Influenza Vaccination Implementation and Timing for Sri Lanka: A Cost-Effectiveness Analysis

by

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Thesis submitted in partial fulfillment of
the requirements for the degree of Master of Science
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ABSTRACT

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Abstract

Influenza causes an estimated 3 to 5 million cases of severe illness annually, along with substantial morbidity and mortality, particularly among low and middle-income countries (LMICs). The most effective way to decrease the burden of influenza is vaccination. Currently, Sri Lanka has no influenza vaccination policies and does not offer vaccination within the public healthcare sector. Therefore, a cost-effectiveness analysis of influenza vaccine implementation for the Sri Lankan population was performed.

A static Markov model that did not account for transmission dynamics was used for this study. The model followed a theoretical cohort of Sri Lankans from all ages through two potential scenarios: universal influenza vaccination and no influenza vaccination across twelve-monthly cycles. Cost-effectiveness was analyzed using a governmental perspective at the national level.

Costs for the study were broken down into three categories: direct, indirect, and vaccine costs. All costs were identified from previous literature for the local context. Vaccine efficacy was expressed as a range (48% to 72%) identified from a previous meta-analysis investigating similar settings. One model arm was considered cost-effective if the ICER was below a three-fold gross domestic product (GDP) per capita per DALY averted limit and highly cost-effective if below a one-fold GDP per capita per DALY averted limit. Utilizing TreeAge Pro software, we conducted both probabilistic sensitivity analyses and one-way sensitivity analyses for all model variables.

The vaccination model arm reduced all influenza outcomes by approximately 60% (170,283 episodes, 3,167 hospitalizations, and 152 deaths) compared to no vaccination. By implementing vaccination earlier in the year, this reduction in the influenza disease burden was maximized. Vaccination was considered cost-effective compared to no vaccination, with a base case incremental cost-effectiveness ratio (ICER) estimated at Rs. 968,071.45 /DALY (5,418.62 USD/DALY).

Sensitivity analysis identified that the ICER was sensitive to implementation month, monthly probability of contracting influenza, cost of vaccination, and years of life disabled. Due to only considering a one-year period, the implementation month had the most substantial effect on the ICER because no potential rollover effects of vaccination could be seen for the later implementation months. Probabilistic sensitivity analyses were performed on all variables, and there was a 99% probability that vaccination was cost-effective below a WTP threshold of 1,157,047.92 Rs/DALY (6,476.38 USD/DALY). No value for a variable within our estimated ranges resulted in ICERs above the WTP threshold of Rs. 2,066,157 (USD 11,556) per DALY averted.

In conclusion, vaccination was considered cost-effective when compared to the implementation of no vaccine. However, due to a lack of national data, large-scale national studies are needed to determine better the influenza disease burden, at-risk population, and implementation cost.

Contents

List of Tables

List of Figures

Acknowledgments

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1. Introduction

Seasonal influenza is an acute respiratory infectious disease that has been known to cause a substantial burden on public health systems globally.[1] Influenza viruses cause an estimated 3 to 5 million cases of severe illness annually,[2] along with substantial morbidity and mortality, particularly in low and middle-income countries (LMICs).[3] In 2017, an estimated 297,000 influenza cases and 6,000 hospitalizations were experienced within Sri Lanka alone.[4]

The most effective way to substantially decrease the annual burden from seasonal influenza epidemics is through equitable access to influenza vaccines.[2] Without readily available influenza vaccinations for all citizens, a country is missing a substantial disease prevention opportunity.[5] Influenza vaccines have been in use since 1936 and have since been integrated into numerous national immunization programs. As of 2016, seventy-four tropical and subtropical countries, representing 60% of the world's population, did not have national vaccination policies regarding seasonal influenza.[6] Sri Lanka currently does not routinely administer influenza vaccines in its public healthcare sector and does not include them in its National Immunization Programme (NIP).[6]

For a country to implement a national influenza vaccination policy, policymakers need to consider country-specific information. Factors to consider include seasonality and disease burden within the country. In temperate regions, influenza is a seasonal disease that typically occurs in the winter months; however, tropical areas have no clearly defined seasonal patterns and can experience year-round influenza circulation with multiple peaks.[7] Even with differing seasonality

in tropical and subtropical regions, vaccinations have proven to be a cost-effective solution for reducing the influenza burden in tropical and subtropical regions.[8,9]

For this study, we constructed a Markov model to determine the cost-effectiveness of influenza vaccinations for the Sri Lankan population from a governmental perspective. Through this work, we hope to provide Sri Lankan policymakers with valuable information on vaccine implementation and timing for any future decisions on including influenza vaccines in the Sri Lankan NIP.

2. Methods

2.1 Model setting

Sri Lanka is a middle-income, tropical country that experiences year-round influenza cases[10] with two peak circulation periods, occurring roughly between April to June and November to February.[11 - 13] Sri Lanka is made up of 21.9 million people,[14] of whom approximately 89.2% are under the age of 65.[15] As for healthcare, Sri Lanka offers publicly financed public healthcare that is free to all citizens.[16] The public healthcare sector makes up approximately 50% of outpatient services, 90% of inpatient admissions, and nearly all preventive services.[16]

2.1.1 Influenza surveillance

Founded in 2005, the influenza surveillance program within Sri Lanka tracks influenza in humans and animals with the mission of serving as an early warning system for potential pandemic influenza situations.[17] Human influenza surveillance in Sri Lanka consists of influenza-like illness (ILI) and severe acute respiratory infection (SARI) surveillance. There are currently twenty sentinel sites for ILI surveillance and three ILI sentinel sites for SARI surveillance.[17] Most sentinel sites are found in tertiary hospitals throughout the country, focusing on highly populated areas with few secondary hospital locations. Figure 1 shows the location of influenza surveillance sentinel sites in relation to the population of each province. Sri Lanka is made up of 9 provinces, with the Western province having the highest population primarily

because of Colombo, the capital city.[18] In Figure 1, clustering of sentinel sites on the left-hand side of the map can be found in Colombo due to its high population.

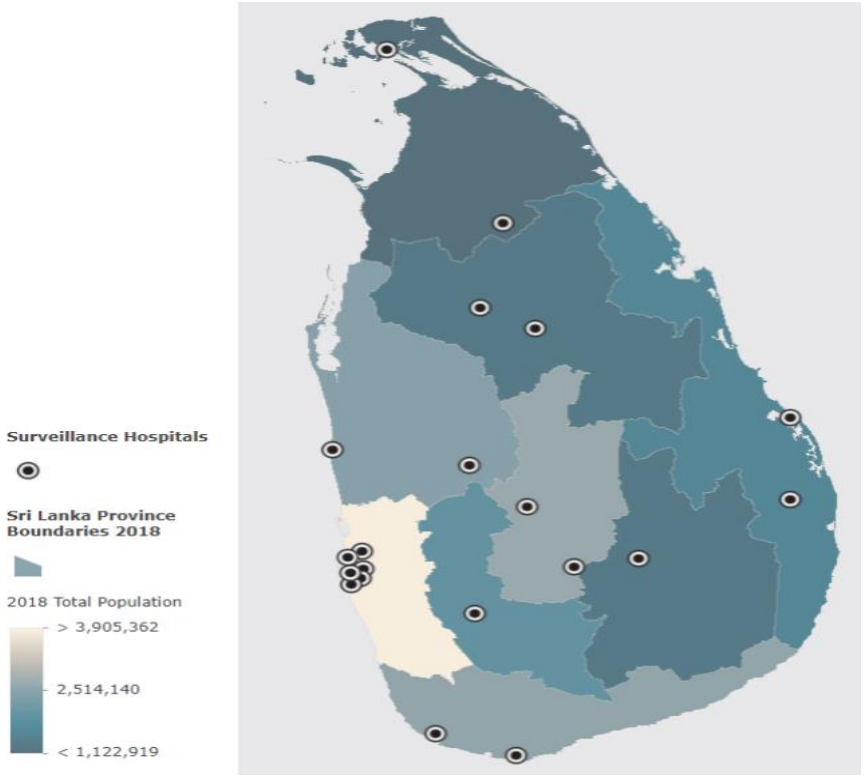

Figure 1. Map of Sri Lanka influenza sentinel sites in relation to population density

2.2 Model design and structure

A static Markov model (Figure 2) that did not account for transmission dynamics was used for this study. The model followed a theoretical cohort of Sri Lankans from all ages through two potential scenarios: universal influenza vaccination and no influenza vaccination across twelve-monthly cycles.

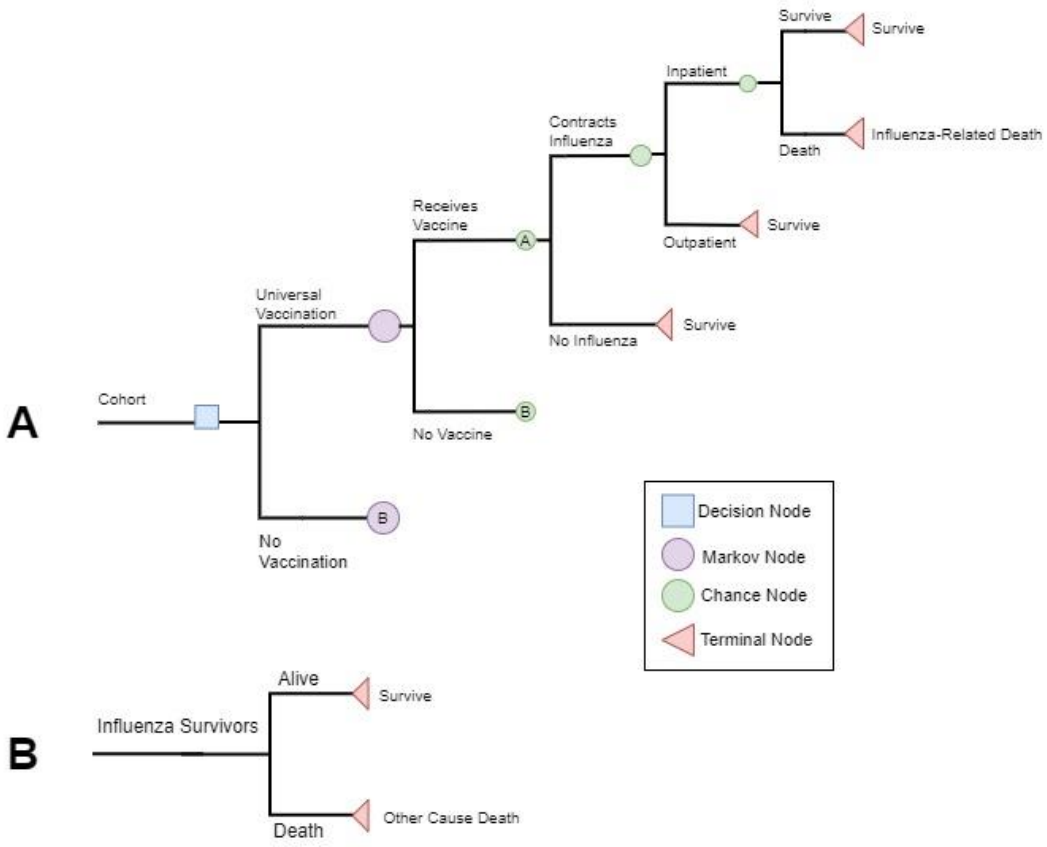

Figure 2. A: Overview of model structure; B: Influenza survivor event pathways. In Figure 2A, nodes labeled B follow along the same decision pathway as that of node A.

All participants entered the model alive. They would receive an influenza vaccine based on model arm and vaccine coverage rates. The participants would then contract influenza or not based on defined influenza incidence rates. Those that did not contract influenza remained alive for the current cycle and were pushed to the next cycle. Because the influenza data used for the model only included those that sought medical care, potential asymptomatic influenza cases were not considered within those that contracted influenza in this model. If participants were not hospitalized, they were automatically considered to receive care in the outpatient setting. Once participants received inpatient or outpatient care, they would survive the infection or pass away.

Because we worked under the assumption that participants could only contract influenza once in the model, all influenza survivors were placed in their own branch within each model arm (Figure 2B), where they either died from other causes or remained alive. All survivors who were alive at the end of each cycle were forced to move on to the next monthly transition until they either died or the twelve-month cycle concluded. TreeAge Pro software (version 2021; TreeAge, Inc, Williamstown, MA); was used to develop the model and conduct all analyses.

2.3 Model parameters

2.3.1 Influenza incidence

A three-step process was used to calculate influenza incidence estimates. We first obtained existing ILI and SARI surveillance data from 2012 to 2016.[19 - 24] The years of 2012 to 2016 were chosen due to data availability and completion. We calculated the monthly influenza-associated SARI estimates, influenza-associated ILI estimates, and influenza burden percentages using the national surveillance data. The method used to calculate influenza-associated SARI and ILI estimates came from the guidelines provided in *A Manual for Estimating Disease Burden Associated with Seasonal Influenza*.[25] Data on surveillance location catchment populations and age-specific estimates were not readily available, so these factors were excluded from estimates. After viewing these estimates and consulting previous influenza estimates in related literature, it was decided to use only the calculated monthly influenza burden percentages. Calculated monthly influenza burden percentages were then multiplied by Sri Lankan annual influenza episode estimates[4] to calculate each month's influenza burden.

To calculate inpatient monthly influenza estimates, we followed the same process as previously discussed for monthly influenza burden; however, we only used national SARI surveillance data to calculate inpatient monthly influenza burden percentages. We multiplied these percentages by annual influenza hospitalization estimates[4] to obtain monthly influenza hospitalization estimates. Because our model did not consider individuals who did not seek care, influenza-associated outpatient estimates were calculated by subtracting monthly hospitalizations from monthly episode estimates. All calculated influenza estimates can be found in Table 1.

For those who received a vaccine within the vaccinated model arm, the influenza infection rate was calculated with the following formula: $R(t)_{Vaccination} = R(t)_{No\ Vaccination} * (1 - VE)$, where $R(t)_{No\ Vaccination}$ is the rate of influenza infection in unvaccinated populations and VE is the vaccine effectiveness.

Table 1. Input data for monthly influenza model parameters

Parameter	Base Case	Range	Distribution Type
Episodes			**Beta**
January	34,161	23,830 - 46,647	
February	28,966	20,014 - 39,931	
March	16,399	11,186 - 22,985	
April	9,015	5,948 - 13,083	
May	18,621	12,604 - 26,225	
June	36,877	25,743 - 50,300	
July	34,705	24,167 - 47,420	
August	16,856	11,381 - 23,814	
September	17,425	11,804 - 24,543	
October	13,815	9,254 - 19,698	
November	33,804	23,679 - 45,990	

December	25,651	17,7559 - 35,336	
Hospitalizations			**Beta**
January	297	91 - 889	
February	416	136 - 1,169	
March	364	119 - 1,033	
April	529	181 - 1,419	
May	478	160 - 1,311	
June	290	86 - 884	
July	592	209 - 1,524	
August	557	192 - 1,482	
September	437	141 - 1,227	
October	516	175 - 1,394	
November	546	191 - 1,437	
December	306	93 - 918	

2.3.2 Mortality

We used a previously published annual influenza-related mortality estimate (1.2 per 100,000), with a range of 07 to 2.2 per 100,000.[4] We calculated the annual influenza-related mortality by multiplying the estimate by the average population per 100,000 from 2012 to 2016 (207.92).[26] To obtain the monthly influenza-related mortality estimates from the annual estimate, we multiplied the annual influenza-related by the monthly percentage of influenza-related hospitalizations for each month that we had previously calculated. We assumed that influenza-related mortality trends would closely follow influenza-related hospitalization trends due to the limited available data regarding influenza-related mortality in Sri Lanka.

Mortality from other causes was calculated by dividing the annual death rate per 100,000 (645.90)[27] by twelve to obtain the monthly death rate per 100,000. We multiplied the monthly

death rate per 100,000 (53.83) by the average population per 100,000 from 2012 to 2016 (207.92)[26] to estimate the number of monthly deaths in the Sri Lankan population. Finally, the monthly other cause mortality estimates were obtained by subtracting the monthly influenza mortality estimates (Table 2) from the estimated total monthly deaths (11,191.40). All mortality estimates used for the model can be found in Table 2.

Table 2. Input data for monthly mortality model parameters

Parameter	Base Case	Range	Distribution Type
Influenza-Related Mortality			**Beta**
January	14	8 – 28	
February	20	12 – 37	
March	18	10 – 33	
April	25	15 – 45	
May	23	14 – 41	
June	14	8 – 28	
July	28	18 – 48	
August	27	16 – 47	
September	21	12 – 39	
October	25	15 – 44	
November	26	16 – 45	
December	15	8 – 29	
Other Cause Mortality			**Beta**
January	11,178	11,164 - 11,184	
February	11,172	11,155 - 11,181	
March	11,175	11,160 - 11,182	
April	11,167	11,148 - 11,177	
May	11,169	11,151 - 11,179	
June	11,178	11,164 - 11,185	
July	11,164	11,145 - 11,175	

August	11,166	11,146 - 11,176
September	11,171	11,154 - 11,180
October	11,168	11,148 - 11,178
November	11,166	11,147 - 11,176
December	11,178	11,163 - 11,184

2.3.3 Vaccine coverage and effectiveness

All vaccine model parameters can be found in Table 3. Vaccine coverage rates were assumed based on existing vaccination coverage rates within the Sri Lankan NIP. The program currently experiences very high coverage rates for all vaccines, including a 99% vaccination rate for childhood vaccines and a 100% vaccination rate for the newly added HPV vaccine.[28] In addition to this, we also considered vaccination rates from other countries to get a more reasonable estimation. Based on these factors, we chose a base case of 80% with a uniform distribution range of 60 to 100%.

Estimates for vaccine effectiveness were derived from a meta-analysis investigating vaccine effectiveness (VE) in similar tropical settings across a wide range of ages, risk categories, and outcomes. The pooled VE estimate range for overall laboratory-confirmed influenza for the trivalent inactivated vaccine (TIV)[6] (48 - 72%) within the model. This range was chosen over that of the live attenuated influenza vaccine (LAIV) or combined ranges due to TIV being more commonly used in LMICs over LAIV.[29] Using a Beta distribution, we found the mean to be 60%, with a range of 48% to 72%

Table 3. Input data for vaccine model parameters

Vaccine Parameters	Base Case	Range	Distribution Type	Mean (SD)	Source

Vaccine Effectiveness	0.60	0.48 - 0.72	Beta	0.60 (0.0612)	6
Vaccine Coverage	0.80	0.60 - 1.00	Uniform		Assumption

2.3.4 Cost parameters

Cost data were found from prior literature and local corporations. All costs were adjusted to 2019 values using annual inflation rates[30] and then exchanged to United States dollars (USD) using the average 2019 exchange rate for USD to Rs. (Rs. 178.6566/1 USD).[31] Summarized cost parameters for the model can be found in Table 4.

The model's direct medical cost included any cost directly related to the patient seeking care, such as medical visit/stay cost, commonly prescribed prescriptions, and transportation. All prescriptions were identified from previous research[32 – 34] and verified by medical professionals with prior experience in Sri Lanka. Prescription costs were based upon standard dosages. The Sri Lankan mean birth weight (2.854 kg)[35] was used to obtain minimum prescription dosages and costs.

When looking at the cost for inpatients with influenza, we estimated a base cost of Rs. 13,168.75 (USD 73.71), including transportation (Rs. 111.10, USD 0.62),[36] medical stay cost (Rs. 11,827.35, USD 66.20), and a prescription for oseltamivir (Rs 1,230.30, USD 6.89). Medical stay costs were calculated using the hospital cost per day for primary (Rs. 2,298.10, USD 12.86), secondary (Rs. 2,998.09, USD 16.78), and tertiary (Rs. 4,095.05, USD 22.92) hospitals,[37] and an average hospital stay length of 3.66 days.[38] The prescription cost for oseltamivir was calculated by multiplying the wholesale cost per pill of oseltamivir 75 mg

capsule (Rs. 220.88, USD 1.24)[39] and the average pill count for a standard prescription using child and adult dosage recommendations (5.57 pills).[40]

The estimated base cost for outpatients with influenza was calculated as Rs. 470.60 (USD 2.63), including transportation (Rs. 111.10, USD 0.62),[36] medical visit cost (Rs. 322.42, USD 1.80),[37] and the following prescriptions: amoxicillin (Rs. 25.76, USD 0.14),[39] paracetamol (Rs. 9.89, USD 0.06),[39] and chlorpheniramine (Rs. 1.43, USD 0.01).[39] Previous studies conducted in Southern Sri Lanka identified that the average influenza patient treated in the outpatient setting receives a mean of three prescriptions, with the above prescriptions being the most commonly administered.[32] All outpatient prescriptions were calculated based on a three-day prescription due to Sri Lankan doctors only being allowed to prescribe three-day prescription dosages within the outpatient setting.

In addition to direct costs, we also considered the indirect costs one might acquire if they contracted influenza in Sri Lanka. Included in the indirect costs were income and productivity losses due to work absenteeism and presenteeism. The cost of absenteeism and presenteeism was calculated by multiplying the average number of days of total productivity loss (6.95)[41] and the daily per capita income (Rs. 623.67, USD 3.49). The daily per capita income was calculated by dividing the per capita monthly income (18,982.51, USD 106.25)[42] by the average number of days per month (30.44).

The cost for vaccination was defined as the cost of the vaccine per dose (Rs. 391.71, USD 2.19),[43] a disposable 2 mL syringe (Rs. 3.80, USD 0.02),[44] and a 22-gauge disposable

needle (Rs. 2.57, USD 0.01).[44] Vaccination cost came out to Rs. 398.08 (USD 2.22) per vaccine administered.

Table 4. Input data for cost model parameters.
*All cost data presented as Sri Lankan Rs (USD)

Cost Parameters	Base Case*	Range*	Distribution Type	Mean (SD)	Source
Inpatient Direct Costs					
Hospital Cost per Day	3,196.58 (17.89)	2,298.10 - 4,095.05 (12.86 – 22.92)	Uniform		37
Average Hospital Stay Length	3.66	2.96 - 4.44	Gamma	3.66 (0.38)	38
Oseltamivir 75mg Capsule	220.88 (1.24)	176.70 - 265.06 (0.99 – 1.48)	Gamma	218.68 (22.56)	39
Oseltamivir Pill Count	5.57	1.14 – 10	Uniform		40
Travel Expense	111.10 (0.62)	8.37 – 343.11 (0.05 – 1.92)	Gamma	111.10 (89.70)	36
Outpatient Direct Costs					
Medical Visit Cost	322.42 (1.80)	208.14 - 436.70 (1.17 – 2.44)	Uniform		37
Amoxicillin 500mg Tablet	4.96 (0.03)	4.73 – 5.12 (0.03 – 0.03)	Gamma	4.92 (0.10)	39
Amoxicillin Pill Count	5.19	1.37 – 9	Uniform		
Paracetamol 500mg Tablet	1.05 (0.01)	0.84 – 1.27 (0.00 – 0.01)	Gamma	1.04 (0.11)	39
Paracetamol Pill Count	9.38	0.77 – 18.00	Uniform		
Chlorpheniramine 4mg Tablet	0.14 (0.00)	0.11 - 0.16 (0.00 – 0.00)	Gamma	0.13 (0.01)	39

Chlorpheniramine Pill Count	10.50	3.00 – 18.00	Uniform		
Travel Expense	111.10 (0.62)	8.37 - 343.11 (0.05 – 1.92)	Gamma	111.10 (89.70)	36
Indirect Costs					
Days Lost for Absenteeism & Presenteeism	6.95	0.00 - 46.67	Gamma	6.95 (13.55)	41
Daily per Capita Income	623.67 (3.49)	498.93 - 748.40 (2.79 – 4.19)	Uniform		42
Vaccine Costs					
Vaccine per dose	391.71 (2.19)	195.63 - 587.78 (1.10 – 3.29)	Uniform		43
22-gauge, disposable needle	2.57 (0.01)	2.08 - 3.12 (0.01 – 0.02)	Gamma	2.57 (0.27)	44
2 mL disposable syringe w/o needle	3.80 (0.02)	3.07 - 4.61 (0.02 – 0.03)	Gamma	3.80 (0.39)	44

2.3.5 Disability-adjusted life years

We estimated disability-adjusted life years (DALYs) averted by implementing a universal vaccination program compared to the current context of no influenza vaccination policy. In this analysis, both years of life lost (YLL) due to premature death from influenza and years lived with disability (YLD) from contracting influenza were accounted for. The following equation was used to get the total DALYs for each month: DALY = YLL + YLD.

YLL estimates due to premature death were calculated for each month. Monthly YLL estimates were derived from 2012-2016 national influenza death data,[45 - 49] annual influenza death estimates,[4] and weighted age group life expectancy. Age groups were defined as 0-1, 1-4,

5-19, 20-49, 50-69, and 70+. The proportion of influenza deaths for each age group were calculated first by dividing the average influenza deaths for each age group by the average influenza deaths across all age groups. Because of limited national mortality data, the proportions for each age group were multiplied by the monthly influenza death estimates that we calculated using mortality rates obtained from the Global Burden of Disease Study 2017[4] to obtain the number of deaths within the age group for each month. Age group-specific monthly YLL estimates were then calculated by multiplying each age group's number of deaths by the weighted life expectancy for the said age group. Weighted age group life expectancies were found using age-specific national population and life expectancy estimates.[50] To calculate the total YLL for each month, we added YLL estimates from all age groups for that month.

Monthly YLD estimates from contracting influenza were derived from influenza disability weight estimates and the estimated monthly non-fatal influenza episodes. For disability weights, we used two previously defined influenza disability weights, 0.131 and 0.279.[51, 52] Disability weights were then divided by twelve to get two monthly disability weight estimates. Calculated monthly disability weight estimates were multiplied by the non-fatal influenza episodes for each month to calculate the monthly YLD.

2.4 Cost-effectiveness analysis and sensitivity analysis

Cost-effectiveness and sensitivity analyses were performed using TreeAge Pro Healthcare 2020 (TreeAge Software Inc., Williamstown, MA). One model arm was considered dominated when it offered lower DALYs averted and was more expensive than the other option. When universal vaccination was considered dominant (higher DALY averted) at a higher cost

compared to no vaccination, the following equation was used to calculate the incremental cost-effectiveness ratio (ICER) of universal vaccination: ICER = ($Cost_{Vaccination}$ - $Cost_{No\ Vaccination}$) / ($DALY\ averted_{Vaccination}$ - $DALY\ averted_{No\ Vaccination}$).

One model arm was considered cost-effective if the ICER was below a three-fold gross domestic product (GDP) per capita per DALY averted limit and highly cost-effective if below a one-fold GDP per capita per DALY averted limit.[53] The 2019 GDP per capita at market prices (Rs. 688,719, USD 3,852) for Sri Lanka was obtained from the Central Bank of Sri Lanka.[54] With this data, the willingness-to-pay (WTP) threshold used in this study was defined as Rs. 2,066,157 (USD 11,556) per DALY averted (three-fold of GDP per capita at market price). The highly cost-effective threshold was defined as less than Rs. 688,719 (USD 3,852) per DALY averted (one-fold the GDP per capita at market price).

We performed probabilistic sensitivity analyses to explore parameter influence on the resulting incremental cost-effectiveness ratios (ICERs). Probabilistic sensitivity analyses were done using Monte Carlo sampling using distributions (95% CI or ± 20% of base-case values) for all model parameters (Table 1, Table 2, Table 3, Table 4), running 10,000 simulations, and then calculating the mean and 95% CI for the ICERs based on these 10,000 simulations. In addition to this, we completed one-way sensitivity analyses for all parameters over variable ranges (95% CI of base-case values) to identify any influential parameters on the base-case results.

3. Results

The estimated number of individuals who either contracted, died, or were hospitalized from influenza for each model arm is shown in Table 5.

Table 5. Expected clinical outcome of no vaccination and vaccination model arms.

	No Vacc	Vacc	Difference (No Vacc – Vacc)
Number of influenza episodes (seeking medical treatment)	284, 518	114, 235	170, 283
Number of hospitalizations for influenza	5, 293	2, 126	3, 167
Number of influenza deaths	255	103	152

No Vacc: No vaccination model arm; Vacc: Vaccination model arm

3.1 Base-case analysis

Under the base case assumptions, vaccinations resulted in an overall decrease in influenza cases, hospitalizations, and death. Vaccinations would be expected to reduce the number of influenza episodes by 170,283, hospitalizations by 3,167, and deaths by 152 compared to no vaccination (Table 5). As a result, the use of vaccinations showed that the cost reduction due to the reduced influenza disease burden would exceed the cost increase due to the cost of vaccination, resulting in cost savings. The ICER for vaccination compared to no vaccination was estimated to be 968,071.45 Rs/DALY (5,418.62 USD/DALY) (Table 6).

Table 6. Base case analysis (per-person costs and effectiveness).

	Cost per person	Incremental cost	Effectiveness	Incremental effectiveness	Incremental cost-effectiveness ratio
	Rs. (USD)		DALY		Rs/ DALY (USD/DALY)
No Vacc	69 (0.39)	-	0.000616	-	-

Vacc	426 (2.38)	357 (2.00)	0.000247	0.000369	968,071.45 (5,418.62)

No Vacc: No vaccination model arm; Vacc: vaccination model arm

3.2 Sensitivity analyses

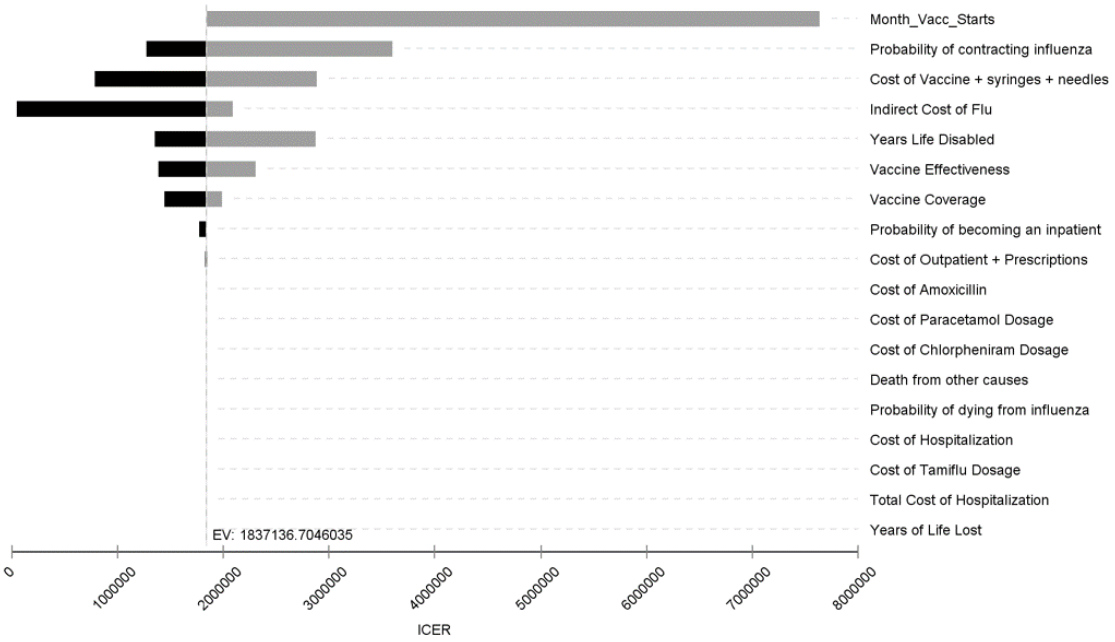

Figure 3. One-way sensitivity analysis.

Figure 3 shows the one-way sensitivity analysis for vaccination. Results were sensitive to the implementation month, monthly probability of contracting influenza, cost of vaccination, and years of life disabled. Among these parameters, the implementation month had the most substantial effect on the ICER (Figure 3). Since the model only considered a one-year period, no potential rollover effects to future years were shown, leading the later implementation months to protect fewer people from influenza within the one-year timeframe. Probabilistic sensitivity analyses were performed on all variables, and there was a 99% probability that vaccination was cost-effective below a WTP threshold of 1,157,047.92 Rs/DALY (6,476.38 USD/DALY)

(Figure 4). No value for a variable within our estimated ranges resulted in ICERs above the WTP threshold of Rs. 2,066,157 (USD 11,556) per DALY averted.

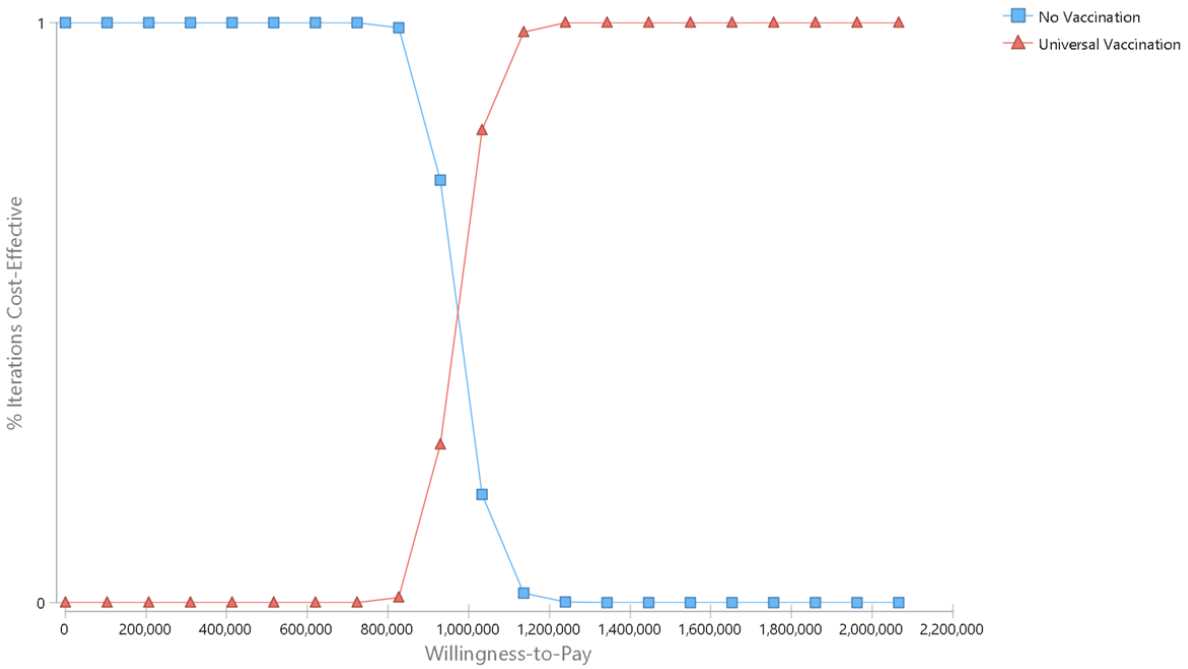

Figure 4. Probabilistic sensitivity analysis. Vaccination was favored over 99% for WTP 1,157,047.92 Rs./DALY (6,476.38 USD/DALY) compared to no vaccination.
Willingness to pay; WTP

3.3 Vaccine timing

Varying assumptions about vaccine implementation timing influenced the estimated disease reduction in the population. Earlier implementation months were found to have a more considerable impact on all influenza-related outcomes. While implementing the influenza vaccine in any month was more effective than not implementing the vaccine, there was a substantial effect associated with effectiveness and earlier implementation times (Figure 5). This effect is associated with the number of people that would be receiving the benefit from vaccination. The later the vaccination implementation time would allow for fewer people to

benefit; therefore, the difference in DALYs between the vaccinated and unvaccinated groups decreases compared to early implementation months. When looking at the costs of vaccination, there was not a considerable difference between the months (Figure 6).

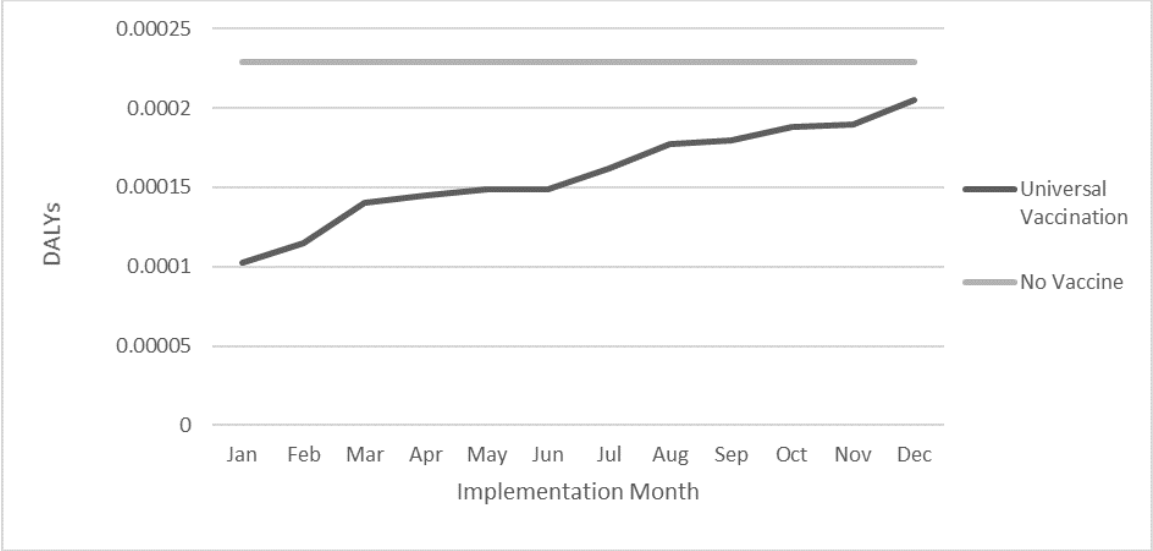

Figure 5. Effect of vaccine implementation timing on effectiveness.

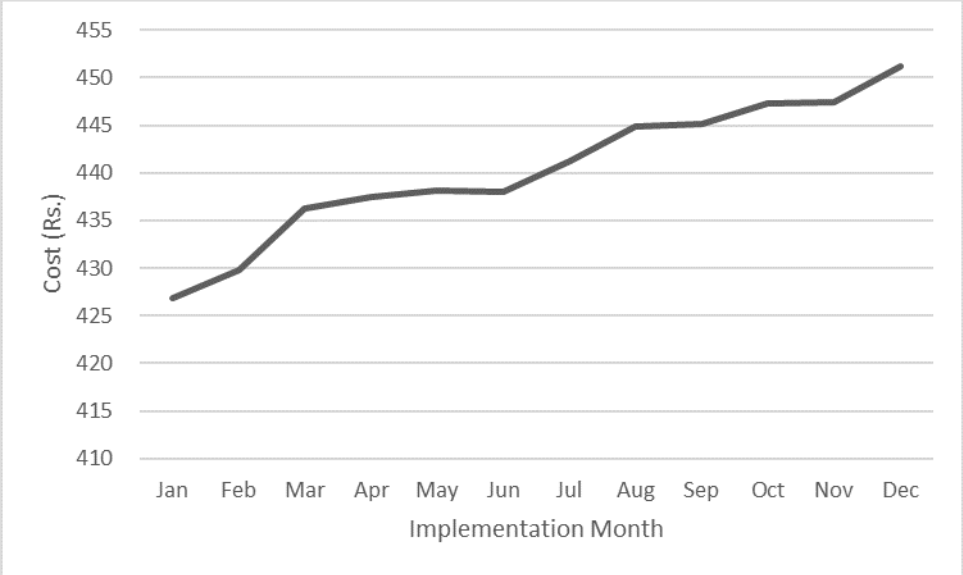

Figure 6. Effect of vaccine implementation timing on vaccination cost.

4. Discussion

This study estimated the disease burden of influenza using previous estimates and Sri Lankan national data and analyzed the cost-effectiveness of the influenza vaccine at a national level. To determine the priority of influenza vaccine implementation, we conducted a cost-effectiveness analysis for the Sri Lankan population. This study showed that the inclusion of influenza vaccinations into the NIP could represent good value for money in Sri Lanka despite its increase in cost. It also found that Sri Lanka can reduce the burden of influenza the most by implementing vaccination earlier in the year. This was most likely due to our study only considering a one-year period and not accounting for potential rollover effects of vaccination into future years.

Due to limited access to data, we made a few assumptions within the model. The first assumption was that once participants received immunity against influenza from surviving influenza, they would not contract influenza again within the 12-month cycle. We also used the assumption that influenza mortality followed a similar monthly pattern to monthly influenza hospitalizations. Adverse events related to vaccination and influenza-related complications were not considered.

We are not aware of other studies evaluating the cost-effectiveness of influenza vaccination in Sri Lanka. While there have been cost-effectiveness studies evaluating influenza vaccination programs, most are in high-income settings, with few in LMICs.[55] Cost-effectiveness analyses must occur for local health authorities to demonstrate how vaccination can be used to

reduce disease transmission and burden, especially in LMIC settings with limited or no access to influenza vaccines.

Influenza vaccines have been in use since the creation of the first monovalent influenza vaccine in 1936[56] and have since been integrated into numerous national immunization programs. Because of multiple circulating strains of the influenza virus, influenza vaccines have always required adaptations. These adaptations have led to the creation of the current influenza vaccines, LAIV, TIV, and quadrivalent inactivated vaccine (QIV). TIV and LAIV are antigenically equivalent, and each contains three influenza strains- two subtypes of influenza A and one subtype of influenza B.[57] QIV includes the three influenza strains in the TIV and LAIV and an additional subtype of influenza B strain.[57]

Each year, the WHO provides formal recommendations for which influenza strain subtypes should be included in the vaccines based on surveillance data from the WHO Global Influenza Surveillance and Response System (GISRS). These recommendations are broken up into Northern Hemisphere and Southern Hemisphere, based on the country's location and influenza activity. LAIV, TIV, and QIV effectiveness differ between influenza seasons and are based on how well of a match the recommendation is and the recipient's age and health status.[58] In tropical settings, LAIV tends to have an overall effectiveness of 63% - 83%, while TIV tends to be 48% - 72% when looking at laboratory-confirmed influenza as the outcome.[6] QIV has been shown to be 53% (95% CI, 45–59) effective against any influenza B illness.[59] Currently, there is research into the development of universal influenza vaccines, which would provide long-lasting protection against multiple influenza subtypes. With the development of a universal influenza

vaccine, influenza vaccines would prove to be more cost-effective due to the increase in vaccine effectiveness and the protective period's duration.

In addition to the cost savings shown in this study, the implementation of influenza vaccines into the Sri Lankan NIP would provide further cost savings due to the decrease in antimicrobial resistance. Influenza vaccinations have been found to decrease antimicrobial resistance in both HICs and LMICs.[60 - 62] This decrease in antimicrobial resistance would occur due to the reduction in antibiotics being prescribed for 1) patients with influenza and 2) patients that contract secondary infections due to influenza. A previous study from Southern Sri Lanka estimated that antibiotic resistance costs $229,120,600 per year from a societal perspective.[34] Another study found that antibiotics were over-prescribed for acute lower-respiratory illnesses in the outpatient setting for various reasons, such as patient demand for antibiotics, lack of awareness of antimicrobial resistance, and minimal diagnostic testing usage.[32] Studies have found seasonal influenza patients are more susceptible to developing secondary bacterial infections, which greatly contributes to influenza-related mortality and morbidity.[63 - 65] Podewils et al. found the rate of secondary bacterial infections in adult and children influenza patients to be roughly 2.0% and 1.6% respectively.[66] By decreasing the number of influenza episodes with vaccines, the amount of secondary bacterial infections would be reduced, allowing for a reduction in antibiotic prescriptions. Because of this, influenza vaccinations could provide more considerable cost savings than what this study suggests.

Because this study is the first of its kind for Sri Lanka, there are limitations. One of the most important limitations is that the study uses a static model. Because the study uses a static

model and not a dynamic model, the model cannot consider potentially important factors, such as attack rates and vaccination herd immunity effects. By doing so, the model serves as a conservative estimate and underestimates the cost-effectiveness of influenza vaccinations.

Second, the input data used for the model may have marginally underestimated the disease burden of influenza. Patients with mild infections might not have sought medical care, or patients might have sought care in the traditional or private healthcare sectors. The private healthcare sector has been growing in popularity within Sri Lanka and has received a notable boost in popularity since the end of the civil war in 2009.[16] However since the study goal was to verify an influenza vaccination program's cost-effectiveness from a governmental perspective, we believe this serves well as a conservative estimate.

Additionally, not much data could be found regarding age structure for influenza patients in Sri Lanka. Thus, it was not possible to include alternative vaccination strategies, other than universal vaccination, into the model. However, since universal vaccination was found to be cost-effective, alternative vaccination strategies, such as targeted or high-risk-only vaccination programs, would likely prove more cost-effective due to decreased program cost while still reducing a large majority of influenza hospitalizations and deaths.

Finally, to avoid overestimating the costs attributable to influenza, we excluded some treatment costs, including various diagnostic tests, additional medical visits, and the indirect costs of caregivers. Therefore, the cost of the influenza disease burden provided in the study serves as a conservative estimate. Since we wanted to estimate the local context within Sri Lanka, these costs were excluded due to uncertainty, limited data, or not having routine usage.

Despite these limitations, this study has the advantage of reflecting the local context. A limited number of studies have been conducted to investigate seasonal influenza in Sri Lanka.[4, 11 – 13, 32 – 34] The contribution of previous studies was the estimation of influenza disease burden and available treatment options and costs. However, some studies have been limited to mainly Southern Sri Lanka and the outpatient setting.[12, 32 - 34] Other studies, such as Rafeek et al.[11] and Jayasinghe et al.,[13] describe Sri Lankan influenza trends on a national level. The Global Burden of Disease Study 2017[4] provided an influenza disease burden estimate at the national level; however, this estimate is only an annual estimate. This study addressed these limitations by developing a method to estimate the monthly influenza disease burden at a national level.

In conclusion, this study showed that including influenza vaccinations in the NIP would be cost-effective in Sri Lanka and suggests that vaccine implementation should be considered due to the vaccination ICER being much lower than the WHO cost-effectiveness threshold. However, to further determine if a universal vaccination strategy is optimal for Sri Lanka, a cost-effectiveness analysis comparing various implementation strategies should be performed. In addition to this, large-scale national studies are needed to better determine the influenza disease burden, risk-group population, and costs.

References

1. Lee, V. J., Ho, Z. J. M., Goh, E. H., Campbell, H., Cohen, C., Cozza, V., Fitzner, J., Jara, J., Krishnan, A., & Bresee, J. (2018). Advances in measuring influenza burden of disease. Influenza and Other Respiratory Viruses, 12(1), 3–9. https://doi.org/https://doi.org/10.1111/irv.12533Du Pont, H.A. *The Campaign of 1864 in the Valley of Virginia and the Expedition to Lynchburg*. New York: National Americana, 1925.

2. World Health Organization. (2018, November 6). Influenza (Seasonal). https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal)

3. Newall AT, Chaiyakunapruk N, Lambach P, Hutubessy RCW. *WHO guide on the economic evaluation of influenza vaccination. Influenza and Other Respiratory Viruses*. 2018 Mar;12(2):211-219. DOI: 10.1111/irv.12510.

4. Troeger, C. E., Blacker, B. F., Khalil, I. A., Zimsen, S. R. M., Albertson, S. B., Abate, D., Abdela, J., Adhikari, T. B., Aghayan, S. A., Agrawal, S., Ahmadi, A., Aichour, A. N., Aichour, I., Aichour, M. T. E., Al-Eyadhy, A., Al-Raddadi, R. M., Alahdab, F., Alene, K. A., Aljunid, S. M., … Reiner, R. C. (2019). Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017. *The Lancet Respiratory Medicine*, 7(1), 69–89. https://doi.org/10.1016/S2213-2600(18)30496-X

5. Bresee, J. S., Lafond, K. E., McCarron, M., Azziz-Baumgartner, E., Chu, S. Y., Ebama, M., Hinman, A. R., Xeuatvongsa, A., Bino, S., Richardson, D., Porter, R. M., Moen, A., & McKinlay, M. (2019). The partnership for influenza vaccine introduction (PIVI): Supporting influenza vaccine program development in low and middle-income countries through public-private partnerships. *Vaccine*, 37(35), 5089–5095. https://doi.org/10.1016/j.vaccine.2019.06.049

6. Hirve, S., Lambach, P., Paget, J., Vandemaele, K., Fitzner, J., & Zhang, W. (2016). Seasonal influenza vaccine policy, use and effectiveness in the tropics and subtropics – a systematic literature review. *Influenza and Other Respiratory Viruses*, 10(4), 254–267. https://doi.org/https://doi.org/10.1111/irv.12374

7. World Health Organization. (n.d.). Seasonal Influenza. Retrieved January 6, 2021, from http://158.232.12.119/ith/diseases/influenza_seasonal/en/

8. Peasah, S. K., Azziz-Baumgartner, E., Breese, J., Meltzer, M. I., & Widdowson, M.-A. (2013). Influenza cost and cost-effectiveness studies globally – A review. *Vaccine*, 31(46), 5339–5348. https://doi.org/10.1016/j.vaccine.2013.09.013

9. Yue, M., Dickens, B. L., Yoong, J. S., Chen, M. I.-C., Teerawattananon, Y., & Cook, A. R. (2019). Cost-Effectiveness Analysis for Influenza Vaccination Coverage and Timing in Tropical and Subtropical Climate Settings: A Modeling Study. *Value in Health*, 22(12), 1345–1354. https://doi.org/10.1016/j.jval.2019.07.001

10. Newman, L. P., Bhat, N., Fleming, J. A., & Neuzil, K. M. (2018). Global influenza seasonality to inform country-level vaccine programs: An analysis of WHO FluNet influenza surveillance data between 2011 and 2016. *PLOS ONE*, 13(2), e0193263. https://doi.org/10.1371/journal.pone.0193263

11. Rafeek, R. A. M., Divarathna, M. V. M., & Noordeen, F. (2017). History and current trends in influenza virus infections with special reference to Sri Lanka. *Virus Disease*, *28*(3), 225–232. https://doi.org/10.1007/s13337-017-0390-8

12. Shapiro, D., Bodinayake, C. K., Nagahawatte, A., Devasiri, V., Kurukulasooriya, R., Hsiang, J., Nicholson, B., Silva, A. D. D., Østbye, T., Reller, M. E., Woods, C. W., & Tillekeratne, L. G. (2017). c. *The American Journal of Tropical Medicine and Hygiene*, 97(1), 88–96. https://doi.org/10.4269/ajtmh.17-0032

13. Jayasinghe, C., Ginige, S., & Jayamaha, J. (2019, September 19). *Influenza surveillance activities in Sri Lanka*. [Paper presentation]. 1st South East Asia Regional Group Meeting of the International Epidemiological Association, Colombo. https://www.researchgate.net/publication/335991317_Infleunza_surveillance_activities_in_Sri_Lanka

14. Institute for Health Metrics and Evaluation. (2017, September 19). Sri Lanka. Retrieved from http://www.healthdata.org/sri-lanka

15. H. Plecher. (2020, November 03). *Sri Lanka: Age structure from 2009 to 2019*. Retrieved from https://www.statista.com/statistics/728538/age-structure-in-sri-lanka/

16. Kumar, R. Public–private partnerships for universal health coverage? The future of "free health" in Sri Lanka. *Global Health* 15, 75 (2019). https://doi.org/10.1186/s12992-019-0522-618.

17. Epidemiology Unit. (n.d.). *Introduction Influenza Surveillance* [PDF]. Epidemiology Unit-Ministry of Health.

18. Sri Lanka, Registrar General's Department. (n.d.). *Mid-year Population Estimates by District & Sex, 2015 - 2020*. Retrieved from http://www.statistics.gov.lk/Population/StaticalInformation/VitalStatistics/ByDistrictandSex

19. Sri Lanka, Ministry of Health, Medical Statistics Unit. (n.d.). *Annual Health Bulletin 2012*. Retrieved from http://www.health.gov.lk/moh_final/english/public/elfinder/files/publications/AHB/Annual Health Bulletin - 2012.pdf

20. Sri Lanka, Ministry of Health and Indigenous Medicine, Medical Statistics Unit. (n.d.). *Annual Health Bulletin 2013*. Retrieved from http://www.health.gov.lk/moh_final/english/public/elfinder/files/publications/AHB/AHB 2013.pdf

21. Sri Lanka, Ministry of Health, Nutrition and Indigenous Medicine, Medical Statistics Unit. (2016). *Annual Health Bulletin 2014*. Retrieved from http://www.health.gov.lk/moh_final/english/public/elfinder/files/publications/AHB/AHB 2014.pdf

22. Sri Lanka, Ministry of Health, Nutrition and Indigenous Medicine, Medical Statistics Unit. (2017). *Annual Health Bulletin 2015*. Retrieved from http://www.health.gov.lk/moh_final/english/public/elfinder/files/publications/AHB/2017/AHB 2015.pdf

23. Sri Lanka, Ministry of Health, Nutrition and Indigenous Medicine, Medical Statistics Unit. (2018). *Annual Health Bulletin 2016.* Retrieved from http://www.health.gov.lk/moh_final/english/public/elfinder/files/publications/AHB/2017/AHB_2016.pdf

24. Sri Lanka, Ministry of Health, Nutrition and Indigenous Medicine, Epidemiology Unit. (2013, August). *Epidemiological Component*. Retrieved from https://www.epid.gov.lk/web/index.php?option=com_content&view=article&id=180&Itemid=494&lang=en

25. World Health Organization, Global Influenza Programme, University of Edinburgh, & World Health Organization. (2015*). A manual for estimating disease burden associated with seasonal influenza.* http://apps.who.int/iris/bitstream/10665/178801/1/9789241549301_eng.pdf?ua=1

26. The World Bank. (n.d.). Population, total - Sri Lanka. Retrieved from https://data.worldbank.org/indicator/SP.POP.TOTL?locations=LK

27. The World Bank. (n.d.). Death rate, crude (per 1,000 people) - Sri Lanka. Retrieved from https://data.worldbank.org/indicator/SP.DYN.CDRT.IN?locations=LK

28. UNICEF ROSA. (2019). *Continued national commitment to primary health care with a strong focus on community engagement: A case study from Sri Lanka (Sustaining Vaccination Coverage).* https://www.unicef.org/rosa/reports/sustaining-vaccination-coverage

29. Hendriks, A., Hutubessy, R. C., Grohmann, G., Torelli, G., Friede, M., & Kieny, M. (27 june 2018). Quadrivalent influenza vaccines in low and middle income countries: Cost-effectiveness, affordability and availability. *Vaccine,* 36(28), 3993-3997. doi:https://doi.org/10.1016/j.vaccine.2018.05.099

30. International Monetary Fund (IMF. World Economic Outlook Database, October 2020. Washington, D.C., United States of America: International Monetary Fund (IMF).

31. US Dollar to Sri Lankan Rupee Spot Exchange Rates for 2019. (n.d.). Retrieved from https://www.exchangerates.org.uk/USD-LKR-spot-exchange-rates-history-2019.html

32. Tillekeratne, L. G., Bodinayake, C. K., Dabrera, T., Nagahawatte, A., Arachchi, W. K., Sooriyaarachchi, A., Stewart, K., Watt, M., Østbye, T., & Woods, C. W. (2017). Antibiotic overuse for acute respiratory tract infections in Sri Lanka: a qualitative study of outpatients and their physicians. *BMC family practice*, 18(1), 37. https://doi.org/10.1186/s12875-017-0619-z

33. Tillekeratne, L. G., Bodinayake, C. K., Nagahawatte, A., Vidanagama, D., Devasiri, V., Arachchi, W. K., Kurukulasooriya, R., De Silva, A. D., Østbye, T., Reller, M. E., & Woods, C. W. (2015). Use of Rapid Influenza Testing to Reduce Antibiotic Prescriptions Among Outpatients with Influenza-Like Illness in Southern Sri Lanka. *The American journal of tropical medicine and hygiene*, 93(5), 1031–1037. https://doi.org/10.4269/ajtmh.15-0269

34. Tillekeratne, L. G., Bodinayake, C., Nagahawatte, A., Kurukulasooriya, R., Orlando, L. A., Simmons, R. A., Park, L. P., Woods, C. W., & Reed, S. D. (2019). Use of clinical algorithms and rapid influenza testing to manage influenza-like illness: A cost-effectiveness analysis in Sri Lanka. *BMJ Global Health*, 4(2), e001291. https://doi.org/10.1136/bmjgh-2018-001291

35. Nanayakkara, K. K., Samarakoon, A. B., Perera, B. H., De Silva, A. W., & Nanayakkara, C. D. (2011). Size of Sri Lankan newborns at birth. *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology*, 31(4), 311–314. https://doi.org/10.3109/01443615.2011.563332

36. Tillekeratne, L. G., Bodinayake, C. K., Nagahawatte, A., Vidanagama, D., Devasiri, V., Arachchi, W. K., Kurukulasooriya, R., De Silva, A. D., Østybe, T., Reller, M. E., & Woods, C. W. (2015). An under-recognized influenza epidemic identified by rapid influenza testing, southern Sri Lanka, 2013. *The American journal of tropical medicine and hygiene*, 92(5), 1023–1029. https://doi.org/10.4269/ajtmh.14-0708

37. World Health Organization. (2010, December 06). *Estimates of Unit Costs for Patient Services for Sri Lanka*. Retrieved from https://www.who.int/choice/country/lka/cost/en/

38. Chamikara Perera, Ravi P. Rannan-Eliya, Sunil Senanayake, Shanti Dalpatadu, Hirushaka de Silva and Ruki Wijesinghe. 2009. *Public Hospital Inpatient Discharge Survey 2005*. IHP Health Statistics Reports Series Number 1. Colombo: Institute for Health Policy.

39. State Pharmaceuticals Corporation of Sri Lanka Products. (2021, January 27). Retrieved from https://www.spc.lk/products.php

40. Center for Disease Control and Prevention. (2021, January 25). *Influenza Antiviral Medications: Summary for Clinicians*. Retrieved from https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

41. Fernando, M., Caputi, P., & Ashbury, F. (2017). Impact on Employee Productivity From Presenteeism and Absenteeism: Evidence From a Multinational Firm in Sri Lanka. *Journal of occupational and environmental medicine*, 59(7), 691–696. https://doi.org/10.1097/JOM.0000000000001060

42. DEPARTMENT OF CENSUS AND STATISTICS. (2017, October). *Household Income and Expenditure Survey – 2016 Final Results* [PDF]. DEPARTMENT OF CENSUS AND STATISTICS.

43. Pan American Health Organization. (n.d.). *EXPANDED PROGRAM OF IMMUNIZATION VACCINE PRICES FOR YEAR 2019* [PDF]. Pan American Health Organization.

44. Gunawardane, Damitha & Karnon, Jonathan & Rowel, Dhammica & Lucas, Nishani & N.Gamaethige, & C.Mathota, & U.D.P.Ratnasiri, & Hemachandra, Nilmini & Jayakody, Hemali. (2018). *Cost Analysis of Sri Lanka Every Newborn Action Plan to End Preventable Morbidity and Mortality*.

45. Sri Lanka, Ministry of Health, Medical Statistics Unit. (n.d.). *Indoor Morbidity and Mortality Report - 2012*. Retrieved from http://www.health.gov.lk/moh_final/english/others.php?pid=110

46. Sri Lanka, Ministry of Health, Medical Statistics Unit. (n.d.). *Indoor Morbidity and Mortality Report - 2013*. Retrieved from http://www.health.gov.lk/moh_final/english/others.php?pid=110

47. Sri Lanka, Ministry of Health, Medical Statistics Unit. (n.d.). *Indoor Morbidity and Mortality Report - 2014*. Retrieved from http://www.health.gov.lk/moh_final/english/others.php?pid=110

48. Sri Lanka, Ministry of Health, Medical Statistics Unit. (n.d.). *Indoor Morbidity and Mortality Report - 2015*. Retrieved from http://www.health.gov.lk/moh_final/english/others.php?pid=110

49. Sri Lanka, Ministry of Health, Medical Statistics Unit. (n.d.). *Indoor Morbidity and Mortality Report - 2016*. Retrieved from http://www.health.gov.lk/moh_final/english/others.php?pid=110

50. World Health Organization. (2020, December 06). Life tables by country - Sri Lanka. Retrieved from https://apps.who.int/gho//data/view.main.LT62220?lang=en

51. Ock, M., Lee, J. Y., Oh, I. H., Park, H., Yoon, S. J., & Jo, M. W. (2016). Disability Weights Measurement for 228 Causes of Disease in the Korean Burden of Disease Study 2012. *Journal of Korean medical science,* 31 Suppl 2(Suppl 2), S129–S138. https://doi.org/10.3346/jkms.2016.31.S2.S129

52. World Health Organization. (n.d.). *GLOBAL BURDEN OF DISEASE 2004 UPDATE: DISABILITY WEIGHTS FOR DISEASES AND CONDITIONS* [PDF].

53. World Health Organization. *The World Health Report 2002: reducing risks, promoting healthy life*. Geneva; 2002.

54. Statistics Department, C. B. of S. L. (2020). *Sri Lanka Socio-Economic Data Folder- 2020*. https://www.cbsl.gov.lk/en/publications/other-publications/statistical-publications/sri-lanka-socio-economic-data-folder

55. de Francisco Shapovalova N, Donadel M, Jit M, Hutubessy R. A systematic review of the social and economic burden of influenza in low and middle-income countries. *Vaccine*. 2015 Nov 27;33:6537-6544.

56. Ray, R., Dos Santos, G., Buck, P. O., Claeys, C., Matias, G., Innis, B. L., & Bekkat-Berkani, R. (2017). A review of the value of quadrivalent influenza vaccines and their potential contribution to influenza control. *Human vaccines & immunotherapeutics*, 13(7), 1640–1652. https://doi.org/10.1080/21645515.2017.1313375

57. Pan American Health Organization, & World Health Organization. (n.d.). About the influenza vaccine. Retrieved from https://www.paho.org/hq/index.php?option=com_content&view=article&id=6207:about-the-influenza-vaccine&Itemid=4322&lang=en#:~:text=Influenza vaccine is available in,Attenuated Influenza Vaccine (LAIV).

58. Center for Disease Control and Prevention. (2020, December 16). Key Facts About Seasonal Flu Vaccine. Retrieved from https://www.cdc.gov/flu/prevent/keyfacts.htm

59. Gaglani, M., Vasudevan, A., Raiyani, C., Murthy, K., Chen, W., Reis, M., Belongia, E. A., McLean, H. Q., Jackson, M. L., Jackson, L. A., Zimmerman, R. K., Nowalk, M. P., Monto, A. S., Martin, E. T., Chung, J. R., Spencer, S., Fry, A. M., & Flannery, B. (2020). Effectiveness of Trivalent and Quadrivalent Inactivated Vaccines against Influenza B in the United States, 2011-2012 to 2016-2017. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, ciaa102. Advance online publication. https://doi.org/10.1093/cid/ciaa102

60. Johan Vekemans, Mateusz Hasso-Agopsowicz, Gagandeep Kang, William P Hausdorff, Anthony Fiore, Elizabeth Tayler, Elizabeth J Klemm, Ramanan Laxminarayan, Padmini Srikantiah, Martin Friede, Marc Lipsitch, Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance: A World Health Organization Action Framework, *Clinical Infectious Diseases*, 2021;, ciab062, https://doi.org/10.1093/cid/ciab062

61. Eili Y Klein, Emily Schueller, Katie K Tseng, Daniel J Morgan, Ramanan Laxminarayan, Arindam Nandi, The Impact of Influenza Vaccination on Antibiotic Use in the United States, 2010–2017, *Open Forum Infectious Diseases*, Volume 7, Issue 7, July 2020, ofaa223, https://doi.org/10.1093/ofid/ofaa223

62. Gwenan M Knight, Madeleine Clarkson, Thushan I de Silva, Potential impact of influenza vaccine roll-out on antibiotic use in Africa, *Journal of Antimicrobial Chemotherapy*, Volume 73, Issue 8, August 2018, Pages 2197–2200, https://doi.org/10.1093/jac/dky172

63. Metzger, D. W., & Sun, K. (2013). Immune dysfunction and bacterial coinfections following influenza. *Journal of immunology (Baltimore, Md. : 1950)*, 191(5), 2047–2052. https://doi.org/10.4049/jimmunol.1301152

64. Gupta, R. K., George, R. C., & Nguyen-Van-Tam, J. S. (2008). Bacterial Pneumonia and Pandemic Influenza Planning. *Emerging Infectious Diseases*, 14(8), 1187-1192. https://dx.doi.org/10.3201/eid1408.070751.

65. Metersky, M. L., Masterton, R. G., Lode, H., File, T. M., & Babinchak, T. (2012). Epidemiology, microbiology, and treatment considerations for bacterial pneumonia

complicating influenza. *International Journal of Infectious Diseases*, *16*(5), e321–e331. https://doi.org/10.1016/j.ijid.2012.01.003

66. Laura Jean Podewils, Laura A. Liedtke, L. Clifford McDonald, Jeffrey C. Hageman, Larry J. Strausbaugh, Thea K. Fischer, Daniel B. Jernigan, Timothy M. Uyeki, Matthew J. Kuehnert, A National Survey of Severe Influenza-Associated Complications among Children and Adults, 2003–2004, *Clinical Infectious Diseases*, Volume 40, Issue 11, 1 June 2005, Pages 1693–1696, https://doi.org/10.1086/430424