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TITLE: Modelling the health and economic impact of the influenza vaccine in Kenya

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Declaration

This thesis is my original work and has not been presented for a degree in any other University.

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Dedication

I dedicate this work to the individuals who participated in surveillance and research activities in order to help improve our population's health, and the researchers who shared the data they collected and the methods they utilised to enable others build on their findings.

Acknowledgements

Disclaimer: *The statements made and views expressed are solely the responsibility of the student and do not necessarily represent the views of the Kenya Medical Research Institute, the African Population and Health Research Centre, the University of the Witwatersrand, Wellcome Trust (UK), the Carnegie Corporation of New York, the Swedish International Development Corporation Agency or the Centers for Disease Control and Prevention.*

Table of contents

List of tables

List of figures

x

Abbreviations

A(H1N1)pdm09	influenza A H1N1pdm09
A(H3N2)	influenza A H3N2
ARI	acute respiratory illness
ALRTI	acute lower respiratory tract infection
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CI	credible interval
DALY	disability adjusted life year
EPI	expanded Programme of Immunization
ERC	ethics review committee
GP	general practitioner
HDSS	Health Demographic and Surveillance Site
HI	haemagglutination inhibition
HA-ILI	hospital acquired influenza like illness
Hib	*Haemophilus influenza* type b
HIV	Human immunodeficiency virus
ICER	incremental cost-effectiveness ratio
ILI	influenza like illness
INMB	incremental net monetary benefit
IRB	institutional review board
IPT	in-patient
KEMRI	Kenya Medical Research Institute
KENITAG	Kenya National Immunization Technical Advisory Group
LAIV	live attenuated inactivated vaccine
LMIC	low and middle income countries
LRTI	lower respiratory tract infection
MCMC	Markov Chain Monte Carlo
NIP	national immunization programme
NITAG	national immunization technical advisory group
NH	northern hemisphere
NP	nasopharyngeal
OP	oropharyngeal
OPT	out-patient
rRT-PCR	real time reverse transcription-polymerase chain reaction
PCR	polymerase chain reaction
RHAI	respiratory hospital acquired infections
RT	reverse transcriptase
SAGE	Strategic Advisory Group of Experts
SARI	severe acute respiratory illness
SEIR	Susceptible-Exposed-Infectious-Recovered
SH	southern hemisphere
sSA	sub-Saharan Africa
UK	United Kingdom
UoN	University of Nairobi
US	United States
URTI	upper respiratory tract infection
VE	vaccine effectiveness
VPD	vaccine preventable diseases
WHO	World Health Organization
WTP	willingness-to-pay

Definition of operational terms

Cost effectiveness analysis – a method of comparing the costs and benefits of an intervention to another intervention or the status quo/doing nothing. In this type of economic evaluation, benefits are usually defined in terms of a single measure e.g. infections averted, deaths averted etc.

Herd immunity - a form of indirect protection from infectious disease infection whereby susceptible individuals in a population have a reduced chance of being infected because a sufficient proportion of individuals in the population are immune either due to past infection or effective vaccination and cannot be infected or transmit infection.

Influenza associated severe acute respiratory illness (SARI) – refers to cases where individuals with severe acute respiratory illness have influenza detected following testing of nasopharyngeal and oropharyngeal samples.

Severe acute respiratory illness (SARI) – acute onset illness (within 14 days), reported fever (or recorded temperature of ≥38° Celsius), and a cough occurring among individuals who are hospitalised (hospitalised SARI) or not (non-hospitalised SARI).

Severe acute respiratory illness (SARI) surveillance system – a system of monitoring the number of individuals admitted with acute onset respiratory illness and their causes in a network of hospitals across Kenya run by the Ministry of Health in collaboration with funders.

Vaccine effectiveness – the percent reduction in the number of infections among those who are vaccinated compared to those who are not vaccinated.

Abstract

Background: There is substantial burden of seasonal influenza in sub-Saharan Africa. In Kenya, national rates of influenza-associated respiratory illness were considerable during the emergence of the 2009 influenza pandemic. However, since then there have been no published national estimates of influenza burden in the post-pandemic period. Furthermore, an economic evaluation of the benefits of influenza vaccination in Kenya has not been conducted.

Objectives: We set out to update estimates of the national burden of hospitalized and non-hospitalized influenza-associated severe acute respiratory illness (SARI) during a post-pandemic period (2012-2014) and describe the incidence of disease by narrow age categories. In addition, we estimated the cost-effectiveness of seasonal influenza vaccination among children using a dynamic transmission model to inform policy discourse on implementation of a national influenza vaccination program in Kenya.

Methods: To determine the burden of hospitalised and non-hospitalised influenza associated SARI, we used data from Siaya County Referral Hospital from 2012-2014 to estimate age-specific base rates of SARI. We extrapolated these base rates to other regions within the country by adjusting for regional risk factors for acute respiratory illness (ARI), regional health-care utilization for ARI and the proportion of influenza positive SARI cases in each region, so as to obtain region specific rates of influenza-associated hospitalized and non-hospitalized SARI.

For the economic evaluation I fitted an age-stratified dynamic transmission model to surveillance data from patients with influenza-associated severe acute respiratory illness (SARI) at five county referral hospitals in Kenya from 2010-2018. Using a societal perspective, we developed a decision-tree cost-effectiveness model and estimated the incremental cost-effectiveness ratio (ICER) per disability-adjusted life year (DALY) averted for three vaccine target groups: children 6-23 months (strategy I), 2-5 years (strategy II) and 6-14 years (strategy III) with either the Southern Hemisphere influenza vaccine (Strategy A) or Northern Hemisphere vaccine (Strategy B) or both (Strategy C: twice-yearly vaccination campaigns, or Strategy D: year round vaccination campaigns). To compare strategies we calculated the incremental net monetary benefits (INMB)

using a willingness-to-pay (WTP) threshold of 1-51% of the annual gross domestic product per capita ($17-872).

Results: For the period 2012-2014, the mean annual rate of hospitalized influenza-associated SARI among all ages was 21 (95% CI 19-23) per 100,000 persons, while rates of non-hospitalized influenza-associated SARI were approximately 4 times higher at 82 (95% CI 74– 90) per 100,000 persons. Mean annual rates of influenza-associated SARI were highest in children <2 years of age with annual hospitalization rates of 147 (95% CI of 134-160) per 100,000 persons and non-hospitalization rates of 469 (95% CI 426-517) per 100,000 persons. From 2012-2014, there were 8,929 (95% CI 8,153-9,751) cases of hospitalized influenza-associated SARI and 35,041 (95% CI 31,785-38,546) cases of non-hospitalized influenza-associated SARI per year.

Using the dynamic transmission model we estimated the mean number of total infections to be 2-15 million per year. When vaccination was well timed to influenza activity, the annual mean ICER per DALY averted for vaccinating children 6-23 months ranged between $749-1,385 for strategy IA, $442-1,877 for strategy IB, $678-4,106 for strategy IC and $1,147-7,933 for strategy ID. For children 2-5 years it ranged between $945-1,573 for strategy IIA, $563-1,869 for strategy IIB, $662-4,085 for strategy IIC, and $1,169-7,897 for strategy IID. For children 6-14 years it ranged between $923-3,116 for strategy IIIA, $1,005-2,223 for strategy IIIB, $883-4,727 for strategy IIIC and $1,467-6,813 for strategy IIID.

Overall, no vaccination strategy was cost-effective at the minimum ($17) and median ($445) WTP thresholds. Vaccinating children 6-23 months once a year had the highest mean INMB value at $872 (WTP threshold upper limit), however this strategy had very low probability of highest net benefit.

Conclusions: Influenza virus was associated with substantial disease burden in Kenya, especially among very young children, <2 years of age. Vaccinating children 6-23 months once a year was the most favourable vaccination option, however, the strategy is unlikely to be cost-effective given the current WTP thresholds.

1   Introduction

Sections of this chapter are available in a peer reviewed article published January 2019: Dawa, J., S. S. Chaves, A. Ba Nguz, R. Kalani, E. Anyango, D. Mutie, P. Muthoka, C. Tabu, M. Maritim, E. Amukoye and F. Were (2019). "Developing a seasonal influenza vaccine recommendation in Kenya: Process and challenges faced by the National Immunization Technical Advisory Group (NITAG)." Vaccine 37(3): 464-472 and an advisory report presented to the Ministry of Health, Kenya dated May 2016: "Kenya National Immunization Technical Advisory Group (KENITAG) Influenza Vaccine Recommendation Note (28 May 2016)".

The number of vaccines recommended for regular use is increasing [1, 2]. In the 1970s, the World Health Organisation (WHO) recommended only 6 vaccine preventable diseases (VPDs) for inclusion in National Immunization Programs (NIPs): diphtheria, whooping cough, tetanus, measles, poliomyelitis and tuberculosis [1]. By 2019, there were 22 vaccine preventable diseases, including the influenza vaccine, recommended for routine immunization by WHO [2]. Given the limited resources available, policy makers must prioritise which vaccines to be included in their NIPs.

It is estimated that a billion cases of influenza occur annually, with up to 5 million severe cases and approximately 650,000 deaths per year [3, 4]. The greatest burden of influenza disease is thought to occur in the developing world, where higher prevalence of malnutrition, immunosuppression and co-morbidities, as well as unique socio-cultural factors, increase the likelihood of infection and the risk of developing severe disease [5].

In 2010, lower respiratory tract infections accounted for 1 in 10 deaths in Kenya [6]. Influenza in particular, is an important cause of morbidity among Kenyan patients with respiratory illness [7-9]. It is postulated that the influenza virus accounts for over 20% of all medical attended cases of acute respiratory illness in Kenya [8, 10].

The World Health Organisation (WHO) recommends the prioritisation of pregnant women for influenza vaccination [11]. Other groups that are recommended for annual vaccination include children 6 to 59 months of age, the elderly, those with co-morbidities and health

care workers [11, 12]. Despite the WHO recommendation, the influenza vaccine is not currently included in the NIP in Kenya. Vaccination is a potential means of reducing illness, health care worker load and health care provision costs associated with seeking influenza related medical care at health facilities [11].

The influenza vaccine is the most effective preventive measure available against influenza infection, however, less than half of the world's population are able to access the influenza vaccine as part of their NIP, in part, due to limited evidence to justify introduction of the vaccine [13]. Use of the vaccine in the Eastern Mediterranean, Southeast Asian and African regions remains remarkably low. In particular, the Africa region is thought to receive less than 1% of influenza vaccines supplied by the International Federation of Pharmaceutical Manufacturers and Associations [14]. Furthermore, unlike other vaccines, the influenza vaccine is reformulated yearly to match vaccine contents to circulating strains, and must be administered every year, which has significant cost implications for a national program.

The potential impact of influenza vaccination in reducing morbidity and health care related costs in Kenya, has yet to be quantified. Understanding the cost-effectiveness of introducing influenza vaccination in our setting is an important component in the decision-making process. In addition, unlike most countries in the world, significant influenza transmission occurs year round in Kenya and there is no clearly defined primary peak in activity [15]. As a result, the most appropriate vaccination timing is not known. Timing of vaccination could affect the overall effectiveness of a NIP and is an important element to include in evaluation of vaccination strategies.

This research study seeks to describe the burden of severe influenza in the Kenyan population, model the transmission of influenza in the country, and recommend appropriate cost-effective strategies for influenza vaccination. This introductory chapter provides a justification of the research project, describes the conceptual framework that was adopted and defines the objectives of the research project.

1.1   Conceptual framework

Evidence-based decision-making in the health sector refers to the use of available scientific knowledge, to identify the most appropriate intervention to address a health problem [16].

The concept was first published in the early 1990's as 'evidence-based medicine', to support the use of scientific knowledge in clinical decisions. In time, this approach was adopted in the fields of public health and policy making as 'evidence-based decision-making' and 'evidence-based' or 'evidence-informed policy-making' [17]. In this approach to decision-making, evidence is collected in a systematic and transparent way to identify all relevant scientific knowledge. This systematic method of gathering evidence limits the influence of bias and errors in the identification, selection and appraisal of evidence and the resulting conclusions and recommendations derived from it [16]. An evidence-based decision-making approach is currently recommended when making the decision to introduce a vaccine into a NIP.

The concept of evidence-based decision-making has received criticism from both scholars and policy makers [16, 17]. Individuals have criticized this approach because of its perceived emphasis on scientific evidence as the sole driver of decisions. Decision-making is also thought to be affected by the decision maker's characteristics, the external environment and research system [18]. The personal experiences and values of decision makers, the available resources, political influence, public perception, media coverage, influence of special interest groups and how well research is tailored to address the questions that matter to policy makers, all influence the decision-making process [16, 18].

Notwithstanding its weaknesses, the evidence-based decision-making approach is currently used in the immunization field when selecting new vaccines to be included in NIPs. The **immunization recommendation framework** as described by the World Health Organisation (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization, and used by a number of National Immunization Technical Advisory Groups (NITAGs) around the world, seeks to identify and consider a wide variety of factors, both scientific and 'non-scientific' in the decision-making process [19, 20].

1.1.1   Concept map

The immunization policy advisory framework adopted by the WHO SAGE on Immunization provides a list of factors that should be considered in the vaccine recommendation process. These factors include epidemiologic features of the disease, clinical characteristics of the disease, alternative options for disease control and prevention, the vaccine and immunization characteristics and the economic, health system, implementation, social, legal

and ethical considerations of the proposed vaccine program [20]. Of these considerations, Nohynek and colleagues [21] advocate for the prioritization of local disease burden data and national economic benefit in deciding whether to introduce new vaccines into NIPs (Figure 1). As such, this research project explored two main factors of the immunization recommendation framework: the epidemiologic features of the disease and the economic impact of introducing an influenza vaccination. Specifically, the research project was designed to estimate the overall disease burden in the general population and in different age groups as well as the population health and economic impact of different vaccination strategies. **Table *1*** provides a summary of some of the specific data elements that may be considered during the vaccine decision-making process using the example of the recommendation framework adopted locally by the Kenya National Immunization Technical Advisory Group (KENITAG), which advises the government on which vaccines to be included in the NIP.
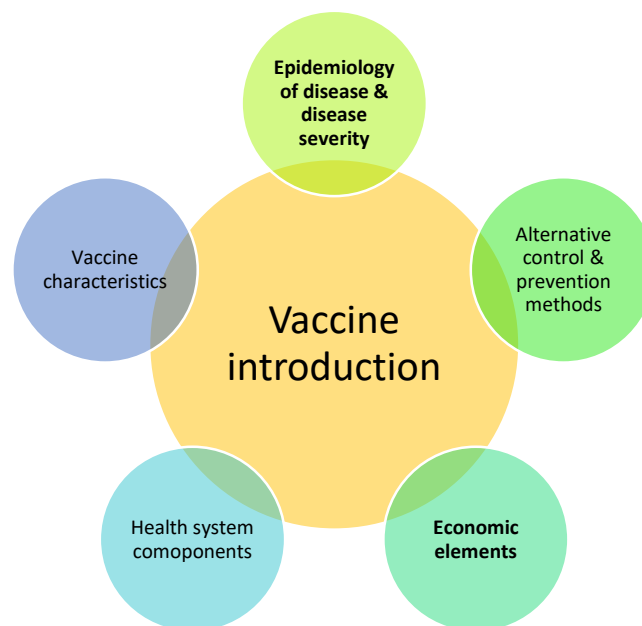
Figure 1: Concept map of elements considered in development of evidence-based vaccine related recommendations.
Emphasis placed on epidemiology of disease and economic elements as suggested by Nohynek et al. Adapted from [21, 22]

Table 1: A description of some of the specific data elements to be considered during the vaccine decision making process as used by the Kenya National Immunization Technical Advisory Group [23]

ISSUE	ELEMENT	EXAMPLE OF DATA REQUIRED
1. DISEASE	Burden of disease	Local data on the morbidity in general population, data from surveillance sites (total number infected, rates of illness), hospital based surveillance data, position in priority disease list, seasonality and mortality curve, epidemiology over time/trends over time (5 to 10 years)
	Use and costs of health care	Local data health facility attendance, increased workload for health care worker, admissions
		Drug use (e.g. effect on inappropriate use of antimicrobials)
	Social impact of disease	School and work absenteeism
		Indirect costs to patients and families
		Productivity losses
	Alternative preventive and control measures	Pharmaceutical and non-pharmaceutical prevention and control measures
2. VACCINE AND IMMUNIZATION CHARACTERISTICS	Vaccine characteristics	Vaccine presentation and formulation
		Dosage and route of administration
		Administration schedule and possibility of co-administration with other vaccines and drugs
		Flexibility of vaccination schedules
	Vaccine indirect effects	Impact on antibiotic use
	Safety	Type, consequences and frequency of short and long-term adverse events following vaccination including adverse effects on foetus and new-born
		Risk groups or risk factors for adverse events
		Contraindications
	Efficacy and effectiveness	Efficacy worldwide
		Efficacy against strains circulating locally
		Duration of protection and waning of immunity in general and risk groups
		Impact on incidence of illness, admissions, outpatient attendance, mortality
3. ECONOMIC AND OPERATIONAL CONSIDERATIONS	Vaccine related costs and resource use	Local data on the direct and indirect costs to administer the vaccine as they compare to those of other existing vaccines or other prevention or control measures
	Vaccine availability	Local data on cost to the government
		Local data on sources of funding
		Availability in private sector

	Economic impact of intervention on immunization program as well as health sector	Cost benefit analysis, cost effectiveness, cost per disability adjusted life year averted, cost per quality adjusted life year gained
4. HEALTH POLICY AND PROGRAMMATIC ISSUES	Feasibility	Local data on accessibility of target population and risk groups, number of individuals in target population and risk groups
		Local data on human, technical and financial requirements that is cold chain, supply chain requirements
		Local data on possibility of inclusion into regular immunization schedule
		Reliability and sustainability of surveillance system for disease
	Ability to evaluate	Adverse events following immunization (AEFI) monitoring
		Local data on availability of information systems to measure coverage and vaccine utilization
	Acceptability	Perception of the public and medical community about the disease and the vaccine
		Health seeking behaviour
	Equity	Accessibility for all the inhabitants in the country

1.2 Research justification

WHO recommends annual vaccination for seasonal influenza in temperate as well as tropic and sub-tropic regions [12, 24] due to the recognised morbidity and mortality associated with the disease. In addition to the burden of seasonal influenza, the threat of an influenza pandemic is an important consideration - widespread use of a seasonal influenza vaccine could lead to increased manufacturing capacity for influenza vaccines, and result in improved availability of pandemic influenza vaccines during the emergence of a highly pathogenic pandemic influenza strain [12].

Notably, evidence of clinical effect alone is insufficient to lead to introduction of an intervention. In addition to clinical benefit, evidence of cost-effectiveness should be considered [25]. The immunization evidence-based decision-making approach as proposed by the WHO, considers several elements [22]. Of these elements, Nohynek and colleagues [21] advocate for the prioritization of evidence of local disease burden and national economic benefit in deciding which vaccine to include in a NIP.

In low and middle income countries (LMICs), data on national burden of disease and the potential health and economic benefits of vaccination are not readily available. In these settings, decision makers often do not have the benefit of robust nationwide surveillance data to determine the national health and economic burden of a disease within a population, nor do they have the resources for large population based studies to establish a vaccine's health and economic effects. Yet in the face of these limitations, appropriate decisions regarding which vaccines to introduce into NIPs must still be made. Mathematical models are beneficial because they make use of available local data – even where limited – to estimate the potential impact of vaccination.

Infectious disease transmission models are mathematical representations of reality that have been ''simplified, idealised, approximated and abstracted'' to provide reasonable predictions of how diseases are transmitted within a population [26]. By accurately replicating the way diseases spread, the models can then be used to examine the potential impact of different control interventions [26]. Mathematical models have been used to develop and evaluate

strategies to control the spread of numerous infectious diseases including influenza, rabies, HIV, schistosomiasis, salmonella, malaria, varicella, polio, dengue, hepatitis C, diphtheria, trypanosomiasis, tuberculosis, measles, and human papilloma virus among others [27-48]. However, in 2013, only half of European NITAGS used results from mathematical models in the vaccine decision making process [21]. Since then transmission models are increasingly utilised to determine the most appropriate vaccination strategy, and estimate the impact and cost-effectiveness of vaccination [49-54].

Infectious disease models are one of the few tools available that can assess the direct and indirect effects of vaccination [26]. The indirect effect of vaccination refers to the additional protection of vaccinated and unvaccinated individuals due to reduced transmission of disease in the population. It is argued that the indirect effect of influenza vaccination, rather than the direct protection provided by vaccination, is the more significant contributor to the observed decline in influenza cases following vaccination [55]. Preventing transmission of the influenza virus among those who are effectively vaccinated has the additional benefit of protecting other vaccinated and unvaccinated individuals from being infected, because propagation of the virus is interrupted. Indirect protection from influenza vaccination is thought to be best achieved with higher vaccine efficacy and coverage among children [56]. Health policy decisions that do not take into account the indirect effect of influenza vaccination could therefore potentially underestimate its overall benefits.

Cost-effectiveness data is an important consideration in the vaccine decision-making process. However, there are no published studies that present economic evaluation data on influenza vaccine use in Kenya. A systematic review of economic evaluations of influenza vaccine in low and middle income countries, observed that few economic evaluations have been carried out in low income countries [57]. In a few middle income countries in South America and Asia the influenza vaccine has been found to be cost-effective, especially when administered to specific target groups including the elderly, children with co-morbidities, young children <2 years of age, patients with chronic obstructive pulmonary disease and health care personnel in contact with cancer patients [57]. In some cases, when administered to particular high risk groups, influenza vaccination has also been found to be cost saving [57-59].

This research project will be useful in establishing the national burden of influenza each year, identifying the most at-risk age groups in Kenya, and identifying the most cost-effective strategy for seasonal influenza vaccination to better inform national policy decisions on influenza control strategies.

1.2.1 Research gap

The national burden of severe influenza illness in Kenya has previously been described by Fuller *et al* [9]. Although Fuller's study was important in describing the national burden of influenza-associated disease in Kenya, the findings had three key constraints. Fuller's method described the burden of influenza in only two broad age groups: children <5 years of age, and persons aged ≥5 years of age. From studies conducted in the developed world, the risk of severe disease is known to vary between age groups with children <5 years of age, specifically those <2 years of age, and the elderly (≥65 years of age) being at highest risk of severe disease [24]. Secondly, during the years in which Fuller's method was applied (July 2009 to August 2011), the pandemic influenza A virus subtype H1N1 (influenza A(H1N1)pdm09) was in circulation at markedly higher levels of activity than is present during a normal influenza season [60]. The years captured by Fuller's method would therefore represent a higher than normal level of influenza activity in the community. Lastly, since the method was developed, updated data have become available for most of the input parameters that were used in Fuller's method. In order to address these issues, Fuller's method was applied in calculating the burden of hospitalized and non-hospitalized severe influenza-associated during a recent non-pandemic period (2012 to 2014) and in describing the incidence of severe influenza disease in finer age groups (including children <2 years and individuals ≥65 years old).

Mathematical models can be used to estimate the potential impact of health interventions such as vaccination [61]. Mathematical models though beneficial, are not routinely utilized in the decision-making process [21]. It is thought that the underutilization of this technique is as a result of lack of expertise, time and resources [21]. This research made use of a mathematical model to determine the burden of disease and economic benefit of an influenza vaccination program in order to generate data that can inform evidence-based decision-making in support of or against the introduction of influenza vaccines in Kenya.

Economic evaluations of influenza vaccination are generally lacking in low income countries [57]. I adapted the dynamic transmission model described by Baguelin *et al* in the United Kingdom (UK) [53] to estimate the potential health and economic impact of introducing the influenza vaccine in Kenya. The dynamic model depicts transmission across the entire population and therefore takes into account both the direct and indirect effects of influenza vaccination, which can then more accurately estimate vaccine impact. The recommendations from Baguelin's model for the UK could not be directly applied to Kenya without first adapting the model to suit our local context. There are differences in disease epidemiology between the UK and Kenya, including differences in seasonality, with year round transmission of influenza observed in tropical climates such as Kenya [62], as opposed to seasonal transmission of influenza in temperate climates [62, 63]. Differences in health systems, costs of treatment, and indirect costs of illness in the two settings have important implications in determining the economic impact of influenza disease and the cost-effectiveness of any preventive measure. There are also likely to be differences in social contact mixing patterns between the two settings, which would determine how the disease spreads within each population. In addition, the type of surveillance data for influenza differs between the two countries. Whereas influenza surveillance in the UK makes use of influenza like illness (ILI) cases recorded at outpatient general practitioner (GP) practices [64], influenza surveillance in Kenya is implemented through severe acute respiratory illness (SARI) surveillance among inpatients at selected influenza surveillance sites [15]. The model developed by Baguelin *et al* was adapted to the local epidemiology of influenza disease, the local health system and available influenza surveillance data in Kenya, in order to identify the most appropriate vaccination policy.

1.3 Study question

What is the health burden of influenza and what would be the impact and cost-effectiveness of introducing annual influenza vaccination in Kenya?

1.3.1 Overall objective

The primary objective of this study was to determine the health burden of influenza-associated illness in Kenya and the potential impact and cost-effectiveness of annual influenza vaccination.

1.3.2 Specific objectives

The specific objectives were:

- **Objective 1:** To determine the annual health burden of influenza-associated respiratory illness in Kenya for the period 2012-2014
    - 1.1. To estimate the annual incidence of influenza-associated severe respiratory disease among the general population and specific age groups in Kenya for the period 2012-2014
- **Objective 2:** To describe the transmission of influenza in the Kenyan population for the period 2010-2018
    - 2.1. To define and collect data on the input parameters to be included in an infectious disease model of influenza transmission in Kenya
    - 2.2. To adapt a dynamic transmission model of influenza transmission to the Kenyan population
- **Objective 3:** To recommend an appropriate and cost-effective influenza vaccination policy to prevent the morbidity and mortality due to influenza-associated respiratory illness in Kenya
    - 3.1 To evaluate the potential health impact of different vaccination strategies in reducing influenza-associated respiratory illness among the general population as well as specific target groups in Kenya
    - 3.2 To conduct a cost utility analysis of the impact of different vaccination strategies in reducing influenza-associated respiratory illness among the general population as well as specific target groups in Kenya

1.4   Ethical considerations

This study made use of influenza surveillance data originally collected by the Ministry of Health, Kenya Medical Research Institute and Centers for Disease Control and Prevention at the Kenyatta National Teaching and Referral Hospital (KNH) as well as the following county referral hospitals: Siaya, Nyeri, Mombasa, Nakuru, Kakamega. The study protocol at Siaya County Referral Hospital was approved by both the ethics review committee (ERC) of the Kenya Medical Research Institute (KEMRI) (SSC-1801), and the institutional review board (IRB) of the U.S. Centers for Disease Control and Prevention (CDC) (CDC-3308) as SCRH falls within a health and demographic surveillance site (HDSS) where more detailed information is collected from patients attending the health facility (Appendix 1: Ethical approval). Surveillance for influenza within the other 5 influenza sentinel surveillance sites (Kenyatta National Hospital, Nyeri County Referral Hospital, Mombasa County Referral Hospital, Nakuru Country Referral Hospital, and Kakamega County Referral Hospital) was part of routine disease surveillance by the Kenya Ministry of Health. Verbal consent to collect samples from patients at these sites was therefore considered adequate. At the commencement of this doctoral research project, I received ethical exemption from the KNH/University of Nairobi (UoN) ERC to perform secondary data analysis on de-identifiable surveillance data collected from the above mentioned health facilities within the national influenza surveillance network (Appendix 1: Ethical approval).

1.5   Overview of thesis

Chapter 2 presents a comprehensive literature review of the burden of influenza in Kenya, starting from one of the first reported cases of laboratory confirmed influenza in the 1970's. We provide summaries of the rates of influenza-associated illness in different age groups and regions in Kenya, data on locally identified risk factors for severe disease, the timing of epidemics and economic burden of illness. At the end of the chapter I highlight some of the gaps in influenza data in Kenya.

The main results of the research project are presented in Chapters 3 and 4. Each of these chapters has an introduction, methods, results and discussion section in the same format as the

research publications that were developed from the work. As there was no methodology common to each chapter, we did not include a separate methods chapter. The methods and limitations specific to each research objective were incorporated in detail in both Chapters 3 and 4.

In **Chapter 3,** we describe the methods and findings of the first objective of the thesis. We utilize available influenza surveillance data to illustrate the national burden of hospitalized and non-hospitalized severe acute respiratory illness (SARI) from 2012-2014 in more discrete age groups than have previously been described in Kenya. We also update national estimates of the burden of hospitalized and non-hospitalized influenza-associated SARI after emergence of the 2009 influenza A(H1N1) pandemic. This provides a more accurate account of the burden of seasonal influenza in the absence of a pandemic. We identify the age groups and regions with the highest rates of hospitalized and non-hospitalized SARI, and compare our research findings with data from other countries. At the end of the chapter, we identify the age group that should be prioritized for influenza prevention strategies.

In **Chapter 4**, we combine the second and third objectives of the study to develop an age-stratified transmission model adapted to our setting. We use the number of infections obtained from the model to conduct an economic evaluation from a societal perspective. Using a decision tree model, we calculate the number of mild illnesses, severe illnesses, deaths, DALYS and health care utilization events per year. We assign costs to each of the disease states based on health care utilization data and previously published data on the cost of influenza in Kenya. We also model the effect of different vaccination strategies targeted towards children. At the end of the chapter, we identify the most cost-effective target group, vaccine formulation, and vaccination period.

The overall conclusion of the study is presented in **Chapter 5**. In this chapter we integrate data from all the individual results chapters and discuss the overall picture that emerges from the thesis and the recommendations arising from the study.

The appendices contain additional information on the studies identified in the literature review, calculations used in the research, and detailed supplementary text, tables and figures not presented within the main text.

2 Literature review

Sections of this chapter are available in a peer reviewed article published January 2019: Dawa, J., S. S. Chaves, A. Ba Nguz, R. Kalani, E. Anyango, D. Mutie, P. Muthoka, C. Tabu, M. Maritim, E. Amukoye and F. Were (2019). "Developing a seasonal influenza vaccine recommendation in Kenya: Process and challenges faced by the National Immunization Technical Advisory Group (NITAG)." Vaccine 37(3): 464-472 and an advisory report presented to the Ministry of Health, Kenya dated May 2016: "Kenya National Immunization Technical Advisory Group (KENITAG) Influenza Vaccine Recommendation Note (28 May 2016)".

The literature review was conducted to provide an overview of the burden of influenza in Kenya. Searches were conducted in PubMed and PMC in 2015 and 2016. The following search terms were used:

PubMed search 2015 (search 1):

1. (Influenza[Title/Abstract] OR flu[Title/Abstract] OR flu-like illness[Title/Abstract] OR flu like illness[Title/Abstract] OR pneumonia[Title/Abstract] OR respiratory illness[Title/Abstract])
2. Influenza[MeSH Terms]
3. Kenya[Title/Abstract]
4. Kenya[MeSH Terms]
5. Search (1 OR 2) AND (3 OR 4). Filter: Human

PubMed search 2016 (search 2):

1. flu[Title/Abstract] OR influenza[Title/Abstract] OR influenza like illness[Title/Abstract] OR flu like illness[Title/Abstract])) OR (flu-like illness[Title/Abstract] OR influenza-like illness[Title/Abstract])) OR influenza[MeSH Terms]) OR human influenza[MeSH Terms]
2. Kenya[Title/Abstract]) OR Kenya[MeSH Terms]) OR republic of Kenya[MeSH Terms]
3. 1 AND 2. Filter: Human studies, studies within 10 years

PMC search 2016 (search 3):

1. flu[Title] OR influenza[Title] OR influenza like illness[Title] OR flu like illness[Title] OR flu-like illness[Title] OR influenza-like illness[Title])) OR influenza[MeSH Terms]) OR human influenza[MeSH Terms]) OR (flu[Abstract] OR influenza[Abstract] OR influenza like illness[Abstract] OR flu like illness[Abstract] OR flu-like illness[Abstract] OR influenza-like illness[Abstract])

2. Kenya[Abstract]) OR Kenya[Title]) OR Kenya[MeSH Terms]) OR republic of Kenya[MeSH Terms]

3. Search 1 AND 2

Local researchers were asked to provide additional research studies that had been conducted but were unpublished at the time of the literature review (search 4). The studies identified were assessed for relevance to the aim of the literature of review. The quality of relevant studies identified was assessed using the Critical Appraisal Skills Programme (CASP) tool. The CASP tool is a set of checklists that are used to review the methods used in different types of studies, as well as the credibility and relevance of results to local decision-making [65]. Studies that scored less than half of the total score were not considered. Thirty-two studies were selected for inclusion in the literature review (Table 2). Results from the selected studies were categorised as either describing the epidemiology of disease (health burden, risk factors, seasonality), health care use associated with illness or economic impact of illness.

Table 2: Number of studies identified during each step of the literature search process

Number of studies	Search 1	Search 2	Search 3	Search 4
No. of studies identified before screening of titles and abstracts	172	52	31	1
No. of relevant studies after screening of titles and abstracts	32	31	21	1
No. of studies retrieved in full text	26	31	21	1
No. of studies found relevant after reviewing full text	26	30	19	1
No. of studies utilized after assessing quality of evidence	25	29	18	1
Final number of studies after removal of duplicates	32			

2.1 Health burden of influenza in Kenya

2.1.1 Proportion of medically attended respiratory illness due to influenza in Kenya

One of the earliest records of laboratory confirmed influenza infection in the Kenyan population was published approximately 50 years ago [66]. In 1970, a sero-survey of 57 randomly selected patients attending hospitals in Mombasa was conducted to detect antibodies to the globally circulating influenza A and B virus strains. The antibodies were detected by the haemagglutination inhibition method. It was observed that 37% of samples tested positive for influenza A2/Hong Kong/68 antibodies, and 7% were positive for influenza B/Mass/3/66. At the time, little was known regarding the epidemiology of influenza in East Africa. This study was one of the first to highlight influenza as an important cause of respiratory illness in the region.

The next published study of influenza epidemiology was conducted in the 1980s. In this study conducted from 1 November 1981 to 31 October 1982, influenza was detected by immunofluorescence in only 1.1% of patients up to 5 years of age admitted with respiratory illness at the paediatric wards of Kenyatta National Hospital [67]. At the time, researchers concluded that influenza was not a significant cause of severe respiratory illness among children. However, immunofluorescence tests only have moderate sensitivity in detecting influenza, as compared to viral culture and molecular assays such as reverse transcription polymerase chain reaction (RT-PCR) and other nucleic acid amplification tests [68]. It is important to note that studies conducted in later years using molecular assays, present markedly different findings.

In later years, it has been shown that when testing both nasopharyngeal (NP) and oropharyngeal (OP) specimens for presence of the influenza virus by PCR, influenza is detected in 7 – 13% of all cases of medically attended respiratory illness in children <5 years of age [7, 69-74], and 12 – 39% of all cases of medically attended respiratory illness in individuals ≥5 years of age [7, 71, 72, 74, 75]. These differences in results may be due to differences in diagnostic test performance, duration of illness, quality and source of specimen, and time from collection to testing [68]. Aside from differences in laboratory testing, the wide variation in prevalence of influenza in Kenyan studies may also be due to differences in the types of studies, the timing of

the studies in regards to influenza peak activity, the region in which the study was conducted, the case definitions used, and the influenza strains tested (Table 3). A description of each of the studies that have described the proportion of individuals with influenza is provided in the appendices (Appendix 2: Description of burden of disease published articles).

Table 3: Summary of proportion of individuals who test positive for influenza virus in Kenya from published data

Age group	Region	Years covered	Sample	Test method	Prevalence of influenza*	Reference
<5 years	Nyanza, Rift Valley, North Eastern, Nairobi, Coast	2007 – 2010 1981 – 1982	NP swab &/or OP swabs, serum, NP aspirate	PCR, serology, indirect immunofluorescence	Cases Influenza: 1.1 – 62.1% Influenza A: 0.0 – 10.8% Influenza B: 0.0 – 5.2% Influenza C: 0.0 – 0.4% Controls Influenza: 3.7% Influenza A: 0.0 – 4.3% Influenza B: 0.0 – 1.5% Influenza C: 0.0 – 0.9%	[7, 10, 67, 69, 70, 72-74, 76, 77]
≥5 years	Nyanza, Rift Valley, North Eastern, Nairobi, Coast, Western	2007 – 2012	NP swab &/or OP swabs, serum, nasal swab	PCR, haemagglutination inhibition assays	Cases Influenza: 12.0-37.9% Influenza A: 9.0-40.9% Influenza B: 0.1-18.1% Controls Influenza: 4.3% Influenza A: 4.0% Influenza B: 1.0%	[10, 70-72, 74, 75, 78, 79]
All ages	Nyanza, Rift Valley, North Eastern, Nairobi, Coast Western, Nairobi, Eastern, Central	2007 – 2012	NP swab &/or OP swabs, NP wash or aspirate, nasal wash, throat swab, serum	RT-PCR, haemagglutination inhibition assay, Immunofluorescence	Cases Influenza: 3.9-37.6% Influenza A: 0.0-49.0% Influenza B: 0.3-7.7% Influenza C: 0.9-37.6% Controls Influenza: 0.5-7.6% Influenza A: 0.5% Influenza B: 0.0% Influenza C: 0.09%	[7, 8, 10, 60, 70, 80-84]

Cases refers to both in and outpatients with severe acute respiratory illness (SARI), acute respiratory illness (ARI), influenza like illness (ILI), severe acute respiratory disease (SARD), pneumonia, severe pneumonia, very severe pneumonia. Controls refers to patients without respiratory tract infection symptoms

2.1.2   Incidence of influenza in Kenya

2.1.2.1   Incidence of influenza-associated respiratory illness in the community

Few studies describe the incidence of influenza disease in the community [69, 75, 76]. Of the 3 published studies available, two articles refer to a population-based infectious disease

surveillance site in the former Nyanza province [75, 76], and the third article refers to a population-based infectious disease surveillance site in an informal urban settlement in Kibera, Nairobi [69] (

Table 4).

In the studies conducted in the former Nyanza province, researchers from the Centers for Disease Control and Prevention (CDC) and Kenya Medical Research Institute (KEMRI) conducted clinic and community based surveillance for respiratory illness from March 2007 to February 2010 in Asembo to identify causes of respiratory illness [75, 76]. The incidence of severe influenza among children <5 years of age was 5,800 (95% CI 3,800-7,800) per 100,000 person years observed [76], while the incidence of influenza A associated acute respiratory illness (ARI) among individuals ≥5 years was 2,600 (95% CI 2,280-2,920) per 100,000 person years observed and the incidence of influenza B associated acute respiratory illness was 200 (95% CI 150-250) per 100,000 person years of observation [75]. Among individuals ≥18 years of age, incidence of influenza acute respiratory illness (ARI) was much higher among individuals who were HIV positive (4,490 (95% CI 2,800-6,180) cases of influenza A per 100,000 person years of observation) compared to individuals who were HIV negative (1,420 (95% CI 1,040-1,800) cases of influenza A per 100,000 person years of observation) [75].

A team of researchers from the Centers for Disease Control and Prevention (CDC) conducted a similar study in Kibera, Nairobi from 2007 to 2011. Among children <5 years of age, the incidence of severe influenza was 1,300 (95% CI 600-2,000) per 100,000 person years of observation [69]. Despite the fact that the studies conducted in Nyanza and Nairobi collected data around the same time period that is 2007 to 2010 in Nyanza and 2007 to 2011 in Nairobi, collected both NP and OP samples from participants and tested for the presence of influenza with PCR, the incidence rates of influenza among the under 5 population appear to be slightly different. These findings could suggest regional differences in the epidemiology of influenza.

Table 4: Summary of data available on incidence of influenza disease in Kenya from published studies

Age group	Region	Years covered	Risk calculated	Mean rates per 100,000 person years of observation	Reference
<5 years	Nairobi, Nyanza	2007 – 2011	Incidence of influenza-associated SARI	Influenza A: 1,000-4,000 Influenza A & B: 1,300-5,800	[69, 76]
≥5 years	Nyanza	2007 – 2010	Incidence of influenza-associated ARI	Influenza A: 2,600 (95% CI 2,280-2,920) Influenza B: 200 (95% CI 150-250)	[75]

2.1.2.2 Incidence of medically and non-medically attended influenza-associated respiratory illness

In Kenya the incidence of medically and non-medically attended influenza-associated respiratory illness is dependent on the case definitions used in each study. In general, cases of upper respiratory tract illness that is influenza like illness are more common than lower respiratory tract illness, the incidence of disease is higher in the <5 years age group as compared to individuals ≥5 years of age, and non-medically attended rates of disease are higher than medically attended rates, underlying the fact that most individuals with influenza do not seek medical care for their illness (Table 5).

From 2007 to 2009 researchers from the Centers for Disease Control and Prevention (CDC) and Kenya Medical Research Institute (KEMRI), conducted a study to determine the causes of hospitalized acute respiratory illness in Bondo district (located in the former Nyanza province). By setting up surveillance systems at all the inpatient health facilities within the district, researchers were able to prospectively collect and test 2,079 oropharyngeal and nasopharyngeal samples from patients admitted with symptoms of acute respiratory illness (ARI) [7].

During this period, the rate of influenza-associated hospitalization was 56.2 (95% CI 50.0-62.4) per 100,000 population, with a rate of 143.7 cases (95% CI 119.6–167.8) per 100,000 population for children aged less than 5 years compared to 36.7 cases (95% CI 33.0-44.4) per 100,000 population for individuals 5 years of age and older. The rates of influenza-associated hospitalization observed among young adults were similar to the rates among the elderly. The comparatively low influenza-associated hospitalization rate among the elderly was postulated

to be as a result of low levels of health care utilization among this age group. The relatively higher incidence of influenza-associated hospitalization among young adults was thought to be due to higher prevalence of HIV among this population. However, researchers could not confirm this hypothesis as no HIV status data were presented in the study.

Fairly similar influenza hospitalisation incidence rates were observed from 2009 to 2012, when researchers from CDC, KEMRI and the United States Public Health Service conducted surveillance for influenza-associated ARI at two health facilities within a health demographic surveillance site (HDSS) in Karemo Division (located in the former Nyanza province). The average annual adjusted incidence of influenza-associated hospitalized SARI was 70 (95% CI 50–90) per 100,000 population. Among children <5 years of age, the rates of influenza-associated hospitalised SARI were 270 (95% CI 180-390) compared to 30 (95% CI 20-40) per 100,000 population for those ≥5 years of age [80]. The rates of medically-attended ILI associated with influenza were markedly high at 720 (95% CI 550-940) per 100,000. As was the case for medically attended SARI, the rates of medically attended influenza-associated ILI were higher in children <5 years of age (2180 (95% CI 1,510–3,160) per 100,000 population) compared to those ≥5 years of age (430 (95% CI 280-640) per 100,000 population [80].

Few studies in Kenya have attempted to describe the differences in incidence of influenza illness within older age groups. However, the varying incidence of influenza within younger age groups was illustrated during influenza surveillance carried out between 2007 and 2009 at the Kilifi Demographic Health Surveillance System (located in the former Coast province) [85]. During this surveillance period, researchers obtained nasopharyngeal samples of 2,956 children aged 1 day to 12 years presenting with symptoms of ARI. Influenza was detected in 3.9% of outpatients, while among inpatients admitted with features of severe or very severe pneumonia, influenza was detected in 4.9% of samples. The incidence of influenza-associated severe or very severe pneumonia among inpatients was 154 (95% CI 116-204) per 100,000 for children <1 year of age, 60 (95% CI 49-74) per 100,000 for children <5 years of age and 28 (95% CI 23-34) per 100,000 for children <13 years of age.

These differences in disease incidence among younger age groups were corroborated in a study conducted in Western Kenya by researchers from the Centers for Disease Control and Prevention and United States Public Health Service who also demonstrated the varying incidence of hospitalised and non-hospitalised influenza-associated SARI with age. Rates of hospitalised influenza-associated SARI were highest in children <6 months (570 (95% CI 240-1,380) per 100,000 persons), then children 6-11 months (470 (95% CI 180-1,190) per 100,000 persons) followed by children 12-23 months (440 (95% CI 230-850) per 100,000 persons) and children 2-4 years of age, 140 (95% CI 70-270) per 100,000 persons [80].

Among individuals ≥5 years, the change in rates of hospitalised influenza-associated SARI have been less frequently defined. In Western Kenya individuals 5-17 years of age were observed to have hospitalised influenza-associated SARI incidence rates of 20 (95% CI 10-50) per 100,000 persons, individuals 18-34 years rates of 30 (95% CI 10-70) per 100,000 persons, individuals 35-49 years rates of 40 (95% CI 10-120) per 100,000 persons and individuals ≥50 years 20 (95% CI 10-90) per 100,000 persons [80].

Although the findings of the studies conducted in Western Kenya (that is the former Nyanza province) differ from the studies conducted in Coastal Kenya (that is Kilifi), the results cannot be directly compared as they use different risk definitions. However, it is likely that the researchers underestimated the true prevalence of influenza in the Kilifi study by using nasopharyngeal samples alone in diagnosing presence of the virus. Oropharyngeal samples would have increased the diagnostic capacity to detect influenza by 22% (95% CI 9–42%) [85]. Despite this shortcoming, the Kilifi study was able to demonstrate variations in influenza incidence among children of different ages.

Studies in Kenya have consistently observed higher incidence of severe influenza disease among the <5 years age group when compared to older age groups [7, 80, 85]. Among children <5 years of age, there is additional evidence to suggest that the highest burden of disease occurs in children <1 year of age [80, 85]. In a study conducted in Kilifi in 2007, nasal wash samples were used to detect influenza among children presenting with features of respiratory illness. Among those presenting with severe pneumonia or very severe pneumonia, the rates of

influenza A were: 0.31 per 1,000 live births for neonates <28 days of age, 244 per 100,000 population for children <1 year of age, and 82 per 100,000 for children <5 years of age [86]. As with the previous study in Kilifi that used only nasal samples, the use of nasal wash samples alone may have underestimated the true prevalence of disease.

In refugee settings within Kenya, the incidence of influenza-associated hospitalization is several times higher than that observed in other settings. In Dadaab and Kakuma refugee camps surveillance was carried out from September 2007 to August 2010 to determine the causes of influenza like illness (ILI) and severe acute respiratory illness (SARI) among patients attending health facilities within the camps. For children <5 years of age, researchers were able to determine the population rates of SARI. Annual rates of influenza-associated hospitalisation were 500 per 100,000 children under 5 years of age, while annual rates of influenza B associated hospitalisation were 100 per 100,000 children under 5 years of age. The rates of influenza-associated hospitalisation were considerably higher among children less than 1 year of age compared to those 1 to 5 years of age [84]. The markedly higher rates of influenza-associated hospitalisation observed in refugee camps could be explained by higher rates of malnutrition, poor living conditions, and overcrowding [5].

In a systematic review of the incidence of influenza-associated medically attended influenza up to the year 2013, Emukule et al summarised that the annual incidence of influenza-associated medically attended respiratory illness was 570 per 100,000 persons or person years among children <6months of age, 140-1,230 per 100,000 persons or person years for children 1 year of age, 60-560 per 100,000 persons or person years for children <5 years of age and 20-40 per 100,000 persons or person years for individuals ≥5 years of age and 60-110 per 100,000 persons or person years across all ages [10].

It is worth noting that most Kenyan studies have typically provided provincial level or district level estimates of disease incidence [7, 8, 69, 70, 72, 73, 75-77, 79-81, 84, 86-88] with no attempt to extrapolate the findings to national level statistics. Yet data on the national burden of disease is often required in making decisions on whether to introduce a vaccine into a NIP.

In 2013, Fuller and colleagues [9] proposed a novel methodology for the calculation of national incidence using data from a few health facilities. The method was developed specifically for the limited resource setting. Using health facility surveillance data from one health facility with a defined catchment population within a province, and taking into account differences in risk factors for respiratory illness and health seeking behaviour between provinces, researchers were able to estimate the national disease burden. It was estimated that between August 2009 and July 2011 there were 17,129-27,659 cases per year of hospitalized influenza-associated severe acute respiratory illness (SARI) (2.9–4.7 per 1,000 persons) and 19,798-30,275 cases per year of non-hospitalized influenza-associated SARI among children less than 5 years old (3.3–5.1 per 1,000 persons). Among individuals aged 5 years and older, there were 6,882-7,836 cases per year of hospitalized influenza-associated SARI (0.21–0.24 per 1,000 persons), and 13,592-15,270 cases per year of non-hospitalized influenza-associated SARI (0.42–0.47 per 1,000 persons) [9]. Fuller's research provided useful country specific national data that would be essential in discussing the need for and potential impact of influenza control measures in Kenya at a national level.

Table 5: Summary of data on annual incidence of medically attended influenza disease in Kenya from published studies

Risk calculated	Dates covered	Region	Mean rates per 100,000 persons	References
Medically attended influenza like illness	2009 - 2012	Nyanza	<5 years: 2,180 ≥5 years: 430 All ages: 720	[80]
Non medically attended influenza like illness	2009 - 2012	Nyanza	<5 years: 3,010 ≥5 years: 540 All ages: 910	[80]
Medically attended acute lower respiratory illness	2007 - 2010	Nyanza, Nairobi	<5 years: data not available ≥5 years: data not available All ages : 1,630#	[8]
Hospitalised severe respiratory illness*	2007 - 2012	National, Nyanza, Rift Valley, North Eastern, Coast, Nairobi	<5 years: 60-610 ≥5 years: 20-40 All ages : 56-110	[7, 9, 10, 80, 84-86]
Non-hospitalised severe respiratory illness*	2008 - 2012	National, Nyanza	<5 years: 290-510 ≥5 years: 42-50 All ages: 120	[9, 80]

*Severe respiratory illness refers to severe or very severe pneumonia or severe acute respiratory illness
#Results refer to findings per 100,000 person years

2.1.3 Mortality associated with influenza in Kenya

The mortality associated with influenza is usually described among patients admitted to hospital. Mortality associated with the disease can vary from 0-4.3% among inpatients, depending on the infecting strain, age group affected and presence of co-morbidities [7, 73, 75].

During six years of influenza surveillance carried out between 2007 and 2013, only 0.9% of patients admitted with influenza died [15]. However, during the H1N1 pandemic of 2009, of 49 patients confirmed to have been infected with pandemic H1N1, two patients died (4%), both of whom had co-infections (malaria and secondary bacterial infection) [89].

In Bondo, Kenya the case fatality rate among patients of all ages admitted with influenza from 2007 to 2009 was 2%. In this study, a higher rate of mortality was observed among children <5 years of age (7.6 (95% CI 0.5-2.5) influenza deaths per 100,000 population) as compared to individuals ≥5 years of age (0.2 (95% CI 0.0-0.6) influenza deaths per 100,000 population) [7].

In a study conducted in Kilifi among admitted patients 1 to 12 years of age, 4% of children infected with influenza died. All deaths were recorded in patients with co-morbidities such as HIV, severe malnutrition or chronic heart disease [85].

The differences in mortality among children less than 5 years of age, and the effect co-morbidities have on mortality in children are not clearly described in local studies. Among the under 5 years' age group, researchers in a study conducted in Western Kenya observed that while no child aged 0-23 months admitted with influenza infection died, 4.3% of children infected with the influenza virus aged 24-59 months died. Among children co-infected with malaria and influenza 2.4% of children aged 0-23 months died, while no child 24-59 months of age died [73].

2.2 Risk factors for influenza disease in Kenya

The surveillance data described above suggests that young age and HIV, increase the risk of severe influenza disease. There are few studies reported in Kenya that are specifically designed to identify risk factors for influenza disease. However, where appropriately designed studies are

reported, they are able to demonstrate that HIV and chronic lung disease are important risk factors for severe influenza disease in Kenya [90]. Researchers in Kenya identified these two conditions as important risk factors for influenza among the >5 years' age group. From March 2006 to August 2008, a neighbourhood matched case control study was conducted by the Ministry of Health, CDC and KEMRI to identify risk factors for hospitalized seasonal influenza in rural western Kenya [90].   During primary analysis, HIV, chronic lung disease, current tuberculosis and ownership of cattle and chicken were associated with increased odds of hospitalized influenza infection. However, in multivariate analysis, only chronic lung disease and HIV were found to be associated with hospitalized influenza (aOR 6.83, 95% CI 1.37-34 and aOR 3.56 95% CI 1.25-10.07 respectively) [90].

In addition to the findings described above, the researchers provided data on the population attributable fraction of these exposures, that is the contribution each of these risk factors made to the national burden of influenza disease. Researchers were able to show that although chronic lung disease was more strongly associated with the odds of influenza hospitalization, because of the relatively lower prevalence of chronic lung disease in the general Kenyan population, it was found that chronic lung disease accounted for only 8% of the population burden of hospitalized influenza. Whereas HIV, though less strongly associated with influenza hospitalization, but a relatively more common disease in Kenya, accounted for 15% of the population burden of hospitalized influenza. As a result of their findings the researchers called for targeted influenza immunization of HIV positive patients in Kenya.

Identifying risk factors for disease and those most at-risk for disease is an important component of the immunization decision-making process. Those at increased risk for disease may be prioritized for vaccination. Targeting the most at-risk group, may result in greater impact in reducing disease burden and possibly greater cost savings as compared to a generalized approach to vaccination [57]. Based on the available Kenyan studies so far, patients with HIV and chronic lung disease as well as children <5 years of age have been observed to be at increased risk of severe influenza disease.

2.3 Influenza seasonality

Influenza transmission is present throughout the year [60, 69], however transmission varies according to the influenza strains and geographic location. Over 6 years of national surveillance it was observed that most activity seemed to occur in the second half of the year [15]. The table below presents data on reported influenza peak activity, nationally and across regions for studies where data was collected for at least 12 continuous months.

Table 6: Summary of peaks in influenza activity across regions in Kenya from published data of research conducted over one year

Region	Peaks of activity
National	Mar [60], Jul [60], Aug [60], Jul - Aug & Oct [60], Jul to Nov [15], Oct to Nov [83]
Nairobi	June - Jul (inf A) [69], Jul – Aug [8], Oct - Dec (inf A) [69]
Nyanza	Jan – Feb [7], Jan - Jul (inf A) [91], July – Aug [7], July – Aug [8], Apr - Dec (inf B) [91], May – Oct [7], May - Oct (inf A) [91]
Coast	Apr - Jul [85], Jul – Dec [85], Oct - Nov (inf A) [92]
North Eastern	Nov – Dec (inf A) [84]

Due to the limited number of studies, it was not possible to describe distinct differences in seasonality between regions. However, across all regions, peak influenza activity was described from May to August and October to November.

2.4 Health care use associated with influenza disease in Kenya

Studies in Kenya have not yet described the proportion of patients with influenza who seek medical attention. However, it has been observed that among patients with influenza who attend outpatient clinics, the proportion of patients admitted will vary from 0% to 10% [8, 88]. The frequency of admission is higher among children <5 years of age (27%) than among individuals ≥5 years of age (7%) [8]. A cross sectional study of acute febrile illness conducted in Western Kenya (in the former Nyanza province), observed that among children <5 years of age

seen at the outpatient clinic with influenza, 28.2% of children 0-23 months of age and 9.4% children 24-59 months of age were admitted [73]. It is worth noting that in some cases, admission rates not only vary with the severity of illness, but with the capacity of the health facility to admit patients [8].

Among patients admitted with influenza, the median duration of stay for hospitalised patients is 4 days [15]. The duration of admission can vary between age groups. In Western Kenya, the mean duration of hospitalisation for children 0-23 months of age with influenza was 3.7 days (SD 1.8), and 1.6 days (SD 0.5 days) for children 24-59 months of age [73].

2.5   Economic impact of influenza disease and vaccination in Kenya

One published study estimates the national annual direct and indirect cost of influenza to be between US $2.96–5.37 million for inpatients and US $5.96–26.35 million for outpatients in Kenya [93]. In this study conducted from July 2013 to August 2014, the mean cost per episode of influenza-associated illness was US$117.86 (standard deviation [SD], 88.04) among inpatients and US$ 19.82 (SD, 27.29); among outpatients. However, due to the higher number of outpatient visits, the overall outpatient cost of treating influenza was higher than the overall inpatient cost of treatment. Indirect costs of influenza (that is due to productivity losses) were lower than direct medical costs for inpatient cases, while indirect costs were higher than direct medical costs for outpatients [93].

There were no economic evaluation studies of influenza vaccine conducted in Kenya or Africa at the time of the search. In addition, no studies on cost-effectiveness of influenza vaccines were found from low-income countries in any systematic reviews of published literature on the subject [57]. Nonetheless, studies conducted in high and middle income countries find influenza vaccination to be cost effective and/or cost saving for populations at highest risk of severe disease that is children and the elderly [57-59, 94, 95]. From both societal and payer's perspective, routine vaccination of children (healthy or ill) with live attenuated influenza vaccine (LAIV) was associated with increased cost effectiveness compared to use of the inactivated influenza vaccine though the initial cost of LAIV is higher [58, 59]. From both the

societal perspective and family perspective, vaccinating children against influenza is cost saving with a benefit/cost ratio of 1.8 and 2.15 respectively. However from the provider perspective there are no cost savings [95]. Vaccinating against influenza for patients with mild moderate or severe COPD is very cost effective, more so in those with severe COPD [57, 94]. If immunization programs targeted children under two years and the elderly over 65, influenza infection associated costs could be reduced by 59% [57].

In Thailand, the incremental cost effectiveness ratio is between 2,000-5,000 international dollars per disability adjusted life year (DALY) averted [96].Vaccinating children aged between 6 months to 15 years at high risk of influenza complications in Argentina was cost-effective with US$ 57.36 saved per influenza episode averted [57]. Evidence from Europe shows that following influenza vaccination, the cost per episode of acute febrile respiratory process avoided was 5 euros while the cost per paediatric visit avoided was 6.87 euros following influenza vaccination among children. The cost per episode of antibiotic consumption avoided was 25.18 euros and cost per QALY gained equaled 18.26 euros [95]. Influenza vaccination among the elderly population has been found to be cost effective from both the third party and societal perspective and could save between 7,454 and 11,169 life years, leading to net costs per life year saved between US$ 1,210 and 1,910, respectively [57]. In Columbia, the payer was observed to experience cost saving through reduced hospitalizations by vaccinating health care workers in close contact with hospitalized oncological patients [57]. There were no systematic reviews identified describing the economic impact of influenza vaccination in healthy adults and pregnant women.

2.6   Summary

Substantial research has been conducted in Kenya describing the health burden of disease, more so in children <5. Few national level studies have been conducted, with most studies conducted in the former Nyanza province and Coastal region. Few studies describe the burden of disease in those with comorbidities, pregnant women and the elderly, all of whom are influenza vaccination priority groups identified by the World Health Organization (WHO). There

is limited data on local risk factors for severe influenza disease however there is data to suggest that HIV positive individuals and those with chronic respiratory illness are at higher risk of severe illness. Mortality is variable but has been shown to be as high as 4% among those hospitalized with influenza. Influenza is transmitted year round with variable peaks in activity, although differences between regions cannot as yet be clearly ascertained. The virus leads to substantial health care utilization, with direct medical costs reaching US $ 5 million per year. The annual direct and indirect cost of influenza ranges between US $8-32 million per year. Influenza vaccination can be cost effective and potentially cost saving, however no economic evaluations have been conducted in African countries.

2.7   List of supplementary material available in Appendix 2

Table 19: Proportion of cases positive for influenza virus among children less than 5 years of age

Table 20: Proportion of cases positive for influenza among individuals ≥5 years of age

Table 21: Proportion of cases positive for influenza across all age groups

Table 22: Incidence of influenza disease

Table 23: Incidence of medically attended influenza disease

3 Results: Objective 1 - National annual burden of hospitalized and non-hospitalized influenza-associated severe acute respiratory illness in Kenya, 2012 to 2014

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3.1 Abstract

Background: Influenza-associated respiratory illness was substantial during the emergence of the 2009 influenza pandemic. Estimates of influenza burden in the post-pandemic period are unavailable to guide vaccine policy in Kenya.

Objectives: To update estimates of the burden of hospitalized and non-hospitalized influenza-associated severe acute respiratory illness (SARI) during a post-pandemic period (2012-2014) and describe the incidence of disease by narrow age categories.

Methods: We used data from Siaya County Referral Hospital to estimate age-specific base rates of SARI. We extrapolated these base rates to other regions within the country by adjusting for regional risk factors for acute respiratory illness (ARI), regional health-care utilization for ARI and the proportion of influenza positive SARI cases in each region, so as to obtain region specific rates of influenza-associated hospitalized and non-hospitalized SARI.

Results: The mean annual rate of hospitalized influenza-associated SARI among all ages was 21 (95% CI 19-23) per 100,000 persons, while rates of non-hospitalized influenza-associated SARI were approximately 4 times higher at 82 (95% CI 74– 90) per 100,000 persons. Mean annual rates of influenza-associated SARI were highest in children <2 years of age with annual hospitalization rates of 147 (95% CI of 134-160) per 100,000 persons and non-hospitalization

rates of 469 (95% CI 426-517) per 100,000 persons. For the period 2012-2014, there were between 8,153-9,751 cases of hospitalized influenza-associated SARI and 31,785-38,546 cases of non-hospitalized influenza-associated SARI per year.

Conclusions: Influenza virus was associated with substantial disease burden in Kenya, especially among very young children, <2 years of age. This highlights the need for strategies to prevent influenza infections in this age group.

3.2   Background

Influenza is an important cause of respiratory illness in Kenya, accounting for up to 27% of all medically attended cases of respiratory illness [10]. Most Kenyan studies have focussed on providing sub-national estimates of influenza disease burden [8, 69, 75, 76, 80, 84, 85, 92]. The only national estimates of the incidence of influenza-associated severe acute respiratory illness (SARI) were calculated for the period July 2009-August 2011 [9], when the influenza A(H1N1)pdm09 (H1N1pdm09) virus circulated at markedly high levels [97] and presented with unusual epidemiology, affecting younger adults and sparing those ≥65 years of age [98]. As H1N1pdm09 virus circulated in subsequent years, the severity and epidemiology of illness associated with the pandemic influenza strain could have changed, as has been observed for other pandemic viruses [99].

Previous national estimates of the incidence of influenza-associated SARI described the burden of severe influenza in children <5 years of age, and persons aged ≥5 years. From studies conducted in temperate countries, the risk of influenza is known to vary by age, being highest at extremes of age [11]. Moreover, the World Health Organization (WHO) recommends vaccination for children 6-23 months of age [11]. The influenza vaccine is not included as part of the national immunization program in Kenya. More current information could inform Kenyan health authorities about the relative value of introducing influenza vaccination in specific age groups.

3.3 Objectives

We adapted a methodologic approach used previously [9], to:

i. Update estimates of the burden of hospitalized and non-hospitalized influenza-associated severe acute respiratory illness (SARI) during a non-pandemic period (from 2012 through 2014), and;

ii. Describe the incidence of severe influenza disease by narrow age categories to include individuals <6 months of age, <2 years of age and ≥65 years of age which would be useful when considering interventions

3.4 Methods

We adapted a previously described method used to estimate the burden of severe influenza disease in Kenya [9]. We calculated base rates of hospitalized SARI from Siaya County Referral Hospital (SCRH) in Nyanza region. These rates were extrapolated to the other regions in the country, by adjusting for regional risk factors for SARI and hospitalization. To calculate rates of non-hospitalized SARI, non-hospitalized SARI cases were indirectly estimated from healthcare utilization data on the proportion of acute respiratory illnesses that were hospitalized in Nyanza region. Region-specific data on the proportion of influenza-associated SARI were used to estimate regional rates of hospitalized and non-hospitalized influenza-associated SARI cases.

3.4.1 Base site

SCRH is located in Nyanza region which has the highest HIV prevalence at 15% [100] and the highest mortality among children aged <5 years within the country at 82 deaths per 1000 live births [101]. SCRH is embedded in a Health and Demographic Surveillance System (HDSS) in Karemo division. The Karemo division of the HDSS has a population of approximately 80,000 inhabitants [80].

We used SCRH and HDSS data from January 2012 through December 2014 as the basis for estimating the incidence of hospitalized SARI in the Nyanza region (henceforth referred to as base rates), which were then extrapolated to the other regions using the steps outlined further below.

3.4.2 Calculation of base rates of hospitalized SARI

Hospitalized SARI was clinically defined as a patient hospitalized with acute onset illness (within 14 days), reported fever (or recorded temperature of ≥38°C), and a cough. We calculated the annual age-specific base rates of hospitalized SARI by dividing the age-specific number of hospitalized SARI patients at SCRH who were enrolled in the HDSS, by the age-specific population of Karemo residents within the HDSS. These base rates of hospitalized SARI, which were assumed to be representative of the Nyanza region, were calculated for each of the following age groups: 0-5 months, 6-11 months, 12-23 months, 2-4 years, 5-14 years, 15-49 years, 50-64 years, and ≥65 years ((1).

> *Annual base rates of hospitalized severe acute respiratory illness (SARI) for the years 2012 to 2014 were calculated for the population of Karemo division enrolled in the Health and Demographic Surveillance System (HDSS). The number of hospitalized SARI patients at Siaya County Referral Hospital (SCRH) was divided by the age-specific population of HDSS residents in Karemo Division. The base rate of hospitalized SARI was calculated for each of the age groups and years under study.*

$$I_B = \frac{SARI_B}{Pop_B},$$

(1)

where,

I_B	=	Base rate of hospitalized SARI
$SARI_B$	=	Total number of cases meeting SARI case definition hospitalized in base region per year
Pop_B	=	Population of surveillance catchment area

3.4.3 Calculation of regional rates of hospitalized SARI

To obtain region-specific rates of hospitalized SARI, we first calculated an adjustment factor for each of the other 7 regions in Kenya. Calculation of the adjustment factor used the population prevalence of region-specific risk factors for SARI [101-103], the relative risk of each of the risk factors [104-106], and region-specific health care seeking practices for acute respiratory illness (ARI) [107].

An adjustment factor for hospitalized SARI within each region was calculated. The net prevalence of risk factors within each region (after deduction of the base region prevalence), was multiplied by each risk factor's relative risk value and summed. This figure was multiplied by the health care seeking practices in each region divided by the base region to account for differences in health care seeking practices between regions.

$$Adj_Y = \left(1 + \sum_i (P_{i,Y} - P_{i,B}) \times (RR_i - 1)\right) \times \frac{DHS_Y}{DHS_B},$$

(2)

where,

Adj_Y	=	Adjustment factor for region Y
$P_{i,Y}$	=	Prevalence of risk factor i in region Y
$P_{i,B}$	=	Prevalence of risk factor i in base region
RR_i	=	Relative risk of SARI due to risk factor i
DHS_Y	=	Proportion of ARI cases seeking care in region Y (from DHS)
DHS_B	=	Proportion of ARI cases seeking care in base region (from DHS)

For children <5 years old, 6 risk factors for SARI were used for adjustment: malnutrition (weight for age Z-score ≤-2), low birth weight (<2500 g), non-exclusive breastfeeding (during the first 4 months of life), household pollution (as indicated by use of solid fuels for cooking), crowding (≥5 persons in a household), and HIV prevalence. For individual's ≥5 years old, 3 SARI risk factors were used for adjustment: household air pollution, crowding and HIV prevalence. The regional adjustment factor was multiplied by the base SARI rate to estimate the region-specific hospitalized SARI rates ((3).

The incidence of hospitalized SARI in each region was calculated by multiplying the base rate of hospitalized SARI by the adjustment factor for the region

$$I_{H,Y} = I_B \times Adj_Y$$

(3)

where,

$I_{H,Y}$	=	Incidence of hospitalized SARI in region Y

36

3.4.4 Calculation of regional rates of non-hospitalized SARI

The rates of non-hospitalized SARI were estimated using data on self-reported episodes of pneumonia from a healthcare utilization survey (HUS) that was conducted in the Nyanza region [107]. In the HUS, pneumonia was defined as reported episodes of acute respiratory illness (ARI) characterized by cough and difficulty breathing for more than two days, or a diagnosis of pneumonia by a healthcare worker within the last 12 months. For the purposes of this study, non-hospitalized pneumonia as described in the HUS was equated to non-hospitalized SARI. The definition of pneumonia in the HUS could have included cases of ARI that do not require hospitalization, consequently the definition of SARI in the current study differs from the WHO definition that all cases of SARI require hospitalization [108]. The HUS provided data for 2 broad age groups: individuals <5 and ≥5 years of age.

As the HUS data was only available for the base region, we extrapolated the percentage of all those who reported pneumonia that resulted in hospitalization to the other regions by multiplying this percent by the proportion of individuals seeking healthcare for ARI for each region, compared to the base region ((5).

The total rates of regional SARI (combining hospitalized and non-hospitalized SARI) in the community were calculated by multiplying the region-specific rate of hospitalized SARI by the reciprocal of the estimated proportion of those with pneumonia who were hospitalized. In the final step, the rate of non-hospitalized SARI was calculated as the difference of the overall SARI rates in the community and the rate of hospitalized SARI ((4).

The rates of non-hospitalized SARI in the base region were calculated by applying findings from a health care utilization survey specific to hospitalization for pneumonia [107] . The proportion of individuals hospitalized for pneumonia in the other regions was obtained by applying an adjustment that took into account health care seeking for acute respiratory illness (ARI) in each region as compared to the base region.

$$I_{NH,Y} = \left(I_{H,Y} \times \frac{1}{HUS_Y} \right) - I_{H,Y}$$

Where,

$I_{NH,Y}$ =   Incidence of non-hospitalized SARI in region Y

HUS_Y =   Proportion of all SARI cases that are hospitalized in region Y

$$HUS_Y = HUS_B \times \frac{DHS_Y}{DHS_B}$$

Where,

HUS_B =   Proportion of all SARI cases that are hospitalized in the base region

HUS_Y =   Proportion of all SARI cases that are hospitalized in region Y

3.4.5 Calculation of regional rates of hospitalized and non-hospitalized influenza-associated SARI

The proportion of SARI due to influenza was collected from six influenza surveillance sites spread across the country: SCRH representing Nyanza region, Kakamega County Referral Hospital (CRH) representing the Western region, Mombasa CRH representing the Coast region, Nakuru CRH representing the Rift Valley region, Nyeri CRH representing the Central region and Kenyatta National Hospital (KNH) representing the Nairobi region. As surveillance data was not available in the Eastern and North Eastern regions during the study period, surveillance data from the sites in the neighbouring regions were used to estimate the average proportion of hospitalized influenza-associated SARI that was assigned to these two regions.

The region-specific rates of hospitalized and non-hospitalized influenza-associated SARI were calculated by applying the proportion of SARI cases that tested positive for influenza virus in each site to the regional rates of both hospitalized and non-hospitalized SARI ((6, (7).

The percentage of SARI due to influenza in each of the regional influenza surveillance sites was applied to the regional adjusted rate of hospitalized SARI, to obtain the region-specific rates of hospitalized influenza-associated SARI. As the annual number of specimens was limited, the percent positivity of SARI due to influenza was only calculated in two broad age groups: children <5 years and persons aged ≥5 years. The percent positivity for children aged <5 years was applied to all age groups aged <5 years.

Similarly, the percent positivity for influenza for persons aged ≥5 years was applied to all age groups five years and older.

$$IF_{H,Y} = I_{H,Y} \times F_Y$$

<div align="right">(6)</div>

Where,

$IF_{H,Y}$ =   Incidence of hospitalized influenza-associated SARI in region Y

F_Y =   Proportion of pneumonia due to influenza

As surveillance data was not available in the Eastern and North Eastern regions over the study period, surveillance data from the sites in the neighbouring regions were used to estimate the average proportion of hospitalized influenza-associated SARI that was assigned to these two regions. For the Eastern region, an average proportion of influenza positivity from the Coast, Rift Valley, Central and Nairobi regions was used, while for North Eastern region an average proportion of influenza positivity from Eastern and Coast regions was used.

The region specific rates of non-hospitalized influenza-associated SARI were calculated by multiplying the incidence of non-hospitalized SARI by the percent positivity for influenza at each surveillance site.

$$IF_{NH,Y} = I_{NH,Y} \times IF_{,Y}$$

<div align="right">(7)</div>

Where,

$IF_{NH,Y}$ =   Incidence of non-hospitalized influenza-associated SARI in region Y

F_Y =   Proportion of pneumonia due to influenza

3.4.6   Calculation of the number of hospitalized and non-hospitalized SARI cases

To obtain the number of cases, the region-specific rates of hospitalized and non-hospitalized SARI were multiplied with regional population data from the national census [103] ((8, (9). The national census data of 2009 were projected to the study period using the annual population

growth rate [109]. A similar approach was used to estimate the region-specific number of hospitalized and non-hospitalized influenza-associated SARI cases ((10, 11).

To obtain the number of hospitalized and non-hospitalized cases of SARI and influenza-associated SARI, the rates in each region were multiplied with the regional population data.

$$NI_{H,Y} = I_{H,Y} \times Pop_Y$$

(8)

$$NI_{NH,Y} = I_{NH,Y} \times Pop_Y$$

(9)

$$NF_{H,Y} = IF_{H,Y} \times Pop_Y$$

(10)

$$NF_{NH,Y} = IF_{NH,Y} \times Pop_Y$$

(11)

Where,

$NI_{H,Y}$	=	Number of hospitalized SARI cases in region Y
$NI_{NH,Y}$	=	Number of non-hospitalized SARI cases in region Y
$NF_{H,Y}$	=	Number of hospitalized influenza-associated SARI cases in region Y
$NF_{NH,Y}$	=	Number of non-hospitalized influenza-associated SARI cases in region Y
Pop_Y	=	Population in region Y

3.4.7 Differences in methodology between original and current study

There were a few differences between the original method described by Fuller *et al.* [9] and the current method. In the current study the catchment population of Karemo division was used to determine the base rates of SARI among those enrolled within the HDSS. In the method proposed by Fuller, base rates of SARI were calculated using a catchment population within 5 kilometres (km) of SCRH. However, an exploratory analysis of SARI rates calculated using

patients and residents within a 5 km radius of SCRH versus the whole of Karemo division produced similar results. Considering the finer age groups investigated and the potential for recording very few SARI cases for some age groups, the larger population of Karemo was chosen over a subset residing within a 5 km radius of SCRH.

Given the previous lack of data on HIV prevalence in children, Fuller and colleagues had proposed an algorithm for calculation of HIV prevalence in children. This algorithm took into account the prevalence of HIV positive mothers in each region, enrolment in prevention to mother to child transmission programs per region, and the HIV mother to child transmission rates. At the time of the current study, the Kenya HIV Estimates 2014 provided the number of children 0 to 14 years of age living with HIV in each region. By dividing this number with the population of each region, a rough estimate of the prevalence of HIV in children per region was obtained. The national estimate obtained from this approach (1.0%) was similar to published results from the Kenya AIDS Indicator Survey 2012 (0.9%) [100].

Lastly, when calculating the rates of non-hospitalized influenza-associated SARI, health care utilization survey data on the proportion of individuals with pneumonia who were admitted in the past 12 months was used, rather than the proportion of individuals with pneumonia who visited a hospital in the past 12 months as was used in the original study. It was felt that in calculating the rate of non-hospitalized influenza-associated SARI cases, using the proportion who were admitted rather than the proportion who visited a hospital would more accurately reflect the ratio of hospitalized to non–hospitalized cases. It was observed by the research team that a visit to the hospital though indicative of access to a health facility as explained in the original Fuller method, would not necessarily equate to hospitalization. Within the Kenyan setting, hospitalization is not only dependent on the severity of illness but also on whether in-patient facilities are available within the health facility, as well as the ability of the patient to afford admission. For these reasons it was argued that the proportion of individuals with pneumonia who were admitted in the past 12 months would more accurately reflect the difference between hospitalized and non-hospitalized influenza cases as compared to the proportion of individuals who visited a hospital. This change in input parameter would change the ratio of hospitalized to non-hospitalized patients. Table 7 provides a summary of the

differences in methodology between the original study conducted by Fuller *et al* and the current study and Table 8 presents the risk factors' relative risk values and the sources of data for both the original and current study.

Table 7: Differences in methodology between original study and current study

Difference in method	Original study	Current study
Catchment population of SCRH (hospital within base region) for calculation of base SARI rates	Population enrolled in HDSS within 5 km of SCRH in Karemo division	Population enrolled in HDSS residing in Karemo division
Estimation of HIV prevalence in children	Algorithm developed by authors that took into account regional differences in prevalence of HIV positive mothers, enrolment in prevention to mother to child transmission programs, and HIV mother to child transmission rates	Number of HIV positive children 0-14 years of age in each region divided by number of children of 0-14 years of age in each region
Calculation of rates of non-hospitalized influenza-associated SARI	Used health care utilization findings on proportion of individuals with pneumonia who visited a hospital in the past 12 months	Used health care utilization findings on proportion of individuals with pneumonia who were admitted in the past 12 months

Table 8: Risk factors, relative risks values and sources of data for the prevalence of risk factors in each region

Risk factor	Relative risk (reference number)	Source of risk factor prevalence data in the original study (reference number)	Source of risk factor prevalence data in the current study (reference number)
Malnutrition (weight for age Z-score ≤2)	1.8 [104]	Kenya Demographic Health Survey (DHS) 2009 [110]	Kenya DHS 2014 report and dataset [101, 102]
Low birth weight (<2500 g)	1.4 [104]	Kenya DHS 2009 [110]	Kenya DHS 2014 report and dataset [101, 102]
Non-exclusive breastfeeding (during first 4 months of life)	1.9 [104]	MICS UNICEF 2000 (8)	Kenya DHS 2014 dataset [102]
Household air pollution (use of solid fuels for cooking)	1.8 [104]	Kenya DHS 2009 [110]	Kenya DHS 2014 report [101] and Kenya population census 2009 [103]
Crowding (≥5 per household)	1.4 [104]	Kenya DHS 2003 [111]	Kenya DHS 2014 dataset [102]
HIV prevalence (children 0 - 14 years)	7.2 [105]	Algorithm provided in Appendix 2 of original paper [9]	Kenya HIV estimates 2014 (12)
HIV prevalence (≥ 15 years)	5.64 [106]	Kenya DHS 2009 (5)	KAIS 2012 (14) and Kenya population census 2009 (9)

3.4.8   Data analysis

Data analysis was performed using Microsoft Excel, R version 3.3.1 [112] and Stata version 13.0 [113]. Confidence intervals (CIs) of the regional SARI rates were estimated by running 1,000

iterations of each of the risk factors for hospitalized SARI by allowing the specific risk factor to vary within their 95% CI limits, while keeping all the other risk factors constant. The 2.5th and 97.5th values of these outputs were presented respectively as the lower and upper limits of the 95% CI of the regional hospitalized SARI rates. All rates were reported per 100,000 persons.

3.4.9   Ethical review

The study protocol at SCRH was approved by both the ethical review committee of the Kenya Medical Research Institute (KEMRI) (SSC-1801), and the institutional review board (IRB) of the U.S. Centers for Disease Control and Prevention (CDC) (CDC-3308). Surveillance for influenza within the other 5 influenza sentinel surveillance sites was part of routine surveillance by the Kenya Ministry of Health. Verbal consent to collect samples from patients at these sites was therefore considered adequate.

3.5   Results

3.5.1   Rates of hospitalized and non-hospitalized SARI

The national mean annual rate of hospitalized SARI was 228.1 (95% CI 208.1-249.4) per 100,000 persons (Table 25). Rates of hospitalized SARI were highest in Nyanza at 350.8 (95% CI 320.3 – 381.2) per 100,000 persons and lowest in Nairobi at 71.6 (95% CI 57.3-85.3) per 100,000 persons (Table 25). The national annual mean rate of non-hospitalized SARI was 3.7 times higher than the rates of hospitalized SARI at 847.1 (95% CI 768.3 – 932.0) per 100,000 persons (Table 26). Rates of non-hospitalized SARI were highest in Nyanza at 1,183.2 (95% CI 1,079.3-1,285.7) per 100,000 persons and lowest in Nairobi at 265.6 (95% CI 212.7-315.6) per 100,000 persons (Table 26). Rates of hospitalized and non-hospitalized SARI were higher among children <5 years of age compared to the older age groups (Table 25, Table 26). Rates of hospitalized and non-hospitalized SARI were highest in 2012 and lowest in 2014 (Figure 2).
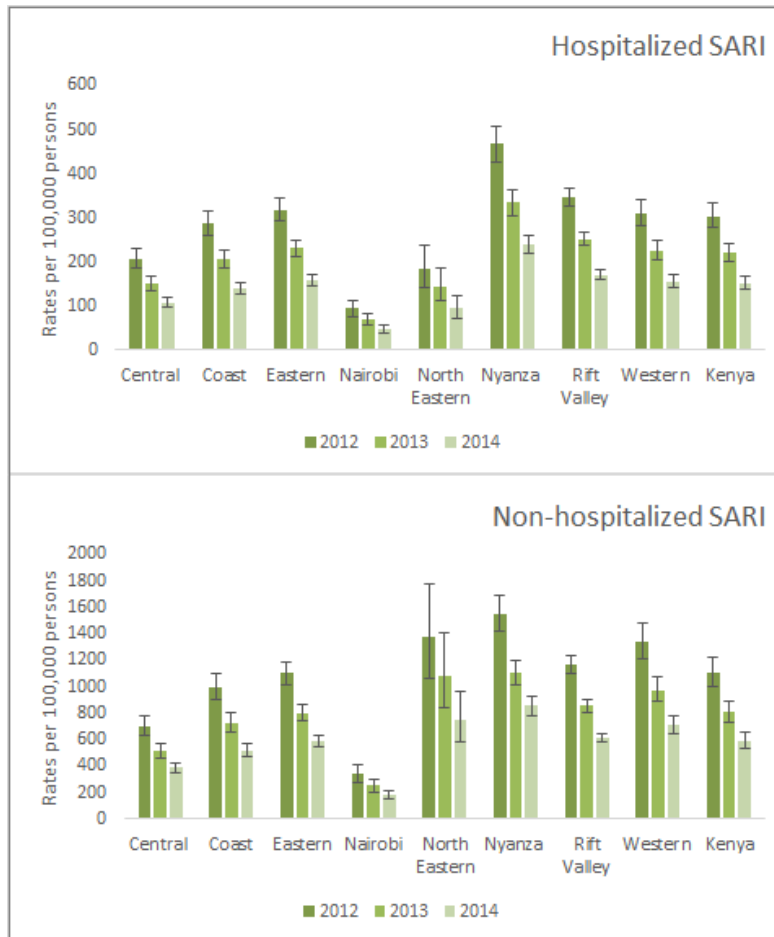
Figure 2: Rates of hospitalized and non-hospitalized severe acute respiratory illness (SARI) per 100,000 population in Kenya by region, 2012 to 2014

3.5.2   Rates of hospitalized influenza-associated SARI

Among children <5 years of age, the average annual influenza positivity was 8% in 2012 and 9% in 2013 and 2014, while among individuals ≥5 years of age, the average influenza positivity was 12% in 2012, 13% in 2013 and 10% in 2014 (Figure 3). The identified circulating influenza subtypes varied throughout the years (Figure 4). Influenza A(H3N2) virus accounted for 48% of viruses detected in 2012, influenza B accounted for 35% of influenza viruses detected in 2013 and H1N1pdm09 accounted for 48% of influenza viruses detected in 2014 (Table 9).
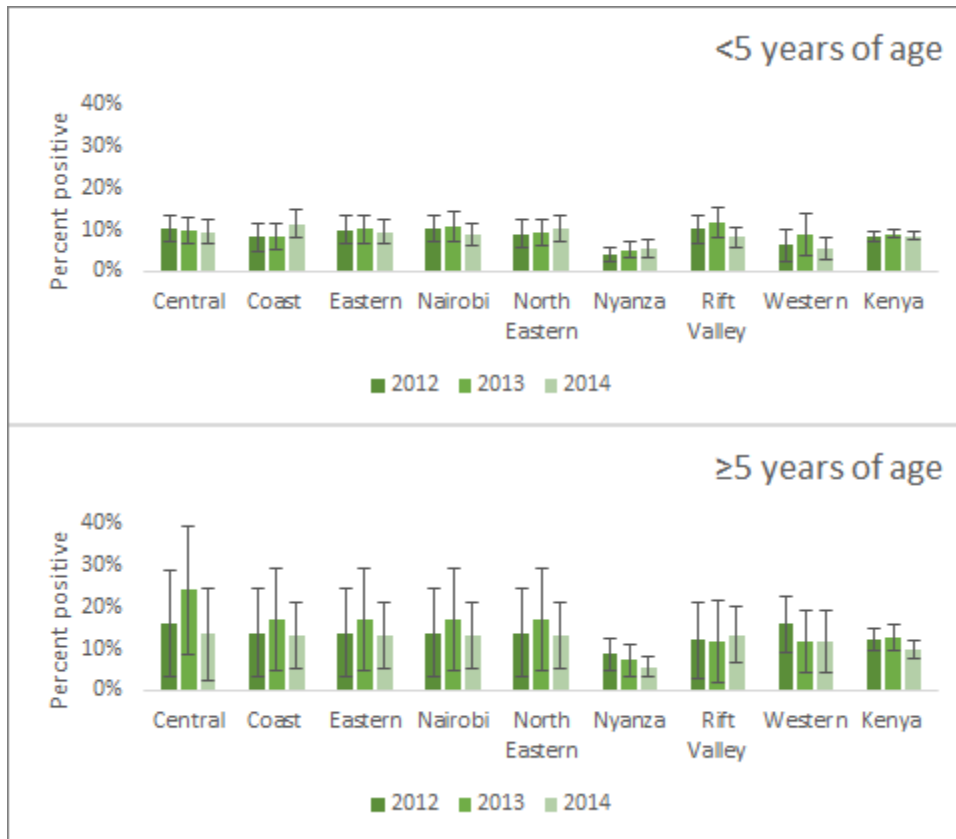
Figure 3: Proportion of severe acute respiratory infections (SARI) among children <5 years of age and individuals ≥5 years of age that tested positive for influenza by region, 2012 to 2014
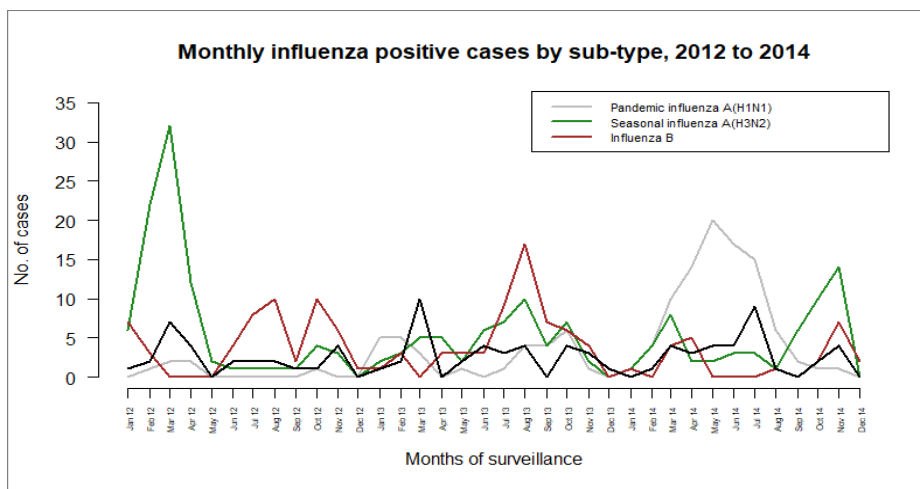
Figure 4: Monthly influenza positive cases by sub-type, 2012 to 2014

Table 9: Circulating influenza sub-types by year, 2012 to 2014

Year	2012		2013		2014	
Influenza Subtype	Number	Percent	Number	Percent	Number	Percent
Influenza B	59	29.4	77	35.0	21	7.8
Pandemic influenza A(H1N1)	7	3.5	32	14.6	129	48.1
Seasonal influenza A(H3N2)	97	48.3	70	31.8	80	29.9
Not subtyped	38	18.9	41	18.6	38	14.2
Total	201	100.0	220	100.0	268	100.00

The national mean annual rate of hospitalized influenza-associated SARI was 20.8 (95% CI 19.0-22.7) per 100,000 persons (Table 10). Rates of hospitalized influenza-associated SARI were highest in Rift Valley region (26.6 [95% CI 25.1-28.2] per 100,000 persons) and lowest in Nairobi (7.8 [95% CI 6.3-9.3] per 100,000 persons) (Table *25*). Overall, rates of hospitalized influenza-associated SARI were higher among children <5 years of age (100.6 [95% CI 91.7-110.3] per 100,000 persons) than among individuals ≥5 years of age (6.3 [95% CI 5.8-6.8] per 100,000 persons) (Table 10). The mean annual rates of hospitalized influenza-associated SARI were highest among children <2 years of age at 146.6 (95% CI 133.8-160.3) per 100,000 persons. Among the <2 years age group, rates among children 0-5 months of age were 112.2 (95% CI 102.5-122.6) per 100,000 persons, while rates among children 6-11 months of age and 12-23 months of age were 169.7 (95% CI 155.1- 185.8) per 100,000 persons and 152.7 (95% CI 139.3-167.1) per 100,000 persons respectively (Table 10). Among individuals ≥5 years of age, the mean annual rates of hospitalized influenza-associated SARI were highest among persons aged ≥65 years (9.8 [95% CI 8.9-10.5] per 100,000 population) and school age children 5-14 years of age (9.4 [95% CI 8.7-10.1] per 100,000 population) (Table 10). Rates of hospitalized influenza-associated SARI were highest in 2012 and lowest in 2014 (Figure 5).

Table 10: Average annual national age-specific rate and number of hospitalized and non-hospitalized influenza-associated severe acute respiratory illness (SARI) in Kenya, 2012 to 2014

Age	Hospitalized SARI cases		Non-hospitalized SARI cases	
	Rate*	No. of Cases	Rate*	No. of Cases
<5 years	100.6	6,642	325.7	21,502
	(91.7-110.3)	(6,055-7,280)	(294.7-360.3)	(19,451-23,782)
<2 years	146.6	3,714	469.0	11,885
	(133.8-160.3)	(3,391-4,063)	(425.7-516.6)	(10,787-13,091)
0-5 months	112.2	755	358.7	2,414
	(102.5-122.6)	(690-825)	(326.0-394.7)	(2,194-2,656)
6-11 months	169.7	1,163	542.6	3,718
	(155.1-185.8)	(1,063-1,273)	(493.0-598.1)	(3,378-4,098)
0-11 months	141.2	1,918	451.5	6,132
	(129.1-154.5)	(1,753-2,098)	(410.3-497.3)	(5,572-6,754)
12-23 months	152.7	1,796	489.2	5,753
	(139.3-167.1)	(1,638-1,965)	(443.4-538.8)	(5,215-6,337)
2-4 years	72.0	2928	236.5	9,617
	(65.5-79.1)	(2,664-3,217)	(213.0-262.9)	(8,664-10,691)
≥5 years	6.3	2,287	37.3	13,539
	(5.8-6.8)	(2,098-2,471)	(34.0-40.7)	(12,334-14,764)
5-14 years	9.4	1,113	56.7	6,695
	(8.7-10.1)	(1,025-1,199)	(51.6-61.8)	(6,103-7,299)
15-49 years	4.1	846	24.1	4,939
	(3.8-4.5)	(772-917)	(21.9-26.3)	(4,485-5,387)
50-64 years	7.3	183	42.4	1,066
	(6.7-8.0)	(169-200)	(39.1-46.7)	(982-1,175)
≥65 years	9.8	145	56.7	839
	(8.9-10.5)	(132-155)	(51.6-61.0)	(764-903)
All ages	20.8	8,929	81.7	35,041
	(19.0-22.7)	(8,153-9,751)	(74.1-89.9)	(31,785-38,546)

Rates calculated per 100,000 persons
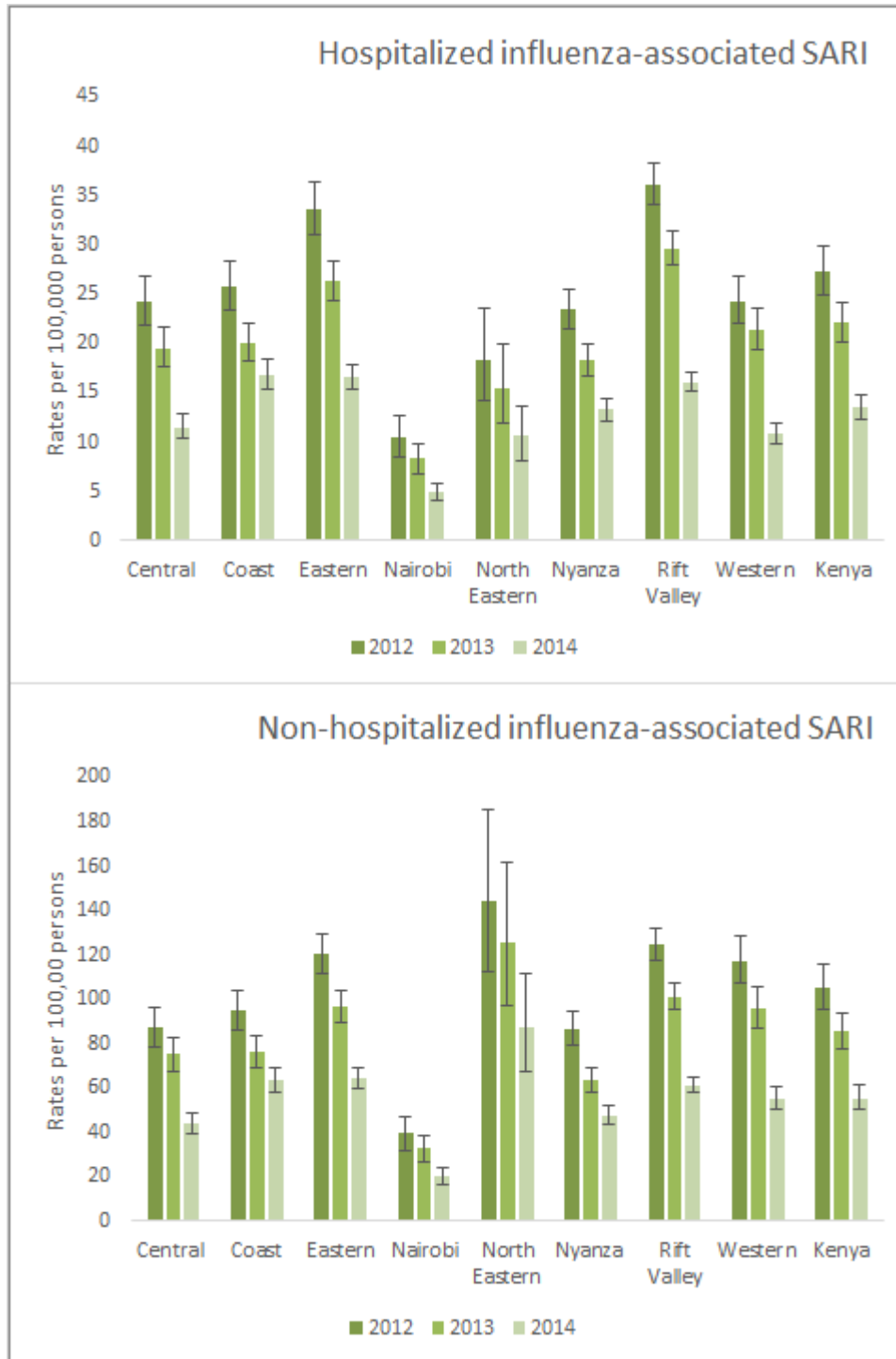
Figure 5: Rates of hospitalized and non-hospitalized influenza-associated severe acute respiratory illness (SARI) per 100,000 population in Kenya by region, 2012 to 2014

3.5.3 Rates of non-hospitalized influenza-associated SARI

The mean annual rate of non-hospitalized influenza-associated SARI was 81.7 (95% CI 74.1 – 89.9) per 100,000 persons (Table 10). Rates of non-hospitalized influenza-associated SARI were

highest in the North Eastern region (120.2 [95% CI 94.0-155.7] per 100,000 persons), and lowest in Nairobi region (30.5 [95%CI 24.4- 36.0] per 100,000 persons) (*Table 28*). Rates were higher among children <5 years of age (325.7 [95% CI 294.7–360.3] per 100,000 persons) as compared to individuals aged ≥5 years of age (37.3 [95% CI 34.0-40.7] per 100,000 persons) (Table 10). Similar to the hospitalized rates, rates of non-hospitalized influenza-associated SARI were highest among children <2 years of age (469.0 [95% CI 425.7-516.6] per 100,000 persons) (Table 10). Among individuals aged ≥5 years, rates of non-hospitalized influenza-associated SARI were highest among children 5-14 years of age (56.7 [95% CI 51.6-61.8] per 100,000 persons) and the elderly ≥65 years of age (56.7 [95% CI 51.6-61.0] per 100,000 persons) (Table 10). Rates of non-hospitalized influenza-associated SARI were also highest in 2012 and lowest in 2014 (Figure 3).

3.5.4   Number of hospitalized and non-hospitalized influenza-associated SARI cases

For the period 2012 through 2014, there were between 8,153-9,751 cases of hospitalized influenza-associated SARI and 31,785-38,546 cases of non-hospitalized influenza-associated SARI per year. Among children <5 years of age, the annual number of influenza-associated SARI hospitalized cases were 6,055-7,280, and non-hospitalized cases were 19,451-23,782 (Table 10). Among those ≥5 years of age, the annual number of influenza-associated SARI hospitalized cases were 2,098-2,471, and of non-hospitalized cases were 12,334-14,764 (Table 10). Overall there was a 30-40% decrease in the number of influenza-associated SARI cases during 2012-2014 compared to previously estimated numbers from the 2009-2011 period described in a study which used a similar methodology [9]. There was a 66-73% decline in the number of hospitalized influenza-associated SARI cases, while the number of non-hospitalized influenza-associated SARI cases dropped 5-15% during the same time frame (Table 11, Table 12).

Table 11: Comparison of average annual national rate and number of hospitalized influenza-associated severe acute respiratory illness (SARI) cases in Kenya during and shortly after the 2009 influenza pandemic (2009-2011) with seasonal influenza (2012-2014)

Age group	Hospitalized SARI cases			
	2009-2011[a]		2012-2014	
	Rate*	No. of cases	Rate*	No. of cases
<5 years	290-470	17,129-7,659	92-110	6,055-7,280
≥5 years	21-24	6,882-7,836	6-7	2,098-2,471
All ages	61-90	24,011-35,495	19-23	8,153-9,751

[a] Data from Fuller et al. [9]; *Rate per 100,000 persons

Table 12: Comparison of average annual national rate and number non-hospitalized influenza-associated severe acute respiratory illness (SARI) cases in Kenya during and shortly after the 2009 influenza pandemic (2009-2011) with seasonal influenza (2012-2014)

Age group	Non-hospitalized SARI cases			
	2009-2011[a]		2012-2014	
	Rate*	No. of cases	Rate*	No. of cases
<5 years	330-510	19,798 –30,275	295-360	19,451-23,782
≥5 years	42-47	13,592-15,270	34-41	12,334-14,764
All ages	84-115	33,390-45,545	74-90	31,785-38,546

[a] Data from Fuller et al. [9]; *Rate per 100,000 persons

3.6 Discussion

From 2012 through 2014, we estimated that the annual rate of hospitalized influenza-associated SARI was 21 per 100,000 population, while the annual rate of non-hospitalized influenza-associated SARI was 4 times higher at 82 per 100,000 population. Despite regional and year to year variation on rates of influenza-associated SARI, the group consistently most at-risk for hospitalization was children <5 years of age, and especially those <2 years of age. Among older age groups, those 5-14 years of age and adults ≥65 years of age had the highest hospitalization rates, though not in the same magnitude as that reported for young children.

Our findings support the hypothesis that the burden of influenza in Kenya during the influenza A(H1N1)pdm09 pandemic period (that is, 2009 to 2010) was higher than during non-pandemic years. Overall there was a 30–40% decline in the number of influenza-associated SARI cases between 2009-2011 and 2012-2014. In our study, the number of hospitalized influenza-

associated SARI cases was higher during 2012 when almost 50% of the samples were positive for H3N2 virus. H3N2 predominant-seasons in the US have been described as causing more severe disease in the very young and the very old [114]. In contrast, in 2014 we saw a resurgence of the H1N1pdm09 virus strain, representing almost 50% of the samples tested. That year was the mildest in terms of influenza-associated SARI hospitalizations. This may indicate a decline in the severity of the H1N1pdm09 virus strain over the years. The 2012-2014 decline in hospitalized influenza-associated SARI rates could also be attributed to a low threshold for admissions combined with increased health care seeking associated with heightened public awareness around the 2009 pandemic. In 2011, the Kenyan government introduced pneumococcal vaccination of children <1 year of age into the routine immunization program [115]. Use of the pneumococcal vaccine reduces all cause pneumonia admissions within the targeted age group [116], and may have contributed to the observed decline in SARI in children <5 years of age.

Based on the findings of the health care utilization survey, hospitalizations were estimated to occur in about 20% of influenza-associated SARI cases. In keeping with this finding, a study conducted in rural Kenya estimated that approximately 10-20% of patients with laboratory confirmed influenza-associated pneumonia were hospitalized [8]. Not all cases of influenza-associated SARI require hospitalization, some cases may be managed in the out-patient setting, however, in countries with relatively low health care utilization rates such as Kenya, where only 48% of children <5 years of age and 34% of individuals ≥5 years of age with pneumonia reportedly seek medical care in hospitals [107], calculating the burden of disease based on SARI cases admitted to hospitals alone would grossly underestimate the true burden of influenza disease in the community.

Using a similar methodology, a South African study estimated rates of hospitalized influenza-associated SARI among children <5 years of age of 58-276 per 100,000 persons [117] which is comparable to our estimates of 92-110 per 100,000 children. Rates of hospitalized influenza-associated SARI among Kenyan children <5 years of age in 2012 and 2013, were approximately twice as high as the influenza-associated hospitalization rates observed among the same age group in the United States [118]. In fact, the average annual rate of influenza-associated

hospitalizations in our study for children <5 years was higher than that reported in European countries or the Americas for the same age group [97], underscoring the need to explore the cost-effectiveness of influenza vaccines among those at highest risk of hospitalization.

Our rates of influenza-associated hospitalization among those <2 years, were twice as high as that among children 2-4 years. Children <2 years of age are at high risk for severe influenza disease [11]. Among the <2 years age group, rates of influenza-associated hospitalization were estimated to be higher in the 6-23 months age group than in the 0-5 months age group. These findings are in contrast to the US, where rates of influenza-associated hospitalization are higher in the 0-5 months age group than in the 6-23 month age group [119], however these differences could reflect an increased likelihood of new-born hospitalizations in the US for potential sepsis workup investigations. Few studies in Kenya have attempted to describe the incidence of hospitalized influenza-associated SARI among very young children [80, 120], yet these findings have an important bearing on the implementation of influenza vaccine policies. While children 6-23 months of age can be directly vaccinated against influenza, it is recommended that protection of children <6 months of age be provided through maternal vaccination [11].

In contrast to the high rates of hospitalized influenza-associated SARI among young children, rates for those ≥65 years of age were 9-11 per 100,000 persons. The rates of influenza-associated hospitalization among adults ≥65 years observed in the US are approximately 20 times higher than what we documented for Kenya [118]. In Kenya, the elderly are least likely to seek medical care when ill [121], and this may have contributed to the lower than expected rates of hospitalization in this age group. The difference between rates in Kenya and the US could also be partially explained by approaches to case ascertainment; in Kenya, only patients meeting SARI case definition were tested for influenza whereas in the US study [118] influenza testing was driven by clinicians' suspicion of influenza, allowing for less typical non-respiratory influenza presentation to be detected. Similarly, ARI and pneumonia definitions used in the HDSS to identify SARI cases could have missed influenza-associated cases if signs/symptoms were associated with pre-existing underlying conditions or resulted in atypical presentations of influenza [122, 123].

We also found that children 5-14 years of age had high rates of influenza-associated hospitalization (9-10 per 100,000 persons) among those ≥5 years of age, similar to rates among the elderly (9-11 per 100,000 persons). Similarly in India, children 5-14 years of age had the second highest rates of influenza-associated hospitalizations among individuals ≥5 years of age [124]. In the India study, rates of hospitalization among school going children were 2 to 5 times higher than those observed among the elderly. While these findings may reflect differences in health care seeking between younger and older individuals, the results also suggest that school going children may be an important risk group to consider for influenza prevention strategies.

Our study had a few limitations. During our study period, patients could have sought care in facilities other than SCRH, leading to an underestimation of our SARI rates. The calculation of non-hospitalized SARI rates is based on a health care utilization survey conducted >10 years ago that described the proportion of individuals aged <5 years and ≥5 years of age who were hospitalized with pneumonia. It is important to note that health care utilization may have changed over the past 10 years and health care seeking behaviour may vary with age, especially among the elderly, which could impact the precision of non-hospitalized case estimation. It may also be argued that hospitalized influenza-associated SARI is in fact a more severe form of respiratory illness than non-hospitalized influenza-associated SARI, because individuals with more severe disease are more likely to seek medical care [107]. The hospitalized and non-hospitalized SARI case definitions used in the study would therefore not refer to illnesses of equal severity. In spite of these limitations, we were able to provide reasonable estimates of rates of hospitalized and non-hospitalized influenza-associated SARI, enabling appreciation of influenza as an important public health matter in Kenya.

3.7   Conclusion

Influenza virus is associated with a substantial amount of severe respiratory disease burden in Kenya, especially among very young children. Children <2 years of age could be considered as a priority group for influenza vaccination in Kenya. As influenza vaccine is not licensed for

children <6 months of age, maternal vaccination of pregnant women could be considered in order to protect this age group.

3.8 List of supplementary material available in Appendix 3

Table 24: Prevalence and 95% confidence interval limits for regional risk factors for severe acute respiratory illness and healthcare seeking behaviour for acute respiratory illness in Kenya

Table 25: Annual regional rate of hospitalized severe acute respiratory illness (SARI) in Kenya by region, 2012 to 2014

Table 26: Annual regional rate of non-hospitalized severe acute respiratory illness (SARI) in Kenya by region, 2012 to 2014

Table 27: Annual regional rate of hospitalized influenza-associated severe acute respiratory illness (SARI) in Kenya by region, 2012 to 2014

Table 28: Annual regional rate of non-hospitalized influenza-associated severe acute respiratory illness (SARI) in Kenya by region, 2012 to 2014

4 Results: Objectives 2 and 3 - Seasonal influenza vaccination in Kenya: an economic evaluation using dynamic transmission modelling

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4.1 Abstract

Background: There is substantial burden of seasonal influenza in Kenya, which led the government to consider introducing a national influenza vaccination program. Given the cost implications of a nationwide program, local economic evaluation data are needed to inform policy on the design and benefits of influenza vaccination. We set out to estimate the cost-effectiveness of seasonal influenza vaccination in Kenya.

Methods: We fitted an age-stratified dynamic transmission model to active surveillance data from patients with influenza from 2010-2018. Using a societal perspective, we developed a decision-tree cost-effectiveness model and estimated the incremental cost-effectiveness ratio (ICER) per disability-adjusted life year (DALY) averted for three vaccine target groups: children 6-23 months (strategy I), 2-5 years (strategy II) and 6-14 years (strategy III) with either the Southern Hemisphere influenza vaccine (Strategy A) or Northern Hemisphere vaccine (Strategy B) or both (Strategy C: twice yearly vaccination campaigns, or Strategy D: year round vaccination campaigns). We assessed cost-effectiveness by calculating incremental net monetary benefits (INMB) using a willingness-to-pay (WTP) threshold of 1-51% of the annual gross domestic product per capita ($17-872).

Results: The mean number of infections across all ages was 2-15 million per year. When vaccination was well timed to influenza activity, the annual mean ICER per DALY averted for vaccinating children 6-23 months ranged between $749-1,385 for strategy IA, $442-1,877 for strategy IB, $678-4,106 for strategy IC and $1,147-7,933 for strategy ID. For children 2-5 years it

ranged between $945-1,573 for strategy IIA, $563-1,869 for strategy IIB, $662-4,085 for strategy IIC, and $1,169-7,897 for strategy IID. For children 6-14 years it ranged between $923-3,116 for strategy IIIA, $1,005-2,223 for strategy IIIB, $883-4,727 for strategy IIIC and $1,467-6,813 for strategy IIID.

Overall, no vaccination strategy was cost-effective at the minimum ($17) and median ($445) WTP thresholds. Vaccinating children 6-23 months once a year had the highest mean INMB value at $872 (WTP threshold upper limit), however this strategy had very low probability of highest net benefit.

Conclusion: Vaccinating children 6-23 months once a year was the most favourable vaccination option, however, the strategy is unlikely to be cost-effective given the current WTP thresholds.

4.2 Introduction

Influenza is an important cause of respiratory illness in Kenya, especially in children under 5 and in particular, young children under 2 [10, 125]. In 2016, the Kenya National Immunization Technical Advisory Group (KENITAG) recommended annual seasonal influenza vaccination for children 6-23 months of age [126]. KENITAG further recommended pilot projects to generate additional local data to inform implementation of a nationwide influenza vaccination policy. In particular, KENITAG requested that local evidence be generated on influenza vaccine cost-effectiveness, because their recommendation largely relied on studies in non-African countries [23, 57, 95]. Given the cost implications of a nationwide program, local economic evaluation data are needed to inform policy on the design and benefits of influenza vaccination in Kenya.

In countries with year-round influenza activity, the World Health Organisation (WHO) recommends vaccination with the most recent influenza vaccine formulation before the primary peak in influenza activity [127, 128]. In Kenya, cases are observed year round [15], with an equal number of cases occurring during the Northern Hemisphere (NH) and Southern Hemisphere (SH) seasons [129]. There are no published influenza vaccine cost-effectiveness

studies in Kenya. In other tropical settings with year-round influenza transmission, there is some quantification of the effect of elderly vaccination [130], but no evidence of the impact of vaccinating children.

Although evidence from intervention and observational studies on the indirect effects of influenza vaccination is limited [131], dynamic transmission models have proven useful to evaluate the effect of public health interventions targeted at infectious diseases, because they incorporate direct and indirect effects of vaccination [132, 133]. By doing so, it is possible to identify the optimal target group and coverage level for vaccination programs, especially where the impact of herd immunity significantly alters disease incidence and outcomes [55].

Using a dynamic transmission model, researchers in the United Kingdom (UK) showed that expanding the influenza vaccination program to include children 5-16 years of age would be the most efficient strategy in further reducing morbidity and mortality associated with influenza in their country [53]. We adapted this age-stratified transmission model to estimate the burden of disease associated with seasonal influenza from 2010-2018 in Kenya. Our objectives were to identify the most cost-effective target group and to estimate the ideal timing and vaccine formulation by comparing the incremental cost-effectiveness ratios (ICER) per disability-adjusted life year (DALY) averted for different vaccination scenarios. This information may assist policy makers in determining optimal seasonal influenza vaccination strategies.

4.3   Methods

We obtained influenza surveillance data among patients hospitalised with severe acute respiratory illness (SARI) in Kenya from 2010 to 2018 and defined peaks in influenza activity. We fitted a transmission dynamic model to these epidemics by fitting the number of SARI cases, the number of tested samples, and the number of influenza virus-positive samples, by week and age group (<1, 1-5, 6-14, 15-19, 20-49 and ≥50 years of age). The virus-positive samples were categorised by influenza type and subtype: influenza B, influenza A H1N1pdm09 (A(H1N1)pdm09) and influenza A H3N2 (A(H3N2)). We set each influenza year from September to August the following year, except at the start of the study period because data were

available from January 2010. Using epidemiological information, we then estimated the number of asymptomatic cases, symptomatic cases, deaths and DALYS due to influenza each year. Using health care utilisation data and costs of illness we determined the number of health care utilisation events and costs of influenza each year. Thereafter, we modelled different influenza vaccination strategies and determined the ICER per DALY averted and incremental net monetary benefit (INMB) of each vaccination strategy.

4.3.1 Influenza surveillance data

We used weekly numbers of patients hospitalised with SARI identified through the Kenyan national SARI surveillance system from 1 January 2010 to 31 December 2018. This system is run by the Ministry of Health in a few health facilities, and supported by the Centers for Disease Control and Prevention (CDC), Kenya [15]. There are approximately 759 hospitals with in-patient capacity in the country, of which 50 have a bed capacity of ≥200 [134]. We used data from 5 of these larger health facilities: Siaya, Nyeri, Mombasa, Nakuru and Kakamega County Referral Hospitals where a well-established SARI surveillance system was in place, and comprehensive data for the full study period was available (Appendix 4, section 7.4.1). We excluded data from circulation of influenza A(H1N1)pdm09 during the pandemic period (January 2010 to December 2011) to focus on seasonal epidemics, because the influenza A(H1N1)pdm09 pandemic did not present normal influenza activity in Kenya and was associated with higher level of severity than other circulating strains [135].

Hospitalized patients with SARI were included in the surveillance system if illness onset was acute (within 14 days from admission date) and they presented with fever (or history of fever) and cough. Nasopharyngeal (NP) and oropharyngeal (OP) samples were tested by real time reverse transcription-polymerase chain reaction (rRT-PCR) from a random subset of these hospitalized patients [15]. Of the 24,480 cases identified through the SARI surveillance system, 80% were tested for influenza virus.

Although catchment populations are defined for each public health facility in Kenya they are more reflective of administrative criteria and often do not reflect actual health care utilization

especially where other private options are available. We therefore defined hospital-specific catchment populations around each SARI surveillance site as the population within 10 kilometers of the hospital. This was informed by a study in Kenya that showed 90% of children admitted with symptoms of a febrile illness, reside within 10 kilometers of the health facility (Appendix 4, section 7.4.1) [136].

Kenya has year-round influenza transmission. To allow fitting and simulation of vaccine impact in the model, we used the following activity-period decision rule. We identified periods of high influenza activity as ≥2 successive weeks where the proportion of subtype-specific test-positive cases was greater than the average weekly proportion during the entire study [137]. A period ended when there were ≥2 consecutive weeks where the proportion of subtype-specific positive cases was less than the weekly average. In addition, influenza-positive cases had to be observed in at least 3 of the 5 surveillance sites during the identified period so that periods identified were of widespread transmission. During model fitting, start and end dates were adjusted to centre the model peak to observed cases. If the posterior mean estimate of the net reproduction number at the start of the simulation was less than 1 (that is little evidence of sustained transmission) the period was excluded.

4.3.2   Transmission model

We modified an age-stratified Susceptible-Exposed-Infectious-Recovered (SEIR) compartmental modelling framework previously used to inform influenza vaccination policy decision-making in the UK (Appendix 4, section 7.4.2)[53, 138]. The main differences between the UK model and Kenya model and their impact on the findings are summarised in the supplementary text (Appendix 4, section 7.4.7).

Mixing between age groups was governed by social contact survey data from Kenya collected from the coastal region [139]. The latent period was fixed at 0.8 days, and the infectious period at 1.8 days [53]. Probability of transmission and the fraction of the population susceptible varied each season, and the values were estimated during fitting. The SEIR compartments were

stratified into vaccine-naïve and vaccinated populations. The model is available in the fluEvidenceSynthesis package in R [112, 140].

4.3.3 Parameter inference

Parameters of the model were fitted to Kenyan surveillance data using Bayesian evidence synthesis [53]. Bayesian evidence synthesis "*combines prior knowledge and data from multiple sources systematically, linking different data sources through equations that describe how data sources, quantities to be estimated, and model parameters relate to each other* [141]." For each season we inferred the transmissibility of the virus, the susceptibility of 3 age groups (≤14 years, 15-49 years, ≥50 years), the initial number of infections, the number of infections introduced from outside Kenya, the probability of identifying an influenza positive patient within the catchment population in each of 3 age groups (<1 years, 1-5 years, ≥6 years), and the number of subtype-specific influenza cases in the whole Kenyan population during each epidemic. We determined the age groupings for susceptibility and ascertainment based on comparisons of the best fit of the model to the observed data.

Where there was more than one circulating subtype during a season, we fitted the model separately to each subtype. We ran 500,000 Markov Chain Monte Carlo (MCMC) iterations after a burn in of 200,000. We thinned the chain of 500,000 iterations to 2% and all results are presented from 10,000 samples from the joint posterior distribution. Posterior mean values and 95% Bayesian credible intervals (CI) are given.

4.3.4 Vaccination component

We considered 12 vaccination strategies using: i) 3 age groups: 6-23 months, 2-5 years, 6-14 years; ii) 4 vaccination timings: vaccination campaigns in April-June, October-December, or both (to coincide with NH or SH vaccine availability), and year-round vaccination (Table 13). Vaccination coverage levels varied by strategy. We assumed that year-round vaccination would achieve higher coverage levels than shorter campaigns due to longer availability of vaccine, and that vaccination coverage of older children would be slightly higher than younger children, based on findings from a demonstration vaccination program in Kenya [142]. For biannual

60

vaccination we assumed that individuals would only be vaccinated once per year, and that in each vaccination period only individuals who had not been vaccinated in the preceding 12 months would receive vaccine. Vaccination was assumed to occur at a constant rate during the vaccination period.

Table 13: Vaccination scenarios modeled in three age groups and four vaccination timings.

		Vaccination timing and uptake			
		A: Apr-Jun SH vaccine	B: Oct-Dec NH vaccine	C: Apr-Jun & Oct-Dec Both vaccines	D: Year-round Both vaccines
Age group	I: 6-23 months	30%	30%	45%	60%
	II: 2-5 years	35%	35%	50%	65%
	III: 6-14 years	40%	40%	55%	70%

Coverage values were set based on influenza vaccination studies in Kenya [142] and local consultation. NH – Northern Hemisphere, SH – Southern Hemisphere

We assumed that the NH and SH vaccines provided "all-or-nothing protection" that is for 80% vaccine effectiveness (VE), 80% of vaccinated people receive 100% protection from infection [143]. Protection lasted from the time of vaccination up to the end of the subtype specific influenza activity period. Vaccine protection was restricted to an epidemic and was not carried forward to future epidemics. We assumed that the NH vaccine provided protection against influenza activity that began between September of the same year to February of the next year and did not protect against influenza activity beginning between March and August. Similarly, the SH vaccine provided protection against influenza activity that began between March to August of the same year and did not provide protection against activity starting either earlier or later than these months.

Influenza vaccine effectiveness varies each year and differs across age groups. To simplify the model, we used sub-type specific published values of overall influenza VE to set a fixed value of

VE in the model as either good (70%) or poor (42%) in all target age groups. If published VE was ≥50%, VE was modelled at 70% across all age groups, however if VE was <50%, VE was set at 42% in the model (Appendix 4, section 7.4.3). The choice of a fixed influenza VE value was informed by a systematic review and was validated in the original UK study [53].

4.3.5 Economic evaluation

We used an economic evaluation decision tree to categorise infected individuals as asymptomatic, symptomatic with mild illness (upper respiratory tract (URT) infections) or symptomatic with severe illness (lower respiratory tract (LRT) infections) based on influenza challenge studies [144]. Those with mild illness were either seen at an outpatient clinic or were not medically attended, while patients with severe illness were either hospitalised or not. All those with mild illness were assumed to recover, while those with severe illness either recovered or died (Appendix 4, section 7.4.4).

We calculated DALYs from disability weights of mild upper respiratory infection, moderate lower respiratory tract infection, severe lower respiratory tract infection, and death [145] (Appendix 4, section 7.4.4). We estimated the proportion of cases that attended outpatient clinics or were hospitalised using representative South African influenza-specific healthcare utilization data [146] (Table 14). To estimate costs from a societal perspective, we used an influenza costing study that described direct medical costs, healthcare-related costs, and indirect costs of influenza illness among patients with influenza attending health facilities in Kenya [93] (Figure 6, Table 15).
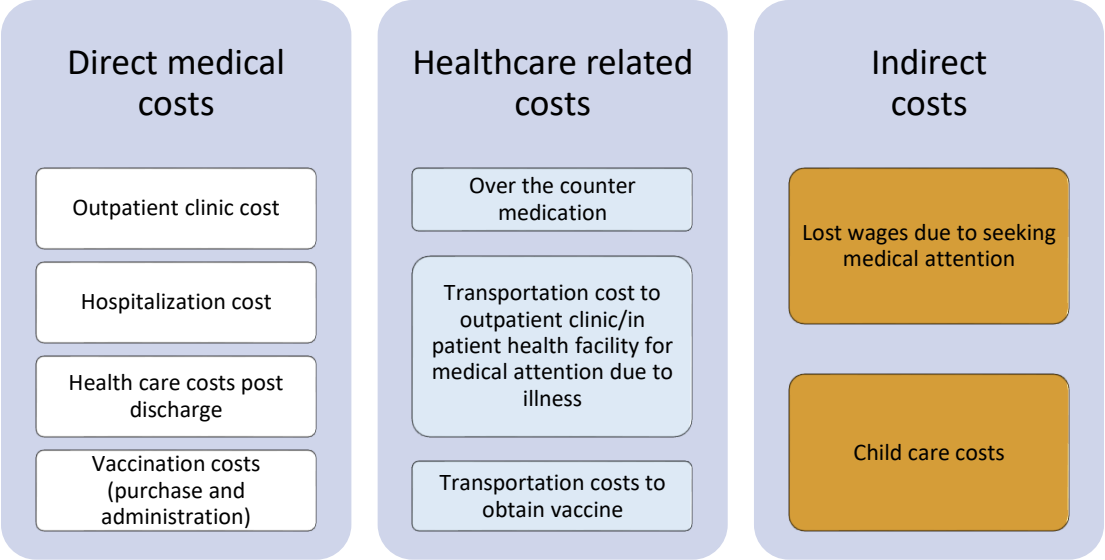
Figure 6: Summary of costs associated with influenza illness and vaccination. *Shading of boxes: white = direct medical costs paid by government (presupposes a universal healthcare scheme with government as the main healthcare payer), blue = healthcare-related costs paid by individual, orange = indirect costs paid by individual.*

Table 14: Values for disease states and heath utilization rates used in economic model. Mean and 95% confidence interval (CI) or proportions are given

Item	Measure	Value	Distribution	Reference
Disease states				
Proportion of influenza cases that develop any clinical symptoms	mean (95% CI)	0.669 (0.583 - 0.745)	Normal	[144]
Proportion of influenza cases that develop upper respiratory tract symptoms/mild illness	mean (95% CI)	0.588 (0.455-0.708)	Normal	[144]
Proportion of influenza cases that develop lower respiratory tract symptoms/severe illness	mean (95% CI)	0.210 (0.140-0.303)	Normal	[144]
Proportion of influenza cases with severe illness that die while hospitalised				
<1 year	mean (95% CI)	0.0274 (0-0.0616)	Truncated normal	Influenza SARI surveillance dataset (2010-2018)
1-5 years	mean (95% CI)	0.0091 (0-0.0322)		
6-14 years	mean (95% CI)	0.0108 (0-0.0902)		
15-20 years	mean (95% CI)	0 (0-0.1116)		
20-49 years	mean (95% CI)	0.0331 (0-0.0818)		
≥ 50 years	mean (95% CI)	0.1818 (0.0909-0.3080)		
All ages	mean (95% CI)	0.0200 (0.0035-0.0373)		
Proportion of deaths due to a respiratory illness that occur in a health facility				
<1 year	mean (95% CI)	0.2794 (0.2451-0.3140)	Normal	Siaya health demographic and surveillance site dataset (2010-2016)
1-5 years	mean (95% CI)	0.2899 (0.2471-0.3349)		
6-14 years	mean (95% CI)	0.4361 (0.3534-0.5278)		
15-20 years	mean (95% CI)	0.5250 (0.3750-0.6795)		
20-49 years	mean (95% CI)	0.5067 (0.4626-0.5525)		
≥ 50 years	mean (95% CI)	0.2715 (0.2421-0.3012)		
All ages	mean (95% CI)	0.3287 (0.3106-0.3474)		
Health care utilization events				
Proportion of symptomatic influenza cases who attend outpatient clinic				
0-5 years	mean (95% CI)	0.475 (0.39-0.60)	Normal	[146]
6-12 years	mean (95% CI)	0.118 (0.09-0.17)		

13-17 years	mean (95% CI)	0.088 (0.06-0.13)		
18-24 years	mean (95% CI)	0.035 (0.02-0.08)		
25-44 years	mean (95% CI)	0.034 (0.02-0.07)		
45-64 years	mean (95% CI)	0.027 (0.01-0.05)		
≥ 65 years	mean (95% CI)	0.036 (0.02-0.07)		
Proportion of symptomatic influenza cases who are hospitalised				
0-5 years	mean (95% CI)	0.0102 (0.0089-0.0117)	Normal	[146]
6-12 years	mean (95% CI)	0.0007 (0.0006-0.0010)		
13-17 years	mean (95% CI)	0.0006 (0.0004-0.0011)		
18-24 years	mean (95% CI)	0.0008 (0.0006-0.0010)		
25-44 years	mean (95% CI)	0.0021 (0.0018-0.0024)		
45-64 years	mean (95% CI)	0.0026 (0.0020-0.0033)		
≥65 years	mean (95% CI)	0.0033 (0.0025-0.0044)		
Proportion of outpatient influenza cases who purchased medication prior to clinic visit	proportion	0.718	Fixed value	[93]
Proportion of hospitalised influenza cases who sought care after discharge from hospital	proportion	0.105	Fixed value	[93]
Proportion of non-medically attended influenza cases where household members missed work due to illness*	proportion	Not known	-	-
Proportion of outpatient influenza cases where household members missed work due to illness	proportion	0.518	Fixed value	[93]
Proportion of hospitalised influenza cases where household members missed work due to illness	proportion	0.848	Fixed value	[93]
Proportion of non-medically attended influenza cases where household members paid for childcare during illness*	proportion	Not known	-	-
Proportion of outpatient influenza cases where household members paid for childcare during illness	proportion	0.18	Fixed value	[93]
Proportion of hospitalised influenza cases where household members paid for childcare during illness	proportion	0.29	Fixed value	[93]

These items were not included in the model as the values were unknown and difficult to estimate in the case of non-medically attended illness

Table 15: Cost of influenza associated illness in US dollars showing year of valuation.

Type of cost	Measure	Value in USD	Year	Distribution	Source
Direct medical costs					
Facility based medical costs among influenza cases attending outpatient clinic	mean (SD)	4.34 (1.30)	2014	Normal	[93]
Facility based medical costs among hospitalised influenza cases	mean (SD)	59.19 (59.39)	2014	Normal	[93]
Health care costs after discharge among hospitalised influenza cases who sought care after discharge	mean (SD)	3.28 (6.19)		Normal	[93]
Influenza vaccine purchase costs per dose (varied in sensitivity analysis)	fixed	3	2018	Fixed value	Assumption
Vaccine administration cost per dose					
Supply chain cost per dose from national level to the health facility	mean	0.43	2012	Fixed value	[147]
Provision of immunization services at the health facility	mean (SD)	1.0 (0.72)	2012	Normal	[147]
Health care related costs					
Transportation costs among influenza cases attending outpatient clinic	mean (SD)	0.40 (0.87)	2014	Normal	[93]
Transportation costs among hospitalised influenza cases	mean (SD)	5.03 (8.32)	2014	Normal	[93]
Transportation costs to receive vaccine at health facility	mean (SD)	0.20 (0.435)	2014	Normal	Assumption*
Health care costs prior to outpatient visit among influenza cases who purchased medication before the outpatient visit	mean (SD)	1.39 (3.90)	2014	Normal	[93]
Indirect costs					
Lost wages among influenza cases not seeking formal health care for mild illness	fixed	0	-	Fixed value	Assumption
Lost wages among influenza cases attending outpatient visit who report that household members missed work	mean (SD)	12.84 (27.17)	2014	Normal	[93]
Lost wages among hospitalised influenza cases who report that household members missed work	mean (SD)	42.02 (41.54)	2014	Normal	[93]
Lost wages among those not hospitalised with severe influenza illness	-	Not known	-	-	-
Childcare costs among influenza cases attending outpatient clinic who report household members paid for childcare	mean (SD)	0.07 (0.57)	2014	Normal	[93]
Childcare costs among hospitalised influenza cases who report household members paid for childcare	mean (SD)	0.11 (0.75)	2014	Normal	[93]
Childcare among those not hospitalised for severe influenza illness	-	Not known	-	-	-

*For this cost no data existed and an assumption was made that the cost would be half of the transportation costs for outpatient care.

In the case where no data was available for costs incurred by non-medically attended cases, these costs were not included in the model. SD = standard deviation

Vaccine administrative costs were obtained from a vaccine delivery costing study in Kenya and Tanzania (Table 15) [147]. We set vaccine purchase price at $3 US dollars (USD) per dose for a multi-dose vial, which was considered a reasonable price based on available market prices for the trivalent inactivated vaccine, if obtained through a negotiated agreement for low- and middle-income countries (LMICs). We tested the sensitivity of our results to this cost. Vaccine wastage was assumed to be 15% [148]. Costs from before 2018 were adjusted to 2018 USD values using the annual Kenya gross domestic product (GDP) deflator values.

We calculated annual ICERs per DALY averted for all 12 strategies compared to no vaccination (base scenario), as influenza vaccination was negligible in Kenya during the study period. We time discounted DALYs by 3% [149]. Average annual ICERs per DALY averted were calculated for each vaccine strategy. A cost saving output resulted in an increase in benefit and overall decrease in total costs incurred. For each strategy, we calculated the probability that it had the highest INMB at willingness-to-pay (WTP) thresholds of 1-51% of the 2018 Kenya GDP per capita (that is between $17-872 per DALY averted), and used the results to construct cost-effectiveness acceptability curves [150]. We then constructed cost-effectiveness acceptability frontiers depicting the highest probability for the most optimal strategy (that is the strategy with highest average INMB) [151].

In sensitivity analysis we calculated DALYs with and without social weighting and time discounting [149]. Social weighting placed greater value on life lost from 9-56 years of age. We tested the impact of changing the vaccine purchase price to $1.5, $3.0, $6.0 and $10.0 per dose. Finally, we tested the impact of maintaining the same vaccine coverage across all age groups that is 30% coverage for once yearly campaigns, 45% coverage for twice yearly campaigns and 60% for year-round vaccination.

4.3.6   Ethics statement

Permission to undertake secondary data analysis of de-identified SARI surveillance data collected from patients admitted at county referral hospitals, was obtained from the Kenyatta National Hospital – University of Nairobi Ethics Review Committee (P18/01/2017).

4.4 Results

4.4.1 Periods of high influenza activity

We fitted 11 periods of high influenza activity in 7 of the 9 years of surveillance data. Five periods were associated with influenza B, four with A(H3N2) and two with A(H1N1)pdm09 (Figure 7). In one year, there were 3 peaks in activity (September 2017-August 2018), and in two years, there were two peaks in activity (September 2010-August 2011, and September 2015-August 2016). September 2014-August 2015 and September 2016-August 2017 had no influenza activity periods that met the activity-period decision rule. The remaining three years had one period of influenza activity each (Table 16, Appendix 4, section 7.4.5).
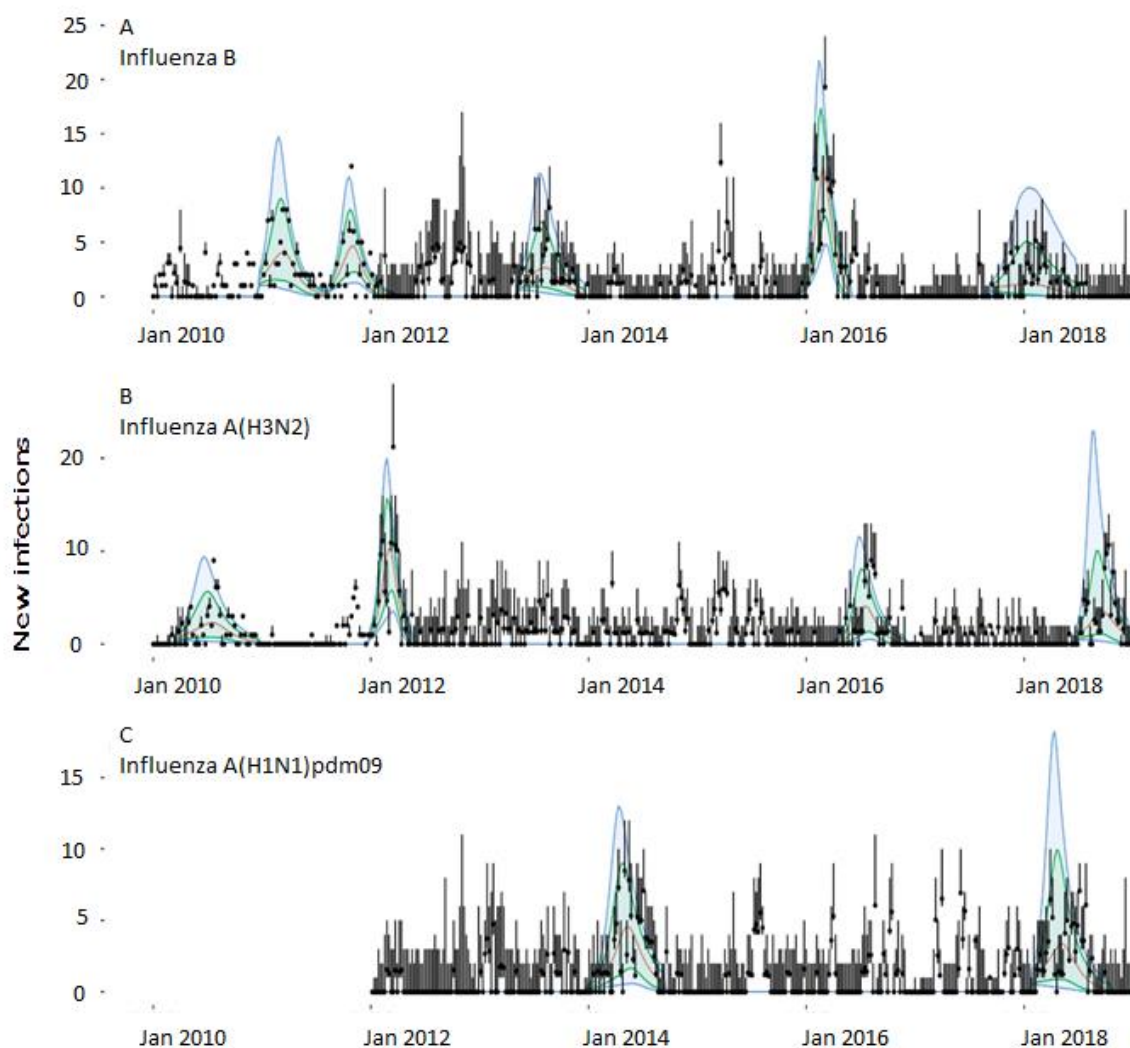
Figure 7: Comparison of the fit of the model to weekly influenza-positive SARI cases in all ages. *Positive cases detected in the influenza surveillance system (black) with hypergeometric 95% confidence interval. Lines and shading represent the median (red) and 50% (green) and 75% credible intervals (blue) of the fitted model. Note that the model is fitted to age-specific data, but age groups are aggregated here for clarity. A: Influenza B; B: Influenza A(H3N2); C: Influenza A(H1N1)pdm09). Influenza A(H1N1)pdm09 data from January 2010 to December 2012 were excluded from the analysis.*

Table 16: Periods of high influenza activity, 2010-2018.

Year	NH season	Subtype	Vaccine match	SH season	Subtype	Vaccine match
Jan 2010-Aug 2010				03/2010-12/2010	A(H3N2)	M
2010-2011	12/2010-08/2011	B	M	08/2011-03/2012	B	M
2011-2012	12/2011-05/2012	A(H3N2)	U			
2012-2013				05/2013-12/2013	B	M
2013-2014	12/2013-09/2014	A(H1N1)pdm09	M			
2014-2015						
2015-2016	11/2015-05/2016	B	M	03/2016-11/2016	A(H3N2)	U
2016-2017						
2017-2018	09/2017-06/2018	B	U	06/2018-12/2018	A(H3N2)*	U
	01/2018-10/2018	A(H1N1)pdm09	M			

*An influenza year begins in September and ends in August the following year. 'M' means the vaccine was well matched to circulating strains (VE = 70%) [53]. 'U' means vaccine was poorly matched to circulating strains (VE = 42%) [53]. Blank cells indicate no detectable peak in influenza activity. *There were no SH VE estimates available at the time, and we used VE values for the NH vaccine.*

Of the 11 periods of high influenza activity, 6 started between September and February and were suited to vaccination with the NH vaccine, and 5 started between March and August and were suited to the SH vaccine (Table 16). There were 8 instances where limited influenza activity did not meet the activity decision criteria (Appendix 4, section 7.4.5).

4.4.2   Disease burden in the absence of vaccination

We estimated that the mean number of infections per year (includes asymptomatic and symptomatic infections) was 2.0-15.0 million (Figure 8, and Appendix 5), corresponding to a mean annual attack rate of 5-32%. For years where more than one period of high influenza activity was modelled, the mean annual number of infections was 5.7-15.0 million and the mean annual attack rate was 12-32%, while for years that had one peak, the yearly average was 2.0-6.7 million infections with a mean annual attack rate of 5-16%.
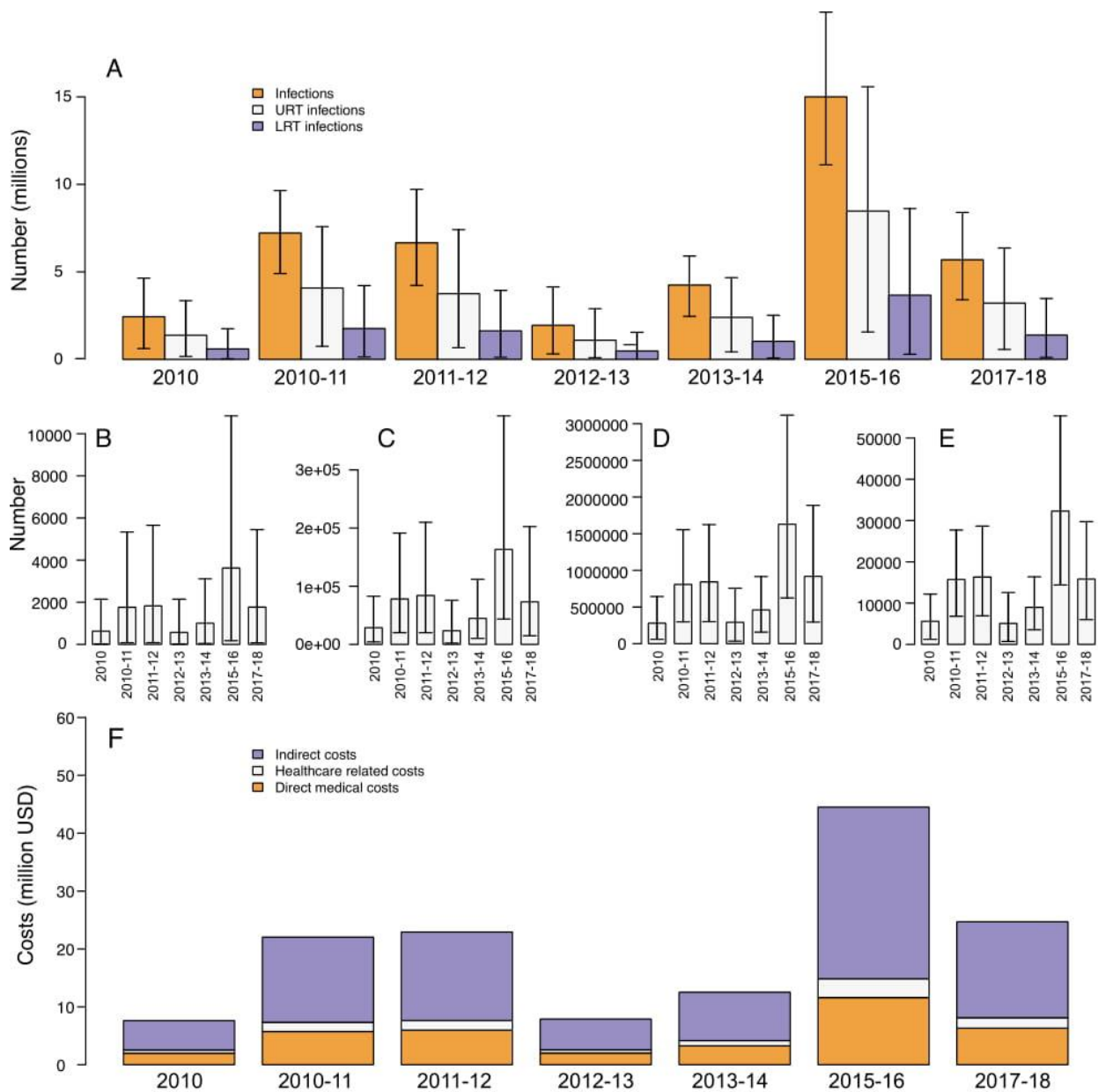
Figure 8: Influenza burden in the absence of vaccination in all age groups, 2010-2018. *Mean and 95% credible interval shown for each calendar year (September-August). A) Influenza infections, upper respiratory tract infections and lower respiratory tract infections, B) Deaths, C) DALYs, D) Outpatient visits, E) Hospitalizations, F) Costs. Note that y-axes vary. There were three periods of high influenza activity in Sep 2017-Aug 2018, two periods of high influenza activity in Sep 2010-Aug 2011 and Sep 2015-Aug 2016. Years with no detectable periods of high influenza activity are not included in the figure.*

We estimated that the average annual rate of infection was 4,547-32,343 per 100,000 population. Rates of infection were highest among children 1-5 years (Appendix 5). There were 1.1-8.5 million respiratory tract infections, 0.5-3.7 million lower respiratory tract infections and 570-3,626 deaths annually (Figure 8). Deaths were highest in the 1-5 and >50 age groups. The average annual mortality rate was 1-8 per 100,000 population. The highest mortality rates were observed in the ≥50, <1 and 1-5 age groups (Appendix 5, table 2). There

were 24,000-163,000 DALYs associated with influenza illness each year. Children 1-5 years of age consistently contributed the highest number of DALYs (Appendix 5, table 1).

There were 0.3-1.6 million outpatient visits and 5,000-32,000 hospitalisations across all age groups each year (Figure 8). The highest number of hospitalisations was observed among children 1-5 years of age (Appendix 5, table 3). The annual mean rate of hospitalisation across all ages was 12-70 per 100,000 population and was highest among children 1-5 years of age followed by those <1 year of age (Appendix 5, table 2).

4.4.3 Costs of influenza illness

We estimated that the direct medical costs associated with outpatient and inpatient care were $2.0-11.6 million per year (Figure 8, and Appendix 5). Of this amount, outpatient costs accounted for approximately three quarters of total direct medical costs. Healthcare-related costs amounted to $0.6-3.2 million annually while indirect costs associated with lost wages and childcare costs equalled $5.1-29.6 million per year. The mean annual total cost of influenza associated illness was $20.3 million each year (annual average ranged between $7.6-44.5 million). Of note, indirect costs accounted for nearly 60% of all influenza associated costs (Figure 8 and Appendix 5).

4.4.4 Comparison of vaccination strategies

There were substantial differences in mean costs and outcomes by strategy (Figure 9). Mean annual vaccination purchase and administrative costs were lower when vaccinating children 6-23 months (strategy I: $4.3-10.5 million) compared to 2-5 year olds (strategy II: $9.9-22.7 million) and 6-14 year olds (strategy III: $25.3-54.4 million) (Appendix 5). Total societal costs associated with vaccination and illness were lowest with strategy I as compared to the other strategies: it cost an annual average of $10.5-53.4 million for strategy I, $14.5-63.2 million for strategy II and $28.7-87.8 for strategy III (Table 17). Strategy III (vaccinating 6-14 year olds) required the highest number of vaccine doses, resulted in the highest costs, and led to the largest decrease in the number of infections (Figure 9).
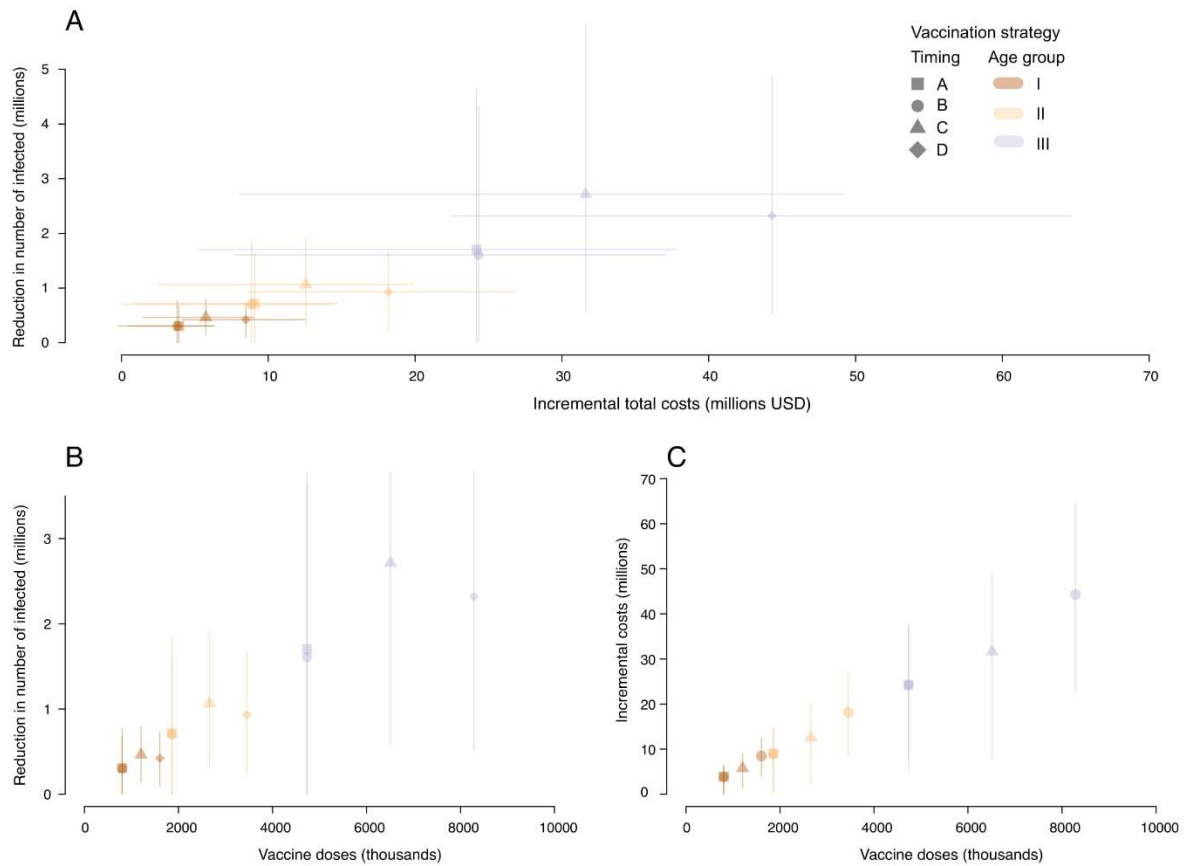
Figure 9: Summary of annual mean incremental cost, reductions in infections and vaccine doses per strategy. *A) Annual reduction in number of infections and incremental total societal costs per strategy. B) Annual reduction in number of infections and vaccine doses per vaccine strategy. C) Annual incremental total societal costs and vaccine doses costs per strategy. Strategies are vaccinating children 6-23 months (strategy I), 2-5 years (strategy II) and 6-14 years (strategy III) with either the Southern Hemisphere influenza vaccine (Strategy A) or Northern Hemisphere vaccine (Strategy B) or both (Strategy C: twice yearly 3-month vaccination periods, or Strategy D: year-round vaccination). The points mark posterior mean estimates and lines 95% credible intervals.*

Table 17: Average annual total societal costs and 95% credible intervals (CIs) per vaccination strategy in millions of USD.

Strategy

Year	I				II				III			
	A	B	C	D	A	B	C	D	A	B	C	D
2010	10.47 (4.99-22.4)	12.3 (5.58-26.8)	13.22 (7.12-26.02)	15.52 (9.08-28.28)	14.53 (9.47-23.82)	18.44 (10.87-33.1)	20.02 (13.42-31.01)	24.77 (17.12-36.28)	28.65 (21.06-38.28)	35.14 (24.28-51.56)	39.53 (29.07-52.79)	50.31 (37.05-66.96)
2010-11	25.7 (9.89-58.27)	25.32 (9.79-57.84)	27.2 (11.9-58.74)	29.96 (14.23-62.08)	30.6 (15.28-61.51)	29.75 (15.14-59.51)	33.38 (18.94-61.44)	39.04 (23.2-68.8)	44.11 (28.7-70.93)	44.27 (28.78-70.65)	50.86 (35.6-72.91)	63.32 (44.63-89.53)
2011-12	27.85 (10.44-63.18)	26.96 (10.19-61.17)	29.64 (12.57-64.32)	32.28 (14.84-67.11)	34.33 (16.4-69.85)	32.08 (15.76-64.48)	37.58 (20.31-70.94)	42.95 (24.54-77.14)	51.94 (31.52-88.39)	45.96 (29.32-74.06)	58.5 (38.79-89.58)	70.68 (48.1-104.96)
2012-13	10.96 (5.05-25.92)	12.94 (5.51-30.84)	13.93 (7.26-29.65)	16.59 (9.34-32.58)	15.3 (9.94-25.72)	19.59 (11.17-37.81)	21.21 (14.09-34.17)	26.68 (18.09-41.05)	30.86 (22.82-40.92)	37.68 (25.53-57.45)	42.45 (31.39-56.29)	54.35 (40.13-72.27)
2013-14	17.72 (7.9-37.94)	15.64 (7.3-32.6)	18.74 (9.82-36.49)	21.31 (12.07-39.21)	24.55 (14-44.98)	19.79 (12.29-33.19)	26.16 (17.02-41.7)	31.41 (21.16-47.5)	43.13 (29.18-64.84)	33.28 (24.47-44.45)	46.15 (33.91-61.7)	58.33 (43.01-77.66)
2015-16	48.3 (16.51-113.91)	48.47 (16.56-114.58)	50.31 (18.88-114.99)	53.37 (21.44-118.68)	52.91 (22.38-115.21)	53.61 (22.69-116.66)	56.94 (27.06-117.17)	63.21 (32.38-124.8)	64.18 (37.24-116.25)	68.06 (38.78-124.43)	73.27 (46.12-121.35)	87.82 (57.09-139.53)
2017-18	28.72 (10.86-68.26)	27.17 (10.44-64.33)	29.46 (12.91-65.93)	32.54 (15.56-69.14)	33.57 (17-68.92)	31.08 (16.29-61.99)	34.85 (20.51-63.09)	41.42 (25.5-71.71)	48.72 (32.39-75.87)	48.1 (31.97-74.92)	52.83 (38.48-70.92)	67.61 (49.24-90.92)

Strategies are vaccinating children 6-23 months (strategy I), 2-5 years (strategy II) and 6-14 years (strategy III) with either the Southern Hemisphere influenza vaccine (Strategy A) or Northern Hemisphere vaccine (Strategy B) or both (Strategy C: twice yearly 3-month vaccination periods, or Strategy D: year-round vaccination).

When vaccination was well timed/aligned to influenza activity, the annual mean ICER per DALY averted ranged between $749-1,385 per DALY averted for strategy IA, $442-1,877 for strategy IB, $678-4,106 for strategy IC and $1,147-7,933 for strategy ID. For II strategies it ranged between $945-1,573 for strategy IIA, $563-1,869 for strategy IIB, $662-4,085 for strategy IIC, and $1,169-7,897 for strategy IID. For III strategies, it ranged between $923-3,116 for strategy IIIA, $1,005-2,223 for strategy IIIB, $883-4,727 for strategy IIIC and $1,467-6,813 for strategy IIID (Appendix 5).

There was considerable overlap between ICER values obtained for each strategy in the 7 years with influenza activity (Figure 10 and Appendix 5). Depending on the strategy 0-3% of outputs were cost saving, and only 15-39% of outputs were equal to or less than the upper limit of the WTP threshold of $872 (51% of annual GDP per capita). Using the average INMB values, vaccination was not cost-effective in 2011-2012 at the tested WTP thresholds (Appendix 4, section 7.4.6). When comparing age-groups, I strategies (vaccinating children 6-23 months of age) had the highest mean INMB values at the lowest WTP values in 5 of 7 years, however in 2015-2016, III strategies (vaccinating 6-14 year olds) had the highest mean INMB at the lowest WTP value (Appendix 4, section 7.4.6 and Appendix 5). In regard to timing of vaccination, A strategies (April-June) and B strategies (October-December) had the highest mean INMB at the lowest WTP values in an equal number of years. C strategies (vaccinating in two 3-month campaigns) were the most cost-effective strategies at the upper WTP limit ($872) in 2010-2011, 2015-2016 and 2017-2018, however D strategies were never cost-effective at Kenya's range of WTP values (Appendix 4, section 7.4.6). On average, across the 7 years of influenza activity, no vaccination strategy was cost-effective at $17 (lower limit of WTP range), and $445 (median value of WTP range). At $872 (upper limit of WTP range), strategy IB had the highest mean INMB, however it had low probability (3%) of being the most optimal strategy (*Figure 11*,

Table 18).
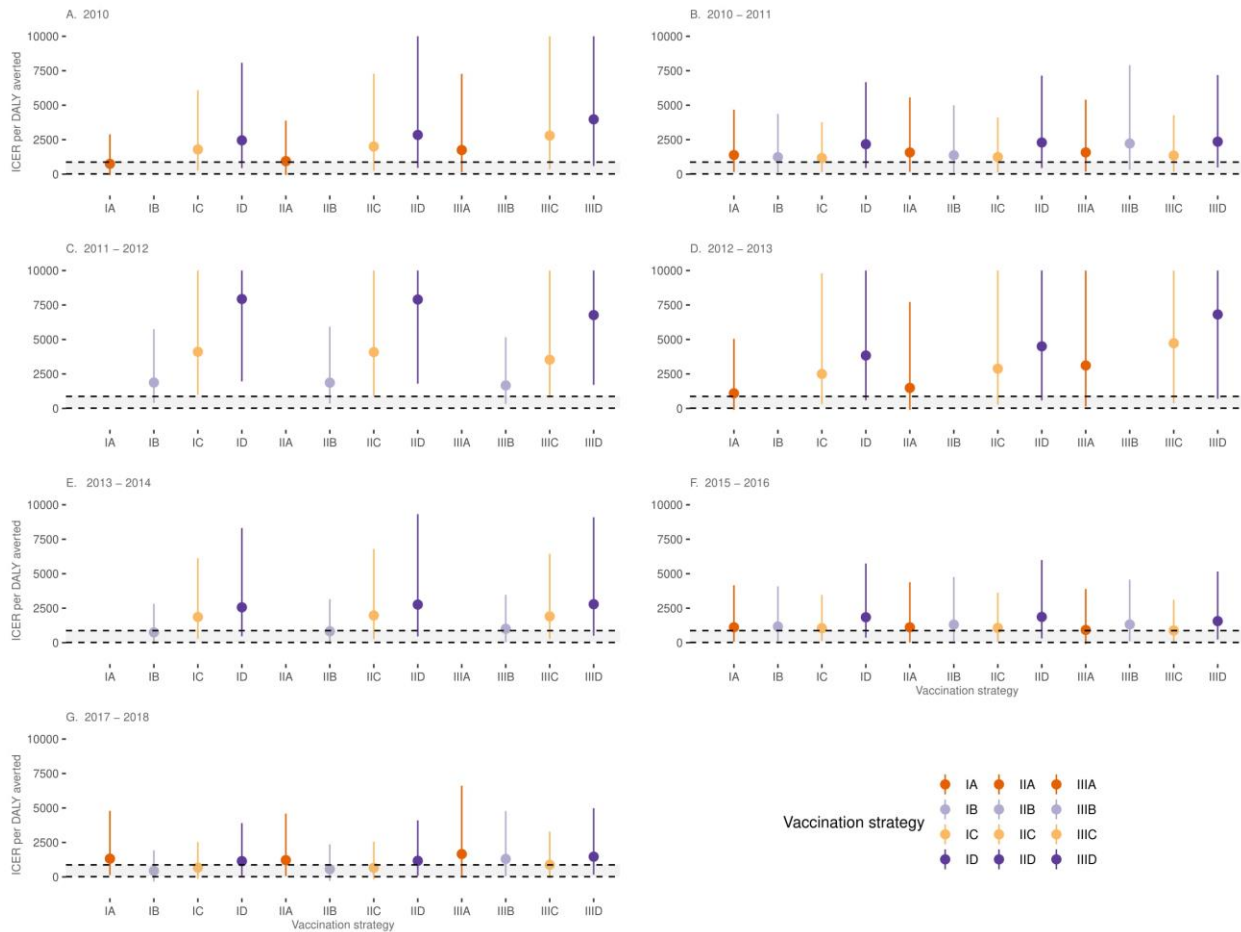
Figure 10: ICER per DALY averted and 95% CI. *Results for 2014-15 and 2016-17 are not shown as there were no periods of high influenza activity detected in these years and calculation of ICER values per DALY averted would produce an infinite value as no DALYs would be averted. Similarly, ICER values are not shown for A and B strategies where vaccine administration was mistimed to influenza activity as vaccination was considered ineffective that year. Note the y-axes are cut off at 10,000 while actual values may exceed this value. Section shaded grey between the horizontal dotted lines represents outputs that fall within a willingness-to-pay threshold of 1-51% of the GDP per capita (that is between $17-872). Values below zero are cost saving. Strategies are vaccinating children 6-23 months (strategy I), 2-5 years (strategy II) and 6-14 years (strategy III) with either the Southern Hemisphere influenza vaccine (Strategy A) or Northern Hemisphere vaccine (Strategy B) or both (Strategy C: twice yearly 3-month vaccination periods, or Strategy D: year-round vaccination)*

Figure 11: Cost-effectiveness acceptability curve and frontier for strategies with the highest incremental net monetary benefit. *A = cost-effectiveness acceptability curve. B = cost-effectiveness acceptability frontier. NB: X axis is limited to 1,000 USD per DALY averted. Strategies are vaccinating children 6-23 months (strategy I), 2-5 years (strategy II) and 6-14 years (strategy III) with either the SH influenza vaccine (Strategy A) or NH vaccine (Strategy B) or both (Strategy C: twice yearly 3-month vaccination periods, or Strategy D: year-round vaccination).*

Table 18: Incremental net monetary benefit values and probabilities for each vaccination strategy at a willingness-to-pay threshold of $872 per DALY averted

Strategy	Mean INMB value in '000s	INMB 95% credible interval in '000s		Probability of highest INMB benefit	Rank
		Lower quantile	Upper quantile		
Strategy IA	- 472	-6,201	10,054	4%	5
Strategy IB	3	-5,975	13,302	3%	1
Strategy IC	-217	-6,976	13,545	0%	3
Strategy ID	- 3,424	-10,351	9,188	0%	8
Strategy IIA	-1,293	-14,377	23,996	11%	7
Strategy IIB	- 581	-13,854	28,726	7%	6
Strategy IIC	-387	-15,597	31,947	2%	4
Strategy IID	-7,507	-22,440	20,834	0%	11
Strategy IIIA	-7,077	-36,674	53,262	12%	10
Strategy IIIB	-7,531	-35,320	44,647	12%	12
Strategy IIIC	-3,633	-39,244	70,255	14%	9
Strategy IIID	-20,326	-54,467	42,876	0%	13
No vaccine	0	-	-	35%	2

INMB – incremental net monetary benefit. Strategies are vaccinating children 6-23 months (strategy I), 2-5 years (strategy II) and 6-14 years (strategy III) with either the Southern Hemisphere influenza vaccine (Strategy A) or Northern Hemisphere vaccine (Strategy B) or both (Strategy C: twice yearly 3-month vaccination periods, or Strategy D: year-round vaccination)

The most favourable vaccination strategy each year was the same regardless of whether total societal costs or only direct medical costs were considered (Appendix 5); however, the WTP value at which vaccination became cost-effective was higher with direct medical costs (Appendix 4, section 7.4.6). Based on the average INMB values across the 7 years of influenza activity, no vaccination strategy was cost-effective at the upper limit of the WTP threshold when only direct medical costs were considered.

4.4.5   Sensitivity analysis

Removing time discounting led to a 49-50% reduction in mean ICER per DALY averted across all strategies, and addition of social weighting led to a slight decrease (5-6%) in mean ICER value. At a vaccine purchase price of $1.50 USD the mean ICER decreased by 44-62%. At a vaccine purchase price of $10.0 USD the mean ICER value increased by 144-178%, at $6.0 USD the mean ICER value increased by 38-43%, while at a vaccine purchase price of $4.50 USD the mean ICER value increased by 31-38%. Maintaining a uniform vaccine coverage across all age groups

led to a 1-4% decrease in mean ICER value for strategies targeting children 2-5 years, and a 7-20% reduction in mean ICER values for strategies targeting children 6-14 years. Using the INMB approach, no vaccination strategy was cost-effective at a vaccine price of $4.5 USD and above. For all other sensitivity analysis outputs, vaccinating children 6-23 months of age with the NH vaccine (strategy IB) remained the most cost-effective strategy.

4.5   Discussion

We set out to identify the most cost effective influenza vaccination strategy using a dynamic transmission model that provided estimates of the burden of influenza associated respiratory illness each year. There were yearly variations in peaks of influenza activity, with at most three periods of increased influenza activity each year. Rates of infection and hospitalisation were highest in the 1-5 year age group, while mortality rates were highest in individuals ≥50 and children <5. As a result, children 1-5 years contributed the highest number of DALYs each year. Given the expected vaccine coverage levels, we found that targeting children 6-23 months in an annual 3-month campaign was the most favourable of the vaccination strategies, although the probability of any vaccination strategy being cost-effective, even at the upper limit of the WTP threshold, was low. Vaccination was most cost-effective when vaccine was well matched to circulating strains and influenza activity occurred after hypothetical vaccination campaigns. Vaccinating children 6-23 months of age was least expensive although the reduction in number of infections was not as substantial as those observed at higher coverage levels attainable by vaccinating more children in older age groups. The provisional KENITAG recommendation to vaccinate children 6-23 months would be the least expensive strategy for the government to adopt and frequently had the highest INMB, although at very low probabilities.

Primary school-going children have the highest contact rates in Kenya [139], and therefore vaccinating this group could yield considerable benefit in all ages due to indirect protection [152]. We found that the overall reduction when vaccinating children 6-14 years old was only more favourable than vaccinating children 6-23 months of age (who have a higher burden of severe disease) in 2015-2016 when the vaccine was poorly matched to circulating strains.

Vaccinating school-going children may be an important strategy when inadequate protection levels are attained in those most susceptible to severe disease [153]. Nonetheless, we found that when the vaccine is well matched to circulating strains, direct protection of the age group with highest burden of severe disease was most favourable. Studies have previously shown that with lower vaccine efficacy the indirect benefit of vaccination exceeds the direct benefits by larger margins [132], and could explain why we obtained more favourable values when vaccinating children 6-14 years of age in years when vaccine effectiveness was lower.

We found that year-round vaccination was always the least cost-effective strategy. For this strategy, vaccination after infection was more likely to occur. Therefore, vaccinating in short 3-month campaigns was a more favourable strategy than year-round vaccination. These findings highlight the need to vaccinate as much of the target population as possible as soon as the influenza vaccine becomes available in order to enjoy the full benefit of vaccination in Kenya. However, evidence of intraseasonal waning immunity and its implications on vaccination timing may lead to changes in recommendations for vaccination timings in future [154-156].

Vaccinating twice a year was most cost-effective at higher WTP values. This strategy would ensure that a proportion of the population has some protection against the currently circulating influenza strains by using the most up-to-date vaccine formulation. Continuous mutations in nucleic acids coding for influenza antigens lead to semi-annual reviews of the components used for the production of influenza vaccine [11]. Over the past 10 years, the strains in the NH vaccine differed from the incoming SH vaccine in 6 years, and differed from the contents of the preceding SH vaccine in 3 years [157]. Despite the possibility of waning protection [158-160], vaccinating once per year should provide some protection over a 12-month period if there is no need for a change in the composition of the NH and SH vaccine. Once-a-year vaccination in short 3-month campaigns should be considered, however, surveillance is needed to monitor whether the vaccine is well matched to circulating strains that circulate in the latter half of the year.

In this study, most of the model outputs were unlikely to be cost-effective given a willingness to pay threshold of 1-51% of the GDP. These findings were contingent on a vaccine price per dose

of $3, which is lower in price than vaccine available in high-income countries [161]. Very few outputs (1% of all simulations) at the price of $3 were cost saving. Overall, vaccination was unlikely to be cost-effective however if we had used previous WHO thresholds for cost-effectiveness of health interventions (that is very cost-effective if less than the annual GDP per capita, ii) cost-effective if 1-3 times the GDP, and iii) not cost-effective if greater than 3 times the GDP [162]), we would have found that vaccination was most likely very cost-effective or cost-effective regardless of the strategy modelled. However, there is debate over the suitability and affordability of the WHO threshold for cost-effectiveness of interventions in LMICs [162, 163] and as an alternative a threshold of 1-51% GDP per capita for LMICs has been proposed [150]. This lower threshold is postulated to better reflect the constraints within the 'supply side' of healthcare funding and considers the opportunity costs of the choice of interventions [150]. Selecting an appropriate ICER threshold value is critical: if interventions that cost more than the appropriate ICER threshold are implemented, they result in a net reduction in health, as more health benefits could be gained by choosing interventions of a lower ICER value [164].

Influenza vaccination of children 6-23 months age was cost-effective at a WTP value of $872 per DALY averted, while vaccines already included in the Kenya expanded programme on immunization (EPI) have considerably lower ICER values. For example rotavirus vaccine and *Haemophilus influenzae* type b vaccine cost approximately $38 per DALY averted [165, 166], while the pneumococcal vaccine costs $59 per DALY averted [167]. Continuing the pneumococcal vaccination program beyond 2022-2027 when Kenya transitions to the full Gavi price ($3.05 per dose) would still result in a cost per DALY averted of $153 (95% prediction intervals of $70–$411) [168].

In 2010, half of the vaccines provided or considered for provision in LMICs cost less than $100 per DALY averted, 25% cost between $100-$500 per DALY averted and 9% cost between $500-$1,000 per DALY averted (2010 dollar values) [169]. A decrease in vaccine price and improved influenza vaccine effectiveness, duration of protection, and if possible, long-term immunity would increase influenza vaccine cost-effectiveness and likely adoption in LMICs [170].

Although the range of ICER values per DALY averted were similar among the strategies, the modelled vaccination strategies substantially differed in vaccine purchase costs. Over the past three years (2016-2019) the government of Kenya allocated approximately $7 million per financial year to the immunization programme, while Gavi contributed $26 million per year [171]. We estimated that at a vaccine price of $3 per dose, the government would spend $4.3-10.5 million in vaccine purchase costs for the least expensive strategy, and $25.3-54.4 million for the most expensive strategy, which represents a significant proportion of the immunization budget. Cost differences between strategies could therefore influence selection of vaccination strategy.

Our findings need to be interpreted in light of several limitations. In 2014-15 and 2016-17 influenza activity did not meet our decision rule for periods of activity. These periods were characterised by nationwide healthcare worker strikes in public hospitals and disruptions in influenza surveillance funding (2014-2015), both of which plausibly led to a decrease in the number of influenza positive SARI patients detected. Therefore, our model could have underestimated the burden of influenza and the impact and cost-effectiveness of seasonal influenza vaccination. Indeed, we were not able to fit all the observed periods of influenza activity, which could also underestimate the impact of vaccination over those periods. More complete and robust surveillance data could improve estimates and give further confidence in the findings presented here.

We limited our burden calculation to periods of high influenza activity. However, the overall rates of hospitalisation across all ages are comparable to past estimates of national disease burden conducted in Kenya covering similar years [9, 125]. Using a simpler methodology that took into account influenza activity throughout the year, we previously estimated the mean annual rates of influenza associated hospitalised SARI to be 21 (95% confidence limit 19-23) per 100,000 population over the period January 2012-December 2014 [125]. For a similar period in our study, September 2011-August 2014, we estimated the mean annual influenza hospitalisation rates to be 24 per 100,000. These similar results may be explained by the fact that the identified periods of high influenza activity frequently lasted 6 or more months, and likely captured most of the annual influenza activity. Although we focussed on peaks in activity,

we obtained comparable rates of illness to studies that considered year-round activity. However, our rates of hospitalised influenza during the early years of this study were slightly lower than previous estimates from August 2010–July 2011, when published rates of influenza-associated hospitalised SARI were 70 (95% confidence limits 50-90) per 100,000 persons [9]. Our estimated rate for the period September 2010-August 2011 was 39 (95% credible interval 17-69) per 100,000 persons. This disparity may be explained by the fact that we excluded circulation of A(H1N1)pdm09 from January 2010-December 2011 during our analysis. We excluded the first two years of circulation of the pandemic strain because these epidemics were not a typical influenza season – there was no single peak and numerous small epidemics occurred. This exclusion could have led to underestimation of vaccine cost-effectiveness if vaccine were matched to the pandemic strain during this time. Additionally, if competitive viral interaction were occurring, the circulation of A(H1N1)pdm09 could have suppressed A(H3N2) or B epidemics, leading to underestimation of vaccine impact.

In this analysis, we assumed that vaccination with SH or NH vaccine did not protect against transmission starting in the alternate hemisphere's vaccination period. This assumption was informed by the potential for waning immunity suggested by declining vaccine antibody titres [172, 173] and/or possible mismatch of vaccine composition to circulating subtypes [157]. If there were lasting protection [174], there would be a higher impact of the vaccine in later seasons and an increase in cost-effectiveness. On the other hand, for periods of influenza activity that fell within a particular vaccination period, we also assumed protection was maintained at a constant level for the duration of influenza activity, regardless of whether the epidemic ran into the next vaccination period, that is even when periods of influenza activity lasted more than 6 months. This could lead to overestimation of the impact of vaccination.

We adopted a societal perspective for costs. However, we did not have local data on over-the-counter medication costs, lost wages, and childcare costs for non-medically attended symptomatic influenza cases, and these costs were not incorporated in the analysis. The lack of local data may have led to underestimation of costs as well as the benefits of vaccination. We assumed vaccine completely protects a proportion of those vaccinated that is "all-or-nothing" protection. However, where the influenza vaccine does not prevent infection, it may still reduce

the severity and duration of illness [175] which could have underestimated the benefit of vaccination. Finally, we did not include non-respiratory influenza illness in our analysis. Although they are important manifestations of severe influenza, they contribute only 7% of the total costs of illness and may not have made significant differences to the ICER values [176].

4.6   Conclusion

Influenza vaccination of children 6-23 months of age once per year was the most favourable vaccination strategy, however it is unlikely to be a cost-effective intervention using a WTP threshold of 1-51% of annual GDP per capita. Targeting children in older age groups led to the largest reduction in the number of cases but was not necessarily the most cost-effective strategy at our WTP threshold. Further reductions in cost per dose and improvements in vaccine effectiveness and long-term immunity would make the influenza vaccine more attractive for inclusion in the EPI.

4.7   List of supplementary material available in appendices 4 and 5

Appendix 4: Supplementary text (Objectives 2 and 3)

Table 40: Average number of influenza associated disease states and DALYs with their 95% credible interval limits, (2010-2018)

Table 42: Average annual rate per 100,000 of influenza associated disease states with their 95% credible interval limits, (2010-2018)

Table 41: Average number of influenza associated health care utilization events with their 95% credible interval limits, (2010-2018)

Table 43a: National cost of influenza associated illness across all ages, 2010-2018

Table 44: Average annual costs and 95% credible intervals (CIs) per vaccination strategy in millions of USD

Table 45a: Incremental cost-effectiveness ratio for influenza vaccination using total societal costs **– Strategy IA-D**

Figure 30: Yearly cost-effectiveness acceptability curves and frontiers for strategies with the highest incremental net monetary benefit considering total societal costs. NB: X axis is limited to 1,000 USD per DALY averted. Strategies are vaccinating children 6-23 months (strategy I), 2-5

years (strategy II) and 6-14 years (strategy III) with either the SH influenza vaccine (Strategy A) or NH vaccine (Strategy B) or both (Strategy C: twice yearly 3-month vaccination periods, or Strategy D: year-round vaccination).
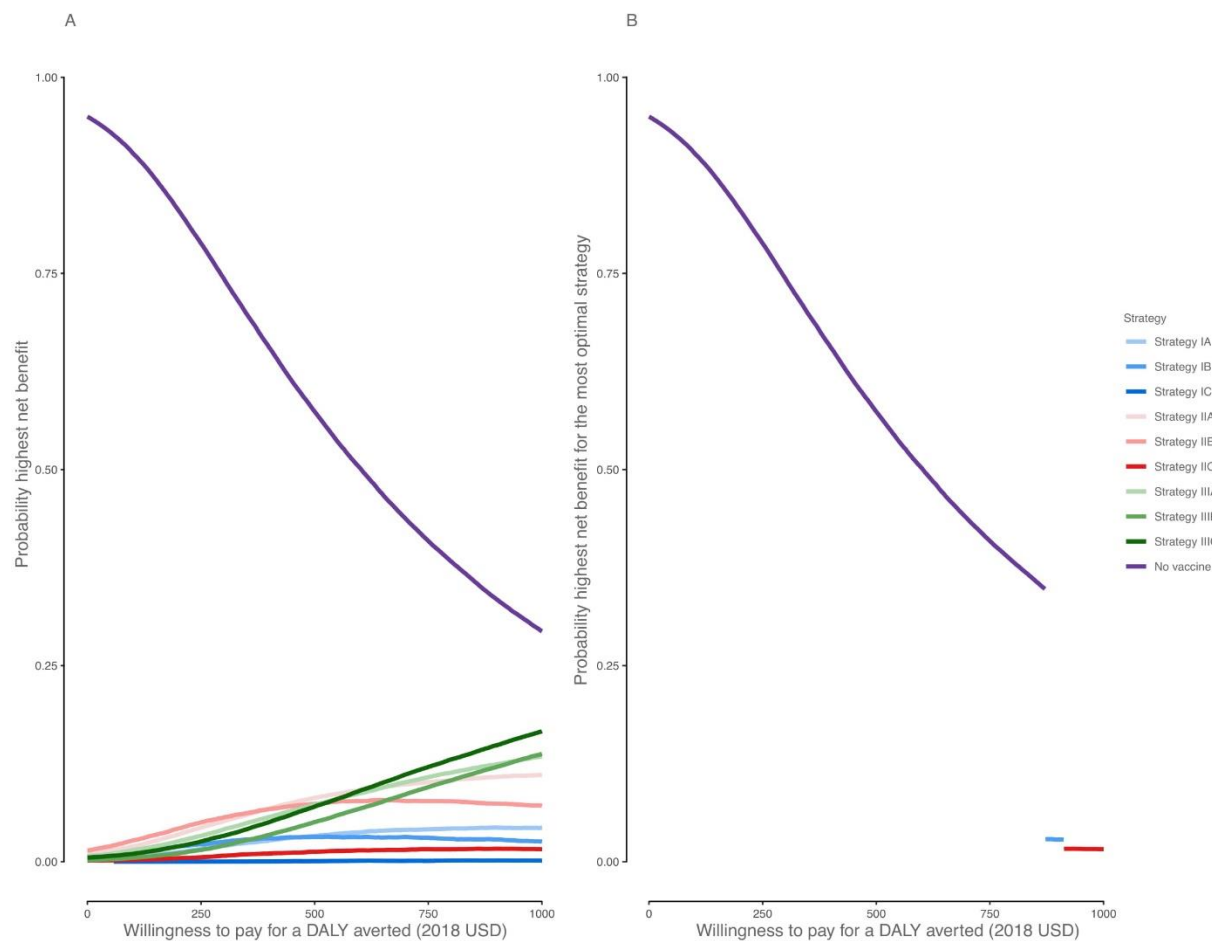
Figure 31: Yearly cost-effectiveness acceptability curves and frontiers for strategies with the highest incremental net monetary benefit considering direct medical costs only. NB: X axis is limited to 1,000 USD per DALY averted. Strategies are vaccinating children 6-23 months (strategy I), 2-5 years (strategy II) and 6-14 years (strategy III) with either the SH influenza vaccine (Strategy A) or NH vaccine (Strategy B) or both (Strategy C: twice yearly 3-month vaccination periods, or Strategy D: year-round vaccination).

5   Conclusion

In 2006, the Ministry of Health established an influenza surveillance system to act as an early warning system to detect pandemic influenza, identify circulating influenza strains that could be used to inform the choice of vaccine strains for the influenza vaccine, and establish the burden of influenza illness in the Kenyan population [15]. We set out to build on the existing data obtained from this surveillance system to quantify the national burden of influenza in Kenya in discrete age groups and determine the most cost-effective influenza vaccine strategy if the influenza vaccine were introduced in Kenya's NIP.

Our study has contributed to the body of work on the burden of influenza in Africa. We were able to demonstrate that influenza-associated illness is an important cause of respiratory illness in Kenya and that the influenza virus caused substantial illness and financial burden each year. Based on the data available, we surmised that nationally, children <5 years of age carry the highest burden of severe influenza disease, particularly those <2 years of age. Despite the underrepresentation of older adults in the influenza surveillance system we were also able to observe high rates of disease among the oldest age group by adjusting for health care seeking among the elderly.

To the best of our knowledge, we provided the first estimates of DALYs associated with influenza illness in Kenya. The availability of national disease specific DALYS is a useful tool for priority setting. When additional DALY estimates for other illnesses are produced, policy makers will be better able to identify which diseases cause the highest health burden in the Kenyan population and prioritise resources accordingly. We also provided ICER values for influenza vaccination, and thereby have provided policy makers a measure to compare the cost-effectiveness of influenza vaccination to other health interventions, and prioritize the most cost-effective interventions for diseases that generate the most DALYs.

The findings of this research project produced results that allow for a more informed discussion of the most appropriate influenza vaccination policy that the Kenyan government could adopt to prevent influenza-associated respiratory illness than has previously been available. We observed that annual vaccination of children 6-23 months of age once a year would cost

approximately $872 per DALY averted, however the probability that this was the most cost-effective strategy to implement was quite low. However according to the previous WHO classification of cost effective interventions, influenza vaccination would likely be a very cost-effective or cost-effective strategy. Interestingly the choice of the most appropriate vaccine target group varied with the WTP threshold, with vaccination of children 2-5 years and then 6-14 years of age being the most optimal strategy at increasingly higher WTP thresholds. Although once-yearly campaigns carried a higher risk of mistiming vaccine administration to influenza activity, we suggest that once-yearly campaigns may be a suitable alternative where financial considerations and programmatic capacity do not allow for twice-yearly campaigns. Of note, further research on the 12-month effectiveness of the SH and NH vaccine would be needed alongside a once-yearly vaccination strategy in countries like Kenya with fairly equal amounts of influenza activity in both the NH and SH seasons.

Ultimately we conclude that although vaccination of children 6-23 months of age in Kenya would be the most favourable vaccination strategy it would not be as cost-effective as the vaccines currently included in the Kenya EPI. A marked reduction in the vaccine price per dose to below $1.50 and improved vaccine effectiveness and duration of protection are important avenues for future developments of the influenza vaccine. These would likely make the vaccine more attractive to countries with lower and middle income economies.

We chose to calculate and present national results in order to inform national policy decisions as previous estimates of influenza burden in Kenya have typically focused on regional estimates. In addition, we calculated age-stratified data in keeping with the knowledge that influenza affects different age groups disproportionately, and that the adopted vaccine policy would likely target specific, discrete, narrow age groups. It was therefore important to present data in more discrete age groups than have previously been provided for national estimates in Kenya. We used a dynamic transmission model in order to adequately incorporate the effects of herd immunity in determining cost-effectiveness of influenza vaccination. The methods we employed have been used in the process of vaccine decision making within countries [54], and the model could be adopted for similar exercises in other countries with year round influenza transmission.

While the methodology we used in objective 1 was adequate in determining the burden of hospitalized and non-hospitalized influenza-associated SARI, it could not capture the number of infections in the community or the outpatient clinic visits associated with less severe influenza infection. Nevertheless, it provided important information to showcase the burden of influenza-associated SARI and is a useful tool in quantifying severe disease burden and identifying high burden age groups and annual age specific hospitalization rates. Notably, Fuller´s method utilized to estimate national burden of influenza-associated SARI in objective 1 was a considerably simpler methodology than the dynamic transmission model we utilized for objective 2 to describe the burden of disease. Nonetheless, we obtained similar rates of influenza-associated hospitalization from both methods.

The dynamic transmission model we utilized in objective 2 was designed to produce the total number of infections in the community, while the economic model utilized in objective 3, made use of the transmission model outputs to calculate the number of mild illnesses, severe illnesses, deaths, DALYs, medical utilization episodes and costs. As such the dynamic transmission model provided a more comprehensive picture of the burden of influenza disease than Fuller's method but utilized a more complicated methodology. Mathematical models often take time and require specific expertise [21] as evidenced in our work, so although they provide more comprehensive information, their complexity can limit their use in national vaccine decision-making processes because policy makers often require results urgently.

Interestingly, by using the dynamic transmission model we were able to observe that vaccinating 6-14 year olds was more cost effective than vaccinating children 6-23 months of age (who have a higher burden of severe disease) in 2015-2016 when the vaccine was poorly matched to circulating strains. These findings may not have been obtained from static models as the effects of herd immunity would need to be incorporated for these results to be observed. When vaccine effectiveness is poor, vaccinating school going children may be the best strategy to protect those at highest risk of severe influenza illness. In our setting, vaccine effectiveness was not only determined by how well vaccine contents were matched to circulating strains but also on how well administration of the vaccine was timed to influenza

activity. Timing to influenza activity is an added dimension to vaccination programs that requires special consideration in countries with year round influenza activity.

We did not incorporate high risk groups in the model, yet these would be another important target group for influenza vaccination. While pregnant women, the elderly and children with co-morbidities such as HIV/AIDS, asthma and chronic heart or lung diseases are considered risk groups for severe influenza outcomes in HICs, high risk groups specific to LMICs are less well defined [11]. Defining the at-risk populations in Kenya would be an important initial step in determining the cost-effectiveness of an influenza vaccination program targeted towards specific at risk groups other than young children, and may possibly lead to more cost-effective and potential cost-saving outputs.

We did not include the costs of non-medically attended influenza. From the first objective we observed that the rates of non-hospitalized influenza-associated SARI were four times higher than the rates of hospitalized influenza-associated SARI. In settings with low health care utilization, the inclusion of non-medically attended indirect costs of influenza illness could potentially impact the results of cost-effectiveness studies from a societal perspective. Therefore, quantifying the economic impact of non-medially attended cases would be useful in further cost-effectiveness studies in our region.

Finally, it is generally accepted that vaccines play a crucial role in disease control and eradication. Despite this fact, they are generally undervalued and underutilised both in the developing and developed world [177]. Lack of data on the burden of vaccine preventable diseases (VPDs) and the potential impact of vaccination, are thought to be major contributors to the underutilisation of vaccines in sub-Saharan Africa (sSA) [177]. This is especially true for influenza in Africa [178]. Our findings confirm the importance of influenza in Africa as a disease that causes significant morbidity. Even so, the decision to introduce the influenza vaccine into Kenya's NIP will be determined by a myriad of factors, some of which have been addressed within this research project, while others have not. Key among them, and relevant to only a few vaccine preventable diseases, is the emergence of a pandemic strain and the potential threat to national and global health security. Country-level initiatives to understand, prevent and

manage seasonal influenza have the additional benefit of enhancing global preparedness to manage future pandemic strains of the influenza virus [179]. Ultimately, this consideration may hold great sway in the decision to introduce the influenza vaccine into the NIPs of countries across the world.

5.1   Recommendations

Vaccine strategy

- Influenza vaccination of children 6-23 months in a 3-month once yearly vaccination campaign would be the most favourable influenza vaccination strategy to implement at the lowest cost per DALY averted
- The 12-month effectiveness of the NH or SH vaccine administered once a year should be monitored in countries with year round influenza activity in order to further inform the suitability of a 3-month once-yearly vaccination strategy

Gaps in disease epidemiology data

- Risk groups for severe influenza disease in the African setting should be defined to inform locally relevant vaccination priority groups
- Additional surveillance data is required on the rates of influenza in pregnant women, individuals with co-morbidities, the elderly and other locally relevant risk groups for severe disease

Gaps in costs of illness

- The costs associated with influenza associated illness among those non medically attended should be quantified to be incorporated into economic evaluations of the influenza vaccine from a societal perspective

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7 Appendices

7.1 Appendix 1: Ethical approval

KENYA MEDICAL RESEARCH INSTITUTE

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KEMRI/RES/7/3/1   September 13, 2016

TO: **HENRY NJUGUNA**
             PRINCIPAL INVESTIGATOR

THROUGH: **DR. STEPHEN MUNGA**
             THE DIRECTOR, CGHR
             KISUMU

Dear Sir,

RE: **SSC 2558** (*REQUEST FOR ANNUAL RENEWAL*) **INTEGRATED SURVEILLANCE
        FOR RESPIRATORY PATHOGENS AND HIV AT SIAYA DISTRICT HOSPITAL
        (SDH), KAREMO DIVISION, NYANZA REGION, KENYA**

Thank you for the continuing review report for the period **21 August, 2015 to 1 August,
2016.**

This is to inform that during the 255th Committee A meeting of the KEMRI Scientific and Ethics
Review Unit (SERU) held on 13 September, 2016, the Committee **conducted the annual
review and approved** the above referenced application for another year.

This approval is valid from **13 September, 2016** through to **12 September, 2017**. Please
note that authorization to conduct this study will automatically expire on **12th September,
2017.** If you plan to continue with data collection or analysis beyond this date please submit an
application for continuing approval to the **SERU** by **31 July, 2017.**

You are required to submit any amendments to this protocol and other information pertinent to
human participation in this study to the SERU for review prior to initiation.

Yours faithfully,

DR. EVANS AMUKOYE,
ACTING HEAD
KEMRI/SCIENTIFIC AND ETHICS REVIEW UNIT

In Search of Better Health

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AFYA HOUSE
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NAIROBI

REF: MOH/ADM/1/1/2

DATE: 17th November, 2016

Dr. Kevin De Cock
Director
Centre for Disease Prevention and Control
Nairobi

Dear Dr. Kevin

RE: INFLUENZA SENTINEL SURVEILLANCE PROTOCOL IN KENYA

Influenza Sentinel Surveillance System was launched in 2006 by the Kenya Ministry of Health and the Centers for Disease Prevention and Control (CDC) Kenya office. Understanding influenza activity in Kenya is an issue of public health concern. Influenza surveillance provides us with an understanding of the **basic epidemiology of this infection in Kenya and allows us to detect new influenza virus strains which may be precursors to a global pandemic.** Because influenza surveillance is part of routine public health surveillance, this activity has never been considered research. In 2006, the Ministry of Health approved the initiation of surveillance immediately, as an issue of public interest, and considered the activity exempt from formal ethics committee review. This continues to support this position because the surveillance, including patient follow-up is part of routine public health surveillance, and verbal consent is considered adequate.

The purpose of this letter is to forward this Influenza Surveillance Protocol for your information.

Yours Sincerely

Dr. Kioko Jackson K., OGW
DIRECTOR OF MEDICAL SERVICES

Encls

ISO 9001:2008
Certified

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Ref: KNH-ERC/A/26

27th January 2017

Dr. Jeanette Dawa
Principal Investigator
KAVI- Institute of Clinical Research
College of Health Sciences
University of Nairobi

Dear Dr. Dawa

Revised Research Proposal: "Modelling the health and economic impact of the influenza vaccine in Kenya(P18/01/2017)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above revised proposal. The approval period is from 27th January 2017 – 26th January 2018.
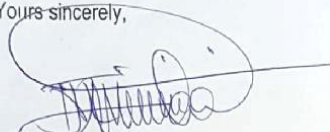
This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study.
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website http://www.erc.uonbi.ac.ke

Protect to discover

Yours sincerely,

PROF M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c.   The Principal, College of Health Sciences, UoN
         The Deputy Director, CS, KNH
         The Assistant Director, Health Information, KNH
         The Chair, KNH- UoN ERC
         Supervisors: Prof. Omu Anzala, Roland Eggo, Edwine Barasa

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7.2 Appendix 2: Description of burden of disease published articles

Table 19: Proportion of cases positive for influenza virus among children less than 5 years of age

Author, publication year	Study design	Region	Dates	Target Age	Outpatient/ Inpatient/ Community	Case definition	Sample	Test method	Samples tested	Influenza findings
Emukule 2015* [10]	Systematic review	Nyanza, Rift Valley, North Eastern, Nairobi, Coast	Before Dec 2013	All ages	OPT, IPT & community	Hospitalized severe or very severe pneumonia, hospitalized SARI, hospitalized ARI, in and outpatient ALRI, in and outpatient SARI, outpatient SARI, in and outpatient ARI, outpatient ILI	Not described	RT-PCR	28,744 (for all ages)	Medically attended patients <5 years 4.9%-13.7% Inf
Breiman, 2015 [69]	Surveillance and case control study	Nairobi	1 Mar 07 - 28 Feb 11	<5 years	OPT & community	SARI at health facility – cough/difficulty breathing & unable to drink or breastfeed/vomits everything/convulsions/lethargic or unconscious/stridor when calm/lower chest wall in drawing/oxygen saturation <90% SARI from household – cough/difficulty breathing & chest in drawing/elevated respiratory rate for age Controls – children at clinic not requiring hospitalization/for Immunizations/medicine refills & no respiratory symptoms or diarrhoea in last 2 weeks	NP & OP	Real time RT PCR	731 cases 115 controls	Cases 10.8% inf A 2.6% inf B Controls 4.3% inf A 0.9% inf B
O'meara, 2015* [70]	Case Control	Western	Nov 11 – Dec 12	1 – 12 years	OPT	Cases - temp > 37.5°C & resident of Webuye Health and Demographic Surveillance System Exclusions: children with	NP swab	PCR	286 cases 118 controls	Cases <5 years 62.1% Inf

Author, publication year	Study design	Region	Dates	Target Age	Outpatient/ Inpatient/ Community	Case definition	Sample	Test method	Samples tested	Influenza findings
						apparent skin or soft-tissue infections Controls - enrolled from eye clinic, follow-up visits for fractures, postoperative visits, or children accompanying parents for other reasons. Exclusions: children accompanying sick family members and those who had objective fever or history of fever within the past 7 days			(all ages)	
Feikin, 2013 [76]	Surveillance & Case control	Nyanza	1 Mar 07 – 28 Feb 10	<5 years	IPT, OPT & community	SARI in health facility – cough/difficulty in breathing & unable to drink or breastfeed/vomits everything/convulsions/lethargic or unconscious/stridor when calm/lower chest wall in drawing/oxygen saturation <90% SARI in community – cough/ difficulty in breathing & either chest in drawing/elevated respiratory rate for age Controls: Patients in health facility with non-severe illness /for immunizations/for medicine refills and no history of fever/respiratory symptoms/diarrhoea in the past 2 weeks	NP & OP	Real time quantitative PCR	*Surveillance* IPT Cases 1,600 OPT cases 1,373 *Case control study* 199 cases 93 controls	*Surveillance* All cases 6.6% Inf A 1.2% Inf B Cases inpatient 6.3% Inf A 0.6% Inf B Cases outpatient 8.6% Inf A 5.2% Inf B *Case control* All Cases 9.0% Inf A 2.2% Inf B All Controls 1.1% Inf A 1.1% Inf B
Murray, 2013 * [72]	Surveillance	Nyanza	Jan 07 – Jul 10	≥2 months	IPT	ARI - cough, difficulty breathing, sore throat, or chest pain	NP & OP swabs	Real time RT–PCR	2-59 months 3,116	2-59 months 7% Inf 6% Inf A

107

Author, publication year	Study design	Region	Dates	Target Age	Outpatient/ Inpatient/ Community	Case definition	Sample	Test method	Samples tested	Influenza findings
										1% Inf B
Fuller, 2013* [74]	Case control	Nyanza	Aug 08 - Dec 10	All ages	OPT & IPT	Cases ILI adults & children- outpatient with temp >38.0^{0}C & cough/sore throat SARD children Inpatient with cough/difficulty breathing & inability to breastfeed or Feed/vomiting/convulsions/lethargy/stridor/chest in drawing/, unconsciousness/low oxygen saturation <90% Controls Afebrile outpatients with no respiratory or gastrointestinal symptoms in previous 2 weeks	NP & OP swab	Quantitative real-time polymerase chain reaction (qRT-PCR)	<5 years 2,280	<5 years All 8.2% Inf Controls 3.7% Inf OPT cases 9.2% Inf IPT cases 6.9% Inf
Thompson, 2012 [73]	Retrospective cross sectional study	Nyanza	1 July 2009 - 31 June 2011	0-59 months	OPT and IPT	SARI - cough or difficulty breathing with an elevated respiratory rate or a respiratory danger sign ILI - temp ≥38.0°C & cough/sore throat Exclusion Fever >7days duration	NP & OP swab	Real time RT PCR	4,052	8.2% inf 6.2% inf A 1.9% inf B
Hammit, 2012 [77]	Case control	Coast	Jan 10 – Feb 11	1-59 months	Cases: IPT Controls: OPT	Cases Admitted with severe pneumonia or very severe pneumonia SP - lower chest-wall in drawing & history of cough/	NP swabs & serum	Serology & multiplex PCR	*Serology* Cases 105 Controls with URTI 121	*Serology of serum* Cases 0.0% Inf A 0.0% Inf B 0.0% Inf C

Author, publication year	Study design	Region	Dates	Target Age	Outpatient/ Inpatient/ Community	Case definition	Sample	Test method	Samples tested	Influenza findings
						difficulty breathing VSP – cyanosis/oxygen saturation < 90%/inability to feed/head nodding/impaired consciousness & history of cough/difficulty in Breathing Controls Outpatients with and without symptoms of URTI. URTI – cough/runny or blocked nose/sore throat			Controls w/out URTI 69 *PCR* Cases 805 Controls with URTI 227 Controls w/out URTI 142	Controls with URTI: 0.0% Inf A 0.0% Inf B 0.0% Inf C Controls w/out URTI: 1.5% Inf A 1.5% Inf B 0.0% Inf C *PCR of NP swabs* Cases 0.9% Inf A 0.3% Inf B 0.4% Inf C Controls with URTI: 1.8% Inf A 0.0% Inf B 0.9% Inf C Controls w/out URTI: 0.7% Inf A 0.0% Inf B 0.0% Inf C
Feikin, 2012* [7]	Surveillance	Nyanza	Jun 07 – May 09	All ages	IPT	Hospitalized for respiratory illness – cough/difficulty breathing or (for patients aged ≥5 years) pleuritic chest pain & duration < 2 weeks Exclusion: Readmission within 3 days	NP & OP swabs	Real time RT-PCR	<5 years 1,213	<5 years 6.8% Inf 6.7% Inf A 0.2% Inf B

109

Author, publication year	Study design	Region	Dates	Target Age	Outpatient/ Inpatient/ Community	Case definition	Sample	Test method	Samples tested	Influenza findings
Hazlett, 1988 [67]	Cross sectional	Nairobi	1 Nov 81 – 31 Oct 82	<5 years	IPT	Severe ARI – admission with nasal flaring/chest retractions/ wheezing with chest retractions or nasal flaring/whooping cough with chest retractions/ nasal flaring/ stridor/ hoarseness with nasal flaring/blue lips, hands, or tongue/weakness great enough to prevent feeding	NP aspirate	Indirect immunofluo rescence	822	1.1% Inf 0.9% Inf A 1.1% Inf B

Table 20: Proportion of cases positive for influenza among individuals ≥5 years of age

Author, publication year	Study design	Region	Dates	Target Age	Outpatient/ Inpatient/ Community	Case definition	Sample	Test method	Samples tested	Influenza findings
Emukule 2015* [10]	Systematic review	Nyanza, Rift Valley, North Eastern, Nairobi, Coast	Before Dec 2013	All ages	OPT, IPT & Community	Hospitalized severe or very severe pneumonia, hospitalized SARI, hospitalized ARI, in and outpatient ALRI, in and outpatient SARI, outpatient SARI, in and outpatient ARI, outpatient ILI	Not described	RT-PCR	28,744 (for all ages)	≥5 years 14.0% - 20.5% Inf
O'meara, 2015* [70]	Case Control	Western	Nov 11 – Dec 12	1-12 years	OPT	Cases - temp > 37.5°C & resident of Webuye Health and Demographic Surveillance System Exclusions: children with apparent skin or soft-tissue infections Controls - enrolled from eye clinic, follow-up visits for fractures, postoperative visits, or children accompanying parents for other reasons. Exclusions: children accompanying sick family members and those who had objective fever or history of fever within the past 7 days	NP swab	PCR	286 cases 118 controls (for all ages)	Cases >5 years 37.9%
Feikin 2013 [76]	Surveillance	Nyanza	1 Jan 09 - 28 Feb 10	≥5 years	OPT	ARI: cough/difficulty breathing/chest pain & Temp ≥38.0°C/oxygen saturation of <90%	NP & OP swabs, acute & convalescent sera	Quantitative real time RT- PCR & haemagglutination inhibition assays	232	Serology 26.7% Inf A 11.6% Inf B PCR 30.2% Inf A 8.6% Inf B PCR or serology

111

Author, publication year	Study design	Region	Dates	Target Age	Outpatient/ Inpatient/ Community	Case definition	Sample	Test method	Samples tested	Influenza findings
										40.9% Inf A 18.1% Inf B
Murray, 2013 * [72]	Surveillance	Nyanza	Jan 07 – Jul 10	≥2 months	IPT	ARI - cough, difficulty breathing, sore throat, or chest pain	NP & OP swabs	Real time RT–PCR	≥ 5 years 1,684	≥5 years 12% Inf 9% Inf A 3% Inf B
Fuller, 2013* [74]	Case control	Nyanza	Aug 08- Dec 10	All ages	OPT & IPT	*Cases* ILI adults & children: outpatient with temp >38.0^{0}C & cough/sore throat SARD children: inpatient with cough/difficulty breathing & inability to breastfeed or Feed/vomiting/convulsions/lethargy/stridor/chest in drawing/, unconsciousness/low oxygen saturation <90% SARD adults: cough/difficulty breathing/chest pain & temp >38.0^{0}C/oxygen saturation <90% *Controls* Afebrile outpatients with no respiratory or gastrointestinal symptoms in previous 2 weeks	NP & OP swab	Quantitative real-time polymerase chain reaction (qRT-PCR)	≥5 years 2,130	≥5 years All 17.0% Inf Controls 4.3% Inf OPT 25.0% Inf IPT 12.3% Inf
Feikin, 2012 [75]	Surveillance & Case control	Nyanza	1 Mar 07 – 28 Feb 10	≥5 years	OPT, IPT & Community	ARI in hospital setting: cough/difficulty breathing/ chest pain & temp ≥38.0°C/oxygen saturation <90%/hospitalization ARI in community: cough/ difficulty breathing/chest pain	NP & OP swabs	Quantitative real time RT- PCR	ARI surveillance: 1,216 Cases: 766 Controls:	ARI surveillance 20% Inf A 6% Inf B Case control Cases 26% Inf A 6% Inf B

Author, publication year	Study design	Region	Dates	Target Age	Outpatient/ Inpatient/ Community	Case definition	Sample	Test method	Samples tested	Influenza findings
						& reported fever Controls: Patients in health facility with non-severe illness /for immunizations/for medicine refills and no history of fever/respiratory symptoms/diarrhoea in the past 2 weeks			273	Controls 4% Inf A 1% Inf B
Feikin, 2012* [7]	Surveillance	Nyanza	Jun 07 – May 09	All ages	IPT	Hospitalized for respiratory illness – cough/difficulty breathing or (for patients aged ≥5 years) pleuritic chest pain & duration < 2 weeks Exclusion: Readmission within 3 days	NP & OP swabs	Real time RT-PCR	≥5 years 866	≥5 years 14.0% Inf 11.1 % Inf A 2.9% Inf B
Waitumbi, 2010 [79]	Cross sectional study	Nyanza	Apr – Jul 07	5 – 10 years	OPT	Fever & malaria like symptoms for ≤ 4 days	Nasal swab	Real time PCR	197	19.3% inf 18.3% inf A 0.1% inf B

Table 21: Proportion of cases positive for influenza across all age groups

Author, publication year	Study design	Region	Dates	Target Age	Outpatient/ Inpatient/ Community	Case definition	Sample	Test method	Samples tested	Influenza findings
Emukule 2015* [10]	Systematic review	Nyanza, Rift Valley, North Eastern, Nairobi, Coast	Before Dec 2013	All ages	OPT, IPT & Community	Hospitalized severe or very severe pneumonia, hospitalized SARI, hospitalized ARI, in and outpatient ALRI, in and outpatient SARI, outpatient SARI, in and outpatient ARI, outpatient ILI	Not described	RT-PCR	28,744	Medically attended patients All ages 9.8% - 26.7% Inf
O'meara, 2015* [70]	Case Control	Western	Nov 11 – Dec 12	1 – 12 years	OPT	Cases - temp > 37.5°C & resident of Webuye Health and Demographic Surveillance System Exclusions: children with apparent skin or soft-tissue infections Controls - enrolled from eye clinic, follow-up visits for fractures, postoperative visits, or children accompanying parents for other reasons Exclusions: children accompanying sick family members and those who had objective fever or history of fever within the past 7 days	NP swab	PCR	286 cases 118 controls	All cases 20.3% Inf Controls 7.6% Inf
Emukule 2014 [80]	Surveillance	Nyanza	Aug 09 – Jul 12	All ages	IPT & OPT	ILI – outpatient & temp ≥38^{0}C & cough/sore throat & onset within last 14 days SARI - hospitalization & cough/difficulty breathing/ pleural chest pain & onset within last 14 days	NP & OP swabs	Real time RT PCR	ILI 1,508 SARI 4,387	SARI 7.9% Inf 5.8% Inf A 0.1% Inf A s(H1N1) 1.4% Inf A (H3N2) 2.1% Inf A p(H1N1) 0.2% Inf A unsubtyped

114

Author, publication year	Study design	Region	Dates	Target Age	Outpatient/ Inpatient/ Community	Case definition	Sample	Test method	Samples tested	Influenza findings
						ARI - cough and difficulty in breathing within last 14 days				1.8% Inf A not subtyped 2.2% Inf B ILI 13.7% Inf 10.5% Inf A 0.1% Inf A s(H1N1) 3.4% Inf A (H3N2) 5.4% Inf A p(H1N1) 0.2% Inf A unsubtyped 1.2% Inf A not subtyped 3.4% Inf B
Katz, 2014	Surveillance	Nairobi, Coast, Eastern, North Eastern, Western, Nyanza, Central, Rift Valley, North Eastern	Aug 06 - Dec 11	All ages	OPT & IPT	SARI <5 years – cough/difficulty breathing & chest in-drawing/stridor/unable to breastfeed or drink/vomits everything/convulsions/lethargy, or unconsciousness & hospitalisation SARI - ≥5 years axillary temperature >38.0°C & cough/difficulty breathing/shortness of breath & hospitalisation ILI - axillary temperature >38.0°C & cough/sore throat in an outpatient	NP & OP swab	Real time RT PCR	24,762 SARI 14,013 ILI	SARI 9.6% Inf 7.5% Inf A 2.2% Inf B ILI 14.6% Inf 11.6% Inf A 3.3% Inf B
Ndegwa 2014 [81]	Surveillance	Nyanza, Nairobi	1 Apr 10 – 30	All ages	IPT	Respiratory health care associated infections (RHAIs) - new hospital onset	NP & OP swabs	Real time RT PCR	rHAI 153 HA-ILI	RHAI 9.3% Inf A 7.1% Inf B

Author, publication year	Study design	Region	Dates	Target Age	Outpatient/ Inpatient/ Community	Case definition	Sample	Test method	Samples tested	Influenza findings
			Sep 12			(≥3 days after admission) fever (≥380C) or hypothermia (<350C) with concurrent signs or symptoms of acute respiratory infection: crackles, rhonchi, decreased breath sounds, crepitus, need for supplemental oxygen in non-ventilated patients, clinician documentation of upper respiratory infection, clinician request for sputum culture, and oxygen saturation (by pulse oximetry) <90% in ventilated patients or concurrent patient or family report of cough or sore throat Hospital-associated ILI - new-onset fever or hypothermia with concurrent patient or family report of cough or sore throat			121	HA-ILI 8.7% Inf A 7.7% Inf B
Majanja, 2013 [60]	Surveillance	Nairobi, Nyanza, Coast, Western, Eastern, Rift Valley	Jan 08 – Jul 11	> 2 months	OPT	Temp >38°C & cough/sore throat & symptoms <72 hours Exclusions: exudative pharyngitis/tonsillitis	NP swab	Real time RT PCR	11,592	17.9% Inf 13.1% Inf A 3.0% Inf A pH1N1 3.3% Inf A H3N2 1.2% Inf A sH1N1 6.0% Inf A unsubtyped 4.7% Inf B
Bulimo, 2012	Surveillance	Nyanza Nairobi, Coast, North Eastern,	Jan 07 – Nov 08	> 2 months	OPT	Temp > 38°C & cough/sore throat & symptoms < 72 hours Exclusions: exudative pharyngitis/tonsillitis	NP swab	Real time RT PCR	5,898	20% Inf A

116

Author, publication year	Study design	Region	Dates	Target Age	Outpatient/ Inpatient/ Community	Case definition	Sample	Test method	Samples tested	Influenza findings
		Rift Valley, Western								
Katz 2012 [8]	Surveillance	Nyanza, Nairobi	1 Mar 07 - 28 Feb 10	All ages	IPT & OPT & Community	Acute LRTI <5 – cough/difficulty breathing & oxygen saturation ≤90%/ convulsions/ inability to drink or breast-feed/vomiting everything/lethargy, unconsciousness/lower-chest wall in drawing/stridor Acute LRTI > 5 – cough/difficulty breathing/ chest pain & temp ≥38.0°C/ oxygen saturation level of ≤90% ILI clinic - temp ≥38°C & cough/sore throat ILI community – reported fever/temp ≥38°C & cough/sore throat NB: ILI data not included in calculating prevalence of Influenza	NP & OP	Real time RT PCR	Kibera 1,197 Lwak 1,641	Kibera 26.7% Inf 21.9% Inf A 10.4% Inf A (H1N1) pdm09 5.4% Inf A H1N1 3.8% Inf A unsubtyped 2.7% Inf A H3N2 4.3% Inf B 21.9% Inf 17.3% Inf A 8.8% Inf A (H1N1) pdm09 2.3% Inf A H1N1 2.9% Inf A unsubtyped 2.0% Inf A H3N2 4.4% Inf B
Wong, 2012 [83]	Surveillance	Nairobi, Nyanza, Rift Valley, Western, North Eastern, Coast	1 Jun 09 – 31 Aug 10	2 months – 18 years	OPT	ILI - temp >38.0°C & cough/sore throat & presented within 72 hours of symptom onset	NP swab	Real time RT PCR	4,251	26% Inf 4.5% Inf A(H1N1)pdm09 4.3% Inf A(H3N2) 1.7% Inf A(H1N1)
Feikin,	Surveillance	Nyanza	Jun 07	All ages	IPT	Hospitalized for respiratory	NP & OP	Real time	All 2,079	All

117

Author, publication year	Study design	Region	Dates	Target Age	Outpatient/ Inpatient/ Community	Case definition	Sample	Test method	Samples tested	Influenza findings
2012* [7]			– May 09			illness – cough/difficulty breathing or (for patients aged ≥5 years) pleuritic chest pain & duration < 2 weeks Exclusion: Readmission within 3 days	swabs	RT-PCR	<5 years 1,213 ≥5 years 866	9.8% Inf 8.5% Inf A 1.3% Inf B <5 years 6.8% Inf 6.7% Inf A 0.2% Inf B ≥5 years 14.0% Inf 11.1 % Inf A 2.9% Inf B
Ahmed 2012 [84]	Surveillance	North Eastern & Rift Valley	1 Sep 07 – 31 Aug 10	All ages	IPT & OPT	ILI all ages - temp ≥ 38°C & cough/sore throat SARI children > 1 week and < 2 months old – hospitalisation & respiratory rate > 60 per minute/severe chest in drawing/nasal flaring/ grunting/temp ≥38°C or < 35.5°C/pulse oxygenation < 90% SARI children 2 months to <5 years – hospitalisation & cough/difficulty breathing & respiratory rate >50/min for infants 2 months to <1 year old or >40/min for children 1 to <5 years old/ chest in drawing or stridor in a calm child/unable to drink or breast feed/vomiting/ convulsions/lethargic or unconscious/pulse oxygen saturation < 90%	NP & OP swabs	RT-PCR	ILI 1,815 SARI 4,449	ILI 10.9% Inf A 3.0% Inf B SARI 9.2% Inf A 2.4% Inf B

Author, publication year	Study design	Region	Dates	Target Age	Outpatient/ Inpatient/ Community	Case definition	Sample	Test method	Samples tested	Influenza findings
						SARI for individuals ≥5 years – hospitalisation & temp ≥ 38°C & cough/sore throat & shortness of breath/difficulty breathing				
Onyango 2012 [85]	Cross sectional	Coast	Jan 07 – Dec 10	1 day – 12 years	IPT & OPT	Inpatients – cough/difficulty breathing & lower chest-wall in drawing/cyanosis/prostration/unconsciousness/oxygen saturation level <90% Exclusion - children not residing in the Kilifi Health and Demographic Surveillance System/admitted in extremis/admitted for elective surgery/received a diagnosis of neonatal tetanus Outpatients with URTI – cough/ difficulty breathing/nasal discharge/ runny or blocked nose/sore throat Outpatients non-ARI - no signs of acute respiratory infection	NP wash or aspirate	Real time RT-PCR	Inpatients 2,002 Outpatients with URTI 331 Outpatients non ARI 196	In patients 4.9% Inf 3.5% Inf A 0.9% Inf B 0.8% Inf C Outpatients with URTI: 3.9% Inf 3.3% Inf A 0.3% Inf B 0.9% Inf C Outpatients non-ARI Inf 0.5% Inf A 0.5% Inf B 0.0% Inf C 0.0%
Waiboci 2011 [88]	Surveillance	Nairobi	14 Oct 09 - 25 Nov 09	All ages	OPT	ILI - case was defined as a patient with fever $38uC and cough or sore throat for all ages SARI <5 years – cough/ difficulty breathing & unable to drink or breast feed/lethargic or unconscious/vomiting everything/convulsions/nasal flaring/ grunts/chest in	NP & OP swabs	Real time RT- PCR	285	49% Inf A p(H1N1)

Author, publication year	Study design	Region	Dates	Target Age	Outpatient/ Inpatient/ Community	Case definition	Sample	Test method	Samples tested	Influenza findings
						drawing/stridor in a calm child/oxygen saturation <90%.				
Berkley, 2010 [86]	Case control	Coast	1 Jan 07 - 30 Apr - 08	1 day – 13 years	IPT & OPT	Cases (severe disease) Severe pneumonia – admitted with cough/difficult breathing & lower chest wall in drawing Very severe pneumonia – admitted with cough/difficult breathing & oxygen saturation <90%/inability to drink or breast feed/inability to sit/impaired consciousness Controls (non-severe disease) URTI - cough, runny or blocked nose, sore throat or sneezing being managed as outpatients and not meeting any criteria for pneumonia Well children: no signs of URTI or LRTI/ attending for routine immunization at the hospital.	Nasal wash	Real time PCR	Cases 759	5.8% Inf A
Bulimo, 2008 [180]	Surveillance	Nairobi, Nyanza, Coast, North Eastern, Rift Valley	06 - 07	≥ 2 months	OPT	ILI - sore throat/cough + fever < 72 hours Exclusion: Exudative pharyngitis, tonsillitis	NP swab	Haemagglutination inhibition (HI) assay	1,014	0.9% inf A H3N2
Gachara 2006 [87]	Surveillance	Nairobi	Jan – Aug 05	Not described	Not described	Not described	Throat swab	Immunofluorescence	660	37.6% Inf 0.0% Inf A 37.6% Inf B
Montefiore 1970 [66]	Cross sectional study	Coast	Feb 1970	All ages	Health facility (not specified whether IPT or OPT)	Patients attending hospital	Serum sample	HI assays	57	36.8% Inf A 7.0% Inf B

Table 22: Incidence of influenza disease

Author, publication year	Region	Dates covered	Risk calculated	Findings
Breiman, 2015 [69]	Nairobi	1 Mar 07 – 28 Feb 11	Incidence of influenza-associated SARI	Influenza A <5 years: 1,000 (95% CI 400 – 1,700) per 100,000 person years of observation Influenza A & B <5 years: 1,300 (95% CI 600 – 2,000) per 100,000 person years of observation
Feikin, 2013 [76]	Nyanza	1 Mar 07 – 28 Feb 10	Incidence of influenza-associated SARI	Influenza A <5 years: 4,000 (2,500 – 5,500) per 100,000 person years observed Influenza A & B <5 years: 5,800 (3,800 – 7,800) per 100,000 person years observed
Feikin, 2012 [75]	Nyanza	1 Mar 07 – 28 Feb 10	Incidence of influenza-associated ARI	Influenza A ≥5 years: 2,600 (95% CI 2,280 – 2,920) per 100,000 person years of observation ≥ 18 years HIV –ve: 1,420 (95% CI 1,040 – 1,800) per 100,000 person years of observation ≥ 18 years HIV +ve: 4,490 (95% CI 2,800 – 6,180) per 100,000 person years of observation Influenza B ≥5 years: 200 (95% CI 150 – 250) per 100,000 person years of observation ≥ 18 years HIV –ve: 440 (95% CI 250 – 630) per 100,000 person years of observation ≥ 18 years HIV +ve: 920 (95% CI 320 – 1,520) per 100,000 person years of observation

Table 23: Incidence of medically attended influenza disease

Author, publication year	Region	Dates covered	Risk calculated	Findings
Emukule 2015* [10]	Nyanza, Rift Valley, North Eastern, Nairobi, Coast	Before Dec 2013	Annual incidence rates of hospitalization with influenza for different respiratory syndromes - hospitalized severe or very severe pneumonia, hospitalised SARI, hospitalised ARI	<6 months: 570 per 100,000 persons or person years < 1 year: 140–1,230 per 100,000 persons or person years <5years: 60 – 560 per 100,000 persons or person years ≥5 years: 20 – 40 per 100,000 persons or person years All ages: 60 – 110 per 100,000 persons or person years
Emukule 2014 [80]	Nyanza	Aug 09 – Jul 12	Rates of influenza-associated hospitalised SARI Rates of influenza-associated non hospitalised SARI Rates of influenza-associated medically attended ILI Rates of influenza-associated non-medically attended ILI	Rates of influenza-associated hospitalised SARI Annual unadjusted rates < 6 months: 450 (95% CI 190 – 1,090) per 100,000 persons 6-11 months: 380 (95% CI 150 – 970) per 100,000 persons 12-23 months: 370 (95% CI 190 – 710) per 100,000 persons 2-4 years: 110 (95% CI 60 – 210) per 100,000 persons 5-17 years: 20 (95% CI 10 – 40) per 100,000 persons 18-34 years: 30 (95% CI 10 – 70) per 100,000 persons 35-49 years: 30 (95% CI 10 – 110) per 100,000 persons ≥50 years: 20 (95% CI 0 – 80) per 100,000 persons <5 years: 210 (95% CI 150 – 310) per 100,000 persons ≥5 years: 20 (95% CI 10 – 40) per 100,000 persons All ages: 50 (95% CI 40 – 70) per 100,000 persons Annual adjusted rates < 6 months: 570 (95% CI 240 – 1,380) per 100,000 persons 6-11 months: 470 (95% CI 180 – 1,190) per 100,000 persons 12-23 months: 440 (95% CI 230 – 850) per 100,000 persons 2-4 years: 140 (95% CI 70 – 270) per 100,000 persons 5-17 years: 20 (95% CI 10 – 50) per 100,000 persons 18-34 years: 30 (95% CI 10 – 70) per 100,000 persons 35-49 years: 40 (95% CI 10 – 120) per 100,000 persons ≥50 years: 20 (95% CI 10 – 90) per 100,000 persons <5 years: 270 (95% CI 180 – 390) per 100,000 persons ≥5 years: 30 (95% CI 20 – 40) per 100,000 persons All ages: 70 (95% CI 50 – 90) per 100,000 persons Rates of influenza-associated non-hospitalised SARI Annual Adjusted rates < 6 months: 620 (95% CI 290 – 1,320) per 100,000 persons

Author, publication year	Region	Dates covered	Risk calculated	Findings
				6-11 months: 50 (95% CI 220 – 1,140) per 100,000 persons 12-23 months: 480 (95% CI 270 – 850) per 100,000 persons 2-4 years: 150 (95% CI 90 – 270) per 100,000 persons 5-17 years: 40 (95% CI 20 – 70) per 100,000 persons 18-34 years: 60 (95% CI 30 – 110) per 100,000 persons 35-49 years: 70 (95% CI 30 – 160) per 100,000 persons ≥50 years: 40 (95% CI 20 – 110) per 100,000 persons <5 years: 290 (95% CI 210 – 400) per 100,000 persons ≥5 years: 50 (95% CI 40 - 70) per 100,000 persons All ages: 120 (95% CI 90 – 140) per 100,000 persons Rates of influenza-associated medically attended ILI Unadjusted annual rates < 6 months: 150 (95% CI 30 – 690) per 100,000 persons 6-11 months: 380 (95% CI 150 – 970) per 100,000 persons 12-23 months: 310 (95% CI 150 – 640) per 100,000 persons 2-4 years: 180 (95% CI 110 – 300) per 100,000 persons 5-17 years: 60 (95% CI 40 – 100) per 100,000 persons 18-34 years: 20 (95% CI 10 – 60) per 100,000 persons 35-49 years: - ≥50 years: - <5 years: 220 (95% CI 150 – 320) per 100,000 persons ≥5 years: 40 (95% CI 20 - 50) per 100,000 persons All ages: 70 (95% CI 50 – 90) per 100,000 persons Adjusted annual rates < 6 months: 1,620 (95% CI 350 – 7,380) per 100,000 persons 6-11 months: 3,770 (95% CI 1,470 – 9,670) per 100,000 persons 12-23 months: 3,170 (95% CI 1,560 – 6,440) per 100,000 persons 2-4 years: 1,730 (95% CI 1,030 – 2,900) per 100,000 persons 5-17 years: 610 (95% CI 390 – 980) per 100,000 persons 18-34 years: 20 (95% CI 70 – 530) per 100,000 persons 35-49 years: - ≥50 years: -

Author, publication year	Region	Dates covered	Risk calculated	Findings
				<5 years: 2,180 (95% CI 1,510 – 3,160) per 100,000 persons ≥5 years: 430 (95% CI 280 - 640) per 100,000 persons All ages: 720 (95% CI 550 – 940) per 100,000 persons Rates of influenza-associated non-medically attended ILI Annual rates < 6 months: 2,230 (95% CI 1,500 – 3,320) per 100,000 persons 6-11 months: 5,210 (95% CI 4,040 – 6,710) per 100,000 persons 12-23 months: 4,380 (95% CI 3,630 – 5,300) per 100,000 persons 2-4 years: 2,390 (95% CI 2,080 – 2,750) per 100,000 persons 5-17 years: 780 (95% CI 690 – 890) per 100,000 persons 18-34 years: 250 (95% CI 190 – 340) per 100,000 persons 35-49 years: - ≥50 years: - <5 years: 3,010 (95% CI 2,730 – 3,330) per 100,000 persons ≥5 years: 540 (95% CI 490 - 600) per 100,000 persons All ages: 910 (95% CI 850 – 980) per 100,000 persons
Fuller 2013 [9]	National	Aug 08- Dec 10	Incidence of hospitalised and non-hospitalised SARI	Hospitalised influenza-associated SARI <5 years: 290-470 per 100,000 persons per year ≥5 years: 21-24 per 100,000 persons Non hospitalised influenza-associated SARI <5 years: 330-510 per 100,000 persons per year ≥5 years: 42-47 per 100,000 persons
Feikin, 2012* [7]	Nyanza	Jun 07 – May 09	Incidence of hospitalised influenza-associated respiratory illness	Influenza < 1 year: 137.8 (95% CI 92.6 – 183.0) per 100,000 per year 1 year: 263.1 (95% CI 187.9 – 338.3) per 100,000 per year 2 years: 114.7(95% CI 64.2 – 165.2) per 100,000 per year 3 years: 115.0 (95% CI 63.5 – 166.5) per 100,000 per year 4 years: 76.2 (95% CI 35.1 – 117.3) per 100,000 per year <5 years: 143.7 (95% CI 119.6 – 167.8) per 100,000 per year 5 – 19 years: 18.8 (95% CI 13.1 – 24.4) per 100,000 per year

Author, publication year	Region	Dates covered	Risk calculated	Findings
				20 − 34 years: 55.2 (95% CI 41.2 − 69.2) per 100,000 per year 35 − 39 years: 65.1 (95% CI 44.9 − 85.3) per 100,000 per year ≥50 years: 57.3 (95% CI 38.6 − 76.0) per 100,000 per year All ages: 56.2 (95% CI 50.0 − 62.4) per 100,000 per year Influenza A All ages: 50.3 (95% CI 44.4 − 56.1) Influenza B All ages: 6.1 (95% CI 4.1 − 8.2)
Onyango 2012 [85]	Coast	Jan 07 − Dec 10	Incidence of admission with severe or very severe pneumonia due to influenza and influenza A	Influenza <1 year: 154 (95% CI 116–204) per 100,000 per year <5 years: 60 (95% CI 49–74) per 100,000 per year <13 years: 28 (95% CI 23–34) per 100,000 per year Influenza A <1 year: 106 (95% CI 75–149) per 100,000 per year <5 years: 43 (95% CI 34–55) per 100,000 per year <13 years: 20 (95% CI 16–25) per 100,000 per year Adjusted rates for children w/in 5 km of hospital Influenza <5 years: 106 (95% CI 78–144) per 100,000 per year Influenza A <5 years: 70 (95% CI 48–102) per 100,000 per year
Katz 2012 [8]	Nyanza, Nairobi	1 Mar 07 - 28 Feb 10	Crude and adjusted incidence of medically attended acute lower respiratory tract influenza-associated illness	Crude rate <1 year: 780 (95% CI 530 − 1,110) per 100,000 person years 1-<2 years: 770 (95% CI 560 − 1,030) per 100,000 person years 2-≤4 years: 490 (95% CI 390 − 620) per 100,000 person years 5 - ≤ 17 years: 830 (95% CI 750 − 920) per 100,000 person years 18 - ≤ 34 years: 290 (95% CI 240 − 350) per 100,000 person years 35 - 49 years: 170 (95% CI 110 - 250) per 100,000 person years

Author, publication year	Region	Dates covered	Risk calculated	Findings
				≥50 years: 110 (95% CI 60 – 180) per 100,000 person years All ages: 480 (95% CI 450 – 520) per 100,000 person years Adjusted rate <1 year: 3,670 (95% CI 3,100 – 4,320) per 100,000 person years 1 - <2 years: 3,250 (95% CI 2,800 – 3,750) per 100,000 person years 2 - ≤4 years: 2,620 (95% CI 2,370 – 2,890) per 100,000 person years 5 - ≤ 17 years: 2,530 (95% CI 2,390 – 2,690) per 100,000 person years 18 - ≤ 34 years: 810 (95% CI 240 – 350) per 100,000 person years 35 - 49 years: 480 (95% CI 380 - 590) per 100,000 person years ≥50 years: 300 (95% CI 210 – 410) per 100,000 person years All ages: 1,630 (95% CI 1,570 – 1,700) per 100,000 person years
Ahmed 2012 [84]	North Eastern & Rift Valley	1 Sep 07 – 31 Aug 10	Incidence of SARI hospitalisation	Influenza A < 1 year: 1,680(95% CI 1,310-2,160) per 100,000 per year 1-5 years: 390 (95% CI 300 – 490) per 100,000 per year <5years: 610 (95% CI 510 – 730) per 100,000 per year Influenza B < 1 year: 1,110(95% CI 820-1,510) per 100,000 per year 1-5 years: 340 (95% CI 270 – 440) per 100,000 per year <5years: 480 (95% CI 390 – 580) per 100,000 per year
Berkley, 2010 [86]	Coast	1 Jan 07 - 30 Apr - 08	Incidence of admission with severe or very severe pneumonia due to Influenza A	< 28 days: 31 per 100,000 live births < 1 year: 244 per 100,000 1 – 2 years: 97 per 100,000 2 – 5 years: 32 per 100,000 <5 years: 82 per 100,000 5 to < 13 years: 15 per 100,000 < 13 years: 39 per 100,000

7.3 Appendix 3: Supplementary tables (Objective 1)

Table 24: Prevalence and 95% confidence interval limits for regional risk factors for severe acute respiratory illness and healthcare seeking behaviour for acute respiratory illness in Kenya

Region	Malnutrition	Low birth weight	Non-exclusive breastfeeding	Household air pollution	Household crowding	HIV prevalence (children)*	HIV prevalence (adults)	Health care seeking
Central	0.052 (0.041-0.067)	0.092 (0.067-0.125)	0.218 (0.098-0.417)	0.768 (0.762-0.773)	0.230 (0.214-0.246)	0.0065	0.038 (0027-0.049)	0.703 (0.595-0.792)
Coast	0.136 (0.119-0.155)	0.127 (0.099-0.162)	0.262 (0.158-0.401)	0.685 (0.679-0.691)	0.355 (0.339-0.372)	0.0094	0.043 (0.030-0.056)	0.661 (0.572-0.740)
Eastern	0.121 (0.108-0.137)	0.084 (0.063-0.112)	0.352 (0.237-0.487)	0.833 (0.828-0.837)	0.378 (0.363-0.394)	0.0063	0.0378 (0.023-0.051)	0.677 (0.606-0.740)
Nairobi	0.038 (0.023-0.062)	0.089 (0.058-0.136)	0.131 (0.031-0.410)	0.457 (0.448-0.465)	0.175 (0.155-0.198)	0.0122	0.049 (0.037-0.061)	0.652 (0.459-0.806)
North Eastern	0.190 (0.166-0.216)	0.079 (0.046-0.133)	0.416 (0.263-0.588)	0.857 (0.853-0.861)	0.666 (0.640-0.691)	0.0019	0.008 (0.000-0.020)	0.370 (0.241-0.520)
Nyanza	0.075 (0.065-0.086)	0.035 (0.024-0.050)	0.340 (0.214-0.494)	0.823 (0.819-0.828)	0.468 (0.452-0.483)	0.0262	0.151 (0.114-0.188)	0.711 (0.644-0.769)
Rift Valley	0.153 (0.142-0.165)	0.066 (0.054-0.081)	0.291 (0.205-0.395)	0.807 (0.802-0.812)	0.396 (0.385-0.407)	0.0081	0.037 (0.024-0.050)	0.689 (0.642-0.733)
Western	0.091 (0.076-0.107)	0.048 (0.031-0.074)	0.245 (0.131-0.411)	0.864 (0.860-0.868)	0.488 (0.468-0.508)	0.0086	0.047 (0.030-0.065)	0.568 (0.494-0.639)

*95% confidence interval limits were not available for the prevalence of HIV in children

Data on the prevalence of these risk factors was obtained from the Kenya Demographic Health Survey 2014 report [101] and dataset [102], the Kenya population census 2009 [103], the Kenya HIV estimates 2014 [181], and the Kenya AIDS Indicator Survey 2012 [100]

Table 25: Annual regional rate of hospitalized severe acute respiratory illness (SARI) in Kenya by region, 2012 to 2014

Year	Central n(95% CI)	Coast n(95% CI)	Eastern n(95% CI)	Nairobi n(95% CI)	North Eastern n(95% CI)	Nyanza n(95% CI)	Rift Valley n(95% CI)	Western n(95% CI)	Kenya n(95% CI)
2012									
<5 years	**1,345.7 (1,205.2-1,510.5)**	**1,522.7 (1,380.9-1,680.1)**	**1,864.5 (1,709.0-2,021.9)**	**625.5 (500.1-748.8)**	**1,073.5 (831.0-1,387.5)**	**2,155.3 (1,970.4-2,341.0)**	**1,814.2 (1,706.4-1,925.9)**	**1,482.8 (1,339.9-1,649.2)**	**1,644.1 (1,498.4-1,801.7)**
<2 years	2,116.2 (1,895.1-2,375.5)	2,370.5 (2,149.7-2,615.7)	2,949.7 (2,703.9-3,198.8)	950.5 (760.0-1,137.8)	1,929.0 (1,494.7-2,493.0)	3,385.0 (3,094.7-3,676.7)	2,872.9 (2,702.3-3,050.0)	2,325.4 (2,101.5-2,586.4)	2,600.3 (2,372.4-2,845.9)
0-5 months	1,814.6 (1,625.2-2,037.7)	2,034.7 (1,846.1-2,245.9)	2,527.6 (2,316.7-2,740.8)	817.9 (654.7-979.2)	1,654.9 (1,283.9-2,138.5)	2,904.5 (2,655.9-3,155.0)	2,467.6 (2,320.9-2,619.6)	1,993.6 (1,802.0-2,217.5)	2,229.1 (2,034.3-2,439.2)
6-11 months	2,260.7 (2,024.8-2,538.0)	2,533.9 (2,297.9-2,795.2)	3,147.6 (2,885.8-3,413.9)	1,017.8 (813.1-1,218.6)	2,059.7 (1,597.0-2,661.6)	3,618.7 (3,308.4-3,930.8)	3,074.2 (2,891.7-3,263.8)	2,482.7 (2,244.0-2,761.5)	2,776.5 (2,533.7-3,038.1)
0-11 months	2,039.6 (1,826.8-2,290.1)	2,286.5 (2,074.0-2,523.0)	2,840.4 (2,603.8-3,080.4)	918.7 (734.6-1,100.0)	1,859.1 (1,441.9-2,402.4)	3,264.8 (2,985.0-3,546.3)	2,773.6 (2,608.8-2,944.6)	2,240.4 (2,025.0-2,491.9)	2,505.2 (2,286.3-2,741.3)
12-23 months	2,201.3 (1,971.1-2,470.6)	2,467.4 (2,237.1-2,722.6)	3,066.5 (2,810.8-3,325.3)	990.7 (792.1-1,185.6)	2,007.2 (1,553.9-2,594.5)	3,524.4 (3,221.9-3,827.9)	2,994.3 (2816.5-3,178.8)	2,418.1 (2,185.0-2,689.5)	2,710.1 (2,471.8-2,966.7)
2-4 years	852.4 (763.4-956.6)	955.4 (866.3-1,053.9)	1,187.1 (1,088.1-1,287.2)	383.8 (306.9-459.5)	7,76.3 (600.4-1,003.4)	1,364.7 (1,247.6-1,482.2)	1,159.3 (1,090.4-1,230.7)	936.4 (846.0-1,041.4)	1,048.3 (953.9-1,151.1)
≥5 years	**49.4 (44.6-53.4)**	**47.3 (43.0-51.3)**	**61.5 (57.5-65.1)**	**18.9 (15.2-22.0)**	**36.0 (27.9-46.6)**	**112.0 (101.6-122.1)**	**60.7 (57.8-63.5)**	**61.1 (56.0-66.0)**	**60.4 (55.4-65.3)**
5-14 years	76.7 (69.2-82.9)	72.2 (65.7-78.2)	84.8 (79.5-89.6)	48.5 (38.8-56.4)	50.5 (39.1-65.3)	105.1 (98.5-110.7)	86.2 (82.6-89.7)	77.9 (71.3-84.0)	80.8(74.6-86.7)
15-49 years	33.7 (30.5-36.5)	32.4 (29.4-35.1)	43.1 (40.3-45.7)	10.9 (8.7-12.7)	22.6 (17.5-29.2)	101.6 (90.6-112.4)	42.4 (40.2-44.5)	45.1 (41.3-48.7)	44.1 (40.2-47.9)
50-64 years	39.7 (36.0-43.1)	38.2 (34.8-41.5)	50.6 (47.4-53.8)	13.4 (11.3-16.2)	26.6 (21.3-34.6)	119.3 (106.5-132.0)	49.8 (47.3-52.4)	53.0 (48.5-57.5)	54.7 (50.0-59.5)
65+ years	94.0 (85.3-101.9)	90.2 (82.0-98.3)	120.2 (112.4-127.6)	31.4 (26.2-36.7)	63.3 (49.9-82.5)	282.9 (252.4-313.4)	118.0 (112.0-124.0)	125.9 (115.7-136.2)	133.4 (122.0-144.7)
All ages	**207.9 (186.5-231.5)**	**286.1 (259.5-314.9)**	**319.1 (293.5-344.7)**	**95.7 (76.6-114.1)**	**183.3 (142.0-237.0)**	**468.0 (427.2-508.7)**	**345.7 (325.8-366.2)**	**309.7 (280.5-342.9)**	**304.2 (277.5-332.6)**
2013									
<5 years	**967.7 (866.9-1,086.2)**	**1,089.3 (987.9-1,201.9)**	**1,344.7 (1,232.7-1,458.2)**	**442.4 (353.8-529.7)**	**822.0 (636.3-1062.5)**	**1,548.1 (1,415.3-1,681.4)**	**1,307.6 (1,229.9-1,388.1)**	**10,65.0 (962.5-1,184.5)**	**1,185.0 (1,079.7-1,299.0)**
<2 years	1,267.0 (1,135.5-1,422.5)	1,417.4 (1,285.8-1,564.1)	1,767.3 (1,620.3-1,916.6)	567.7 (454.3-680.1)	1,153.7 (893.4-1,491.5)	2,023.6 (1,850.1-2,197.9)	1,715.2 (1,613.4-1,820.9)	1,392.6 (1,258.7-15,49.1)	1,554.9 (1,418.8-1,701.9)
0-5 months	517.1 (464.4-581.2)	577.7 (524.4-637.4)	718.8 (659.0-779.8)	233.6 (187.6-279.5)	470.8 (365.3-608.8)	825.6 (755.5-897.5)	701.1 (659.7-744.6)	566.6 (513.0-630.7)	633.7 (578.8-693.8)
6-11 months	1,790.5 (1,604.5-2,010.4)	2,007.7 (1,821.2-2,215.9)	2,494.0 (2,286.7-2,704.6)	806.7 (645.0-966.6)	1,630.7 (1263.9-2,109.2)	2,866.4 (2,620.5-3,113.1)	2,435.1 (2,290.7-2,585.2)	1,967.4 (1,778.5-2,188.4)	2,199.5 (2,007.5-2,406.9)
0-11 months	1,159.5 (1,039.5-1,302.2)	1,299.1 (1,178.6-1,433.7)	1,614.4 (1,480.2-1,750.8)	522.7 (418.4-626.1)	1,056.0 (818.6-1,365.7)	1,855.2 (1,696.4-2,015.2)	1,575.9 (1,482.5-1,673.2)	1,273.3 (1,151.4-1,416.6)	1,423.6 (1,299.5-1,558.0)
12-23 months	1,386.6 (1,242.3-1,556.3)	1,553.8 (1,409.4-1,714.4)	1,930.7 (1,770.0-2,093.7)	624.7 (499.8-748.4)	1,263.1 (977.2-1,632.4)	2,219.0 (2,028.5-2,409.9)	1,885.5 (1,773.3-2,001.5)	1,522.8 (1,375.9-1,693.7)	1,706.5 (1,556.6-1,868.1)
2-4 years	776.0 (694.9-870.9)	869.7 (788.6-959.5)	1,080.9 (990.8-1,172.1)	349.3 (279.1-417.9)	706.8 (547.0-913.5)	1,242.4 (1,135.7-1,349.3)	10,55.5 (992.8-1,120.4)	852.5 (770.4-948.1)	954.4 (868.4-1,047.9)

128

Year	Central n(95% CI)	Coast n(95% CI)	Eastern n(95% CI)	Nairobi n(95% CI)	North Eastern n(95% CI)	Nyanza n(95% CI)	Rift Valley n(95% CI)	Western n(95% CI)	Kenya n(95% CI)
≥5 years	**36.6** **(33.1-39.6)**	**36.6** **(33.3-39.7)**	**46.1** **(43.2-48.8)**	**15.1** **(12.2-17.6)**	**30.3** **(23.5-39.3)**	**78.1** **(71.4-84.5)**	**47.3** **(45.1-49.4)**	**46.5** **(42.6-50.3)**	**45.4** **(41.7-49.0)**
5-14 years	78.3 (70.7-84.6)	73.7 (67.0-79.8)	86.5 (81.2-91.4)	49.4 (39.6-57.6)	51.5 (39.9-66.7)	107.3 (100.5-113.0)	88.0 (84.3-91.6)	79.5 (72.7-85.7)	82.5 (76.1-88.5)
15-49 years	18.5 (16.7-20.0)	17.7 (16.1-19.1)	23.6 (22.0-25.0)	6.0 (4.8-6.9)	12.4 (9.6-16.0)	55.5 (49.5-61.4)	23.2 (21.9-24.3)	24.6 (22.5-26.7)	24.1 (21.9-26.2)
50-64 years	38.9 (35.4-42.2)	37.2 (33.9-40.4)	49.5 (46.4-52.6)	13.0 (11.0-15.8)	26.8(20.7-35.4)	116.7 (104.3-129.4)	48.7 (46.2-51.2)	52.0 (47.6-56.3)	53.5 (48.9-58.3)
65+ years	21.1 (19.0-23.1)	20.4 (18.6-22.2)	26.8 (25.2-28.4)	7.7 (7.7-10.2)	14.9 (13.1-20.5)	63.0 (56.7-69.9)	26.4 (25.2-28.0)	28.3 (26.1-31.1)	29.9 (27.5-32.6)
All ages	**150.4** **(135.0-167.5)**	**207.0** **(187.8-227.7)**	**231.7** **(213.2-250.2)**	**69.3** **(55.5-82.5)**	**142.8** **(110.6-184.6)**	**334.2** **(305.5-362.7)**	**252.1** **(237.7-267.0)**	**224.6** **(203.5-248.6)**	**220.8** **(201.4-241.4)**
2014									
<5 years	**604.5** **(541.7-678.7)**	**682.2** **(618.8-752.9)**	**838.2** **(768.5-909.0)**	**278.9** **(223.2-334.0)**	**502.3** **(389.2-649.7)**	**968.1** **(885.0-1,051.4)**	**817.6** **(769.0-868.0)**	**665.0** **(601.0-739.7)**	**740.0** **(674.4-811.2)**
<2 years	447.1 (400.5-501.7)	500.9 (454.3-552.8)	622.6 (570.7-675.1)	201.3 (160.8-241.1)	407.4 (315.3-526.5)	1,360.9 (1,244.3-1,478.2)	607.9 (571.7-645.3)	490.9 (443.7-546.0)	549.7 (500.2-603.6)
0-5 months	902.3 (808.8-1013.4)	1010.8 (917.1-1,115.2)	1,256.5 (1,151.6-1,362.5)	406.5 (325.9-487.0)	822.1 (639.4-1,064.4)	1,443.7 (1,319.9-1,568.4)	1,226.1 (1,153.4-1,301.9)	990.2 (895.5-1,102.0)	1,107.7 (1,011.2-1,212.4)
6-11 months	819.8 (734.3-921.0)	918.9 (834.4-1,013.9)	1,141.0 (1,046.6-1,237.5)	369.8 (296.2-443.4)	749.0 (581.3-971.4)	1,311.4 (1,199.4-1,424.2)	1,114.0 (1,048.2-1,182.9)	899.8 (813.5-1,000.6)	1,006.5 (918.9-1,101.6)
0-11 months	860.7 (771.2-966.8)	964.4 (875.4-1,064.1)	1,198.2 (1,098.6-1,299.4)	388.0 (311.0-465.0)	785.2 (610.1-1,017.5)	1,377.0 (1,259.1-1,495.6)	1,169.6 (1,100.3-1,241.9)	944.6 (854.1-1,050.9)	1,056.7 (964.7-1,156.5)
12-23 months	839.1 (752.1-942.1)	940.1 (852.4-1,037.6)	1,168.0 (1,071.1-1,266.8)	377.3 (302.1-451.4)	764.5 (592.6-989.2)	1,342.3 (1,227.1-1,458.0)	1,140.6 (1,073.0-1,211.0)	921.2 (832.3-1,024.8)	1,032.4 (941.8-1,130.3)
2-4 years	850.4 (762.2-955.1)	953.1 (864.7-1,051.8)	1,183.6 (1,085.3-1,283.6)	383.3 (307.0-459.0)	775.5 (601.9-1,004.1)	715.5 (654.0-777.0)	1,156.5 (1,088.0-1,228.0)	933.4 (843.7-1,038.4)	1,045.4 (954.1-1,144.4)
≥5 years	**37.5** **(33.9-40.6)**	**36.0** **(32.8-39.0)**	**46.5** **(43.5-49.3)**	**14.4** **(11.6-16.9)**	**27.1** **(21.0-35.1)**	**86.5** **(78.3-94.4)**	**46.0** **(43.8-48.1)**	**46.4** **(42.5-50.2)**	**46.0** **(42.2-49.8)**
5-14 years	54.3 (49.1-58.7)	51.1 (46.5-55.4)	60.0 (56.3-63.5)	34.4 (27.6-40.1)	35.8 (27.8-46.4)	74.5 (69.8-78.5)	61.1 (58.5-63.6)	55.2 (50.5-59.6)	57.2 (52.8-61.5)
15-49 years	27.3 (24.7-29.5)	26.2 (23.8-28.4)	34.9 (32.6-37.0)	8.8 (7.1-10.3)	18.4 (14.2-23.7)	82.2 (73.3-91.0)	34.3 (32.5-36.1)	36.5 (33.4-39.4)	35.7 (32.5-38.8)
50-64 years	47.5 (42.9-51.5)	45.4 (41.4-49.5)	60.6 (56.7-64.2)	15.4 (12.7-18.1)	32.1 (25.3-42.2)	142.5 (127.1-157.9)	59.6 (56.5-62.7)	63.4 (58.1-68.7)	65.4 (59.7-71.1)
65+ years	47.2 (42.8-51.1)	45.1 (41.7-49.5)	59.8 (56.0-63.6)	17.5 (15.0-22.5)	32.9 (25.6-43.9)	141.3 (126.1-156.5)	58.9 (55.9-61.9)	63.0 (58.1-68.4)	66.7 (61.1-72.6)
All ages	**106.8** **(96.0-118.6)**	**140.6** **(127.6-154.5)**	**159.6** **(147.1-172.1)**	**48.0** **(38.4-57.1)**	**94.5** **(73.3-122.4)**	**240.1** **(218.9-261.1)**	**171.4** **(161.7-181.4)**	**154.6** **(140.1-170.7)**	**152.8** **(139.5-167.0)**
2012-2014									
<5 years	**982.3** **(879.7-1102.6)**	**1,109.3** **(1,005.9-1,224.0)**	**1,362.6** **(1,248.9-1,477.6)**	**453.2** **(362.7-542.7)**	**806.8** **(624.3-1043.2)**	1,572.9 (1,437.9-1,708.4)	**1,326.5** **(1,247.7-1,408.1)**	**1,081.6** **(977.5-1,203.0)**	**1,201.6** **(1,095.0-1,317.1)**
<2 years	1,427.1 (1,278.3-1,601.8)	1,598.4 (1,449.5-1,764.1)	1,989.0 (1,823.0-2,157.0)	640.7 (512.8-767.6)	1300.0 (1006.4-1682.0)	2,282.4 (2,086.6-2,479.0)	1,937.1 (1,822.2-2,056.4)	1,567.9 (1,417.2-1,743.9)	1,753.3 (1,599.7-1,919.0)

Year	Central n(95% CI)	Coast n(95% CI)	Eastern n(95% CI)	Nairobi n(95% CI)	North Eastern n(95% CI)	Nyanza n(95% CI)	Rift Valley n(95% CI)	Western n(95% CI)	Kenya n(95% CI)
0-5 months	1,090.0 (976.2-1,223.5)	1,221.6 (1,108.4-1,348.9)	1,517.7 (1,391.1-1,646.5)	490.8 (393.0-588.6)	991.8 (768.2-1284.4)	1,743.8 (1,594.3-1,894.1)	1,481.3 (1,393.6-1,572.7)	1,196.7 (1,082.3-1,331.0)	1,338.2 (1,221.4-1,464.6)
6-11 months	1,652.1 (1,480.4-1,854.5)	1,851.5 (1,678.6-2,043.0)	2,299.9 (2,107.9-2,494.2)	743.9 (595.1-890.7)	1505.3 (1165.9-1948.5)	2,644.0 (2,417.5-2,872.2)	2,246.4 (2,113.3-2,384.8)	1,814.3 (1,639.9-2,018.4)	2,028.9 (1,851.5-2,220.2)
0-11 months	1,373.6 (1,230.6-1,541.9)	1,539.4 (1,396.0-1,699.1)	1,912.3 (1,752.7-2,074.1)	618.5 (495.0-741.0)	1250.8 (968.8-1619.4)	2,197.9 (2,009.6-2,387.6)	1,867.3 (1,756.7-1,982.4)	1,508.3 (1,363.6-1,677.8)	1,686.6 (1,539.3-1,845.8)
12-23 months	1,486.7(1,331.3-1,668.4)	1,666.6 (1,511.2-1,839.1)	2,071.0 (1,898.1-2,245.6)	668.9 (535.4-801.2)	1355.1 (1048.5-1752.0)	2,380.4 (2,176.0-2,585.2)	2,022.3 (1,902.3-2,146.9)	1,633.0 (1,475.8-1,816.1)	1,830.3 (1,669.4-2,003.6)
2-4 years	697.5 (624.5-782.9)	781.9 (709.0-862.6)	971.6 (890.6-1,053.6)	313.8 (251.1-375.4)	635.4 (491.6-821.3)	1,116.7 (1,020.8-1,212.9)	948.8 (892.4-1,007.2)	766.2 (692.4-852.2)	857.9 (780.6-942.0)
≥5 years	**41.5 (37.5-44.9)**	**40.3 (36.7-43.7)**	**51.8 (48.5-54.9)**	**16.3 (13.0-19.0)**	**31.3 (24.3-40.5)**	**93.0 (84.5-101.1)**	**51.7 (49.3-54.1)**	**51.8 (47.4-56.0)**	**51.0 (46.8-55.1)**
5-14 years	70.4 (63.6-76.1)	66.3 (60.3-71.8)	77.9 (73.0-82.3)	44.5 (35.6-51.8)	46.3 (35.8-59.9)	96.6 (90.5-101.7)	79.1 (75.8-82.4)	71.5 (65.4-77.1)	74.2 (68.5-79.7)
15-49 years	26.4 (23.9-28.6)	25.4 (23.1-27.5)	33.7 (31.5-35.8)	8.6 (6.9-10.0)	17.8 (13.7-23.0)	79.5 (70.9-88.0)	33.2 (31.5-34.9)	35.3 (32.3-38.2)	34.5 (31.4-37.5)
50-64 years	43.7 (39.5-47.2)	41.9 (38.1-45.6)	55.8 (52.2-59.1)	14.4 (11.7-17.2)	29.4 (23.3-38.1)	131.2 (117.1-145.3)	54.8 (52.0-57.6)	58.4 (53.7-63.2)	60.2 (55.0-65.4)
65+ years	55.6 (50.3-60.0)	53.3 (48.8-57.7)	71.0(66.4-75.3)	20.4 (17.9-25.6)	37.4 (29.9-48.6)	167.5 (149.6-185.3)	69.9 (66.2-73.5)	74.5 (68.4-80.6)	78.9 (72.3-85.6)
All ages	**156.5 (140.5-174.2)**	**213.3 (193.5-234.7)**	**239.2 (220.1-258.2)**	**71.6 (57.3-85.3)**	**141.5 (109.5-182.9)**	**350.8 (320.3-381.2)**	**258.9 (244.1-274.2)**	**231.9 (210.1-256.5)**	**228.1 (208.1-249.4)**

*Rate per 100,000 persons

Table 26: Annual regional rate of non-hospitalized severe acute respiratory illness (SARI) in Kenya by region, 2012 to 2014

Year	Central n(95% CI)	Coast n(95% CI)	Eastern n(95% CI)	Nairobi n(95% CI)	North Eastern n(95% CI)	Nyanza n(95% CI)	Rift Valley n(95% CI)	Western n(95% CI)	Kenya n(95% CI)
2012									
<5 years	**3,882.1 (3,476.5-4,357.3)**	**4,778.1 (4,332.9-5,271.6)**	**5,667.4 (5,195.0-6,145.9)**	**1,994.9 (1,594.8-2,387.5)**	**7,208.2 (5,579.9-9,316.4)**	**6,134.5 (5,608.3-6,663.0)**	**5,460.7 (5,136.2-5,797.1)**	**5,684.1 (5,136.3-6,322.0)**	**5,285.3 (4,784.7-5,838.5)**
<2 years	6,105.0 (5,466.9-6,852.9)	7,438.5 (6,745.3-8,207.4)	8,966.3 (8,219.3-9,723.5)	3,031.7 (2,423.6-3,627.8)	12,952.9 (10,036.5-16,741.0)	9,634.6 (8,808.2-10,464.8)	8,647.7 (8,133.9-9,180.4)	8,914.1 (8,055.8-9,914.8)	8,281.2 (7,515.2-9,121.6)
0-5 months	5,235.7 (4,687.7-5,878.3)	6,384.7 (5,793.0-7,047.4)	7,683.7 (7,042.8-8,331.5)	2,609.1 (2,088.1-3,122.3)	11,113.4 (8,620.6-14,360.7)	8,267.7 (7,559.1-8,980.0)	7,427.2 (6,986.2-7,885.1)	7,642.8 (6,907.6-8,501.3)	7,090.7 (6,437.3-7,808.3)
6-11 months	6,521.4 (5,842.0-7,322.0)	7,951.7 (7,210.5-8,770.4)	9,568.0 (8,772.3-10,377.4)	3,246.4 (2,593.7-3,885.7)	13,832.4 (10,724.4-17,874.0)	10,299.7 (9,416.4-11,187.6)	9,253.7 (8,703.9-9,823.9)	9,517.0 (8,602.0-10,586.0)	8,831.6 (8,017.3-9,725.0)
0-11 months	5,884.3 (5270.0-6,606.6)	7,175.2 (6,508.1-7,916.6)	8,634.3 (7,915.3-9,363.6)	2,930.6 (2,343.1-3,507.4)	12,485.0 (9,681.9-16,133.0)	9,292.8 (8,496.0-10,093.7)	8,348.6 (7,852.7-8,863.2)	8,588.3 (7,762.4-9,553.0)	7,968.9 (7,234.4-8,775.2)
12-23 months	6,350.4 (5,685.9-7,126.7)	7,742.1 (7,018.9-8,542.8)	9,321.0 (8,543.9-10,107.8)	3,159.7 (2,525.5-3,780.2)	13,476.7 (1,0433.6-17,421.7)	10,031.1 (9,170.3-10,895.2)	9,013.0 (8,477.4-9,568.0)	9,269.7 (8,376.0-10,309.7)	8,641.8 (7,839.5-9,521.6)
2-4 years	2,458.8 (2,202.0-2,759.4)	2,997.5 (2,718.3-3,306.8)	3,608.4 (3,307.4-3,912.9)	1,223.9 (978.5-1,465.1)	5,212.4 (4,031.6-6,736.9)	3,884.1 (3,551.0-4,218.6)	3,489.5 (3,282.0-3,704.3)	3,589.4 (3,243.0-3,992.0)	3,418.6 (3,083.3-3,792.9)
≥5 years	**262.2 (237.1-283.6)**	**270.9 (246.3-293.5)**	**342.0 (320.2-362.1)**	**109.8 (88.0-128.0)**	**415.3 (322.3-537.3)**	**588.2 (533.4-640.8)**	**334.7 (318.9-350.1)**	**419.0 (383.6-452.6)**	**351.9 (320.7-383.2)**
5-14 years	407.3 (367.8-440.2)	413.5 (375.8-447.5)	471.7 (442.4-498.4)	281.4 (225.3-327.8)	582.2 (450.8-753.0)	552.1 (517.4-581.4)	475.4 (455.4-495.0)	533.8 (488.6-575.7)	479.9 (439.1-520.9)
15-49 years	179.2 (162.0-193.8)	185.4 (168.5-200.7)	239.8 (224.1-254.1)	63.4 (50.7-73.8)	260.9 (202.3-337.2)	533.3 (475.8-590.2)	233.9 (221.5-245.7)	309.0 (282.8-334.1)	253.4 (229.8-276.7)
50-64 years	211.2 (191.5-228.9)	218.5 (199.4-237.6)	281.7 (264.0-299.4)	78.1 (65.5-94.3)	307.9 (245.7-399.1)	626.4 (559.5-693.2)	275.0 (261.0-289.0)	363.4 (332.6-394.3)	313.2 (285.6-342.2)
65+ years	499.6 (453.4-541.6)	516.4 (470.0-562.9)	669.0 (626.0-709.9)	183.4 (154.6-214.9)	730.9 (575.6-953.5)	1,485.5 (1,325.5-1,646.0)	651.4 (618.2-684.2)	863.4 (793.3-934.1)	758.9 (693.0-826.2)
All ages	**704.8 (633.2-781.7)**	**1,000.3 (907.6-1,099.1)**	**1,103.0 (1,016.8-1,188.6)**	**348.6 (279.0-414.3)**	**1,380.0 (1,069.0-1784.0)**	**1,554.5 (1,417.6-1,690.1)**	**1,167.9 (1,101.9-1235.4)**	**1,339.7 (1,214.7-1,479.0)**	**1,111.2 (1,007.8-1,222.8)**
2013									
<5 years	**2,791.7 (2,500.9-3,133.5)**	**3,418.1 (3,100.1-3,771.3)**	**4,087.7 (3,747.2-4,432.6)**	**1,410.7 (1,128.6-1,689.2)**	**5,519.8 (4,272.9-7,134.5)**	**4,406.2 (4,028.4-4,785.9)**	**3,935.9 (3,702.1-4,178.2)**	**4,082.5 (3,689.6-4,540.9)**	**3,818.8 (3,455.2-4,221.8)**
<2 years	3,655.4 (3,276.0-4,103.9)	4,448.1 (4,034.8-4,907.7)	5,372.7 (4,925.7-5,826.1)	1,810.2 (14,49.2-2,169.1)	7,747.7 (6,000.1-10,015.8)	5,759.7 (5,266.3-6,256.3)	5,163.0 (4,856.4-5,481.0)	5,338.6 (4,825.4-5,938.5)	4,952.4 (4,495.0-5,455.5)
0-5 months	1,491.9 (1,340.4-1,677.9)	1,813.3 (1,645.3-2,000.1)	2,185.8 (2,004.2-2,370.9)	744.7 (599.2-892.1)	3,161.9 (2,455.7-4,091.4)	2,350.3 (2,150.9-2,555.1)	2,110.8 (1,986.1-2,241.3)	2,172.0 (1,966.8-2,418.0)	2,016.1 (1,832.2-2,221.5)
6-11 months	5,166.0 (4,629.0-5,800.1)	6,300.8 (5,714.8-6,953.1)	7,581.7 (6,951.0-8,221.3)	2,572.5 (2,057.2-3,082.1)	10,952.5 (8,488.5-14,162.1)	8,158.5 (7,459.3-8,861.2)	7,329.7 (6,894.9-7,781.7)	7,542.1 (6,817.2-8,389.5)	6,996.5 (6,352.0-7,704.9)
0-11 months	3,345.4 (2,999.4-3,757.5)	4,077.1 (3,698.3-4,498.8)	4,907.9 (4,499.5-5,322.3)	1,666.8 (1,334.8-1,996.9)	7,092.0 (5,499.0-9,171.7)	5,280.4 (4,828.9-5,736.4)	4,743.6 (4,462.5-5,036.3)	4,881.1 (4,413.8-5,430.5)	4,528.6 (4,112.3-4,987.8)
12-23 months	4,000.1 (3,583.6-4,489.2)	4,875.9 (4,422.9-5,379.2)	5,869.0 (5,380.5-6,364.1)	1,991.8 (1,594.2-2,387.0)	8,481.8 (6,561.1-10,960.8)	6,315.7 (5,773.7-68,59.3)	5,675.4 (5,337.7-6,024.3)	5,837.8 (5,274.7-6,493.0)	5,441.8 (4,936.9-5,995.6)
2-4 years	2,238.7 (2,004.6-2,512.2)	2,728.8 (2,474.5-3,010.7)	3,285.7 (3,011.7-3,562.9)	1,113.6 (890.1-1,332.4)	4,745.7 (3,672.8-6,133.5)	3,536.0 (3,232.4-3,840.4)	3,176.9 (2,988.2-3,372.4)	3,267.8 (2,953.0-3,634.5)	3,112.4 (2,807.3-3,453.0)
≥5 years	**194.3 (175.7-210.2)**	**209.7 (190.7-227.1)**	**256.6 (240.5-271.6)**	**87.9 (70.7-102.5)**	**350.0 (271.5-453.5)**	**410.3 (374.9-443.8)**	**260.9 (249.1-272.7)**	**319.1 (292.1-344.7)**	**265.9 (242.6-289.4)**
5-14 years	415.8 (375.6-449.3)	422.1 (383.7-457.0)	481.4 (451.6-508.7)	287.1 (229.7-334.3)	594.5 (460.5-769.1)	563.4 (527.8-593.4)	485.2 (464.9-505.3)	544.7 (498.3-587.3)	489.9 (448.2-531.7)

131

Year	Central n(95% CI)	Coast n(95% CI)	Eastern n(95% CI)	Nairobi n(95% CI)	North Eastern n(95% CI)	Nyanza n(95% CI)	Rift Valley n(95% CI)	Western n(95% CI)	Kenya n(95% CI)
15-49 years	98.1 (88.7-106.1)	101.2 (92.0-109.5)	131.1 (122.5-138.9)	34.7 (27.9-40.3)	143.2 (110.9-185.2)	291.2 (259.9-322.3)	127.8 (121.1-134.3)	168.8 (154.5-182.7)	138.5 (125.6-151.3)
50-64 years	207.0 (188.1-224.6)	212.7 (194.2-231.3)	275.6 (258.4-292.9)	76.1 (63.7-91.8)	309.2 (239.2-408.5)	612.7 (547.6-679.4)	268.7 (255.1-282.5)	356.3 (326.2-386.3)	306.8 (279.4-335.7)
65+ years	112.2 (101.3-122.7)	117.1 (107.3-127.7)	149.4 (140.2-158.5)	45.9 (45.9-61.2)	173.7 (151.3-237.2)	331.2 (297.9-367.3)	146.0 (139.2-154.3)	194.2 (179.2-213.1)	170.4 (156.9-187.0)
All ages	**511.9 (460.0-567.6)**	**728.9 (661.5-800.6)**	**804.1 (741.6-866.2)**	**255.5 (204.7-303.6)**	**1,084.2 (839.8-1,402.4)**	**1,106.5 (1,011.5-1,200.3)**	**858.3 (810.3-907.5)**	**977.1 (886.2-10,78.5)**	**812.7 (737.0-894.6)**

2014

Year	Central n(95% CI)	Coast n(95% CI)	Eastern n(95% CI)	Nairobi n(95% CI)	North Eastern n(95% CI)	Nyanza n(95% CI)	Rift Valley n(95% CI)	Western n(95% CI)	Kenya n(95% CI)
<5 years	**1,744.2 (1,562.9-1,958.0)**	**2,140.9 (1,942.0-2,362.4)**	**2,548.0 (2,336.1-2,763.1)**	**889.7 (712.1-1,065.3)**	**3,372.8 (2,613.5-4,362.6)**	**2,755.4 (2,519.2-2,992.7)**	**2,460.9 (2,314.9-2,612.8)**	**2,549.3 (2,304.2-2,835.8)**	**2,382.7 (2,156.7-2,633.7)**
<2 years	2,453.8 (2,199.0-2,755.6)	2,991.1 (2,713.9-3,300.5)	3,598.4 (3,299.4-3,902.1)	1,222.5 (979.8-14,64.2)	5,207.8 (4,042.5-6,743.1)	3,873.7 (3,542.2-4,207.5)	3,481.4 (3,275.2-3,696.5)	3,578.4 (3,234.7-3,980.8)	3,329.3 (3,022.7-3,668.1)
0-5 months	2,603.7 (2,333.0-2,924.3)	3,172.1 (2,878.7-3,499.3)	3,820.4 (3,501.3-4,141.7)	1,296.3 (1,039.7-1,552.9)	5,520.5 (4,293.3-7,148.8)	4,109.4 (3,757.6-4,463.9)	3,690.8 (3,472.1-3,918.8)	3,796.5 (3,433.7-4,224.3)	3,523.8 (3,200.4-3,881.3)
6-11 months	2,366.0 (2,119.1-2,657.2)	2,883.4 (2,619.3-3,182.1)	3,468.4 (3,182.1-3,762.4)	1,179.4 (945.8-1,415.0)	5,032.6 (3,905.1-6,522.8)	3,732.9 (3,414.5-4,054.0)	3,353.3 (3,155.4-3,560.9)	3,450.1 (3,118.4-3,836.7)	3,202.2 (2,908.5-3,527.6)
0-11 months	2,483.8 (2,225.1-2,789.5)	3,026.5 (2,747.9-3,339.3)	3,642.8 (3,340.3-3,950.3)	1,237.3 (992.3-1,483.3)	5,274.3 (4,097.5-6,833.0)	3,919.5 (3,584.5-4,257.1)	3,520.5 (3,312.4-3,738.2)	3,621.7 (3,274.7-4,028.7)	3,361.6 (3,053.2-3,702.9)
12-23 months	2,420.5 (2,170.1-2,717.9)	2,950.3 (2,674.7-3,255.8)	3,550.9 (3,255.8-3,850.6)	1,203.7 (963.9-1,439.9)	5,133.3 (3,981.1-6,642.4)	3,820.7 (3,493.0-4,149.9)	3,433.5 (3,229.8-3,645.4)	3,531.0 (3,191.1-3,928.4)	3,292.1 (2,987.5-3,628.0)
2-4 years	1,289.9 (1,155.6-1,447.3)	1,571.8 (1,425.3-1,734.5)	1,892.4 (1,734.9-2,052.2)	642.2 (513.0-768.7)	2,735.3 (2,117.0-3,535.5)	2,036.4 (1,861.6-2,211.6)	1,829.8 (1,720.9-1,942.5)	1,882.0 (1,700.8-2,093.2)	1,792.8 (1,617.1-1,989.1)
≥5 years	**199.2 (180.1-215.5)**	**206.2 (187.5-223.5)**	**258.8 (242.3-274.1)**	**83.9 (67.5-98.1)**	**312.2 (242.7-404.9)**	**454.2 (411.2-495.5)**	**253.7 (241.7-265.5)**	**318.1 (291.2-343.9)**	**267.9 (244.1-291.9)**
5-14 years	288.6 (260.8-311.9)	292.8 (266.1-317.0)	334.2 (313.4-353.3)	199.9 (160.4-233.0)	413.1 (320.7-534.8)	391.2 (366.5-412.0)	336.9 (322.9-350.9)	378.3 (346.0-408.3)	340.1 (311.3-369.4)
15-49 years	145.0 (131.2-156.9)	149.9 (136.3-162.4)	194.1 (181.4-205.7)	51.3 (41.2-60.0)	211.7 (164.3-273.9)	431.6 (385.0-477.5)	189.4 (179.4-198.9)	250.0 (228.6-270.4)	205.1 (186.0-224.0)
50-64 years	252.5 (228.1-273.7)	260.4 (236.8-283.6)	337.2 (315.3-357.5)	89.8 (74.4-105.3)	370.9 (293.2-487.6)	748.5 (667.5-829.2)	328.9 (311.8-346.1)	434.4 (398.4-470.7)	374.4 (340.7-409.1)
65+ years	250.9 (227.5-271.9)	258.6 (238.6-283.7)	332.9 (311.5-354.3)	102.4 (87.4-132.3)	380.2 (296.1-506.3)	742.1 (662.1-821.7)	325.3 (308.8-341.9)	432.2 (398.5-469.1)	380.0 (347.2-415.0)
All ages	**388.1 (349.2-428.5)**	**519.2 (471.4-569.6)**	**586.0 (541.5-629.8)**	**186.0 (149.2-220.6)**	**746.9 (579.4-966.9)**	**855.1 (778.5-930.6)**	**612.5 (578.6-647.0)**	**708.3 (643.2-779.6)**	**593.4 (538.5-652.4)**

2012-2014

Year	Central n(95% CI)	Coast n(95% CI)	Eastern n(95% CI)	Nairobi n(95% CI)	North Eastern n(95% CI)	Nyanza n(95% CI)	Rift Valley n(95% CI)	Western n(95% CI)	Kenya n(95% CI)
<5 years	**2,833.8 (2,537.9-3,180.7)**	**3,480.7 (3,156.4-3,840.6)**	**4,142.2 (3,796.5-4,491.5)**	**1,445.6 (1,156.7-1,730.8)**	**5,417.4 (4,192.3-7,004.5)**	**4,476.9 (4,092.7-4,862.6)**	**3,992.6 (3,755.8-4,238.5)**	**4,146.3 (3,747.4-4,611.5)**	**3,867.3 (3,500.1-4,273.7)**
<2 years	4,117.1 (3,687.7-4,620.9)	5,015.6 (4,548.3-5,535.1)	6,046.6 (5,541.7-6,556.8)	2,043.7 (1,635.5-2,448.2)	8,731.1 (6,758.7-11,294.0)	6,496.4 (5,939.2-7,056.3)	5,830.6 (5,485.1-6,190.0)	6,010.7 (5,433.1-6,685.2)	5,583.8 (5,067.5-6,151.0)
0-5 months	3,144.6 (2,816.5-3,530.5)	3,832.9 (3,477.6-4,232.2)	4,614.1 (4,228.7-5,005.1)	1,566.4 (1,253.9-1,877.0)	6,662.1 (5,158.1-8,625.3)	4,963.4 (4,537.7-5,391.8)	4,458.8 (4,195.1-4,734.1)	4,588.4 (4,149.4-5,102.2)	4,256.8 (3,864.8-4,688.7)
6-11 months	4,766.8 (4,271.2-5,349.9)	5,809.4 (5,267.4-6,410.1)	6,992.0 (6,408.1-7,581.4)	2,372.8 (1,898.2-2,841.7)	10,109.8 (7,829.9-13,084.4)	7,525.5 (6,880.8-8,175.5)	6,761.7 (6,361.3-7,178.3)	6,955.4 (6,286.8-7,737.6)	6,453.6 (5,858.7-7,107.5)
0-11 months	3,963.0 (3,550.4-4,448.4)	4,830.0 (4,380.5-53,30.9)	5,813.7 (5,328.2-6,304.8)	1,973.2 (1,578.9-2,363.6)	84,01.3 (6505.9-10,874.8)	6,255.9 (5,719.8-6,796.2)	5,620.6 (5,287.9-5,967.2)	5,782.5 (5,227.7-6,431.7)	5,365.0 (4,870.7-5,908.9)
12-23 months	4,288.4	5,229.7	6,295.5	2,133.0	9,100.3	6,775.4	6,087.3	6,259.8	5,836.4

Year	Central n(95% CI)	Coast n(95% CI)	Eastern n(95% CI)	Nairobi n(95% CI)	North Eastern n(95% CI)	Nyanza n(95% CI)	Rift Valley n(95% CI)	Western n(95% CI)	Kenya n(95% CI)
	(3,840.4-4,812.8)	(4,741.8-5,770.5)	(5,769.8-6,825.9)	(1,707.1-2,555.2)	(7,041.7-11,763.2)	(6,193.8-7,358.0)	(5,725.9-6,462.1)	(5,657.4-6,962.0)	(5,294.9-6,430.5)
2-4 years	2,012.2 (1,801.7-2,258.5)	2,453.5 (2,224.8-2,706.5)	2,953.6 (2,707.2-3,202.5)	1,000.7 (800.6-1,197.3)	4,266.1 (3,300.7-5,514.3)	3,178.4 (2,905.5-3,452.1)	2,855.8 (2,686.2-3,031.5)	2,937.1 (2,654.2-3,266.6)	2,797.7 (2,523.5-3,103.9)
≥5 years	**220.5 (199.3-238.4)**	**230.8 (210.0-250.0)**	**288.5 (270.2-305.4)**	**94.4 (75.8-110.3)**	**361.5 (280.3-467.8)**	**488.3 (443.5-531.1)**	**285.3 (271.9-298.4)**	**355.3 (325.3-383.7)**	**297.7 (271.3-324.1)**
5-14 years	374.2 (338.0-404.5)	379.5 (345.2-410.8)	433.3 (406.3-458.0)	258.3 (206.5-300.8)	534.2 (413.2-691.1)	506.9 (475.0-534.0)	436.5 (418.2-454.6)	490.3 (448.6-528.7)	440.7 (403.2-478.4)
15-49 years	140.4 (126.8-151.8)	145.2 (132.1-157.2)	187.7 (175.5-199.0)	49.7 (39.9-58.0)	204.8 (158.5-265.2)	417.5 (372.3-462.0)	183.2 (173.5-192.4)	241.9 (221.4-261.8)	198.4((179.9-216.8)
50-64 years	232.0 (210.1-251.0)	240.0 (218.6-260.9)	310.6 (290.9-328.9)	83.7 (67.9-100.2)	339.9 (269.8-439.3)	688.9 (615.2-763.0)	302.4 (286.8-318.0)	400.7 (368.2-433.1)	344.6 (314.0-376.0)
65+ years	295.3 (267.3-319.2)	305.5 (279.8-331.3)	395.4 (369.9-419.0)	120.1 (104.8-150.8)	432.1 (346.1-561.2)	879.4 (785.6-973.2)	385.6 (365.0-405.9)	510.7 (469.0-552.4)	449.2 (410.4-488.9)
All ages	**540.0 (485.2-598.2)**	**756.7 (686.8-831.0)**	**839.2 (774.1-903.6)**	**265.6 (212.7-315.6)**	**1079.5 (835.9-1396.1)**	**1183.2 (1079.3-1285.7)**	**887.9 (838.2-938.8)**	**1,018.1 (923.6-1,123.0)**	**847.1 (768.3-932.0)**

*Rate per 100,000 persons

Table 27: Annual regional rate of hospitalized influenza-associated severe acute respiratory illness (SARI) in Kenya by region, 2012 to 2014

Year	Central n(95% CI)	Coast n(95% CI)	Eastern n(95% CI)	Nairobi n(95% CI)	North Eastern n(95% CI)	Nyanza n(95% CI)	Rift Valley n(95% CI)	Western n(95% CI)	Kenya n(95% CI)
2012									
<5 years	**141.1** (126.4-158.1)	**125.2** (113.4-138.1)	**184.5** (169.0-200.0)	**64.8** (52.2-77.8)	**98.5** (76.5-127.2)	**88.0** (80.4-95.6)	**184.1** (173.1-195.4)	**92.9** (84.0-103.3)	**135.3** (123.4-148.2)
<2 years	221.9 (199.0-248.8)	195.1 (176.7-215.2)	292.1 (267.5-316.4)	98.5 (79.5-118.7)	177.8 (138.6-229.1)	138.3 (126.4-150.3)	291.7 (274.2-309.5)	145.8 (131.9-161.9)	213.6 (195.0-233.6)
0-5 months	191.1 (170.8-213.1)	167.7 (151.6-185.4)	250.3 (229.5-271.2)	84.5 (68.8-102.2)	154.2 (120.9-195.9)	118.7 (108.4-129.0)	250.7 (235.5-266.0)	125.7 (113.7-138.9)	183.6 (167.6-200.5)
6-11 months	237.5 (212.6-265.8)	209.0 (188.5-229.6)	311.9 (285.7-338.1)	106.2 (85.0-127.5)	188.4 (147.4-245.7)	147.8 (135.0-160.7)	312.1 (293.4-331.4)	155.2 (141.1-172.9)	228.4 (208.5-249.8)
0-11 months	214.5 (191.9-239.7)	188.5 (170.2-207.7)	281.4 (257.9-304.9)	95.5 (77.0-115.0)	171.5 (134.3-221.0)	133.4 (121.8-145.0)	281.7 (264.7-299.0)	140.6 (127.6-156.0)	206.2 (188.2-225.4)
12-23 months	230.2 (206.9-259.1)	202.7 (184.3-223.9)	303.6 (277.8-328.7)	102.4 (82.7-123.4)	185.0 (143.4-238.2)	144.0 (131.6-156.4)	303.9 (285.8-322.4)	151.5 (136.6-168.4)	222.2 (202.8-243.1)
2-4 years	89.3 (80.0-100.0)	78.5 (71.0-86.5)	117.4 (107.5-127.4)	39.7 (32.0-47.4)	70.9 (55.0-91.7)	55.7 (50.9-60.5)	117.6 (110.6-124.8)	58.6 (53.0-65.3)	86.5 (78.7-94.9)
≥5 years	**8.0** (7.2-8.6)	**6.6** (6.0-7.1)	**8.5** (7.9-9.0)	**2.6** (2.2-3.1)	**5.1** (4.0-6.5)	**9.9** (9.0-10.8)	**7.4** (7.1-7.8)	**9.8** (9.0-10.5)	**7.6** (7.0-8.2)
5-14 years	12.4 (11.2-13.4)	10.0 (9.1-10.8)	11.7 (11.0-12.3)	6.7 (5.3-7.8)	7.0 (5.4-9.1)	9.3 (8.7-9.8)	10.6 (10.1-11.0)	12.4 (11.3-13.4)	10.4 (9.6-11.2)
15-49 years	5.4 (5.0-5.9)	4.5 (4.1-4.8)	5.9 (5.6-6.3)	1.5 (1.2-1.8)	3.2 (2.5-4.0)	9.0 (8.0-9.9)	5.2 (4.9-5.5)	7.2 (6.6-7.8)	5.5 (5.0-5.9)
50-64 years	6.5 (5.9-7.0)	5.2 (4.8-5.7)	7.0 (6.6-7.5)	2.1 (2.1-2.8)	4.4 (3.5-5.3)	10.8 (9.6-11.6)	6.2 (5.8-6.5)	8.7 (8.0-9.4)	6.9 (6.4-7.5)
65+ years	15.4 (13.7-16.6)	12.8 (11.8-13.7)	16.8 (15.4-17.8)	5.2 (5.2-5.2)	9.6 (7.7-11.5)	24.9 (22.5-27.7)	14.5 (13.9-15.5)	19.9 (18.8-21.7)	16.8 (15.4-18.1)
All ages	**24.3** (21.8-26.9)	**25.8** (23.4-28.3)	**33.6** (31.0-36.3)	**10.5** (8.5-12.6)	**18.3** (14.3-23.6)	**23.5** (21.4-25.5)	**36.2** (34.1-38.3)	**24.3** (22.1-26.8)	**27.3** (24.9-29.8)
2013									
<5 years	**96.3** (86.2-107.8)	**91.2** (82.9-100.7)	**137.3** (126.0-148.8)	**48.2** (38.4-57.4)	**77.2** (59.7-99.4)	**78.7** (71.9-85.4)	**153.7** (144.5-163.2)	**96.2** (86.9-107.1)	**110.0** (100.4-120.4)
<2 years	126.3 (113.0-141.3)	118.7 (107.9-131.2)	180.5 (165.8-195.8)	62.0 (49.3-73.7)	109.4 (85.0-140.2)	102.9 (94.2-111.7)	201.7 (189.6-214.0)	125.7 (113.7-140.2)	144.3 (131.8-157.6)
0-5 months	52.7 (46.1-57.6)	48.7 (44.0-53.4)	73.4 (67.7-80.1)	26.8 (21.1-30.6)	44.6 (36.5-56.8)	41.9(39.1-45.5)	82.8 (77.5-87.6)	51.3 (46.6-57.1)	59.2 (54.2-64.4)
6-11 months	177.9 (160.1-200.5)	168. 1(152.7-186.6)	254.9 (233.9-276.0)	88.4 (69.6-105.3)	155.5 (119.6-199.4)	145.7 (133.2-158.3)	286.2 (269.0-303.9)	177.5 (160.3-198.1)	204.3 (186.7-223.4)

134

Year	Central n(95% CI)	Coast n(95% CI)	Eastern n(95% CI)	Nairobi n(95% CI)	North Eastern n(95% CI)	Nyanza n(95% CI)	Rift Valley n(95% CI)	Western n(95% CI)	Kenya n(95% CI)
0-11 months	115.9 (103.6-129.7)	108.9 (98.8-120.6)	165.0 (151.5-178.9)	57.9 (45.5-68.3)	100.6 (78.4-128.7)	94.3 (86.6-102.4)	185.4 (174.1-196.7)	115.0 (104.0-128.3)	132.4 (121.0-144.6)
12-23 months	137.9 (123.4-154.3)	130.1 (118.4-143.5)	197.1 (180.9-213.8)	67.3 (54.1-80.5)	119.3 (92.3-153.1)	113.0 (103.1-122.4)	221.7 (208.5-235.2)	137.5 (124.2-153.2)	157.9 (144.3-172.5)
2-4 years	77.0 (69.0-86.4)	72.8 (66.1-80.3)	110.3 (101.1-119.5)	37.8 (30.4-45.3)	66.1 (50.9-85.3)	63.1 (57.6-68.5)	124.0 (116.6-131.7)	77.0 (69.6-85.6)	88.7 (80.9-97.3)
≥5 years	**8.9** **(8.0-9.6)**	**6.2** **(5.7-6.8)**	**7.8** **(7.3-8.3)**	**2.6** **(2.1-3.0)**	**5.2** **(4.1-6.7)**	**5.7** **(5.2-6.2)**	**5.7** **(5.4-5.9)**	**5.5** **(5.1-6.0)**	**6.1** **(5.6-6.6)**
5-14 years	18.9 (17.1-20.4)	12.5 (11.4-13.5)	14.6 (13.7-15.5)	8.4 (6.8-9.7)	8.7 (6.7-11.3)	7.8 (7.4-8.2)	10.5 (10.1-10.9)	9.4 (8.6-10.1)	11.3 (10.4-12.2)
15-49 years	4.5 (4.0-4.8)	3.0 (2.7-3.3)	4.0 (3.7-4.2)	1.0 (0.8-1.2)	2.1 (1.7-2.8)	4.0 (3.6-4.5)	2.8 (2.6-2.9)	2.9 (2.7-3.1)	3.1 (2.8-3.4)
50-64 years	9.6 (8.5-10.4)	6.5 (6.0-7.0)	8.4 (8.0-9.1)	2.7 (2.1-2.7)	5.2 (4.3-6.0)	8.6 (7.7-9.7)	5.8 (5.5-6.2)	6.4 (5.7-6.7)	7.1 (6.5-7.7)
65+ years	5.3 (4.9-5.7)	3.5 (3.5-4.4)	4.6 (4.2-4.9)	2.6 (2.6-2.6)	3.7 (3.7-3.7)	4.6 (4.1-5.5)	3.4 (3.1-3.4)	3.3 (3.3-3.9)	4.1 (3.8-4.5)
All ages	**19.5** **(17.6-21.6)**	**20.0** **(18.2-22.0)**	**26.3** **(24.3-28.4)**	**8.4** **(6.7-9.9)**	**15.4** **(12.0-19.9)**	**18.4** **(16.8-20.0)**	**29.7** **(28.0-31.5)**	**21.4** **(19.4-23.6)**	**22.1** **(20.2-24.1)**
2014									
<5 years	**57.4** **(51.5-64.7)**	**78.5** **(71.4-86.8)**	**79.2** **(72.5-85.9)**	**25.0** **(20.1-29.6)**	**52.8** **(40.7-67.8)**	**53.2** **(48.8-57.9)**	**67.4** **(63.5-71.6)**	**36.4** **(33.0-40.5)**	**59.3** **(54.0-65.1)**
<2 years	80.7 (72.7-91.2)	109.7 (99.9-121.5)	111.9 (102.6-121.5)	34.8 (28.0-41.0)	82.1 (63.4-105.0)	74.9 (68.7-81.5)	95.4 (89.9-101.3)	51.3 (46.3-56.9)	83.5 (76.3-91.7)
0-5 months	85.4 (77.3-96.7)	116.7 (106.0-129.0)	119.2 (109.3-129.2)	37.5 (30.0-43.1)	87.4 (67.5-111.2)	79.3 (73.0-86.4)	101.3 (95.0-107.5)	54.8 (49.1-60.5)	88.7 (80.9-97.1)
6-11 months	77.5 (69.6-88.6)	105.6 (96.6-117.7)	107.4 (98.7-117.1)	33.1 (27.6-40.5)	78.0 (62.4-101.4)	72.6 (66.5-78.7)	91.8 (86.7-97.4)	49.3 (44.8-54.9)	80.3 (73.6-88.4)
0-11 months	81.4 (73.5-92.6)	111.1 (101.2-123.3)	113.3 (104.0-123.1)	35.3 (28.8-41.8)	82.7 (64.9-106.3)	75.9 (69.7-82.5)	96.5 (90.8-102.4)	52.0 (46.9-57.7)	84.5 (77.2-92.7)
12-23 months	79.9 (71.9-89.7)	108.0 (98.3-119.4)	110.4 (101.1-119.8)	34.1 (27.0-40.0)	81.5 (61.7-103.5)	73.7 (67.6-80.4)	94.0 (88.7-100.0)	50.6 (45.7-56.1)	82.5 (75.2-90.5)
2-4 years	42.5 (38.0-47.6)	57.6 (52.4-63.6)	58.7 (53.8-63.7)	17.7 (14.3-21.2)	42.6 (32.9-54.9)	39.3 (36.0-42.7)	50.2 (47.2-53.2)	26.8 (24.3-29.8)	44.1 (40.1-48.6)
≥5 years	**5.1** **(4.6-5.5)**	**4.9** **(4.4-5.2)**	**6.2** **(5.8-6.6)**	**2.0** **(1.6-2.3)**	**3.7** **(2.8-4.7)**	**4.9** **(4.4-5.3)**	**6.1** **(5.8-6.4)**	**5.5** **(5.0-6.0)**	**5.2** **(4.8-5.6)**
5-14 years	7.3 (6.7-8.0)	6.9 (6.3-7.4)	8.0 (7.5-8.5)	4.6 (3.8-5.4)	4.8 (3.8-6.2)	4.2 (4.0-4.4)	8.1 (7.8-8.4)	6.5 (5.9-7.0)	6.7 (6.2-7.2)
15-49 years	3.7	3.5	4.7	1.2	2.5	4.7	4.6	4.3	3.9

Year	Central n(95% CI)	Coast n(95% CI)	Eastern n(95% CI)	Nairobi n(95% CI)	North Eastern n(95% CI)	Nyanza n(95% CI)	Rift Valley n(95% CI)	Western n(95% CI)	Kenya n(95% CI)
	(3.4-4.0)	(3.2-3.8)	(4.4-4.9)	(1.0-1.4)	(1.9-3.2)	(4.1-5.1)	(4.3-4.8)	(4.0-4.7)	(3.6-4.2)
50-64 years	6.4 (5.9-7.0)	6.4 (5.9-6.8)	8.2 (7.6-8.7)	2.7 (2.0-2.7)	5.1 (3.4-5.9)	8.1 (7.3-8.9)	8.0 (7.6-8.3)	7.6 (6.9-8.3)	7.2 (6.6-7.7)
65+ years	6.3(5.9-7.1)	6.1 (6.1-6.9)	8.0 (7.7-8.6)	2.5 (2.5-5.0)	5.5 (3.7-7.3)	8.0 (7.2-8.9)	7.8 (7.5-8.4)	7.6 (7.1-8.1)	7.3 (6.8-8.1)
All ages	**11.5** **(10.4-12.8)**	**16.8** **(15.3-18.4)**	**16.7** **(15.4-17.9)**	**4.9** **(4.0-5.8)**	**10.7** **(8.2-13.7)**	**13.3** **(12.2-14.5)**	**16.1** **(15.2-17.0)**	**10.9** **(9.9-12.0)**	**13.5** **(12.3-14.8)**
2012-2014									
<5 years	**97.9** **(87.7-109.8)**	**106.4** **(96.4-117.3)**	**133.7** **(122.6-144.9)**	**45.1** **(36.2-53.9)**	**78.7** **(61.2-101.8)**	**75.9** **(69.6-82.5)**	**130.0** **(122.3-138.0)**	**69.5** **(62.8-77.1)**	**100.6** **(91.7-110.3)**
<2 years	142.4 (127.4-159.6)	153.5 (138.9-169.0)	195.2 (179.0-211.7)	63.7 (51.5-76.4)	127.7 (100.0-164.9)	110.4 (101.2-119.8)	189.9 (178.6-201.6)	100.8 (91.2-111.7)	146.6 (133.8-160.3)
0-5 months	108.8 (97.3-122.0)	117.9 (106.9-128.9)	149.2 (136.7-161.6)	49.8 (40.3-59.4)	97.6 (77.2-126.0)	84.8 (77.5-92.0)	145.1 (136.6-154.1)	77.1 (70.1-85.2)	112.2 (102.5-122.6)
6-11 months	165.2 (147.4-184.6)	177.6 (160.6-196.1)	225.3 (207.6-245.3)	73.4 (60.3-88.5)	147.7 (115.8-191.7)	128.0 (117.3-138.8)	220.3 (207.3-233.9)	117.0 (105.5-129.6)	169.7 (155.1-185.8)
0-11 months	137.3 (122.6-153.6)	148.0 (134.0-162.8)	187.6 (172.5-203.8)	61.8 (50.4-74.1)	122.9 (96.7-159.1)	106.6 (97.6-115.6)	183.0 (172.2-194.4)	97.2 (87.9-107.6)	141.2 (129.1-154.5)
12-23 months	148.1 (132.7-166.3)	159.9 (144.6-176.1)	203.3 (186.0-220.1)	66.2 (52.9-79.4)	133.0 (103.7-171.4)	114.7 (105.3-124.7)	198.2 (186.3-210.4)	104.8 (94.7-116.2)	152.7 (139.3-167.1)
2-4 years	69.4 (62.3-78.0)	74.8 (67.9-82.7)	95.3 (87.4-103.2)	31.2 (24.9-37.1)	61.7 (47.7-79.8)	53.8 49.3-58.5)	93.0 (87.4-98.7)	49.1 (44.4-54.6)	72.0 (65.5-79.1)
≥5 years	**7.3** **(6.6-7.9)**	**5.8** **(5.3-6.3)**	**7.5** **(7.0-7.9)**	**2.4** **(1.9-2.8)**	**4.5** **(3.6-5.9)**	**6.5** **(5.9-7.1)**	**6.6** **(6.3-6.9)**	**7.1** **(6.5-7.7)**	**6.3** **(5.8-6.8)**
5-14 years	12.3 (11.2-13.4)	9.5 (8.7-10.3)	11.2 (10.5-11.8)	6.5 (5.2-7.5)	6.6 (5.2-8.6)	6.7 (6.3-7.1)	10.1 (9.6-10.5)	9.7 (8.9-10.5)	9.4 (8.7-10.1)
15-49 years	4.6 (4.2-5.0)	3.7(3.3-3.9)	4.8 (4.5-5.1)	1.2 (1.0-1.5)	2.6 (2.1-3.4)	5.5 (4.9-6.1)	4.2 (4.0-4.4)	4.8 (4.4-5.2)	4.1(3.8-4.5)
50-64 years	7.7(7.1-8.5)	6.0 (5.6-6.5)	8.2 (7.5-8.6)	2.1 (2.1-2.7)	4.3 (3.5-6.1)	9.1 (8.3-10.2)	7.1 (6.7-7.4)	8.1 (7.4-8.8)	7.3 (6.7-8.0)
65+ years	10.1 (8.9-10.5)	8.0 (7.1-8.9)	10.5 (9.8-10.8)	5.1 (2.6-5.1)	5.6 (5.6-7.5)	11.9 (10.5-13.3)	8.9 (8.6-9.5)	10.6 (9.4-11.1)	9.8 (8.9-10.5)
All ages	**18.4** **(16.5-20.4)**	**22.1** **(20.0-24.3)**	**25.5** **(23.5-27.5)**	**7.8** **(6.3-9.3)**	**15.1** **(11.8-19.5)**	**18.6** **(17.0-20.2)**	**26.6** **(25.1-28.2)**	**18.0** **(16.3-19.8)**	**20.8** **(19.0-22.7)**

*Rate per 100,000 persons

Table 28: Annual regional rate of non-hospitalized influenza-associated severe acute respiratory illness (SARI) in Kenya by region, 2012 to 2014

Year	Central n(95% CI)	Coast n(95% CI)	Eastern n(95% CI)	Nairobi n(95% CI)	North Eastern n(95% CI)	Nyanza n(95% CI)	Rift Valley n(95% CI)	Western n(95% CI)	Kenya n(95% CI)
2012									
<5 years	**407.2** (365.1-456.4)	**393.4** (356.2-433.5)	**561.1** (513.9-608.3)	**207.1** (166.9-248.4)	**661.7** (514.2-854.1)	**250.7** (229.2-272.3)	**554.3** (521.2-588.3)	**356.4** (322.3-396.1)	**436.4** (395.1-482.1)
<2 years	640.7 (574.9-718.3)	613.2 (555.0-675.6)	888.2 (813.2-962.4)	315.2 (254.2-378.9)	1,195.8 (931.8-1,539.5)	394.1 (360.2-428.1)	878.2 (825.5-931.9)	559.2 (505.9-621.1)	682.2 (619.3-751.1)
0-5 months	551.3 (493.8-615.6)	527.2 (475.6-582.0)	761.4 (697.7-825.2)	271.3 (220.2-326.4)	10,38.0 (812.9-1,317.3)	338.4 (309.4-367.4)	754.9 (709.1-800.7)	482.5 (437.0-532.8)	586.2 (532.3-644.0)
6-11 months	686.0 (614.6-767.4)	657.2 (592.3-720.6)	948.3 (868.6-1027.9)	339.9 (272.3-407.5)	1265.3 (991.0-1,650.2)	421.5 (384.7-458.2)	939.6 (883.4-998.0)	595.1 (541.0-663.3)	728.3 (661.4-802.4)
0-11 months	619.3 (554.7-692.2)	592.8 (534.5-651.9)	855.7 (783.9-927.5)	305.9 (246.5-367.3)	1,152.7 (902.7-1,485.2)	380.3 (347.4-413.2)	848.1 (797.1-900.2)	539.3 (489.5-598.7)	657.9 (597.4-723.9)
12-23 months	664.5 (597.4-747.4)	636.7 (578.6-703.0)	923.0 (844.5-999.7)	326.9 (264.0-393.6)	1,244.1 (964.3-1,600.2)	410.0 (375.1-445.5)	915.1 (860.3-970.5)	580.9 (523.9-645.7)	710.3 (644.5-782.5)
2-4 years	257.7 (230.8-288.7)	246.3 (223.1-271.5)	356.9 (327.1-387.3)	126.7 (102.0-151.4)	476.1 (369.2-616.0)	158.5 (144.9-172.1)	354.0 (332.9-375.8)	224.9 (203.2-250.2)	283.2 (255.5-314.5)
≥5 years	**42.5** (38.5-45.9)	**37.6** (34.4-40.6)	**47.2** (44.2-49.9)	**15.3** (12.6-18.1)	**58.6** (45.8-74.8)	**52.0** (47.2-56.6)	**41.1** (39.2-43.0)	**66.9** (61.4-72.3)	**45.1** (41.1-49.1)
5-14 years	65.9 (59.8-71.1)	57.2 (52.3-61.9)	65.0 (61.0-68.6)	38.8 (31.0-45.5)	81.1 (62.7-104.5)	48.8 (45.6-51.3)	58.3 (55.9-60.6)	85.1 (77.7-91.5)	62.6 (57.1-68.1)
15-49 years	28.9 (26.3-31.3)	25.8 (23.5-27.7)	33.0 (31.0-34.9)	8.8 (7.2-10.4)	36.5 (28.7-46.5)	47.1 (41.9-52.1)	28.7 (27.1-30.2)	49.3 (45.2-53.4)	31.8 (28.9-34.7)
50-64 years	34.6 (31.5-37.5)	30.1 (27.7-32.9)	39.3 (36.8-41.8)	12.7 (12.7-16.9)	51.4 (41.7-62.1)	56.7 (50.7-61.2)	34.2 (32.2-36.2)	59.6 (54.7-64.4)	40.6 (37.2-44.1)
65+ years	81.9 (73.2-88.6)	73.8 (68.3-78.3)	93.7 (85.9-99.0)	31.4 (31.4-31.4)	111.3 (90.2-134.3)	130.9 (118.7-145.5)	80.2 (76.7-85.5)	136.8 (129.4-148.7)	97.0 (89.3-105.1)
All ages	**87.1** (78.5-96.1)	**95.2** (86.5-104.2)	**120.6** (111.4-129.7)	**39.6** (32.1-47.2)	**144.3** (112.3-185.5)	**86.6** (78.9-94.2)	**124.5** (117.5-131.7)	**117.5** (107.1-128.9)	**105.3** (95.6-115.7)
2013									
<5 years	**278.1** (248.9-311.3)	**286.3** (260.3-316.4)	**417.6** (383.1-452.6)	**154.0** (123.0-183.6)	**518.8** (401.6-667.8)	**224.0** (205.0-243.3)	**462.7** (435.1-491.2)	**369.0** (333.5-410.7)	**356.3** (323.0-393.2)
<2 years	365.2 (326.5-408.2)	372.9 (339.1-412.5)	549.3 (504.2-595.5)	198.2 (158.0-235.9)	735.1 (572.6-942.3)	293.1 (268.6-318.3)	607.4 (571.0-644.4)	482.4 (436.3-537.9)	461.9 (420.1-507.8)

137

Year	Central	Coast	Eastern	Nairobi	North Eastern	Nyanza	Rift Valley	Western	Kenya
	n(95% CI)	n(95% CI)	n(95% CI)	n(95% CI)	n(95% CI)	n(95% CI)	n(95% CI)	n(95% CI)	n(95% CI)
0-5 months	153.1 (133.4-166.3)	153.9 (138.2-168.0)	223.4 (206.5-243.7)	86.2 (68.9-99.6)	300.4 (247.6-381.5)	119.2 (112.0-130.2)	249.5 (233.5-263.8)	197.0 (179.5-219.2)	189.6 (173.0-207.4)
6-11 months	514.3 (462.6-579.0)	527.4 (479.6-586.0)	775.9 (711.6-839.1)	282.1 (221.9-336.6)	1,044.6 (805.4-1,339.7)	414.9 (380.0-450.6)	861.7 (810.1-914.9)	681.4 (615.0-760.4)	653.5 (593.9-718.9)
0-11 months	335.4 (299.5-374.5)	342.3 (310.4-378.9)	502.1 (461.3-544.1)	185.0 (146.1-219.1)	675.8 (529.0-864.9)	268.4(247.2-291.8)	558.3 (524.4-592.3)	441.4 (399.2-492.2)	423.6 (385.3-465.5)
12-23 months	398.4 (356.6-445.6)	408.2 (372.3-451.3)	599.6 (550.0-650.3)	215.0 (173.0-257.1)	801.6 (621.4-1029.0)	321.8 (293.5-349.0)	667.4 (627.8-708.2)	527.2 (476.7-587.7)	506.2 (460.2-556.8)
2-4 years	222.3 (199.2-249.2)	228.4 (207.5-252.1)	335.4 (307.5-363.4)	121.0 (97.0-144.7)	443.6 (342.1-572.5)	179.6 (164.2-195.1)	373.2 (351.1-396.4)	295.4 (266.9-328.3)	290.5 (262.5-321.8)
≥5 years	**47.1 (42.5-50.9)**	**35.7 (32.5-38.8)**	**43.5 (40.8-46.1)**	**15.3 (12.4-17.6)**	**60.3 (47.2-77.5)**	**30.0 (27.5-32.6)**	**31.2 (29.7-32.6)**	**37.8 (34.7-40.9)**	**36.3 (33.0-39.7)**
5-14 years	100.3(90.7-108.5)	71.6 (65.1-77.5)	81.6 (76.4-86.1)	49.0 (39.6-56.6)	100.5 (77.8-130.4)	41.1 (38.6-43.2)	57.8 (55.5-60.2)	64.2 (59.0-69.5)	67.9 (61.7-74.3)
15-49 years	23.7 (21.4-25.6)	17.2 (15.6-18.7)	22.2 (20.8-23.5)	6.0(4.9-7.0)	24.8 (19.4-32.4)	21.3 (18.9-23.6)	15.3 (14.4-16.0)	19.9 (18.2-21.5)	18.2 (16.5-19.9)
50-64 years	51.0 (45.2-55.4)	37.6 (34.8-39.9)	46.9 (44.4-50.6)	16.4 (12.3-16.4)	60.5 (50.1-69.9)	45.0 (40.8-50.8)	32.4 (30.5-34.4)	44.2 (39.5-46.6)	41.7 (37.9-45.2)
65+ years	28.4 (25.9-30.4)	20.4 (20.4-25.7)	25.5 (23.9-27.5)	15.3 (15.3-15.3)	44.8 (44.8-44.8)	24.2(21.9-29.2)	18.7 (17.2-18.7)	23.3 (23.3-26.6)	24.1 (22.7-26.4)
All ages	**75.3 (67.7-82.7)**	**76.3 (69.4-83.7)**	**96. 9(89.7-104.2)**	**32.9 (26.4-38.6)**	**125.4 (97.5-161.4)**	**63.8 (58.4-69.3)**	**101.3 (95.6-107.1)**	**95.7 (86.9-105.5)**	**85.5 (77.6-94.1)**
2014									
<5 years	**165.9 (148.8-186.9)**	**246.5 (224.4-272.6)**	**240.8 (220.6-261.4)**	**80.1 (64.6-95.1)**	**355.1 (273.9-455.6)**	**151.7 (139.0-164.9)**	**203.0 (191.2-215.7)**	**139.8 (126.5-155.4)**	**192.7 (173.9-213.9)**
<2 years	233.3 (210.2-264.0)	344.5 (313.9-381.6)	340.5 (311.9-369.9)	111.5 (90.2-131.7)	553.0 (427.2-705.8)	213.5 (196.0-232.5)	287.1 (270.6-305.2)	197.1 (177.9-218.6)	268.0 (242.9-296.3)
0-5 months	246.5 (224.0-280.3)	367.1 (333.3-405.5)	363.3 (332.4-393.1)	119.9 (97.4-138.6)	587.8 (456.7-746.7)	226.2 (208.4-246.7)	304.8 (286.1-324.1)	209.9 (188.2-232.7)	284.3 (257.6-313.7)
6-11 months	224.7 (201.0-256.4)	331.9 (303.3-369.7)	326.5 (300.4-356.8)	106.7 (88.3-130.6)	526.7 (421.3-682.7)	207.3 (189.8-224.8)	276.5 (261.2-293.3)	189.4 (172.6-210.7)	257.3 (234.4-285.5)
0-11 months	235.5 (212.4-268.3)	349.4 (318.2-387.4)	344.7 (316.2-374.8)	113.2 (92.8-134.6)	557.0 (438.9-714.4)	216.7 (199.0-235.7)	290.5 (273.5-308.5)	199.5 (180.3-221.6)	270.6 (245.9-299.5)
12-23 months	230.9 (207.8-259.3)	338.8 (309.0-374.8)	336.0 (307.4-364.6)	109.3 (87.0-128.1)	548.6 (414.2-696.2)	209.9 (192.5-228.8)	283.0 (266.9-301.2)	194.4 (175.2-215.3)	264.9 (239.5-292.6)
2-4 years	122.7 (109.6-137.5)	180.9 (164.5-199.7)	178.7 (163.7-193.6)	56.7 (45.5-67.9)	286.4 (220.7-368.7)	112.0 (102.4-121.5)	151.0 (142.1-160.3)	102.7 (93.2-114.4)	145.8 (130.9-162.5)

Year	Central n(95% CI)	Coast n(95% CI)	Eastern n(95% CI)	Nairobi n(95% CI)	North Eastern n(95% CI)	Nyanza n(95% CI)	Rift Valley n(95% CI)	Western n(95% CI)	Kenya n(95% CI)
≥5 years	**27.0 (24.6-29.4)**	**27.9 (25.5-30.0)**	**34.7 (32.5-36.7)**	**11.6 (9.4-13.5)**	**42.6 (32.9-54.8)**	**25.7 (23.4-28.0)**	**33.7 (32.2-35.3)**	**37.6 (34.6-40.8)**	**30.6 (27.9-33.3)**
5-14 years	39.1 (35.4-42.6)	39.4 (35.9-42.2)	44.6 (41.8-47.1)	26.8 (22.2-31.4)	55.1 (43.3-71.4)	22.0 (20.9-23.2)	44.8 (42.9-46.6)	44.6 (40.8-48.3)	40.3 (36.9-44.0)
15-49 years	19.7 (17.8-21.4)	20.2 (18.3-21.7)	26.0 (24.3-27.5)	7.1 (5.6-8.1)	28.5 (22.2-36.9)	24.5 (21.8-26.9)	25.1 (23.9-26.5)	29.5 (27.2-32.1)	22.7 (20.7-24.7)
50-64 years	34.3 (31.4-37.3)	36.8 (34.1-39.1)	45.9 (42.2-48.2)	16.1 (12.1-16.1)	59.1 (39.7-68.4)	42.6 (38.3-47.0)	44.0 (42.1-45.9)	52.2 (47.5-56.8)	42.2 (38.1-45.2)
65+ years	33.7 (31.7-38.0)	35.6 (35.6-39.9)	44.8 (42.9-48.3)	15.0 (15.0-30.0)	64.0 (43.9-85.9)	42.5 (38.0-47.4)	43.3 (41.5-46.6)	52.1 (48.9-55.9)	42.4 (39.5-47.2)
All ages	**44.0 (39.7-48.7)**	**63.3 (57.7-69.3)**	**64.2 (59.4-68.8)**	**20.3 (16.4-23.8)**	**87.0 (67.1-111.8)**	**47.7 (43.5-51.9)**	**61.2(58.0-64.6)**	**55.5 (50.7-60.9)**	**55.5 (50.4-61.1)**
2012-2014									
<5 years	**282.8 (253.3-317.1)**	**334.1 (302.8-368.2)**	**406.6 (372.9-440.7)**	**144.0 (115.9-172.1)**	**529.4 (411.2-684.1)**	**216.3 (198.2-235.0)**	**391.5 (368.1-415.5)**	**266.5 (241.0-295.8)**	**325.7 (294.7-360.3)**
<2 years	411.8 (368.3-460.8)	482.3 (436.8-530.7)	594.0 (544.5-643.7)	203.8 (165.1-244.2)	859.6 (672.4-1109.6)	314.6 (288.2-341.5)	571.8 (537.6-607.0)	386.8 (349.6-428.7)	469.0 (425.7-516.6)
0-5 months	315.0 (282.0-352.9)	371.0 (336.4-405.6)	454.3 (415.9-491.6)	159.1 (128.5-189.8)	658.5 (520.3-849.5)	241.6 (220.6-262.5)	436.9 (411.4-464.0)	295.4 (268.5-326.9)	358.7 (326.0-394.7)
6-11 months	477.8 (426.0-532.9)	557.5 (505.0-616.1)	686.0 (631.6-745.9)	235.4 (194.0-282.5)	994.2 (778.6-1289.7)	365.3 (334.0-395.7)	663.5 (623.9-704.3)	448.4 (404.8-497.7)	542.6 (493.0-598.1)
0-11 months	397.1 (354.6-443.7)	465.1 (421.5-511.8)	571.2 (524.7-619.9)	197.6 (161.5-236.6)	827.8 (650.6-1071.6)	304.0(277.8-329.7)	551.2 (518.6-585.2)	372.6 (337.3-413.1)	451.5 (410.3-497.3)
12-23 months	428.0 (383.5-479.8)	502.2 (454.6-552.5)	618.4 (565.7-669.2)	211.7 (169.6-253.8)	895.2 (696.7-1152.2)	327.0 (300.2-355.2)	596.9 (560.8-633.6)	402.2 (363.1-445.8)	489.2(443.4-538.8)
2-4 years	200.3 (179.6-225.1)	234.8 (213.1-259.4)	289.7 (265.7-313.9)	99.5 (79.3-118.4)	414.7 (320.5-536.3)	153.2 (140.4-166.6)	279.9 (263.2-297.1)	188.6 (170.5-209.5)	236.5 (213.0-262.9)
≥5 years	**38.8 (35.2-42.1)**	**33.3 (30.4-36.1)**	**41.7 (39.0-44.0)**	**14.0 (11.1-16.3)**	**52.4 (41.5-68.2)**	**34.0 (30.9-37.1)**	**36.3 (34.7-38.0)**	**48.7 (44.4-52.5)**	**37.3 (34.0-40.7)**
5-14 years	65.6 (59.6-71.1)	54.5 (49.8-59.3)	62.4 (58.5-65.9)	37.8 (30.2-43.5)	76.7 (59.9-99.5)	35.4 (32.9-37.2)	55.5 (53.1-57.8)	66.7 (61.0-72.0)	56.7 (51.6-61.8)
15-49 years	24.6 (22.3-26.7)	21.0 (19.1-22.6)	27.0 (25.3-28.5)	7.3 (5.7-8.6)	30.2 (23.7-38.9)	28.9 (25.8-32.1)	23.3 (22.1-24.4)	33.2 (30.2-35.8)	24.1(21.9-26.3)
50-64 years	40.9 (38.2-45.3)	34.9 (32.1-37.7)	45.6 (42.1-48.3)	12.4 (12.4-16.5)	50.2 (40.6-70.0)	48.1 (43.6-53.9)	39.2 (37.2-41.2)	55.7 (51.0-60.5)	42.4 (39.1-46.7)
65+ years	53.9 (47.5-56.4)	46.2 (40.9-51.5)	58.6 (54.7-60.2)	30.7 (15.3-30.7)	65.5 (65.5-87.9)	62.7 (55.4-70.0)	49.2 (47.7-52.9)	72.8 (65.0-76.7)	56.7 (51.6-61.0)

Year	Central	Coast	Eastern	Nairobi	North Eastern	Nyanza	Rift Valley	Western	Kenya
	n(95% CI)	n(95% CI)	n(95% CI)	n(95% CI)	n(95% CI)	n(95% CI)	n(95% CI)	n(95% CI)	n(95% CI)
All ages	68.6 (61.9-75.7)	82.0 (74.4-89.9)	93.8 (86.7-100.7)	30.5 (24.4-36.0)	120.2 (94.0-155.7)	65.8 (60.0-71.6)	94.1 (88.9-99.4)	86.8 (78.8-95.1)	81.7 (74.1-89.9)

*Rate per 100,000 persons

7.4 Appendix 4: Supplementary text (Objectives 2 and 3)

7.4.1 Further information on health facilities within influenza surveillance system

7.4.1.1 Map of influenza surveillance system

From 2010 to 2018 the Centers for Disease Control and Prevention (CDC) in collaboration with the Ministry of Health conducted influenza surveillance in Kenya at each of the largest public health facilities in the following counties: Kakamega, Siaya, Nyeri, Nakuru, Mombasa, and Nairobi. Influenza surveillance also took place within refugee camps. The analysis was limited to data from the county referral hospitals (CRH) in Kakamega, Siaya, Nyeri, Nakuru and Mombasa from where we were able to define catchment populations.
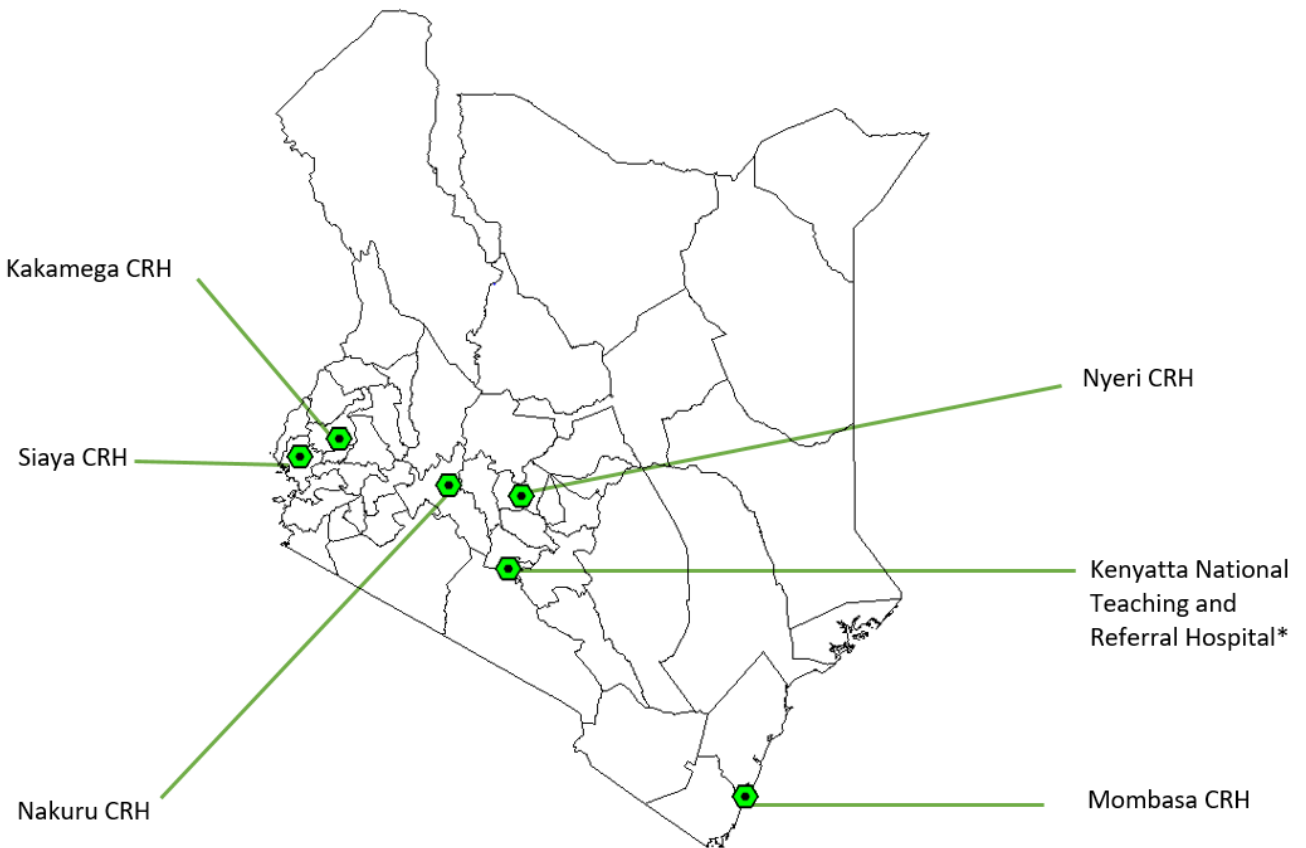
Figure 12: Map of influenza surveillance sites in Kenya. CRH – county referral hospital.
Data from Kenyatta National Teaching and Referral Hospital not included in the analysis.

7.4.2 Defining the catchment population

We obtained Kenyan age group specific population density data for the years 2010 and 2015 [182]. We plotted each sentinel site on ArcGIS (ESRI) using its longitude and latitude (Table 1) and calculated the catchment population within a 10 kilometre radius of each health facility. This was informed by a local study that showed that ninety percent of children admitted in a health facility with symptoms of a febrile illness, reside within 10 kilometres of the health facility [136].

The annual population for each age group was estimated by assuming a constant growth rate between 2010 and 2015. The 2016 to 2018 population was obtained by applying the World Bank annual population growth estimate [109]. We then assumed that only 5-20% of ill patients within the whole catchment population requiring hospitalisation were admitted at the county referral hospital, given the low levels of health care seeking [107] and presence of alternative inpatient health facilities within the community. Although Kenyatta National Teaching and Referral Hospital is part of the influenza surveillance system, using a 10-kilometre radius round this facility to define its catchment population is not appropriate. The national hospital serves a much larger population than the other county referral hospitals in the influenza surveillance system. For this reason, data from Kenyatta National Teaching and Referral Hospital was excluded from the model.

7.4.3 Summary of surveillance data from health facilities

For the period 2010 to 2018 there were 24,480 cases of severe acute respiratory illness (SARI) identified across the five surveillance sites. Of these cases, 80% (19,547) had respiratory samples tested for the presence of influenza. The influenza virus was detected in 8.6% (1,690) of samples tested.
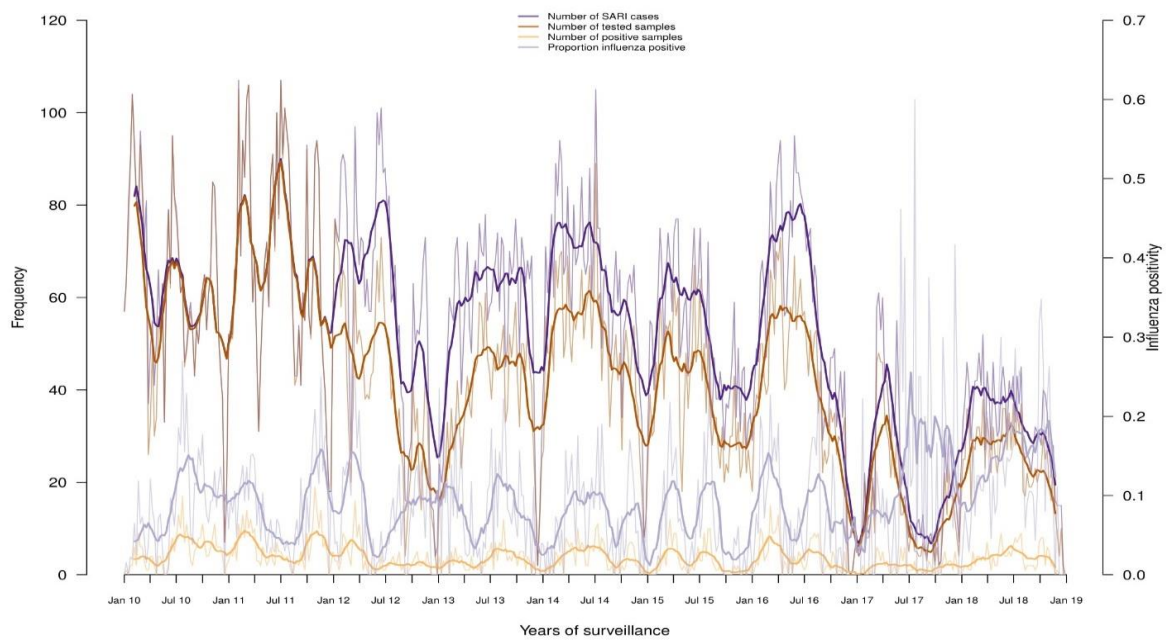
Figure 13: Weekly number of severe acute respiratory illness (SARI) cases, tested samples, positive samples (on left axis) and proportion of tested samples that were influenza positive (right axis) that were identified across the surveillance sites over the period 2010 to 2018. *Darker lines represent the rolling mean. Lighter lines represent the weekly number/proportion.*

7.4.4 Further details on the epidemiological model
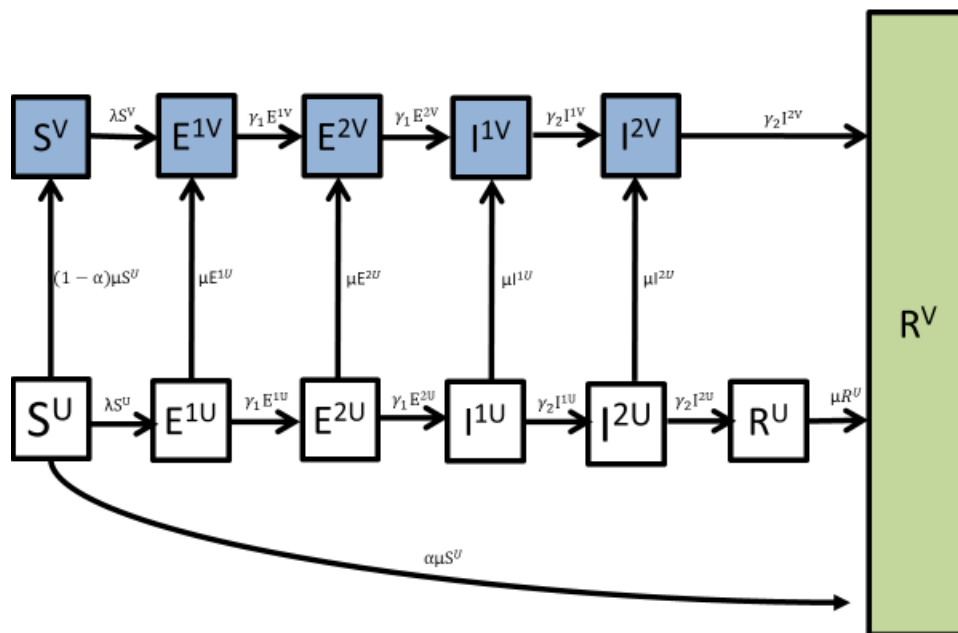
Figure 14: Epidemiological model of influenza transmission [53]. *S = susceptible population; E¹= first compartment of the exposed population; E²= second compartment of the exposed population; I¹ = first compartment of infectious population; I² = second compartment of the infectious population; R = recovered population; V = vaccinated population; U =unvaccinated population; α = vaccine effectiveness; λ =the force of infection; γ₁ = rate of onset of infectiousness; γ₂ = recovery rate, μ = vaccination rate*

The model uses a basic Susceptible-Exposed-Infectious-Recovered (SEIR) structure with two E and I compartments (SEEIIR structure). This was adopted to make the latent and infectious periods gamma distributed, rather than exponential [53]. The differential equations of the transmission model are provided below while full details of the model are provided in Baguelin, 2013 and van Leeuwen, 2017 [53, 140]:

$$\frac{dS_{ik}^U}{dt} = -\lambda_i S_{ik}^U - \mu_{ik} S_{ik}^U \qquad ; \qquad \frac{dS_{ik}^V}{dt} = -\lambda_i S_{ik}^V + (1-\alpha_i)\mu_{ik} S_{ik}^U$$

$$\frac{dE_{ik}^{1U}}{dt} = \lambda_i S_{ik}^U - \gamma_1 E_{ik}^{1U} - \mu_{ik} E_{ik}^{1U} \qquad ; \qquad \frac{dE_{ik}^{1NU}}{dt} = \lambda_i S_{ik}^V - \gamma_1 E_{ik}^{1V} + \mu_{ik} E_{ik}^{1U}$$

$$\frac{dE_{ik}^{2U}}{dt} = \gamma_1 (E_{ik}^{1U} - E_{ik}^{2U}) - \mu_{ik} E_{ik}^{2U} \qquad ; \qquad \frac{dE_{ik}^{2V}}{dt} = \gamma_1 (E_{ik}^{1V} - E_{ik}^{2V}) + \mu_{ik} E_{ik}^{2U}$$

$$\frac{dI_{ik}^{1U}}{dt} = \gamma_1 E_{ik}^{2U} - \gamma_2 I_{ik}^{1U} - \mu_{ik} I_{ik}^{1U} \qquad ; \qquad \frac{dI_{ik}^{1V}}{dt} = \gamma_1 E_{ik}^{2V} - \gamma_2 I_{ik}^{1V} + \mu_{ik} I_{ik}^{1U}$$

$$\frac{dI_{ik}^{2U}}{dt} = \gamma_2 (I_{ik}^{1U} - I_{ik}^{2U}) - \mu_{ik} I_{ik}^{2U} \qquad ; \qquad \frac{dI_{ik}^{2V}}{dt} = \gamma_2 (I_{ik}^{1V} - I_{ik}^{2V}) + \mu_{ik} I_{ik}^{2U}$$

$$\frac{dR_{ik}^U}{dt} = \gamma_2 I_{ik}^{2U} - \mu_{ik} R_{ik}^{1U} \qquad ; \qquad \frac{dR_{ik}^{1V}}{dt} = \gamma_2 I_{ik}^{2V} + \mu_{ik}(R_{ik}^U + \alpha_i S_{ik}^U)$$

where,

S	=	susceptible population
E¹	=	first compartment of the exposed population
E²	=	second compartment of the exposed population
I¹	=	first compartment of infectious population
I²	=	second compartment of the infectious population
R	=	recovered population
V	=	vaccinated population
U	=	unvaccinated population
i	=	age class
k	=	risk group
λ	=	the force of infection
γ₁	=	rate of onset of infectiousness
γ₂	=	recovery rate
μ	=	vaccination rate
α	=	vaccine effectiveness

7.4.4.1 Age and risk groupings in modelling framework

Table 29: Age and risk groups in model framework

Data	Values	Basis
Age groups	<1 year 1-5 years 6-14 years 5-19 years 20-49 years ≥ 50 years	Based on age groupings used in Kenyan contact survey [139]
Age specific susceptibility profiles	<15 years 15-49 years ≥50 years	Three age groups used to avoid overfitting of data. The age groups were identified over the process of fitting the model to the data.
Ascertainment probability age groupings	<1 year 1-5 years ≥6 years	Three age groups used to avoid overfitting of data. The age groups were identified over the process of fitting the model to the data. These age groupings had least correlation between parameters. Due to difference in healthcare seeking behaviour between age groups, the best fit of model to the observed data was obtained by allowing children <1 and 1-5 years to have their own ascertainment probability values, rather than maintaining the same susceptibility age groupings.

The fluEvidenceSynthesis package allows specification of high-risk groups within age groups. Unfortunately, there were limited national data on the proportions of each age group that were high risk, and thus all individuals were considered equally at risk of severe outcomes

7.4.4.2 Data inputs

Table 30: Assumptions of main data inputs in adapted Baguelin framework

Data	Source	Assumptions
Weekly SARI counts stratified by age group	KEMRI/CDC influenza surveillance data, 2010-2018 from Siaya, Kakamega, Nakuru, Nyeri and Mombasa influenza sentinel surveillance sites	Data adequately represents influenza activity in the country. Data from Kenyatta National Teaching and Referral Hospital was not included because the catchment population of the national referral hospital could not be adequately estimated.
Weekly virological data stratified by age group	KEMRI/CDC influenza surveillance data, 2010-2018 from Siaya, Kakamega, Nakuru, Nyeri and Mombasa influenza sentinel surveillance sites	As above
Population size by age	2009 population census data projected to the years under study using the world bank annual population growth rates	Population growth is uniform across regions and age groups
Contact data by age group	[139]	Contact patterns of rural and semi-urban Kilifi, Kenya are similar to the rest of Kenya. Contact patterns are constant throughout the year and do not vary between dry and wet seasons or school terms and school holidays
Monitored population around each influenza sentinel surveillance site	World population map density data projected to the years under study using world bank annual population growth rates	Population within a 10 kilometre radius of each health facility represents the catchment population of the health facility. It is informed by Noor, 2003 that states 90% of admissions within a health facility arise from the population within 10 km of the health facility [136]
Weekly monitored population	World population map density data projected to the years under study using world bank annual population growth rates	A random value with a minimum value from the expected population at the start of the season and a maximum value from the expected population at the end of the season given a uniform increase in population size throughout the year
Vaccine effectiveness	Published literature	Among those who are effectively vaccinated, protection is assumed to be complete whereas those who are not effectively vaccinated carry the same risk of infection as non-vaccinated individuals

146

Table 31: Data sources and assumptions for priors in epidemiological model

Data	Value	Source	Notes
Ascertainment probability priors			
<1 year of age	Log normal distribution; mean log -4.856275807, SD log 0.85064645	Refer to Table 5	The priors on ascertainment probability are generated by combining the mean and ranges of the 5 constituent probabilities, i to v given in Table **32**.
1-5 years of age	Log normal distribution; mean log -4.913483683, SD log 0.85956516		
≥6 years of age	Log normal distribution; mean log -5.319344699, SD log 0.981261173		
Susceptibility prior			
0-14 years age group	Normal distribution, mean = 0.6, SD = 0.1	Assumption	
15-49 and ≥50 years age groups	No prior provided		
Transmissibility prior			
All ages	Normal distribution, mean = 0.165, SD = 0.055	Assumption	Uses the UK values on transmissibility Baguelin, 2013 (8) but incorporates a SD that is twice as wide

SD = standard deviation

Table 32: Data sources and assumptions for ascertainment probability priors in epidemiological model

Component of ascertainment probability prior	Mean and 95% confidence limit	Source	Notes
i. Probability of an infected case developing lower respiratory tract (LRT) symptoms	0.21(0.14-0.303)	[144]	We assume that the probability of severe infection is the same across influenza strains and sub-types
ii. Probability of a case with LRT being hospitalised			
<1 year of age	0.26(0.159-0.396)	[107]	
1-5 years of age	0.24(0.14-0.37)	Calculated	Based on the data from [107]
≥6 years of age	0.16(0.08-0.29)	[107]	
iii. Probability of people within a 10 km radius of the surveillance site being hospitalised at the surveillance site	0.125(0.05-0.2)	Assumption	
iv. Probability of being picked up by surveillance officer			
0-5 years of age	0.7(0.6-0.8)	Assumption	The assumption is based on the fact that in the surveillance sites, the surveillance officers aim to record every case of SARI, however it is likely that during weekends/staff changes/staff absence a few cases may be missed. The robustness of surveillance is assumed to be 0.7(0.6-0.8) in children ≤5 years of age and 0.5(0.3-0.7) in older individuals. NB: We later take into account that not all SARI cases are tested when we fit the modelled data to the 'observed data' where in this case 'observed data' is the number of positive cases we would expect to see if all cases were tested.
≥6 years of age	0.5(0.3-0.7)	Assumption	
v. Probability of a positive influenza case testing positive	0.55(0.3-0.8)	Assumption	The assumption is informed by the Feikin 2013 [71] paper that showed that approximately 48-74% of samples that were positive for influenza by either PCR or serology were positive by PCR.

7.4.5 Vaccine effectiveness values for each vaccination period for modelled influenza seasons

Northern hemisphere and southern hemisphere vaccine effectiveness (VE) was assumed to be either good (70% VE) or poor (42% VE) in all target age groups based on published estimates of vaccine effectiveness. If VE was ≥50% the vaccine was considered well matched to the circulating strain and unmatched if vaccine effectiveness was <50%.

Table 33: Vaccine effectiveness values for each vaccination period for modelled influenza season

Year	Subtype	Vaccine effectiveness (95% confidence interval)	Matched (M) or Unmatched (U)	Source
Northern Hemisphere vaccine match to circulating strains				
2010/2011	B	50% (14-71%)	M	[183]
2011/2012	A(H3N2)	39% (23-52%)	U	[184]
2013/2014	A(H1N1)pdm09	54% (46-61%)	M	[185]
2015/2016	B	55% (44-64%)	M	[186]
2017/2018	A(H1N1)pdm09	67% (54-76%)	M	[187]
2017/2018	B	42% (25-56%)	U	[187]
Southern hemisphere vaccine match to circulating strains				
2010	A(H3N2)	72% (−26–94%)*	M	[188]
2011	B	72% (−26–94%)*	M	[188]
2013	B	For SARI patients, VE against influenza B was 76% (95% CI: 54 to 87); For ILI patients, VE against influenza B was 54% (95% CI: 19 to 75)	M	[189]
2016	A(H3N2)	4% (-40-36%)	U	[190]
2018	A(H3N2)	25% (13-36%)†	U	Uses NH vaccine effectiveness value for 2017/2018 period [187]

Values shown represent VE against all subtypes. †No vaccine effectiveness (VE) values available for this period, as such the VE values for the preceding NH vaccine are used

7.4.6 Further information on the economic evaluation

7.4.6.1 Economic evaluation decision tree

We used an economic evaluation decision tree to categorise infected individuals as asymptomatic, symptomatic with mild illness (upper respiratory tract (URT) infections) or symptomatic with severe illness (lower respiratory tract (LRT) infections) based on published data from influenza challenge studies [144]. Those with mild illness were either seen at an outpatient clinic or were not medically attended, while patients with severe illness were either hospitalised or not. All those with mild illness were assumed to recover, while those with severe illness either recovered or died. The values of the disease states, and healthcare utilisation events associated with each stage are presented in the main text.
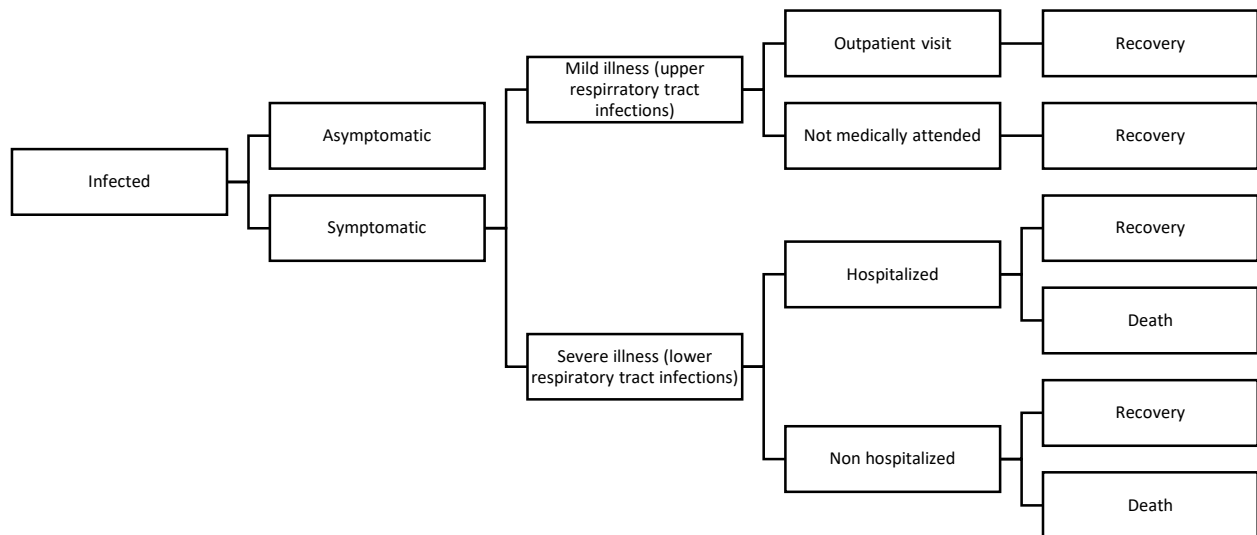
Figure 15: Economic evaluation decision tree of influenza infection and healthcare utilization

7.4.6.2   Additional inputs in the economic model

Table 34: Gross domestic product (GDP) per capita values, GDP deflator values and currency exchange rated

Input	Value	Source
Gross Domestic Product (GDP) per capita		
GDP per capita 2018	1,710.5	[191]
GDP deflator		
2018 GDP deflator	192.255	[192]
2014 GDP deflator	140.613	
2012 GDP deflator	123.721	
Kenya shilling to US dollar exchange rate		
2017 exchange rate for one dollar	103.2317 KES	[193]
2014 exchange rate for one dollar	90 KES	[93]
2012 exchange rate for one dollar	83 KES	[147]

KES – Kenya shillings

Table 35: Life expectancy values used in calculation of disability adjusted life years (DALYs) that were obtained from the Global Health Observatory data repository [194]

Life expectancy	2018*	2017*	2016	2015	2014	2013	2012	2011	2010
<1 year	66.2	66.1	66.7	66.0	65.6	65.3	64.9	64.0	62.9
1-4 years	67.8	67.7	68.2	67.7	67.2	67.0	66.7	65.7	64.6
10-14 years	60.3	60.1	60.6	60.1	59.8	59.6	59.4	58.5	57.5
15-19 years	55.6	55.5	55.9	55.4	55.1	55.0	54.8	53.9	53.0
30-34 years	42.5	42.4	42.8	42.3	42.1	41.9	41.7	41.0	40.1
70-74 years	11.7	11.7	11.7	11.7	11.7	11.7	11.6	11.6	11.4

*Estimated value based on average of three previous years

Table 36: Disability adjusted life year (DALY) weights used in economic model obtained from the Global Burden of Disease Study, 2016 [145]

DALY weights	Value	Additional notes
Influenza cases with mild illness/upper respiratory tract infection	0.006 (0.002-0.012)	Disability weight for mild upper respiratory infection is used
Influenza cases with lower respiratory tract illness that are not hospitalised	0.051 (0.032-0.074)	Disability weight for moderate lower respiratory infection is used
Influenza cases with lower respiratory tract illness that are hospitalised	0.133 (0.088-0.19)	Disability weight for severe lower respiratory infections is used

7.4.7 Further information on fitted model

7.4.7.1 Fitted periods of influenza activity

We identified periods of high influenza activity as >2 successive weeks where the proportion of subtype-specific test-positive cases was greater than the average weekly proportion during the entire study. A period ended when there were ≥2 consecutive weeks where the proportion of subtype-specific positive cases was less than the weekly average. In addition, influenza-positive cases had to be observed in at least 3 of the 5 surveillance sites so that periods identified were of widespread transmission. Periods were included if the posterior mean estimate of the net reproduction number at the start of the simulation was greater than or equal to 1.

There were 4 peaks in influenza B activity, 3 peaks in influenza A(H3N2) activity and 2 peaks in influenza A(H1N1)pdm09 activity. Influenza A(H1N1)pdm09 data from January 2010 to December 2011 was excluded from the analysis as this coincided with the emergence of the pandemic A(H1N1)pdm09 virus.
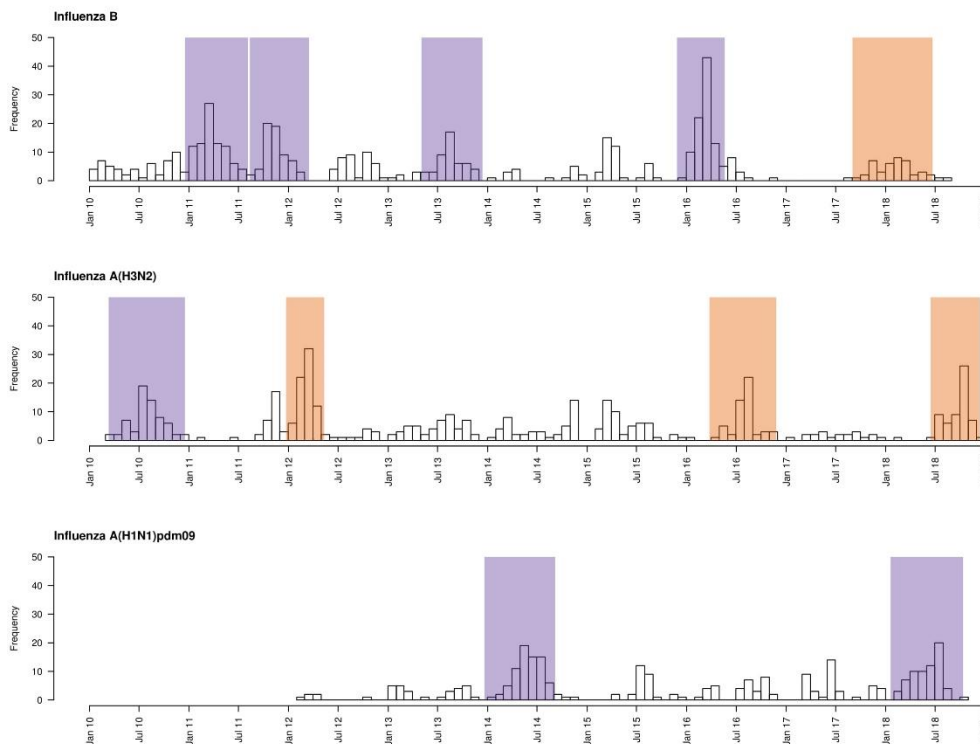
Figure 16: Epidemic curve of modelled peaks in influenza activity by influenza subtype and vaccine effectiveness. *Shaded area refers to the identified peaks in influenza activity. Purple shading refers to seasons where the vaccine was well matched to the circulating strains (vaccine effectiveness (VE) = 70%). Orange shading refers to seasons where the vaccine was poorly matched*

to circulating strains (VE = 42%). There was no influenza activity detected between September 2014-August 2015 and September 2016-August 2017. There was no Southern Hemisphere VE data available for the A(H3N2) season in June 2018-December 2018, so the Northern Hemisphere VE data for the 2017 to 2018 period was used.

7.4.7.2   Periods that did not meet decision rule criteria

The periods listed below had >2 successive weeks where the proportion of subtype-specific test-positive cases was greater than the average weekly proportion during the entire study, however, they did not meet the decision rule criteria because either transmission was recorded in less than 3 of the surveillance sites or the mean net reproduction number at the start of the period was less than 1.

Table 37: Periods that did not meet decision rule criteria

Period	Flu type/subtype
Jan 2010 to Dec 2011	A H1N1pdm09
Oct 2011 to Dec 2011	A H3N2
Jun 2012 to Sep 2012	B
Sep 2012 to Dec 2012	B
Jan 2015 to Jun 2015	B
Feb 2015 to May 2015	A H3N2
Jun 2015 to Sep 2015	A H1N1pdm09
Sep 2017 to Jun 2018	B

7.4.8 Fit of model to data and distribution of posteriors

7.4.8.1 Influenza B

7.4.8.1.1 17 September 2010 to 05 August 2011
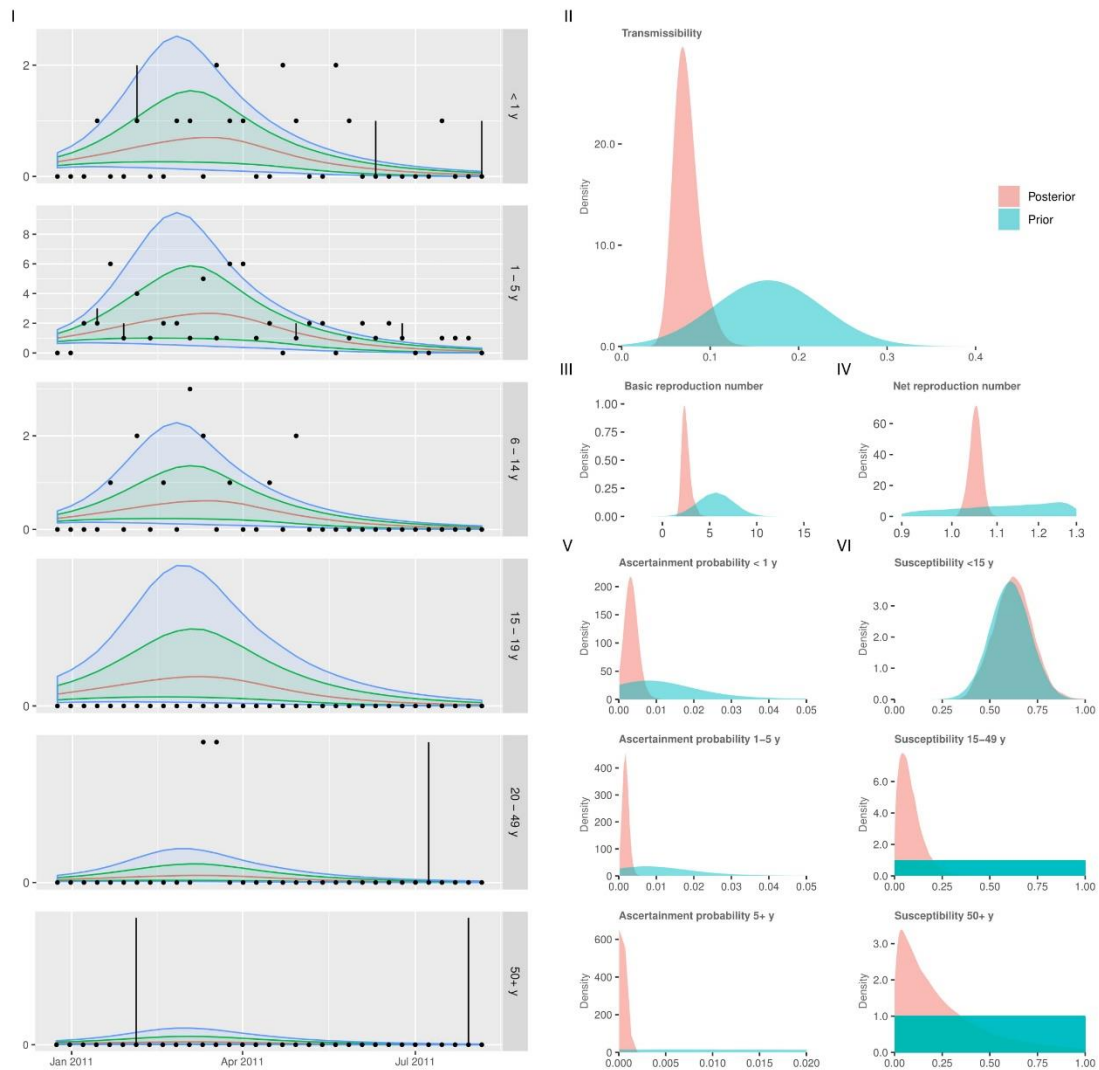
Figure 17: Inference results for influenza B activity, September 2010 to August 2011. *I. Comparison of the fit of the model to the age specific time series of influenza positive SARI cases detected in the influenza surveillance system (black dots) with hypergeometric 95% confidence interval. The median (red) and 50 and 75% credible intervals (shaded green and blue respectively) from the fitted model. II. Transmissibility of the virus. III. Basic reproduction number. IV. Net reproduction number. V. Ascertainment probability in 3 age groups. VI. Susceptibility in 3 age groups. For II to VI the prior distributions are in blue and posterior outputs in pink.*
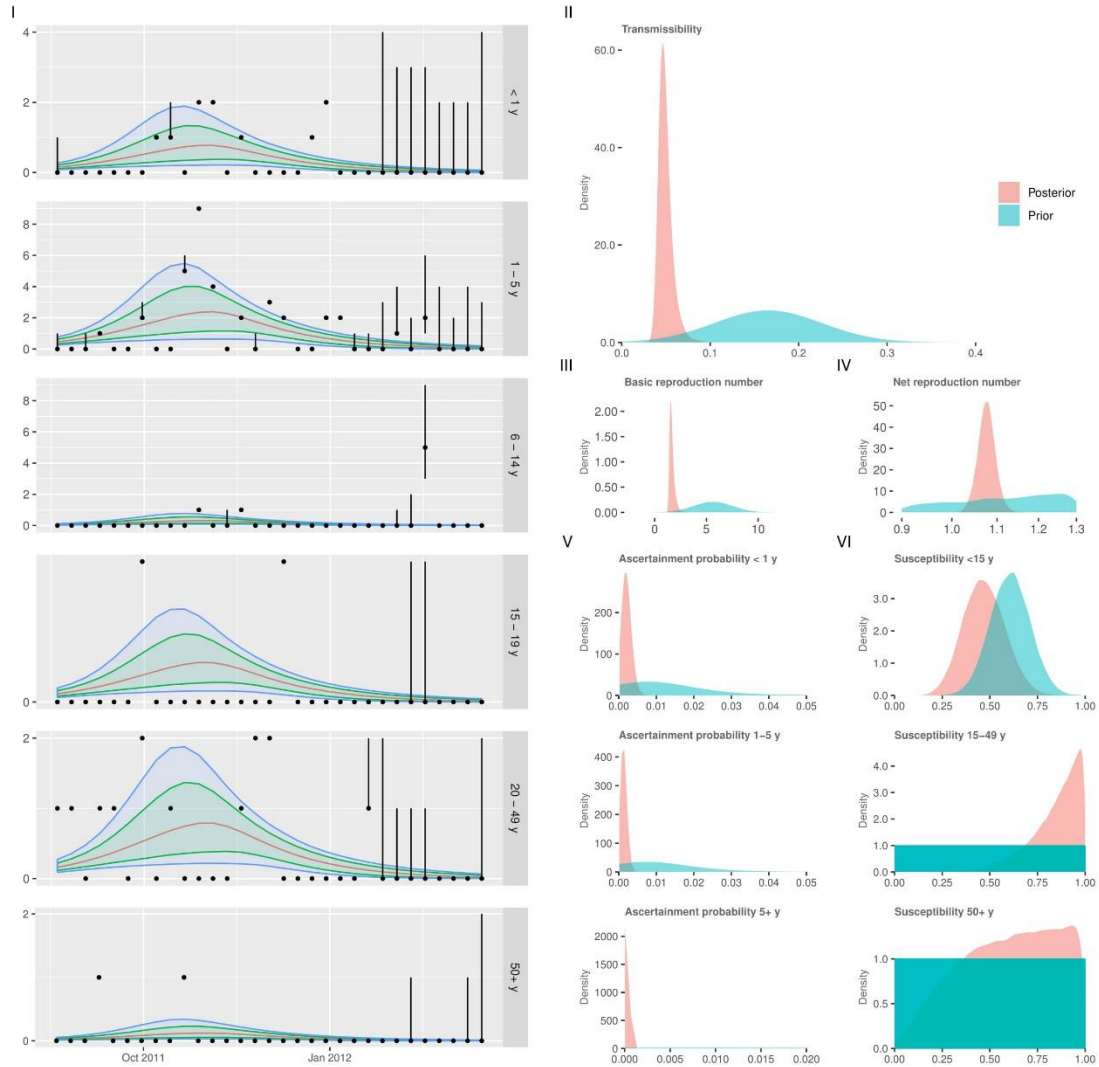
Figure 18: Inference results for influenza B activity, August 2011 to March 2012. *I. Comparison of the fit of the model to the age specific time series of influenza positive SARI cases detected in the influenza surveillance system (black dots) with hypergeometric 95% confidence interval. The median (red) and 50 and 75% credible intervals (shaded green and blue respectively) from the fitted model. II. Transmissibility of the virus. III. Basic reproduction number. IV. Net reproduction number. V. Ascertainment probability in 3 age groups. VI. Susceptibility in 3 age groups. For II to VI the prior distributions are in blue and posterior outputs in pink.*
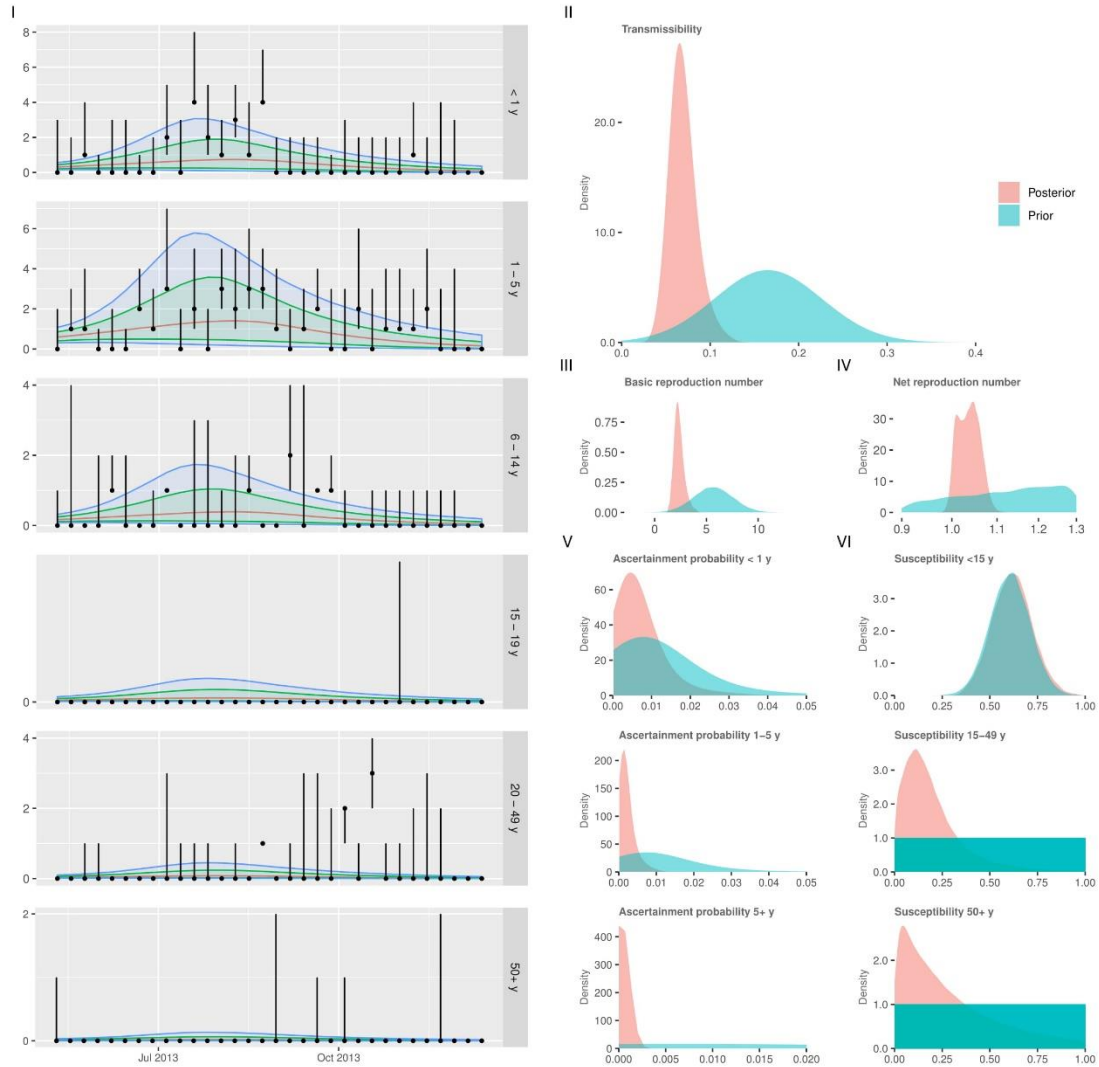
Figure 19: Inference results for influenza B activity, May to December 2013. *I. Comparison of the fit of the model to the age specific time series of influenza positive SARI cases detected in the influenza surveillance system (black dots) with hypergeometric 95% confidence interval. The median (red) and 50 and 75% credible intervals (shaded green and blue respectively) from the fitted model. II. Transmissibility of the virus. III. Basic reproduction number. IV. Net reproduction number. V. Ascertainment probability in 3 age groups. VI. Susceptibility in 3 age groups. For II to VI the prior distributions are in blue and posterior outputs in pink.*
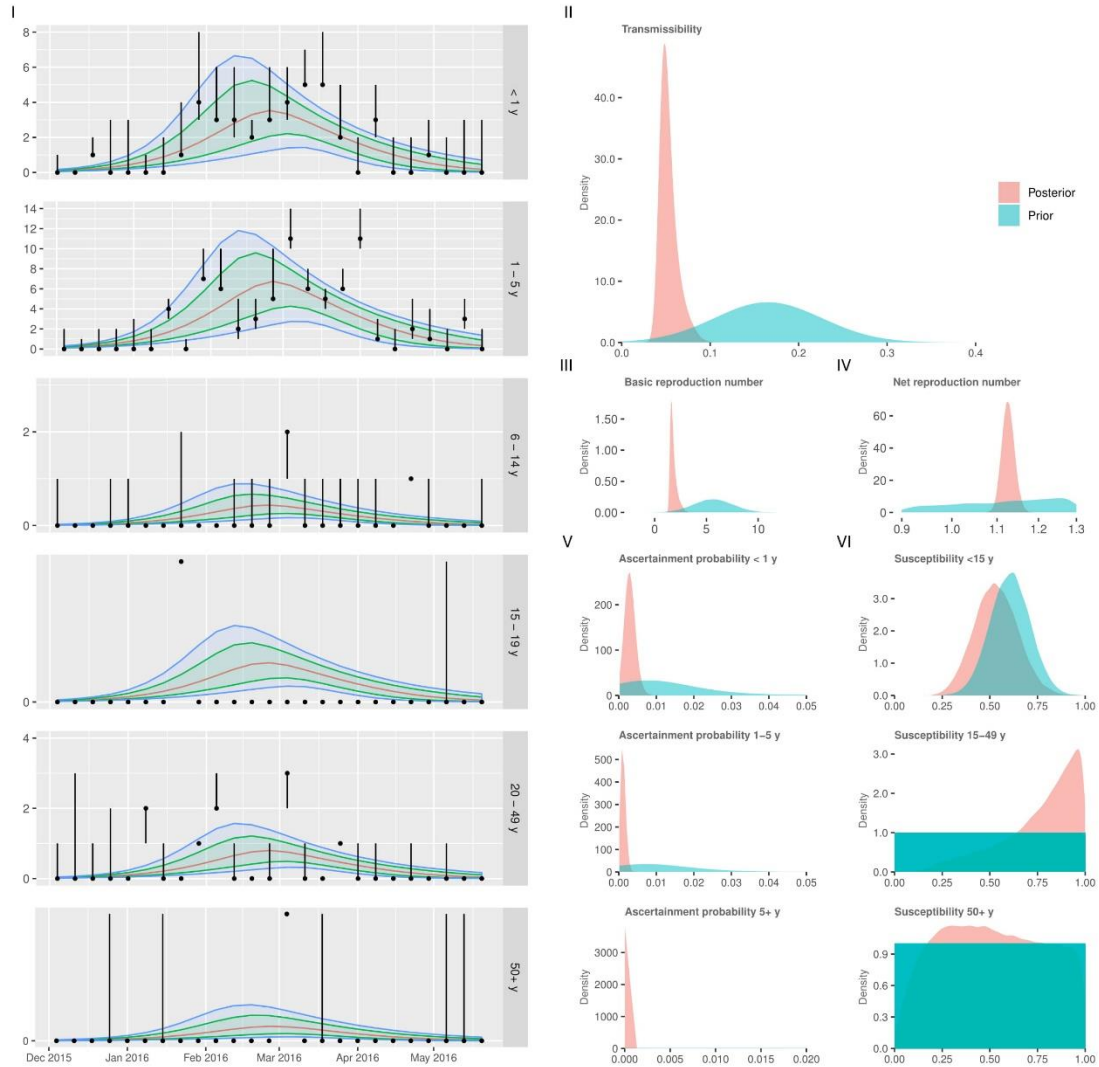
Figure 20: Inference results for influenza B activity, November 2015 to May 2016. *I. Comparison of the fit of the model to the age specific time series of influenza positive SARI cases detected in the influenza surveillance system (black dots) with hypergeometric 95% confidence interval. The median (red) and 50 and 75% credible intervals (shaded green and blue respectively) from the fitted model. II. Transmissibility of the virus. III. Basic reproduction number. IV. Net reproduction number. V. Ascertainment probability in 3 age groups. VI. Susceptibility in 3 age groups. For II to VI the prior distributions are in blue and posterior outputs in pink.*
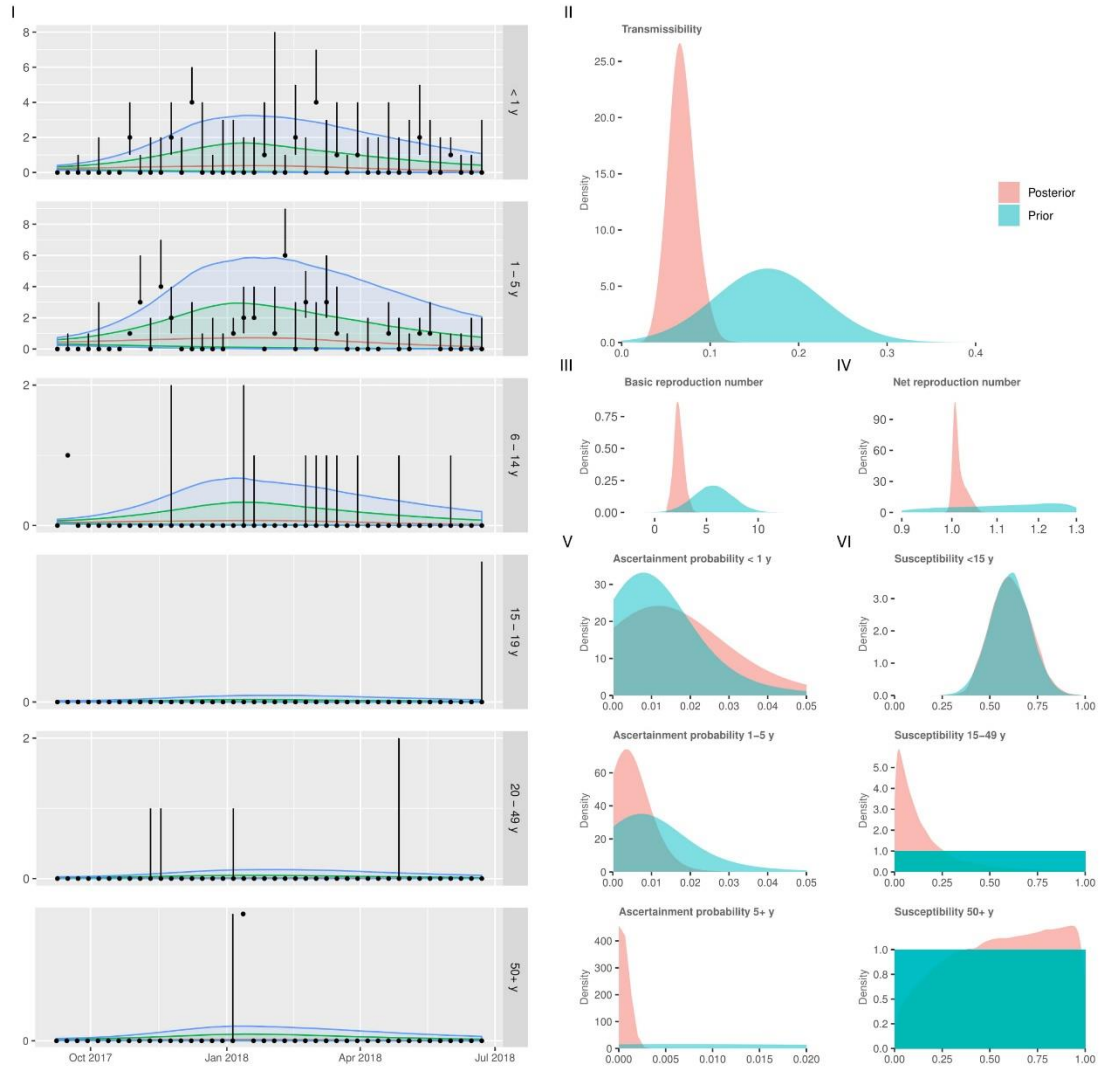
Figure 21: Inference results on influenza B activity, September 2017 to June 2018. *I. Comparison of the fit of the model to the age specific time series of influenza positive SARI cases detected in the influenza surveillance system (black dots) with hypergeometric 95% confidence interval. The median (red) and 50 and 75% credible intervals (shaded green and blue respectively) from the fitted model. II. Transmissibility of the virus. III. Basic reproduction number. IV. Net reproduction number. V. Ascertainment probability in 3 age groups. VI. Susceptibility in 3 age groups. For II to VI the prior distributions are in blue and posterior outputs in pink.*

7.4.8.2   Influenza A(H3N2)

7.4.8.2.1   12 March 2010 to 17 December 2010
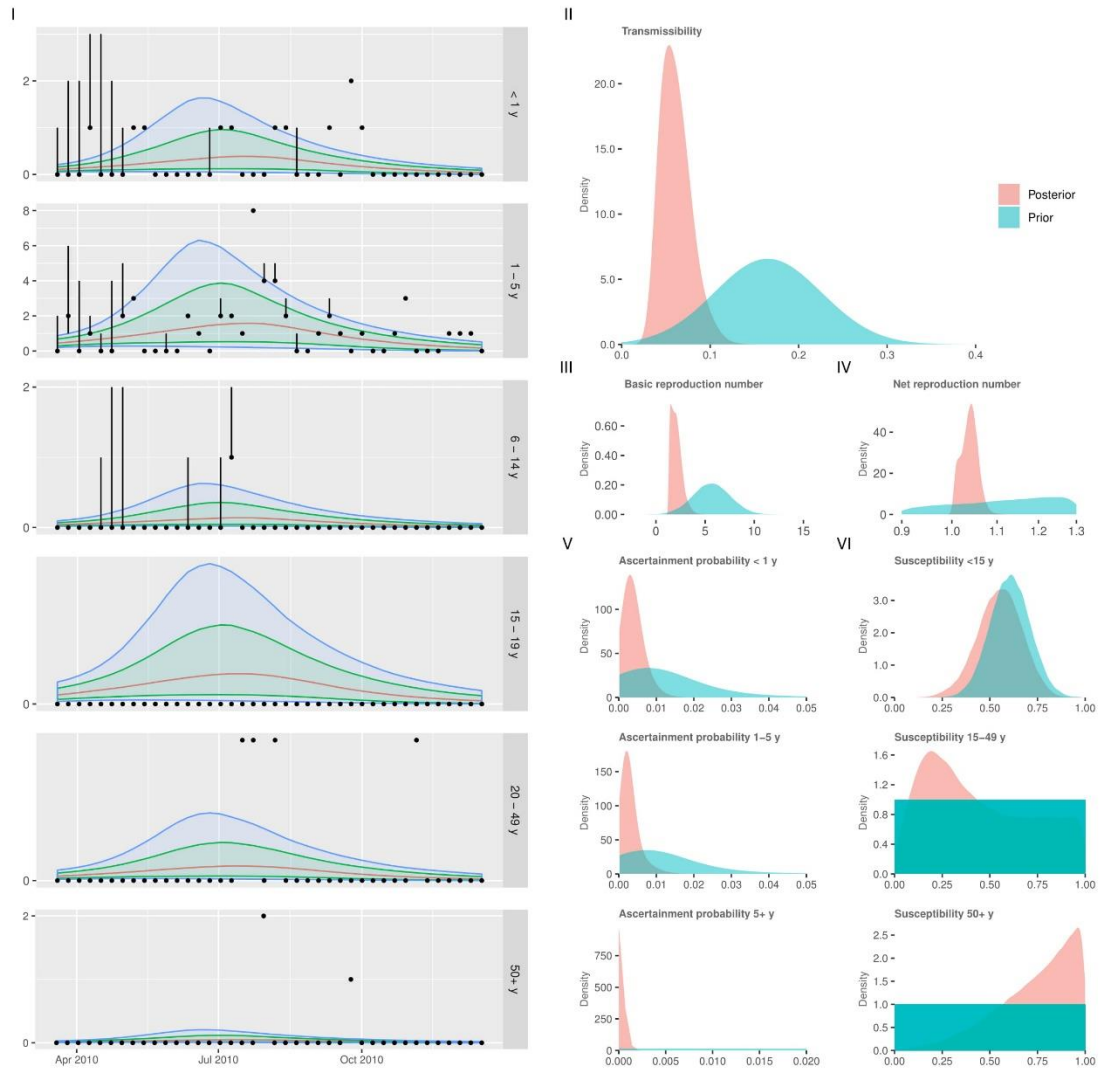
Figure 22: Inference results for influenza A(H3N2) activity, March to December 2010. *I. Comparison of the fit of the model to the age specific time series of influenza positive SARI cases detected in the influenza surveillance system (black dots) with hypergeometric 95% confidence interval. The median (red) and 50 and 75% credible intervals (shaded green and blue respectively) from the fitted model. II. Transmissibility of the virus. III. Basic reproduction number. IV. Net reproduction number. V. Ascertainment probability in 3 age groups. VI. Susceptibility in 3 age groups. For II to VI the prior distributions are in blue and posterior outputs in pink.*
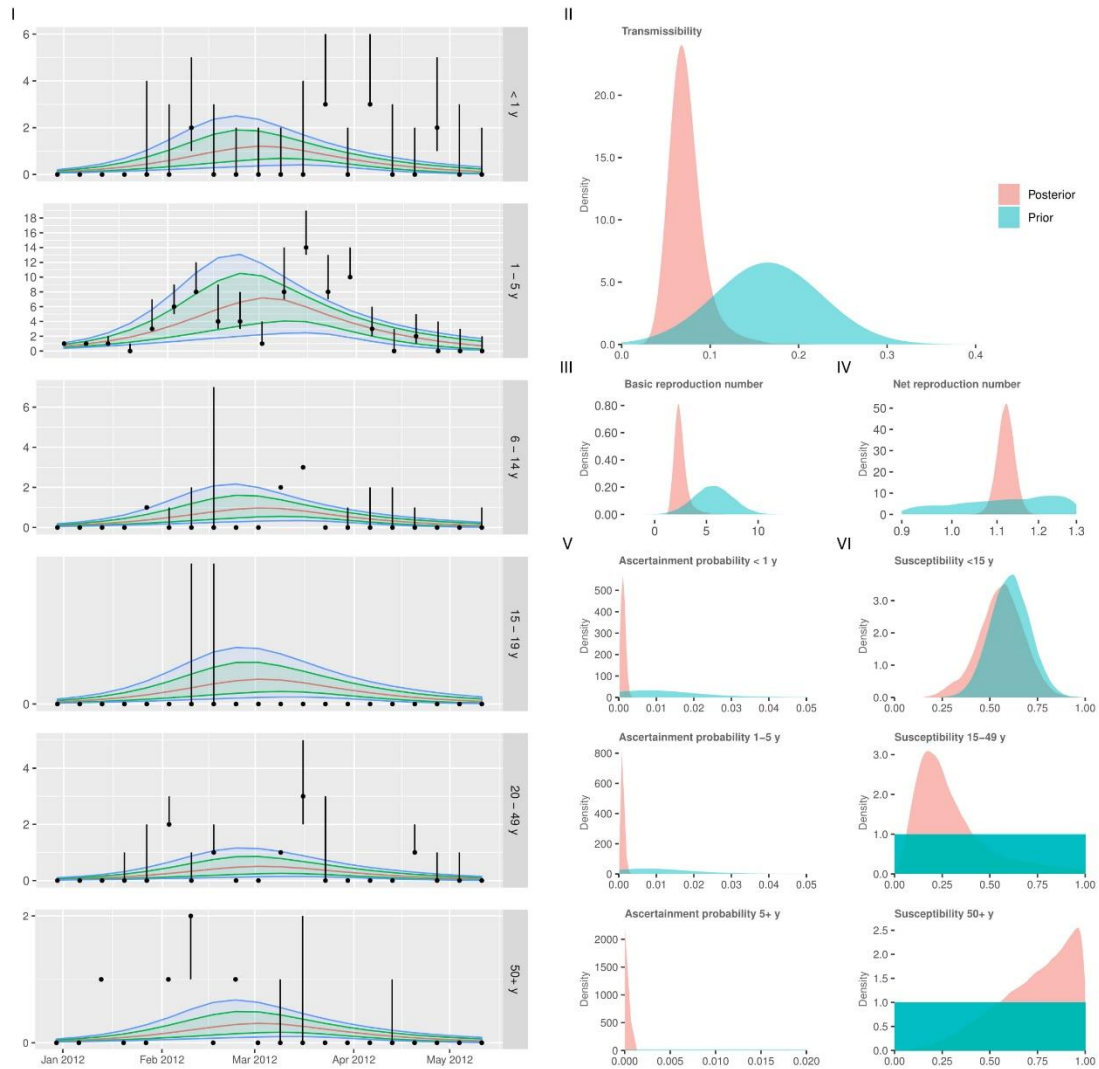
Figure 23: Inference results for influenza A(H3N2) activity, December 2011 to May 2012. *I. Comparison of the fit of the model to the age specific time series of influenza positive SARI cases detected in the influenza surveillance system (black dots) with hypergeometric 95% confidence interval. The median (red) and 50 and 75% credible intervals (shaded green and blue respectively) from the fitted model. II. Transmissibility of the virus. III. Basic reproduction number. IV. Net reproduction number. V. Ascertainment probability in 3 age groups. VI. Susceptibility in 3 age groups. For II to VI the prior distributions are in blue and posterior outputs in pink.*
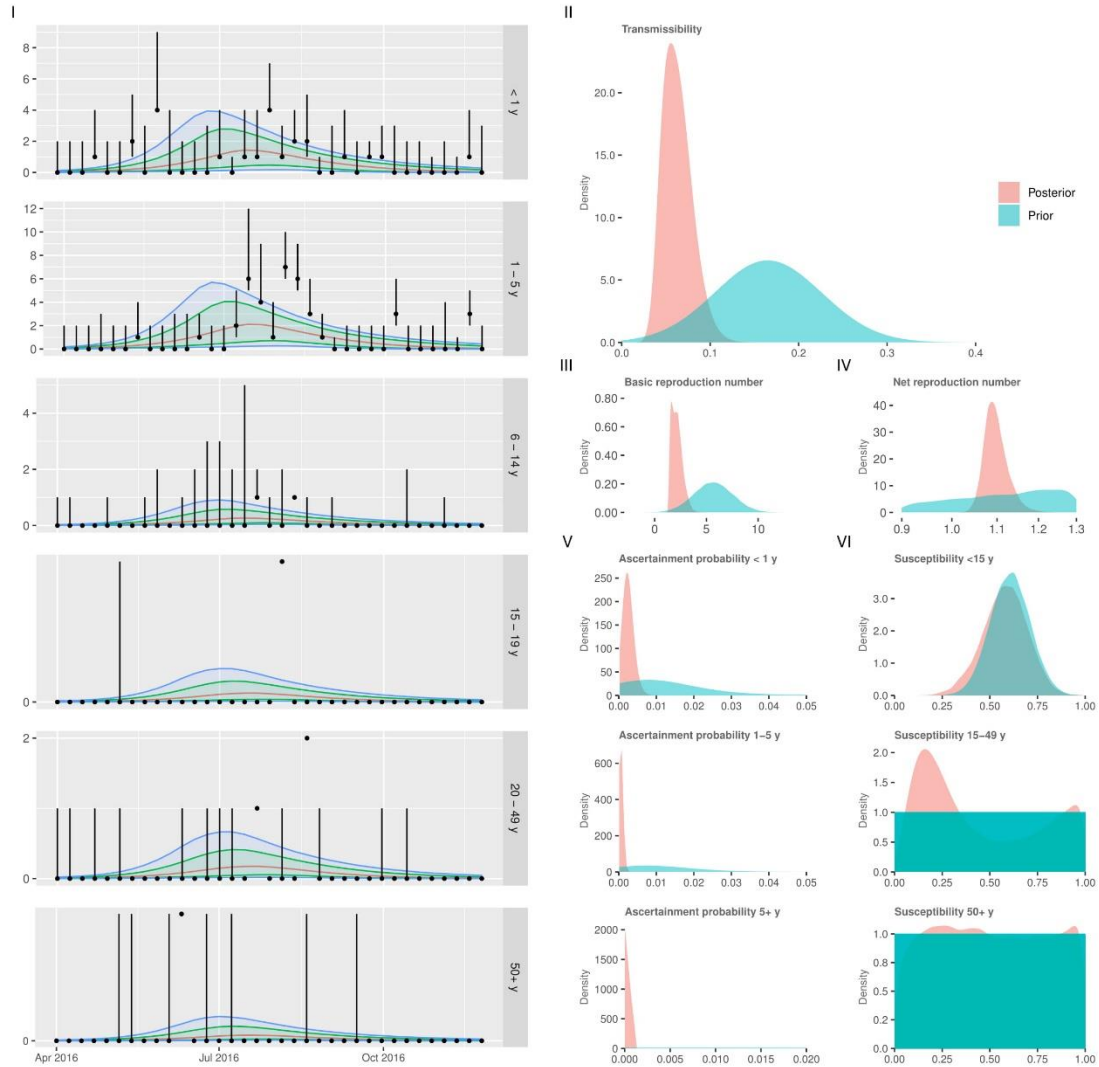
Figure 24: Inference results for influenza A(H3N2) activity, March to November 2016. I. *Comparison of the fit of the model to the age specific time series of influenza positive SARI cases detected in the influenza surveillance system (black dots) with hypergeometric 95% confidence interval. The median (red) and 50 and 75% credible intervals (shaded green and blue respectively) from the fitted model. II. Transmissibility of the virus. III. Basic reproduction number. IV. Net reproduction number. V. Ascertainment probability in 3 age groups. VI. Susceptibility in 3 age groups. For II to VI the prior distributions are in blue and posterior outputs in pink.*
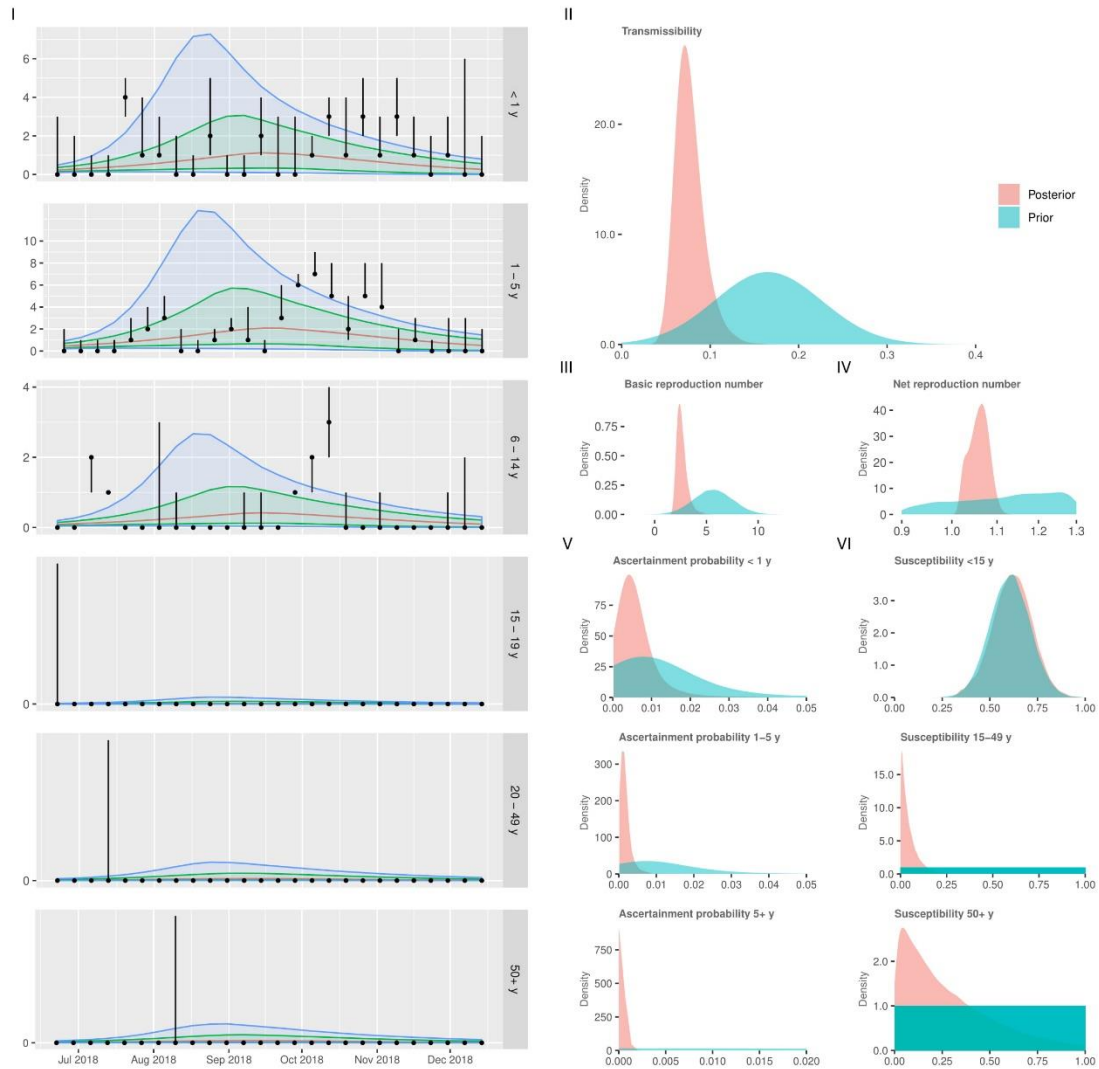
Figure 25: Inference results for influenza A(H3N2) activity, June to December 2018. *I. Comparison of the fit of the model to the age specific time series of influenza positive SARI cases detected in the influenza surveillance system (black dots) with hypergeometric 95% confidence interval. The median (red) and 50 and 75% credible intervals (shaded green and blue respectively) from the fitted model. II. Transmissibility of the virus. III. Basic reproduction number. IV. Net reproduction number. V. Ascertainment probability in 3 age groups. VI. Susceptibility in 3 age groups. For II to VI the prior distributions are in blue and posterior outputs in pink.*

7.4.8.3 Influenza A(H1N1)pdm09

7.4.8.3.1 20 December 2013 to 5 September 2014
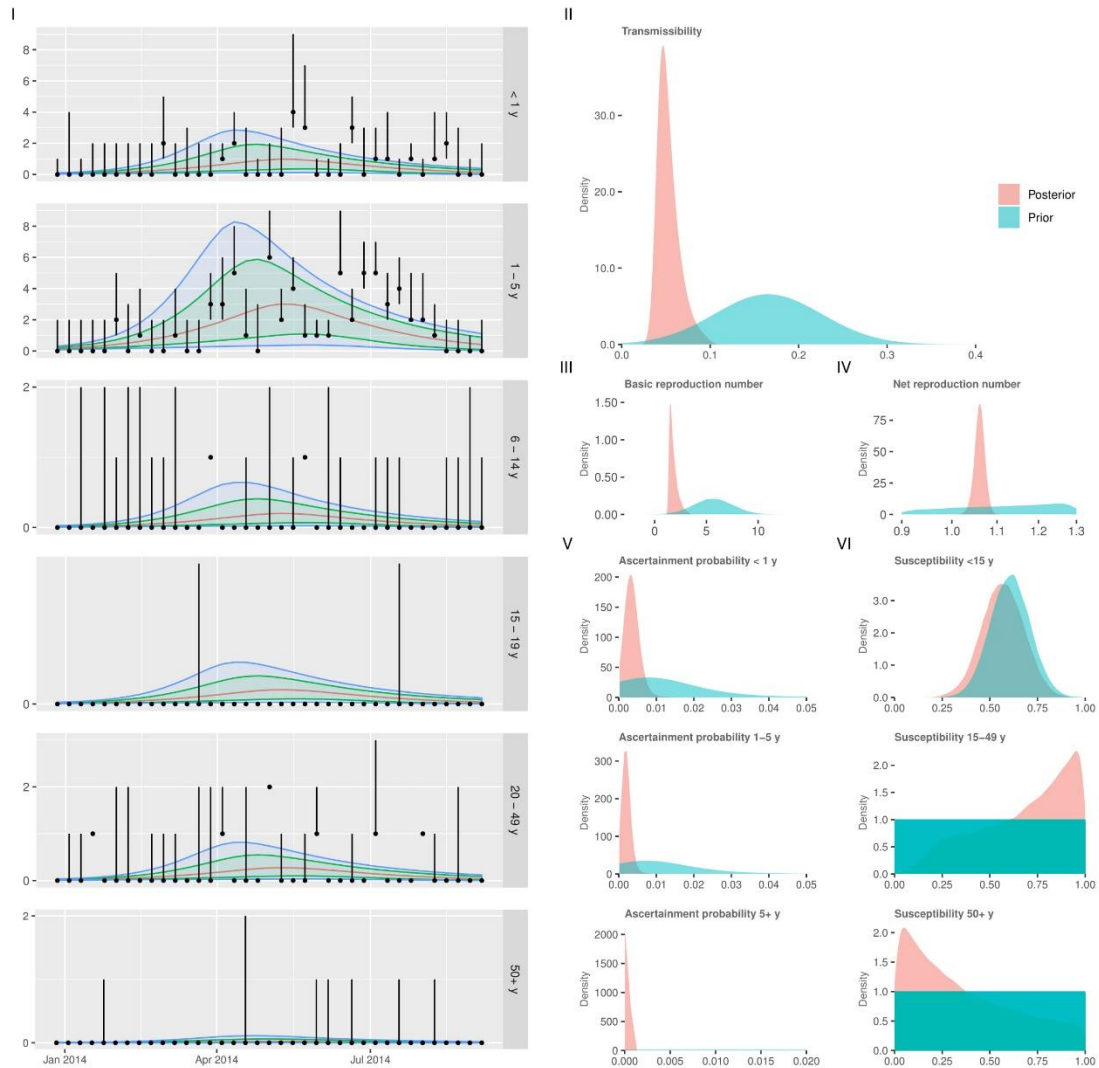
Figure 26: Inference results for influenza A(H1N1)pdm09 activity, December 2013 to September 2014. *I. Comparison of the fit of the model to the age specific time series of influenza positive SARI cases detected in the influenza surveillance system (black dots) with hypergeometric 95% confidence interval. The median (red) and 50 and 75% credible intervals (shaded green and blue respectively) from the fitted model. II. Transmissibility of the virus. III. Basic reproduction number. IV. Net reproduction number. V. Ascertainment probability in 3 age groups. VI. Susceptibility in 3 age groups. For II to VI the prior distributions are in blue and posterior outputs in pink.*
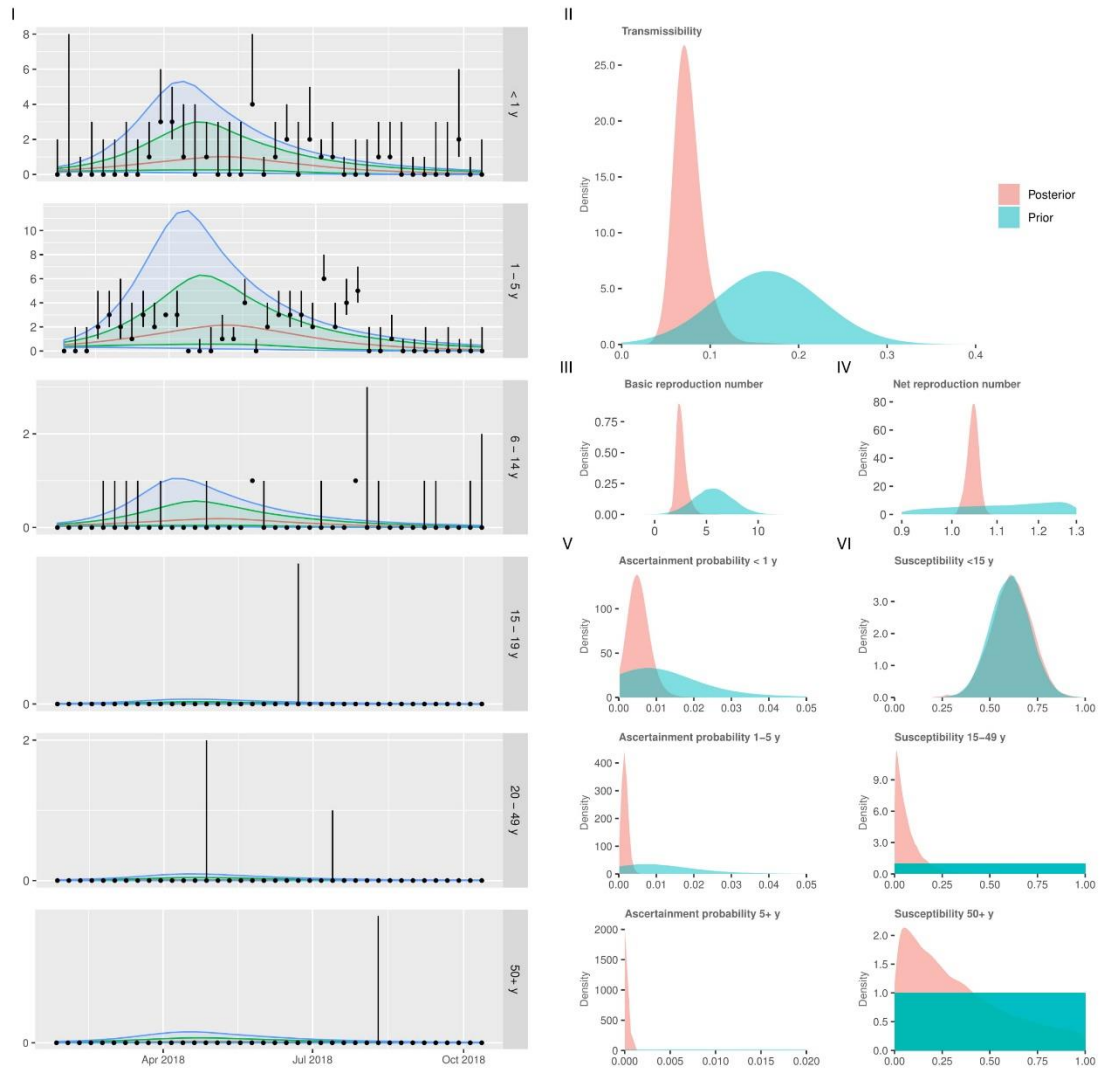
Figure 27: Inference results for influenza A(H1N1)pdm09 activity, January to October 2018. *I. Comparison of the fit of the model to the age specific time series of influenza positive SARI cases detected in the influenza surveillance system (black dots) with hypergeometric 95% confidence interval. The median (red) and 50 and 75% credible intervals (shaded green and blue respectively) from the fitted model. II. Transmissibility of the virus. III. Basic reproduction number. IV. Net reproduction number. V. Ascertainment probability in 3 age groups. VI. Susceptibility in 3 age groups. For II to VI the prior distributions are in blue and posterior outputs in pink.*

7.4.9 Additional results

This section provides additional information on the incremental net monetary benefits (INMB) obtained for each strategy using total societal costs and direct medical costs only, as well as the ICER values obtained from the sensitivity analysis.

7.4.9.1.1 Results of incremental net monetary benefit analysis

Table 38: Annual willingness-to-pay threshold values at which influenza vaccination was cost-effective using total societal costs and direct medical costs only

Year	2010	2010-2011	2011-2012	2012-2013	2013-2014	2015-2016	2017-2018
WTP USD value at which vaccination resulted in a positive INMB value using **total societal costs**	$428	$736	NA*	$511	$428	$478	$246
WTP USD value at which vaccination resulted in a positive INMB value **using direct medical costs only**	$574	$901	NA*	$687	$581	$639	$441
Most optimal strategy at the WTP value	IA	IB	NA*	IA	IB	IIIA	IB

INMB – incremental net monetary benefit; WTP – willingness-to-pay; USD – US dollar. *In this year, vaccination was not cost effective using a WTP threshold of $18-872 per DALY averted

Table 39: Vaccination strategy with the highest positive incremental net monetary benefit in the year using costs calculated from total societal costs and direct medical costs

Year	Willingness-to-pay threshold using **total societal costs**			Willingness-to-pay threshold using **direct medical costs** only		
	Minimum value	Median value	Maximum value	Minimum value	Median value	Maximum value
	$17	$445	$872	$17	$445	$872
2010	None	IA	IIA	None	None	IIA
2010-2011	None	None	IIC	None	None	None
2011-2012	None	None	None	None	None	None
2012-2013	None	None	IIA	None	None	IIA
2013-2014	None	IB	IIIB	None	None	IIIB
2015-2016	None	None	IIIC	None	None	IIIA
2017-2018	None	IIB	IIIC	None	IB	IIIC

7.4.9.2   Results of sensitivity analysis

During one-way sensitivity analysis, strategy IB (vaccinating children 6-23 months of age between October-December) remained the most cost-effective strategy that is attained the highest INMB value at the lowest willingness-to-pay WTP value. However, no vaccination strategy was cost effective at the upper limit of the WTP threshold ($872) when vaccine price was increased to $4.5, $6 and $10. The following sections describe the ICER values obtained during sensitivity analysis.

7.4.9.2.1   Social weighting and time discounting

During the sensitivity analysis we maintained the vaccine purchase price at $3.0 per dose and calculated DALYs with and without social weighting and time discounting. Social weighting placed greater value on life lost from 9-56 years of age. Removing time discounting led to a 49-50% reduction in mean ICER per DALY averted across all strategies, and addition of social weighting led to a slight decrease (5-6%) in mean ICER value.
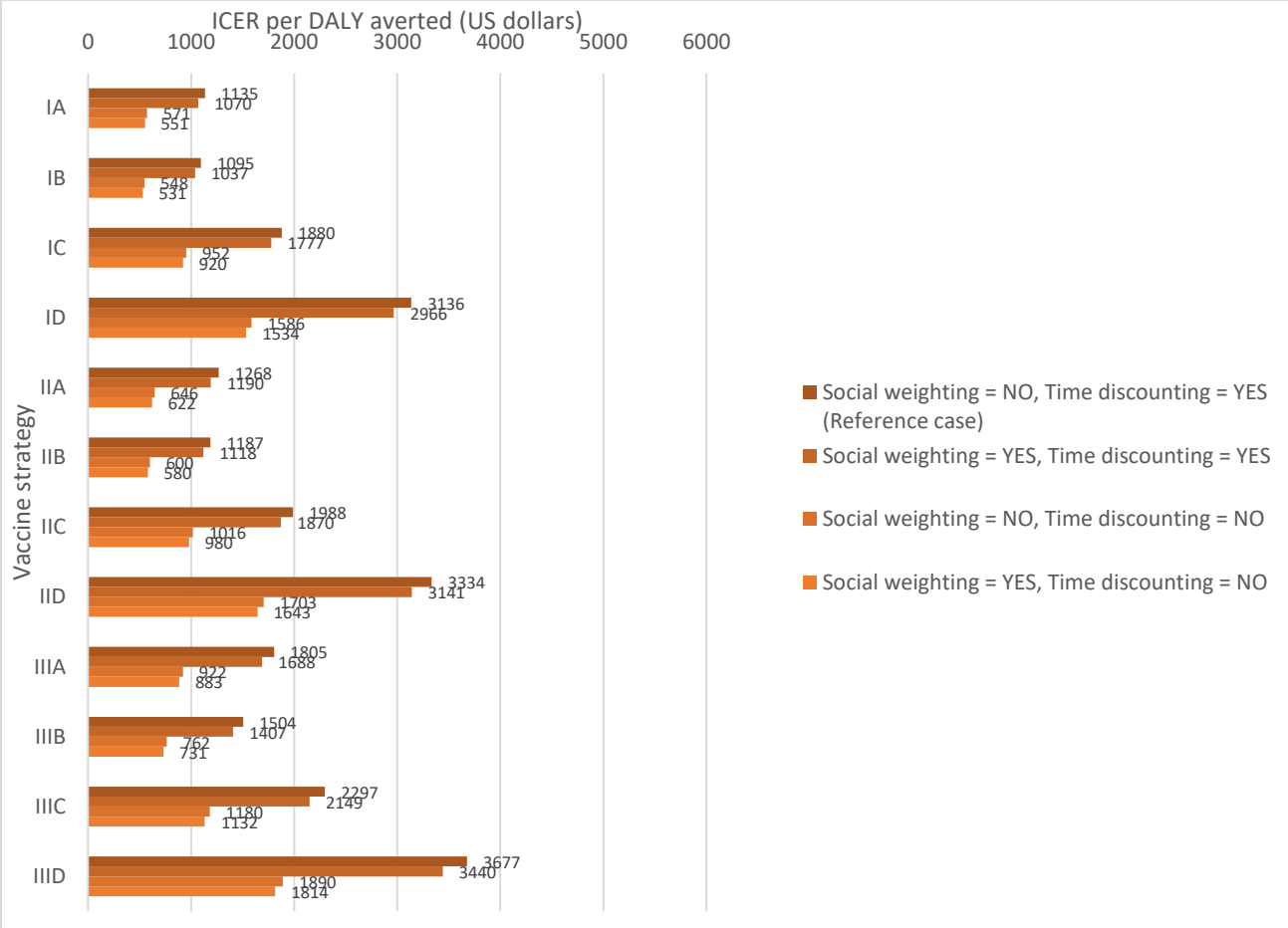
Figure 28: Mean annual ICER values per DALY averted per strategy with and without time discounting and social weighting. *Strategies are vaccinating children 6-23 months (strategy I), 2-5 years (strategy II) and 6-14 years (strategy III) with either the Southern Hemisphere influenza vaccine (Strategy A) or Northern Hemisphere vaccine (Strategy B) or both (Strategy C: twice yearly 3-month vaccination periods, or Strategy D: year-round vaccination).*

7.4.9.2.2 Changes in vaccine price

In the reference case we calculated the ICER per DALY averted with time discounting at 3% and no social weighting. During sensitivity analysis we varied the vaccine purchase price per dose to be $1.5, $4.5, $6.0 and $10.0. At a vaccine purchase price of $10.0 USD the mean ICER value increased by 144-178%, at $6.0 USD the mean ICER value increased by 38-43%, while at a vaccine purchase price of $4.5 USD the mean ICER value increased by 31-38%. At a vaccine

purchase price of $1.5 USD the mean ICER decreased by 44-62%.
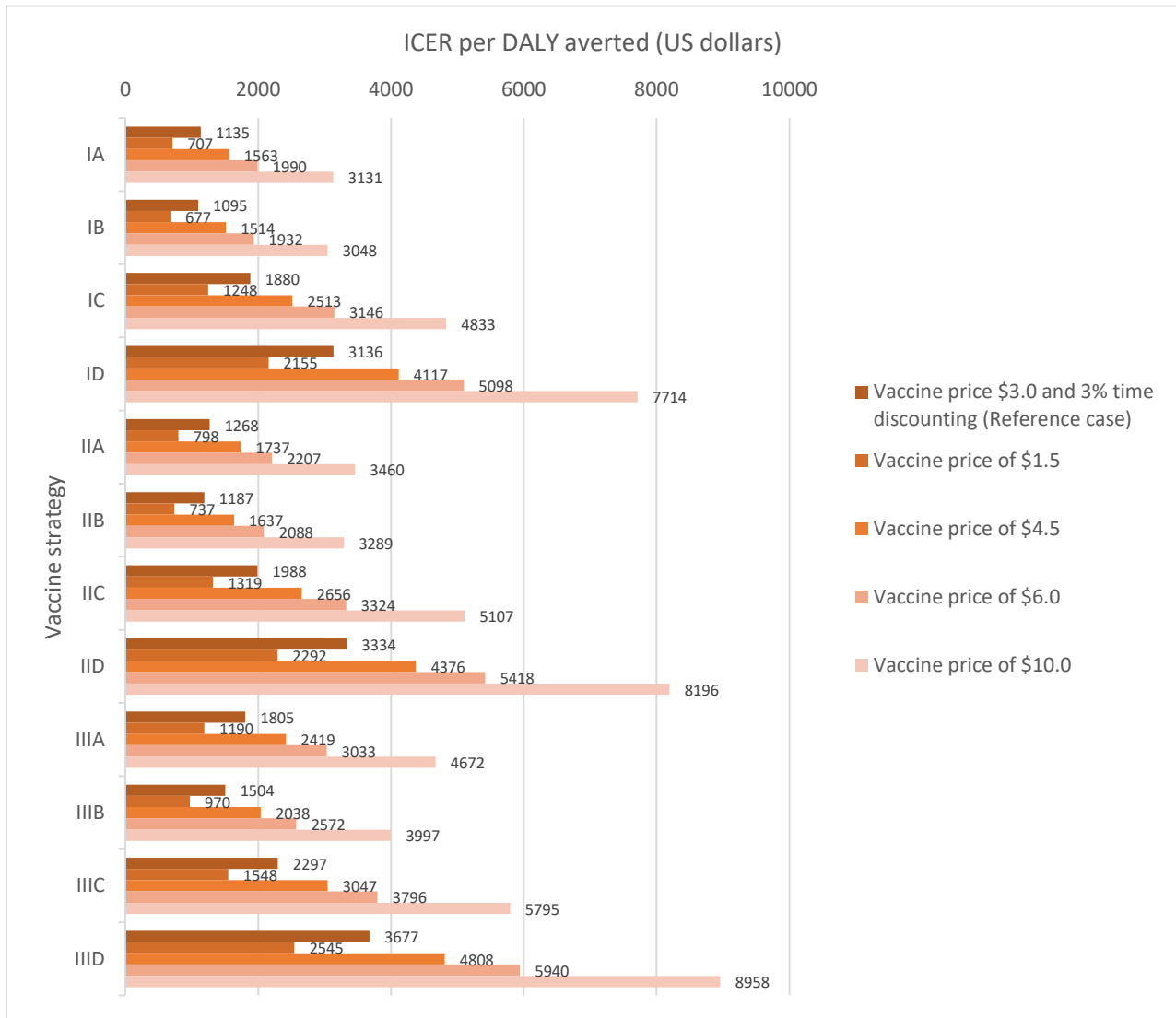
Figure 29: Mean annual ICER values per DALY averted per strategy at different vaccine prices. *Strategies are vaccinating children 6-23 months (strategy I), 2-5 years (strategy II) and 6-14 years (strategy III) with either the Southern Hemisphere influenza vaccine (Strategy A) or Northern Hemisphere vaccine (Strategy B) or both (Strategy C: twice yearly 3-month vaccination periods, or Strategy D: year-round vaccination).*

7.4.9.2.3 Changes in vaccine coverage

We assessed the impact of maintaining vaccination coverage across all age groups at the same level of coverage attained in strategy I that is 30% for once yearly vaccination, 45% for twice yearly vaccination and 60% for year-round vaccination. The mean ICER value decreased by 1-4% for II strategies and 7-20% for III.

7.4.9.3 Comparison between UK model and Kenya model

This section compares key inputs and outputs of the transmission model for the original paper [53, 140] fitted to UK surveillance data, and the adaption to Kenya.

Difference	United Kingdom	Kenya	Impact
Epidemic timing	Well defined annual peak of influenza activity in Northern Hemisphere season	No defined primary peak in influenza activity. Equal activity in Northern Hemisphere and Southern Hemisphere season. Significant year-round activity.	We identified several periods of high influenza activity in Kenya throughout the year using defined criteria and modelled each period separately. As a result, more than one period of high influenza activity of a particular influenza type/subtype was modelled in some years in Kenya. Because of significant year-round activity, the start and stop dates of each season were not easily ascertained and were selected based on the best fit of the model to the peak in activity. Dates of periods of high influenza activity may have started later than the true start date and ended earlier than the actual end date as these were not easily ascertainable.
Source of surveillance data	Influenza-like illness records from GP practices	Severe acute respiratory illness records from hospitalised patients	Ascertainment probability adjusted to reflect the probability of a hospitalised patient being detected. As a result, fitted model to surveillance data in Kenya has much lower numbers than that in the United Kingdom.
Age groups	0–4, 5–14, 15–44, 45–64, 65+ years	0-1, 1-5, 6-14, 15-19, 20-49, 50+ years	Kenya age groups were informed by the age groupings in the local social contact survey, the age-specific distribution of burden of illness, and the demographic pyramid in Kenya. Findings for the elderly age group are not as well defined in Kenya as compared to the United Kingdom because the ascertainment rate is much lower in this group.
Risk groups	Population stratified into high risk groups based on age and pre-existing conditions	No high-risk groups were included due to insufficient data on type and prevalence of influenza high-risk groups relevant in Kenya	Lack of stratification into high-risk groups in Kenya could lead to an underestimation of overall severe disease outcomes, which would be higher in high risk groups.

7.5 Appendix 5: Supplementary tables and figures (Objectives 2 and 3)

Table 40: Average number of influenza associated disease states and DALYs with their 95% credible interval limits, (2010-2018)

	Jan 10 - Aug 10			Sep 10 - Aug 11			Sep 11 - Aug 12			Sep 12 - Aug 13			Sep 13 - Aug 14			Sep 15 - Aug 16			Sep 17 - Aug 18		
	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit
Infections																					
<1	74,643	21,406	134,863	207,109	135,560	297,481	229,401	149,679	312,920	78,957	12,768	158,583	120,417	63,098	180,155	418,857	280,152	574,686	248,191	149,092	360,412
1-5	423,428	114,987	785,863	1,181,440	773,038	1,695,167	1,365,245	826,451	1,811,216	507,950	82,032	995,956	650,740	302,929	1,021,290	2,335,725	1,427,886	3,321,445	1,685,132	1,008,582	2,409,124
6-14	739,462	193,672	1,391,387	2,080,704	1,361,984	2,974,116	2,361,838	1,429,523	3,115,029	924,029	143,448	1,795,885	1,129,873	519,850	1,796,468	4,010,169	2,420,314	5,747,836	3,020,509	1,806,080	4,300,199
15-19	244,099	14,467	661,175	865,106	491,108	1,238,906	498,786	96,183	1,252,802	100,816	3,921	402,557	580,111	131,030	926,019	1,891,957	842,908	2,973,470	123,136	20,695	437,163
20-49	685,485	38,699	1,865,548	2,412,665	1,349,899	3,472,007	1,422,892	260,517	3,637,153	261,165	8,497	1,047,900	1,570,123	340,756	2,536,414	5,318,034	2,281,194	8,405,602	323,295	51,224	1,166,931
>50	273,712	40,845	656,590	475,213	120,915	903,776	783,073	233,802	1,493,800	78,349	2,821	333,703	197,920	5,103	590,682	1,030,767	276,693	1,948,084	295,220	60,097	713,444
All ages	2,440,827	619,950	4,644,883	7,222,237	4,904,833	9,649,051	6,661,234	4,226,348	9,717,858	1,951,266	314,303	4,144,596	4,249,183	2,461,103	5,905,593	15,005,510	11,115,652	19,843,767	5,695,483	3,408,170	8,393,809
Upper respiratory tract (URT) infections																					
<1	42,193	5,675	97,647	116,995	21,224	225,345	129,461	24,099	243,408	44,519	3,963	114,129	68,005	11,710	138,580	236,592	42,481	446,350	140,193	24,961	276,455
1-5	239,446	32,357	574,561	667,452	123,431	1,284,010	770,512	138,452	1,437,873	286,444	24,837	723,069	367,319	61,204	777,784	1,319,338	231,883	2,564,879	951,925	170,204	1,868,445
6-14	417,989	55,092	1,006,756	1,175,846	218,331	2,265,507	1,333,351	240,349	2,490,985	520,948	44,645	1,320,392	637,693	105,100	1,353,509	2,265,271	397,665	4,440,310	1,706,352	310,386	3,337,456
15-19	138,260	5,111	466,311	488,364	88,119	948,667	281,070	26,137	864,076	56,227	1,537	246,114	328,389	37,502	716,270	1,068,183	182,814	2,290,691	69,619	5,908	264,381
20-49	388,372	13,730	1,332,028	1,362,043	246,833	2,639,308	801,539	74,027	2,469,208	145,617	3,195	630,229	889,027	101,292	1,951,591	3,001,275	505,783	6,386,126	182,841	14,504	692,471
>50	154,795	12,200	444,853	268,689	32,304	654,831	441,872	58,515	1,054,019	44,085	1,093	206,059	112,270	2,029	404,795	581,197	72,361	1,419,479	166,890	16,944	482,991
All ages	1,381,054	169,169	3,355,404	4,079,389	749,032	7,583,366	3,757,806	667,812	7,414,902	1,097,841	98,256	2,898,220	2,402,703	431,109	4,670,022	8,471,857	1,568,317	15,575,788	3,217,819	572,062	6,365,855
Lower respiratory tract (LRT) infections																					
<1	18,281	1,124	52,129	50,618	3,995	121,747	56,175	4,450	135,045	19,385	946	60,825	29,393	2,250	73,971	102,432	8,437	245,672	60,698	4,893	150,678
1-5	103,657	6,119	297,871	288,806	23,023	697,524	334,485	26,459	797,027	124,572	6,086	388,228	158,927	12,036	411,768	571,246	47,232	1,397,658	411,810	33,108	1,018,673
6-14	180,981	10,696	520,379	508,360	39,976	1,229,738	578,472	45,275	1,385,194	226,519	10,730	698,528	276,017	20,365	712,663	980,748	80,236	2,404,881	738,300	58,988	1,821,331
15-19	60,066	1,239	233,713	211,182	17,173	514,462	122,129	5,420	424,578	25,033	440	119,369	141,531	8,280	376,928	463,013	34,340	1,205,676	30,294	1,396	130,608
20-49	168,785	3,368	662,928	589,051	48,039	1,430,184	348,529	15,498	1,233,225	64,847	916	315,837	382,991	22,356	1,026,638	1,300,654	96,792	3,378,775	79,482	3,478	344,573
>50	67,064	2,840	227,342	116,378	6,831	339,754	190,749	12,267	533,892	19,240	304	96,656	48,387	558	198,186	251,609	15,520	729,113	72,222	3,537	243,151
All ages	598,834	33,942	1,752,717	1,764,396	140,567	4,214,897	1,630,539	124,438	3,941,250	479,595	23,270	1,548,826	1,037,246	80,644	2,519,428	3,669,702	296,751	8,618,752	1,392,805	113,537	3,478,509
Deaths																					
<1	121	3	468	333	11	1,217	369	12	1,321	127	3	527	195	6	731	673	22	2,438	400	12	1,467
1-5	342	8	1,433	963	27	3,508	1,108	31	4,136	417	8	1,768	536	15	2,024	1,879	56	7,026	1,361	39	5,128
6-14	98	1	424	265	3	1,106	303	4	1,290	117	1	560	147	2	637	515	6	2,242	388	5	1,640
15-19	61	-	253	220	1	796	133	-	473	28	-	113	152	1	559	492	2	1,775	30	-	127
20-49	172	2	843	611	18	2,233	358	7	1,605	66	-	366	398	10	1,544	1,340	39	4,777	81	1	412

	Jan 10 - Aug 10			Sep 10 - Aug 11			Sep 11 - Aug 12			Sep 12 - Aug 13			Sep 13 - Aug 14			Sep 15 - Aug 16			Sep 17 - Aug 18		
	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit
>50	695	13	3,089	1,208	30	4,823	1,996	51	8,059	196	1	1,122	509	3	2,685	2,623	64	10,355	746	15	3,292
All ages	627	23	2,145	1,763	81	5,335	1,829	86	5,652	570	17	2,146	1,007	47	3,114	3,626	174	10,848	1,771	78	5,448
Years lived with disability																					
<1	18	2	57	49	8	138	54	9	152	19	1	64	29	4	81	99	16	278	59	9	170
1-5	101	11	323	280	44	781	324	51	903	121	9	412	154	22	460	554	87	1,577	399	63	1,139
6-14	171	16	568	479	63	1,380	545	71	1,553	214	14	734	260	31	803	927	118	2,683	696	90	2,024
15-19	57	2	250	199	25	563	115	8	449	23	-	113	133	12	412	436	53	1,329	28	2	125
20-49	161	5	706	557	73	1,566	331	23	1,294	60	1	295	363	33	1,128	1,229	156	3,697	75	5	331
>50	64	4	240	111	10	359	182	19	579	18	-	91	46	1	200	239	24	770	69	5	247
All ages	571	54	1,943	1,674	238	4,651	1,551	211	4,465	455	33	1,593	985	135	2,791	3,484	506	9,821	1,327	186	3,889
Years of life lost																					
<1	3,417	89	13,227	9,467	291	34,621	10,544	337	37,738	3,632	75	15,084	5,604	170	20,967	19,393	622	70,260	11,509	349	42,175
1-5	9,756	234	40,896	27,612	784	100,640	31,930	906	119,200	12,036	222	51,039	15,476	426	58,501	54,534	1,613	203,924	39,436	1,123	148,619
6-14	2,698	27	11,621	7,298	88	30,484	8,402	104	35,755	3,250	29	15,549	4,077	45	17,707	14,386	176	62,612	10,812	136	45,692
15-19	1,613	3	6,721	5,873	29	21,265	3,563	12	12,709	763	1	3,053	4,085	16	15,066	13,332	60	48,123	822	2	3,440
20-49	4,019	40	19,674	14,398	428	52,642	8,524	163	38,183	1,568	11	8,728	9,509	232	36,899	32,271	924	115,060	1,950	34	9,900
>50	6,689	126	29,715	11,789	291	47,089	19,557	501	78,953	1,931	14	11,030	5,001	29	26,400	25,886	636	102,176	7,346	153	32,420
All ages	28,191	3,999	82,117	76,437	18,718	189,166	82,519	18,968	207,460	23,180	2,148	75,297	43,753	9,535	111,093	159,803	40,533	387,705	71,876	13,691	199,993
Total DALYs																					
<1	3,434	101	13,233	9,516	334	34,715	10,598	381	37,773	3,651	86	15,113	5,633	196	21,003	19,492	707	70,332	11,568	397	42,222
1-5	9,857	319	41,039	27,892	1,077	100,917	32,254	1,275	119,703	12,157	305	51,189	15,630	569	58,624	55,089	2,133	204,929	39,836	1,531	148,974
6-14	2,869	110	11,759	7,777	406	31,166	8,947	477	36,222	3,464	102	16,037	4,337	210	18,085	15,313	801	63,646	11,508	597	46,764
15-19	1,669	13	6,800	6,072	160	21,431	3,678	53	12,888	786	4	3,137	4,219	76	15,260	13,768	335	48,424	851	12	3,480
20-49	4,179	76	19,912	14,955	896	53,093	8,855	332	38,627	1,628	18	9,039	9,872	472	37,229	33,500	1,947	116,507	2,025	66	10,086
>50	6,753	161	29,879	11,900	386	47,331	19,739	626	79,397	1,949	17	11,041	5,047	36	26,560	26,125	822	102,421	7,415	193	32,501
All ages	28,761	4,225	82,732	78,111	20,197	191,351	84,071	20,109	209,921	23,634	2,270	75,899	44,738	10,370	111,884	163,287	43,628	392,914	73,203	14,878	202,528

171

Table 41: Average number of influenza associated health care utilization events with their 95% credible interval limits, (2010-2018)

	Jan 10 - Aug 10			Sep 10 - Aug 11			Sep 11 - Aug 12			Sep 12 - Aug 13			Sep 13 - Aug 14			Sep 15 - Aug 16			Sep 17 - Aug 18		
	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit
Outpatient clinic visits																					
<1	23,510	2,742	61,513	65,331	10,182	147,120	72,299	11,582	161,653	24,934	1,963	71,626	37,965	5,623	88,887	131,981	21,372	292,431	78,270	11,716	177,235
1-5	133,022	15,902	350,385	373,454	64,811	851,994	431,256	71,945	955,335	161,246	12,975	459,785	205,166	30,572	495,628	737,543	123,627	1,688,695	531,772	89,684	1,214,457
6-14	67,049	3,246	213,769	189,333	11,012	510,603	214,865	12,522	579,080	84,647	2,970	286,407	103,059	5,796	300,331	364,722	21,738	995,857	274,930	16,434	755,439
15-19	16,586	293	71,906	59,106	2,874	169,505	34,005	1,049	132,917	6,964	84	35,546	39,869	1,518	126,141	129,291	5,682	389,905	8,379	224	37,412
20-49	29,542	393	132,772	102,849	4,656	300,839	60,339	1,790	232,765	11,109	114	56,706	66,503	2,226	208,638	226,433	9,297	697,833	13,804	353	63,670
>50	10,288	295	38,477	17,954	750	59,247	29,484	1,294	94,520	2,969	34	16,221	7,446	74	32,760	38,829	1,585	123,812	11,147	398	40,728
All ages	279,997	59,028	643,138	808,026	297,634	1,554,900	842,249	300,886	1,623,528	291,869	34,936	755,927	460,009	157,187	915,603	1,628,800	623,483	3,116,436	918,302	295,069	1,886,881
Hospitalizations																					
<1	504	99	1,196	1,394	458	2,726	1,547	509	3,017	534	67	1,392	812	247	1,659	2,823	946	5,488	1,672	536	3,342
1-5	2,860	543	6,859	7,975	2,698	15,547	9,218	3,060	17,820	3,445	420	8,819	4,396	1,239	9,305	15,772	5,187	31,260	11,380	3,724	22,629
6-14	367	24	1,127	1,034	89	2,615	1,175	100	3,009	457	23	1,456	560	46	1,537	1,989	168	5,144	1,502	129	3,960
15-19	132	3	541	464	29	1,261	267	10	1,005	54	1	263	311	15	919	1,018	63	2,876	66	2	280
20-49	1,052	41	3,710	3,695	915	7,848	2,182	249	6,859	402	10	1,798	2,410	345	5,668	8,152	1,790	18,228	492	50	1,929
>50	679	49	2,178	1,174	127	3,284	1,934	225	5,297	193	4	931	493	8	1,998	2,552	265	7,175	730	63	2,329
All ages	5,593	1,221	12,174	15,737	6,813	27,707	16,323	6,934	28,661	5,085	709	12,574	8,982	3,557	16,381	32,306	14,400	55,364	15,842	6,003	29,735

*No values included for 2014-2015 and 2016-2017 when no influenza activity was modelled

172

Table 42: Average annual rate per 100,000 of influenza associated disease states with their 95% credible interval limits, (2010-2018)

	Jan 10 - Aug 10			Sep 10 - Aug 11			Sep 11 - Aug 12			Sep 12 - Aug 13			Sep 13 - Aug 14			Sep 15 - Aug 16			Sep 17 - Aug 18		
	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit
Infections																					
<1	6,084	1,745	10,993	16,438	10,759	23,611	17,729	11,568	24,183	5,942	961	11,934	8,823	4,623	13,200	29,155	19,500	40,002	16,427	9,868	23,855
1-5	8,744	2,375	16,228	23,756	15,544	34,085	26,730	16,181	35,461	9,684	1,564	18,987	12,080	5,623	18,958	41,188	25,179	58,570	28,256	16,912	40,396
6-14	7,419	1,943	13,960	20,328	13,306	29,056	22,467	13,599	29,632	8,559	1,329	16,635	10,190	4,689	16,202	34,358	20,737	49,246	24,608	14,714	35,034
15-19	5,401	320	14,628	18,637	10,580	26,689	10,463	2,018	26,279	2,059	80	8,222	11,537	2,606	18,417	35,744	15,925	56,177	2,212	372	7,854
20-49	4,516	255	12,291	15,477	8,660	22,273	8,888	1,627	22,719	1,588	52	6,374	9,299	2,018	15,021	29,919	12,834	47,290	1,730	274	6,243
>50	7,047	1,052	16,905	11,914	3,031	22,658	19,115	5,707	36,465	1,862	67	7,932	4,581	118	13,671	22,663	6,083	42,831	6,172	1,256	14,915
All ages	6,161	1,565	11,724	17,750	12,055	23,715	15,941	10,114	23,256	4,547	732	9,658	9,641	5,584	13,399	32,343	23,959	42,771	11,673	6,985	17,203
Upper respiratory tract (URT) infections																					
<1	3,439	463	7,959	9,286	1,685	17,886	10,005	1,862	18,811	3,350	298	8,588	4,983	858	10,154	16,468	2,957	31,069	9,279	1,652	18,298
1-5	4,945	668	11,865	13,421	2,482	25,818	15,086	2,711	28,152	5,461	473	13,785	6,818	1,136	14,438	23,265	4,089	45,229	15,962	2,854	31,330
6-14	4,194	553	10,101	11,487	2,133	22,133	12,684	2,286	23,696	4,825	414	12,230	5,751	948	12,207	19,408	3,407	38,044	13,902	2,529	27,190
15-19	3,059	113	10,317	10,521	1,898	20,437	5,896	548	18,125	1,148	31	5,027	6,531	746	14,245	20,181	3,454	43,277	1,251	106	4,750
20-49	2,559	90	8,776	8,738	1,583	16,931	5,007	462	15,424	886	19	3,833	5,265	600	11,558	16,885	2,846	35,928	978	78	3,704
>50	3,985	314	11,454	6,736	810	16,417	10,786	1,428	25,730	1,048	26	4,898	2,598	47	9,369	12,778	1,591	31,209	3,489	354	10,098
All ages	3,486	427	8,469	10,026	1,841	18,638	8,993	1,598	17,745	2,558	229	6,753	5,452	978	10,596	18,260	3,380	33,572	6,595	1,172	13,047
Lower respiratory tract (LRT) infections																					
<1	1,490	92	4,249	4,018	317	9,663	4,341	344	10,437	1,459	71	4,577	2,154	165	5,420	7,130	587	17,100	4,017	324	9,973
1-5	2,141	126	6,151	5,807	463	14,025	6,549	518	15,605	2,375	116	7,401	2,950	223	7,644	10,073	833	24,646	6,905	555	17,081
6-14	1,816	107	5,221	4,966	391	12,014	5,503	431	13,177	2,098	99	6,470	2,489	184	6,428	8,403	687	20,604	6,015	481	14,838
15-19	1,329	27	5,171	4,549	370	11,083	2,562	114	8,906	511	9	2,438	2,815	165	7,496	8,748	649	22,778	544	25	2,346
20-49	1,112	22	4,368	3,779	308	9,175	2,177	97	7,703	394	6	1,921	2,268	132	6,080	7,317	545	19,009	425	19	1,843
>50	1,727	73	5,853	2,918	171	8,518	4,656	299	13,033	457	7	2,297	1,120	13	4,587	5,532	341	16,030	1,510	74	5,083
All ages	1,512	86	4,424	4,336	345	10,359	3,902	298	9,432	1,118	54	3,609	2,353	183	5,716	7,910	640	18,577	2,855	233	7,129
Deaths																					
<1	10	0	38	26	1	97	29	1	102	10	0	40	14	0	54	47	2	170	26	1	97
1-5	7	0	30	19	1	71	22	1	81	8	0	34	10	0	38	33	1	124	23	1	86
6-14	1	0	4	3	0	11	3	0	12	1	0	5	1	0	6	4	0	19	3	0	13
15-19	1	0	6	5	0	17	3	0	10	1	0	2	3	0	11	9	0	34	1	0	2
20-49	1	0	6	4	0	14	2	0	10	0	0	2	2	0	9	8	0	27	0	0	2
>50	18	0	80	30	1	121	49	1	197	5	0	27	12	0	62	58	1	228	16	0	69
All ages	2	0	5	4	0	13	4	0	14	1	0	5	2	0	7	8	0	23	4	0	11

	Jan 10 - Aug 10			Sep 10 - Aug 11			Sep 11 - Aug 12			Sep 12 - Aug 13			Sep 13 - Aug 14			Sep 15 - Aug 16			Sep 17 - Aug 18		
	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit
Outpatient clinic visits																					
<1	1,916	224	5,014	5,185	808	11,677	5,587	895	12,493	1,876	148	5,390	2,782	412	6,513	9,187	1,488	20,355	5,181	775	11,731
1-5	2,747	328	7,236	7,509	1,303	17,131	8,443	1,409	18,704	3,074	247	8,765	3,808	568	9,200	13,006	2,180	29,778	8,917	1,504	20,364
6-14	673	33	2,145	1,850	108	4,988	2,044	119	5,509	784	28	2,653	929	52	2,709	3,125	186	8,532	2,240	134	6,155
15-19	367	6	1,591	1,273	62	3,652	713	22	2,788	142	2	726	793	30	2,509	2,443	107	7,366	151	4	672
20-49	195	3	875	660	30	1,930	377	11	1,454	68	1	345	394	13	1,236	1,274	52	3,926	74	2	341
>50	265	8	991	450	19	1,485	720	32	2,307	71	1	386	172	2	758	854	35	2,722	233	8	851
All ages	707	149	1,623	1,986	732	3,822	2,016	720	3,885	680	81	1,761	1,044	357	2,077	3,511	1,344	6,717	1,882	605	3,867
Hospitalizations																					
<1	41	8	97	111	36	216	120	39	233	40	5	105	59	18	122	196	66	382	111	35	221
1-5	59	11	142	160	54	313	180	60	349	66	8	168	82	23	173	278	91	551	191	62	379
6-14	4	0	11	10	1	26	11	1	29	4	0	13	5	0	14	17	1	44	12	1	32
15-19	3	0	12	10	1	27	6	0	21	1	0	5	6	0	18	19	1	54	1	0	5
20-49	7	0	24	24	6	50	14	2	43	2	0	11	14	2	34	46	10	103	3	0	10
>50	17	1	56	29	3	82	47	5	129	5	0	22	11	0	46	56	6	158	15	1	49
All ages	14	3	31	39	17	68	39	17	69	12	2	29	20	8	37	70	31	119	32	12	61

*No values included for 2014-2015 and 2016-2017 when no influenza activity was modelled

* Rates per 100,000 population

174

Table 43a: National cost of influenza associated illness across all ages, 2010-2018

	Jan 10 - Aug 10			Sep 10 - Aug 11			Sep 11 - Aug 12			Sep 12 - Aug 13		
	Mean	**Lower limit**	**Upper limit**	**Mean**	**Lower limit**	**Upper limit**	**Mean**	**Lower limit**	**Upper limit**	**Mean**	**Lower limit**	**Upper limit**
Outpatient clinic costs all ages	1,478,621	249,056	3,813,241	4,264,212	1,136,749	9,397,189	4,450,524	1,163,875	9,858,220	1,547,485	156,113	4,514,938
Hospitalization costs all ages	520,075	25,839	1,679,925	1,470,924	89,586	4,180,903	1,522,246	90,425	4,323,426	473,433	17,211	1,682,379
Direct medical costs	**1,998,696**	**375,651**	**4,908,769**	**5,735,135**	**1,795,524**	**11,940,351**	**5,972,770**	**1,873,966**	**12,319,761**	**2,020,917**	**229,180**	**5,645,813**
	0.74			**0.74**			**0.75**			**0.77**		
Outpatient transport costs all ages	293,339	10,285	1,062,152	849,033	34,893	2,752,093	882,489	36,424	2,834,710	306,095	7,531	1,193,197
Hospitalization transport costs all ages	59,452	2,172	203,328	167,712	7,409	511,222	173,874	7,761	536,686	54,457	1,566	208,870
Over the counter medication costs	204,274	6,286	726,774	588,708	22,967	1,894,876	615,169	22,077	2,010,823	213,073	4,987	847,261
Health care related costs	**557,065**	**72,102**	**1,620,808**	**1,605,453**	**312,113**	**4,104,216**	**1,671,532**	**322,304**	**4,341,211**	**573,625**	**47,100**	**1,876,997**
OPC lost wages	4,737,695	165,193	16,817,576	13,742,259	569,024	43,850,686	14,289,449	596,917	45,541,719	4,979,650	127,445	19,598,325
Hospitalized lost wages	311,701	15,403	1,011,996	877,481	57,361	2,485,068	908,797	57,023	2,550,714	283,939	10,767	1,012,823
OPC child care costs	29,312	768	109,100	84,372	2,809	277,377	88,108	2,941	294,426	30,372	639	121,992
Hospitalized child care costs	1,257	35	4,586	3,540	122	11,403	3,659	125	11,933	1,135	27	4,467
Indirect costs	**5,079,966**	**355,499**	**17,366,814**	**14,707,652**	**1,326,176**	**45,208,537**	**15,290,012**	**1,386,556**	**46,514,482**	**5,295,096**	**260,667**	**20,214,241**
Total costs	**7,635,727**	**1,222,454**	**22,102,684**	**22,048,240**	**5,544,645**	**56,718,719**	**22,934,314**	**5,538,666**	**58,483,936**	**7,889,639**	**750,048**	**25,729,887**

2018 dollar rate used

No values included for 2014-2015 and 2016-2017 when no influenza activity was modelled

Table 43b: National cost of influenza associated illness across all ages, 2013-2018

	Sep 12 - Aug 13			Sep 13 - Aug 14			Sep 15 - Aug 16			Sep 17 - Aug 18		
	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit
Outpatient clinic costs all ages	1,547,485	156,113	4,514,938	2,428,176	631,664	5,534,670	8,599,068	2,349,461	18,890,793	4,847,612	1,142,078	11,499,044
Hospitalization costs all ages	473,433	17,211	1,682,379	840,833	50,501	2,446,038	3,018,979	187,563	8,514,517	1,480,046	84,137	4,310,139
Direct medical costs	**2,020,917**	**229,180**	**5,645,813**	**3,269,009**	**979,595**	**7,032,997**	**11,618,047**	**3,815,095**	**23,771,095**	**6,327,659**	**1,825,103**	**13,968,634**
	0.77			0.74			0.74			0.77		
Outpatient transport costs all ages	306,095	7,531	1,193,197	482,470	20,310	1,591,137	1,709,864	74,300	5,566,385	961,795	37,371	3,195,582
Hospitalization transport costs all ages	54,457	1,566	208,870	95,686	4,171	298,675	344,357	15,856	1,025,954	168,591	7,505	525,838
Over the counter medication costs	213,073	4,987	847,261	335,679	12,919	1,113,849	1,189,527	45,375	3,791,514	671,935	23,966	2,271,612
Health care related costs	**573,625**	**47,100**	**1,876,997**	**913,836**	**170,462**	**2,416,848**	**3,243,747**	**652,900**	**8,398,692**	**1,802,321**	**319,756**	**4,969,587**
OPC lost wages	4,979,650	127,445	19,598,325	7,797,892	309,153	25,274,834	27,666,365	1,160,924	87,257,407	15,585,428	614,683	51,375,114
Hospitalized lost wages	283,939	10,767	1,012,823	501,365	31,141	1,452,505	1,802,371	117,570	5,036,558	884,104	53,163	2,592,811
OPC child care costs	30,372	639	121,992	48,091	1,578	158,645	170,278	5,617	563,584	96,097	3,074	334,012
Hospitalized child care costs	1,135	27	4,467	2,015	66	6,627	7,252	250	22,967	3,546	122	11,723
Indirect costs	**5,295,096**	**260,667**	**20,214,241**	**8,349,362**	**733,526**	**26,107,753**	**29,646,266**	**2,707,708**	**89,577,508**	**16,569,176**	**1,350,961**	**52,728,596**
Total costs	**7,889,639**	**750,048**	**25,729,887**	**12,532,207**	**2,945,009**	**32,633,498**	**44,508,060**	**11,421,335**	**112,760,453**	**24,699,155**	**5,685,880**	**66,924,013**

*2018 dollar rate used

*No values included for 2014-2015 and 2016-2017 when no influenza activity was modelled

Table 44: Average annual costs and 95% credible intervals (CIs) per vaccination strategy in millions of USD

Strategy	I				II				III			
Jan 10 - Sep 10	A	B	C	D	A	B	C	D	A	B	C	D
Vaccine costs	4.28 (3.16-5.72)	4.28 (3.16-5.72)	6.42 (4.74-8.58)	8.56 (6.32-11.44)	9.92 (7.33-13.25)	9.92 (7.33-13.25)	14.17 (10.47-18.93)	18.42 (13.61-24.61)	25.25 (18.66-33.74)	25.25 (18.66-33.74)	34.72 (25.66-46.4)	44.19 (32.66-59.05)
Direct medical costs	5.8 (3.85-8.61)	6.28 (4.1-9.46)	8.05 (5.6-11.32)	10.18 (7.27-13.93)	10.9 (7.95-14.65)	11.92 (8.56-16.21)	15.37 (11.3-20.52)	19.65 (14.52-26.16)	25.56 (18.92-34.14)	27.25 (20.19-36.15)	35.18 (26.07-47.02)	44.77 (33.19-59.81)
Health care related costs	0.81 (0.18-1.84)	0.94 (0.23-2.13)	1.03 (0.23-2.26)	1.22 (0.26-2.68)	1.16 (0.19-2.68)	1.44 (0.33-3.11)	1.6 (0.26-3.71)	1.99 (0.29-4.71)	2.33 (0.17-5.96)	2.81 (0.46-6.53)	3.22 (0.24-8.2)	4.1 (0.32-10.44)
Indirect costs	3.86 (0.22-13.8)	5.08 (0.36-17.37)	4.15 (0.25-14.56)	4.12 (0.25-14.49)	2.48 (0.12-9.58)	5.08 (0.36-17.37)	3.05 (0.16-11.36)	3.13 (0.17-11.46)	0.76 (0.04-3.27)	5.08 (0.36-17.37)	1.13 (0.06-4.99)	1.44 (0.08-5.85)
Total costs	10.47 (4.99-22.4)	12.3 (5.58-26.8)	13.22 (7.12-26.02)	15.52 (9.08-28.28)	14.53 (9.47-23.82)	18.44 (10.87-33.1)	20.02 (13.42-31.01)	24.77 (17.12-36.28)	28.65 (21.06-38.28)	35.14 (24.28-51.56)	39.53 (29.07-52.79)	50.31 (37.05-66.96)
Sep 10 - Aug 11												
Vaccine costs	4.39 (3.25-5.87)	4.39 (3.25-5.87)	6.59 (4.87-8.81)	8.79 (6.49-11.74)	10.18 (7.53-13.61)	10.18 (7.53-13.61)	14.55 (10.75-19.44)	18.91 (13.98-25.27)	25.94 (19.17-34.66)	25.94 (19.17-34.66)	35.66 (26.35-47.65)	45.39 (33.54-60.65)
Direct medical costs	9.83 (5.83-15.76)	9.74 (5.77-15.6)	11.8 (7.66-17.69)	14.09 (9.51-20.34)	15.25 (10.53-21.42)	15.05 (10.41-21.12)	19.12 (13.78-25.74)	23.72 (17.34-31.63)	30.06 (22.32-39.65)	30.13 (22.4-39.77)	38.81 (29.05-51.23)	49.02 (36.7-64.66)
Health care related costs	1.91 (0.57-4.34)	1.89 (0.56-4.3)	2.05 (0.62-4.47)	2.27 (0.68-4.83)	2.33 (0.7-4.87)	2.27 (0.67-4.76)	2.57 (0.72-5.3)	3.03 (0.8-6.32)	3.47 (0.81-7.44)	3.48 (0.74-9.34)	4.05 (0.74-9.34)	5.06 (0.89-11.76)
Indirect costs	13.95 (1.25-42.9)	13.69 (1.24-42.29)	13.36 (1.2-41.19)	13.6 (1.23-41.98)	13.02 (1.18-40.12)	12.43 (1.12-38.54)	11.69 (1.05-36.31)	12.3 (1.1-38.16)	10.59 (0.95-33.3)	10.66 (0.96-33.18)	7.99 (0.73-24.86)	9.24 (0.84-28.91)
Total costs	25.7 (9.89-58.27)	25.32 (9.79-57.84)	27.2 (11.9-58.74)	29.96 (14.23-62.08)	30.6 (15.28-61.51)	29.75 (15.14-59.51)	33.38 (18.94-61.44)	39.04 (23.2-68.8)	44.11 (28.7-70.93)	44.27 (28.78-70.65)	50.86 (35.6-72.91)	63.32 (44.63-89.53)
Sep 11 - Aug 12												
Vaccine costs	4.51 (3.34-6.03)	4.51 (3.34-6.03)	6.77 (5-9.05)	9.03 (6.67-12.06)	10.46 (7.73-13.98)	10.46 (7.73-13.98)	14.94 (11.04-19.97)	19.42 (14.35-25.96)	26.64 (19.68-35.59)	26.64 (19.68-35.59)	36.62 (27.06-48.94)	46.61 (34.45-62.28)
Direct medical costs	10.49 (6.11-17.04)	10.25 (6.02-16.57)	12.57 (7.99-19.2)	14.87 (9.9-21.74)	16.43 (11.12-23.58)	15.85 (10.79-22.54)	20.49 (14.45-28.1)	25.1 (18.07-33.85)	32.61 (23.92-43.48)	31.06 (22.94-41.21)	41.48 (30.82-54.9)	51.81 (38.56-68.53)
Health care related costs	2.07 (0.59-4.75)	2.01 (0.58-4.6)	2.23 (0.66-4.88)	2.44 (0.72-5.2)	2.6 (0.77-5.46)	2.44 (0.71-5.13)	2.89 (0.81-5.98)	3.32 (0.9-6.91)	4.05 (1.03-8.51)	3.61 (0.83-7.79)	4.62 (0.98-10.17)	5.61 (1.12-12.57)
Indirect costs	15.29 (1.39-46.51)	14.7 (1.32-45.01)	14.84 (1.34-45.34)	14.97 (1.35-45.64)	15.29 (1.39-46.51)	13.8 (1.23-42.44)	14.21 (1.27-43.49)	14.53 (1.3-44.58)	15.29 (1.39-46.51)	11.28 (0.98-34.83)	12.39 (1.09-38.36)	13.26 (1.17-40.69)
Total costs	27.85 (10.44-63.18)	26.96 (10.19-61.17)	29.64 (12.57-64.32)	32.28 (14.84-67.11)	34.33 (16.4-69.85)	32.08 (15.76-64.48)	37.58 (20.31-70.94)	42.95 (24.54-77.14)	51.94 (31.52-88.39)	45.96 (29.32-74.06)	58.5 (38.79-89.58)	70.68 (48.1-104.96)
Sep 12 - Aug 13												
Vaccine costs	4.64 (3.43-6.19)	4.64 (3.43-6.19)	6.95 (5.14-9.29)	9.27 (6.85-12.39)	10.74 (7.94-14.35)	10.74 (7.94-14.35)	15.35 (11.34-20.5)	19.95 (14.74-26.66)	27.36 (20.21-36.55)	27.36 (20.21-36.55)	37.61 (27.79-50.26)	47.87 (35.38-63.97)
Direct medical costs	6.15 (4.03-9.48)	6.66 (4.25-10.52)	8.58 (5.91-12.47)	10.93 (7.71-15.32)	11.66 (8.52-15.72)	12.76 (9.05-17.75)	16.49 (12.11-22.06)	21.21 (15.64-28.32)	27.63 (20.48-36.88)	29.38 (21.73-39.08)	37.99 (28.18-50.71)	48.44 (35.93-64.62)
Health care related costs	0.84 (0.16-2.04)	0.99 (0.2-2.41)	1.08 (0.19-2.51)	1.3 (0.22-2.95)	1.22 (0.17-2.87)	1.53 (0.29-3.44)	1.69 (0.23-4)	2.14 (0.28-5.12)	2.52 (0.18-6.44)	3.01 (0.44-7.11)	3.46 (0.26-8.87)	4.43 (0.34-11.33)
Indirect costs	3.97 (0.15-16.14)	5.3 (0.26-20.21)	4.27 (0.17-17.13)	4.36 (0.17-17.54)	2.42 (0.08-10.51)	5.3 (0.26-20.21)	3.02 (0.1-12.8)	3.32 (0.12-13.91)	0.71 (0.04-2.75)	5.3 (0.26-20.21)	0.99 (0.05-3.92)	1.48 (0.06-6.07)

Total costs	10.96 (5.05-25.92)	12.94 (5.51-30.84)	13.93 (7.26-29.65)	16.59 (9.34-32.58)	15.3 (9.94-25.72)	19.59 (11.17-37.81)	21.21 (14.09-34.17)	26.68 (18.09-41.05)	30.86 (22.82-40.92)	37.68 (25.53-57.45)	42.45 (31.39-56.29)	54.35 (40.13-72.27)
Sep 13 - Aug 14												
Vaccine costs	4.76 (3.52-6.36)	4.76 (3.52-6.36)	7.14 (5.28-9.54)	9.52 (7.04-12.72)	11.03 (8.15-14.74)	11.03 (8.15-14.74)	15.76 (11.65-21.06)	20.49 (15.14-27.38)	28.09 (20.76-37.54)	28.09 (20.76-37.54)	38.63 (28.55-51.62)	49.16 (36.33-65.69)
Direct medical costs	8.03 (5.27-12)	7.49 (5.03-11.02)	10 (7-14.01)	12.37 (8.91-16.88)	14.3 (10.3-19.46)	13.06 (9.6-17.48)	18.11 (13.44-24.01)	22.86 (17.02-30.25)	31.36 (23.36-41.45)	28.8 (21.41-38.34)	39.7 (29.55-52.85)	50.42 (37.51-67.17)
Health care related costs	1.34 (0.4-2.93)	1.19 (0.35-2.58)	1.44 (0.4-3.03)	1.65 (0.44-3.47)	1.9 (0.51-3.97)	1.55 (0.36-3.32)	2.06 (0.46-4.5)	2.49 (0.5-5.55)	3.42 (0.71-7.61)	2.7 (0.27-6.77)	3.74 (0.4-9.39)	4.73 (0.49-11.89)
Indirect costs	8.35 (0.73-26.11)	6.97 (0.6-21.88)	7.3 (0.63-22.81)	7.29 (0.63-22.77)	8.35 (0.73-26.11)	5.18 (0.41-16.39)	6 (0.51-18.87)	6.06 (0.51-19.11)	8.35 (0.73-26.11)	1.78 (0.12-6.61)	2.71 (0.18-9.75)	3.18 (0.23-10.76)
Total costs	17.72 (7.9-37.94)	15.64 (7.3-32.6)	18.74 (9.82-36.49)	21.31 (12.07-39.21)	24.55 (14-44.98)	19.79 (12.29-33.19)	26.16 (17.02-41.7)	31.41 (21.16-47.5)	43.13 (29.18-64.84)	33.28 (24.47-44.45)	46.15 (33.91-61.7)	58.33 (43.01-77.66)
Sep 15 - Aug 16												
Vaccine costs	5.01 (3.7-6.7)	5.01 (3.7-6.7)	7.52 (5.55-10.04)	10.02 (7.41-13.39)	11.61 (8.58-15.52)	11.61 (8.58-15.52)	16.59 (12.26-22.17)	21.57 (15.94-28.82)	29.57 (21.85-39.52)	29.57 (21.85-39.52)	40.66 (30.05-54.34)	51.75 (38.24-69.15)
Direct medical costs	16.2 (8.46-28.03)	16.24 (8.48-28.2)	18.51 (10.68-30.24)	21.1 (12.96-33.16)	22.13 (14.11-33.82)	22.3 (14.15-34.01)	26.74 (18.08-38.59)	31.94 (22.31-44.81)	37.95 (27.57-51.47)	38.95 (28.15-52.68)	48.27 (35.74-64.42)	60 (44.7-79.39)
Health care related costs	3.57 (1-8.57)	3.58 (1-8.6)	3.74 (1.11-8.69)	3.99 (1.21-9.05)	3.97 (1.22-8.87)	4.02 (1.23-8.92)	4.31 (1.3-9.2)	4.82 (1.45-10.01)	4.97 (1.36-10.34)	5.25 (1.47-10.76)	5.74 (1.4-12.26)	6.91 (1.62-14.97)
Indirect costs	28.53 (2.62-86.29)	28.65 (2.62-86.81)	28.06 (2.56-84.99)	28.28 (2.59-85.62)	26.81 (2.45-81.47)	27.29 (2.51-82.78)	25.89 (2.37-78.36)	26.46 (2.41-80.04)	21.26 (1.92-66.59)	23.86 (2.2-73.57)	19.26 (1.74-60.19)	20.92 (1.91-64.8)
Total costs	48.3 (16.51-113.91)	48.47 (16.56-114.58)	50.31 (18.88-114.99)	53.37 (21.44-118.68)	52.91 (22.38-115.21)	53.61 (22.69-116.66)	56.94 (27.06-117.17)	63.21 (32.38-124.8)	64.18 (37.24-116.25)	68.06 (38.78-124.43)	73.27 (46.12-121.35)	87.82 (57.09-139.53)
Sep 17 - Aug 18												
Vaccine costs	5.27 (3.89-7.04)	5.27 (3.89-7.04)	7.9 (5.84-10.56)	10.54 (7.79-14.08)	12.21 (9.02-16.32)	12.21 (9.02-16.32)	17.45 (12.89-23.31)	22.68 (16.76-30.31)	31.1 (22.98-41.56)	31.1 (22.98-41.56)	42.76 (31.6-57.14)	54.43 (40.22-72.73)
Direct medical costs	11.16 (6.57-18.5)	10.76 (6.42-17.72)	13.24 (8.59-20.2)	15.93 (10.72-23.3)	17.41 (11.98-24.95)	16.76 (11.7-23.65)	21.5 (15.53-29.14)	26.96 (19.72-36.23)	34.91 (25.9-46.32)	34.74 (25.79-46.12)	44.37 (33.11-58.88)	56.57 (42.23-75.05)
Health care related costs	2.15 (0.59-5.12)	2.03 (0.56-4.84)	2.23 (0.63-5.06)	2.48 (0.7-5.41)	2.57 (0.71-5.52)	2.39 (0.65-5.04)	2.71 (0.68-5.75)	3.24 (0.77-6.99)	3.86 (0.8-8.61)	3.81 (0.77-8.49)	4.27 (0.56-10.46)	5.46 (0.72-13.37)
Indirect costs	15.42 (1.26-49.59)	14.38 (1.17-46.16)	13.99 (1.14-45.15)	14.13 (1.15-45.69)	13.6 (1.1-44.16)	11.93 (0.96-38.81)	10.64 (0.83-34.63)	11.22 (0.88-36.63)	9.95 (0.8-32.48)	9.54 (0.75-31.24)	4.19 (0.33-13.94)	5.59 (0.43-18.6)
Total costs	28.72 (10.86-68.26)	27.17 (10.44-64.33)	29.46 (12.91-65.93)	32.54 (15.56-69.14)	33.57 (17-68.92)	31.08 (16.29-61.99)	34.85 (20.51-63.09)	41.42 (25.5-71.71)	48.72 (32.39-75.87)	48.1 (31.97-74.92)	52.83 (38.48-70.92)	67.61 (49.24-90.92)

NB: Vaccine costs include the costs of administration and purchase. Direct medical costs are inclusive of vaccine costs. Total costs are made up of direct medical costs, healthcare related costs and indirect costs. 2018 US dollar value is used

Table 45a: Incremental cost-effectiveness ratio for influenza vaccination using total societal costs – Strategy IA-D

	Strategy IA			Strategy IB			Strategy IC			Strategy ID		
	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit
Cost per DALY averted												
Jan '10 - Aug '10	749	-77	2,892	NA	NA	NA	1,792	272	6,092	2,452	436	8,078
Sep '10 - Aug '11	1,385	159	4,677	1,235	92	4,367	1,176	150	3,765	2,175	444	6,672
Sep '11 - Aug '12	NA	NA	NA	1,877	392	5,746	4,106	983	11,978	7,933	1,959	22,841
Sep '12 - Aug '13	1,097	-109	5,040	NA	NA	NA	2,498	304	9,802	3,838	584	14,288
Sep '13 - Aug '14	NA	NA	NA	751	-95	2,821	1,862	280	6,128	2,563	458	8,312
Sep '14 - Aug '15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '15 - Aug '16	1,118	75	4,159	1,172	103	4,089	1,051	116	3,472	1,843	362	5,743
Sep '16 - Aug '17	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '17 - Aug '18	1,324	132	4,795	442	-332	1,926	678	-145	2,529	1,147	81	3,901
Cost per death averted												
Jan '10 - Aug '10	78,522	-3,877	482,538	NA	NA	NA	181,194	10,235	1,094,192	248,760	16,285	1,463,761
Sep '10 - Aug '11	139,277	5,791	914,809	101,231	3,243	614,143	114,484	5,126	687,322	205,944	15,731	1,231,924
Sep '11 - Aug '12	NA	NA	NA	175,448	13,754	1,118,249	365,794	34,472	2,308,005	659,900	67,425	4,194,630
Sep '12 - Aug '13	95,415	-4,619	606,825	NA	NA	NA	211,357	10,325	1,337,137	322,332	20,141	1,976,850
Sep '13 - Aug '14	NA	NA	NA	74,516	-4,109	480,577	180,505	10,345	1,127,105	250,426	16,643	1,564,636
Sep '14 - Aug '15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '15 - Aug '16	111,500	2,526	693,114	123,108	3,810	769,601	114,676	4,297	641,321	194,331	12,923	1,109,445
Sep '16 - Aug '17	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '17 - Aug '18	112,804	4,585	659,876	42,865	-17,015	269,761	65,544	-6,265	375,294	108,161	3,227	597,074
Cost per hospitalization averted												
Jan '10 - Aug '10	2,997	-372	10,052	0	0	0	7,145	1,625	20,451	9,765	2,696	27,320
Sep '10 - Aug '11	5,605	870	15,974	4,025	461	10,735	4,350	742	10,836	8,015	2,661	18,677
Sep '11 - Aug '12	0	0	0	7,301	2,441	17,753	15,944	6,609	36,892	30,776	13,417	70,031
Sep '12 - Aug '13	3,880	-424	16,499	0	0	0	8,763	1,713	31,573	13,432	3,491	45,157
Sep '13 - Aug '14	0	0	0	2,886	-374	9,260	7,119	1,564	19,748	9,789	2,682	26,371
Sep '14 - Aug '15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '15 - Aug '16	4,302	381	14,362	4,614	526	12,983	4,063	607	10,732	7,096	2,123	17,616
Sep '16 - Aug '17	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

	Strategy IA			Strategy IB			Strategy IC			Strategy ID		
	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit
Sep '17 - Aug '18	4,313	630	11,339	1,542	-1,156	5,500	2,323	-563	6,875	3,930	470	10,426
Cost per case averted												
Jan '10 - Aug '10	6	-1	17	NA	NA	NA	15	5	36	21	9	48
Sep '10 - Aug '11	11	2	26	10	2	19	10	2	19	19	9	32
Sep '11 - Aug '12	NA	NA	NA	19	9	33	42	25	69	82	51	132
Sep '12 - Aug '13	9	-2	35	NA	NA	NA	21	6	67	33	12	98
Sep '13 - Aug '14	NA	NA	NA	6	-1	15	15	5	31	20	8	43
Sep '14 - Aug '15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '15 - Aug '16	10	1	26	11	2	24	10	2	19	17	7	31
Sep '16 - Aug '17	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '17 - Aug '18	11	2	20	4	-4	10	6	-2	12	10	2	18

NA refers to years where no influenza activity was modelled or periods where once-yearly vaccination was mistimed to influenza activity and was therefore found to be ineffective

Table 45b: Incremental cost-effectiveness ratio for influenza vaccination using total societal costs – Strategy IIA-D

	Strategy IIA			Strategy IIB			Strategy IIC			Strategy IID		
	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit
Cost per DALY averted												
Jan '10 - Aug '10	945	-65	3,881	NA	NA	NA	2,006	261	7,281	2,844	451	10,159
Sep '10 - Aug '11	1,573	172	5,570	1,371	109	5,001	1,240	140	4,097	2,296	442	7,145
Sep '11 - Aug '12	NA	NA	NA	1,869	353	5,934	4,085	900	12,440	7,897	1,794	23,835
Sep '12 - Aug '13	1,488	-105	7,719	NA	NA	NA	2,881	280	12,894	4,503	578	18,864
Sep '13 - Aug '14	NA	NA	NA	825	-104	3,155	1,973	256	6,791	2,762	452	9,318
Sep '14 - Aug '15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '15 - Aug '16	1,115	8	4,388	1,308	82	4,765	1,067	69	3,627	1,867	307	5,985
Sep '16 - Aug '17	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '17 - Aug '18	1,217	49	4,589	563	-289	2,365	662	-193	2,547	1,169	76	4,101
Cost per death averted												
Jan '10 - Aug '10	103,378	-3,226	583,566	NA	NA	NA	218,152	9,970	1,235,056	307,512	17,075	1,739,649
Sep '10 - Aug '11	161,666	6,388	1,009,593	122,270	3,634	697,861	127,813	5,007	712,406	233,219	15,829	1,310,766
Sep '11 - Aug '12	NA	NA	NA	193,950	12,257	1,150,599	401,415	31,535	2,410,316	718,823	63,134	4,425,060
Sep '12 - Aug '13	140,382	-4,339	834,114	NA	NA	NA	264,058	9,483	1,575,288	404,293	19,430	2,425,551
Sep '13 - Aug '14	NA	NA	NA	85,417	-4,311	503,446	199,340	9,538	1,212,694	279,316	16,091	1,663,865
Sep '14 - Aug '15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '15 - Aug '16	122,162	124	689,506	133,360	2,862	816,559	120,749	2,615	641,463	206,339	11,084	1,113,654
Sep '16 - Aug '17	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '17 - Aug '18	108,297	1,841	644,378	57,764	-13,134	342,412	66,861	-8,202	367,384	118,925	2,902	619,601
Cost per hospitalization averted												
Jan '10 - Aug '10	3,696	-292	13,390	0	0	0	7,814	1,511	24,011	11,055	2,674	32,681
Sep '10 - Aug '11	5,958	901	17,189	4,334	525	11,776	4,361	717	11,139	8,025	2,606	18,966
Sep '11 - Aug '12	0	0	0	6,780	2,034	17,429	14,765	5,755	36,063	28,468	11,813	67,743
Sep '12 - Aug '13	5,207	-422	24,719	0	0	0	9,981	1,461	41,266	15,527	3,307	60,270
Sep '13 - Aug '14	0	0	0	3,052	-438	9,909	7,237	1,360	20,626	10,109	2,507	27,810
Sep '14 - Aug '15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '15 - Aug '16	4,039	32	14,637	4,682	406	13,656	3,823	310	10,697	6,669	1,718	17,461
Sep '16 - Aug '17	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

	Strategy IIA			Strategy IIB			Strategy IIC			Strategy IID		
	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit
Sep '17 - Aug '18	3,845	275	10,699	1,928	-1,019	6,652	2,207	-678	6,827	3,887	365	10,519
Cost per case averted												
Jan '10 - Aug '10	8	-1	24	NA	NA	NA	17	5	43	24	9	60
Sep '10 - Aug '11	12	3	28	11	2	21	10	2	19	19	8	32
Sep '11 - Aug '12	NA	NA	NA	17	8	32	38	22	67	74	46	127
Sep '12 - Aug '13	12	-1	55	NA	NA	NA	24	5	90	37	12	133
Sep '13 - Aug '14	NA	NA	NA	6	-1	16	15	4	33	21	8	45
Sep '14 - Aug '15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '15 - Aug '16	9	0	27	11	1	25	9	1	18	16	6	30
Sep '16 - Aug '17	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '17 - Aug '18	10	1	19	5	-3	12	5	-2	12	10	1	18

NA refers to years where no influenza activity was modelled or periods where once-yearly vaccination was mistimed to influenza activity and was therefore found to be ineffective

Table 45c: Incremental cost-effectiveness ratio for influenza vaccination using total societal costs – Strategy IIIA-D

	Strategy IIIA			Strategy IIIB			Strategy IIIC			Strategy IIID		
	Mean	**Lower limit**	**Upper limit**	**Mean**	**Lower limit**	**Upper limit**	**Mean**	**Lower limit**	**Upper limit**	**Mean**	**Lower limit**	**Upper limit**
Cost per DALY averted												
Jan '10 - Aug '10	1,748	139	7,271	NA	NA	NA	2,796	354	11,012	3,977	590	15,225
Sep '10 - Aug '11	1,578	183	5,403	2,223	318	7,910	1,348	179	4,268	2,357	479	7,187
Sep '11 - Aug '12	NA	NA	NA	1,668	324	5,163	3,533	835	10,565	6,770	1,707	19,794
Sep '12 - Aug '13	3,116	143	16,105	NA	NA	NA	4,727	382	23,303	6,813	695	32,636
Sep '13 - Aug '14	NA	NA	NA	1,005	39	3,478	1,907	281	6,449	2,789	502	9,093
Sep '14 - Aug '15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '15 - Aug '16	923	-101	3,895	1,320	88	4,573	886	-14	3,101	1,563	225	5,161
Sep '16 - Aug '17	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '17 - Aug '18	1,658	81	6,608	1,304	60	4,778	883	-78	3,282	1,467	158	4,982
Cost per death averted												
Jan '10 - Aug '10	201,810	6,139	1,136,347	NA	NA	NA	330,189	14,378	1,775,587	451,979	23,573	2,490,554
Sep '10 - Aug '11	193,280	7,502	1,141,183	223,695	11,279	1,215,613	162,149	6,768	869,667	277,140	17,754	1,465,302
Sep '11 - Aug '12	NA	NA	NA	206,916	12,164	1,156,194	427,907	31,384	2,416,353	792,817	63,045	4,552,467
Sep '12 - Aug '13	304,119	4,887	1,785,622	NA	NA	NA	462,446	13,029	2,734,590	671,626	24,185	4,003,129
Sep '13 - Aug '14	NA	NA	NA	121,656	1,535	647,328	223,509	10,641	1,184,483	325,936	18,854	1,754,530
Sep '14 - Aug '15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '15 - Aug '16	128,486	-4,469	662,949	172,129	3,695	950,590	125,373	-472	622,798	216,870	8,357	1,053,728
Sep '16 - Aug '17	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '17 - Aug '18	161,498	3,501	966,566	141,608	2,304	762,726	94,747	-3,291	524,681	158,554	6,243	823,369
Cost per hospitalization averted												
Jan '10 - Aug '10	6,935	807	25,846	NA	NA	NA	11,130	2,146	38,642	15,841	3,691	52,677
Sep '10 - Aug '11	6,593	1,086	19,400	7,276	1,776	19,104	5,163	985	12,944	8,962	2,863	21,143
Sep '11 - Aug '12	NA	NA	NA	6,828	2,028	17,452	14,450	5,603	35,150	27,678	11,656	65,820
Sep '12 - Aug '13	11,054	718	53,001	NA	NA	NA	16,750	2,082	76,713	24,129	3,901	105,651
Sep '13 - Aug '14	NA	NA	NA	3,878	195	11,240	7,381	1,611	20,592	10,790	3,011	28,939
Sep '14 - Aug '15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '15 - Aug '16	3,711	-410	14,815	5,440	439	16,788	3,559	-66	10,750	6,254	1,238	17,853
Sep '16 - Aug '17	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

	Strategy IIIA			Strategy IIIB			Strategy IIIC			Strategy IIID		
	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit	Mean	Lower limit	Upper limit
Sep '17 - Aug '18	5,369	411	16,785	4,540	308	13,109	3,020	-318	8,820	5,021	850	13,304
Cost per case averted												
Jan '10 - Aug '10	14	2	50	NA	NA	NA	23	6	74	33	10	102
Sep '10 - Aug '11	11	3	24	17	6	35	10	3	19	18	8	32
Sep '11 - Aug '12	NA	NA	NA	14	6	26	29	17	52	56	35	97
Sep '12 - Aug '13	25	2	114	NA	NA	NA	39	6	166	56	12	232
Sep '13 - Aug '14	NA	NA	NA	7	0	16	13	4	29	20	8	40
Sep '14 - Aug '15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '15 - Aug '16	7	-1	22	9	1	22	6	0	15	12	3	24
Sep '16 - Aug '17	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sep '17 - Aug '18	13	1	36	11	1	24	7	-1	16	12	3	23

NA refers to years where no influenza activity was modelled or periods where once-yearly vaccination was mistimed to influenza activity and was therefore found to be ineffective
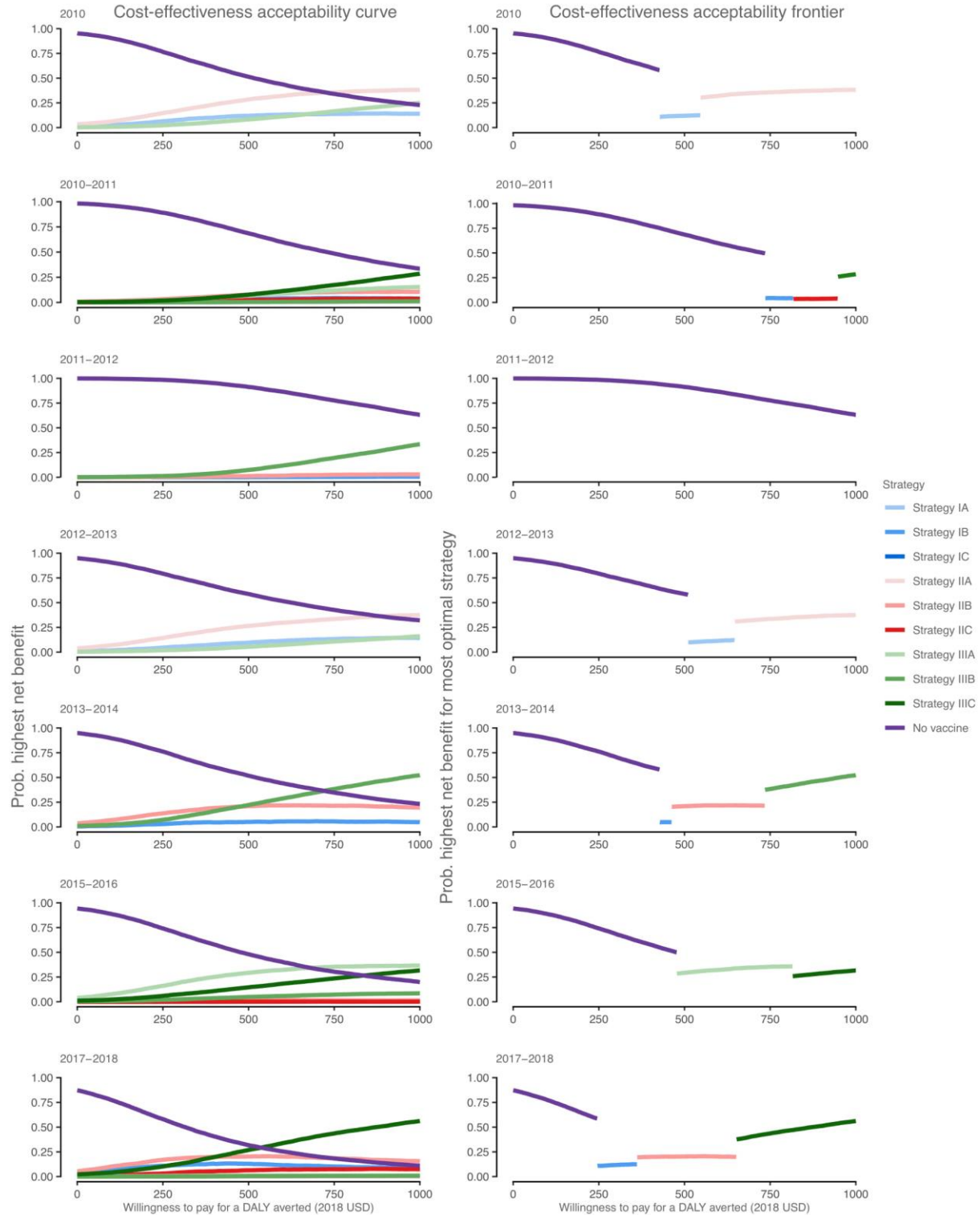
184

Figure 30: Yearly cost-effectiveness acceptability curves and frontiers for strategies with the highest incremental net monetary benefit considering total societal costs. *NB: X axis is limited to 1,000 USD per DALY averted. Strategies are vaccinating children 6-23 months (strategy I), 2-5 years (strategy II) and 6-14 years (strategy III) with either the SH influenza vaccine (Strategy A) or NH vaccine (Strategy B) or both (Strategy C: twice yearly 3-month vaccination periods, or Strategy D: year-round vaccination).*
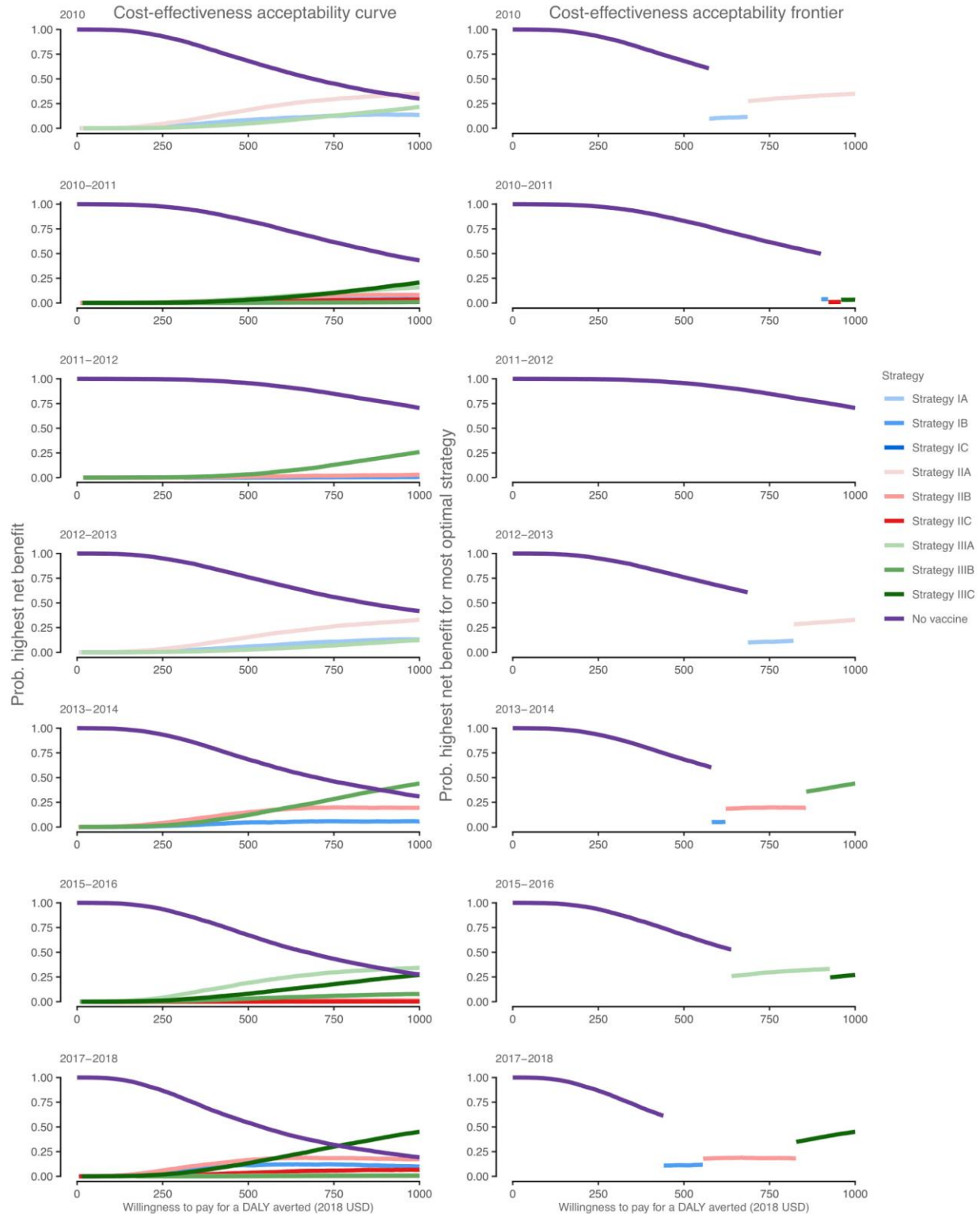
185

Figure 31: Yearly cost-effectiveness acceptability curves and frontiers for strategies with the highest incremental net monetary benefit considering direct medical costs only. *NB: X axis is limited to 1,000 USD per DALY averted. Strategies are vaccinating children 6-23 months (strategy I), 2-5 years (strategy II) and 6-14 years (strategy III) with either the SH influenza vaccine (Strategy A) or NH vaccine (Strategy B) or both (Strategy C: twice yearly 3-month vaccination periods, or Strategy D: year-round vaccination).*

186