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Cost-effectiveness of influenza vaccination in prior pneumonia patients

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Abstract

Pneumonia is a common complication of influenza infection, and accounts for the majority of influenza mortality. Both the WHO and the Ministry of Health in Israel prioritize seasonal influenza vaccination primarily on the basis of age and specific co-morbidities. Here we consider whether the targeting of individuals previously infected with pneumonia for influenza vaccination would be a cost-effective addition to the current policy. We performed a retrospective cohort data analysis of 163,990 cases of pneumonia hospitalizations and 1,305,223 cases of outpatient pneumonia from 2004–2012, capturing more than 54% of the Israeli population. Our findings demonstrate that patients infected with pneumonia in the year prior had a substantially higher risk of becoming infected with pneumonia in subsequent years (Relative risk >2.34, $p < 0.01$). Results indicated that the benefit of targeting for influenza vaccination patients hospitalized with pneumonia in prior year would be cost-saving regardless of age. Complementing the current policy with the targeting of prior pneumonia patients would require vaccination of only a further 2.3% of the Israeli population to save an additional 538 quality-adjusted life years (QALYs) annually at a mean price of only 1,238-2,033USD/QALY saved. Global uncertainty analysis demonstrates that the cost-effectiveness of adding this policy is robust over a vast range of conditions. As prior pneumonia patients are currently not prioritized for influenza vaccination in Israel, nor elsewhere, this study suggests a novel supplement of current policies to improve cost-effectiveness of influenza vaccination.

Keywords

Influenza vaccination; cost-effectiveness; influenza and pneumonia

Introduction

Pneumonia, an inflammatory condition of the lung, causes greater mortality than any other respiratory disease globally [1]. More than AIDS, malaria and tuberculosis combined, pneumonia is responsible for about 19% of all deaths in children below five years [1]. Pneumonia is the primary complication of influenza infection and, as such, accounts for the

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majority of influenza mortality [1]. Even when pneumonia is caused by bacteria and respiratory viruses other than influenza, influenza has nonetheless been shown to increase the susceptibility for other etiologies of pneumonia [2,3]. For example, a recent study found a strong but brief interaction between bacterial and influenza infection that can elevate susceptibility to pneumococcal pneumonia by 100-fold [2]. Consequently, interventions that effectively reduce influenza will concomitantly impact pneumonia arising either directly from influenza or indirectly from bacterial etiologies [3,4].

Influenza responsible for about 801,200 reported infections (around 10% of the population), 4130 hospitalizations, 1140 deaths, 2.7 million work days lost annually in Israel, and an overall cost to the Israeli economy of 261 million dollars (~0.1 of the GDP) [5,6] . Influenza and pneumonia are most prevalent in children under five, while complications occur predominately in the elderly and in individuals with co-morbidities [3]. Thus, in the vast majority of developed countries, including Israel, the current influenza vaccination policy offers vaccination to everyone older than six months with a focus on those over 50 and on children between six months and four years of age[3,7].

In addition to age, immunologic, socioeconomic and behavioral factors, as well as co-morbidities, contribute to the likelihood of contracting pneumonia and developing complications. Immunologically, pneumonia is caused by an under- or over-reaction of the immune system to a pathogen [8–10], because pro-inflammatory factors damage tissue. Socioeconomically, level of income, education, nutrition, gender and even race serve as markers for risk [1,8,9,11,12]. For example, in the U.S., rates of pneumonia are known to be higher among Native Americans and African Americans [8]. Behavioral factors are fundamental to risk of exposure due to the social contacts of individuals, as well as elevated susceptibility due to smoking habits or poor nutrition. For example, in the US, a spike in pneumonia occurs annually the week after Christmas, likely arising from a combination of greater human movement and social interactions [13].

It would be impractical to specifically target vaccination based on all these risk factors, particularly as some risk factors may still be unknown, difficult to identify or politically challenging to target. Given that these risk factors are likely to remain relatively constant from year to year for each individual, prior infection could feasibly serve as a confounder for risks that could be used to identify individuals who would be predisposed to infection and complications in subsequent years. We show that even in the absence of information about specific risk factors, some individuals are at higher risk of contracting pneumonia and can thus be identified as being disproportionately represented in the pool of individuals who were previously infected.

Here we evaluate a policy, which we term “current policy PLUS” (PLUS) that maintains the current influenza vaccination strategy but devotes additional resources to recruiting individuals previously infected with pneumonia. Through large scale data analysis, we show that targeting individuals in Israel who have been previously infected with pneumonia would be a highly effective and cost-effective addition. This is the first study to consider the value of previous pneumonia infection history to the design of vaccination policy.

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Materials and Methods

Data collection

We analyzed patient records between 2004–2012 from 'Clalit Healthcare Services' (Clalit), the primary Health Maintenance Organization (HMO) in Israel, serving above 54% of the country, representative demographically, ethnically and socio-economically [14]. There was a total of 1,305,223 records[1] of outpatient pneumonia (P_O), 1,162,968 of which were classified as pneumonia (code R81 by the International classification of primary care, CPC), 117,771 as Lobar pneumonia (reported by the ninth international classification of disease code, ICD-9, unspecified, named with Code 486), 42,859 as viral pneumonia (ICD9, code 480), 17,560 as mycoplasma pneumonia (ICD9, code 483), and 10,256 as pneumococcal pneumonia (ICD9, code 481). The data also included 163,990 hospitalizations[2] (P_H), 153,587 of which were unspecified (ICD9, as code 486) and 31,983 of which were specified as ICD9 codes 481-484. The data further indicated a total of 5,600,250 influenza vaccinations.

To prevent double counting we considered an individual as a P_O patient only if not hospitalized with pneumonia in the same season. We divided our population into the five age-groups (0–3, 4–24, 25–49, 50–64, ≥65) that correspond to U.S. CDC, as well as Israeli Ministry of Health, age-specific targets [3], also taking into account age-dependent rates of infection and vaccination coverage. The age of an individual on September 1 was considered the age of that individual for the season. To avoid biases that could arise from birth, death, or switching HMOs, we excluded individuals who were not members of Clalit for the entirety of each two year period evaluated.

Influenza is seasonal, with highest prevalence from September 1 through April 30. Weekly laboratory diagnostic confirmation of influenza and influenza-related complications in Israel outside this timeframe demonstrate that less than 10% of cases identified by physicians are correctly diagnosed, whereas 35 to 90% is correctly diagnosed within this timeframe [15]. Thus, we focused on pneumonia records diagnosed in the mentioned timeframe of peak influenza activity.

Data analysis

We evaluated the extent to which individuals previously infected with pneumonia are at elevated risk for infection in the subsequent influenza season, distinguishing outpatient treatment from hospitalization. For this purpose, we stratified our ten seasons of data into nine pairs of two consecutive seasons and calculated the proportion of P_O in season *i* previously diagnosed as P_O in season *i-1* (P_O to P_O), the proportion of P_H previously diagnosed as P_H in season *i-1* (P_H to P_H), as well as the proportion of P_O previously diagnosed as P_H in season *i-1* (P_H to P_O), and that of P_H previously diagnosed as P_O in season *i-1* (P_O to P_H) (See Supplement).

[1]We define a record as each time a physician reported a pneumonia case. To prevent double counting in our analysis we consider a new case only if the duration from new case is longer than two months.
[2]Hospitalization refers to pneumonia patients hospitalized for more than 24 hours.

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Cost-effectiveness

To determine the cost-effectiveness of influenza vaccination in prior pneumonia patients, we considered five clinical outcomes associated with influenza infection: 1) homecare for influenza with no assistance from medical personnel, 2) outpatient visit consultation for influenza, 3) outpatient visit consultation for pneumonia, 4) hospitalization, and 4) death, taking into account the probabilities and costs for each outcome. We analyzed both a base case scenario of conservative parameter values (defined in Table 1), as well as performed one-way sensitivity analysis and global uncertainty analysis over empirical ranges (see Appendix A and Table 1) of each input parameter to determine the effect of parameter variability on the evaluations of cost-effectiveness. For example, we assumed a 5% and 25% effectiveness of influenza vaccination in reducing P_O and P_H visits, respectively, for pneumonia in the base case, varying over the range 0–10% and 10–40% in the sensitivity analysis [3,4,16–18].

Our data indicated that age-specific vaccination coverage has been relatively stable since 2007 and also that individuals who were previously infected with pneumonia were more likely to be vaccinated in the subsequent year (see Appendix A and Table 1), while there remains much room to expand coverage. We assumed that these age-specific coverage would continue to be maintained under the current policy. Beyond these group-specific coverage, we evaluated the effectiveness of further vaccine uptake of prior pneumonia patients by the addition of the PLUS policy.

Medical care costs were derived from an Israeli government pricelist and were translated into January 2014 U.S. dollars. In the range of our sensitivity analysis, we also included prices from the US and the EU [19–21]. We assumed that the daily costs of medical outcomes are fixed across all age-groups. This assumption is consistent with previous studies in the US and Europe for homecare [22], and consistent with the Ministry of Health policy to reimburse healthcare providers for hospitalization per day and outpatient visit, regardless of age [21]. The duration of hospitalization and the probability of seeking treatment vary with age, and therefore were taken into account as age-dependent parameters (Table 1).

We included the costs of the vaccine and its administration, as well as additional costs for intervention programs shown to be effective in increasing vaccine uptake that could be used to promote vaccination in prior pneumonia patients [23,24]. Such vaccination promotion programs included automatic telephone reminders, telephone reminders from medical personnel, mailing pamphlets with information about risk of influenza, pneumonia and the benefit of vaccination to previously infected individuals (Table 1). In the sensitivity analysis, medical costs were varied over a range of ±20% from the baseline.

Cost-effectiveness analysis of medical intervention is the balance between the cost of the intervention and the incremental health benefits attributable to the intervention. We calculated cost per QALY saved by vaccination to quantify the cost of purchasing a year of good health. We used the terminology suggested by the WHO that defines “cost-effective” as lower than three times the annual per capita gross domestic product (GDP) and “very cost-effective” as lower than the GDP [27].

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The detail and quantity of the medical records we analyzed makes it feasible to stratify QALY losses according to the severity of each clinical outcome, as performed previously in QALY calculations [28]. Specifically, we determined the QALY losses with respect to the five clinical outcomes considered. In the base-case, we assumed 0.0046 QALY losses for homecare influenza, 0.0084 for outpatient visit consultation influenza, 0.0086 for outpatient visit consultation for pneumonia, and 0.0144 for hospitalizations. As our data indicates that the duration of hospitalization increases with age (Table 1), and consistent with [29], we standardized the QALY losses of hospitalization for each age-group based on the age-specific durations of hospitalization. Losses in quality life years as a result of death were estimated from the age-specific quality of life norms and discounted by 3.5% annually [28]. Given that there is variation in the literature regarding the quantification of QALY losses for influenza and pneumonia [29–34], in our sensitivity analysis, we varied QALYs over plausible ranges of ±15%, which spans beyond the values assumed in previous studies [28–31,33].

We divided the PLUS policy into ten non-competing [35] targets based on age and infection history (i.e. P_O and P_H patients in each of the five age-groups). For every group, we calculated program costs, benefits, and incremental cost-effective price per QALY saved (ICER) beyond the current policy. These divisions provide public health authorities with evaluations to inform the decision of whether to implement the entire PLUS policy or only the most cost-effective targets, such as targeting only P_H patients in specific age-group(s) depending on the willingness to pay [35] of public health authorities.

Results

We found that individuals previously infected with pneumonia were more susceptible both to become infected and to be hospitalized in the subsequent season regardless of age-group, for both outpatient treatment and hospitalization, with the exception of the risk of children under four years being hospitalized given that they were treated as outpatients for pneumonia in the season prior (Table 2). These findings were consistent throughout the eight year time series analyzed. For example, among individuals older than 65, 24.5 per 1000 were diagnosed as P_O, whereas for individuals in this same age-group who were treated as outpatients with pneumonia in the prior season, the risk was 96.8 per 1000. In the age-group of 25–50 years, the risk of being hospitalized with pneumonia was relatively low at 0.8 per 1000, whereas for individuals in this same age-group who were diagnosed with pneumonia in the prior season, the risk was 3.3 per 1000.

Our data indicate that elderly above 65 have the highest risk of hospitalization due to pneumonia with 11.8 cases per 1000. However, individuals hospitalized with pneumonia in the prior season, irrespective of age, had an even higher risk of hospitalization with pneumonia in the current season (25.9–51.6 per 1000) than the elderly above 65.

To evaluate whether medical history, stratified by outpatient treatment and hospitalization, further back than one year can also be used to identify elevated risk for future infection, we calculated the mean and confidence interval of the relative risk of infection in a current season given an infection in the previous k^{th} season (Figure 1). Our results suggest that, on

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average, P_H patients are at higher risk to be hospitalized for pneumonia even after six years following infection, and that P_H and P_O patients are at higher risk of pneumonia infection that requires outpatient treatment in the subsequent two years. Thus, in addition to age, an individual's medical history from several years in the past is a predictor of future risk.

Cost-effectiveness

Base case—The PLUS policy is composed of ten non-competing targets based on age-group and prior P_O and P_H infection. We first evaluated the incremental costs and benefits for vaccination in each intervention program beyond the current policy (Table 3). The incremental gain in the vaccination program that targets P_H patients is cost-saving for base case values regardless of age (Table 3). The break-even prices at which vaccination programs targeting P_H patients become cost-saving range from $20 to $47, depending on age-group, which are well within the estimated costs of both influenza vaccination and its promotion (Table 1). The targeting of *Po* individuals is cost-saving for elderly above 65 at a break-even price of $22. For *Po* individuals below 65, intervention program prices were found to be cost-effective with ICERs ranging from $2,909 to 40,123 per QALY saved, depending on the age-group(s) targeted.

For the ten potential targets composing the PLUS policy, we determined prioritization of the targets ranked by ICERs [35] (Figure 2A) and the corresponding vaccination coverage that would be achieved by this prioritization (Figure 2B). Further, we determined the target combinations that would be optimally implemented depending on the health authorities' willingness to pay per QALY saved (Figure 2C). Cost-saving policies (grouped in target A of Figure 2) should be implemented at any level of willingness to pay. For prior P_H patients, the older the individual, the higher the cost-saving threshold price of the vaccine program. This finding is regardless of the factor that vaccination efficacy in the elderly is lower than other age-groups.

Health authorities may employ different criteria to decide whether to implement a policy. Two such common criteria are in terms of optimizing a budget limit or thresholds of the willingness to pay for a QALY saved [35]. As an illustrative example of the former, given a total budget constraint of $200,000 and a goal of achieving an additional 75% vaccination coverage in the target groups beyond the coverage that is reached by current policies, authorities should optimally target all prior P_H and P_O patients between six months to four years and above 50 years (targets A-C in Figure 2). Alternatively, if the criteria of health authorities for implementing policies are based on a willingness to pay per QALY saved of $10,000, programs A-C should be implemented (Figure 2C).

The overall PLUS policy would require vaccinating a further 2.26% of the Israeli population, but can save an additional 538 QALYs at a mean price of only $1,278/QALY. Even if the additional vaccination uptake for the targeted population is imperfect at, for example 50%, the ICER would increase to $2,200/QALY saved, which is still a relatively low cost per QALY saved (Figure 2). Implementation of only the cost-saving policies, namely targeting P_H patients in all age-groups and P_O patients in the elderly as a supplement to the current policy can save 400 QALYs as well as $513,550 each year (Figure 2A).

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Sensitivity analysis—As our cost-effectiveness analysis includes some unknown parameters; and several, such as vaccination efficacy and infection rate, vary among seasons, we conducted one-way sensitivity analysis for uncertain values of all parameters (See Appendix B), as well as global uncertainty analysis which integrates all parameter uncertainties for each of the ten potential target groups that compose the PLUS policy (Figure 3).

We found that the most influential parameters in determining policy cost-effectiveness were the age-specific influenza attack rates and vaccine efficacies. For example, lowering the influenza attack rate from the baseline of 9% to 5% for the total population will reduce incidence of complications associated with influenza, such as pneumonia and death. Consequently, cost-saving threshold prices of targeting vaccination different in prior P_H age-groups would decline to a range of $8.60–25.90, depending on age-group, and to $11.40 in prior P_O elderly above 65. Sensitivity analysis predicts that for the lowest vaccine effectiveness evaluated (Table 1), the cost-saving threshold price of vaccinating prior P_H patients drops to a range of $10.20–33.40, depending on age-group, and to $14.78 in prior elderly P_O above 65.

To evaluate the robustness of our findings we conducted a global uncertainty analysis which integrates uncertainty in all parameters (Figure 3), including costs of medical outcomes, the evaluation of QALY losses, vaccine effectiveness, and infection risks (Table 1). Our global uncertainty analysis suggests that targeting prior P_H patients is likely to be cost-saving, meaning that the policy would likely save QALYs for no additional costs as a result of the reduction in clinical outcomes, with a probability ranging from 0.74 to 0.99, depending on the age-group (Figure 3). Targeting prior P_O patients was found to be cost-saving for elderly above 65 with a probability as high as 0.97. In age-groups that are currently not being prioritized for vaccination (Figure 3 B, C and D), targeting P_O patients was found to be cost-effective at $50,000 per QALY saved with a probability ranging from 0.8 to 1. This level of cost-effectiveness is favorable relative to those of other health policies recently implemented in Israel (see Discussion). Taken together, applying the PLUS policy for both prior P_H and P_O patients in any age-group would be beneficial both economically and in terms of disease burden.

Discussion

We show that individuals previously infected with pneumonia have a much higher risk of pneumonia infection in subsequent years. Specifically, those previously hospitalized, irrespective of age, have a substantially elevated risk of infection and are even more likely to become hospitalized with pneumonia than an average elderly individual above 65. Consequently, we found that the overall PLUS policy is very cost-effective in the vast range of conditions. In addition, the most cost-effective components of the PLUS policy, which are in fact even cost-saving, are the targeting all prior hospitalized patients, irrespective of age, and prior outpatients elderly above 65. Whereas recommendations from the WHO and the Ministry of Health in Israel prioritize seasonal influenza vaccination primarily on the basis of age and specific co-morbidities, we found that infection histories of individuals should also be considered when targeting influenza vaccination.

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Variable diagnosis and pneumonia etiologies, as well as incomplete surveillance, are potential complications for the policies that we evaluate. Firstly, diagnostic criteria of pneumonia varies among health care providers, countries and international classification codes [36] (see, for example, ICD9 versus ICD10); some diagnoses require only the presence of infiltrates on a chest radiograph, whereas others require certain respiratory symptoms. Additionally, diagnosis is particularly challenging in young children, because pneumonia and bronchiolitis are both common in this age-group, and the symptoms of these two diseases often overlap [37]. Nevertheless, we found that even given the misdiagnosis inherent in the data, and varying widely over rates of false positives and true negatives, the policy of targeting individuals previously diagnosed with pneumonia remains effective. Taking into consideration the misclassifications, we assumed a conservative vaccine efficacy in reducing pneumonia.

The PLUS policy could be achieved via pamphlets, telephone reminders or primary physician recommendations. As vaccination decisions are highly affected by perceived risk of infection and the perceived hazard upon infection [38], a high compliance to adopt the PLUS policy is expected as it would also be motivated by the self-interest of the individuals. Following recommendations, vaccination uptake in elderly above 65 reached 60–70%. Similarly, uptake in the PLUS policy is likely given that the targeted population is even more likely to develop manifestations. Recent policies of rotavirus and HPV vaccination in Israel were adopted at prices of $31,000/QALY saved and 55,000$/QALY saved, respectively [39–41]. Even with an additional vaccine compliance of 50%, applying the overall PLUS policy will be cost-effective at $2,200 per QALY saved, which is considered very cost-effective by the WHO [27].

Our analysis was based on medical records from Israel, but our findings may be applicable in other developed countries. Whereas influenza vaccination policy in developed countries focuses on ages and comorbidities [3,42], the suggested policy has yet to be implemented in any developed countries. The cost-effectiveness of the recommended policy in each country depends on the combination of the current vaccination uptake in each age-group and the costs of medical outcomes. Trends in coverage of influenza vaccination in Israel are similar to those of several others countries within the Organization for Economic Co-operation and Development (OECD) [14,43]. Although Israel has a younger demographic structure, exacerbating influenza transmission and disease burden relative to the majority of the OECD countries, outpatient visits and hospitalization fees are significantly more costly in the U.S. and other countries. Consequently, the PLUS policy is likely to be cost-effective in the U.S. and other OECD countries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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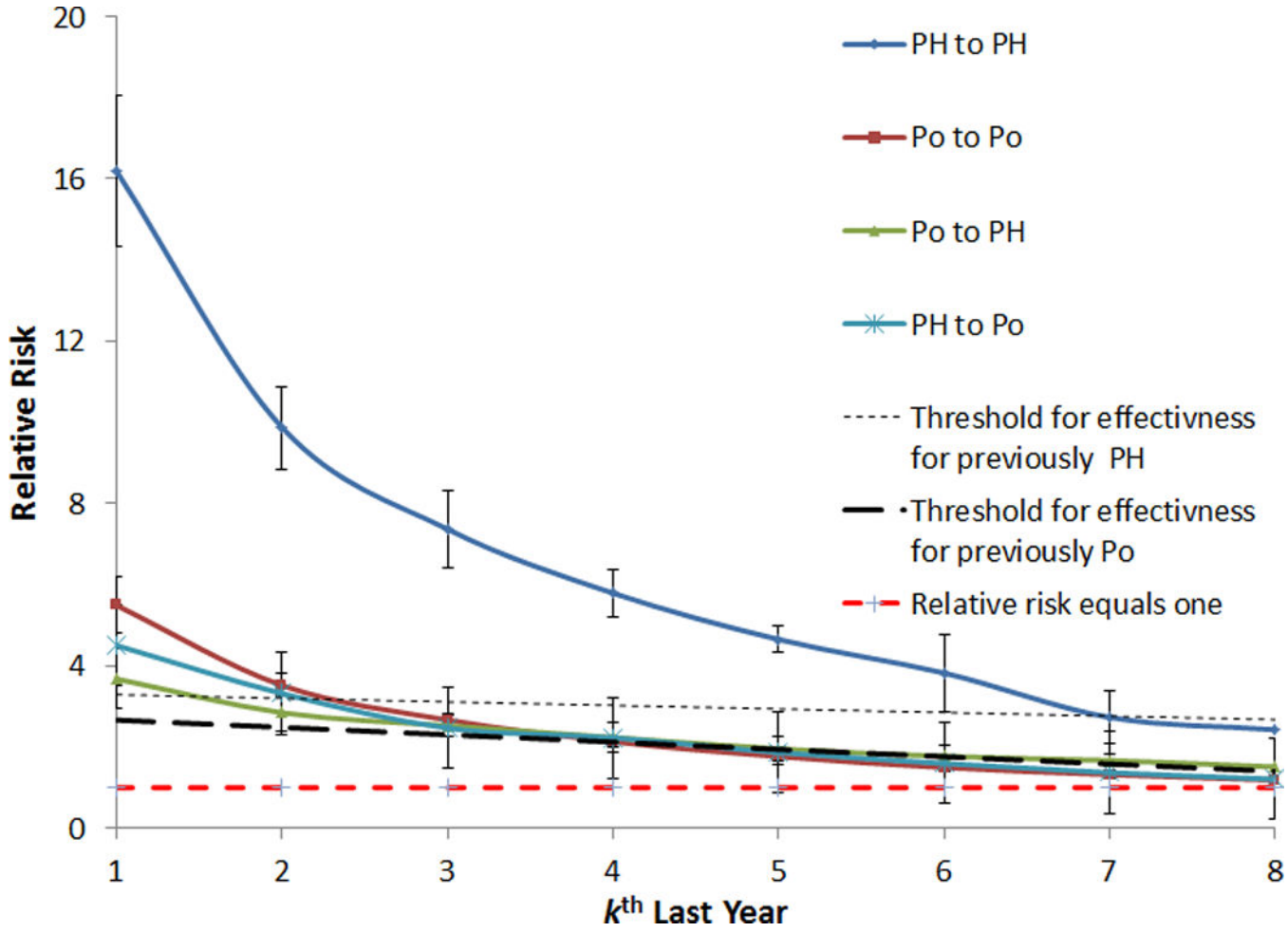

Figure 1.

Mean relative risk of infection given illness in k^{th} prior season in the four scenarios, distinguishing between outpatient treatment and hospitalization. Dash lines reflect the lower bound above which the prior season's patients risk is higher than others, adjusting for the effect of age, and a reference line in which the relative risk equals one. 95% Confidence intervals between years performed under the assumption of normal distribution.

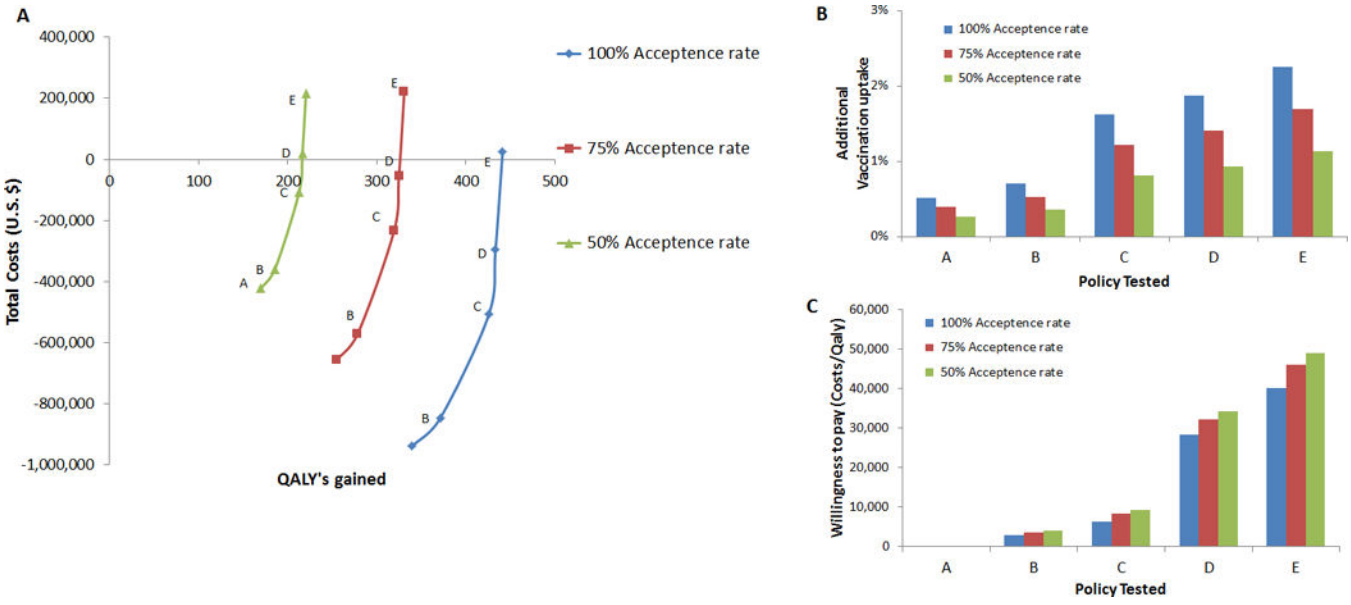

Figure 2.

(A) Costs and QALYs saved given the implementation of target groups in optimal order of prioritization (B) Corresponding additional vaccination coverage on top of the current policy (C) Willingness to pay per QALY saved for each vaccination program. The vaccination programs ranked by cost-effective order are A) Targeting P_H patients and P_O outpatients >65 B) Targeting additionally prior P_O 50–65 C) Targeting additionally prior P_O 0–4 D) Targeting additionally prior P_O 25–50 E) Targeting additionally prior P_O 4–25.

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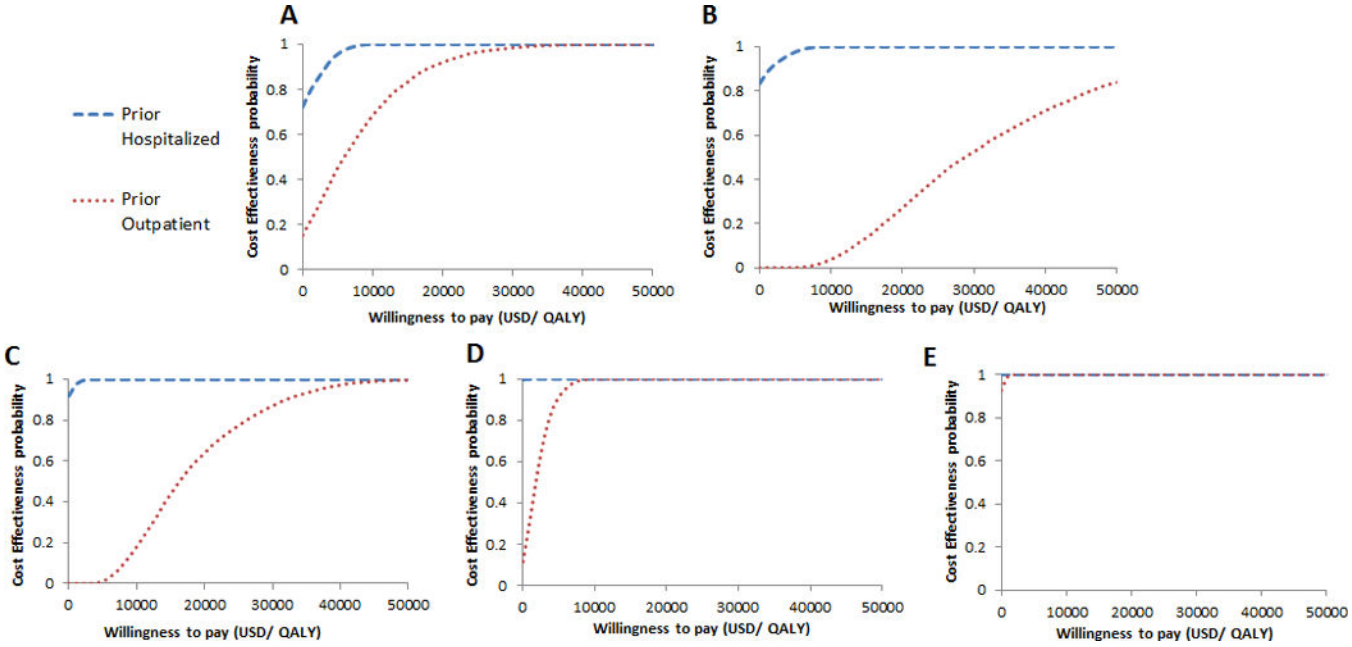

Figure 3.

Probabilities in which targeting P_O and P_H in each age-group is cost-effective given level of willingness to pay per QALY in ages A) 0–4 B) 4–25 C) 25–50 D) 50–65 E) >65 relative to the current policy. The vertical dashed line reflects the 2012 GDP per capita, (i.e. 32,000$).

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Table 1

Health outcomes, probabilities, and costs used as the base case and sensitivity analysis.

	0–3	4–24	25–49	50–64	65	Total	Range evaluated in sensitivity analysis	Source
Health outcome probabilities								
Influenza gross attack rate	0.203	0.102	0.066	0.066	0.09	0.09	0.05–0.15*	[19,20]
Pr(outpatient visit / influenza infection)	0.48	0.32	0.36	0.42	0.72	0.41	0.1–0.6*	[19,20,25]
Pr(death/infected)	0.00004	0.0001	0.0009	0.00134	0.0117	0.0017		[19]
Efficacy against outpatient pneumonia during flu season	0.05	0.05	0.05	0.05	0.05	0.05	0–0.1*	[3,4,16,17,26]
Efficacy against hospitalization during flu season	0.25	0.25	0.25	0.25	0.25	0.25	0.1–0.4	[3,4,16,17,26]
Efficacy against influenza	0.7	0.7	0.7	0.6	0.5	0.68	0.4–0.75*	[3]
Efficacy in reducing death in influenza cases	0.4	0.4	0.4	0.4	0.4	0.4	0.33–0.48*	[3,4]
Duration of hospital stay (days) due to pneumonia in Israel	3.34	3.79	4.63	5.56	6.05	5.08		This study
mean (SD) of current vaccination uptake between 2008–2012								This study
Overall population	0.26 (0.04)	0.07 (0.01)	0.1 (0.02)	0.31 (0.03)	0.62 (0.02)	0.19 (0.02)		
Prior outpatient, P_O	0.25 (0.04)	0.14 (0.02)	0.16 (0.02)	0.43 (0.03)	0.67 (0.02)	0.25 (0.02)		
Prior hospitalized, P_H	0.3 (0.03)	0.23 (0.02)	0.27 (0.02)	0.44 (0.03)	0.44 (0.02)	0.3 (0.02)		
Health outcome-costs (translated to U.S. dollar)							**−15% +15%****	
Additional promotion costs to encourage vaccination (per individual in the targeted population)						1.12		See Appendix A
Costs per unit (per vaccinated)								[19–21]
Influenza vaccination						13.5		
Vaccination administration						1.25		
Total vaccination cost						14.75	12.75–16.75	
Health outcomes								
Hospitalization fee/day						605.2		
Outpatient visit for influenza						61.8		
Outpatient visit for pneumonia (including lab tests and medication)						76.15		

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	0–3	4–24	25–49	50–64	65	Total	Range evaluated in sensitivity analysis	Source
Home care						5.56		
Transportation						3.06		
Death***						8696.58		
Health outcomes-QALY losses							**−15% +15%****	
Hospitalizations	0.0095	0.0108	0.0131	0.0158	0.0171	0.0144		
Outpatient visits for influenza						0.0084		
Outpatient visit for pneumonia						0.0086		
Home care						0.0046		

* The values stated for the sensitivity analysis represent changes in the total. We assumed the same relative changes for each age-group as for overall.

** For sensitivity analysis, the same change was assumed for all outcomes in each iteration.

*** Costs of deaths were estimated as additional costs to hospitalization.

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Table 2

Incidences and risks of future pneumonia infection given prior pneumonia infection by age.

Mean Incidence (SD) (per 1000)		0–3	4–24	25–49	50–64	≥65	Total
P_O to P_O	Outpatient in current season	89.9(6)	11.7(1.6)	7.7(1.1)	13(1.9)	24.5(3.7)	19.9(2.1)
	Outpatient in current season given outpatient in prior season	151.4(7.9)	70.6(7)	50.7(6.5)	71.8(9.2)	96.8(9.8)	75.3(5.7)
	Outpatient in current season given not outpatient in prior season	87.3(6)	11.2(1.7)	7.6(1)	12.6(2)	22.8(3.8)	19.2(1.7)
	Relative Risk	1.7(0.1)	6.4(1)	6.7(0.4)	5.7(0.4)	4.3(0.5)	3.9(0.5)
P_O to P_H	Hospitalization in current season	7.2(1.4)	0.7(0.2)	0.8(0.3)	2.1(0.5)	11.8(2.3)	2.7(0.5)
	Hospitalization in current season given outpatient in prior season	5.8(1.1)	3.7(0.7)	3.3(0.5)	7(1.1)	21.3(2.2)	6.1(0.6)
	Hospitalization in current season given not outpatient in prior season	7.3(1.7)	0.6(0.2)	0.7(0.3)	1.8(0.5)	11.4(2.6)	2.6(0.6)
	Relative Risk	0.79*(0.07)	6.16(1.33)	4.71(1.05)	3.89(0.38)	1.86(0.1)	2.34(0.3)
P_H to P_O	Outpatient in current season	89.9(6)	11.7(1.6)	7.7(1.1)	13(1.9)	24.5(3.7)	19.9(2.1)
	Outpatient in current season given not hospitalizationin prior season	122.6(10.3)	67.8(4.1)	47.2(3.8)	50.2(8.7)	35(4.3)	60.96(2.46)
	Outpatient in current season given not hospitalizationin prior season	89.6(5.5)	11.5(1.7)	7.5(1.1)	12.7(2)	24.3(3.9)	19.6(1.7)
	Relative Risk	1.36(0.12)	5.9(0.73)	6.3(0.65)	3.96(0.78)	1.44(0.13)	3.11(0.3)
P_H to P_H	Hospitalization in current season	7.2(1.4)	0.7(0.2)	0.8(0.3)	2.1(0.5)	11.8(2.3)	2.7(0.5)
	Hospitalization in current season given hospitalization in prior season	25.9(4.5)	38(12.7)	39(12.2)	50.6(11.8)	51.6(10.8)	40.27(9.8)
	Hospitalization in current season given not hospitalization in prior season	7(1.6)	0.7(0.19)	0.8(0.3)	2.1(0.5)	12(2.4)	2.7(0.5)
	Relative Risk	3.7(1)	53.45(13.8)	48.8(9)	24.1(4.5)	4.3(0.2)	14.8(1.1)

*All relative risks except for children 0–4 in P_O to P_H are significant (p-value <0.01).

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Table 3

Cost-effectiveness analysis for vaccination of P_H and P_o patients relative to the current policy

Cost-effectiveness analysis	0–3	4–24	25–49	50–64	≥65	Total
P_H Patients (incremental costs and benefits)						
Overall direct costs no vaccination	416,578	178,834	242,624	470,412	2,255,095	3,563,543
Overall direct costs following vaccination	383,847	160,974	211,189	381,823	1,768,951	2,906,783
Overall direct gain	32,731	17,859	31,435	88,589	486,145	656,760
Threshold price to be cost saving	20.29	24.34	30.00	51.39	65.65	
QALYs saved	6.07	1.62	6.00	34.66	155.36	203.71
ICER	<0	<0	<0	<0	<0	
P_O Patients (incremental costs and benefits)						
Overall direct costs no vaccination	2,354,799	529,033	311,278	511,517	2,119,277	5,825,904
Overall direct costs following vaccination	2,693,448	848,884	522,472	603,284	1,838,255	6,506,343
Overall direct gain	−338,649	−319,851	−211,194	−91,766	281,022	−680,439
Threshold price to be cost saving	10.16	4.47	4.11	8.62	28.92	
QALYs saved	54.27	7.97	7.48	31.55	136.04	237.31
Threshold price to be cost effective at GDP per QALY	33.18	12.48	15.89	74.54	243.53	
ICER	6,240	40,123	28,243	2,909	<0	

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