A(H1N1) influenza pandemic resulted in mostly milder, self-limiting illness.[43]

1.1.5.2 Severity

The severity of a pandemic is assessed based on the impact it has in terms of outcomes in infected individuals. Case fatality ratio (CFR), case hospitalisation ratio (CHR), death-to-hospitalisation ratio, intensive care unit (ICU) admissions as a proportion of hospitalisations, laboratory-based genetic markers of virulence are some methods of ascertaining the severity of an outbreak.[49] Of these, CFR and CHR are most commonly used. CFR and CHR are the ratio of the number of deaths and the number of hospitalisations, respectively, to the number of cases within a specified population. The advantage of using CFR and CHR is that they represent robust outcomes with little scope for misclassification. On the other hand, CFR and CHR may be difficult to estimate early on during the outbreak, particularly when the outbreak is not very severe and there have not been many deaths or hospitalisations.[49] It is also possible to overestimate the CHR and CFR when milder illness in the community are being missed, and the more severe hospital cases are being detected. Furthermore, thresholds for hospitalisations can vary widely between countries and settings making comparisons between CHR estimates difficult.[49]

In August 2010, the WHO reported 18,449 deaths in patients with laboratory-confirmed 2009 A(H1N1) influenza[52] with a CFR of 0.05%[43] making this pandemic less severe when compared to previous pandemics. The low CFR is in contrast to early reports of the pandemic from the Mexico that suggested that the CFR could be as high as 1.5%.[38] In the UK, 128 deaths were reported out of an estimated 540,000 symptomatic A(H1N1)pdm09 infections (CFR: 0.026%).[48] In 2013, a modelling-based study stated that the WHO estimate of 18,449 deaths is likely to have underestimated the true mortality estimate of the

2009 pandemic by approximately 10 times.[53] The mortality rates were highest in the older adults, contrasting with the highest attack rates being observed in children and young adults.[48,51] In the UK, most of the patients who died from A(H1N1) pandemic influenza had been hospitalised.[48] The highest rates of hospitalisation in the UK was observed in children under five years of age.[44] A total 5,376 laboratory-confirmed pandemic influenza-related hospitalisations were reported in the UK over the course of the two pandemic waves.[44] Studies based on serology of infected patients indicate that while the second wave of the pandemic caused a greater number of infections, it was associated with a lower CHR when compared to the first wave.[44]

Risk groups: Increased susceptibility to influenza-related serious illness or death has been consistently observed in young children under six months of age and the elderly aged 65 years or older.[54-58] People with one or more of the following comorbidities are four to ten times more likely to be admitted to hospital due to an influenza infection when compared to otherwise healthy people: asthma and any other chronic respiratory disease, immunosuppression, renal, hepatic, cardiovascular, haematologic, neurologic and metabolic disease.[59] Adverse outcomes have also been reported in pregnant women infected with pandemic as well as seasonal influenza. Pregnant women infected with influenza can experience decreased neonatal birthweight, prematurity, perinatal mortality and even death.[60,61] A study based on data from the USA showed that morbid obesity (BMI≥40) was independently associated with an increase in likelihood of hospitalisation by 4.7 times and an increase in likelihood of death by 7.6 times, from 2009 A(H1N1) pandemic influenza.[62]

1.1.6 Pandemic influenza mitigation

Strategies employed to mitigate an ongoing influenza pandemic will be guided by several factors including the epidemiological nature of the pandemic, the stage of the outbreak, the characteristics of the population, the structure of the healthcare system and the resources available. Broadly, pandemic mitigation strategies can be divided into non-pharmaceutical and pharmaceutical strategies, and successful mitigation of a pandemic frequently entails a combination of both pharmaceutical and non-pharmaceutical measures.

1.1.6.1 Non-pharmaceutical measures

Non-pharmaceutical measures range from actions aimed at personal protection to interventions that are aimed at changing behaviour. Below are brief descriptions of some important non-pharmaceutical measures.

Personal protection and infection control: Personal protection measures are aimed primarily at reducing person-to-person transmission of influenza. The most basic, yet effective, personal protection measures are maintaining hand hygiene and following appropriate respiratory etiquette (such as using a fresh tissue as a barrier whilst coughing or sneezing).[43] Isolation of infected patients, including voluntary domestic isolation, can be effective in minimising contact between uninfected and infected persons.[63] Another in-hospital infection control measure is the establishment of "cohort nursing", where infected patients are all treated together in one ward.[63] While there is some evidence to suggest that the use of face masks or respirators can reduce the risk to transmission in close contact settings in a healthcare facility, the effectiveness

of face masks and respirators in reducing influenza transmission outside of healthcare settings is not supported by evidence.[43]

Societal restrictions: Societal restrictions such as school closures and restrictions of air travel and social gatherings can be enforced as reactive measures, to control the spread of the disease, after an outbreak has occurred.[43] For pandemic influenza mitigation, school closures can be effective in controlling outbreaks, however, their effectiveness can vary greatly depending on their timing.[64] The impact of school closures is seen in the reduction of the peak attack rates during the pandemic, the extent of the reductions, however, is not very clear and is known to vary.[64] While most school closure interventions tend to be reactive, i.e. are enforced after an outbreak has occurred, there is evidence to suggest effectiveness of proactive school closures as well, although proactive school closures can be more disruptive.[64] Restrictions on mass gatherings feature in some pandemic preparedness plans as non-pharmaceutical mitigation measures. Its effectiveness for pandemic influenza depends greatly on the nature of the mass gathering and the duration of contact between attending participants.[65] The role of air travel in propagating infectious disease outbreaks is recognised.[66] However, modelling studies indicate that restricting air travel by 90% to 99.9% would only delay the outbreak by one or two weeks, to 2 months respectively.[67] Restricting air travel is an intervention that has very high costs attached to it; therefore, economic, social and other practical implications of such a measure will have to be considered.

Interventions aimed at improving uptake of pharmaceutical interventions: Public attitudes towards antiviral medications and influenza vaccinations can greatly affect the overall impact of an influenza pandemic. Uptake of influenza

vaccination has been found to be sub-optimal in many high-risk populations such healthcare professionals, pregnant women, children and those with clinical risk conditions.[68] Similarly, evidence from the UK indicate that over a third of antiviral drug prescriptions for pandemic influenza went uncollected.[69] The reasons for the relatively low uptake of vaccinations and antiviral drugs, according to the available evidence, include a lack perceived lack of susceptibility, concerns about side-effects of pharmaceutical interventions, and the belief that infected persons will make an easy recovery.[68,70] Public health interventions aimed at increase uptake of vaccinations and antiviral drugs can, therefore, be effective in pandemic influenza mitigation. The interventions include influenza awareness campaigns, targeted vaccination strategies and clear and transparent reporting of the burden of the ongoing pandemic.[68]

1.1.6.2 Pharmaceutical measures

Vaccination: Vaccines are an important pharmaceutical countermeasure to pandemic influenza. Depending on the timing of vaccine development, there can be three main types of pandemic influenza vaccines: a) vaccines developed during the interpandemic period, b) vaccines developed during the pre-pandemic period (when an influenza pandemic seems imminent), and c) vaccines developed during an influenza pandemic.[43] The first influenza vaccines were introduced in 1945 and were inactivated influenza vaccines (IIV).[71] IIVs are available in adjuvanted and non-adjuvanted formulations. Adjuvants increase the immunogenicity of highly purified antigens that have inadequate immunostimulatory properties. The most commonly used seasonal influenza vaccine adjuvant is MF59 with AS03 and was used in the 2009

pandemic influenza vaccine as well. Moreover, adjuvants have an antigen dose-sparing function as less viral antigen is required per dose, and thus global vaccine production capacity may be increased during a pandemic.[72] Live attenuated influenza vaccines (LAIVs) utilise a single attenuated vaccine virus or master donor viruses (MDV) containing a mutation for attenuation. LAIVs have been recommended for children due to the low immunogenicity of IIVs in this group[72] and ease of administration.

The vaccine response to the 2009 A(H1N1) influenza pandemic was the first ever global deployment of pandemic influenza vaccines. Two vaccine types were approved by the US Food and Drug Administration (FDA) against the 2009 A(H1N1)pdm09 virus– a inactivated unadjuvanted monovalent influenza vaccine, and a LAIV.[73] Although both vaccines were used in during the 2009 pandemic influenza vaccine response, the LAIV accounted for <5% of overall vaccine production in the world.[74] A recent meta-analysis of vaccine effectiveness found that of adjuvanted and unadjuvanted monovalent influenza A(H1N1)pdm09 vaccines were effective not only in preventing laboratory-confirmed pandemic influenza, but also in preventing influenza-related hospitalisations.[75] For a pandemic vaccination strategy to achieve maximum public health impact, early availability of the vaccine is crucial. However, during the 2009 pandemic, vaccines were only available for widespread deployment during the second peak of the pandemic (October 2009), and this delay in vaccine distribution lead to a diminished public health impact.[73,76]

In planning vaccination strategies for an influenza pandemic, it is also important that the critical vaccination threshold is taken into consideration. The critical

vaccination threshold is the minimum proportion of the population that would need to be immunised to induce herd immunity.[77] Herd immunity is the population-level protection conferred on non-immune individuals by the immunised proportion of the population.[77]

Antiviral drugs: Effective vaccines against pandemic influenza can take several months to develop. Antiviral drugs are, therefore, likely to be the main pharmaceutical mitigation measure against pandemic influenza, particularly during the early stages of the outbreak during which an effective vaccine has not yet been developed. Up until 1999, the adamantanes (amantadine and rimandatine) were the only antiviral drugs available for prophylaxis and treatment of influenza. These drugs inhibit M2-ion channel activity in influenza A viruses and interfere with the uncoating of influenza A virions, thereby inhibiting nuclear migration of virus ribonucleoprotein and replication.[78,79] A major limitation of these drugs was the rapid emergence of resistance (especially when used for treatment and prophylaxis in the same setting). In recent years the S31N mutation among circulating influenza A(H3N2) and pandemic A(H1N1) influenza strains have resulted in more widespread resistance to adamantanes.[80] Other limitations include the absence of activity against influenza B virus, and frequent central nervous system side-effects (e.g. anxiety, hallucinations, nightmares and confusion), particularly so in elderly subjects in whom the elimination half-life may be doubled.[79,80]

From 1999 onwards, the neuraminidase inhibitors (NAIs), zanamivir (tradename Relenza®, available as a powder for oral inhalation and licensed for treatment and prophylaxis in patients aged 5 years and over) and oseltamivir

(tradename Tamiflu® available as oral capsules and suspension, and licensed for treatment and prophylaxis in patients of all ages) have been the most widely used antivirals for influenza treatment and prophylaxis.[79,81,82] NAIs block replication of both influenza A and B viruses by preventing the release of influenza virions from the surface of infected cells,[83] albeit studies suggest slightly lower effectiveness against influenza B.[84] NAIs were used widely during the 2009 influenza pandemic, and feature in pandemic preparedness plans worldwide.[85] Their use usually includes both prophylactic and therapeutic use.[43] NAIs are described in more detail in Section 1.1.7.

National Pandemic Flu Service: The earliest confirmed cases of 2009 A(H1N1) pandemic influenza in the UK were identified in April 2009, with the numbers of infected individuals rising sharply soon after.[41] In response, the National Pandemic Flu Service (NPFS). The NPFS was instated in England in July 2009 as a means of dispensing NAIs to low-risk, symptomatic patients with uncomplicated influenza-like illness (ILI) in the community and subsequently relieving pressure off primary care services.[69] Over the course of the 2009 A(H1N1) influenza pandemic, 5,376 pandemic influenza-related hospitalisations occurred in the UK, along with 474 deaths.[44] The NPFS, which operated between 23rd July 2009 and 18th February 2010, authorised over 1.8 million prescriptions for NAIs, however over 35% authorised NAI prescriptions remained uncollected (Figure 3).[86]

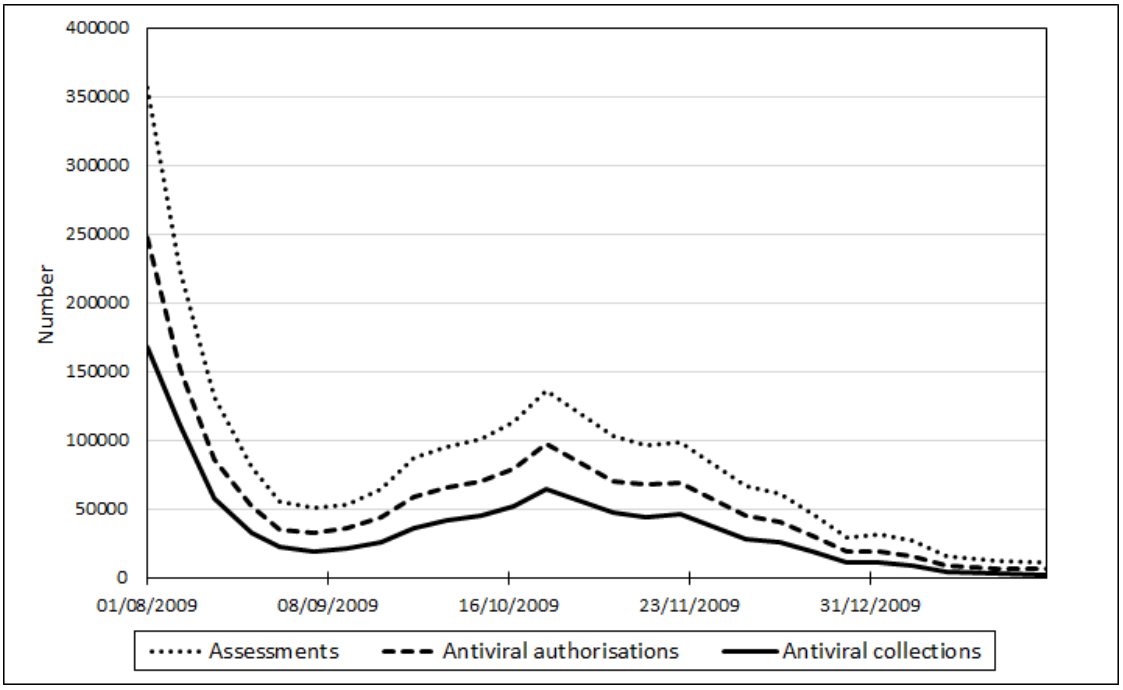


Figure 3: Number of assessments completed, antivirals authorised and collected through the NPFS, England, data from[44]

1.1.7 NAI treatment for influenza

1.1.7.1 Treatment effectiveness

An updated Cochrane review and meta-analysis of randomised placebo controlled trials of oseltamivir conducted between 1997 and 2004 for regulatory purposes found faster symptom relief by about one day and a significant reduction in self-reported pneumonia in previously healthy adults with naturally occurring influenza.[87] Subsequently, a more rigorous individual participant data (IPD) meta-analysis of the same data commissioned by the European Multiparty Group for Advice on Science (MUGAS) foundation confirmed faster symptom relief (25.2 hours), 44% fewer lower respiratory tract infections and 63% fewer hospitalisations associated with influenza in oseltamivir treated adults.[88] A systematic review of observational data for both seasonal and pandemic influenza commissioned by WHO showed that both oseltamivir and zanamivir reduced hospitalisation and duration of symptoms.[89] Finally, an IPD meta-

analysis of observational data on nearly 30,000 hospitalised pandemic influenza patients from 78 centres found that NAI use was associated with a significant 18% reduction in mortality among adults, with early administration (within 2 days of symptom onset) halving mortality. There was a decreasing effect with each day that treatment initiation was delayed; however, later treatment could still benefit critically ill patients, reducing the odds of mortality by 35%.[90] In a follow-up analysis, the authors also reported that early NAI treatment significantly reduced the need for ventilator support and mortality in influenza-related pneumonia cases.[91] It is important to note that none of these studies has been able to establish a statistically significant effect of NAIs with regard to more serious influenza-related outcomes in children; thus clinical judgment should be exercised when prescribing these drugs in children. A double-blind randomised controlled trial (RCT) conducted in Bangladesh on influenza patients diagnosed within 5 days of symptom onset reported that oseltamivir was associated with a reduction in duration of major symptoms by 1 day and reduced viral shedding[92] suggesting that the therapeutic window might extend beyond the licensed 2 days after symptom onset to about 5 days. A more recent meta-analysis of RCT data in children reported that oseltamivir was associated with a reduction in duration of illness, and decrease in likelihood of developing otitis media.[93]

1.1.7.2 Adverse effects

Oseltamivir has been associated with nausea and vomiting in some users but no serious adverse effects have been reported.[88] In 2007, Japan suspended the use of oseltamivir in patients aged 10-19 years due to concerns about neuropsychiatric adverse effects including hallucinations and delirious

behavior, resulting in some self-harming incidents and fatal falls. An investigation into these concerns using Japanese vital statistics data for 10-19 year olds from 1995 to 2005 revealed no significant increases in deaths by accident or suicide after the introduction of oseltamivir in 2001.[94] The investigation suggested that any possible abnormal behavior could be linked to the influenza virus infection itself, rather than to oseltamivir. Major public health authorities recommend the use of NAIs in patients at increased risk of influenza complications or who are seriously unwell with influenza.[95-97]

1.1.7.3 Resistance

The first reports of widespread resistance to oseltamivir in Europe emerged in 2007-08 when about 14% of seasonal (pre-pandemic) influenza A (H1N1) viruses in surveillance specimens carried the H275Y neuraminidase mutation that is associated with oseltamivir resistance;[98,99] however, this did not seem to be linked to oseltamivir use.[100,101] The H275Y mutation is a histidine-to-tyrosine substitution at position 275 of the NA surface protein, and is seen in N1 influenza viruses.[102,103] Resistant strains were seen more commonly in oseltamivir treated children infected with pre-pandemic A (H1N1) viruses (>99%) with low resistance to A(H3N2) and A(H1N1)pdm09 (<3%), and almost no resistance observed among A(H5N1) viruses.[104] By the end of 2008, oseltamivir-resistant A(H1N1) had completely displaced oseltamivir-sensitive A(H1N1) viruses across the globe, until displaced by the oseltamivir-sensitive A(H1N1)pdm09 pandemic virus in 2009, which remains in seasonal circulation.[105] Surveillance data on seasonal influenza virus strains show that resistance to all NAIs is currently low (~2%) and NAIs remain an appropriate choice for influenza treatment and prophylaxis.[106] However, previous

experience has indicated that emergence oseltamivir-resistant viral strains can occur unexpectedly and in a manner that is unrelated to the use of the drug.[103] A slow clinical response, or relapse of symptoms, or a slow virological response as evidenced by quantitative PCR should alert clinicians to the possibility of resistance. A coordinated and sustained monitoring for NAI-resistance is, therefore, crucial to the success of public health and pandemic preparedness plans.

1.1.7.4 Other NAIs

Zanamivir aqueous solution, although not licensed, was used during the 2009 pandemic on a compassionate-use basis for the treatment of serious illness.[107] The Zanamivir aqueous solution was available to be administered through nebulization or through the intravenous (IV) route; however data on safety and efficacy of treatment through these routes are limited.[107] Other NAIs include Peramivir (licensed for use in Japan as Rapiacta®, in South Korea as Peramiflu® and more recently by the US FDA in 2014 as an intravenous administration of a single dose of 600mg in adults aged 18 years and older under the tradename Rapivab™).[108] Clinical trial data show that a single intravenous dose of peramivir may be an alternative to a 5-day oral dose of oseltamivir in patients unable to tolerate an oral dose as well as improve compliance and provide stable pharmacokinetics in other patients with uncomplicated influenza.[109,110] Diarrhoea, nausea and vomiting are the commonly reported adverse effects, though a phase III trial found no significant difference in adverse effects experienced due to peramivir and oseltamivir. Laninamivir was approved for influenza treatment in Japan in 2010 and for prophylaxis in 2013

(tradename Inavir®) and available as a long-acting NAI administered in a single dose by nasal inhalation.

1.2 Modelling and simulation

Modelling can be thought of as a conceptual tool that helps understand the behaviour of an object or system.[111] Simulation is the process of designing a model of a real system and conducting experiments with this model for the purpose of understanding the behaviour of the system and /or evaluating various strategies for the operation of the system.[112] The processes of modelling and simulation are interrelated and a well-designed model can significantly improve the performance of a simulation.[113]

A general expectation of most modelling endeavours is prediction. Indeed, many models, including statistical models based on fixed distributions, have prediction as their primary goal.[114] However, not all models attempt to make predictions about future events. Epstein (2008) has identified the following as 16 reasons other than prediction to build models:[114]

1) Explaining a phenomenon
2) Guiding data collection
3) Illuminating core dynamics
4) Illuminating core uncertainties
5) Suggesting dynamical analogies
6) Discovering new questions
7) Promoting a scientific habit of the mind
8) Bracketing outcomes to reasonable ranges
9) Offering crisis options in near-real time
10) Demonstrating trade-offs
11) Challenging robustness of prevailing theories through perturbations

12) Exposing prevailing theories as being incompatible with available data
13) Training practitioners
14) Disciplining the policy dialogue
15) Education of the general public
16) Revealing the apparently simple (complex) to be complex (simple)

Computer simulations are of particular value in the study of complex systems whose behaviour cannot be inferred from its individual components.[115] While computer simulations are not substitutes for experimentation, they may be preferred over experiments with a real system for four main reasons: cost, time, control of the conditions of the experiment and in instances where the real system may not yet exist.[113] Simulation models enhance our understanding of a particular system in several ways,[114] but their primary application has been to aid in strategic decision-making.[116] In computer science literature, modelling and simulation is usually divided into three main paradigms: System Dynamics (SD), Discrete Event Simulation (DES) and Agent-based Modelling and Simulation (ABM&S).[116] A fourth modelling and simulation paradigm is one that combines elements of more than one paradigm, and is referred to as 'hybrid modelling' or 'multi-method modelling and simulation'.[117] The choice a particular method of modelling should depend on system being modelled, the intended purpose of the model and the level of abstraction desired.[113] Each of the three main computer simulation paradigms are briefly described in the following sections.

1.2.1 Computational modelling and simulation paradigms

1.2.1.1 System dynamic modelling and simulation

Introduced by Jay Forrester in the 1950s, SD modelling employs a combination of feedback loops, stocks, and flows between stocks.[117] Stocks are frequently used to represent tangible physical entities such as people, animals, money, vehicles, or items in an inventory. But they can also be used to represent more abstract concepts such as the level of fear (or any other emotion), knowledge, or experience. Flows are usually rates that represent the change in the state of the stocks, expressed per unit time.[117,118] Based on the nature of the relationship between model input parameters and model output, SD simulations can be either open or closed. In open SD simulations, the outputs are affected by the input parameters, but the opposite would not occur. A closed SD simulation is one where the outputs not only respond to changes in input parameters, but are also capable of influencing them.[118] Feedback loops are used to express the influence of model inputs and output on each other in closed SD simulations. Positive feedback loops are reinforcing influences, whereas negative feedback loops have system balancing effects.[118] Compartmental epidemic models and the Bass diffusion model are examples of real-life SD simulations.

SD modelling is a continuous, top-down simulation approach that employs a very high level of abstraction and are well-suited for models to aid in strategic decisions.[113,116,117] Computationally, SD modelling is rather efficient in dealing with the challenges of parallel synchronisation of the various elements of a simulation model.[118] SD models are typically deterministic, or rule-based, unless a stochastic term is explicitly specified in the model.[119] Mathematically,

SD models are a system of first order differential equations. A basic SD model can be described mathematically as follows:

$$\frac{d(X)}{dt} = F(X, P)$$

X= Stocks; P= set of parameters; F= non-linear vector-valued function[117]

1.2.1.2 Discrete event modelling and simulation

The earliest DES tool is believed to have been introduced by Geoffrey Gordon in 1961.[117] The idea underpinning the DES method is that a system is modelled as a process, in other words, as an orderly sequence of events occurring over time.[117] Queueing systems are especially well-suited to investigation using DES. DES models represent the changes that occur continuously in real world systems as divided, discrete entities.[117,120] DES may be deterministic or stochastic; randomness is explicitly specified in stochastic DES models. Entities are modelled passively as they move through a system, and intelligence (if people are being modelled) is modelled as a component of the larger system; in other words, with DES, macro behaviour is being modelled as opposed to the micro-level behaviour of individual entities.[121]

While DES is still a top-down modelling approach, in comparison to SD simulation, DES employs a lower level of abstraction. Healthcare systems in particular, as Robinson notes, lend themselves well to being modelled by both SD and DES.[113] The decision of whether to use DES or SD for a particular problem, often depends on the level of detail required in the models, with DES being better suited to represent systems where detailed tracking of individual entities is required.[113] Besides healthcare-related fields, DES are used

extensively to aid decision-making in supply chain management, operations research, planning of manufacturing and production lines.[118]

1.2.1.3 Agent-based modelling and simulation

ABM&S is a bottom-up modelling approach with a low level of abstraction that is particularly suitable to systems that comprise heterogeneous, autonomous, decision-making entities, such as human populations.[116] Applications of ABM&S span several disciplines from economics and social science to biology and ecology. ABM is a more recent modelling and simulation method when compared to SD and DES.[117] While most agent-based models (ABM) work in discrete time, it is also possible for ABMs to support discrete/continuous (hybrid) time as well.[117] ABM&S differs from DES in that the thread of control in ABM&S is decentralised, and marcro-level behaviour emerges from agent-level behaviour (i.e. macro-level behaviour is not explicitly modelled).[121]

The history of ABM&S is not very well documented and there is no general agreement over precisely what constitutes an "agent"– definitions of "agent" are known to vary across displines.[116] Nevertheless, agents can, in simple terms, be described as "conscious software entities" with some degree of autonomy in their interactions with other agents and with the environment.[122] Based on practical considerations for the purposes of modelling and simulation, Macal and North (2010) have identified the following set of essential characteristics of an agent: it is self-contained, autonomous, has a state that varies over time, and is social having dynamic interactions with other agents.[123] In addition to the essential characteristics, an agent may also have adaptiveness, goal-directedness, and heterogeneity.[123] Increasingly, ABMs are also being integrated with machine learning algorithms such as neural networks and

progressive algorithms to inform the agents' ability to adapt to its environment.[118]

1.2.1.4 Hybrid modelling and simulation

Hybrid modelling and simulation, also known as multi-method modelling simulation, integrates more than one modelling and simulation paradigm in a simulation model.[118] Depending on the nature of the problem being modelled and the level of abstraction desired, hybrid models can comprise agents interacting with a DES, a DES linked to an SD model, SD stocks and flows inside agents in an ABM, processes represented by DES embedded within agents, and agents that temporarily act as entities in a DES.[117] From representing a patient with a chronic disease going through a hospital system to modelling a call centre with flow of incoming calls from a diverse client base, hybrid modelling and simulation has several real world applications.[117]

1.2.2 Developing agent-based models and simulations

Typically, ABMs have three fundamental elements: a population of agents, a set of relationships (interactions) between the agents, and the agents' environment; successfully building an ABM involves identifying these three elements and programming them.[123] Despite the increasing popularity of ABM&S in various disciplines, the literature on systematic and standardised frameworks for ABM development is scant, and most model-development tends to be *ad hoc*.[124] Software engineering presents opportunities to apply more formal methods to standardise ABM development and implementation.[124] One such contribution of software engineering to ABM development is the Unified Modeling Language (UML).[124,125] UML is a set of graphical representations

used for designing and developing object oriented software systems.[126] As most ABM tend to be implemented using object-oriented languages, the usage of UML in ABM development seems natural.[124] The four most relevant UML elements to ABM development are:

1) **Use case diagrams:** to show interactions with the system
2) **Class diagrams:** to show how classes are composed
3) **State and activity diagrams:** to capture dynamics and behaviour
4) **Sequence diagrams:** to show interactions between agents.[124,127]

The ABM development process is necessarily multi-disciplinary and can often involve a range of stakeholders from different backgrounds. Application of UML to the development of ABMs can help demystify the modelling process, particularly for those stakeholders unfamiliar with modelling, and helps engage varied, multi-disciplinary teams.[127,128] Using UML and other principles and tools from software engineering, Siebers and Klügl (2017) have developed a structured ABM development framework that involves following a defined set of processes, in an iterative fashion.[124] Figure 4 provides an overview of the model development framework developed by Siebers and Klügl.

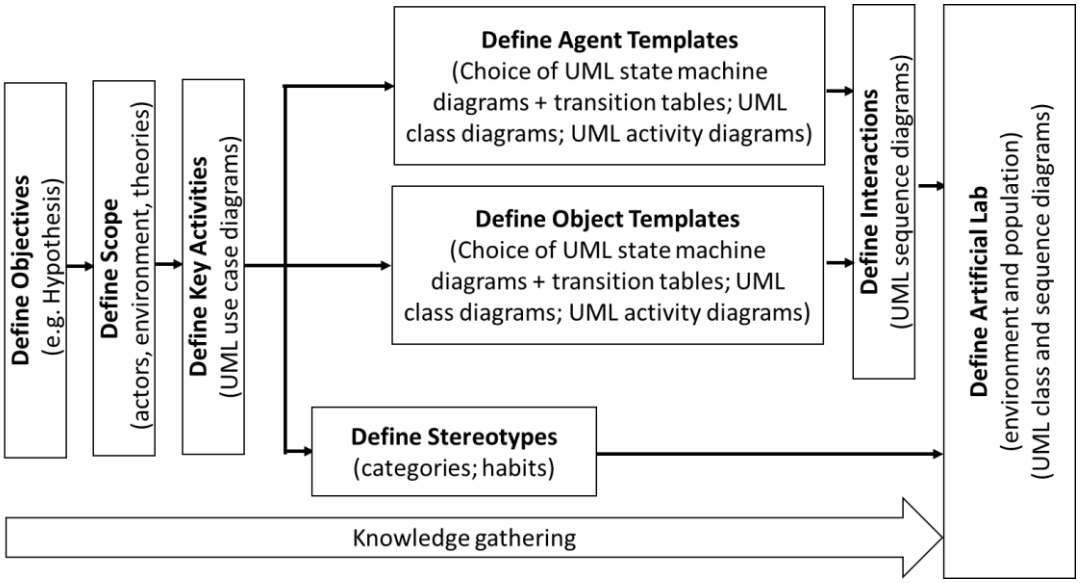


Figure 4: Overview of the ABM development framework by Siebers and Klügl[124]

1.2.3 Calibration and model validation

Simulation models are simplified representations of reality.[113] Therefore, to expect simulation models to reproduce reality perfectly is not reasonable.[114] Instead, simulation models are most helpful when they are built for specific objectives, applications or scenarios.[129] The challenge then turns to a question of how one can ascertain the "correctness" of a simulation model, given its intended purpose. This is usually done by comparing model output to some set of empirical data observed in a real world system (referred to as validation). However, a number of model input parameters are frequently calibrated to ensure that model output matches real world data, raising concerns about the extent to which the calibrated input parameters influenced the apparent 'good fit' to observed data.[130] This section will briefly outline some common model calibration and validation techniques used in social simulation.

1.2.3.1 Calibration

Calibration refers to the process of selecting model input parameter values that maximise the agreement between the model output and that of a real-world system.[131] Depending on the scenario being modelled, a modeller might note that for a number of parameters, their value in a real world system is known and fairly well-established (e.g. duration of a disease, attack rate of an outbreak, population size). Such parameter values can be directly input into a simulation model. But there are other parameters for which real-world values are unknown (e.g. probability of transmission of an unfolding outbreak, behavioural parameters). Such parameters can be estimated indirectly through use of computer simulation by calibrating them. A review on calibration approaches found that three calibration techniques are commonly used in the ABM&S literature– the indirect calibration approach, the Werker-Brenner approach and the history friendly approach.[132]

The indirect calibration approach: In the indirect calibration approach, first a macro-level behaviour is identified that the simulation model is intended to reproduce. Following this, empirical evidence on the macro-level behaviour is used to restrict the parameter space. The final step is to investigate the subspace of parameter values that produce model output that differs from what would be expected. The biggest disadvantage of the indirect calibration approach is that model parameters are not calibrated using empirical data, rather the focus is on the macro-level model output matching empirical behaviour.[132]

Werker-Brenner approach: This is a three-step calibration method. First, empirical data is used to define values, ranges and distributions of known model

parameters. Those parameters where no data are available are left as general as possible in the model (i.e. wide ranges). The second step is to empirically validate the model by using a statistical likelihood function to only retain those model realisations (outputs) that have been assigned a certain probability of being within the empirical output observed; parameters combinations that fall outside this range are rejected. The final step is to analyse the refined parameter space on the unknown parameters and use subjective/expert testimony to further restrict the possible parameter space and perform another round of calibration. The final step is called methodological abduction. One disadvantage of the Werker-Brenner approach is that this methods does not take into account the extent to which values that fall outside the estimated parameter space influence the observed data.[132]

The history friendly approach: This approach to calibration of ABMs attempts to reduce parameter dimensionality by using specific case studies of the phenomenon being investigated through use of the ABM&S, to guide calibration. This type of calibration is more commonly used in ABMs of economics.[132]

1.2.3.2 Validation

'Validation', with respect to simulation models, has been defined in a number of different ways.[130] Common to all of them is the concept of scrutinising the different parts of a simulation model to ascertain the extent to which it could be considered a valid representation of the phenomenon that the model is seeking to investigate. Heath et al. have put forth a useful guide to the validation of simulation models. According to them, validation of a simulation model can, in

the most basic sense, be broken down into the validation of the conceptual model underpinning the simulation, and the validation of the simulation output.[133] Figure 5 shows the basic process involved in developing a simulation model along with the stages at which the conceptual and simulation validation occur.

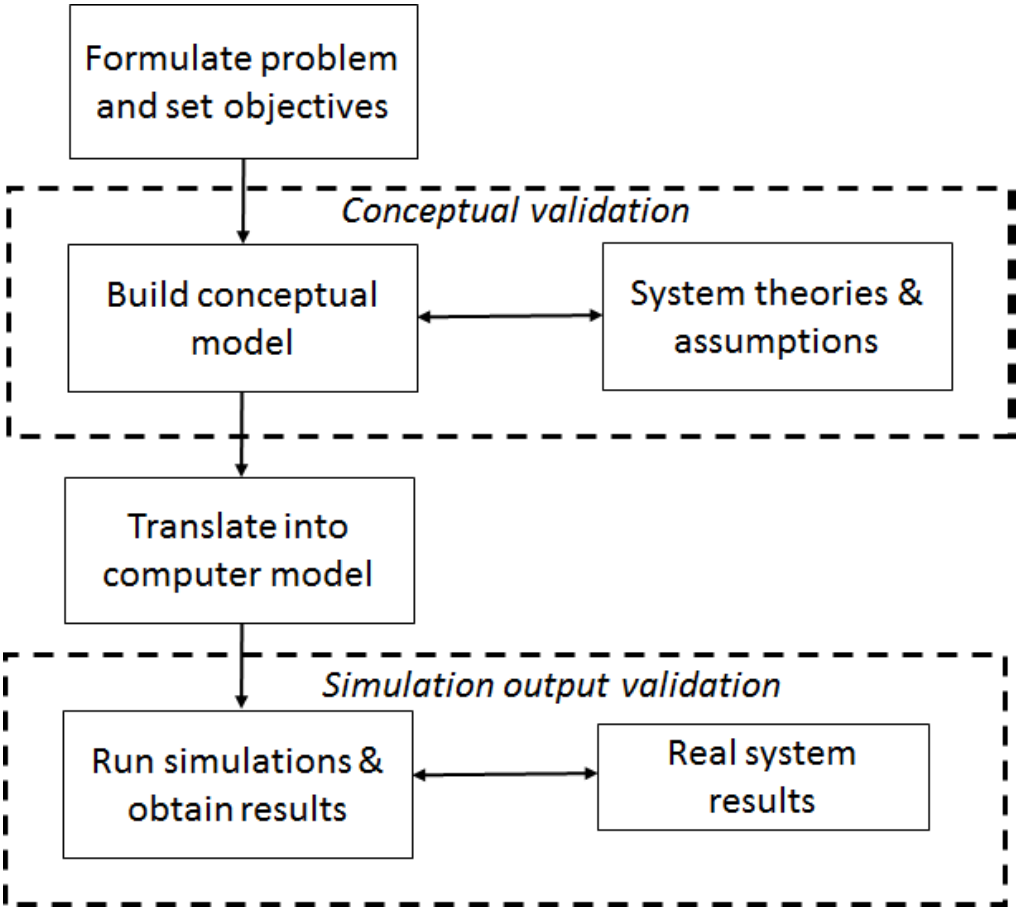


Figure 5: A basic simulation development process as described by Heath et al.[133]

Conceptual model validation involves validating the assumptions and theories that guide agent behaviour in the simulations. Conceptual models relying on established sociological/psychological models, and model assumptions rooted in empirical data can point to a sufficiently valid conceptual model.[133] Validating simulation output can be done either using graphical techniques (i.e. plotting model output and comparing to its real-world counterpart), comparison

to other valid simulation models, and extreme condition tests (i.e. do extreme parameter values produce the expected extreme output?).[129] However, given that most simulation models, particularly ABMs, frequently calibrate several model input parameters, model validation also involves an assessment of the impact of the calibrated parameter values on the simulation output. Testing the model output's sensitivity to calibrated input parameters are a good way of assessing model validity, especially for models with calibrated parameters.[129,133] The disappearance of an apparent match of the dynamics observed in the model output with empirical data as soon as one of the calibrated parameters indicates that the seeming model fit was driven more by the calibration of the parameter, rather than the model structure.[133] Sensitivity analyses can also help check if the simulation output is consistent with the underpinning conceptual model, as in a valid simulation model, the change in the model output in response to change in the input parameters, will usually be expected to be qualitatively and quantitatively consistent with what would be expected in the real world.[129]

1.2.4 Modelling and simulation in epidemiology and public health

Approaches to collecting and analysing evidence within epidemiology and public health depends on the nature of the question being considered. In the most general sense, analytical techniques used in epidemiology may be either qualitative or quantitative. Qualitative methods are generally better suited to explore the *why* and *how* questions through structured interviews and focus groups.[134] Quantitative methods involve using statistics and mathematics to describe an effect (of a drug or another type of exposure), or the behaviour of a system (like the spread of an epidemic). Both qualitative and quantitative methods employ "models" as investigative techniques. This thesis will focus on

quantitative methods in epidemiology as the main aim of the research is to investigate the effectiveness and impact of NAI drugs. Quantitative methods in epidemiology and public health can be divided into two main types: static and dynamical modelling methods.

1.2.4.1 Static models (Statistical models)

A large proportion of quantitative evidence in epidemiology draw from reductionist analytical methods. These methods employ statistical techniques that study one particular component of a system in great detail.[135] Hassmiller Lich et al. (2012), in a review of analytical paradigms in epidemiology and public health, have identified two main improvements in static statistical methods have been made in recent times:

1) In estimation of the magnitude of an effect in public health interventions,
2) In the analysis of change over time.[135]

Static methods in epidemiology can further be of two types: frequentist statistical methods and Bayesian statistical methods. Frequentist methods use frequencies to describe the underlying data but the associated parameters are fixed. Commonly used frequentist statistical techniques include various regression analyses (linear, logistic, Poisson, negative binomial, Cox etc.). Bayesian methods treat unknown quantities and parameters probabilistically and allow for their state to be updated.[136]

A typical statistical model usually studies the association between a dependent variable (the outcome being considered), and a set of independent variables (the main exposure and other variables of interest). A key strength of such statistical methods is that they allow study of individual components of a system in great detail.[135] These methods allow for adjustment of the so-called ‘confounding

variables', which are variables that can cause a 'blurring' of the association between an exposure variable and an outcome variable because these 'confounding variables' are independently associated with both.[137] Because of this, such statistical methods are particularly valuable in the measurement of the effectiveness of preventive interventions.[135] In addition to analysis of raw data pertaining to individual study settings, evidence synthesis methods known as meta-analyses are also widely used in epidemiology and public health.

Conventional meta-analyses in epidemiology and public health use aggregate data (often study/trial level) from published studies that are combined statistically to produce an overall measure of effect. IPD meta-analyses differ from the conventional approach to synthesising quantitative evidence in that, rather than using aggregate data from studies, the raw individual-level data from each contributing study are used to produce an overall measure of effect.[138] The greatest advantage of the IPD approach to data synthesis, when compared to the conventional "aggregate approach", is that the IPD approach facilitates standardisation across included study datasets and makes it possible to have the variables of interest derived directly from the data.[138] While combining data obtained from different studies, each of which report data collected from different population across settings, it is important to statistically account for clustering within individual studies. Failure to so do would result in the incorrect assumption that all the data were sampled from a single homogenous population.[138] Controlling for the clustering between included studies can be done using mixed effects models that allow for specification of the level of clustering that needs to be accounted for.[138,139] While IPD meta-analysis are commonly done for synthesising evidence from RCTs, the Preferred Reporting

Items for Systematic Reviews and Meta-Analyses of Individual Participant Data (PRISMA) statement acknowledges the legitimacy of the IPD approach for observational studies as well.[140]

However, despite the insights that these reductionist methods provide, there has been a growing recognition in the field of the fact that these methods may not be suitable to understand system-level behaviour. While these approaches are well-suited for studying individual components of a system, they fail to account for interactions between components. Often, key issues in epidemiology, particularly of infectious diseases, require understanding of system-level behaviour such as interconnectedness, non-linear dynamics, delays and adaptation.[135] To address these issues, evidence obtained from static methods is often integrated with dynamical models.

1.2.4.2 Dynamical models

Dynamical modelling methods are a collection of approaches that are particularly suitable for studying system-level behaviour. These methods make it possible to study relationships between individual components of a system and how they change over time, and are particularly relevant to infectious disease epidemiology. The methods described in earlier sections (1.2.1.1, 1.2.1.2, 1.2.1.3, 1.2.1.4) are all dynamical methods. While epidemiology has a long tradition of using such methods, the terminology used can differ from that used in standard computer science literature. In fact, the term "system dynamic models" is rarely used in epidemiological literature even if a majority of dynamical models in epidemiology tend to be deterministic or stochastic SD models.[77]

Daniel Bernoulli's work on small pox in 1790 and Sir Ronald Ross's work on Malaria in the late-nineteenth century were amongst the earliest mathematical models used in epidemiology.[141] The simplest dynamical epidemic models are the ones based on the work of Kermack and McKendrick (1927).[142] These are SD models where people, or populations, represent "stocks" and rates of infection and recovery represent "flows". A population is divided into sub-populations (or states) based on the natural history of the infection. For example: "Susceptible"– those people who are naïve to the infection; "Infected"– those people who have been infected at a certain point in time and are capable of passing on their infection to other susceptible people; and "Recovered"– those people who have recovered from the infection and have now developed immunity to it. This type of model is commonly referred to as Susceptible-Infected-Recovered (SIR) models (Figure 6). Here, the transition between states are fixed, or rule-based, and are described using differential equations.[77]

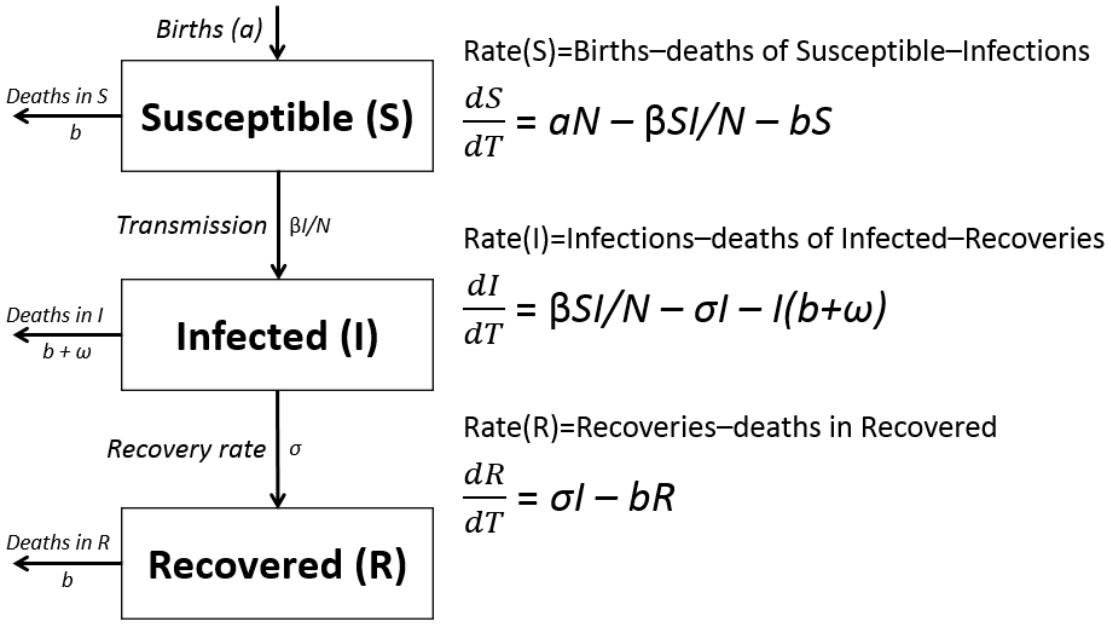


Figure 6: A typical SIR model with the associated differential equations– the simplest type of SD model commonly used in epidemiology

SIR models may be deterministic or stochastic. Stochastic SIR models allow for the transition between states to occur by chance, i.e. the transitions are allowed to vary randomly.[77]

A systematic review published in the Journal of Public Health Medicine in 2003 looked at the extent of "computer simulation modelling" in healthcare delivery systems emphasised the important role that computer simulations, particular DES and Markov models, can play in studying a number of problems in healthcare delivery.[143] Another review noted that DES was principally used in public health to address healthcare delivery problems.[144] The authors of the review noted that DES is particularly well-suited to studying three aspect of healthcare systems:

1. Patient scheduling
2. Patient routing and patient flows
3. Scheduling and availability of resources[144]

A more recent review of literature concurs with the above and adds that most DES models in healthcare delivery tend to be unit specific or facility specific, rather than whole hospital simulations, of which there were very few studies[145]. Jun et al (1999) suggest that improvements be made to DES models used in public health, emphasising the need to work with real operations and empirical data.[144]

Increasingly, ABMs are also being used widely in epidemiology, although the term "individual-based models" is more commonly used in epidemiological literature. ABMs used in epidemiology are described in more detail in section 1.2.4.4.

1.2.4.3 Decision models

Computer-aided decision support systems are technological solutions that help individuals or organisations in complex decision making.[146] Outputs from both static and dynamical models can greatly aid decision making. Decisions can be divided into three main types: strategic decisions, decisions related to management control and decisions related to operational control.[146] Over the years, numerous computer science tools have been incorporated into decision support systems like data mining, the web environment and collaborative decision systems.[146] Shim et al (2002) state that decision support systems in the next millennium should exploit modern tools such as artificial intelligence to create "semi-expert systems" and maximise a decision tool's capacity.[146]

Within epidemiology and public health, where populations are studied rather than individual patients, health economic analyses frequently drive decision making. Traditionally, methods such as cost benefit analysis (CBA) and cost effectiveness analysis (CEA) are commonly used in epidemiology, primarily as evaluation techniques. CBA tends to be used when benefits from one program or policy is being evaluated against its costs, and CEA tends to be used when outcomes from one program or policy are compared with the same outcomes from alternatives against their costs.[147] Decision tree models are commonly used in public health to perform health economic evaluations. They allow public health policy makers to compare the expected costs and consequences of multiple public health interventions.[148,149] Decision tree models comprise three basic components– branches, nodes and outcomes (or payoffs).[149] The branches are alternative public health interventions (or treatment options) and the nodes represent decisions and chance events (Figure 7). Probabilities are assigned to

the nodes in the tree and outcomes are specified, either in natural units (deaths, hospitalisations), or in standardised units (QALYs). Decision trees are then analysed by comparing the weighted average of the values of the outcomes in one branch with the alternative(s).[149] Decision tree models are routinely used by international public health agencies, such as the US Centers for Disease Control and Prevention (CDC), to carry out health economic evaluations of infectious disease intervention strategies.[150-153] Decision tree models are valued for being fairly simple to analyse, and for their transparency. An addition benefit is that they are easy to extend.[148]

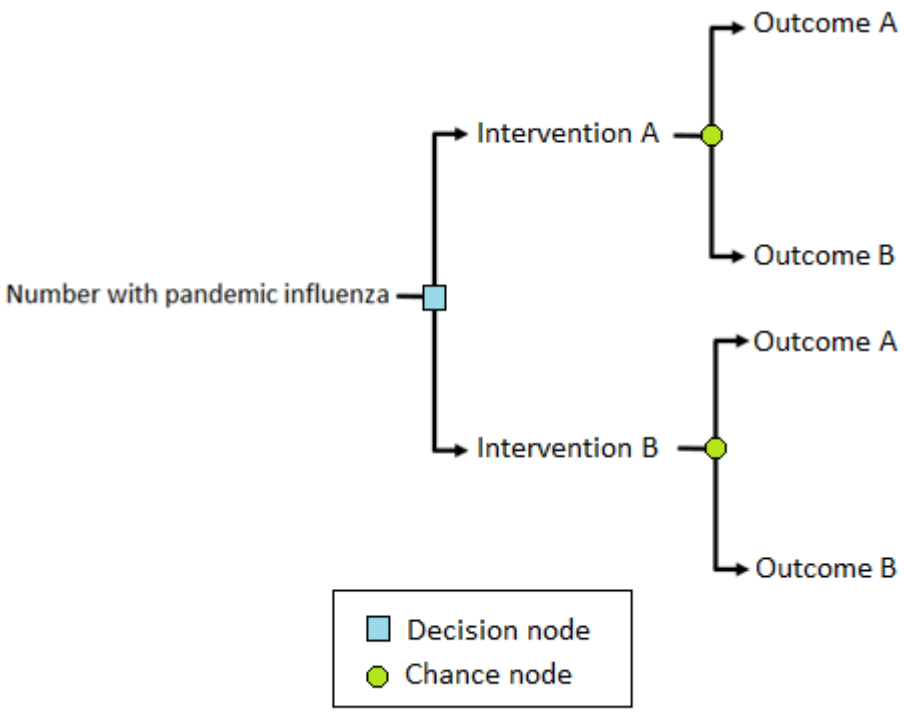


Figure 7: A simple decision tree model

1.2.4.4 Agent-based modelling in epidemiology

The terminology "individual-based model" is more commonly used to refer to ABMs in the epidemiology and ecology literature.[154] ABMs in epidemiology tend to be spatially structured stochastic models expressed in continuous space,

or as meta-population models. The utility of ABM&S in epidemiology can be attributed to their ability to capture complex dynamics, including spatial elements, that are often more biologically realistic than SD models. There is also a recognition of the computational expense that is frequently an issue with running ABMs of large populations, mainly because of all the individual agent interactions that the simulation will need to account for. To this effect, two common computational shortcuts are used in epidemiological ABMs: simulating ABMs in discrete space (as opposed to continuous space), and simulating ABMs in discrete time (as opposed to continuous time).[111] In fact, two of the most widely cited ABMs in epidemiology– both looking at pandemic influenza mitigation strategies– simulated large populations (one simulated the entire population of the USA, and the other entire populations of select Southeast Asian countries), have both used discrete time implementations of the model to achieve computational feasibility.[155,156]

In addition to being able to represent models in continuous time and space, ABMs offer another key feature to epidemiological modelling– the ability to account for heterogeneity.[135] Agents are, by most definitions, heterogeneous and autonomous decision-making entities.[116] Exploiting this characteristic of ABM has obvious benefits for modelling population systems. An epidemiological modeller is likely to encounter two main types of heterogeneity– epidemic heterogeneity, and behavioural heterogeneity. The following sections will discuss how ABMs can help account for epidemic and behavioural heterogeneities.

Incorporating epidemic heterogeneities: One important limitation of SD compartmental SIR epidemic models is the simplifying assumption of identical

contact rates between all members of the population being modelled.[77] In reality, however, contact rates vary significantly by individuals, and these heterogeneities in population are known to have a profound impact on the emerging dynamics of the infectious disease outbreak. This variation in contact rates can arise from a mix of several biological and social factors.[157] ABMs relax the assumption of homogenous mixing and allow for epidemic heterogeneities to be incorporated into the model. Rather than assuming that the probability of contacting another individual is identical for the entire population being modelled, ABMs allow for the network structure (between agents) to be made explicit.[158] Contact network types that could be specified in an ABM include random, spatial (distance-based), small-world, scale-free or lattice networks.[77] This makes it possible for certain agents to be more likely to contact certain other agents, mimicking reality to a greater degree than SD models in this regard.

In each individual, or agent, being modelled there are four important sources of epidemic heterogeneity– the contact rate, infectivity, latent period and the illness duration. Accounting for these individual heterogeneities and network structure has been known to appreciably affect the emergent disease dynamics.[158] These differences in epidemic dynamics may not be practically relevant in some situations, and therefore, the increased computational expense involved in implementing an ABM, rather than an SD model, may not be difficult to justify in those situations. However, in investigating problems to which individual contact structures are important, such as spatial spread of disease, or targeted vaccination programmes within specific population

networks, ABMs have a distinct advantage over SD models in simulating more realistic conditions.[158]

Incorporating behavioural heterogeneities: Although it is perhaps underutilised in epidemiology for this purpose, one of the biggest benefits of using ABM to simulate epidemics is the opportunity to investigate the impact of human behaviour on outbreaks. Simulating human behaviour is a complex endeavour; while differential equations can be used to represent simple behaviour, it can become intractably difficult to model more complex behaviour using ordinary differential equations.[159] ABMs can be especially useful in representing behaviour that is non-linear, exhibits path-dependence, memory and hysteresis, and involves heterogeneous interactions.[159] Clearly, individual behaviour and decision making can have a big impact on overall disease dynamics[160,161] and ABMs' bottom-up approach lends itself as the most natural way to model a system.[159] The challenge for modellers then turns to a question of *how* individual decision making is incorporated into an ABM. In a review of decision making models used in ABM literature, An (2011) has identified nine types of decision models:[162]

1) Microeconomic models
2) Space theory-based models
3) Psychological and cognitive models
4) Institution-based models
5) Rules of thumb models
6) Participatory models
7) Heuristic rules
8) Evolutionary programming

9) Calibration-based rules

Most behavioural models used in ABMs of social science tend to be based on psychological and cognitive models (type 3 above). The health belief model, the theory of planned behaviour and protection motivation theory are three commonly used psychological models in ABMs.[163] An extension of cognitive models, called fuzzy cognitive maps (FCM), are increasingly being used in ecological modelling but have not yet been applied to an epidemic context.[162]

More specific to epidemiological models that also incorporate behaviour change, Funk et al. (2010) propose two possible ways of model classification:[161]

1) **Based on the type/source of information used to make decisions**: In these models, agents make decisions by either updating their associated beliefs, or they do so because the prevalence of the disease (caused by the outbreak) has exceeded a threshold.
2) **Based on the effect of behaviour change**: Three types of such models have been identified in epidemiological literature: 1) where a change in agent behaviour changes the disease state of the agent, 2) where a change in agent behaviour modifies model parameters, and 3) where a change in agent behaviour modifies the contact structure.

In the same review, Funk et al. (2010) later note that while there have been numerous studies in the sociological and psychological literature that have sought to understand human behaviour in response to disease outbreaks, rarely have they been incorporated into epidemiological models. One of chief challenges for using coupled epidemic-behavioural models has been

parametrising behavioural parameters in the models with empirically collected data.[52]

1.3 Thesis motivation, aims and objectives

To summarise the 'Background and literature review' Chapter, influenza pandemics are relatively rare global events that occur when a novel influenza A virus spreads easily within human populations that have little or no immunity to it.[21,43] So far, there have been four confirmed influenza pandemics in the twentieth century– the 1918 'Spanish flu', the 1957 'Asian flu', the 1968 'Hong Kong flu', and, most recently, the 2009 A(H1N1) or 'Swine flu' pandemic.[43] Many argue that a fifth influenza pandemic occurred in 1977, although it was not declared as one at the time.[1] Preventing influenza pandemics from occurring, or even containing them at the source are both considered highly unlikely, however, pandemics can be mitigated once they have occurred through a combination of pharmaceutical and non-pharmaceutical intervention strategies.[43] Antiviral drug treatment was an important part of the pandemic response during the 2009 A(H1N1) influenza pandemic for a number of countries.[86] The antiviral drugs most widely used for pandemic influenza mitigation were NAIs.[164] Although NAI use in 2009 was aimed at reducing complications from pandemic influenza, the evidence for their effectiveness against such outcomes was not well established. Reviewing data from the 2009 A(H1N1) influenza pandemic to establish the effectiveness of NAIs on outcomes such as hospitalisations is important to inform future pandemic preparedness plans.

Given the lack of evidence for the effectiveness of NAIs on pandemic-influenza-related public health outcomes from clinical trials, their impact must

be assessed through observational data. Beyond absolute drug effectiveness estimates derived from clinical studies, outputs from computer simulations and health economic analyses can help public health practitioners understand the impact of various antiviral treatment strategies and their cost-effectiveness across a range of pandemic influenza scenarios.

1.3.1 Aims and objectives

The overall aim of this thesis is to ascertain the impact of NAI treatment on hospitalisation, and on subsequent hospital length of stay (LoS) in patients with influenza A(H1N1)pdm09 virus infection.

This thesis will seek to address this aim by using an interdisciplinary approach that draws from different analytical techniques to answer the following questions regarding the impact of NAI treatment:

1) What is the effectiveness of community-based NAI treatment in reducing hospitalisations in patients with influenza A(H1N1)pdm09 virus infection?
2) What is the effectiveness of in-hospital NAI treatment in reducing hospital LoS with influenza A(H1N1)pdm09 virus infection?
3) How can a behavioural model be integrated with an epidemic model to gain insights into NAI collection rates during an influenza pandemic?
4) How can NAI effectiveness estimates be extrapolated to assess the impact of NAI treatment on hospitalisations?
5) Is it cost-effective to use NAI treatment to avert hospitalisations?

1.3.2 Structure of the thesis

Chapter 2: The development of the modelling methods used in this thesis are described. This chapter first describes the data standardisation and pooling for the IPD meta-analysis, and then describes the development of a novel behavioural model for integration with an agent-based model.

Chapter 3: This is the first analysis of empirical data to ascertain NAI effectiveness estimates. This chapter describes an IPD meta-analysis investigating the impact of community-based NAI treatment on the risk of subsequent hospitalisation in patients with A(H1N1)pdm 09 infection.

Chapter 4: This is the second of analysis of empirical data to ascertain NAI effectiveness estimates. This chapter describes an IPD meta-analysis investigating the impact of in-hospital NAI treatment on hospital LoS in patients with A(H1N1)pdm09 infection.

Chapter 5: This chapter describes the proof-of-concept implementation and validation of the behavioural model developed in Chapter 2, exploring the impact of possible public health interventions on NAI collection rates during an influenza pandemic.

Chapter 6: In this chapter, the validated behavioural-epidemic ABM from Chapter 5 is extended to incorporate a DES. This "hybrid" model is then used to extrapolate point estimates of NAI effectiveness derived from IPD meta-analysis to evaluate the public health impact of NAI treatment strategies.

Chapter 7: This chapter describes results from a spreadsheet-based decision tree model exploring the impact and cost-effectiveness of community-based

NAI treatment, based on drug effectiveness estimates derived from IPD meta-analysis, on averting hospitalisations and deaths.

Chapter 8: This chapter summarises the thesis findings, outlines thesis contributions and makes recommendations for future research.

Chapter 9: Closing Remarks

Chapter 10: References

Chapter 11: Appendices

2 Overview of thesis methodology

Investigating the impact of NAI treatment on hospitalisation and LoS involves two broad processes: obtaining an estimate of drug effectiveness, and using the estimate of drug effectiveness in a model to explore the public health impact of the treatment strategy. This thesis takes an interdisciplinary approach where these two processes are embedded into a broader framework where the rigorous analysis of individual-level patient data, rooted in epidemiology and biostatistics, informs input parameters for a computational social simulation model, and a health economic decision tree model. The computational models in this thesis are not suited for precise forecasting of future events. Rather, their purpose is guided by the principles outlined by a pioneer of computational modelling, Joshua Epstein, who, amongst others, argues that computational models can serve several purposes other than prediction including: aiding understanding of the core dynamics of a system, discovering potential new drivers of system behaviour, and also to inform future data collection.[114,165-167]

In this thesis, the public health impact of NAI treatment is evaluated by sequentially addressing a set of questions (Section 1.3.1), each using different analytical techniques, to gain a broader understanding of NAI impact. The methodology used in this thesis can be divided in to two main parts: the IPD meta-analysis (analysis of empirical data to establish treatment effectiveness), and the modelling and simulation (extrapolation of IPD effectiveness estimates to assess the impact of NAI treatment strategies and their cost-effectiveness). In order to effectively study the public health impact of NAI treatment strategies,

the epidemic component of the computational models will need to be coupled with an appropriate behavioural model.

The remainder of this section will provide a brief overview of the thesis methodology by first describing the development of, and the empirical data used in the IPD meta-analysis, followed by a description of the novel behavioural model that was developed for use in the computational models subsequently.

2.1 Individual participant data meta-analysis

For the IPD meta-analyses described in this thesis, data from the PRIDE Research Consortium was used. The Post-pandemic Review of anti-Influenza Drug Effectiveness (PRIDE) Research Consortium was established in October 2011 with the aim of investigating the effectiveness of NAI treatment on a range of public health outcomes in patients with 2009 A(H1N1) pandemic influenza through the conduct of a series IPD meta-analyses. The PRIDE Consortium is headed and coordinated by researchers based at the Health Protection and Influenza Research Group, University of Nottingham (including the author of this thesis). The identification of potential data contributors was guided by the systematic search strategy that was employed in a systematic review and meta-analysis of published evidence, conducted by the PRIDE study team from Nottingham, on the effectiveness of NAI treatment on mortality and severe outcomes in hospitalised patients with 2009 A(H1N1) pandemic influenza.[168] On the basis of this systematic search, 401 potential data contributors were identified. The 401 potential data contributors included corresponding authors of multiple articles that analysed a common dataset. Additional research centres were identified through word-of-mouth, publicity at conferences and through professional networks of the PRIDE study team. Datasets that satisfied the

minimum dataset requirement (Appendix 1) were requested from the contacted authors. The study population of interest was patients with a laboratory confirmation, or clinical diagnosis, of A(H1N1)pdm09 infection until March 14, 2011 (to capture data up to three pandemic waves). Clinically diagnosed patients were those patients in whom laboratory-confirmation was not performed but had symptoms that were judged by the attending physician to be representative of ILI. 32% (121) of the contacted study centres responded, of which 60% (77) agreed to participate in the project. Data were neither requested from, nor provided by pharmaceutical companies. Four additional study centres were identified through the PRIDE study teams' professional networks. After exclusion of duplicate study centres (i.e. instances where multiple contacted authors had used the same dataset), a total of 170,858 individual patient records were disclosed by 81 study centres from 38 different countries.

The PRIDE study was granted an exemption from full ethical review by the University of Nottingham Medical School Research Ethics Committee, as individual contributing study centres had obtained ethical approval from their respective institutional review boards. The protocol for the PRIDE study has been registered at the PROSPERO register of systematic reviews (CRD42011001273).[169]

Prior to the commencement of this PhD, two IPD meta-analyses had been performed using data from the PRIDE Consortium, that respectively looked at the effectiveness of NAI treatment on in-hospital mortality, and influenza-related pneumonia (IRP).[90,91] As stated in earlier sections, this thesis will include IPD meta-analysis, using data from the PRIDE Consortium, to look at NAI effectiveness of hospitalisation and hospital LoS. Specifics about the

identification of the study population and statistical analyses used are described in the subsequent chapters (Chapters 3 and 4).

2.2 Development of a novel behavioural model

Over the past decade, different approaches to coupling behavioural and epidemic models have been proposed including game theoretic models to establish baseline equilibria,[160] belief-based models where model agents make decisions based on *a priori* beliefs, and simple extensions to models.[161,170] In computer science and multi-agent systems communities, frameworks such as the Belief-Desire-Intention (BDI) model and layered software frameworks are extensively used to model human decision-making.[171]

An effective behavioural model will allow individuals within a simulation to dynamically alter their behaviour in response to an unfolding infectious disease outbreak using decision algorithms to guide their behaviour.[172,173] The importance of ensuring that decision algorithms are based on established sociological and psychological frameworks has been recognised,[163,174] but few attempts have been made to formalise such frameworks for use in epidemiological models. Moreover, for a behavioural model to be useful to public health practitioners, it will also have to satisfy the requirement of relatively easy parametrisation of the model. One behavioural model that fulfils both these criteria is the mathematical interpretation of the health belief model (HBM) as proposed by Durham and Casman.[173]

According to the HBM, health-related behaviour is a result of four main constructs: perceived severity, perceived susceptibility, perceived barriers to action, and perceived benefits of the behaviour. HBM is primarily a cognitively oriented theory of behaviour change that is known to have its limitations.[175,176]

With a view to improve intervention design and healthcare policy, and to overcome limitations of previously proposed health behaviour theories, the COM-B (Capability Opportunity Motivation- Behaviour) behaviour model was developed in 2011.[177] The COM-B behaviour model posits that behaviour change arises from the interaction of the three essential components (C, O and M), and for an intervention to successfully bring about behaviour change, one or more of the three interacting components will have to be altered. One of the biggest advantages of the COM-B behaviour model is that it is intervention oriented, i.e. its constructs are linked to a set of interventions and healthcare policies. The linking of theory to intervention design is in line with recommendations given by the Medical Research Council of the UK (MRC) for intervention design, and this facilitates easy evaluation of the impact of various interventions on behaviour change.[178]

The NPFS, and the lack of NAI drug collection by over a third of patients with ILI who were authorised it, have described in Section 1.1.6.2. In this section, a simple behavioural model based on the COM-B model of behaviour change is developed. Its application to help identify potential interventions that could help improve collection rates for NAI medications, authorised through the NPFS, during an influenza pandemic is described in a subsequent chapter (Chapter 5).

It is important to clarify at the outset that the behavioural model outlined in the following section, and the analyses described in Chapters 5 and 6 are not intended to evaluate the performance of the NPFS, or its effectiveness in relieving pressure off primary or secondary healthcare services. Rather, they sought to address the question: If NPFS-related NAI collection rates could be improved (amongst those authorised) by specific public health interventions,

how might that impact on resulting hospitalisations? A thorough evaluation of the NPFS will also require comparison data on ILI consultation and NAI prescription from GP practices. Only ILI patients not at high-risk of complications from pandemic influenza were authorised NAIs through the NPFS; high-risk ILI patients who consulted the NPFS were referred back to their GPs.[179] Additionally, NPFS-consulting non-high-risk ILI patients were also referred to their GPs if they had symptoms suggestive of severe illness.[179] Therefore, while some reviews of the NPFS report that the service was successful in achieving its objectives,[69,179] the real impact of the NPFS in reducing GP workload is not entirely clear. However, that is beyond the scope of this thesis. Nevertheless, understanding the impact of certain drivers of healthcare seeking behaviour can help devise effective public health strategies that, for a given rate of NAI authorisation, seek to maximise collection.

In 2015, a qualitative study was undertaken in which people were interviewed about their experience with NAIs and vaccinations during the 2009 influenza pandemic. A list of factors that are likely to influence a person's uptake of vaccines under each component of the COM-B behaviour model was identified.[70] This list has been adapted to inform the novel behavioural model and to guide the links between drivers of behaviour and behaviour change (Table 2).

Capability	Opportunity	Motivation
Psychological: **Knowledge of the disease (Awareness of disease and transmission rates)** ***Physical:*** **Not salient**	*Physical:* Access to treatments *Social:* Social influences (seeing that others are being treated)	*Automatic:* Fear of infection and consequences (Physical and emotional proximity) *Reflective:* Optimistic bias

Table 2: Adapted list of factors that can influence antiviral drug uptake from[70]

Formalising a behavioural theory involves expressing the influence of a set of variables, using the logic of a particular behavioural theory, to produce an estimate of the likelihood of a behaviour. This often means weighting constructs of a behavioural theory and combining them mathematically. A few different ways of achieving this combination of constructs have been reported in literature including additive models,[163] multiplicative models,[180] and logistic regression models,[181] Building on the work done by Durham and Casman,[173] a logistic model will be developed to express the decision framework owing to its binary classification of the COM-B constructs, the ease of parametrising from public health literature and its terse representation of behaviour probability.

In the logistic expression of the COM-B model, each construct of the model (C, O and M) is classified as being in either a 'high' state or a 'low' state. The odds ratios (OR) of the behaviour when being in a particular state ('high' or 'low') are obtained either from literature or from analysing data. These values are then combined using the formula below to obtain a probability (p) of behaviour (b).

$$p(b) = \frac{OR_0 * \prod OR_i^{x_i}}{1 + (OR_0 * \prod OR_i^{x_i})}, i = 1,2,3 \qquad (1)$$

In equation (1), i corresponds to each of the three constructs of the COM-B model– C, O and M respectively. OR_i represents the odds ratio of the behaviour when one of the COM-B constructs in the 'high' state (relative to the 'low' state). For example, if one were to assume that NAI authorisations to people with 'high' Capability (to collect NAI drugs) are 3.1 times as likely to result in collections when compared to those with 'low' Capability, the OR_1 in equation (1) would be 3.1. Once similar OR estimates for the O and M constructs are obtained, they can be combined using equation (1) to get a probability estimate

for NAI collection. OR_0 is a constant that will be derived from fitting the model to data. It describes *p(b)* when C, O and M are in the 'low' state. Solving the logistic equation above will give us a value between 0 and 1. Agents with a *p(b)* value of ≥0.5 will engage in a particular behaviour (collect NAI drugs).

During an ongoing pandemic, people are likely to fluctuate between states of 'high' and 'low' capability, opportunity and motivation respectively depending on the state of the disease around them and also on the behaviour of their peers. Hence, it is essential that agents in the simulation are able to update their C, O and M scores dynamically. Using the information presented in table 2, decision rules for the updating of the COM-B constructs can be formulated as follows.

2.2.2 Capability

Using the COM-B behaviour model, Rubinstein et al. (2015) identified that a person's capability to engage in the thought process necessary to enact a particular behaviour (collect NAI drugs) is influenced by awareness of the disease rates of the ongoing outbreak.[70] The capability of a person to make a particular decision is more likely to be influenced by local disease activity in their immediate networks, rather than global-level prevalence estimates. Indeed, the importance of local awareness during an outbreak has been reported before.[182] Even within local networks, disease activity is a combination of new infections occurring each day, and the total number (cumulative) of infections that have occurred in a local network over the course of the outbreak. Therefore, in the context of the case study considered, an agent's Capability to collect authorised NAI drugs would depend on its level of awareness of local disease activity, both incident cases and prevalent cases. However, it is unlikely all individuals would actively seek out

information on disease rates during a pandemic. Further, there is evidence to suggest the possibility of a cognitive discounting of earlier hazards in favour of more recent events.[183]

In this behavioural model, the effects of awareness of disease activity are incorporated using both the cumulative as well as daily incidence of influenza cases. The biases that can affect an agent's perception of local disease rates are modelled using a weighted discount rate (δ) that can take any value between 0 and 1 (Equation 2).

$$C = \sum_{i=0}^{t-2} \delta^i * I_{t-i-1} \quad (2)$$

Capability *C* is represented as the weighted sum of the number of new influenza cases *I* at time *t,* discounted at the rate δ. This approach to calculating discounted cumulative incidence is consistent with previous behaviour models.[163,173] Once an agent has determined its Capability score, it then compares it with a threshold α to determine if it is in the 'high' or 'low' state of Capability (Equation 3).

$$C = \begin{cases} high, & C > \alpha \\ low, & else \end{cases} \quad (3)$$

2.2.3 Opportunity

According to the COM-B model, the Opportunity to engage in a particular behaviour represents all of the factors that influence the behaviour but are outside the control of the individual.[177] Rubinstein et al. (2015) identified 'access to treatments' and 'seeing other being treated' as affecting an individual's opportunity to engage in behaviour change (Table 2). An ecological study performed in the UK also reported that the likelihood of NAI collection significantly reduced with increasing distance to an ACP[184]. For this

case study, Opportunity is modelled as a function of the distance to an ACP and seeing others in their community who have collected NAIs (C_n), with the distance to an ACP having an inverse association with Opportunity (i.e. a decreasing likelihood of NAI collection with an increasing distance to an ACP). Agents in the simulation then compare their respective Opportunity scores (O) to a threshold η to determine if they are in a state of 'low' or 'high' Opportunity (Equation 4). There is also evidence for the association between socioeconomic depravation (SED) and access to influenza treatment.[184,185] This is not explicitly included in the current formulation of the behavioural model due to the lack of available data. However, a measure of SED, such as the English Index of Multiple depravation (IMD),[186] could easily be incorporated into the Opportunity score as a multiplicative factor.

$$O = \begin{cases} high, & (\frac{C_n}{Distance}) > \eta \\ low, & else \end{cases} \quad (4)$$

2.2.4 Motivation

'Motivation' includes the mental processes that direct behaviour beyond conscious decision-making.[177] According to the COM-B model, Motivation is comprised of an automatic and a reflective component. In the study by Rubinstein et al. (2015), fear from proximity (physical and emotional) to the pandemic, and beliefs about consequences of being ill from pandemic influenza was identified as the automatic component of Motivation that influenced people's decision to take NAI drugs (Table 2). The belief amongst some people that, because they followed an active lifestyle, they would make an easy recovery from pandemic influenza without needing to take NAI treatment was found to be the reflective component of Motivation.[70] In the

behavioural model, the case hospitalisation risk (CHR) was used to represent the severity of the outbreak. The physical and emotional proximity to severe outcomes from the disease was represented by the CHR and a variable, *OB*, which was used to account for optimistic bias. *OB* can take any value between 0 and 1 with higher values indicating an increased optimistic bias. Each agent's Motivation (*M*) will be evaluated against a threshold θ to determine if they were associated with an 'high' or 'low' state of Motivation (Equation 5).

$$M = \begin{cases} high, & (\frac{No.hosptialisations}{No.illnesses})/OB > \theta \\ low, & else \end{cases} \quad (5)$$

2.3 Extrapolation of IPD estimates using modelling and simulation

The models developed in this thesis combine three modelling and simulation methods to extrapolate the NAI effectiveness measures obtained from the IPD meta-analyses (described in Section 2.1) to aid in public health decision-making– an agent-based simulation model, a discrete event simulation model and a health economic decision tree model.

In assessing the population-level impact of NAI treatment, it is important to account for epidemic and behavioural heterogeneities. An important limitation of SD models (compartmental SEIR epidemic models) is that they assume homogenous mixing of individuals in a population. ABMs, on the other hand, relax this assumption, and are extremely well-suited for incorporating the effects of epidemic and behavioural heterogeneity (Section 1.2.4.4). Therefore, a coupled behavioural-epidemic ABM that integrates the formalised COM-B behavioural model described in Section 2.2 with an agent-based epidemic

model, will be used in this thesis. The implementation and validation of this coupled behavioural-epidemic model are presented in Chapters 5. The extension of this coupled behavioural-epidemic model with a DES to evaluate the impact of NAI treatment on hospitalisation and LoS is presented in Chapter 6. A DES is used in Chapter 6 to represent a hospital where infected patients spend a specified amount of time depending on their treatment status before being discharged, representing time spent by a patient at a hospital. A DES is appropriate here since once patients enter a hospital, they can be modelled as passive entities that flow through a system (Section 1.2.1.2). It must be borne in mind that the models described in Chapters 5 and 6 are not specifically about the potential value of the NPFS. Rather, they serve as frameworks to extrapolate NAI effectiveness estimates to understand the value of community NAI treatment.

The health economic decision tree model described in Chapter 7 evaluates the potential hospitalisations and deaths averted through community-based NAI treatment, compared to no NAI treatment, and associated cost-effectiveness. The health economic analysis is based on the UK's experience of the 2009-10 influenza pandemic and is performed from the perspective of the healthcare payer [National Health Service (NHS)]. The decision tree model is decoupled from the behavioural model, as implementing a large-scale ABM of an entire country is computationally expensive. Instead, important parameters related to healthcare-seeking a varied in sensitivity analyses.

The descriptions of the parametrisation, implementation, and results of the simulation models are provided in the subsequent individual study chapters (5, 6, and 7).

3 Study 1: What is the effectiveness of community-based NAI treatment in reducing hospitalisations in patients with influenza A(H1N1)pdm09 virus infection?

3.1 Introduction

This study will seek to answer the first of the thesis objectives regarding the effectiveness of community-based NAI treatment in reducing hospitalisation in patients with A(H1N1)pdm09 virus infection by performing an IPD meta-analysis of observational data. As discussed in Section 1.1.7, data on the effectiveness of NAI treatment pertaining to important public health outcomes, such as reductions in mortality and hospital admissions, for patients with A(H1N1)pdm09 influenza are lacking from RCTs. Notwithstanding, observational evidence suggest that NAI treatment may have reduced mortality in hospitalised patients during the 2009-10 pandemic.[90,187] Similarly, a meta-analysis of (aggregate) observational data on seasonal influenza prior to 2009, also suggests that NAIs given to high-risk community patients with influenza may reduce the risk of subsequent hospitalisation.[188] To the best of my knowledge, similar data on hospitalisation during the 2009-10 pandemic period are currently absent.

3.2 Methods

The PRIDE research consortium: Details regarding the PRIDE consortium and identification data contributors has been provided in Section 2.1. In total, the PRIDE consortium obtained data on 170,858 potentially eligible patients

from 81 research centres in 38 countries across six WHO regions. A smaller group, from the total 81 study centres, provided community or outpatient data, which were then used for the current study. No data were provided or funded for collection by pharmaceutical companies.

Data standardisation, exposure, outcome and covariates: For this study, data on patients in the community or those seeking care in outpatient clinics with laboratory-confirmed or clinically diagnosed influenza A(H1N1)pdm09 virus infection were available from nine centres in as many countries (Argentina, Canada, France, Germany, Israel, Saudi Arabia, Singapore, Slovenia and the UK). The obtained data were standardised using a data dictionary (Appendix 2) before pooling for analysis. Influenza-related hospital admission as determined by case records was the primary outcome variable. Treatment with an NAI started in any community or outpatient setting, as compared to no NAI treatment, was the primary exposure variable. An additional exposure based on timing of NAI treatment was defined– early NAI treatment (treatment started ≤2 days after symptom onset) versus later NAI treatment (>2 days after symptom onset) where data were available. Patients in whom the data of NAI treatment was recorded as being the same as the date of hospital admission were excluded from the analyses on the basis that treatment would have not had sufficient time to work in these patients. The exclusion of these patients also accounts for any NAI prescriptions that may have been given after a decision to admit the patient to hospital was made– amounting to confounding by indication. Variables adjusted for in the final multivariable model were outpatient or community-based antibiotic treatment (yes/no) and propensity score (by quintile) for receiving NAI treatment in the community.

Propensity scoring: Propensity scores were computed for the likelihood of community-based NAI treatment for individual patients within each contributing dataset using the method described by Hirano and Imbens.[189] Multivariable logistic regression models developed to calculate propensity scores included the following covariates: age, sex, presence of a comorbid condition (yes/no) and an indicator of disease severity (in order of preference: documented severe respiratory distress or shortness of breath). The resulting propensity scores were then categorised into quintiles for use in subsequent analyses.

Statistical analysis: A mixed-effects logistic regression model was used in the primary analysis to investigate the association between community-based NAI treatment and subsequent hospital admission using the 'xtmelogit' command in Stata (version 14.2; StataCorp LP, College Station, TX, USA). To account for differences in baseline outcome between individual datasets, individual study centres were included as a random intercept. Both unadjusted and adjusted models were run, the latter adjusting for community-based antibiotic treatment and propensity scores. Missing data were included as a dummy variable category to allow for comparisons between the unadjusted and the adjusted models The C-statistic (area under the receiver operating characteristic curve) was used to assess model fit. Where data were available, the potential impact of timing of NAI administration (early NAI treatment versus later NAI treatment) on hospitalisation was also explored. Stratified analysis were performed in patients with laboratory-confirmed A(H1N1)pdm09 influenza and adults (≥16 years) and children.

Furthermore, an additional analysis restricted to patients with high-risk conditions was carried out. Patients were classified as having a high-risk condition if they had at least one chronic illnesses recorded that would trigger seasonal influenza vaccination,[190] or were aged ≥65 years.

Results from the mixed-effects logistic regression models are presented as OR with 95% CI.

3.3 Results

Outpatient data on 130,077 patients in total with clinically or laboratory-confirmed influenza from 25 contributing centres were obtained. However, 16 out of the 25 centres (n=125,049 patients) contributed surveillance data without clinical data on either NAI use or subsequent hospitalisation status. Therefore, the final study population comprised 3,376 patients from nine study centres (Figure 8). Seven out of the nine included study centres (n=1,183 patients) were outpatient (ambulatory care) clinics attached to hospitals. Of the remaining two study centres, one provided community surveillance data collected by the Ministry of Health (n=1,762), and the other provided data from primary care (n=431). Three out of the nine included centres (Canada, Germany and Israel; total n=535) were from paediatric outpatient clinics and comprised entirely of patients under the age of 18 years. Patients from the German study centre (one of the three paediatric study centre) were especially young with a median age of 1.4 years (Appendix 3).

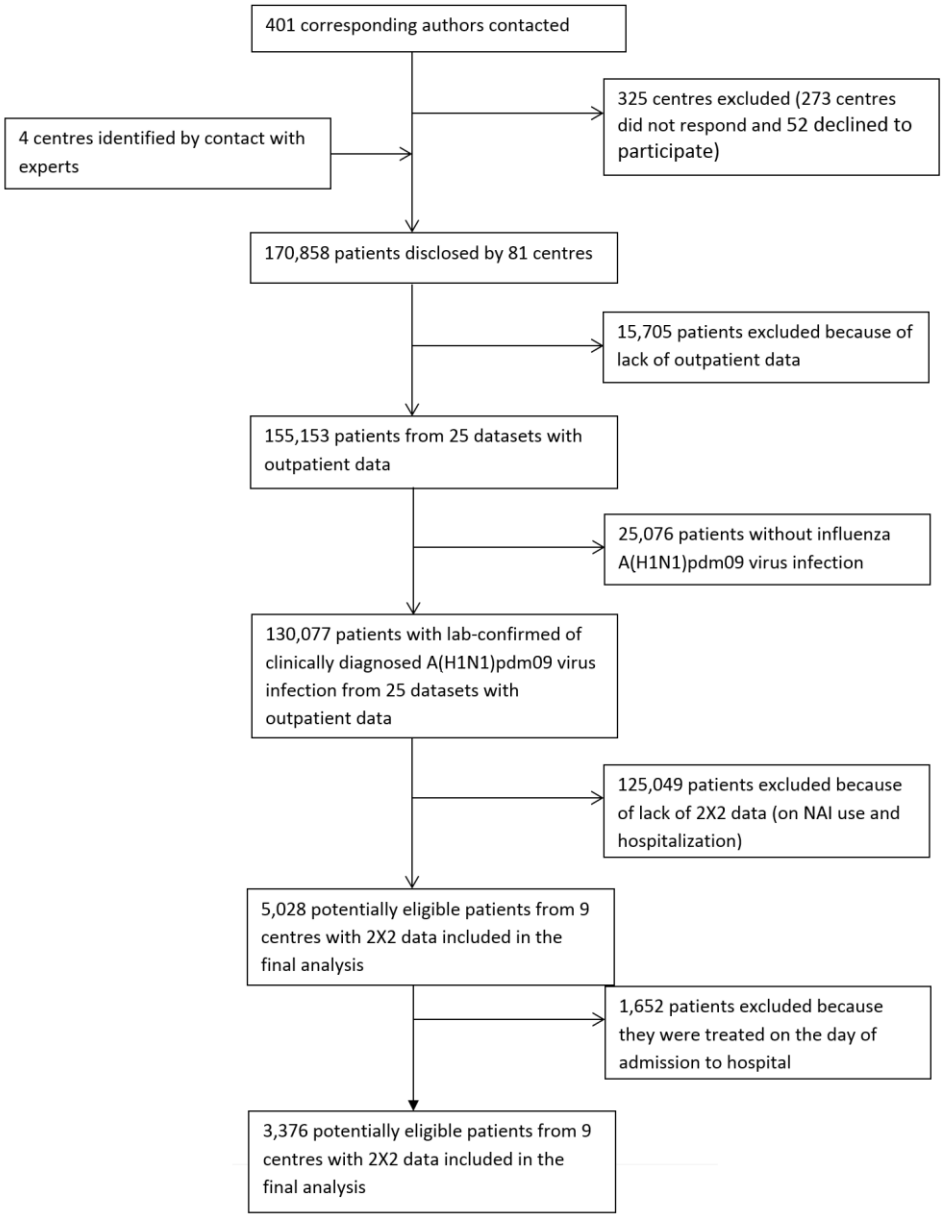


Figure 8: Study flow diagram for IPD meta-analysis investigating NAI effectiveness for hospitalisation

Out of the 3,376 patients included in the pooled dataset: 3,085 (91.4%) patients had laboratory confirmed A(H1N1)pdm09 virus infection; 1,747 (51.8%) were children (<16 years); 67 (2%) were over 64 years old. Overall, 1,705 (50.1%) hospital admissions and 928 (928/2,395; 38.7%) patients with clinically observed shortness of breath or respiratory distress (as a marker of severity)

were observed in the study population. Where data were available (n=473), the median time duration between date of symptom onset and the date of starting NAI treatment was 1 day (interquartile range (IQR): 0-3) for the whole study population, 1 day (IQR: 0-2) for non-hospitalised patients, and 1 day (IQR: 0-4) for hospitalised patients. Out of the hospitalised patients, where data were available (n=1,363), the median interval between date of symptom onset and date of hospitalisation was 2 days (IQR: 1-3). General characteristics of the study population are presented in Table 3. About half (50.1%) of the study population was eventually admitted to hospital and one or more indications of severe respiratory illness (shortness of breath or respiratory distress) were recorded in 38.8% of the study population. Additionally, less than 2% of the study population were elderly (aged ≥ 65 years) and 72% had no recorded comorbidities indiacting that patients were mainly young and previously healthy. Indeed 51.8% were children and 37.1% of women aged 15 to 44 years were pregnant, reflecting the inclusion of one obstetric clinic (n=81) within the pooled dataset.

Variable	**All patients** (n=3,376)	**Non-hospitalised** (n=1,671)	**Hospitalised** (n=1,705)
Number of male cases	1,712 (50.71)	859 (51.41)	853 (50.03)
Age: median (IQR) in years (n=3,253)	14 (4.95 to 27.88)	14 (6.24 to 27)	15 (3.85 to 28.47)
Population groups (no. of persons)			
Adults (≥16 years)	1,506 (44.61)	730 (43.69)	776 (45.51)
Children (<16 years)	1,747 (51.75)	879 (52.60)	868 (50.91)
Aged≥ 65 years	67 (1.98)	22 (1.32)	45 (2.63)
Pregnant women† (n=741)	237/639 (37.09)	121/278 (43.53)	116/361 (32.13)
Countries			
Argentina	17 (0.50)	13 (0.78)	4 (0.23)
Canada	148 (4.34)	113 (6.76)	35 (2.05)
France	81 (2.40)	55 (3.29)	26 (1.52)
Germany	314 (9.29)	161 (9.63)	153 (8.95)
Israel	73 (2.16)	36 (2.15)	37 (2.16)
Saudi Arabia			

Singapore Slovenia UK	1,762 (52.11) 490 (14.49) 60 (1.77) 431 (12.77)	613 (36.68) 242 (14.48) 24 (1.44) 414 (24.78)	1,149 (67.19) 248 (14.50) 36 (2.11) 17 (1.00)
A(H1N1)pdm09 diagnosis Laboratory confirmed Clinically diagnosed	 3,085 (91.38) 291 (8.61)	 1,522 (91.08) 149 (8.92)	 1,563 (91.67) 142 (8.33)
Severe disease (n=2,395) (Severe respiratory distress or shortness of breath at presentation)	928/2,395 (38.75)	321/991 (32.39)	607/1,404 (43.23)
Comorbidities Any comorbidity (n=2,945) Asthma (n=1,172) COPD (n= 902) Other chronic lung disease (n= 2,257) Heart disease (n=614) Renal disease (n= 2,299) Liver disease (n=541) Cerebrovascular disease (n=490) Neurological disease (n= 2,448) Diabetes (n= 2,449) Immunosuppression (n= 2,390)	 824/2,945 (27.98) 214/1,172 (18.26) 120/902 (13.30) 290/2,257 (12.85) 20/614 (3.26) 92/2,299 (4.00) 11/541 (2.03) 7/490 (1.43) 57/2,488 (2.33) 135/2,449 (5.51) 97/2,390 (4.06)	 302/1,257 (24.03) 91/634 (14.35) 38/471 (8.07) 98/871 (11.25) 4/294 (1.36) 40/879 (4.55) 5/258 (1.94) 1/242 (0.41) 9/963 (0.93) 47/964 (4.88) 36/918 (3.92)	 522/1,688 (30.92) 123/538 (22.86) 82/431 (19.03) 192/1,386 (13.85) 16/320 (5.00) 52/1,420 (3.66) 6/283 (2.12) 6/248 (2.42) 48/1,485 (3.23) 88/1,485 (5.93) 61/1,472 (4.14)
Community/outpatient NAI treatment Any NAI treatment Oseltamivir* (n=2,945)	873 (25.82) 590 /2,94 (20.03)	653 (39.08) 385/1,257 (30.63)	220 (12.90) 205/1,688 (12.14)

Percentages presented in this table are column percentages unless other denominators are specified

† Proportions were calculated as a percentage of pregnant patients among female patients of reproductive age; the broader age range was selected in preference to the WHO definition (15–44 years) after consultation with data contributors to reflect the actual fertility experience of the sample. This includes data from an obstetric outpatients clinic (n=81).

* Where it was explicitly stated that the NAI administered was oseltamivir.

Table 3: General characteristics of the study population (n=3,376)

Out of the 1,705 patients who were admitted to hospital, data were available on the subsequent course in 1,433 patients. Of these 1,433 hospitalised patients, 1,155 (80.6%) were treated with NAIs in-hospital, 147 patients (10.3%) were subsequently admitted to critical care facilities [of which 119 (80.9%) treated, 28 (19.1%) untreated] and 14 patients (1%) died [13 (92.9%) treated, 1 (7.1%) untreated]. Data relating to pneumonia were available in a smaller subgroup of

1,392 patients; of these patients 215 (15.5%) were recorded to have clinical signs of pneumonia, with radiographic confirmation of pneumonia in 101 (7.3%) patients (64 (63.4%) treated, 37 (36.6%) untreated). Further, data on length of subsequent hospital stay were available in a smaller subgroup of 522 patients where the median LoS was 3 days (IQR: 2-5 days) (median: 3 days (IQR: 2-5 days) in treated, median: 2 days (IQR: 1.5-5 days) untreated). Of the 1,647 patients who were excluded from the analyses because they were hospitalised on the same day of NAI treatment initiation, 116 (7%) were admitted to critical care facilities and 23 (1.4%) died. In 1,595 of these patients on whom pneumonia data were available, 154 (9.7%) were found to have had clinical signs of pneumonia, 31 (1.9%) of whom radiologically-confirmed pneumonia. The median length of hospital stay in an even smaller sub-group (n=186 where data were available) was found to be 3 days (IQR: 2-5).

In patients with laboratory-confirmed or clinically diagnosed A(H1N1)pdm09 influenza, after adjusting for community-based antibiotic treatment and propensity score to receive NAI treatment in the community, the OR for hospital admission in patients with outpatient or community-based NAI treatment was 0.24 (95% CI: 0.20-0.30) when compared to no NAI treatment in the community (Table 4). A C-statistic of 0.813 (95% CI: 0.799-0.827) suggested that the predictive performance of the mixed-effects logit model used in this study was acceptable.

When restricted to laboratory-confirmed A(H1N1)pdm09 patients, the NAI effectiveness estimate was very similar to the estimate for the overall study population (Table 4). NAI treatment, when compared to no treatment, was associated with reduced odds of hospitalisation in both children (adjusted OR:

0.25; 95% CI 0.18-0.34) and adults (adjusted OR: 0.26; 95% CI: 0.19-0.35). In the sub-group of 473 patients in whom data on the interval between symptom onset and initiation of NAI treatment were available, early NAI treatment was associated with an adjusted OR of 0.44 (95% CI: 0.23-0.86) when compared to later NAI treatment.

In the pooled dataset, 1,019 patients (30.1%) were recorded to have at least one high-risk condition. In this sub-population of higher-risk patients, a reduction in the odds of hospital admission (OR: 0.27; 95% CI: 0.19-0.38) in those who received community-based NAI treatment, compared with no NAI treatment, was observed. The results of all analyses conducted in this study are summarised in Table 4.

Population	Unadjusted analysis		Adjusted analysis †	
	Unadjusted OR (95% CI)	**p-value**	**Adjusted OR (95% CI)**	**p-value**
Main analysis				
Patients with laboratory-confirmed or clinically diagnosed A(H1N1)pdm09 influenza (n=3,376)	0.23 (0.19 - 0.28)	<0.001	0.24 (0.20 - 0.30)	<0.001
Patients with laboratory-confirmed A(H1N1)pdm09 influenza (n=3,085)	0.23 (0.19 - 0.28)	<0.001	0.24 (0.19 - 0.29)	<0.001
Additional sub-group analyses				
Adults (16 years and above) (n=1,506)	0.26 (0.19 - 0.35)	<0.001	0.26 (0.19 - 0.35)	<0.001
Children (below 16 years) (n=1,747)	0.22 (0.17 - 0.30)	<0.001	0.25 (0.18 - 0.34)	<0.001
Patients with at least 1 high-risk condition (n=1,019)	0.26 (0.19 - 0.37)	<0.001	0.27 (0.19 - 0.38)	<0.001
Early NAI Treatment (≤2 days after onset) VS. Later (>2 days) in patients with laboratory-confirmed or clinically diagnosed A(H1N1)pdm09 influenza (n=473)	0.51 (0.28 - 0.93)	0.031	0.44 (0.23 - 0.86)	0.016

†adjusted for treatment propensity (by quintile) and community-based antibiotic use

Table 4: Association between NAI administration and hospital admission

The proportion of patients admitted to hospital varied widely between each of the 9 included study centres ranging from 3.94% to 69.3%. To disentangle any effects that hospital admission rates between centres may have had on the association between NAIs and hospitalisation, a post-hoc stratified analysis by median hospitalisation rate (50.6%) was carried out. After adjusting for community-based antibiotic treatment and propensity score, the pooled OR for the association between NAI treatment and subsequent hospitalisation in study centres with a hospital admission rate <50.6% (n=991) was 1.00 (95% CI: 0.61-1.64), whereas in centres where the admission rate was >50.6% (n=2,385), the OR was 0.17 (95% CI: 0.14-0.22).

3.4 Discussion

In this study, data were assembled from a large cohort of community-based patients, who had pandemic influenza in 2009-10, of whom 91% had laboratory confirmation of influenza A(H1N1)pdm09 virus infection. The demographic and clinical findings (Table 3) reveal that the patients studied were mainly young, mostly previously healthy, yet with relatively severe influenza (indicated by the presence of either documented severe respiratory distress or shortness of breath at presentation). As such, the results of this study are not generalisable to a wider population of community-based patients with mild pandemic influenza. These results may also not be generalisable to the elderly.

The main findings (Table 4) suggest that NAI treatment in the community for patients with severe pandemic influenza substantially reduced the likelihood of hospital admission due to influenza A(H1N1)pdm09. In a pandemic context, individuals generally have little or no pre-existing cross-reactive immunity to the infecting virus; therefore effect size might be lower for seasonal

(interpandemic) influenza, and the findings from this study should be interpreted with more caution in that context. In a sensitivity analysis restricted to patients with laboratory-confirmed A(H1N1)pdm09 virus infection this finding remained the same; and in patients with underlying at-risk conditions, a greater risk reduction was observed. A limitation of the analysis performed is that there were no data on body mass index (BMI), therefore, obesity could not be included as a high-risk condition.

Potential differences in effect size between adults and children were also explored in this study. This revealed that the effect of NAIs in reducing the likelihood of hospital admission was maintained and broadly consistent in both age groups. These findings contrast with a previous IPD meta-analysis of the PRIDE mortality data, in which a statistically significant reduction in mortality in hospitalised children treated with NAIs was not observed.[90] This discrepancy is potentially explained by the relatively high attack ,[191] and hospitalisation rates in children with A(H1N1)pdm09,[192] compared with a relatively low case fatality rate,[193] but could also relate to reduced statistical power in the mortality study.[90]

A question of considerable clinical relevance relates to the timing of antiviral treatment in relation to the magnitude of benefit obtained, especially since data already exist suggesting that symptom alleviation and mortality reduction are both diminished by delayed treatment.[90,194] A sensitivity analysis was performed on 473 NAI treated patients in whom there were specific data on the timing of symptom onset and antiviral treatment. This revealed that earlier treatment (within 48h of symptom onset) was significantly more beneficial than delayed treatment.

Because the dataset contained so few elderly patients, perhaps reflecting the low incidence of A(H1N1)pdm09 virus infection in the elderly,[195,196] this study was unable to lend further insight on the effectiveness of NAIs in this particular subgroup of patients.

NAI effectiveness estimates have been presented in this study as ORs, with associated 95% CI, as a natural way of expressing results from a mixed-effects logistic regression model, i.e. by exponentiation of the model coefficients. Odds ratios tend to approximate relative risks when the outcome being studied is rare.[197] However, the outcome in the current study, hospitalisation, is rather common with more than 50% of the study population experiencing it. In such an instance, the OR cannot be interpreted in the same way as a relative risk as the OR is likely to significantly overestimate the relative risk.[197] Applying simplistic conversion formulae to get relative risks from the ORs obtained in this study may not be appropriate as the outcome may not be equally common (or rare) across the data, now further sub-grouped along different levels of the adjustment covariates.[198] For example, while hospitalisation may be quite common in the overall study population, it may not be as common in a sub-group of NAI-untreated patients at low propensity to receive treatment who also received community-based antibiotic treatment. The clustered nature of data (within individual study centres) make application of simplistic 'OR to relative risks' conversion formulae even more problematic. Therefore, expressing NAI effectiveness as ORs, and 95% CI, in this study does have its advantages. However, the ORs presented in this study must always be interpreted as the ratio of the odds of hospitalisation in the NAI treated vs NAI untreated group, rather than as a ratio of the risk of hospitalisation in the two groups. The true relative

risk of hospitalisation associated with NAI treatment is likely to be much lower (closer to 1) than the OR reported in this study.

Although the current study is smaller than the previous PRIDE IPD meta-analysis that focused on mortality reduction in hospitalised patients [90], one of the strengths of this study is still the relatively large number of patients included from nine geographically diverse clinical centres. Although disease severity could not explicitly be adjusted for in the multilevel models because of the heterogeneity of severity measures used across individual datasets, physician recorded breathlessness and severe respiratory distress were, nevertheless, included when deriving propensity scores. However, confounding by indication [199] may still be present in this study. If it is, it can be surmised that physicians may have been more likely to treat severe cases than milder ones or putative at-risk groups like pregnant women with NAIs. Therefore the treated group would have a higher underlying likelihood of being admitted to hospital, which in turn would produce a bias in the analysis tending towards underestimation of any treatment effect. Likewise, it is possible that some NAI treatment may have been given immediately prior to hospital admission when there was no practical window in which an antiviral drug could have had time to work; or perhaps even when the physician had already decided that the patient needed to be admitted. Therefore there is sound clinical rationale for excluding patients in whom NAI treatment was initiated on the day of hospital admission.

Another potential limitation of the propensity scoring approach is the lack of data on vaccination, albeit knowledge of vaccination status might be associated

with physicians' decisions to prescribe NAIs and hospitalise. To explore this further, it was determined that patients whose illness onset was on or before 15th October 2009 could not have been vaccinated due to non-availability prior to this date; and even vaccinated, they would not have had time to seroconvert. Subsequently, a stratified analysis was performed around this date by dividing the overall pooled dataset into 'early pandemic' and 'later pandemic'. Onset dates were available in 2,175 patients of whom 903 were on or before 15th October 2009. The adjusted ORs (95% CI) in both groups were very similar [Early pandemic group: 0.12 (0.06-0.24) & Late pandemic group: 0.11 (0.07-0.18)]. On this basis, vaccination is unlikely to have been a major confounder in this study. Other residual confounding is nevertheless possible as these are observational data.

Two obvious drawbacks in these data, are the overall high rate of hospitalisation in the cohort studied, which limits generalisability to patients at high risk of hospitalisation; and the substantial variability between hospitalisation rates across individual centres ranging from 4% to 70%. The dataset with the lowest hospitalisation rate was from a surveillance system in the UK where a national policy operated in 2009-10 to offer NAI treatment to all patients with clinically apparent influenza, irrespective of severity. Stratifying the analysis around median hospitalisation rate revealed no effect of NAIs in centres below the median, but a strong positive effect in centres above the median. It can be surmised that these data confirm the beneficial effect of NAIs (beyond symptom relief) in patients who are severely unwell and at high risk of hospitalisation, versus those with milder illness.

To my knowledge, this is the first IPD meta-analysis investigating the association between pre-admission NAI antiviral use and hospitalisation relating to the 2009-10 influenza pandemic. As such, these data have potential importance for future pandemic stockpiling and treatment policies; but may possibly be of relevance to seasonal epidemics, especially for community patients with relatively severe influenza and those with underlying comorbidities. It was noted that the point estimates of treatment effectiveness are somewhat higher than the 25% reduction in hospitalisation for the treatment of seasonal influenza previously reported by Hsu and colleagues.[89] However the disparity in effect size might be explained by the fact that the four studies [200] meta-analysed by Hsu contained patients with generally milder influenza than in the present study; in addition three of these four studies were based on diagnoses of ILI without laboratory confirmation, therefore highly vulnerable to misclassification bias. An earlier pooled analysis of clinical trial data from patients with laboratory-confirmed seasonal influenza also observed a 59% reduction in hospitalisation.[201] This was confirmed in recent IPD analysis of seasonal influenza patients which reported a risk reduction of 63% in treated patients (intention-to-treat infected population),[88] which is somewhat similar to the findings of this study. A further paper not included in Hsu's meta-analysis also suggested a 29% reduction in hospitalisation associated with oseltamivir but was again based on diagnoses of ILI without laboratory confirmation.[202] A recent study from British Columbia, based on clinically diagnosed cases of pandemic influenza A(H1N1)pdm09, also noted 16% effectiveness of NAIs in reducing hospitalisation;[203] however the hospitalisation rate is this cohort was 0.6% suggesting cases were comparatively very mild. The findings from the

present study reflect the experience of NAI use in a cohort of community patients at high risk of hospitalisation. In addition higher effectiveness were observed in patients with one or more comorbidities that would have placed them in a target group for annual seasonal influenza vaccination.

Placed in the context of the limited previous work on this subject, the findings of this study suggest that greatest benefit from community use of NAIs is likely to be achieved by targeting individuals for treatment who have clinically suspected or proven influenza, and who are also in a recognised at risk-group, or clinically assessed to have severe influenza (irrespective of comorbid status). In these two groups of patients, substantial reductions in the likelihood of hospitalisation can be achieved, especially if treatment is commenced within 48 hours of symptom onset. These findings support current advice on NAI treatment given by major public health agencies[204,205] and the findings of a recent independent report from the UK Academy of Medical Sciences and the Wellcome Trust, which recommend against using NAIs in the community for the treatment of mild influenza, but advise that patients with severe influenza should be treated as soon as possible.[206]

4 Study 2: What is the effectiveness of in-hospital NAI treatment in reducing hospital LoS with influenza A(H1N1)pdm09 virus infection?

4.1 Introduction

The previous chapter investigated the effectiveness of community-based NAI treatment on the risk of hospitalisation in patients with A(H1N1)pdm09 virus infection. This chapter will address the second objective of this thesis and use an IPD meta-analysis approach to investigate the impact of in-hospital treatment on subsequent hospital LoS in patients with A(H1N1)pdm09 virus infection.

Seasonal influenza epidemics and pandemics can create surges in healthcare demand, particularly on hospital bed capacity. The evidence is currently less clear, whether NAIs reduce LoS in hospitalised influenza patients. Existing studies offer mixed evidence for the association between NAIs, compared to supportive care without antiviral treatment, and reduced LoS.[207-213] Minimising LoS is an important factor in managing surges in demand for hospital care and limiting healthcare costs due to severe seasonal influenza epidemics and pandemics.

4.2 Methods

Details regarding identification of study centres and inclusion of patients have been described in Section 2.1.

Data Standardisation, Exposure and Outcome: Data were standardised from individual datasets prior to pooling (Appendix 2). The primary outcome was length of hospital stay (in whole days), calculated as the difference between hospital admission and discharge dates (unless explicitly provided in pre-calculated format). Patients known to have had pre-admission treatment were excluded to ensure uniform potential for treatment to influence LoS in included patients. Patients with post-discharge NAI treatment were omitted. Patients with length of hospital stay <1 day were also excluded on the grounds that they would have received a maximum two doses of NAI treatment and their admission may have been precautionary; and so were patients with nosocomial influenza (symptom onset after hospital admission date, see Figure 9). Finally, since rapid deterioration and early death in hospital would be an adverse outcome associated with paradoxically short LoS, those who died in hospital were excluded from analysis.

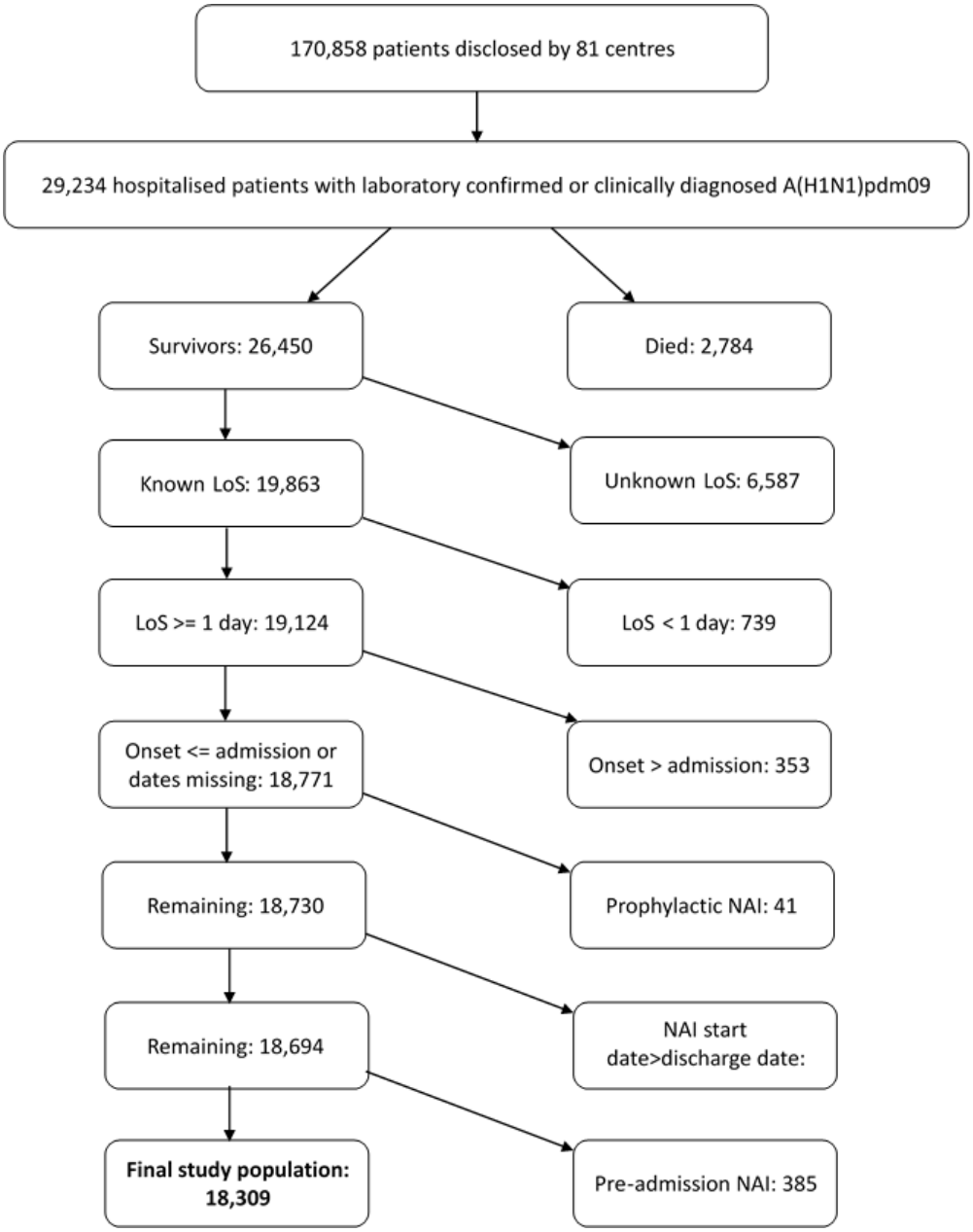


Figure 9: Study flow diagram for IPD meta-analysis investigating NAI effectiveness for hospital LoS

The primary exposure variable was in-hospital NAI treatment received on the day of hospital admission, compared to later NAI treatment or no NAI treatment. Additionally, where data were available, three further exposure variables were defined: NAI treatment (at any time) versus no NAI treatment; early NAI treatment (initiated within ≤2 days after symptom onset) versus no

NAI treatment; and early NAI treatment versus later treatment (initiated >2 days after symptom onset).

Propensity scores: Propensity scores were derived via multivariable logistic regression for each of the exposure variables using the approach described by Hirano and Imbens,[214] separately for individual study centres, based on patient characteristics recorded on admission. Propensity score derivation models included, *a priori*: age, sex, comorbidity (yes/no) and an indicator of disease severity, plus additional covariates that remained statistically significant in a regression model, from: obesity, smoking, pregnancy, asthma, chronic obstructive pulmonary disease, lung disease, heart disease, immunosuppression, neurological disease, renal disease, and diabetes. Variables with >25% missing data were excluded from propensity score derivation.

Statistical analysis: To investigate the impact of NAI treatment on length of hospital stay, a mixed effects negative binomial regression model was used, including study centre as a random intercept, to account for clustering.

The primary analysis, aimed to quantify the potential benefits of a pragmatic 'treat-on-admission' policy, irrespective of the time elapsed since symptom onset (compared to patients who received no NAI treatment and those treated after the day of admission). A sensitivity analysis was also performed where the comparator group was restricted to only those patients who did not receive NAI treatment. Both analyses were adjusted for propensity score quintile, in-hospital antibiotic treatment and in-hospital corticosteroid treatment, and the time delay between symptom onset and hospital admission. In addition, secondary analyses were also performed for the following exposures: NAI treatment (at any time)

versus no NAI treatment, early NAI treatment (≤48h from symptom onset) versus later NAI treatment (>48h from symptom onset), and early NAI treatment versus no NAI treatment. Adjustment for these analyses were done for propensity score, in-hospital antibiotic and corticosteroid treatment.

A priori specified, analyses were performed for the following sub-groups: patients with laboratory-confirmed A(H1N1)pdm09, children (<16 years), elderly patients (≥65 years), patients with chest radiograph-confirmed IRP, and patients with a confirmed absence of IRP. Pregnant women and patients with obesity were also examined as *post hoc* sub-groups. Furthermore, the impact of NAI treatment on total hospital LoS in patients admitted to ICU facilities at any point, and patients managed exclusively using standard ward-based care were explored using stratification.

Both unadjusted and adjusted models were run, and results are presented as incidence rate ratios (IRR/aIRR) with 95% confidence intervals (95% CI). Missing data in the covariates were included in the analysis as dummy variable categories. Using the aIRR point estimates, the difference in LoS (in days) between a treated and untreated patient with similar characteristics was also calculated by scaling the model prediction for LoS without treatment using the following formula:

$$Scaled\ LoS\ prediction = (aIRR - 1)$$

Repeating this for all patients in the dataset gives a distribution of expected changes in LoS due to treatment (with timing as defined for each regression analysis). This did not account for error in the estimates of model covariates, which would likely require a switch to a Bayesian approach; nevertheless it

offers a clinically relevant interpretation of aIRRs. All statistical analyses were performed using Stata (version 14.2; StataCorp LP, College Station, TX, USA).

4.3 Results

As previously reported,[90] 29,234 patients were identified who were admitted to hospital between 2nd January 2009 and 14th March 2011 with laboratory-confirmed or clinically diagnosed A(H1N1)pdm09.[4] The analysis population comprised of 18,309 (62.6%) patients following exclusions as outlined in Figure 9.

The included patients came from 70 clinical centres in 36 countries across all six WHO regions (Appendix 4). The Americas contributed most data (46.2%), followed by Europe (33.3%). The majority of the patients in the final study population were adults (67.4%), who had laboratory-confirmed influenza A(H1N1)pdm09 virus infection (81.1%); the general characteristics of the included population are further described in Table 5. There were relatively few older adults, and the prevalence of clinically recorded obesity and pregnancy was 12% and 23% respectively. Whilst two thirds of patients received NAI treatment, almost the same proportion received antibiotics, one quarter received corticosteroids, and 24% required ICU care at some stage in their illness.

Of 12,234 patients (66.8%) recorded to have received NAI treatment in hospital, oseltamivir was the most commonly specified agent (90.6%). In the 8,621 patients (47.1%) for whom data on timing of NAI treatment were available, 3,678 (42.7%) received early NAI treatment and 4816 (55.9%) had treatment started on the day of admission. The median delay from illness onset to hospital admission was 2 days (IQR: 1-5) and, where data on timing of treatment were

available, 42.7% presented within 48h of symptom onset; length of hospital stay was 5 days (IQR: 3-9). The distribution of LoS is presented in Figure 10. In patients in whom NAI treatment was initiated on the day of hospital admission, the median interval between symptom onset and admission was 2 days (IQR: 1-4).

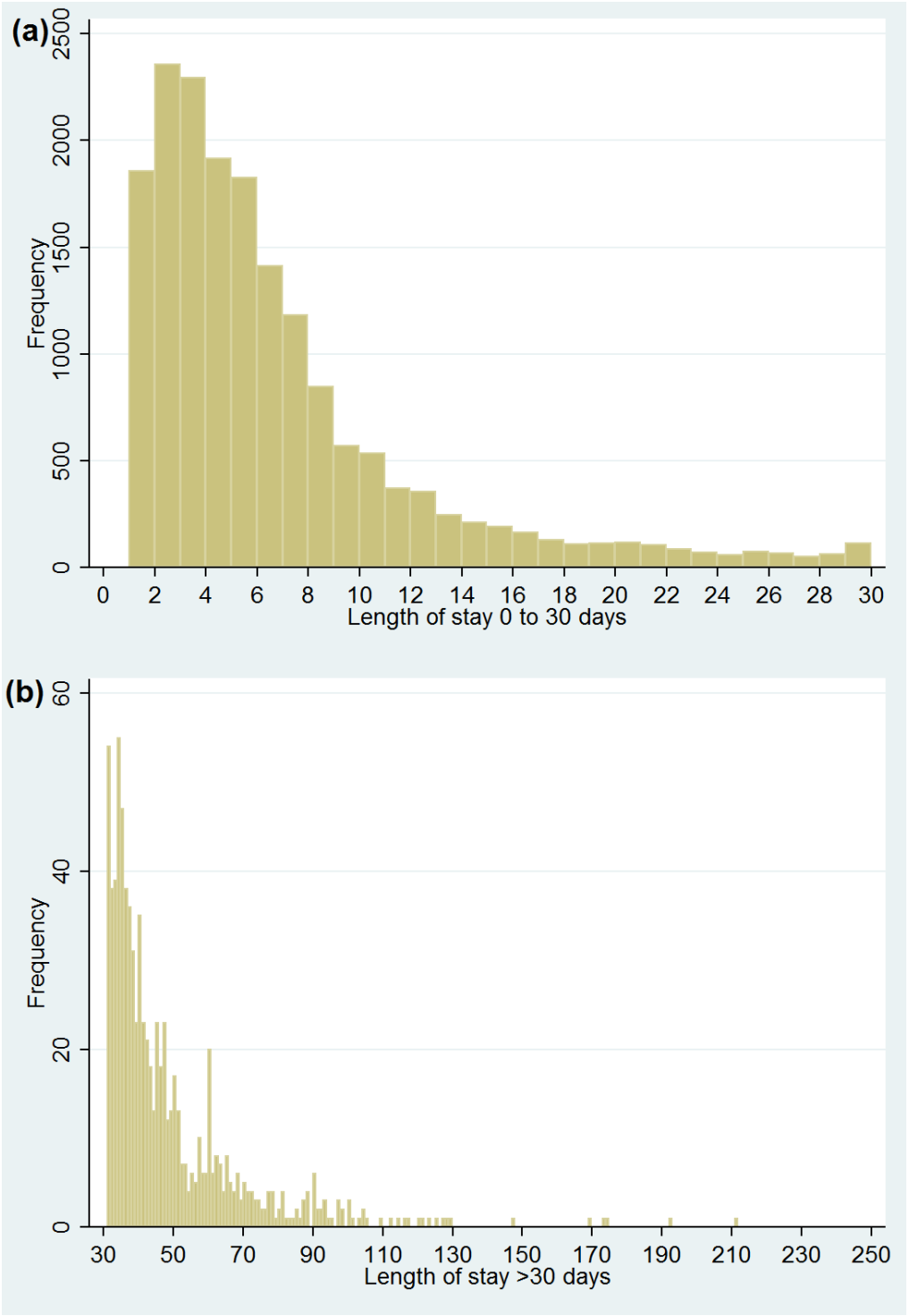


Figure 10: Histogram showing the distribution of hospital LoS for the study population (a) distribution of length of stay from 0 to 30 days (b) distribution of length of stay >30 days

Characteristic (denominator)*	Total study population n (%)	No NAI treatment n (%)	In-hospital NAI treatment n(%)
Number of patients	18,309 (100)	6,075 (33.2)	12,234 (66.8)
Number of male cases (n=18,306)	9,114 (49.8)	2,852 (47)	6,262 (51.2)
Age: median (IQR) in years (n=18,238)	26 (10 to 44)	24 (6 to 41)	27 (12 to 46)
Adults (≥16 years)	12,331 (67.4)	3,686 (60.8)	8,645 (70.7)
Children (<16 years)	5,907 (32.3)	2,344 (38.6)	3,563 (29.1)
Elderly (≥65 years)	1,035 (5.7)	304 (5)	731 (6)
Obese (n=13,695)	1,677 (12.3)	475 (8.9)	1,202 (14.4)
Smoking (n=12,851)	1,728 (13.5)	429 (8.2)	1,299 (17.1)
Pregnant women‡ (n=5,318)	1,197 (22.5)	380 (21.1)	817 (23.2)
WHO Regions (n=18,309)			
African Region	23 (0.1)	0 (0)	23 (0.19)
Region of the Americas	8466 (46.2)	4,606 (75.8)	3,860 (31.6)
Eastern Mediterranean Region	1649 (9.)	41 (0.7)	1,608 (13.1)
European Region	6090 (33.3)	918 (15.1)	5,172 (42.3)
South-East Asia Region	180 (1)	107 (1.8)	73 (0.6)
Western Pacific Region	1901 (10.3)	403 (6.6)	1,498 (12.2)
A(H1N1)pdm09 diagnosis (n=18,309)			
Laboratory confirmed	14,844 (81.1)	3,588 (59.1)	11,256 (92)
Clinically diagnosed	3,465 (18.9)	2,487 (40.9)	978 (8)
Comorbidities			
Any comorbidity (n=18,282)	7,017 (38.4)	1,749 (28.8)	5,268 (43.2)

Asthma (n=16,625)	2,461 (14.8)	607 (10.2)	1,854 (17.4)
COPD (n=13,812)	792 (5.7)	187 (3.6)	605 (7.1)
Other chronic lung disease (n=9,800)	1,393 (14.2)	190 (12.9)	1,203 (14.5)
Heart disease (n=12,146)	1,030 (8.5)	140 (8.2)	890 (8.5)
Renal disease (n=11,373)	401 (3.5)	44 (3.1)	357 (3.6)
Liver disease (n=9,564)	187 (2)	24 (1.7)	163 (2)
Cerebrovascular disease (n=7,751)	239 (3.1)	32 (3.2)	207 (3.1)
Neurological disease (n=8,929)	743 (8.3)	105 (7)	638 (8.6)
Diabetes (n=17,377)	1,375 (7.9)	418 (7.3)	957 (8.2)
Immunosuppression (n=17,180)	1,051 (6.1)	245 (4.3)	806 (7)
Chest radiograph-confirmation of influenza-related pneumonia (n=7,611) Confirmed presence of influenza-related pneumonia Confirmed absence of influenza-related pneumonia	 4,591 (60.3) 3,020 (39.7)	 426 (46.1) 498 (53.9)	 4,165 (62.3) 2,522 (37.7)
Pandemic H1N1 vaccination (n=5,371)	292 (5.4)	33 (4.7)	259 (5.5)
Time from symptom onset to hospital admission (days), median (IQR) (n=16,736)	2 (1 to 5)	2 (1 to 5)	2 (1 to 5)
Antiviral agents used			
No NAI treatment	6,075 (33.2)	6075 (100)	-
Any NAI	12,234 (66.8)	-	12,234 (100)
Treated with oral oseltamivir (n=12,234)	11,082 (90.6)	-	11,082 (98.8)
Treated with intravenous/inhaled zanamivir (n=12,234)	295 (2.4)	-	295 (4.3)
Treated with intravenous peramivir (n=12,234)	13 (0.1)	-	13 (0.2)
Early NAI (≤2 days of symptom onset) (n=8,621)	3,678 (42.7)	-	3,678 (42.7)
Later NAI (>2 days after symptom onset) (n=8,621)	4,943 (57.3)	-	4,943 (57.3)
Time from symptom onset to antiviral treatment, days, median (IQR) (n=7,433)	3 (2 to 5)	-	3 (2 to 5)

Treated with any NAI on the day of hospital admission (n=12,234)	4,816 (39.4)	-	4,816 (39.4)
Antibiotics (n=14,599)	9,153 (62.7)	2,981 (52.2)	6,172 (69.5)
Corticosteroids (n= 8,075)	2,024 (25.1)	165 (15.3)	1,859 (26.6)
Hospital LoS, days, median (IQR) (n=18,309)	5 (3 to 9)	4 (2 to 6)	6 (3 to 10)
Admission to critical care (n=17,348)	4,243 (24.5)	411 (6.9)	3,832 (33.7)

*IQR: Interquartile range; *Percentages have been calculated using the individual denominators (brackets) for each table row.*

‡*Proportions were calculated as a percentage of pregnant patients among female patients of reproductive age (13–54 years); the broader age range was selected in preference to the WHO definition (15–44 years) after consultation with data contributors to reflect the actual fertility experience of the sample; this also includes data from a hospital obstetrics unit (n=72)*

Table 5: General characteristics of study population (n= 18,309)

Impact of NAI treatment on length of stay: In the primary analysis, NAI treatment started on the day of admission, compared with no treatment or later initiation of NAI treatment, was associated with an 19% reduction in LoS [aIRR:0.81 (0.78-0.85)], median decrease 1.19 days (IQR: 0.85-1.55), in the overall study population. The association between starting NAI treatment on admission, compared to later or no treatment, was of similar magnitude and remained significant in all subgroups: laboratory-confirmed patients [aIRR: 0.81 (0.77-0.85), median decrease: 1.22 days (IQR: 0.87-1.60)], children [aIRR: 0.85 (0.78-0.92), median decrease: 0.98 days (IQR: 0.70-1.25)], non-ICU patients [aIRR: 0.81 (0.78-0.85), median decrease: 1.20 days (0.87-1.50)], the elderly [aIRR: 0.79 (0.67-0.91), median decrease: 1.47 (IQR: 1.09-1.82)], ICU patients [aIRR: 0.79 (0.72-0.87), median decrease: 1.32 days (IQR: 0.99-1.80)], patients with confirmed absence of IRP [aIRR: 0.73 (0.68-0.79), median decrease: 1.70 days (IQR: 1.27-2.26)], patients with a confirmed presence of IRP [aIRR: 0.85 (0.79-0.93), median decrease: 0.92 days (IQR: 0.68-1.24)], pregnant women [aIRR: 0.75 (0.64-0.88), median decrease: 1.56 (IQR: 1.11-2.11)], and in patients with obesity [aIRR: 0.80 (0.69-0.93), median decrease: 1.26 (IQR: 0.91-1.64)] (Table 6).

In the sensitivity analysis, NAI treatment on the day of hospital admission was associated with an 8% reduction in LoS (median decrease: 0.50 days (IQR: 0.43-0.57) compared to no NAI treatment, in non-ICU cases [aIRR: 0.92 (0.85-0.98)], a 19% reduction in patients with a confirmed absence of IRP [aIRR: 0.81 (0.73-0.90) median decrease: 1.24 (IQR: 0.93-1.38)], and a 28% increase in LoS in patients with confirmed presence of IRP [aIRR: 1.28 (1.11-1.48) median increase: 1.73 (IQR: 1.29-2.07)].

Secondary analyses: After adjustment for propensity score, in-hospital antibiotic treatment and in-hospital corticosteroid treatment, NAI treatment at any time was associated with an overall 11% increase in LoS [aIRR: 1.11, (95% CI: 1.07-1.16), median increase: 0.74 days (IQR: 0.60-1.05)], when compared to no NAI treatment. By exploring subgroups corresponding statistically significant findings were identified in laboratory-confirmed cases, children, ICU patients and in patients with confirmed IRP, but not in the elderly, patients requiring non-ICU care, or in patients with a confirmed absence of IRP (Table 6). There was no evidence for effect-modification by pandemic influenza vaccination (p-value: 0.68) or by in-hospital antibiotic treatment (p-value: 0.20); however, a borderline significant effect-modification was observed for in-hospital steroid treatment (p-value: 0.05), with NAI treated patients who were also treated with steroids being associated with a marginally increased LoS [aIRR: 1.17 (1.00-1.36)].

In contrast, early NAI treatment compared to no NAI treatment was associated with a 7% overall reduction in LoS [aIRR: 0.93 (0.87-0.99), median decrease: 0.40 days (IQR: 0.36-0.45)]. Similar or larger reductions were observed in most sub-groups; however, this association was not statistically significant in children, ICU patients, and in patients with confirmed IRP (Table 6). Early NAI treatment compared to later NAI treatment was associated with an overall 23% reduction in LoS [aIRR: 0.77 (0.74-0.80), median decrease: 1.78 days (IQR: 1.34-2.49)], which varied across all a priori specified sub-groups but remained statistically significant (Table 6).

In pregnant women and obesity subgroups, early NAI treatment compared to later NAI treatment was associated with statistically significant reductions in

LoS by 39% [aIRR: 0.61 (0.52-0.70), median decrease: 3.10 days (IQR: 2.34-4.56)] and 27% [aIRR: 0.73 (0.65-0.83), median decrease: 2.11 days (IQR: 1.62-3.10)] respectively . NAI treatment at any time and early NAI treatment, when compared to no NAI treatment, were not statistically significantly associated with LoS (Table 6).

	Unadjusted	Adjusted[a]
	IRR (95%CI)	IRR (95%CI)
Primary analysis: NAI treatment on the day of hospital admission vs Later/No NAI treatment[b]		
Overall	**0.83 (0.79-0.87)**	**0.81 (0.78-0.85)**
Laboratory-confirmed A(H1N1)pdm09	**0.83 (0.79-0.86)**	**0.81 (0.77-0.85)**
Children (age <16 years)	**0.90 (0.83-0.97)**	**0.85 (0.78-0.92)**
Elderly (age ≥65 years)	**0.78 (0.67-0.91)**	**0.78 (0.67-0.91)**
Patients requiring standard ward-based care only	**0.81 (0.77-0.85)**	**0.81 (0.78-0.86)**
ICU patients only[c]	**0.80 (0.73-0.88)**	**0.79 (0.72-0.87)**
Confirmed absence of Influenza-related pneumonia	**0.71 (0.66-0.77)**	**0.73 (0.68-0.79)**
Confirmed presence of Influenza-related pneumonia	**0.91 (0.84-0.98)**	**0.85 (0.79-0.93)**
Pregnant women	**0.80 (0.69-0.93)**	**0.75 (0.64-0.88)**
Patients with obesity	**0.79 (0.68-0.91)**	**0.80 (0.69-0.93)**
Sensitivity analysis: NAI treatment on the day of hospital admission vs No NAI treatment[b]		
Overall	**1.14 (1.07-1.22)**	1.06 (0.99-1.13)
Laboratory-confirmed A(H1N1)pdm09	**1.15 (1.07-1.22)**	1.04 (0.97-1.12)
Children (age <16 years)	1.09 (0.98-1.20)	0.98 (0.88-1.09)
Elderly (age ≥65 years)	0.84 (0.67-1.06)	0.83 (0.65-1.07)
Patients requiring standard ward-based care only	**0.93 (0.87-0.99)**	**0.92 (0.85-0.98)**
ICU patients only[c]	1.14 (0.96-1.36)	1.08 (0.90-1.31)
Confirmed absence of Influenza-related pneumonia	**0.83 (0.75-0.92)**	**0.81 (0.73-0.90)**
Confirmed presence of Influenza-related pneumonia	**1.28 (1.12-1.47)**	**1.28 (1.11-1.48)**
Pregnant women	1.18 (0.96-1.16)	1.05 (0.85-1.29)
Patients with obesity	1.10 (0.86-1.41)	1.13 (0.86-1.48)
Secondary Analyses		
NAI anytime vs No NAI treatment		
Overall	**1.21 (1.17-1.26)**	**1.11 (1.07-1.16)**
Laboratory-confirmed A(H1N1)pdm09	**1.31 (1.25-1.37)**	**1.17 (1.12-1.23)**
Children (age <16 years)	**1.18 (1.11-1.25)**	**1.11 (1.04-1.18)**
Elderly (age ≥65 years)	1.00 (0.86-1.17)	0.98 (0.83-1.14)
Patients requiring standard ward-based care only	**1.06 (1.02-1.10)**	1.02 (0.98-1.05)
ICU patients only[c]	**1.33 (1.19-1.49)**	**1.26 (1.13-1.41)**
Confirmed absence of Influenza-related pneumonia	0.98 (0.90-1.07)	0.97 (0.89-1.06)
Confirmed presence of Influenza-related pneumonia	**1.36 (1.24-1.49)**	**1.28 (1.16-1.40)**
Pregnant women	1.10 (0.95-1.27)	1.03 (0.89-1.19)
Patients with obesity	**1.21 (1.06-1.39)**	1.14 (0.99-1.31)

Early NAI treatment vs Later NAI treatment		
Overall	**0.70 (0.68-0.73)**	**0.77 (0.74-0.80)**
Laboratory-confirmed A(H1N1)pdm09	**0.70 (0.68-0.73)**	**0.77 (0.74-0.80)**
Children (age <16 years)	**0.80 (0.74-0.86)**	**0.87 (0.81-0.93)**
Elderly (age ≥65 years)	**0.71 (0.62-0.81)**	**0.71 (0.62-0.82)**
Patients requiring standard ward-based care only	**0.78 (0.75-0.81)**	**0.83 (0.79-0.86)**
ICU patients only[c]	**0.69 (0.64-0.74)**	**0.74 (0.69-0.80)**
Confirmed absence of Influenza-related pneumonia	**0.80 (0.75-0.86)**	**0.84 (0.78-0.90)**
Confirmed presence of Influenza-related pneumonia	**0.84 (0.78-0.90)**	**0.82 (0.77-0.88)**
Pregnant women	**0.56 (0.48-0.65)**	**0.61 (0.52-0.70)**
Patients with obesity	**0.67 (0.59-0.76)**	**0.73 (0.65-0.83)**
Early NAI treatment vs No NAI treatment		
Overall	1.04 (0.98-1.11)	**0.93 (0.87-0.99)**
Laboratory-confirmed A(H1N1)pdm09	1.05 (0.98-1.11)	**0.93 (0.87-0.99)**
Children (age <16 years)	1.00 (0.91-1.10)	0.92 (0.83-1.01)
Elderly (age ≥65 years)	0.82 (0.67-1.01)	**0.79 (0.63-0.997)**
Patients requiring standard ward-based care only	**0.93 (0.87-0.99)**	**0.88 (0.82-0.94)**
ICU patients only[c]	1.01 (0.86-1.20)	0.93 (0.79-1.10)
Confirmed absence of Influenza-related pneumonia	**0.79 (0.71-0.89)**	**0.76 (0.68-0.85)**
Confirmed presence of Influenza-related pneumonia	1.09 (0.95-1.24)	1.01 (0.88-1.16)
Pregnant women	0.98 (0.80-1.19)	0.90 (0.74-1.10)
Patients with obesity	1.09 (0.88-1.34)	0.95 (0.74-1.21)

IRR: Incidence Rate Ratio; 95%CI: 95% Confidence Interval (bold font indicates statistical significance at the 5% level (p<0.05); a) IRR adjusted for propensity scores (quintiles) for receiving treatment, antibiotic treatment received in hospital, steroid treatment received in hospital; b) IRR further adjusted for time from onset to admission; c) patients admitted to ICU at any point – IRR calculated for total length of hospital stay, not time on ICU. The secondary analyses must be interpreted with caution as they may be affected by various time-dependent biases

Table 6: Association between NAI administration and hospital LoS

4.4 Discussion

This study adds to the existing evidence by offering data on the association between NAI treatment and LoS in over 18,000 adult and paediatric patients, of whom >80% had a laboratory confirmed diagnosis of A(H1N1)pdm09 virus infection. A mixed pattern of association between NAI treatment and LoS was found depending on the delay to initiation of treatment, age, and case severity.

The most pragmatic and important question is whether NAI treatment, started on admission, irrespective of delay since symptom onset, reduces LoS in hospitalised influenza patients. Statistically, by defining the primary exposure variable based on treatment decisions made on admission, this study avoids introducing correlations between exposure and LoS which can lead to survivorship bias in linear regression models of time-to-event data.[215,216] Additionally this approach ensures that the propensity scores, which are modelled on symptom severity at admission, should appropriately correct for treatment bias.[217] However, this choice of exposure variable also reflects the clinical reality, that patients present to hospital with varying delays since symptom onset (in this study, ranging from 0-20 days); and that clinicians and policy makers want to know if a 'treat at the door' policy, applied to patients admitted to hospital with clinically recognised influenza will be beneficial compared with no NAI treatment or a 'watch and see' approach when NAI treatment might be added later. This is what the primary analysis sought to address, and found that NAI treatment started on the day of admission, compared to later or no treatment, was associated with an 19% reduction in LoS (median 1.19 days), with similar statistically significant findings across all patient subgroups including children, pregnant women and obese patients. These findings emphasise the importance of presumptive NAI treatment in patients admitted to hospital with suspected influenza, coupled with early diagnosis using standard laboratory or rapid diagnostic tests.

In the sensitivity analysis a significant reduction in LoS of 19% (median 1.24 days) was seen in patients with a confirmed absence of IRP and reduction in LoS of 8% (median 0.5 days) in patients who required supportive ward-based

care. In contrast, NAI treatment (compared with none) was associated with an increase in LoS by 28% (median 1.73 days) in patients with IRP. These data suggest that NAIs may be more effective in reducing LOS when patients do not have IRP and is consistent with the fact that NAIs have no known antibacterial properties.

In the secondary set of analyses, an 11% increase in LoS associated with NAI treatment, equivalent to about 0.74 days, irrespective of the time between symptom onset and initiation of therapy, was observed in the overall study population. NAI treatment initiated within 48h of symptom onset, compared with no treatment, was associated with an overall 7% reduction in LoS, equivalent to a median reduction by 0.40 days; this effect was more pronounced in non-ICU patients and the elderly, but not observed in children and patients requiring ICU care. This finding is clinically important because it suggests that rapid access to antiviral treatment after symptom onset may influence LoS in adults and the elderly; nevertheless, the same was not observed in patients requiring ICU, possibly due to residual confounding related to baseline illness severity. Although these analyses attempted to adjust for severity using propensity scores, ICU care was found to be very strongly associated with prolonged LoS (IRR =2.96), and NAI treatment to be associated with a higher likelihood of requiring ICU care (aOR: 3.11). Furthermore, patients who presented to hospital >2 days from symptom onset were 73% more likely to eventually require ICU care than patients who presented earlier (OR: 1.73; 95% CI: 1.53-1.95). In addition, patients requiring ICU care have frequently developed extra-pulmonary manifestations of influenza, and multi-organ

decompensation, therefore inhibition of virus replication may not correspond with rapid clinical recovery.

No association was seen between NAI treatment and LoS in hospitalised children with influenza. The study may have been underpowered in children, but other factors might have contributed to the findings. LoS is typically shorter in children than in adults, mortality and serious outcomes are less common in hospitalised children with influenza compared with adults; different discharge policies and thresholds for children could also influence the findings. In addition, vomiting is a recognised side-effect of oseltamivir in children,[93] and this may have prevented discharge in some cases.

Previous studies examining whether use of NAIs in patients hospitalised with influenza affects LoS have generally been of smaller size (n<1300) in comparison to the current study, and reached variable conclusions. Of note, eight studies[209-213,218-220] (of which one was a randomised trial)[210] assessed NAI treatment of hospitalised children, but only two (observational) concluded that total hospital days in the NAI treated hospital cohort were reduced (by 18% and 8.3 days respectively),[209,220] the other six reporting no differences.[210-213,218,219] Only four studies have addressed the same question in adults. In Hong Kong, during 2004 to 2005 a study of 356 adult patients hospitalised with laboratory confirmed seasonal influenza showed that early oseltamivir treatment, compared with none or later treatment, was associated with reduced LoS in both unadjusted and multivariable analyses,[207] median LoS was reduced from six to four days and accords with the primary analysis of this study. A Canadian study of adult patients with seasonal influenza found that oseltamivir treatment was not associated with LoS in surviving patients.[221] A further study in 13 Spanish

hospitals during the 2009-10 pandemic, in 538 patients with laboratory confirmed A(H1N1)pdm09, noted LoS increased by 7% (OR =1.07) after adjustment for confounders, if NAI treatment was instigated <48h after symptom onset; however this was of borderline statistical significance.[208] A recent American study analysed data on 201 adult patients with laboratory-confirmed seasonal influenza reported that NAI treatment was not associated with LoS in the overall study population, but was associated with a reduced LoS in vaccinated individuals [hazard ratio of discharge: 1.6 (1.0-2.4), p-value:0.04].[222] Finally, two studies included patients of all age groups. One of them, performed in 813 hospitalised patients with A(H1N1)pdm09 infection in Spain, found that early NAI treatment reduced LoS by 1.9 days (p-value: <0.001).[223] The other, an American study using insurance claims data from seasonal influenza patients reported that patients treated with NAI spent fewer days in hospital (p-value: <0.0001).[202]

This study has a number of strengths and weaknesses. Data from 70 clinical centres in 36 countries were combined, offering broad geographical generalisability to the findings. Propensity scores were used to adjust for major confounders. By excluding patients who died, the paradoxical possibility that short LoS (a positive outcome in this study) was in fact associated with an extremely unfavourable clinical outcome was eliminated. The primary analysis adjusted for delay from illness onset to admission to address length bias[216] and the main exposure variable was defined to avoid time-dependent/survivorship bias.[215,217] However, the secondary analyses, which use time since onset to define the exposure variable, are subject to time-dependent biases and must therefore be interpreted with caution. Indeed, the benefit of early vs late

treatment (Table 6) will be partially driven by this bias.[215] All of the analyses may be subject to residual competing risk bias which has not been removed through adjustment; for example, a significant difference between propensity scores to receive NAIs in hospital for surviving and non-surviving patients was found in the data set (Kruskall-Wallis: $p<0.05$), signalling that the removal of non-surviving patients alters the aggregate presenting patient characteristics for which these results hold. Exclusion of patients who stayed in hospital <1 day, suggesting that admission may have taken place on a precautionary principle, prevents any biologically implausible inference that NAI treatment for <24 hours (<2 doses), given the median delay of 3 days between illness onset and treatment initiation, would have influenced LoS.

These data were generated during the 2009-10 pandemic period. The included population contained relatively few elderly patients and children, consistent with the known age-specific symptomatic attack rates for A(H1N1)pdm09 virus infection,[224] and differs in profile from seasonal influenza where patients admitted to hospital tend to be much older, and median LoS tends to be higher than the five days that was observed in this study.[225,226] In addition, in the study cohort, the prevalence of clinically recorded obesity (12%) and pregnancy (23%) were both comparatively high.

Optimally, clinicians wish to treat influenza patients within 48h of symptom onset, yet in many cases influenza patients do not seek medical care during this therapeutic window. The subsequent decision to admit to hospital is then often made by a primary or ambulatory care physician, who may not act until the patient further deteriorates. The data from the current study show that 57.3% of included patients were hospitalised >48h after symptom onset. What matters is

whether initiation of treatment upon hospitalisation (on the day of admission) irrespective of the time elapsed since symptom onset is effective, and whether this is preferable to non-treatment or further delays in treatment. This study reveals a 19% reduction in LoS (median 1.19 days) in patients treated with an NAI upon admission, rather than remaining untreated or being treated later on; the trend is observed across all subgroups including children.

The results from this study support current recommendations to treat adults hospitalised with clinically suspected influenza with NAIs upon admission; furthermore, this approach appears superior to no-treatment or delayed treatment in terms of reducing LoS. If applied consistently, this strategy would contribute to the management of surge pressures and healthcare costs during seasonal influenza epidemics and pandemics.

5 Study 3: How can a behavioural model be integrated with an epidemic model to gain insights into NAI collection rates during an influenza pandemic?

5.1 Introduction

The previous chapters analysed observational data from the 2009-10 influenza pandemic to ascertain effectiveness estimates for NAI treatment in reducing the risk of hospitalisation, and subsequent LoS. This chapter will describe a proof-of-concept implementation and validation of the behavioural model developed in Section 2.2, to address the third objective of this thesis. The formalised COM-B behavioural model will be coupled with an agent-based epidemic model to explore possible interventions that could be considered to improve NAI collection rates (amongst those authorised NAI drugs through the NPFS). The primary goal of this ABM is to serve as a tool to conceptually understand important drivers of health-related behaviour and gain insights into potential interventions aimed at improving NAI collection amongst those authorised to collect them. The following section will describe the development of the ABM with which the formalised COM-B model is integrated.

5.2 Methods

An ABM integrating the novel behavioural model described in Section 2.2 with an epidemic model was developed using a combination of literature reviews, interdisciplinary discussion groups and expert consultation, guided by a structured model development framework using a software engineering

approach.[124] One particular strength of this model development framework is that its iterative development process makes it easy to extend models in a transparent way. Model development was done over three interdisciplinary focus groups. Participants of these focus groups included PhD students from the faculties of Computer Science and Epidemiology and Public Health. Each focus group discussion lasted about two hours and range of ideas were discussed and debated guided by the framework mentioned above. Using outputs derived from the focus groups, along with a review of literature and expert consultation, the objectives, scope, key activities and agent templates were defined.

The objectives of the ABM was to integrate a behavioural model describing individual decision to collect NAIs (Section 2.2) with an epidemic model, performing a validation of this coupled behavioural-epidemic model, and then explore possible interventions aimed at improving the proportion of patients collecting NAIs amongst those authorised the drugs. Having defined the main objectives of the ABM, a scope of the model was outlined. Table 7 below summarises various elements considered for the modelling, whether they were included in the final model or not, and the justification for doing so.

Category	Element	Decision	Justification
Actor	Individuals in a population	Include	Basic unit of population
	Fomites (inanimate infection sources)	Exclude	Impact unlikely to be significant for objective considered (from literature); computationally expensive
	Buses/ Other public transport	Exclude	(Same as above)
Buildings	Antiviral collection point(ACP)	Include	Needed to assess 'opportunity' to engage in behaviour change

	Hospital	Exclude	Not relevant to the main aim
	GP practices	Exclude	This model will focus on the NPFS service that operated during the 2009 pandemic in England
Psychological factors	Comparative feedback	Include	COM-B model
	Imitation	Include	COM-B model
	Risk perception	Include	COM-B model
	Capability to engage in behaviour change	Include	COM-B model
	Opportunity to engage in behaviour change	Include	COM-B model
	Motivation to engage in behaviour change	Include	COM-B model
	Stigma	Exclude	Not always pertinent to influenza
Networks	Physical distances to ACPs	Include	Needed to assess 'opportunity' to engage in behaviour change
	Social network	Include	COM-B model
Disease	Infection states of individuals	Include	Modelled using a Susceptible, Exposed, Infected, Recovered (SEIR) epidemic model

Table 7: Scope table for the ABM developed in this study

UML diagrams were then used to summarise ideas obtained from the knowledge gathering processes (focus groups, expert consultation and literature review). The purpose of these UML diagrams is to facilitate easy communication of ideas between stakeholders involved in the modelling process, and also to aid easy, and a more natural, implementation of conceptual model. The conceptual model development was performed in three main steps. In the first step, key activities were defined. In the second step, the agent template was developed. And in the final step, the artificial lab was defines.

5.2.1 Defining key activities

A use case diagram was used to describe key activities that agents in the ABM may perform in collaboration with other agents (Figure 11). Two key activities were identified: one involved evaluating the current epidemic state, the second was comparing and evaluating healthcare-seeking behaviour.

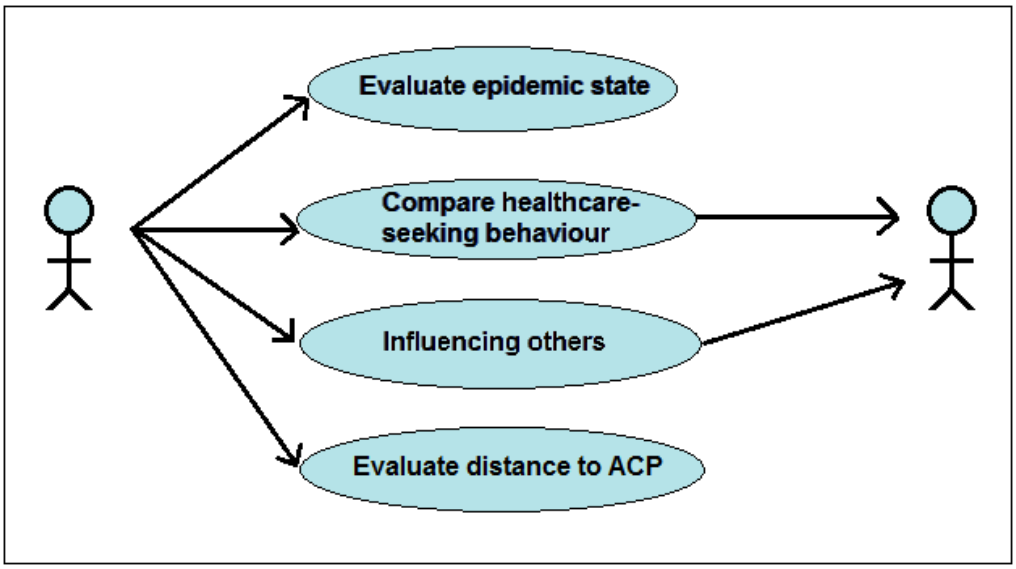


Figure 11: Use case diagram of agent activities

5.2.2 Defining agent template

This section outlines the various states of the agents in the model that will guide their behaviour. As identified in the scope table (Table 7), the main actors/agents in this ABM are individuals within the population being modelled. Individual agent behaviour in the ABM can be classed into two broad groups– one relating to the disease state of the agent, and the other relating to the healthcare-seeking behaviour (decision to collect NAIs if authorised) of the agent. UML state machine diagrams (sometimes called state charts) were used to define agent behaviour with respect to disease state and healthcare-seeking behaviour (Figure 12). A significant advantage to defining agent behaviour in this fashion is that, in addition to being easy to understand, UML state machine

diagrams can be automatically translated into program code by software development environments that support state machine diagrams.[124] A Susceptible-Exposed-Infected-Recovered (SEIR) model is used to model the influenza pandemic. Agents are classed into S, E, I or R states based on their infection status. Except for the probability of transmission, which was calibrated to match the second wave of the 2009 influenza pandemic in England, transitions between states were governed by probabilities derived from epidemiological literature. The behavioural element of agent behaviour is guided by a decision state chart. Agents enter an initial 'no action' state and remain there until they have been infected, and authorised NAIs for collection. Once an agent is authorised NAIs, a transition to the 'Deciding' state is triggered. The transition between the 'Deciding' state and the 'Collect' state is determined by a probability *p(b)* (the formalised COM-B model; Section 2.2)– agents for whom $p(b) \geq 0.5$ enter the 'Collect' state. Table 8 contains the legend for the state machine diagrams described in Figure 12.

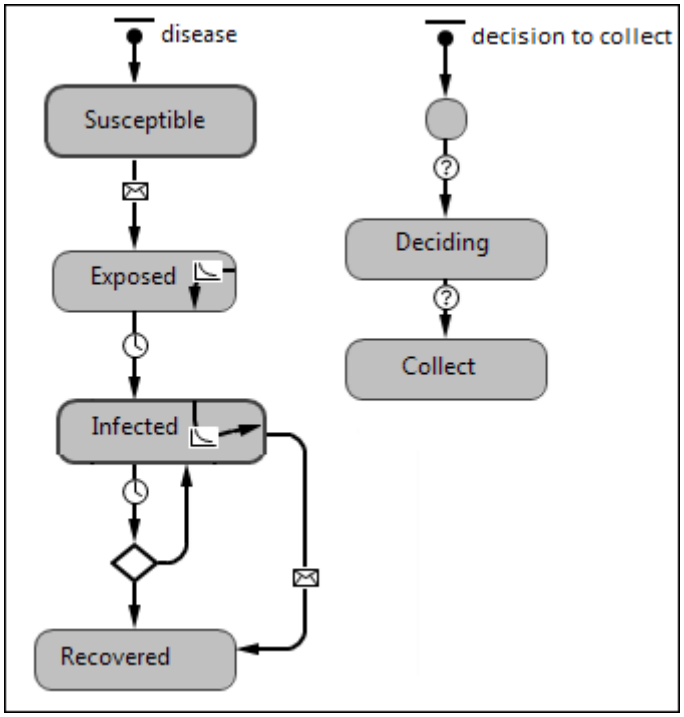


Figure 12: Agent state machine diagrams

: Entry state pointer	: Time out (Incubation period)
: Rate	: Condition (NAI authorised/$p(b)$≥0.5)
: State	: Branch transition
: Message ("Infected")	: 'no action' state

Table 8: Components of the state machine diagram described in Figure 12

For each agent, the process of deciding whether to collect NAIs or not (if authorised) can be represented using a UML activity diagram (Figure 13). This represents the flow of logic for each agent in deciding whether to collect authorised NAIs, or not. In Figure 13, the decision to collect NAI or not ($p(b)\geq 0.5$) is guided by the formalised COM-B model described in Section 2.2.

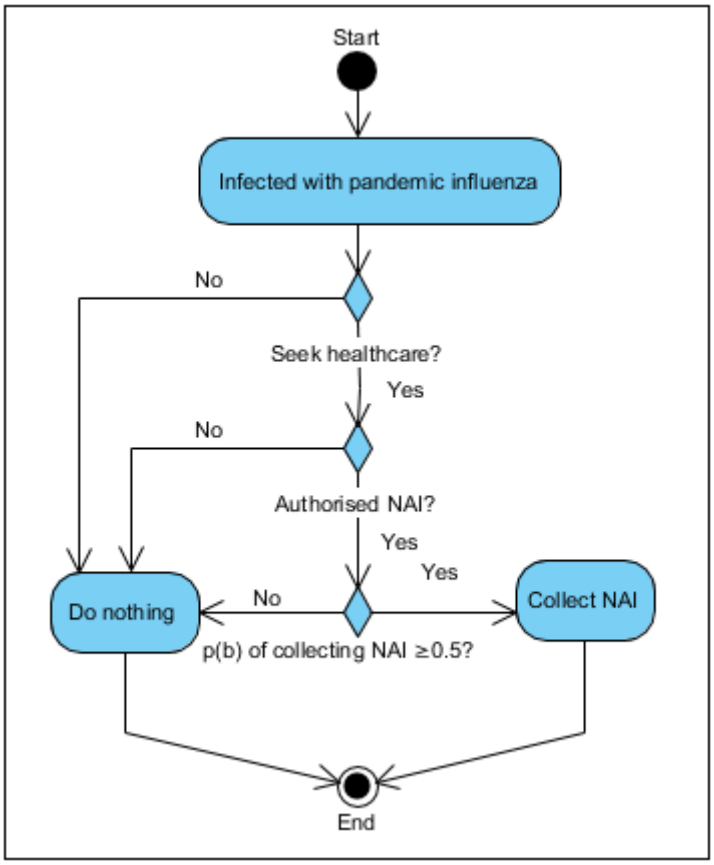


Figure 13: Activity diagram for an agent in the simulation

5.2.3 Defining the artificial lab

The first step in setting-up an artificial lab, is defining the individual agent classes. Given that in the model being considered there is only one type of agent/actor, i.e. individuals within a population (Table 7), an agent class definition will first be developed using a UML class diagram. A UML class is depicted as a large rectangle divided into three sections. The top section displays the name of the class (the name of the agent-type/actor). The middle section is reserved for attributes of the class (e.g. level of optimistic bias, contacts per-day, length of hospital stay etc. for each individual agent). The bottom section contains operations that the agent may be required to perform (e.g. calculating distance to ACP, comparing 'Capability' score with the threshold, calculating *p(b)* etc. for each individual agent). Figure 14 shows the class definition of individual agents in this ABM.

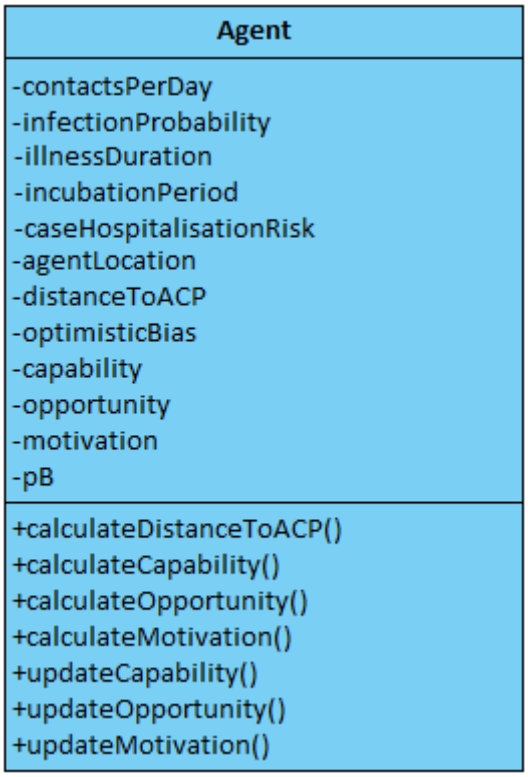


Figure 14: Agent class definition

The artificial lab can be thought of as the environment that embeds all the individual agents and also allows some global functionality.[124] A simple UML class diagram, similar to the one above, can be used to represent the artificial lab. The difference here, however, would be that global-level variables and functions are defined in the artificial lab (as opposed to agent-level variables and functions in Figure 14). Figure 15 outlines the artificial lab for the current model. In the artificial lab class diagram below, the second and third sections represent global variables and global functions respectively.

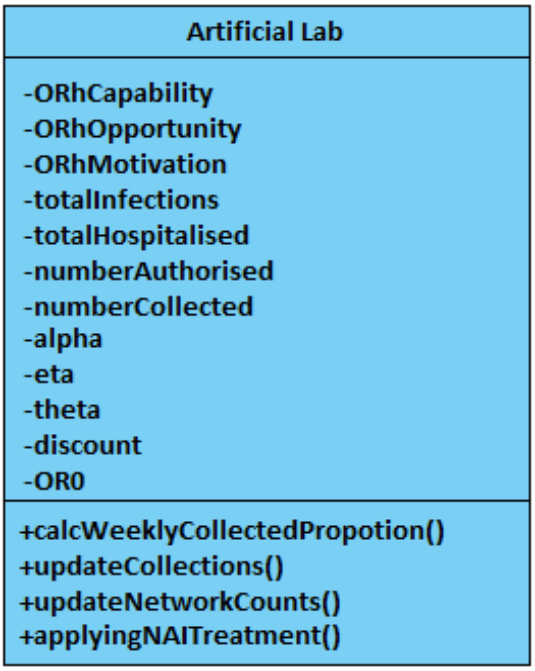


Figure 15: Artificial Lab class diagram

5.2.4 Implementation

Using the model structure described above, 10,000 agents and one ACP were simulated, keeping with the population-to-ACP ratio that was seen in England during the 2009 A(H1N1) influenza pandemic.[69] Epidemic parameters relate mainly to the 2009 influenza pandemic, and most were chosen from literature (Table 9); the probability of transmission was calibrated to match the duration of the second peak of the 2009 influenza pandemic in the UK. Once an agent entered the 'Infected' state, an NPFS call would be made, and based on data from the 2009, 75% of NPFS calls would result in an NAI authorisation.[179] This is a proof-of-concept implementation of the coupled behavioural-epidemic ABM focussing on the decision to collect NAIs. Hence, the actual impact of NAIs in averting outcomes in not considered in this study (that is done in subsequent chapters). Admission to hospital was not explicitly modelled in this study. Rather, once infected, each agent was assigned a probability based on the CHR observed during the second peak of the 2009 influenza pandemic (in the

UK) of being labelled "hospitalised". The number of "hospitalised" agents in an agent network was then used to influence the COM-B Motivation level (Section 2.2.4).

Parameter	Value *Probability distribution*	Source (reference number)
Contact rate, Mean (SD)	11.74 (7.67) *Normal*	[227]
Duration of illness, Median (IQR) in days	6.5 (5 to 8) *Triangular*	[228]
Probability of infection, Range	0.015 to 0.020 *Uniform*	Calibrated
Latency period, Mean (SD) in days	1.6 (0.26) *Normal*	[229]
Case hospitalisation risk	0.55%	[230]
Likelihood of NAI collection for 'high' Capability vs. 'Low', OR (95% CI)	2.80 (2.52 to 3.08) *Triangular*	[231]
Likelihood of NAI collection for 'high' Motivation vs. 'Low', OR (95% CI)	2.71 (2.08 to 3.53) *Triangular*	[232]
Likelihood of NAI 'high' Opportunity vs. 'Low', OR (95% CI)	4 (3 to 5) *Triangular*	Assumed based on [184]

SD: Standard deviation; IQR: Interquartile range; OR: Odds ratio; CI: Confidence Intervals

Table 9: Input parameters for the implementation of the ABM exploring NAI collection rates

Given that several behavioural parameters were unavailable from the literature, four parameters were specified as calibration parameters– the three behavioural thresholds (α, η and θ), and the probability of NAI collection when C, O and M are in the 'low' state (OR_0 from equation 1). Given the high dimensionality of the model parameters, an exhaustive search of the parameter space was not feasible. Therefore, a three-step model calibration method based on the Werker-Brenner calibration approach was followed.[132,233] Existing empirical data were first used for parameters for which they were available. For the four behavioural parameters where no data were available, wide ranges were specified after investigating preliminary model runs. Then, 1,000 model realisations were

performed to narrow down parameter ranges by comparing the model output to empirical data and using an 80% confidence limit (error percent: 0.5%); parameter sets that produced output that fell outside this range were discarded. A confidence limit of 80% was chosen because of the large parameter space. The obtained parameter ranges were then refined using subjective judgement (abduction) and another set of 1,000 calibration runs were performed to further narrow the plausible parameter space. For the calibration, empirical time series data from the 2009 A(H1N1) influenza pandemic on the weekly proportion of NPFS-based NAI authorisations that resulted in collections were used.[44] Given that the NPFS was unavailable for the first half of the first peak of the 2009 influenza pandemic, the model was calibrated to the second wave of the pandemic (from 31 August 2009 to 11 February 2010– 23 weeks and 4 days) to ensure that data availability on an entire epidemic curve. Model parameters were varied over a probability distribution to induce agent heterogeneity (Tables 7-8). A 5,000 iteration Monte Carlo uncertainty analysis was then performed by simultaneously varying all model parameters over the identified plausible ranges to analyse the impact of heterogeneity on the model output. Finally, a set of sensitivity analyses were conducted by examining the model output when α, η and θ were varied by 50%, and when δ was varied from 0 to 1 in increments of 0.1. For the threshold variables, a hypothetical scenario where α, η and θ were set at 0 (i.e. there were no barriers to capability, opportunity, or motivation) was also considered.

The implementation of the ABM and the integrated DES was done using the simulation software AnyLogic 7 which is a Java-based multi-method modelling

IDE (Appendix 5).[234] Visualisations of model output presented in this thesis were produced using Python (IDE: Spyder v.3).

5.3 Results

Using the COM-B behavioural model (Section 2.2), the ABM was able to approximate the dynamics of the number of NAI collections relative to the NPFS-related ILI consultations (Figure 16). The peak of the pandemic was observed on day 50 in the empirical data, whereas the model used in this study predicted that it would occur on day 43. A second smaller peak that occurred on day 80 was consistent the model output. Although the absolute numbers between the model output and the empirical data are not directly comparable, the relative differences and the dynamics between them were similar. Between day 40 and day 100 of the outbreak, the mean model output (over 1,000 iterations) suggested that between 58 and 63% of ILI consultations (that resulted in NPFS authorisations) led to NAI collections. This proportion for the corresponding time period in the empirical data was observed to be slightly higher at 62 to 68%. The final calibration parameter ranges for the ABM are presented in Table 10. Results from the Monte Carlo analysis where all parameters were varied across specified ranges over 5,000 random seeds show that while the model is sensitive to input parameters and model stochasticity, the overall dynamic corresponds with the epidemic curve (Figure 17).

The sensitivity analyses showed that the capability threshold, α, had the biggest impact on the model output. Reducing the α value by 50% of the best-fit range increased NAI collection by almost 36%, and a 50% increase in the best-fit range of α was associated with a reduction in NAI collections by about 40%. Similar associations were found with varying the discount rate δ, by 50%.

Decreasing the best-fit value for the opportunity threshold η was seen to be associated with a 16% increase in antiviral collections. However, an increase in the best-fit η by 50% did not make a significant difference to NAI collections. Varying the motivation threshold was also not seen to have an impact on total NAI collections. Setting the α, η and θ threshold values at 0 was associated with significant increases in NAI collection (Figure 18).

Parameter	Range
α	183 to 185
η	0.15 to 0.20
θ	0.20 to 0.25
OR_0	0.1 to 0.3

Table 10: Final calibrated parameter ranges for the ABM

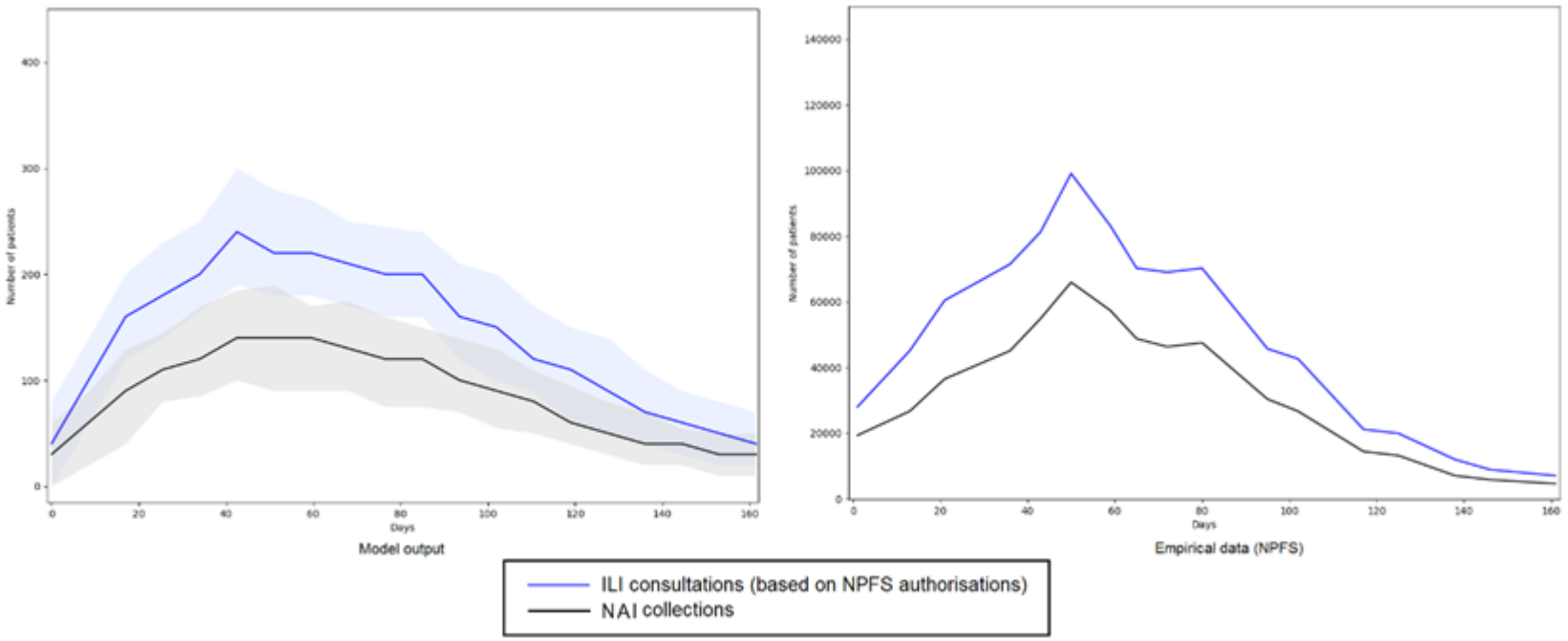


Figure 16: A comparison of NAI treatment collection rates relative to ILI consultations (based on NPFS authorisations) between the model output and empirical data from 2009. For the model output, the solid lines represent the mean model outputs and the shaded regions represent the range of the middle 80% of model output over 1,000 iterations

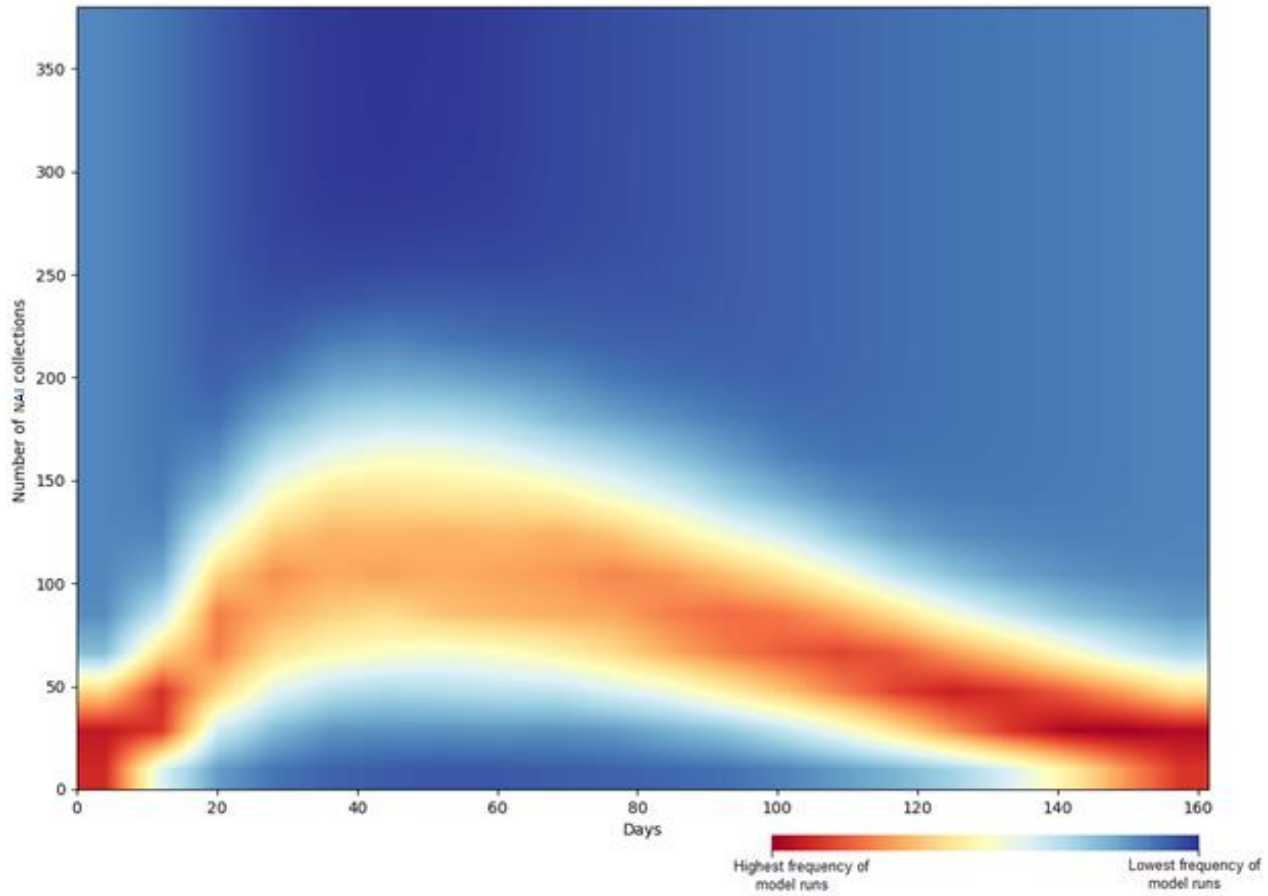


Figure 17: 2D histogram showing output from a 5,000 iteration Monte Carlo uncertainty analysis of the ABM (output: number of NAI collections)

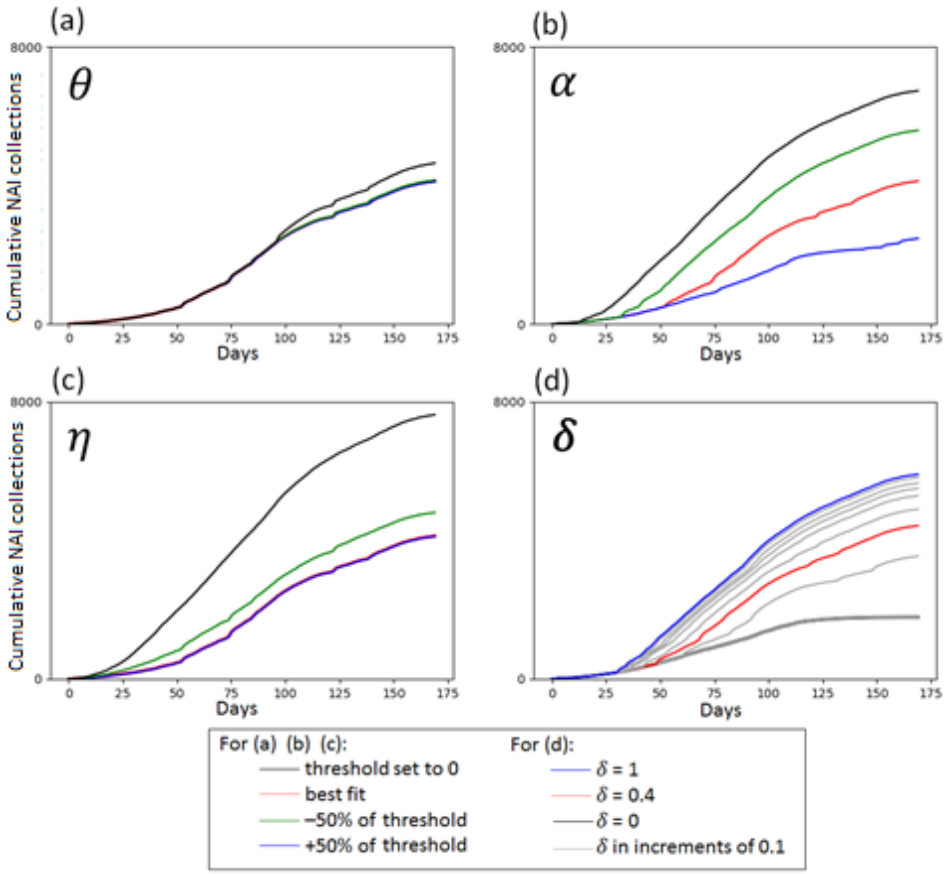


Figure 18: Sensitivity analyses: Impact of varying α, η, θ and δ on NAI collection

5.4 Discussion

In this study a simple behavioural model based on an empirically identified set of constructs[70] has been coupled with an ABM of an influenza pandemic to demonstrate how incorporating the elements of Capability, Opportunity, and Motivation into epidemic models can generate important insights into how interventions can be developed to improve NAI collection rates (and therefore treatment rates) for future pandemics. The proof-of-concept implementation of the behavioural model is based on the UK National Pandemic Flu Service which operated in 2009 and sought to divert pressure away from primary care services. Using this approach 1.2 million treatment courses of NAIs drugs were dispensed.[235] It is intended that this system will be used again in the future,[236] and other countries are now considering similar models.[237]

The coupled behavioural-epidemic ABM output slightly underestimated the proportion collecting authorised NAI drugs in the middle part of the outbreak when compared to data observed from 2009. Although, the dynamics, for the most part, were consistent with empirical data. The sensitivity of the model to the Capability threshold α suggests that a person's awareness of an ongoing epidemic can greatly influence how capable they are of making healthcare decisions. The discounting rate δ was also seen to have had a significant impact on NAI collection rate. This is not surprising as the Capability threshold α is a function of δ. The model is not sensitive to changes in the motivation threshold θ is because a constant CHR has been assumed in the current model.

During an ongoing influenza pandemic, once a patient is infected (and symptomatic), he/she may then choose to call the NPFS, and if authorised NAI drugs, the patient will then have to decide on whether to collect authorised

NAIs. This decision is influenced by the patient's knowledge of the disease (Capability), which includes the ability to differentiate pandemic influenza from seasonal influenza, and awareness of the state of the pandemic at that point in time. Psychological factors that direct the decision to collect NAIs (Motivation) include fear, and beliefs about consequences from pandemic influenza. Also influencing the decision to collect NAIs are factors that lie outside the control of the patient (Opportunity) such as the distance to the nearest ACP, and the community-level attitude towards NAI drugs.

'Capability' to collect NAIs can be strengthened through education campaigns that are aimed at increasing the public's knowledge about the pandemic and associated disease rates.[177] The Department of Health and Social Care (England), state in their evaluation of the NPFS that using social media to monitor the "mood of the public" with respect to pandemic influenza was an important aspect of their pandemic response in 2009-10, and it will remain so for future pandemic responses.[238] The findings from this study support this recommendation and suggest that expanding public engagement and awareness campaigns beyond online media is likely to result in increased NAI collections (by improving Capability). Further, education campaigns also function as persuasion-based interventions that can improve 'Motivation' to collect NAIs.[177] Strengthening 'Opportunity' would require interventions that minimise distance/improve access to ACPs (environmental restructuring) (Section 2.2.2, Table 2). Recommendations from trusted health professionals can also improve treatment uptake by strengthening social Opportunity.[70]

The benefit of using the COM-B model is that Capability, Opportunity and Motivation have already been mapped to a set of interventions that are likely to

influence that particular construct.[177] High threshold values for α, η and θ can be seen as barriers to NAI collection, and low threshold values as facilitators. An educational media campaign during an ongoing pandemic could contribute to an increase in a person's awareness of the pandemic and simultaneously also reduce optimistic bias (increasing motivation). Optimistic bias was modelled by randomly assigning levels of this bias across the population. This could be improved in future work by first identifying specific population groups that are likely to have increased levels of optimistic bias and then accounting for this in the ABM. Increasing the number of ACPs (environmental restructuring) could reduce the Opportunity threshold (by reducing the distance to the ACP, improving access to treatment), and also improve Motivation. Findings from this exploratory analysis reinforce the findings of the qualitative study by Rubinstein et al. that effective interventions to increase NAI uptake are likely to be multidimensional.[70] In deciding the most suitable intervention to increase NAI collection rates, the government will need to consider the cost-effectiveness of each potential intervention.

While the structure of this COM-B-based behavioural model is rooted in the work done by Durham and Casman,[173] it differs from theirs in a number of important ways. Agents within the simulation described in this study make decisions based on information from their local networks, unlike the global approach followed by Durham and Casman.[173] Further, the epidemic and the behavioural components of the model have not been de-coupled as has been done in some previous work.[173,239] But most importantly, in the current behavioural model, the drivers of C, O and M that influence behaviour are based on an empirically validated behaviour model that has already been linked to

policy, whereas the main limitation of decision frameworks based on the HBM is that links between potential drivers of behaviour change and health beliefs are poorly understood.[173] Another behaviour model based on the HBM used parameters such as attitude, norms, and worry to obtain a behaviour score; however, the authors note that their model output fit poorly with empirical data.[163] The difficulty in validating and fitting behaviour models to empirical data has been noted by others as well.[240,241] A systematic review of published studies reported that only 15% of studies involving behaviour change models in epidemiology performed any type of validation with empirical data.[170] The systematic review further noted that most behavioural models used were theoretical models that were developed independently from empirical data. A more practical approach was followed here, and an attempt was made to validate the simulation model output. Validation of a simulation model requires validation of the underlying conceptual model as well as the simulation output (Section 1.2.3.2).[133] The conceptual model used is based on the COM-B model of behaviour change that is widely used within public health and is recommended by leading research organisations.[178] The simulation output was validated against NPFS data from the 2009 influenza pandemic in the UK, noting that the dynamics observed in the simulation output was similar to what was observed in 2009. One important consequence of a lack of suitable behaviour data is that multiple model parameters may have to be calibrated to ensure that model output is consistent with empirical data. This has meant that some previous behaviour models have had to calibrate up to six input parameters.[163,173] An attempt to minimise the number of parameters calibrated by only calibrating the four essential behavioural parameters in the current

study. However, the calibrated parameters were varied over a range in a set of sensitivity analyses to evaluate their impact on the model output. This is one way of validating a model with calibrated parameters.[129,133] The sensitivity analyses produced results that were qualitatively and quantitatively consistent with what would be expected empirically (i.e. a reduction in behavioural thresholds improved the likelihood of behaviour change). Nevertheless, this exploratory study could be used to guide collection of behavioural data in the future. OR_0 can be easily estimated by analysing public health survey data. The three behavioural thresholds can be estimated statistically from behavioural data collected over a period of time.

This study is not without limitations or simplifying assumptions. It was assumed that NAI treatment was not used for prophylaxis and was only given to patients with clinical illness. This is in line with what was observed during the treatment-only phase of the pandemic in 2009 during which the NPFS operated.[44] It was also assumed that NAI treatment does not have an impact on transmission. There is evidence to suggest that the population-level impact of NAI treatment on transmission is likely to be quite small.[242] Further, varying contact rates by agent location (workplace, school, or home), the impact of other pandemic influenza mitigation measures, or the impact of transport disruptions are not accounted for in the model. All modelling endeavours require a compromise between striving for an accurate representation of reality and computational feasibility. The ABM was deliberately implemented as a relatively simple epidemic model on a small population, as the network effects in the behavioural model make modelling larger populations computationally expensive.

This behavioural model, in its current form, is not a perfect representation of the COM-B behaviour change model, and indeed, the COM-B behaviour change model may not be a perfect representation of behaviour change. The COM-B constructs for this proof-of-concept implementation are based on the empirically identified set of factors by Rubinstein et al.[70], but there may be other factors driving healthcare-seeking behaviour that have not been accounted for in this model. Influences such as 'fear' are not straightforward to incorporate into an ABM, but proxies have been used to model the influence of factors that are hard to represent (such as fear) in a dynamic model.

This is, to the best of my knowledge, the first attempt at formalising the COM-B model for use in an ABM. This behavioural model lends itself quite well to easy parameterisation from surveys or other public health data. It is strongly recommend that for future applications of this model, the associations between individual factors driving behaviour change and the COM-B constructs first be empirically identified through a qualitative study, and then the simulation model ideally be informed by behaviour data collected specifically for the case study of interest. Capability, Opportunity and Motivation are also likely to dynamically influence each other. For example, increasing a person's awareness of a disease (Capability) could also influence their optimistic bias (Motivation). Future applications of this behavioural model could explore the dynamic interactions between the COM-B constructs. Finally, this study has assumed a crisp implementation of behaviour probability (behaviour threshold of ≥50% probability). In reality, however, decisions are frequently made under conditions of uncertainty and imprecision. Using fuzzy decision rules[243] to

guide agent behaviour could be a direction for future research to improve upon the current model.

6 Study 4: How can NAI effectiveness estimates be extrapolated to assess the impact of NAI treatment on hospitalisations?

6.1 Introduction

Pandemic events are widespread phenomena that can exert significant pressure of healthcare capacity. The impact of the pandemic is likely to be particularly severe on secondary healthcare services that, in many countries, operate at nearly full capacity even in inter-pandemic periods. Therefore, minimising the impact of a pandemic on hospitals is a public health priority. Devising effective NAI treatment strategies can, therefore, play a crucial role in helping manage surges in healthcare demand. The impact of a pandemic on hospitals can be minimised through community-based NAI treatment (to avert hospitalisations), or through in-hospital NAI treatment (to reduce hospital LoS).

This chapter describes a study that was performed to assess the public health impact of NAI treatment during a pandemic scenario. Community-based NAI treatment dispensed through the NPFS, as well as in-hospital NAI treatment, and their impact on hospitalisations and hospital bed capacity will be examined.

Implications of limited generalisability of the findings in Chapter 3:

Initially, it was intended that this study would take NAI effectiveness estimates derived in Chapters 3 and 4, and extrapolated them using the coupled behavioural-epidemic model described in Chapter 5 to gain insights into potential impact of NAI treatment strategies. However, the main limitation of the NAI effectiveness estimate obtained in Chapter 3 is that the hospitalised

proportion observed in the study population was exceptionally high. The 2009 A(H1N1) influenza pandemic was considered a relatively mild pandemic with a symptomatic CHR of between 0.40 to 0.55%.[41,230] However, even with an extremely severe influenza pandemic, a CHR similar to what was observed in the study population of this IPD meta-analysis is highly unlikely. Notwithstanding, the findings of Chapter 3 are still valuable in evaluating NAI effectiveness in populations at high risk for hospitalisation and formulating public health policy. However, the limited generalisability of the NAI effectiveness measure makes it unsuitable for use in agent-based and health economic models as this estimate depicts drug effectiveness in a group of high-risk patients with severe illness. Other NAI effectiveness estimates relating to the 2009 A(H1N1) influenza pandemic that have been derived using a robust IPD approach are currently lacking. In light of these points, the ABM described in this chapter will use NAI effectiveness estimates for hospitalisation from a published IPD meta-analysis of RCT data based on patients with relatively mild seasonal influenza.[88] The aim of this chapter is: to evaluate the public health impact of a combination of community-based and in-hospital NAI treatment strategies on hospital admission and hospital bed capacity during a pandemic scenario. For model feasibility and to ensure that outputs from the models of community-based treatment (based on NAI treatment dispensed through the NPFS) are comparable to those investigating combination NAI treatment, only patients not at high risk of complications from influenza were considered in both models.

6.2 Methods

6.2.1 Model development

This study used a hybrid ABM-DES model to address its aim. The behaviour-epidemic ABM described in Chapter 6 was extended, using the software engineering-based model development framework described earlier.[124]

The main objective of this ABM was to evaluate the impact of NAI treatment, on hospitalisation and hospital LoS in a pandemic scenario. Similar to what was done in Chapter 6, a scope were developed (Table 11).

Category	Element	Decision	Justification
Actor	Individuals in a population	Include	Basic unit of population
	Fomites (inanimate infection sources)	Exclude	Impact unlikely to be significant for objective considered (from literature); computationally expensive
	Buses/ Other public transport	Exclude	(Same as above)
Buildings	Antiviral collection point(ACP)	Include	Needed to assess 'opportunity' to engage in behaviour change
	Hospital	Include	Relevant to the main aim
	GP practices	Exclude	This model will focus on the NPFS service that operated during the 2009 pandemic in England
Psychological factors	Comparative feedback	Include	COM-B model
	Imitation	Include	COM-B model
	Risk perception	Include	COM-B model
	Capability to engage in behaviour change	Include	COM-B model
	Opportunity to engage in behaviour change	Include	COM-B model
	Motivation to engage in behaviour change	Include	COM-B model
	Stigma	Exclude	Not always pertinent to influenza

Networks	Physical distances to ACPs	Include	Needed to assess 'opportunity' to engage in behaviour change
	Social network	Include	COM-B model
Disease	Infection states of individuals	Include	Modelled using a Susceptible, Exposed, Infected, Recovered (SEIR) epidemic model

Table 11: Scope table for the ABM developed in this study

The main difference in this ABM, when compared to the ABM described in Chapter 5, is that hospitalisation is modelled in the current chapter. A DES (representing a hospital) was integrated with the ABM (Figure 19). The hospital capacity in the DES was assumed to be 22 beds per 10,000 population. This is based on a scaled version of the estimated number of general and acute care hospital beds in England in 2009-10.[244] If an infected agent required hospitalisation, it would be directed to the DES which was embedded in the artificial lab. Upon admission to hospital, the agent would then occupy a hospital bed, so long as full hospital bed capacity was not reached. If the hospital was already at full capacity when an infected agent was directed to hospital, the agent would need to wait until a hospital bed was free to occupy. NAI treatment effectiveness in reducing hospital LoS (in patients requiring standard ward-based care) was informed by the IPD meta-analysis estimates from Chapter 5.

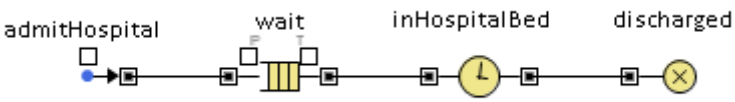


Figure 19: DES representing a hospital

6.2.1.3 Defining the artificial lab

The artificial lab comprised an ABM that simulated pandemic influenza transmission within a population (Figure 20), along with individual decisions to collect NAI drugs (if authorised) and a DES that represented a hospital.

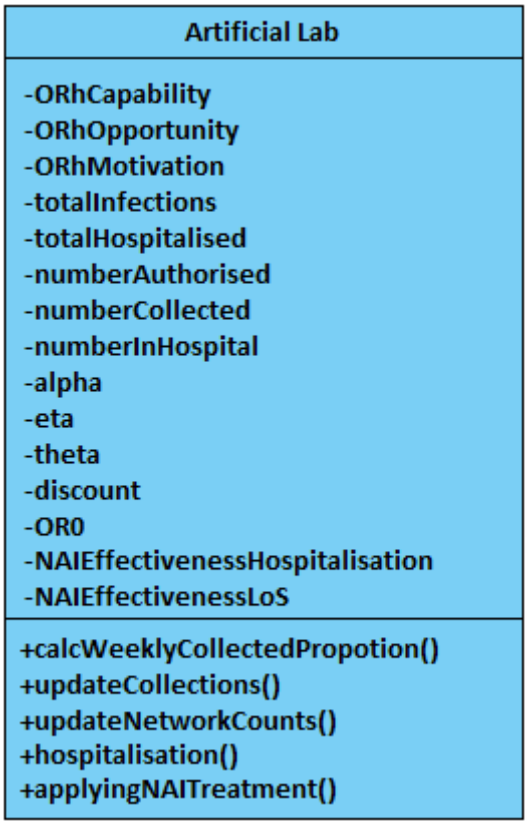


Figure 20: Artificial Lab class diagram

6.2.2 Implementation

The implementation of the ABM was similar to the proof-of-concept implementation of the ABM developed in Chapter 6. Briefly, 10,000 agents and one ACP were simulated for a period of 170 days during an influenza pandemic-like scenario. If infected, an agent sought NAI treatment through a system similar to the NPFS, and, based on data from the 2009 A(H1N1) influenza pandemic in England, 75% of assessments were authorised NAI drugs.[179] If the agent was authorised to collect NAI drugs, the COM-B behavioural model then guided the agent's decision to collect NAI. The CHR for the model was

informed by what was observed during the second peak of the 2009-10 influenza pandemic in the UK (CHR: 0.55%; 95% CI: 0.28 to 0.89).[230] The implementation of the ABM and the integrated DES was done using the AnyLogic modelling software (Version 7). Visualisations of model output presented in this thesis were produced using Python (IDE: Spyder v.3).

Behavioural parameters for this ABM could not be informed by an analysis of empirical data. Instead, they were left unchanged from the model developed in Chapter 6 (derived from literature). Given that the "outpatient" part of the model (the ABM) remained largely unchanged from Chapter 6, the same calibrated behavioural thresholds were retained.

6.2.3 Hypothetical scenarios considered

Pandemic influenza-related hospitalisations, and the total number of hospital beds being occupied (hospital bed occupancy), on a daily basis (by agents admitted with pandemic influenza) were the two outcomes considered in this study. The impact of six different NAI treatment scenarios were considered on the two stated outcomes. Three NAI treatment scenarios focussed on the impact of community-based NAI treatment on subsequent hospitalisations, and three treatment scenarios looked a combination of community-based NAI treatment and a 'treat-at-admission' (in-hospital) NAI treatment strategy. The five NAI treatment scenarios are described below.

a) **Community-based NAI treatment scenario 1:** The impact of community-based NAI treatment on hospitalisation under 2009-like NAI collection behaviour [baseline model: using calibrated behaviour parameters (Chapter 6)].

b) **Community-based NAI treatment scenario 2:** The impact of community-based NAI treatment on hospitalisation with an intervention to improve NAI collection rates by strengthening Opportunity to collect NAIs (η reduced by 50% of baseline).

c) **Community-based NAI treatment scenario 3:** The impact of community-based NAI treatment on hospitalisation with an intervention to improve NAI collection rates by strengthening Capability to collect NAIs (α reduced by 50% of baseline).

d) **Combination NAI treatment scenario 1:** The impact of community-based NAI treatment under 2009-like NAI collection behaviour [using calibrated behaviour parameters (Chapter 6)] + no NAI treatment at hospital admission on hospital bed occupancy.

e) **Combination NAI treatment scenario 2:** The impact of improved community-based NAI treatment (α reduced by 50% of baseline) + no NAI treatment at hospital admission on hospital bed occupancy.

f) **Combination NAI treatment scenario 3:** The impact of improved community-based NAI treatment (α reduced by 50% of baseline) + NAI treatment at hospital admission (treat-at-admission) on hospital bed occupancy.

The main analyses for this study explored the above treatment strategies for the stated outcomes during a pandemic of similar transmissibility and severity as the 2009 influenza pandemic (specifically the UK experience), which had relatively low transmissibility and low severity.[44] In addition, a sensitivity analysis was also carried out to evaluate the impact of the three combination NAI treatment strategies (d, e and f above) on hospital bed occupancy in a

hypothetical pandemic with a higher transmissibility (CAR=30%) and high severity (CHR=4%). This hypothetical pandemic scenario was defined based on a risk assessment framework developed by the CDC.[49,245] For the sensitivity analysis, the behavioural component of the ABM (the formalised COM-B model, Section 2.2) was turned off, and a fixed proportion of NAI authorised patients collecting NAIs was assumed in-line with that was observed in 2009 in the UK. The combination NAI treatment scenarios 2 and 3 in the sensitivity analysis assumed an improvement in community-based NAI collection by 35% (of what was observed in 2009-10). The behaviour thresholds were not used for the sensitivity analysis as they are highly specific to the epidemic/pandemic conditions under which they were calibrated. A full list of input parameters for the hybrid model is provided in Table 12).

Parameter	Value *Probability distribution*	Source (reference number)
Contact rate, Mean (SD)	11.74 (7.67) *Normal*	[227]
Duration of illness, Median (IQR) in days	6.5 (5 to 8) *Triangular*	[228]
Probability of infection, Range	0.015 to 0.020 *Uniform*	Calibrated
Latency period, Mean (SD) in days	1.6 (0.26) *Normal*	[229]
Case hospitalisation risk (95% CI)	0.55% (0.28 to 0.89) *Triangular*	[230]
% Seeking outpatient care	34.5 *Fixed*	[246]
Hospital LoS, in days (IQR)	5 (3 to 9) *Triangular*	Chapter 5
NAI effectiveness for hospitalisation, OR (95% CI)	0.37 (0.19 to 0.81) *Triangular*	[88]
NAI effectiveness for LoS in patients requiring standard ward-based care, IRR (95% CI)	0.81 (0.78 to 0.86) *Triangular*	Chapter 5
Number of hospital beds, number per 10,000 population	22 *Fixed*	[244]

Likelihood of NAI collection for 'high' Capability vs. 'Low', OR (95% CI)	2.80 (2.52 to 3.08) *Triangular*	[231]
Likelihood of NAI collection for 'high' Motivation vs. 'Low', OR (95% CI)	2.71 (2.08 to 3.53) *Triangular*	[232]
Likelihood of NAI 'high' Opportunity vs. 'Low', OR (95% CI)	4 (3 to 5) *Triangular*	Assumed based on [184]

SD: Standard deviation; IQR: Interquartile range; OR: Odds ratio; IRR: Incidence rate ratio; CI: Confidence Intervals

Table 12: Input parameters for the ABM-DES used in this study

6.3 Results

The main results of the impact of community-based NAI treatment strategies (a), (b) and (c) are presented in Figure 21 and Figure 22 below. The mean simulation output from 50 model runs of the baseline treatment scenario [community-based NAI treatment strategy (a)] suggested that, in a population of 10,000 agents during a 2009-like influenza pandemic scenario, hospitalisations would peak around day 25. Improving population attitudes towards NAI treatment, and thereby improving NAI collection rate, by strengthening Opportunity [community-based NAI treatment strategy (b)] could potential delay the peak hospitalisation by about 9 days, and also reduce the number of hospitalisations observed during peak hospitalisation by 12.5%. Finally, for community-based NAI treatment strategy (c), the mean simulation output over 50 model runs suggested that improving NAI collection rates by reducing the Capability threshold (α) by 50% could result in a reduction in peak hospitalisation by about 37.5% when compared to the baseline treatment scenario.

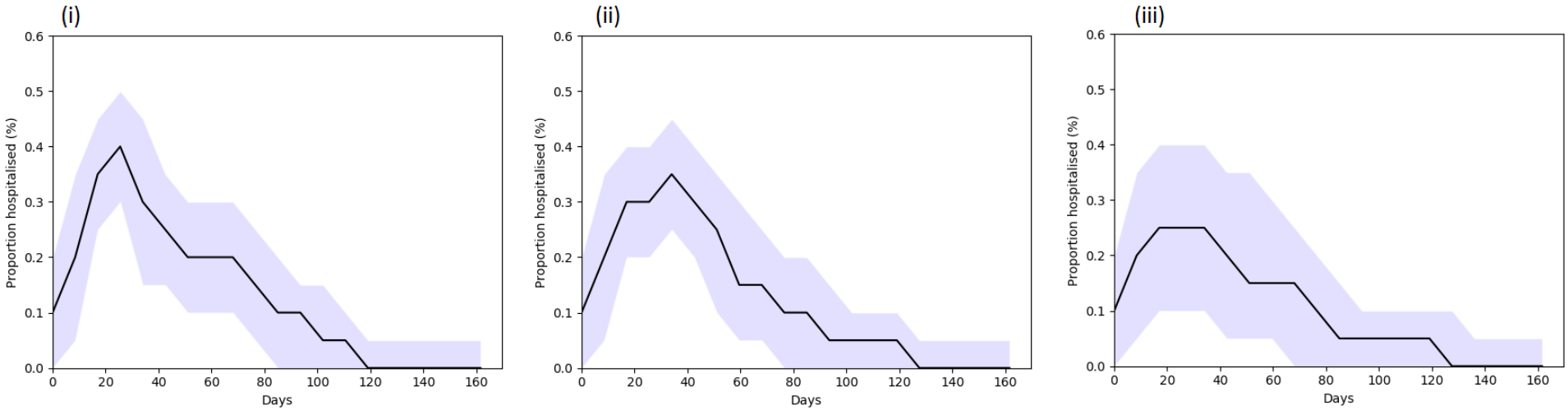


Figure 21: Impact of community-based NAI treatment strategies on hospitalisation. (i), (ii) and (iii) represent community-based NAI treatment scenarios 1, 2 and 3 respectively, under a 2009-like influenza pandemic.

The solid line represents the mean simulation output over 50 model runs; the shaded area represents the range.

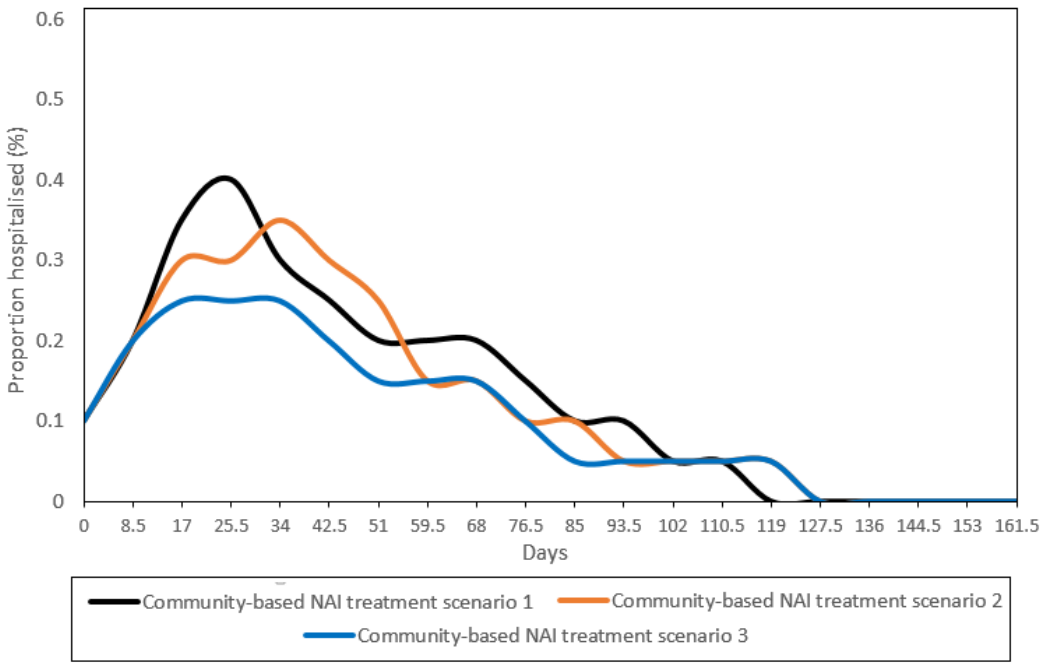


Figure 22: Mean simulation output from 50 model runs for the three community-based NAI treatment strategies overlaid on one plot.

When the combination NAI treatment scenarios were considered, the relatively milder nature of the 2009 A(H1N1) influenza pandemic resulted in low numbers of patients occupying beds in hospital. Due to model stochasticity and the low CHR associated with the 2009 pandemic, wide ranges were associated with the simulation output. Notwithstanding, the mean simulation output after 50 model runs suggested that 'Combination NAI treatment scenario 2' was associated with a decrease in peak bed occupancy (on day 30) from 4 patients to 3 patients when compared to the baseline scenario. This was seen to reduce further to 2 patients when a 'treat-at-admission' NAI strategy was combined with improved community-based NAI collection (Combination NAI treatment scenario 3) (Figure 23).

In the sensitivity analysis, the simulation output suggested that, if population attitudes towards community-based NAI treatment remain the same as was

observed during the 2009 pandemic, hospital capacity may be exceeded (indicated by the upper range crossing the bed limit of 22/10,000 population). An improved NAI collection rate in the community alone would reduce peak bed occupancy by 17.6%. If all hospitalised pandemic-influenza patients were treat at admission, the peak bed occupancy could be reduced by up to 41% (when compared to the baseline scenario). Combination NAI treatment scenarios 2 and 3 were consistently associated with reduced bed occupancy rates (Figure 23).

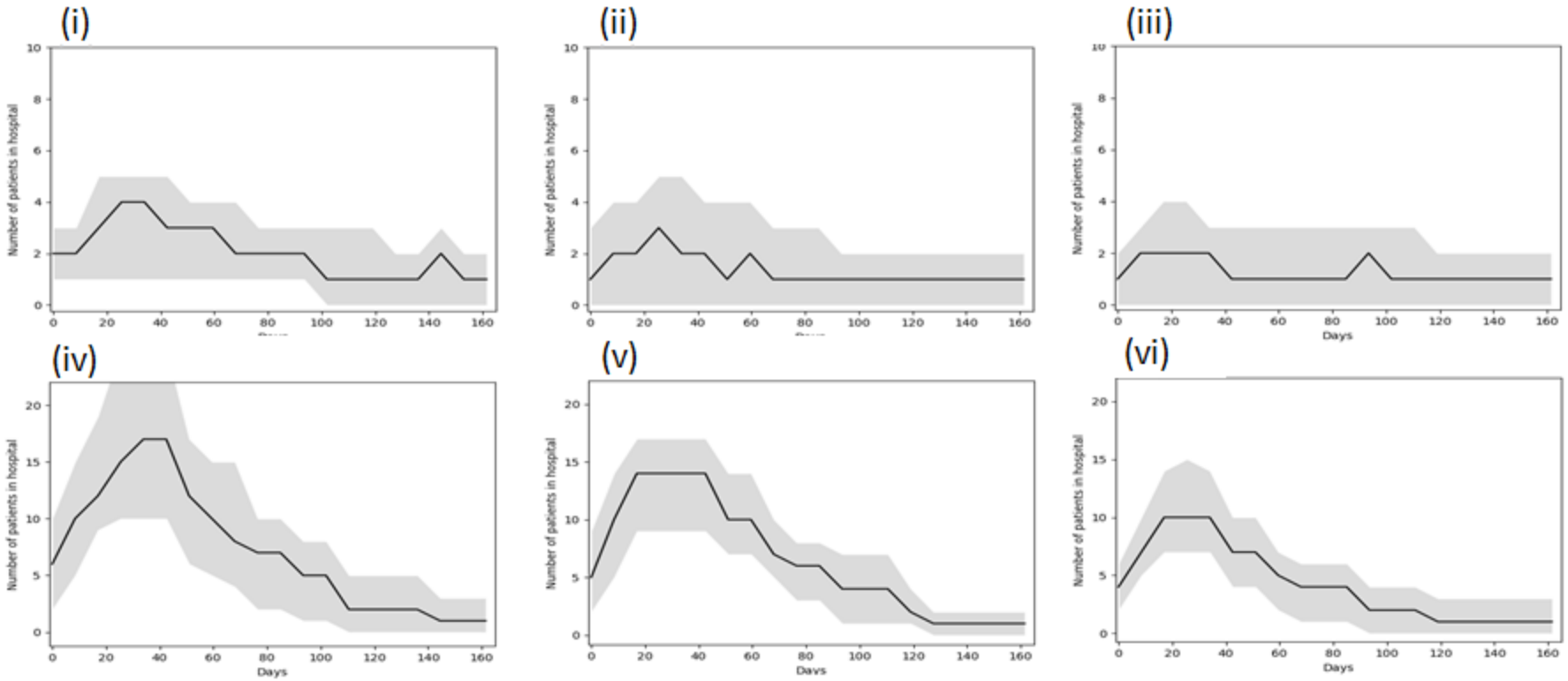


Figure 23: Impact of combination NAI treatment strategies on hospital occupancy. (i), (ii) and (iii) represent Combination NAI treatment scenarios 1, 2 and 3 respectively, under a 2009-like influenza pandemic. (iv), (v) and (vi) represent the same scenarios under a pandemic with a CAR of 30% and a CHR of 4% (sensitivity analysis)

The solid line represents the mean simulation output over 50 model runs; the shaded area represents the range.

6.4 Discussion

The community-based NAI treatment strategies considered in this study are based on NAIs dispensed through the NPFS (Section 2.1.6.2), and the impact of two public health strategies, each aimed at improving NAI collection rates, on resulting hospitalisations, were compared to a baseline scenario. The results of the modelling suggested that public health strategies aimed at improving NAI collection rates through strengthening the 'Capability' construct of COM-B model are likely to avert a greater number of hospitalisations, than strategies that explicitly look to improve 'Opportunity'. The impact of community-NAI scenarios 2 and 3 were seen to be the highest at the peak of the outbreak and less marked during the later stages of the pandemic. The percentage reduction in peak hospitalisation brought about by improving NAI collection rates through community-based NAI treatment scenario 2 and 3 of 12.5% and 37.5% respectively, were consistent with the findings of the sensitivity analysis in Chapter 5. Both, community-based NAI treatment scenarios 2 and 3 were seen to delay peak hospitalisation by about a week; this is significant for a public health planning as the delay allows more time to free-up necessary resources and mount an effective response. The advantage to using a coupled behavioural-epidemic model, such as the one used in this study, is that differences in impact between different types of public health interventions can be ascertained.

The relatively low NAI collection rates observed during the 2009-10 influenza pandemic can be attributed to a number of reasons. One of main barriers to NAI collection during the 2009-10 A(H1N1) pandemic was the perception of the severity of the pandemic. The early pandemic response in the UK was influenced greatly by data from Mexico, based on which a CAR as high as 30%,

and a CFR of up to 0.35% was predicted,[41] and this attracted significant media coverage which in turn translated into a higher number of ILI consultations.[247] But at the end of the first wave, the impact of the pandemic was seen to be much lower than was expected. By the time the second wave occurred, the media interest had decreased.[247] There was a perception amongst the public that the risks from the influenza pandemic were "over-hyped".[248] A consequence of this was that compliance with official recommendations (including treatment with NAIs) was low as the pandemic was not considered serious enough. Evidence from 2009 suggests that many people did not consider pandemic influenza to be a more significant threat than seasonal influenza.[70,248,249] There was also (and continues to be) debate around the effectiveness of NAIs, particularly in averting complications from influenza.[250,251] Finally, there is evidence to suggest that access to an ACP played a role in effecting the low NAI collection rates seen.[184]

Capability can be strengthened through data-driven education/awareness campaigns that are aimed at improving the public's knowledge of the ongoing pandemic. Opportunity to collect NAIs can be improved by improving access to ACPs, particularly in rural areas. There is also evidence to suggest that having GPs adopt a consistent position on NAI treatment can improve social Opportunity as people place faith in recommendations from trusted sources during a pandemic.[70] Ideally, an infected patient who has been authorised an NAI during an influenza pandemic must be able recognise that pandemic influenza is caused by a novel strain (contrary to seasonal influenza), have an understanding of the disease activity in the area of his/her residence, exposed to a consistent set of guidelines and recommendations from the government, and

have reasonable access to an ACP in the local area. During the 2009-10 influenza pandemic, the total number of ACPs was not fixed throughout the pandemic. Instead, it fluctuated on a daily basis based on need.[69] Conceivably, access to ACPs could have been easier in urban areas with a higher population density than in rural areas. Opportunity can be strengthened by increasing the total number of ACPs, however, this is a decision that will need to be made keeping the cost-benefit ratio in mind. Regardless, the Opportunity to collect NAIs is likely to have a stronger influence on the decision to collect NAIs during a perceived milder pandemic than during a severe pandemic.

One of the advantages of using this behavioural model is that the indirect effects of an intervention on other COM-B constructs are also taken into account. For example, an improvement in agents' awareness of pandemic influenza (Capability), results in a greater number of NAI collections, which in turn improves the 'social' Opportunity for agents (by increasing the number of NAI treated agents in a network; Section 2.2.2, Table 2). This is one possible explanation for the higher impact of interventions geared at improving 'Capability', when compared to 'Opportunity'. This also points to the multi-dimensional nature of the interventions that are likely to be successful.

The combination NAI treatment scenarios considered the impact of community-based and in-hospital NAI treatment of patients (not requiring ICU care) on acute care hospital bed occupancy. For a relatively milder pandemic like the 2009 A(H1N1) pandemic, hospitalisations averted through improved community-based NAI treatment was seen to have a greater impact on relieving hospital bed occupancy than in-hospital NAI treatment at admission. However, for a highly transmissible and highly severe influenza pandemic, NAI treatment

at hospital admission could, in combination with improved community-based treatment reduce peak hospital bed occupancy by about 41% (compared to baseline). The findings of this study suggest that even at a relatively 'moderate' level of NAI effectiveness (IRR: 0.81; 95% CI: 0.78 to 0.86; equivalent to a median reduction in LoS of 1.2 days; Chapter 5), a 'treat-at-door' policy could have a substantial impact on reducing hospital (acute care) bed capacity in a high severity pandemic. Previous studies have looked at the impact of NAI treatment on hospital critical care bed capacity; however, they note uncertainties around the NAI effectiveness estimates used in the models.[252,253] The current study focuses on the impact of NAI treatment on LoS in patients requiring ward-based care. This study benefits from the NAI effectiveness estimate that was ascertained specifically for the patient population being modelled (non-ICU patients) from a large individual-level dataset. The hospital model used in this study is not intended to be an operational model of a hospital. Instead, these findings should be interpreted as extrapolations of the NAI effectiveness estimates under different scenarios. Previous studies that have looked at hospital capacity under pandemic scenarios[252-256] have all used the FluSurge model developed by the CDC.[257] The FluSurge model is a static, spreadsheet-based model that is intended to be used as a "training tool" to consider, and prepare for potential pandemic threats.[257] The hospital model used in this study is similar to the FluSurge model in its intended purpose, but has the added advantage that its results are based on a transmission dynamic model that also accounts for the impact of community-based treatment. The 41% reduction in hospital bed demand that was observed in this study was slightly lower than what was observed in a FluSurge model (50% reduction in demand), however, the

FluSurge model also assumed a higher effectiveness of NAI treatment in reducing hospital LoS (1 to 2 days), and a lower attack rate (25%).[257]

There are a number of limitations to the findings reported in this study. The main limitation is that the NAI effectiveness estimate for community-based based treatment could not be derived from pandemic influenza data; estimates based on seasonal influenza have been used instead. Also, the NAI estimates used in this study are based on the assumption that they are taken within 48 hours of symptom onset.[88] This is may not be a realistic assumption. The official evaluation of the NPFS reported that almost two-thirds of the patients who contacted the NPFS did so within 48 hours of symptom onset and almost all of the patients who collected NAIs did so within 48 hours of authorisation.[258] The impact of the promptness in seeking care (relative to symptom onset) is further explored in a sensitivity analysis in Chapter 7. In the models of improved community-based NAI treatment, public health interventions that reduced the Capability and Opportunity thresholds by 50% were considered. While the interventions that could be implemented to address specific constructs of the COM-B model can be easily identified, ascertaining precisely what would comprise a 50% reduction in a particular threshold for any given intervention is difficult to establish at this stage. Further work in behaviour change research, specifically studying pandemic influenza mitigation strategies using the COM-B behavioural model can shed light on this.

Only pandemic influenza-related hospitalisations have been considered in this study as the main aim was to assess the relative impact of NAI treatment on hospital bed occupancy rather than to study hospital resource utilisation. Nevertheless, non-pandemic influenza-related hospitalisations are likely to

contribute to a significant proportion of hospital demand, even during a pandemic. The hospital capacity (number of acute beds) considered in this study are based on a scaled version of total NHS beds in England. However, service prioritisation is an important component of the NHS surge management plan which would see cancellation of all elective procedures in hospital; this could result in increasing the total number of acute beds available for pandemic influenza-related hospitalisations by up to 33%.[259] Finally, results of the sensitivity analysis examining the impact of combination NAI treatment during a pandemic of higher transmissibility and severity must be interpreted with caution, as they are based on NPFS consultation rates observed in 2009 (during a milder pandemic). The extent to which these findings will apply to a more severe pandemic is uncertain, as it is very likely that under a healthcare seeking behaviour during a severe pandemic will be higher. This increase in healthcare seeking behaviour is accounted for in the decision model described in Chapter 7. Nevertheless, findings from the sensitivity analyses are still informative in the sense that they describe the relative benefit of combination NAI treatment under a certain level of healthcare-seeking behaviour.

Overall, the findings of this study suggest that a combination of community-based and in-hospital (treatment at admission) NAI treatment strategies can help reduce the public health impact of an influenza pandemic. However, the extent of their impact will depend on the nature of the pandemic.

7 Study 5: Is it cost-effective to use NAI treatment to avert hospitalisations?

7.1 Introduction

In the event of a severe future pandemic, hospital capacity may be exhausted and therefore reserved for the severely ill who are most likely to benefit.[260] Countries may decide to focus a significant part of their pandemic response plan towards community treatment aimed at averting hospitalisations. Policy makers considering NAI stockpiling for a future pandemic of unknown severity will have to consider both number of hospitalisations averted and the cost-effectiveness of such an intervention. NAI treatment for pandemic influenza has generally been estimated to be cost-effective for higher-income countries.[261-263] However, a review identified that previous health economic evaluations often neglected pandemic uncertainty by only evaluating singular, fixed pandemic scenarios.[264] Moreover, few models have incorporated the increased risks of adverse pandemic influenza-related outcomes for patients with at-risk conditions.

Chapters 3 and 4 used an IPD approach to analyse observational data from the 2009-10 influenza pandemic to estimate NAI treatment effectiveness for hospitalisation and hospital LoS respectively. Chapters 5 and 6 used computational modelling to extrapolate the impact of NAI treatment on public health outcomes. In this chapter, a health economic, decision tree model is used to evaluate the cost-effectiveness of community-based NAI treatment in terms in a range of pandemic influenza scenarios.

7.2 Methods

A decision tree model was developed (Figure 24) to evaluate the impact of community-based NAI treatment for five pandemic scenarios. This decision tree model is decoupled from the behavioural model developed in Section 2.2, and a static mathematical (decision) model is used rather than an ABM. A population of 62.28 million was considered for the decision tree model, based on the UK population in 2009.[265] The network effects in a coupled behavioural-epidemic ABM, like the one described in Chapters 5 and 6, would make simulating a population with over 62 million agents computationally infeasible. Instead, the health economic analyses, using a decision tree model, was performed from the perspective of the healthcare payer (NHS) with a much higher level of abstraction (compared to an ABM). A full cost-utility analysis was not performed in this current study, therefore, outcomes were considered in natural units (deaths and hospitalisations) rather than in standardised units (QALYs).[266] A time horizon of less than one year (one pandemic event) was considered obviating the need for a discounting rate.

Of the five pandemic scenarios considered, the first scenario was based on the UK's experience of the 2009-10 influenza pandemic (CAR of 7% and a CHR of 0.3% and 1.5% among non-high-risk and high-risk patients, respectively). The remaining four scenarios were hypothetical scenarios are based on a risk assessment framework developed by the CDC.[49,245] This risk assessment framework defines a standardised risk space based on past influenza pandemics. The CHRs for the high-risk groups in the four hypothetical pandemics were assumed to be five times the CHR for the non-high-risk group of patients based on estimates from the 2009 A(H1N1) pandemic.[267] It was also assumed that the

proportion of patients seeking outpatient care would increase with the CHR of the pandemic, ranging from 40% among non-high-risk patients in a 2009-type pandemic to approximately 81% among high-risk patients when the CHR is 20%. The number of deaths averted through averting hospitalisations was estimated by multiplying the number of hospitalisations averted with an in-hospital mortality risk that was constant across the scenarios. Detail of the epidemiological parameters of five pandemic scenarios is provided in Table 13.

The definitions of 'NAI' in the decision tree model did not distinguish between Oseltamivir and Zanamivir; however, model input parameters on the NAI cost and treatment effectiveness were based on data specific for Oseltamivir. The model focused on community-based treatment and does not consider NAI prophylaxis. Effectiveness estimates for community-based NAI treatment derived in Chapter 3 of this thesis could not be used to inform the decision tree model in this study due to the limited generalisability of the estimates reported in Chapter 3. Instead, NAI effectiveness estimates from an IPD meta-analysis of clinical trials data on otherwise healthy patients with seasonal influenza based on ITTI analysis (since NAIs are not active against non-influenza respiratory infections) were used to inform the decision tree model (relative risk: 0.37, 95% CI: 0.17-0.81).[88] To account for NAI prescriptions to patients with non-influenza ILI, a 'wastage factor' of 40% was assumed, i.e. patients with non-influenza ILI would be prescribed 40% of the number of regimens that are prescribed to patients with influenza.[153] It was assumed that all patients would start NAI treatment ≤48 hours of symptom onset in the main model. This is an assumption that is implicit in the NAI effectiveness estimates derived from the IPD meta-analysis of RCT data.[88] A sensitivity analysis was performed varying

the promptness of care-seeking within 48 hours of symptom onset from 25% to 75% (percentage of all care-seeking patients who do so ≤48 hours of symptom onset) to test the impact of relaxing this assumption. Based on estimates from 2009, it was assumed that 64% of patients would be compliant with the prescribed NAI regimen.[179]

Unit cost data for the decision tree model were obtained from the British National Formulary and UK-based reports on the cost of health and social care (Table 13). The cost of a physician-based consultation of £24.20 was used. This cost was calculated as a weighted average cost of either a conventional primary care consultation or a phone-based consultation with the 2009 National NPFS.[258] The proportion of assessments routed through each consultation service in 2009 was used to derive the weights for the calculation of the average cost of a physician-based consultation. Details of the costs used in this study are provided in Table 13. All costs were inflated to the 2017 British Pound Sterling (£) using the hospital & community health services (HCHS) index.[268]

In each pandemic scenario, the number of outcomes averted (hospitalisations and deaths) and total costs associated with NAI treatment were compared to no NAI treatment. Cost-effectiveness of community-based NAI treatment was assessed by estimating the cost per averted hospitalisation. The primary analysis was performed using the middle values of the input parameters using formulae provided below (page 169). To account for uncertainty in parameter estimates, sensitivity analyses were performed by probabilistically varying input parameters along pre-defined probability distributions (Table 13) and using Monte Carlo simulations (5,000 iterations using Latin hypercube sampling) to calculate mean output values and 95% confidence intervals for

different combinations of input parameters. The sensitivity analyses were performed using the software @Risk version 7.3 (Palisade Corporation). Further, two-way sensitivity analyses were also performed to assess the impact of varying NAI effectiveness and patient compliance on the outcome (hospitalisations averted). The decision tree tool is provided as an Excel file (Appendix 5).

$$\boldsymbol{Hospitalisations\ averted} = Population * CAR * \%\ RG * \%\ Care\ seeking_{RG} * \%\ Care\ Seeking\ prescribed\ NAI * NAI\ Compliance * CHR_{RG} * (1 - NAI\ effectiveness)$$

$$\boldsymbol{Total\ NAIs\ dispensed} = Population * CAR * \%\ RG * \%\ Care\ seeking_{RG} * \%\ Care\ Seeking\ prescribed\ NAI * (1 + multiplier\ for\ non - influenza\ prescriptions)$$

$$\boldsymbol{Total\ Costs} = (No.\ outpatient\ consultations * cost\ per\ consultation) + (No.\ NAI\ regimens\ dispensed * cost\ per\ NAI\ regimen) + (No.\ Hospital\ admissions * cost\ per\ hospital\ admission)$$

$$\boldsymbol{Cost\ per\ averted\ hospitalisation} = \frac{Total\ cost\ of\ NAI\ stockpile\ scenario - Total\ cost\ of\ no\ stockpile\ scenario}{Hospitalisations\ averted\ by\ NAI\ stockpiling}$$

CAR- Clinical Attack Rate; RG- Risk Group; CHR- Case Hospitalisation Risk; NAI-Neuraminidase inhibitors

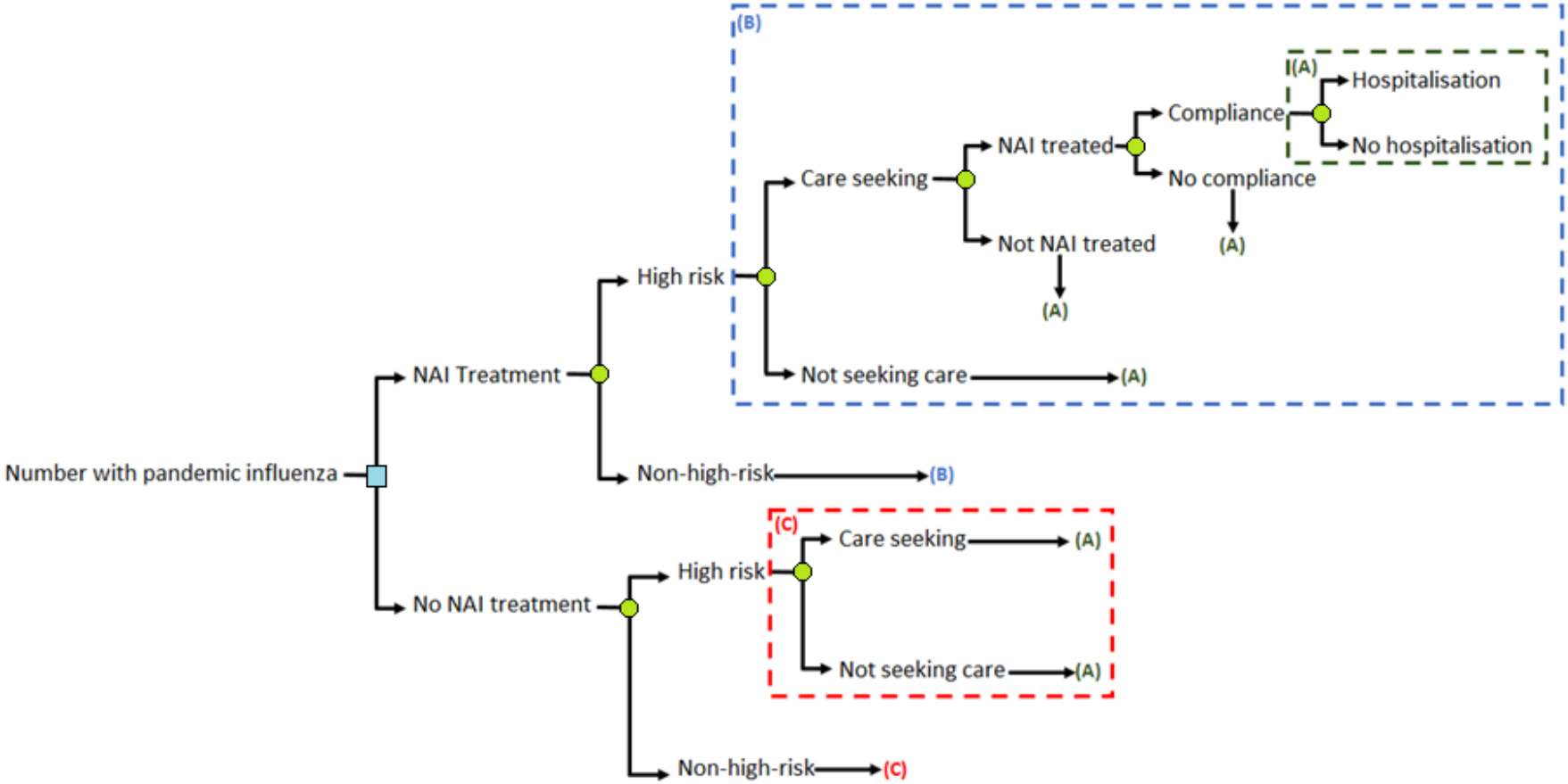


Figure 24: Decision tree model comparing outcomes in 'NAI treatment' and 'no NAI treatment' groups for patients with symptomatic pandemic influenza

A, B and C in the decision tree above indicate repeating arms of the tree

Parameter	Value	Range (probability distribution)	Source
Total population	62280000	Fixed	[265]
Clinical attack rate (CAR)			
2009 pandemic	7%	Fixed	Box A1, page 31 of [269]
Transmissibility scenario 1	20%	Fixed	[245]
Transmissibility scenario 2	30%	Fixed	[245]
% Seeking outpatient care (non-high-risk)*			
2009 pandemic	34.5%	32% to 43% (Uniform)	[246]
Severity 1	60%	Fixed	[245]
Severity 2	70%	Fixed	[245]
% Seeking outpatient care (high-risk)			
2009 pandemic	51.2%	43.2 to 54.2 (Uniform)	Assumed from [270]
Severity 1	71.2%	Fixed	Assumed in line with: [270] and [245]
Severity 2	81.2%	Fixed	Assumed in line with: [270] and [245]
% of high-risk individuals	30%	27% to 33% (Uniform)	[271]
Case hospitalisation risk (non-high-risk)			
2009 pandemic	0.30%	0.27% to 0.33% (Uniform)	From Annex G, page 171 of [41]
Severity 1	1.05%	Fixed	[245]
Severity 2	4.00%	Fixed	[245]
Case hospitalisation risk (high-risk)			
2009 pandemic	1.50%	1.35% to 1.65% (Uniform)	Assumed from page 10 of [267] that at-risk groups would have an increased risk of hospital admission by five times
Severity 1	5.25%	Fixed	Assumed in line with: [245] and [267]
Severity 2	20.00%	Fixed	Assumed in line with: [245] and [267]
% of care-seeking patients prescribed NAI	73%	60% to 85% (Triangular)	[179]
Prescription of NAIs for non-influenza ILI as a % of those receiving NAIs for influenza	40%	30% to 50% (Uniform)	Assumed from [153]
NAI (any time) compliance (as a %)	64%	55% to 70% (Uniform)	[179]

Effectiveness of NAI treatment (<48 hours from symptom onset) on hospitalisation (risk reduction) (Intention-to-treat-infected)	63%	83% to 19% (Triangular)	Assumed for pandemic influenza from [88]
Mortality risk (in-hospital)			
2009 Pandemic	5.3%	Fixed	[272]
Severity 1	5.3%	Fixed	Assumed to be fixed between scenarios
Severity 2	5.3%	Fixed	Assumed to be fixed between scenarios
Costs **Before being input into the model, all costs listed below were inflated to the 2017 UK Pound Sterling (£)** **(The hospital & community health services (HCHS) index)**			
Cost of GP consultation	£ 37		[273] and [274]
Cost of telephone consultation	£ 22		[273] and [274]
Average (weighted) outpatient consultation cost	£24.2	£22 to £37 (Truncated log normal)	
Cost of NAI (+delivery)	£ 16	Fixed	[275]
High-risk patients: Cost of Hospitalisation due to influenza (per patient)	£1,727	£1,263 to £2,075 (Truncated log normal)	[276] and [274]
Low-risk patients: Cost of Hospitalisation due to influenza (per patient)	£436	£307 to £504 (Truncated log normal)	[276] and [274]
This includes consultations made through the National Pandemic Flu Service (NPFS) telephone line			

Table 13: Input parameters used to estimate the number of outcomes averted by NAI treatment and the cost per averted hospitalisation

7.3 Results

The decision tree model estimated that in a 2009-like pandemic scenario, in the base-case scenario (no NAI treatment) there would be 28,773 hospitalisations in the overall population, and an estimated that 1.9 million regimens of NAIs would be dispensed for outpatient treatment. NAI treatment would have averted 4,034 (14%) hospitalisations in a population of 62.28 million (65 hospitalisations averted/million population) at a cost of £7,110 per hospitalisation averted (Table 14). The cost to avert one hospitalisation was £2,238 in high-risk populations and £20,473 in the non-high-risk population

(Table 14). Results from the four hypothetical pandemic scenarios are presented in Table 14.

The sensitivity analysis where the proportion of care-seeking patients who do so within 48 hours of symptom onset was varied, while all other variables were kept constant, suggested that in the 2009-like pandemic scenario, the percentage of averted hospitalisations in the overall population lowered from 14.0% (assuming 100% of care-seeking patients do so ≤48 hours of symptom onset) to 3.5% (assuming 25% of care-seeking patients do so ≤48 hours of symptom onset) (Table 14-15).

The probabilistic sensitivity analyses revealed that using just the middle values of input parameters in a simple multiplicative model without accounting for uncertainty in parameter estimates (by sampling from probability distributions) was likely to overestimate the number of hospitalisations averted and underestimate the cost per averted hospitalisation. For the 2009-like pandemic scenario, multiplying the middle values of input parameters (Table 14) overestimated the overall number of averted hospitalisations by 28% and underestimated the overall cost per-averted hospitalisation by 34% when compared to the mean estimated from the Monte Carlo simulation (Table 16). Similar differences in estimates were observed in the other scenarios as well.

The sensitivity analyses, based on a 2009-like pandemic scenario, indicated that NAI effectiveness had the greatest impact on both the total number of hospitalisations averted, as well as on the cost per hospitalisation averted (see Figure 25 for 2009 scenario). When the NAI effectiveness was varied from 19% to 83%, the resulting overall proportion of averted hospitalisations ranged

between 6% and 15%, at a cost per averted hospitalisation of £6,936 to £19,338. The percentage of care-seeking patients who were prescribed NAI, the proportion of NAI prescriptions to non-influenza patients, and NAI treatment compliance were in the top three influential parameters for one or both outcomes (Figure 25). In the two-way sensitivity analysis, treatment compliance level was varied along with NAI effectiveness beyond the 95% confidence intervals of the input parameters (from 90% effectiveness to 10% effectiveness). Increased compliance levels were consistently associated with an increased number of averted hospitalisations across NAI effectiveness estimates (Figure 26). The impact of prescribing NAIs to non-influenza ILI patients had a considerable effect on the cost per averted hospitalisation. For the 2009-like pandemic scenario, this ranged from £7,983 per averted hospitalisation (wastage factor=30%) to £11,032 per averted hospitalisation (wastage factor=70%).

	NAI regimens dispensed to pandemic influenza patients	NAI regimens dispensed to non-influenza ILI patients	Total NAI regimens dispensed	Total Hospitali-sations	NAI costs (£)	Total costs (£)	Hospitali-sations averted (%)	Increment al cost per averted hospitalisa tion (£)	Deaths averted, No.
2009 A(H1N1) pandemic									
High-risk patients									
No NAI treatment	NA	NA	NA	19,618	NA	56,713,354	NA	NA	NA
NAI treatment	488,833	195,533	684,367	16,662	12,397,546	63,330,048	2,956 (15.1)	2,238	157
Non-high-risk patients									
No NAI treatment	NA	NA	NA	9,155	NA	37,976,039	NA	NA	NA
NAI treatment	891,102	356,441	1,247,543	8,077	22,599,693	60,043,645	1,078 (11.8)	20,473	57
Total population									
No NAI treatment	NA	NA	NA	28,773	NA	94,689,393	NA	NA	NA
NAI treatment	1,379,935	551,974	1,931,910	24,739	34,997,239	123,373,693	4,034 (14.0)	7,110	214
20% CAR- Severity 1									
High-risk patients									
No NAI treatment	NA	NA	NA	196,182	NA	456,499,003	NA	NA	NA
NAI treatment	1,942,239	776,896	2,719,135	155,069	49,258,106	425,367,141	41,113 (21.0)	CS	2,179

Non-high-risk patients								-	
No NAI treatment	NA	NA	NA	91,552	NA	188,534,796	NA	NA	NA
NAI treatment	3,819,010	1,527,604	5,346,613	75,383	96,855,827	277,409,315	16,168 (17.7)	5,497	857
Total population								-	
No NAI treatment	NA	NA	NA	287,734	NA	645,033,798	NA	NA	NA
NAI treatment	5,761,249	2,304,500	8,065,748	230,452	146,113,933	702,776,456	57,281 (19.9)	1,008	3,036
20% CAR- Severity 2									
High-risk patients									
No NAI treatment	NA	NA	NA	747,360	NA	1,544,470,684	NA	NA	NA
NAI treatment	2,215,026	886,010	3,101,036	568,740	56,176,380	1,251,387,276	178,620 (23.9)	CS	9,467
Non-high-risk patients									
No NAI treatment	NA	NA	NA	348,768	NA	339,398,172	NA	NA	NA
NAI treatment	4,455,511	1,782,204	6,237,716	276,910	112,998,465	416,924,159	71,858 (20.6)	1,079	3,808
Total population									
No NAI treatment	NA	NA	NA	1,096,128	NA	1,883,868,856	NA	NA	NA
NAI treatment	6,670,537	2,668,215	9,338,751	845,650	169,174,845	1,668,311,434	250,478 (22.9)	CS	13,275
30% CAR- Severity 1									
High-risk patients									
No NAI treatment	NA	NA	NA	294,273	NA	684,748,504	NA	NA	NA

NAI treatment	2,913,359	1,165,344	4,078,702	232,603	73,887,160	638,050,710	61,670 (21.0)	CS	3,269
Non-high-risk patients									
No NAI treatment	NA	NA	NA	137,327	NA	282,802,193	NA	NA	NA
NAI treatment	5,728,514	2,291,406	8,019,920	113,075	145,283,741	416,113,973	24,252 (17.7)	5,497	1,285
Total population									
No NAI treatment	NA	NA	NA	431,600	NA	967,550,697	NA	NA	NA
NAI treatment	8,641,873	3,456,749	12,098,622	345,678	219,170,901	1,054,164,684	85,922 (19.9)	1,008	4,554
30% CAR- Severity 2									
High-risk patients									
No NAI treatment	NA	NA	NA	1,121,040	NA	2,316,706,026	NA	NA	NA
NAI treatment	3,322,538	1,329,015	4,651,554	853,111	84,264,570	1,877,080,913	267,929 (23.9)	CS	14,200
Non-high-risk patients									
No NAI treatment	NA	NA	NA	523,152	NA	509,097,257	NA	NA	NA
NAI treatment	6,683,267	2,673,307	9,356,574	415,364	169,497,697	625,386,237	107,788 (20.6)	1,079	5,713
Total population									
No NAI treatment	NA	NA	NA	1,644,192	NA	2,825,803,283	NA	NA	NA
NAI treatment	10,005,805	4,002,322	14,008,127	1,268,475	253,762,267	2,502,467,151	375,717 (22.9)	CS	19,913

Table 14: **Outpatient NAI treatment for averting outcomes and the cost per averted hospitalisation**

	Total outpatient consultations			Hospitalisations averted (%)		
	75% seek care within 48 hours	50% seek care within 48 hours	25% seek care within 48 hours	75% seek care within 48 hours	50% seek care within 48 hours	25% seek care within 48 hours
High-risk patients	502,226	334,817	167,409	2,217 (11.3)	1,478 (7.5)	739 (3.8)
Non-high-risk patients	91,5516	610,344	305,172	808 (8.8)	539 (5.9)	269 (2.9)
Total population	1,417,742	945,161	472,581	3,026 (10.5)	2,017 (7.0)	1,009 (3.5)

Table 15: Impact of promptness of care-seeking on hospitalisations averted in a 2009-like pandemic scenario

	Hospitalisations averted (%) (95% Confidence Interval)	Cost per hospitalisation averted (£) (95% Confidence Interval)
2009 A(H1N1) pandemic		
High-risk patients	2,266 (12.2) (1,075 to 3,500)	3,998 (1,698 to 9,171)
Non-high-risk patients	876 (9.4) (410 to 1,370)	28,182 (16,417 to 53,780)
Total population	3,142 (11.2) (1,500 to 4,750)	10,730 (5,944 to 21,229)
20% CAR- Low severity		
High-risk patients	33,169 (17.8) (16,068 to 49,864)	CS (CS to 1,415)
Non-high-risk patients	14,026 (15.0) (6,764 to 21,076)	7,727 (4,579 to 15,027)
Total population	47,195 (16.9) (22,891 to 70,713)	2,233 (787 to 5,454)
20% CAR- High Severity		
High-risk patients	144,027 (20.3) (70,162 to 217,547)	CS*
Non-high-risk patients	62,306 (17.5) (30,372 to 93,491)	1,720 (872 to 3,637)
Total population	206,334 (19.4) (100,419 to 310,061)	CS (CS to 519)
30% CAR- Low Severity		
High-risk patients	49,727 (17.8) (24,116 to 74,453)	CS (CS to 1,433)
Non-high-risk patients	21,026 (15.0) (10,174 to 31,439)	7,731 (4,558 to 14,967)
Total population	70,754 (16.9) (34,238 to 105,421)	2,234 (751 to 5,428)
30% CAR- High severity		
High-risk patients	216,012 (20.3)	CS*

	(104,165 to 321,420)	
Non-high-risk patients	93,423 (17.5) (45,072 to 139,015)	1,507 (879 to 3,598)
Total population	309,434 (19.4) (150,794 to 457,639)	CS (CS to 508)

*CS: Cost Saving; *95% confidence intervals are cost saving as well*

Table 16: Results from the probabilistic sensitivity analysis

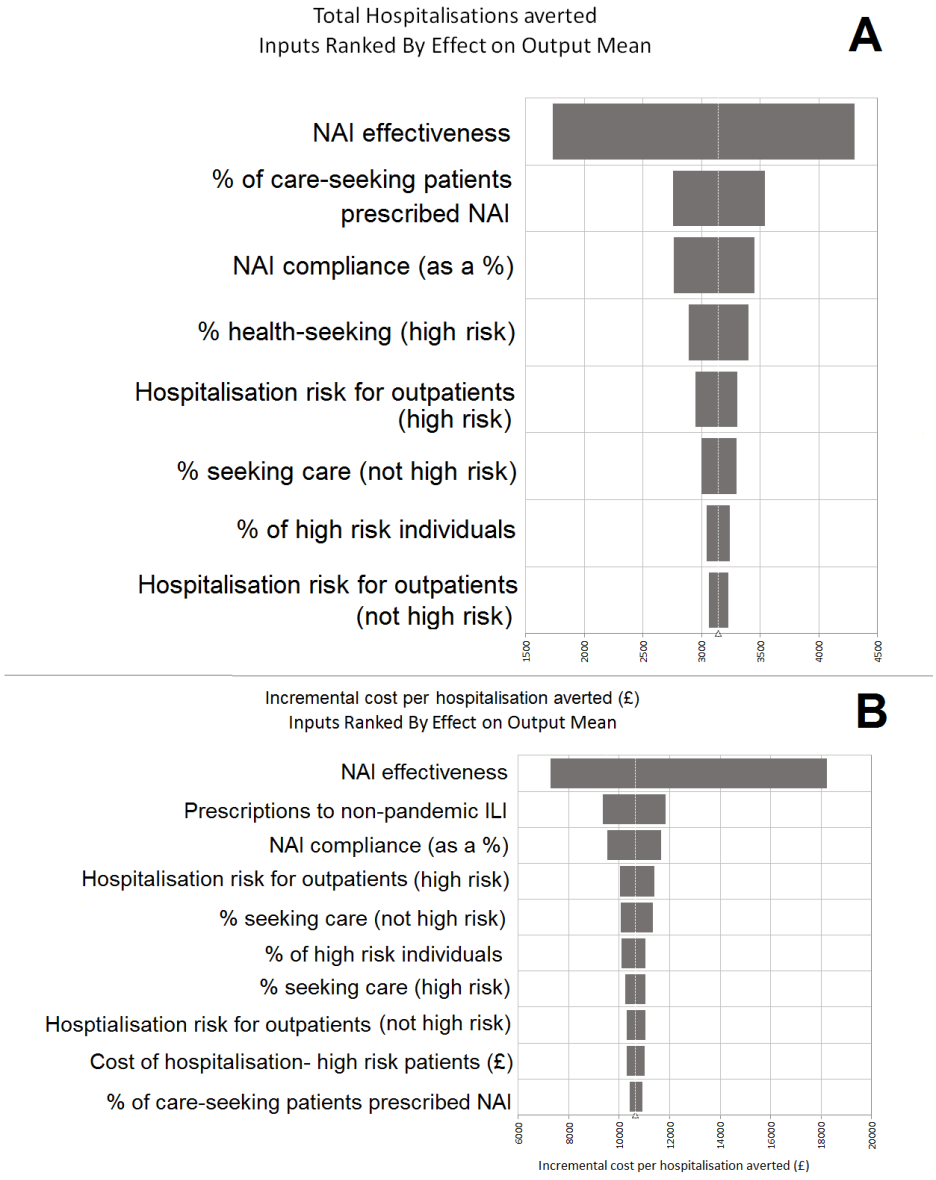


Figure 25: Probabilistic sensitivity analysis. (A) shows the impact of various parameters on total hospitalisations averted, and (B) shows the impact of various parameters on cost-effectiveness (2009-like pandemic scenario).

NAI: Neuraminidase inhibitors; ILI: Influenza-like illness

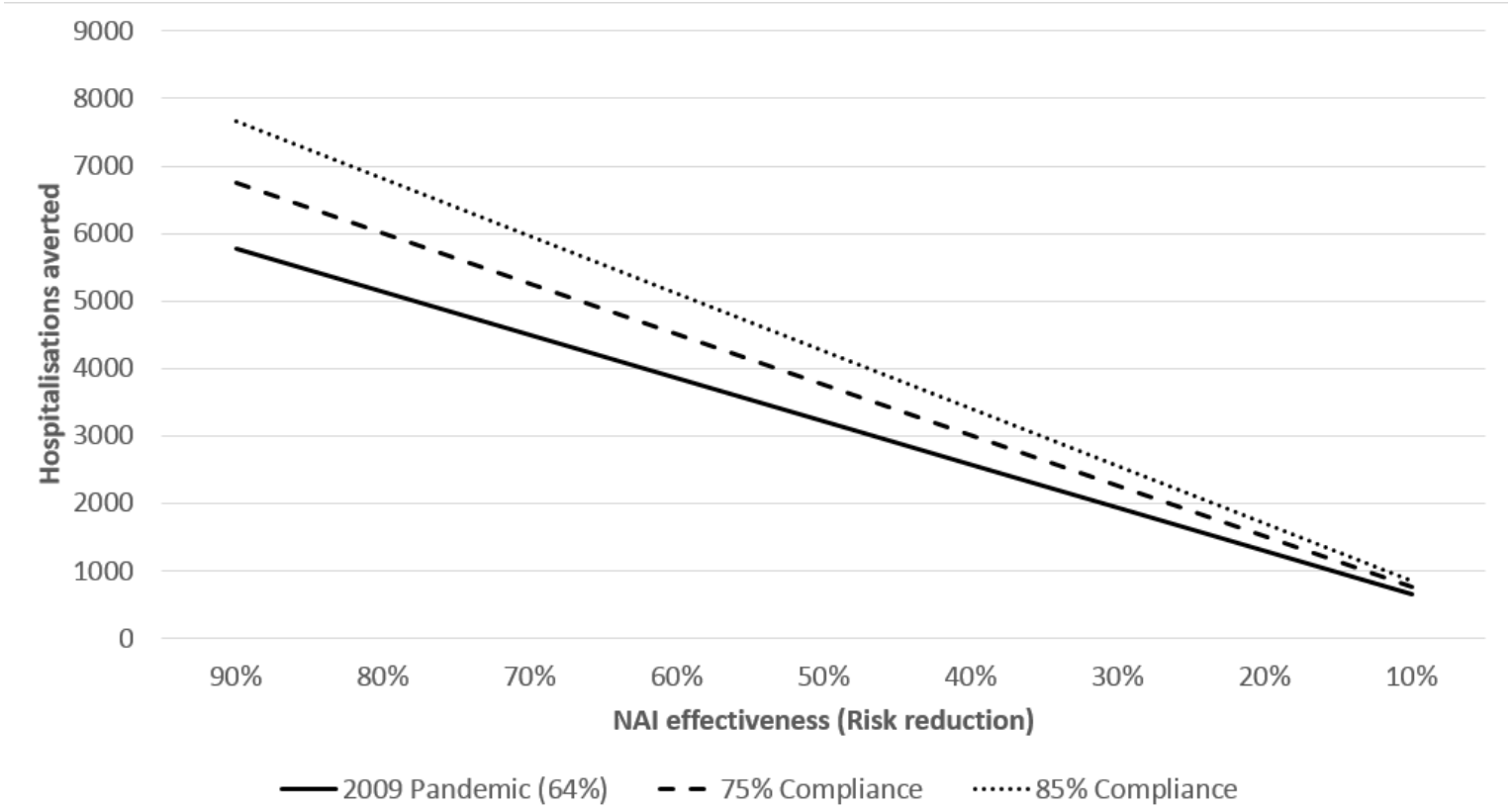


Figure 26: Impact of varying treatment compliance on hospitalisations averted at different NAI effectiveness estimates.

This plot is based on a 2009-like influenza pandemic where the number of hospitalisations in the base-case scenario was estimated to be 24,739; NAI: Neuraminidase inhibitor

7.4 Discussion

The findings of this study suggest that community-based NAI treatment would avert a significant proportion of hospitalisations and deaths, particularly in high-risk patients, across the pandemic scenarios that were explored in this analysis. However, a substantial number of hospitalisations and deaths would continue to occur even with community-based NAI treatment. The proportion of hospitalisations averted by NAIs could be an important consideration while planning for conditions when hospital capacity could be exceeded. Community-based NAI treatment was seen to be cost-saving for the overall population in a pandemic with a high CAR and high severity, and cost-saving for patients at high risk of complications from influenza across all the pandemic influenza scenarios tested. The value of NAI treatment for population groups not at high risk and for milder pandemic scenarios will have to be determined by careful review under country-specific willingness-to-pay thresholds and the desire to reduce the number of hospitalisations and potential hospital capacity issues.

NAI treatment for pandemic influenza has generally been shown to be cost-effective, when compared to no NAI treatment.[261-263,277] Previous studies have found that NAI effectiveness is, by far, the most influential factor affecting the numbers of outcomes averted and the associated cost-effectiveness.[153,261] The sensitivity analysis of the current support this finding. A study based in the United States that used a similar model[153] showed slightly lower proportions of hospitalisations averted due to NAI treatment when compared to the current study, but the difference could be because of the lower level of treatment effectiveness assumed in the U.S. study. The U.S. study further found that while

NAI treatment averted many hospitalisations, large numbers of hospitalisations would remain,[153] which is similar to what the current study suggests.

This study found that variations in NAI prescription rate, treatment compliance and healthcare-seeking behaviour (to include the choice to seek care and the promptness in care-seeking) impacted considerably on the outcomes, suggesting that even with a drug of fixed effectiveness, factors relating to healthcare-seeking and healthcare delivery could significantly influence the total number of hospitalisations and deaths averted. These data indicate that a successful pandemic stockpiling strategy must be linked to operational procedures which optimise timely access to antivirals, widespread treatment implementation, and high levels of compliance in targeted groups.

While NPFS consultations as well as ILI-related GP consultations were considered in the decision tree model, the input parameter for the proportion of any influenza-related consultations (NPFS or GP consultation) that resulted in NAI prescriptions was largely based on data from the NPFS. The decision tree model used in this study focused specifically on patients with symptomatic influenza (the primary node), which meant that the proportion of consultations that resulted in NAI prescriptions was, in fact, the proportion of consultations that resulted in NAI prescriptions within a population of patients with symptomatic influenza. Based on data from the NPFS, this proportion was assumed to be 73% (ranging from 60% to 85%). However, during an ongoing pandemic, laboratory-confirmation of all influenza patients prior to NAI prescription is not practical. Therefore, it is inevitable that patients without pandemic influenza will receive a certain proportion of all prescribed NAIs. Although, data on this from the 2009-2010 pandemic are quite scarce, an 'NAI

wastage factor' of 40% was assumed in this study based on previous modelling studies (Table 13). While this study assumed a fixed 'NAI wastage factor', the proportion of patients without pandemic influenza consulting the NPFS is likely to be linked to the timing during an ongoing pandemic. It likely that the proportion of true influenza patients consulting the NPFS during the peaks of a pandemic is higher than that during the tails of the outbreak. Consequently, the proportion of NAIs being prescribed to non-influenza ILI patients will also vary accordingly; it will likely be lower during the peaks of a pandemic, and higher during the early and late stages. Further influencing the proportion of NAIs prescribed to non-influenza ILI is the timing of the pandemic relative to other seasonal respiratory pathogens like RSV.

One recognised limitation of some previous economic analyses of NAI treatment has been that entire populations have been modelled homogenously without accounting for the increase in the likelihood of influenza-related care-seeking and complications in patients with underlying at-risk conditions.[261,262] In the current study, the propensity to seek care and CHR were varied by patients' at-risk status. The significance of this is that countries with limited resources could consider obtaining smaller antiviral stockpiles to target at-risk population groups and avert a higher number of hospitalisations and deaths for each antiviral course dispensed than if they adopted a treat-all approach.

The CAR was an important factor in determining the number of NAI regimens that would be needed for community-based treatment. The decision tree model used in this study showed that a highly transmissible, but low severity pandemic would require a larger NAI stockpile than a pandemic with lower transmissibility and higher severity. However, across all pandemic scenarios,

the number of NAI regimens dispensed for outpatient treatment was well below the UK's published national NAI stockpile size of almost 40 million courses of the drug.[278]

Updated NAI effectiveness estimates from seasonal influenza data were used in this study, although observational data from the 2009 A(H1N1) pandemic in a high-severity (high risk of hospitalisation) population suggest similar estimates of NAI effectiveness (≤48 hours from symptom onset).[279] NAI effectiveness was assumed to be the same in patients with and without at-risk conditions. While there is some evidence to suggest that the level of effectiveness against hospitalisation is similar for both groups,[279] there is also evidence that suggests a reduction in NAI effectiveness in patients with at-risk conditions.[280]

The limitations of this study are as follows: a decision tree model (not a transmission dynamic model) was used, and it was assumed that NAI treatment had no effect on transmission. There is evidence to suggest that NAI treatment, at a population level, is likely to have minimal impact on influenza transmission.[242] However, decision tree models are known to be limited, especially in their ability to describe the change in influenza attack rates in different risk groups over the course of a pandemic.[277] A comparison of static and dynamic models of NAI treatment for pandemic influenza concluded NAI treatment was seen to be cost-effective with both modelling paradigms; although the associated cost-effectiveness ratios were seen to differ.[277] Due to a lack of evidence specific to hospitalisation, benefits of NAI treatment >48 hours of symptom onset were not considered in the decision tree model. NAI treatment has, however, been shown be beneficial even when started beyond 48 hours from symptom onset.[92] The use of NAIs may be associated with additional costs

to the healthcare system due to possible adverse effects of NAIs[281] but these have not considered as most side effects are known to be minor.[88] Finally, the multiplier for high-risk patients was assumed to remain constant between severity scenarios resulting in a CHR as high as 20%. CHRs of 20%, even for high-risk patients, may be unlikely.

To conclude, findings from this study show that NAI treatment in outpatients can be cost-saving, particularly for population groups at high risk of influenza-related complications. Model-based estimates like these of the potential hospitalisations, deaths and costs associated with different pandemic scenarios can help countries consider different treatment options and inform stockpiling decisions while developing pandemic preparedness plans. NAI stockpiling decisions are also influenced by other costs to the healthcare system related to storage and maintenance of the NAI stockpile. Currently, the shelf-life for the 75 mg hard capsules of oseltamivir phosphate that comprise most of the NAI stockpile is estimated to be 10 years if stored as per instructions.[282] However, influenza pandemics cannot be predicted, and NAI stockpiles could remain unused at the end of their shelf-life, or they may be rendered ineffective or less relevant by the development of antiviral drug resistance or newer, more effective influenza antiviral therapies. Additionally, evidence suggests that in-hospital NAI treatment may also be associated with protective effects[90,283] and NAI treatment has been shown to be cost-effective if the benefits of NAI usage are confined only to those treated in hospital.[284] If a pandemic treatment policy was pursued which combined community use of NAIs to prevent hospital admission and NAI treatment of hospitalised patients to reduce mortality, then cost-effectiveness and stockpile strategies across both scenarios would need to

be considered. Future research in optimising NAI distribution to risk groups during a will further inform the cost-effectiveness of stockpiling.

8 Overall Discussion

The work presented in this thesis draws from concepts in epidemiology, biostatistics, computer science, social simulation and health economics. Using an interdisciplinary approach, five studies were performed using different modelling approaches to address the thesis aim of evaluating the impact of NAI treatment on hospitalisation, and on subsequent hospital length of stay (LoS) in patients with influenza A(H1N1)pdm09 virus infection.

8.1 Thesis contributions

This thesis makes contributions to existing knowledge in three main ways:

1) **Development of a novel coupled behavioural-epidemic model to evaluate the impact of NAI treatment beyond drug effectiveness**: The model consists of a SEIR model and an ABM that has been derived with the help of the EABSS framework and includes the development of a novel behavioural model, which is a simplified version of the well-established COM-B model of behaviour change. NAI drug estimates from rigorous analysis of empirical data, using the IPD approach, were fed into the novel behavioural-epidemic model to quantify, in public health terms, the impact of NAI treatment. The coupled behavioural-epidemic model was then extended to a hybrid model that also included a DES to represent a hospital. It is easy to further extend this hybrid model, as necessary, for future applications; easy extensibility being a core principle adopted from the software engineering community.
2) **Adding to the evidence base on NAI effectiveness estimates for pandemic influenza-related hospitalisation using a large, global**

dataset: The IPD meta-analyses described in Chapters 4 and 5 are, to the best of my knowledge, the first and the only IPD meta-analyses of real-world data investigating NAI effectiveness in reducing hospitalisation and hospital LoS in patients with pandemic influenza. In addition to the effectiveness of NAI treatment for the overall study population of clinically suspected and laboratory-confirmed pandemic influenza patients, these IPD meta-analyses also contribute to the evidence base by reporting NAI effectiveness in a number of clinically meaningful sub-populations.

3) **Development of a spreadsheet-based decision-analytic model to evaluate cost-effectiveness of community-based NAI treatment:** A spreadsheet-based health economic model has been developed in Chapter 7. Input parameters from the UK's experience of the 2009 influenza pandemic were used to inform this model, and the results suggested that community-based NAI treatment would be cost-effective in patients at high-risk of complications from influenza. The spreadsheet tool can be adapted to other settings to evaluate cost-effectiveness of community-based NAI treatment. It has been provided as an Excel file (Appendix 6).

8.2 Summary of main findings

During the 2009-10 A(H1N1) influenza pandemic, NAI drugs were used for treatment of symptomatic patients largely in the expectation that they would help reduce complications from influenza. NAIs were licensed on the basis of reducing duration of symptoms in infected patients, but there was not much *a*

priori evidence at the time to suggest a reduction in complications from influenza. This thesis, using real-world data from the 2009-10 pandemic, contributed new data to the evidence base by evaluating the impact of NAI treatment on hospitalisations and hospital LoS in patients with pandemic influenza. The studies performed to achieve the thesis aim included two IPD meta-analyses of drug effectiveness and three broader studies exploring the public health impact of NAI treatment using computational simulations and a health economic model.

Study 1 (Chapter 3) evaluated the effectiveness of community-based NAI treatment on hospitalisations in patients with severe A(H1N1)pdm09 infection, and found that NAI treatment was associated with a significant reduction in likelihood of hospitalisation (OR: 0.24; 95% CI: 0.20-0.30). The high overall hospitalisation rate observed in the study population meant that these findings may not be generalisable to the wider community-based population. Nevertheless, these findings do suggest that NAI treatment is most likely to benefit influenza patients with severe illness who are at high risk of hosptialisation. The primary analysis in Study 2 (Chapter 4) looked at the effectiveness of a pragmatic 'treat-at-admission' NAI treatment strategy on hospital LoS in patients with pandemic influenza. The study found that when patients with pandemic influenza were treated with NAI on admission to hospital, compared with no treatment or later initiation of NAI treatment, LoS was reduced by 19% [aIRR:0.81 (0.78-0.85)], median decrease 1.19 days (IQR: 0.85-1.55).

Study 3 (Chapter 5) decribed the implementation of a novel behavioural-epidemic coupled model that looked at public health interventions that could

help maximise the impact of a community-based NAI treatment strategy (NPFS). This study demonstrated how using a simple behavioural model, and incorporating elements of Capability, Opportunity and Motivation into an epidemic model, can lend insights into how public health strategies could be devised to improve NAI collection rates. In Study 4 (Chapter 6), the extended behavioural-epidemic model described in Study 3 suggested that public health interventions that are aimed at strengthening Capability are likely to result in a significantly improved impact of community-based NAI treatment. The study also found that treating influenza patients with NAI at hospital admission could ease hospital bed occupancy by reducing petients' subsequent LoS. Finally, Study 5 (Chapter 7) used a decision tree health economic model and found that community-based NAI treatment was cost-effective for the overall population in a pandemic with high transmissibility and high severity, and cost-effective for patients at high risk of complications from influenza across a range of pandemic influenza scenarios.

The findings of this thesis have important implications for pandemic preparedness planning, especially the role of NAI treatment in reducing complications from influenza. Across the five studies performed in this thesis, patients at high risk of complications from pandemic influenza are consistently seen to benefit the most from NAI treatment. While the overall number of NAI regimens required during a future pandemic is unlikely to exceed the UK's current NAI stockpile,[276] the cost-effectiveness of NAI stockpiling could be improved, especially for countries with limited resources, by targeting high-risk patients in the population. Chapters 5, 6 and 7 highlight the importance of NAI uptake during an ongoing pandemic. Beyond the availability of a stockpile, the

success of an NAI treatment strategy during an ongoing pandemic is influenced by antiviral distribution strategies and compliance rates. During the 2009-10 influenza pandemic, while the NPFS helped dispense about 1.8 million courses of NAI,[86] its success in relieving pressure off GP practices is still not clear. It is likely that the primary care consulting experience (NPFS vs GP consultation) from the relatively milder 2009-10 A(H1N1) influenza pandemic may not be generalisable to a more transmissible or more severe infleunza pandemic. More severe pandemics may be associated with heightened levels of public concern and, consequently, higher rates of influenza-related healthcare consultation. Regardless of the severity of the pandemic, findings from this thesis indicate that interventions that prioritise and ensure timely delivery of NAI treatment to patients at increased risk of complications from pandemic influenza are likely to have the greatest population-level impact.

8.3 Limitations

One important limitation of the IPD meta-analyses described in this thesis is that they are based on observational data and are subject to biases that are inherent to the study design. It is not realistic to expect current pandemic preparedness plans to be informed by an RCT of NAI effectiveness in pandemic influenza patients, given that pandemics are rare events. Even if such a trial were to be conducted during the course of a future pandemic, its conclusions would only impact succeeding pandemic preparedness plans. Therefore, much of decision-making regarding the role of NAIs for future pandemics will have to be made using the observational evidence harnessed from the 2009-10 influenza pandemic.

For Studies 3 and 4, the main limitation was related to the data used. Data relating to public attitudes towards antiviral and the NPFS were largely absent. The official NPFS evaluation document states that a survey was conducted amongst members of the public soon after closure of the service (February 2010) to retrospectively evaluate the attitudes of the public towards antiviral medications and towards the NPFS. The raw data from this study have not been published till date. I had originally intended to obtain these data and analyse the survey results to inform the ABM input parameters. In attempting to do so, I first contacted the Service Centre for the NPFS at the NHS. I was then instructed to make an FOI (Freedom of Information) application requesting the data directly to the Department of Health and Social Care. The Department of Health and Social Care confirmed to me that the survey was conducted by the Central Office of Information (COI) in 2010, and that since the COI had recently been merged with the Cabinet Office, the Cabinet Office would be most likely to have the data. I then made an FOI request to the Cabinet Office (FOI Reference: FOI326093), who wrote back to me stating:

"I am writing to advise you that following a search of our paper and electronic records, I have established that the information you requested is not held by the Cabinet Office."

Hence, using empirical data to inform the behavioural model was not possible. Therefore, the COM-B weights for the behavioural model in Studies 3 and 4, were derived from other settings where available,[231,232] and unavailable parameters were calibrated.

8.4 Directions for further research

Literature from behavioural economics consistently indicate that individuals are notoriously poor at predicting future behaviour.[173,285,286] It is, therefore, crucial that behavioural data used to inform model parameters be collected, not retrospectively or for a hypothetical future pandemic, but during an ongoing outbreak. Methodologically, there are several avenues for extending the behavioural model used in Studies 3 and 4. These could include incorporating more elements of the COM-B model within the formalised behavioural model, and also improving the implementation of the model used. Accordingly, directions for further research have been summarised below.

Epidemiology:

1) Strengthening the conduct of observational research for ascertaining NAI effectiveness along the lines that have been reported previously.[250] Briefly, this will require prospective collection of standardised data on illness onset, NAI treatment status, concomitant treatment details, clinical presentation, comorbidities, and outcomes data.
2) Undertaking the development of a more explicitly stated operational model of a hospital to evaluate the impact of NAI treatment on hospital resources (including staff requirements, bed occupancy, ICU capacity, the need for mechanical ventilators etc.).
3) Improving collection of behavioural data during outbreak periods. The COM-B framework can serve as a guide to inform data collection. Better temporal data collected on public attitudes during an ongoing pandemic can help refine behaviour-epidemic models.

4) A health economic evaluation that also accounts for the indirect effects of an influenza pandemic.

Computer simulation:

1) Improving computational efficiency, particularly in improving spatial representation, to allow modelling of larger populations. There are two broad ways of achieving this. The first way is by increasing computational capacity (using high performance clusters). The second way is by modifying the implementation of the ABM. One alternative implementation technique that can be considered for future work is an event-based implementation of the ABM.[287]
2) Applying the formalised behavioural model developed in this thesis to case studies involving other diseases/scenarios, and adjusting the model/implementation structure accordingly.
3) Applying fuzzy logic to model individual decision-making in the behavioural model described in Studies 3 and 4, in an attempt to better represent human decision making under conditions of uncertainty. Indeed, research in applying fuzzy logic to the novel COM-B-based model developed in this thesis is currently being undertaking by a student in the School of Computer Science, University of Nottingham.[288]

9 Closing Remarks

To conclude, it can be claimed that the thesis aims have been achieved through the research carried out in this thesis. The findings from this thesis indicate that NAI treatment given in the community to severe pandemic influenza patients is associated with a decreased likelihood of hospital admission, and NAI treatment given to hospitalised patients with pandemic influenza can reduce their LoS by about 1.19 days. The computational simulations showed that even a seemingly modest reduction in LoS of just a little over a day can have a significant impact on hospital resources. The health economic analysis revealed that community-based NAI treatment is likely to be cost-effective for populations at high-risk for influenza-related complications.

The findings of this thesis are, largely, in agreement with current advice and recommendations by several major public health organisations on NAI treatment for patients with influenza,[204,205,289] and support therapeutic NAI treatment, especially for patients with severe illness, in pandemic preparedness planning. The computational model in Study 4 and the health economic model in Study 5 demonstrate how several factors beyond absolute drug effectiveness estimates can impact on an NAI treatment strategy, and even a modestly effective treatment can potentially avert a significant number of adverse outcomes.

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11 Appendices

Appendix 1: Minimum dataset requirement for the PRIDE IPD meta-analyses

Data variables	**Description/definition**
About the data	
1. Source of data	E.g. hospital or emergency department, community/ GP sentinel data, national surveillance data etc.
2. Patient identifier	A unique identifier for each patient e.g. a specific number that corresponds to each patient
Patient characteristics	
1. Age	Date of birth/ age at hospital admission
2. Sex	Male/ female
3. Any other risk factors	Such as obesity/ BMI, smoking status etc.
4. Seasonal influenza vaccination status	Yes/no
Clinical characteristics	
1. Underlying Co-morbidities a) Asthma b) COPD c) Pneumonia d) Other pulmonary diseases e) Other chronic conditions	List of underlying medical conditions for each individual patient
2. Pregnancy	Pregnancy/ fetal wellbeing assessments e.g. weeks of gestation including pregnancy outcome
3. Clinical examinations a) Influenza presenting symptoms on hospital admission b) Admission laboratory examinations performed	- Date of symptoms onset - List of symptoms presenting at hospital admission - E.g. technique used for laboratory confirmation of influenza AH1N1 e.g. RT-PCR, viral culture, etc.

Data variables	Description/definition
c) Chest x-ray examination	- Date chest x-ray taken - Findings upon x-ray examination
Treatment characteristics	
1. In-hospital antiviral treatment (oseltamivir, zanamivir etc.)	- Date of prescription/treatment including name of antiviral agent (i.e. oseltamivir/ zanamivir), route of administration(e.g. inhaled, oral , IV), dosage and dose frequency, treatment duration
2. In-hospital antibiotics treatment	- List of names of administered antibiotics including route(e.g. inhaled, oral , IV), dose and dose frequency, duration and dates prescribed
3. Other in-hospital additional treatment therapies e.g. corticosteroids, antipyretics etc.	- List of names of other administered treatments including route(e.g. inhaled, oral , IV), dose and dose frequency, duration and dates prescribed
Outcome (please provide data on at least one of the outcome measures)	
1. Hospitalisation	- Dates of admission and discharge - Primary admitting diagnosis for cases admitted to hospital - Secondary diagnoses
2. Pneumonia	- Yes/ no, Unilateral or bilateral etc.
3. Admission to critical care facilities i.e. ICU and/ or HDU	- Specific dates of transfer and discharge to/ from the HDU or ICU - Primary cause of transfer to HDU/ ICU - Need for invasive mechanical ventilation (MV) including non-invasive mechanical ventilation(NIV) and ECMO - Other severity scores e.g. duration MV, NIV, ECMO
4. Mortality in hospital	- Date of death - Primary cause of death

Appendix 2: Standardised data dictionary

Variable name in Stata	Description	Coding
About the data		
study_group_id	Study group identifier	Auto-numbering (_n); string
patid	Study specific patient ID as provided by study groups; this will only be retained in the individual datasets but dropped from the pooled dataset	string
auto_patid	Auto-numbered patient ID generated for each study group dataset; this will only be retained in the individual datasets but dropped from the pooled dataset	Auto-numbering (_n)
pride_patid	Unique patient identifier created by concatenation of study_group_id and auto-numbered patient id (auto_patid)	string
country	Country identifier	string
Patient characteristics		
age_years	Age in years; continuous variable	Place all under 1s in one category (replace <1s as '0')
sex	gender	1=male 0=female
pregnant	Pregnancy (for sub-group analyses including pregnant women, only women of child-bearing age (15-54 years) will be considered)	1= yes 0= no (no separate code for 'not applicable'; men and women not of child-bearing age will be dropped from any analyses

Variable name in Stata	Description	Coding
		including pregnant women)
comorbidity	Whether any co-existing comorbidity was present (either as recorded or derived on the basis of a record of one of the following comorbidities: asthma, COPD, other chronic lung disease, heart disease, cerebrovascular disease (not including uncomplicated hypertension), chronic liver disease, chronic renal disease, diabetes, neurological disease (including neurodevelopmental disorders) and immunosuppression) Note: pregnancy will not be considered a 'comorbidity'	1= any comorbidity 0= no recorded comorbidity
asthma	Asthma as recorded	1= yes 0= no
copd	COPD as recorded	1= yes 0= no
other_lung_ds	Chronic pulmonary diseases (other than asthma or COPD)	1= yes 0= no
heart_ds	Chronic heart disease as recorded (includes congenital heart disease, hypertension with cardiac complications, chronic heart failure, individuals requiring	1= yes 0= no

Variable name in Stata	Description	Coding
	regular medication and/or follow-up for ischaemic heart disease)	
renal_ds	Chronic kidney disease (CKD) as recorded including CKD at stage 3, 4 or 5, chronic kidney failure, nephrotic syndrome, kidney transplantation.	1= yes 0= no
liver_ds	Chronic liver disease as recorded (including cirrhosis, biliary artesia, chronic hepatitis)	1= yes 0= no
cerebrovascular_ds	Cerebrovascular disease as recorded (including stroke, transient ischaemic attack but not including uncomplicated hypertension)	1= yes 0= no
neurological_ds	Neurological disease as recorded (including neurodevelopmental disorders)	1= yes 0= no
diabetes	Diabetes as recorded (including Type 1 diabetes, type 2 diabetes requiring insulin or oral hypoglycaemic drugs, diet controlled diabetes.)	1= yes 0= no
immunosuppression	Immunosuppression due to disease or treatment. Includes patients undergoing chemotherapy leading to immunosuppression; asplenia or splenic dysfunction and HIV infection at all stages.	1=yes 0= no

Variable name in Stata	Description	Coding
clinical characteristics		
onset_date	Date of onset of influenza like illness (ILI)	Recorded as date dd/mm/yy
admission_date	Date of first admission to hospital (whether to a general ward, HDU or ICU)	Recorded as date dd/mm/yy
time_to_admission	Time (in days) from onset of symptoms to hospital admission	Recorded as number of days
fever	Fever on presentation (as recorded)	1= yes 0= no
shortness_of_breath	Shortness of breath at presentation (as recorded)	1= yes 0= no
severe_respiratory_distress	Severe respiratory distress at admission	1= yes 0= no
flu_diag	Method of diagnosis of swine flu whether clinical or laboratory diagnosis (this includes RT-PCR)	1= clinical 2= laboratory diagnosis (not otherwise specified) or RT-PCR confirmed
cxr	Chest x-ray done	1= yes 0= no
cxr_date	Date the chest x-ray was performed	Recorded as dd/mm/yy
treatment		
antiviral_start_date	Date of start of NAI treatment	Recorded as dd/mm/yy
preadmit_antiviral	NAI given in the community/outpatient clinics (either oseltamivir or zanamivir)	1= yes 0= no
oseltamivir_start_date	Date of start of oseltamivir treatment	Recorded as dd/mm/yy

Variable name in Stata	Description	Coding
preadmit_oseltamivir	Oseltamivir given in the community/outpatient clinics	1= yes 0= no
zanamivir_start_date	Date of start of zanamivir treatment	Recorded as dd/mm/yy
preadmit_zanamivir	Zanamivir given in the community/outpatient clinics	1= yes 0= no
antibiotic_start_date	Date of start of antibiotic treatment	Recorded as dd/mm/yy
preadmit_antibiotic	Antibiotic given in the community/outpatient clinics	1= yes 0= no
hospital_oseltamivir	Oseltamivir given in hospital	1= yes 0= no
hospital_zanamivir	Zanamivir given in hospital	1= yes 0= no
hospital_antibiotic	Antibiotics given in hospital	1= yes 0= no
antiviral_anytime	NAI administered at any time (whether in the community or in hospital)	1= yes 0= no
early_preadmit_antiviral	Community/outpatient NAI administered ≤2 days of symptom onset versus late NAI treatment (>2 days from symptom onset)	1= early NAI 0= late NAI
oseltamivir_anytime	Oseltamivir administered at any time (whether in the community or in hospital)	1= yes 0= no
early_preadmit_oseltamivir	Community/outpatient oseltamivir administered ≤2 days of symptom onset versus late oseltamivir treatment (>2 days from symptom onset)	1= early oseltamivir 0= late oseltamivir

Variable name in Stata	Description	Coding
zanamivir_anytime	Zanamivir administered at any time (whether in the community or in hospital)	1= yes 0= no
early_preadmit_zanamivir	Community/outpatient zanamivir administered ≤2 days of symptom onset versus late zanamivir treatment (>2 days from symptom onset)	1= early zanamivir 0= late zanamivir
preadmit_steroid	Steroids given in the community/outpatient clinics	1= yes 0= no
hospital_steroid	New steroids administered in hospital (dexamethasone, hydrocortisone, prednisolone)	1= yes 0= no
steroids_anytime	Steroids administered at any time (whether in the community or in hospital)	1= yes 0= no
Outcomes		
discharge_date	Date of discharge from hospital	Recorded as date dd/mm/yy
length_of_stay	Length of stay in hospital (whether general ward or ICU) in days	Number of days
critical_care	Admission to critical care facilities (ICU)	1= yes 0= no
icu_admit_care	Date of admission to ICU	Recorded as dd/mm/yy
icu_discharge_date	Date of ICU discharge	Recorded as dd/mm/yy
icu_lengthstay	Length of ICU stay	Recorded as a continuous variables (no. of days)
pneumonia	Pneumonia as recorded (whether clinically	1= yes

Variable name in Stata	Description	Coding
	diagnosed or radiologically diagnosed or discerned from free text chest x-ray report findings)	0= no
pneum_diag	Method of diagnosis of pneumonia (clinical or radiological)	1= radiological diagnosis 0= clinical diagnosis
death	Death (as recorded)	1= yes 0= no
dod	Date of death	Recorded as dd/mm/yy
p	Propensity scores for treatment- yes vs. no	Recorded as a continuous variable between 0 and 1
ps_quintile	Propensity scores categorised into quintiles for each individual study for NAI treatment- yes vs. no	Categorical variable with values from 1 to 5 (1=lowest quintile and 5=highest quintile)
p2	Propensity scores for NAI treatment- Early treatment (≤2days) vs. Late treatment (>2 days)	Recorded as a continuous variable between 0 and 1
ps2_quintile	Propensity scores categorised into quintiles for each individual study for early treatment (≤2days) vs. late treatment (>2 days)	Categorical variable with values from 1 to 5 (1=lowest quintile and 5=highest quintile)

Appendix 3: Characteristics of individual studies contributing to the IPD meta-analysis described in Chapter 3 (outcome: hospitalisation)

	Country	Patients source	Total No. of cases supplied	No. of cases used	Median age, years (Range)	Male (%)	No. with any high-risk condition§ (n=1,074) (%)	No. treated with NAI (Outpatient/ community) (%)	No. with early NAI treatment (%)*	Hospitalisation (%)	Outcomes in those hospitalised (n=1,433)† (%)		
											Radiologic pneumonia	Critical care	Death
1	Germany	Hospital outpatients ; Single Centre	315	**314**	1.4 (<1 to 18)	182 (58.0)	123 (39.2)	13 (4.1)	1 (7.1)	153 (48.7)	51 (16.2)	11 (3.5)	1 (0.3)
2	Argentina	Hospital outpatients ; Single Centre	36	**17**	34 (21 to 83)	11 (64.7)	2 (11.8)	3 (17.7)	0 (0)	4 (23.5)	2 (11.8)	1 (5.9)	2 (14.3)
3	Canada	Hospital outpatients ; Single Centre	148	**148**	7.6 (<1 to 18)	90 (60.8)	29 (19.6)	32 (21.6)	-	35 (23.7)	15 (10.1)	7 (4.7)	0 (0)
4	Israel	Hospital outpatients ; Single Centre	73	**73**	9.1 (1 to 17)	42 (57.5)	30 (41.1)	47 (64.4)	-	37 (50.7)	9 (12.3)	2 (2.7)	0 (0)
5	Singapore	Hospital outpatients ; Single Centre	584	**490**	19.1 (<1 to 87.6)	262 (53.5)	187 (38.2)	13 (2.7)	11 (84.6)	248 (50.6)	15 (3.1)	13 (2.7)	3 (0.6)
6	France	Hospital outpatients ; Single Centre	549	**81**	24 (13 to 38)	0 (0)	81 (100)	53 (65.4)	46 (86.8)	26 (32.1)	-	0 (0)	0 (0)

7	Slovenia	Hospital outpatients ; Single Centre	78	**60**	20.85 (<1 to 78)	35 (58.3)	19 (31.7)	9 (15.0)	5 (71.4)	54 (69.23)	9 (15)	1 (1.7)	3 (5)
8	Saudi Arabia	Hospital outpatients & community patients; Surveillance	3,228	**1,762**	17 (<1 to 111)	896 (51.0)	543 (30.82)	446 (25.3)	90 (63.8)	1,149 (65.2)	-	112 (6.4)	5 (0.3)
9	UK	Hospital patients & community patients; Hospitalised	2,741	**431**	15 (<1 to 75.4)	194 (45.01)	5 (1.1)	257 (59.6)	196 (76.3)	17 (3.94)	-	-	-
TOTAL (9 centres)				**3,376**	14 (<1 to 111)	1,712 (50.8)	1,019 (94.9)	873 (25.9)	348 (73.6)	1,705 (50.5)	101 (7.05)	201 (10.3)	14 (1)

ED, Emergency department; IQR, interquartile range (25th and 95th percentile)
§ high-risk condition as a defined in the manuscript and only calculated where data were available; * percentage of all patients who received any NAI treatment; ; † number of hospitalised patients in whom data were available;
1,530 patients (87.8%) of the total 1,762 included from the Saudi Arabia dataset were recorded as being nationals of Saudi Arabia.

Appendix 4: Characteristics of individual studies contributing to the IPD meta-analysis described in Chapter 4 (outcome: hospital LoS)

	Country	Setting/Type of source	Total cases supplied	No. cases used	Median age, years at hospital admission (Range)	Male (%)	Time to hospital admission, days, median (IQR)	No. treated with NAI (%)	Early NAI treatment (≤2 days from symptom onset) (%)	Length of hospital stay, days, median days (IQR)	No. patients admitted to ICU (%)
1	Singapore	ED; Single Centre	110	110	24 (10 to 56)	62 (56.4)	2 (1 to 3)	110 (100)	-	4 (3 to 5)	0 (0)
2	Bangladesh	Hospital; Surveillance	147	121	22 (<1 to 72)	77 (63.7)	3 (2 to 5)	14 (11.6)	2 (14.3)	5 (3 to 6)	-
3	Spain	ICU; Multi-centre	1091	812	46 (1 to 86)	487 (60.2)	4 (2 to 6)	803 (98.9)	192 (23.9)	16 (10 to 30)	812 (100)
4	Mexico	Outpatients, Hospitalised; Multi-centre	446	237	39 (<1 to 81)	140 (59.1)	-	237 (100)	73 (30.8)	15 (11 to 21)	48 (20.3)
5	Hong Kong, China	ICU; Single Centre	17	15	42 (19 to 63)	9 (60)	4 (3 to 7)	15 (100)	3 (20)	46 (26 to 61)	15 (100)
6	Lithuania	Hospital; Multi-centre	121	110	30.5 (18 to 83)	46 (41.8)	2 (1 to 3)	61 (55.5)	31 (52.5)	5 (3 to 8)	3 (2.8)
7	Switzerland	Outpatients, Hospitalised; Single Centre	15	13	43 (30 to 74)	10 (79.9)	5 (1 to 6)	13 (100)	2 (15.4)	9 (8 to 13)	6 (46.2)

8	Germany	Hospital; Single Centre	315	135	1.3 (<1 to 17.7)	78 (57.8)	2 (1 to 4)	39 (28.9)	-	3 (2 to 5)	10 (7.7)
9	China	Outpatients, Hospitalised; Single Centre	65	40	41 (14 to 75)	24 (60)	5 (3.5 to 6)	40 (100)	3 (7.5)	7 (5.5 to 11)	24 (60)
10	China	Hospital; Multi-centre	155	127	39 (15 to 84)	72 (56.7)	5 (3 to 7)	106 (83.5)	12 (12)	11 (5 to 19)	47 (37)
11	Turkey	ICU; Single Centre	20	10	28.5 (15 to 72)	3 (30)	6 (3 to 7)	10 (100)	0 (0)	4.5 (3 to 8)	10 (100)
12	Argentina	Outpatients, Hospitalised; Single Centre	36	17	37 (16 to 82)	9 (52.9)	3 (2 to 4)	17 (100)	7 (41.2)	6 (4 to 10)	3 (17.7)
13	Spain	Outpatients, Hospitalised; Multi-centre	57	45	46 (18 to 84)	26 (57.8)	5 (3 to 7)	45 (100)	5 (11.1)	5 (3 to 8)	9 (20)
14	Iran	Outpatients, Hospitalised; Single Centre	434	121	33 (14 to 86)	52 (43)	4.1 (2.1 to 6.1)	121 (100)	19 (18.5)	3 (2 to 5)	34 (28.1)
15	Canada	ICU, Hospitalised, Outpatients; Single Centre	148	30	5.2 (<1 to 18)	18 (60)	3 (1 to 5)	25 (83.3)	-	4 (2 to 9)	6 (20)
16	South Africa	Hospital; Single Centre	46	23	22 (<1 to 55.7)	1 (4.4)	1 (0 to 3.5)	23 (100)	10 (66.7)	15 (6 to 27)	11 (47.8)

17	Argentina	Hospital; Multi-centre	112	76	26.5 (<1 to 79)	14 (18.4)	2 (1 to 3)	75 (98.7)	40 (53.3)	5 (3 to 9.5)	19 (25)
18	Poland	Hospital; Single Centre	24	18	6.5 (<1 to 16.5)	6 (33.3)	-	18 (100)	13 (72.2)	4 (3 to 5)	1 (5.9)
19	Jordan	Hospital; Single Centre	81	41	7 (1.1 to19)	25 (61)	-	41 (100)	32 (84.2)	4 (3 to 6)	6 (14.6)
20	Israel	Outpatients, Hospitalised; Single Centre	73	37	5.5 (1 to 16.9)	19 (51.4)	-	25 (67.6)	-	3 (2 to 6)	2 (5.4)
21	Australia	Hospital; Single Centre	106	86	28 (1 to 76)	30 (34.9)	-	75 (87.2)	-	2 (1 to 4)	11 (12.8)
22	Turkey	Hospital; Single Centre	204	200	30 (16 to 86)	95 (47.5)	3 (2 to 4)	192 (96)	-	3 (2 to 5)	15 (7.5)
23	Morocco	Outpatients, Hospitalised; Single Centre	640	16	29 (1 to 42)	6 (37.5)	-	16 (100)	-	4 (2.5 to 4)	2 (12.5)
24	France	Hospital; Single Centre	1770	930	35 (<1 to 104)	476 (51.2)	2 (1 to 4)	855 (91.9)	364 (50.5)	5 (3 to 13)	671 (72.2)
25	Spain	Hospital; Multi-centre	698	656	41 (16 to 97)	346 (52.7)	3 (2 to 5)	627 (95.6)	213 (35.1)	6 (3 to 8)	87 (13.3)
26	Singapore	Outpatients, Hospitalised; Single Centre	584	310	19.4 (<1 to 92.5)	160 (51.6)	2 (1 to 3)	258 (83.2)	84 (32.6)	2.5 (2 to 4)	21 (6.8)

27	Canada	Hospital; Multi-centre	300	260	5.2 (<1 to 18.7)	153 (58.9)	2 (1 to 4)	232 (89.2)	103 (44.6)	5 (3 to 10)	111 (42.7)
28	Australia	Hospital; Single Centre	105	102	41.5 (15 to 79)	49 (48)	3 (2 to 6)	87 (85.3)	38 (43.4)	4.5 (3 to 8)	24 (23.5)
29	Hong Kong	Hospital; Single Centre	69	56	46.5 (18 to 95)	22 (39.3)	2 (1 to 3)	51 (91.1)	22 (44.9)	4 (2 to 5.5)	1 (1.8)
30	Argentina	Hospital; Single Centre	197	135	29 (<1 to 71)	67 (49.6)	4 (2 to 7)	135 (100)	37 (28.7)	5 (3 to 8)	24 (17.9)
31	Argentina	ICU, Hospitalised, Outpatients; Single Centre	354	92	34 (<1 to 78)	49 (53.3)	3.5 (1 to 6)	66 (71.7)	-	5 (3 to 8)	8 (8.7)
32	Spain	Hospital; Single Centre	91	64	40.5 (13 to 78)	22 (34.4)	2 (0 to 3)	58 (90.6)	26 (44.8)	6 (4 to 16)	18 (28.1)
33	UK	Hospital; Surveillance	272	169	27 (16 to 44)	0 (0)	2 (1 to 4)	140 (82.8)	59 (47.2)	3 (2 to 6)	33 (19.5)
34	Italy	Hospital; Single Centre	81	78	31 (1 to 81)	43 (55.1)	-	66 (84.6)	50 (75.8)	5 (3 to 7)	7 (9)
35	Turkey	Hospital; Single Centre	15	13	2.2 (<1 to 6)	6 (46.2)	0 (0 to 1)	13 (100)	12 (92.3)	1 (1 to 2)	2 (15.4)
36	Israel	Hospital; Multi-centre	506	480	42 (16 to 89)	229 (47.7)	3 (1 to 4)	426 (88.8)	174 (40.9)	6 (4 to 9)	21 (4.4)

37	Brazil	Hospital; Single Centre	21	20	23.5 (15to 32)	0 (0)	1 (0 to 2)	20 (100)	15 (83.3)	5.5 (3 to 13)	5 (26.3)
38	France	Outpatients, Hospitalised; Single Centre	139	72	25 (16 to 42)	0 (0)	2 (1 to 2)	62 (86.1)	52 (83.9)	4 (3 to 4)	1 (1.4)
39	Greece	Hospital; Single Centre	34	34	33.5 (14 to 65)	23 (67.7)	-	34 (100)	34 (100)	6 (5 to 6)	0 (0)
40	Brazil	ICU; Multi-centre	37	16	36 (18 to 80)	9 (56.3)	7.5 (4 to 10)	15 (93.8)	-	10.5 (6.5 to 29)	16 (100)
41	Finland	ICU; Multi-centre	132	104	45.5 (<1 to 77)	68 (65.4)	3 (1 to 6)	99 (95.2)	39 (40.6)	14 (7 to 25)	104 (100)
42	Egypt	Hospital; Surveillance	1943	822	21 (<1 to 77)	471 (57.3)	1 (1 to 3)	822 (100)	547 (72.1)	6 (5 to 8)	-
43	USA	Hospital; Single Centre	307	263	5.8 (<1 to 21.6)	155 (58.9)	3 (1 to 5)	230 (87.5)	96 (42.1)	3 (3 to 6)	66 (25.1)
44	Turkey	Hospital; Surveillance	114	102	6.3 (<1 to 15.6)	62 (60.8)	2 (2 to 4)	102 (100)	52 (51)	6 (5 to 10)	12 (11.8)
45	Canada	Hospital; Single Centre	81	65	1.1 (<1 to 15)	34 (52.3)	4 (2 to 7)	40 (61.5)	4 (10.3)	4 (2 to 6)	8 (12.3)
46	Denmark	ICU; Surveillance	53	21	41.1 (5.8 to 63.1)	12 (57.1)	4.5 (1 to 7)	21 (100)	6 (30)	12 (3 to 24)	21 (100)

47	Saudi Arabia	Hospital; Single Centre	127	121	27 (10.9 to 79)	97 (80.2)	2.5 (1 to 4)	121 (100)	59 (49.2)	6 (5 to 9)	10 (8.3)
48	Slovenia	Outpatients, Hospitalised; Single Centre	78	40	23.6 (<1 to 87.1)	29 (72.5)	2 (1 to 5)	25 (62.5)	6 (27.3)	4 (2 to 6)	3 (7.5)
49	Japan	Hospital; Single Centre	104	102	7 (<1 to 71)	53 (52)	2 (1 to 3)	102 (100)	76 (74.5)	7 (5 to 9)	4 (3.9)
50	India	Hospital; Single Centre	61	51	20 (<1 to 52)	31 (60.8)	5 (3 to 7)	51 (100)	7 (13.7)	7 (6 to 11)	2 (3.9)
51	Mexico	Outpatients, Hospitalised; Surveillance	127289	5,034	28 (<1 to 99)	2,192 (43.5)	2 (1 to 5)	927 (18.4)	-	4 (2 to 7)	189 (3.8)
52	China	Hospital; Single Centre	72	19	43 (18 to 62)	12 (63.2)	8 (5 to 10)	19 (100)	0 (0)	11 (8 to 22)	8 (42.1)
53	Croatia	Hospital; Single Centre	169	160	29 (<1 to 83)	90 (56.3)	2 (1 to 4)	131 (81.9)	69 (52.7)	6 (4 to 10)	28 (17.5)
54	UK	Hospital; Multi-centre	1520	1,163	26 (<1 to 95)	541 (46.5)	2 (1 to 4)	879 (75.6)	265 (46.3)	4 (2 to 6)	158 (13.6)
55	Poland	Hospital; Single Centre	13	8	18.5 (6 to 75)	3 (37.5)	2 (1 to 2)	6 (75)	2 (50)	9.5 (5.5 to 11.5)	1 (12.5)
56	Slovenia	Hospital; Single Centre	66	60	38.5 (16.6 to 87.2)	29 (48.3)	4 (2 to 6)	58 (96.7)	14 (26.9)	4 (3 to 6)	6 (10)

57	Serbia	Hospital; Single Centre	98	95	27 (14 to 88)	66 (69.5)	2 (1 to 5)	67 (70.5)	31 (46.3)	7 (6 to 8)	4 (4.2)
58	UK	ICU; Single Centre	24	17	50 (22 to 80)	10 (58.8)	6 (3 to 8)	17 (100)	1 (5.9)	32 (14 to 47)	17 (100)
59	Argentina	Hospital; Multi-centre	251	191	0.8 (<1 to 17.7)	98 (51.3)	4 (2 to 7)	156 (81.7)	16 (10.3)	8 (5 to 13)	28 (14.7)
60	China	Hospital; Multi-centre	367	321	20 (<1 to 77)	184 (57.3)	2 (1 to 4)	318 (99.1)	94 (51.1)	7 (5 to 9)	35 (10.9)
61	Austria	Outpatients, Hospitalised; Multi-centre	540	325	20.3 (<1 to 90.8)	230 (70.8)	-	230 (70.8)	-	7 (4 to 9)	34 (10.5)
62	Iran	Hospital; Multi-centre	484	433	31 (1 to 84)	181 (41.8)	3 (2 to 7)	420 (97)	113 (28.1)	3 (1 to 4)	37 (8.6)
63	Mongolia	Hospital; Surveillance	204	180	20 (1 to 76)	89 (49.4)	3 (1 to 5)	96 (53.3)	-	5 (4 to 7)	6 (3.3)
64	Germany	Hospital; Single Centre	92	89	3.6 (<1 to 17.8)	45 (50.6)	2 (1 to 4)	26 (29.2)	18 (69.2)	3 (2 to 5)	6 (6.7)
65	Australia	Hospital; Single Centre	601	433	3.5 (<1 to 14.9)	252 (58.2)	2 (1 to 4)	221 (51)	101 (49.5)	2 (1 to 5)	48 (11.1)
66	Bangladesh	Hospital; Single Centre	28	8	23 (3 to 50)	2 (25)	1 (0 to 4)	8 (100)	4 (57.1)	5.5 (4 to 6)	-

67.1	USA	Hospital; Multi-centre	630	432	47 (13 to 92)	184 (42.6)	3 (2 to 6)	401 (92.8)	1 (16.7)	11 (5.5 to 22)	432 (100)
67.2	USA	Hospital; Multi-centre	838	699	6 (<1 to 20)	412 (58.9)	2 (1 to 4)	628 (89.8)	3 (75)	7 (4 to 15)	699 (100)
68	UK	Hospital; Single Centre	41	20	2 (<1 to 14.4)	9 (45)	3.5 (0.5 to 5)	16 (80)	5 (31.3)	5 (3 to 18.5)	7 (35)
69	Canada	Hospital; Single Centre	1014	899	27 (<1 to 92)	460 (51.2)	3 (2 to 5)	656 (73)	293 (44.7)	3 (2 to 6)	119 (13.2)
70	Norway	Hospital; Single Centre	129	105	43.6 (15.1 to 93.2)	50 (47.6)	4 (1 to 7)	75 (71.4)	29 (38.7)	3 (2 to 6)	7 (6.7)

Appendix 5: The novel behavioural model based on the COM-B model of behaviour change is supplied as a .alp file (AnyLogic file).

Appendix 6: The spreadsheet-based decision tree model used to perform the health economic evaluation in Chapter 7 is provided as an MS Excel file.