Vaccine 31 (2013) 3079–3089

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Optimal targeting of seasonal influenza vaccination toward younger ages is robust to parameter uncertainty

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ARTICLE INFO

Article history:
Received 22 September 2012
Received in revised form 27 March 2013
Accepted 24 April 2013
Available online 16 May 2013

Keywords:
Seasonal influenza
Vaccination
Mathematical modeling
Optimization

ABSTRACT

Identification of the optimal vaccine allocation for the control of influenza requires consideration of uncertainty arising from numerous unpredictable factors, including viral evolution and diversity within the human population's immunity as well as variation in vaccine efficacy. The best policy must account for diverse potential outcomes based on these uncertainties. Here we used a mathematical model parametrized with survey-based contact data, demographic, and epidemiological data from seasonal influenza in the United States to determine the optimal vaccine allocation for five outcome measures: infections, hospitalizations, deaths, years of life loss, and contingent valuation. We incorporated uncertainty of epidemiological parameters and derive probability distributions of optimal age- and risk-specific allocation of vaccine. Our analysis demonstrated that previous recommendations of targeting schoolchildren (ages 5–17 years) and young adults (18–44 years) are generally robust in the face of uncertainty. However, when the outcome measure is to minimize deaths, years of life loss, or contingent valuation, uncertainty analysis identified scenarios under which it is optimal to target people at high risk for complications, even when vaccine are in abundance.

1. Introduction

Despite long-standing vaccination efforts, seasonal influenza continues to be responsible for substantial morbidity and mortality in the United States. It is estimated that seasonal influenza results in an average of 36,000 deaths, more than 200,000 hospitalizations, and an economic burden of approximately US$87 billion annually [1,2]. To minimize the economic and social impact of epidemic and pandemic influenza, optimal allocation of vaccines is imperative [1–3]. A number of studies have developed mathematical models that identify and evaluate the effectiveness of vaccine allocation strategies for different public health objectives such as minimizing mortality, infections, and hospitalizations [3–8].

Previous studies have derived vaccination strategies by using a base-case parameter set [3–8], even though there is considerable uncertainty in influenza epidemiological parameters [9–11]. Influenza epidemics recur yearly in part due to the cyclical evolution of influenza viruses from year to year [9]. This rapid evolution of influenza provides limits the foresight with which a vaccine may be developed and deployed, leading to uncertainty in vaccine efficacy and availability [10]. This evolution also changes the clinical and epidemiological parameters of influenza [9], all of which influence influenza severity and spread. To accommodate this variation, these optimization studies have generally employed a univariate sensitivity analysis to test the robustness of their results with respect to a given epidemiological parameter such as the reproductive number [3,4,6]. However, the performance of models that neglect uncertainty is dependent on assumed parameter values [7,11,12], particularly in models wherein small changes in parameter values may influence the effectiveness of individual strategies. Performance in these models may shift from optimal to highly suboptimal based on real values of parameters within the range of known uncertainty [12]. Though univariate sensitivity analysis helps to assess potential individual parameters that could mislead a base case analysis, univariate analysis does not provide comprehensive study of systems where simultaneous changes in more than one parameter may result in synergistic shifts in outcome arising from real-world nonlinearities [13]. In influenza transmission

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http://dx.doi.org/10.1016/j.vaccine.2013.04.052

Table 1
Epidemiological parameters of the seasonal influenza model and their distributions.

Variable	Distribution	References
Infectious period (ages 0–14)	Gamma(Mean 3.6, Std 1.9)	[19]
Infectious period (ages 15+)	Gamma(Mean 3.9, Std 1.9)	[19]
Latent period	Triangular(Min 1, Mode 2, Max 3)	[20–23]
Susceptibility (ages 0–3)	Normal(Mean 0.83, Std 0.369)	[24]
Susceptibility (ages 4–17)	Normal(Mean 0.49, Std 0.5)	[24]
Susceptibility (ages 18+)	Normal(Mean 0.53, Std 0.49)	[24]
Reproductive number (R)	Normal(Mean 1.3, Std 0.15, Min 1)	[25]
Case mortality (ages 0–4)	Normal(Mean 4×10^{-5}, Std 10^{-5}, Min 0)	[2]
Case mortality (ages 5–17)	10^{-5}	[2]
Case mortality (ages 18–49)	Normal(Mean 9×10^{-5}, Std 3×10^{-5}, Min 0)	[2]
Case mortality (ages 50–64)	Normal(Mean 134×10^{-5}, Std 45×10^{-5}, Min 0)	[2]
Case mortality (ages 65+)	Normal(Mean 117×10^{-4}, Std 39×10^{-4}, Min 0)	[2]
Case hospitalization (ages 0–4)	Normal(Mean 0.0141, Std 0.0047, Min 0)	[2]
Case hospitalization (ages 5–17)	Normal(Mean 0.0006, Std 0.0002, Min 0)	[2]
Case hospitalization (ages 18–49)	Normal(Mean 0.0042, Std 0.0014, Min 0)	[2]
Case hospitalization (ages 50–64)	Normal(Mean 0.0193, Std 0.0064, Min 0)	[2]
Case hospitalization (ages 65+)	Normal(Mean 0.0421, Std 0.0140, Min 0)	[2]
Proportion high risk (ages 0.5–1)	Normal(Mean 0.0415, Std 0.0044, Min 0)	[26]
Proportion high risk (ages 2–5)	Normal(Mean 0.0883, Std 0.0051, Min 0)	[26]
Proportion high risk (ages 5–18)	Normal(Mean 0.1168, Std 0.0030, Min 0)	[26]
Proportion high risk (ages 19–24)	Normal(Mean 0.1235, Std 0.0055, Min 0)	[26]
Proportion high risk (ages 25–49)	Normal(Mean 0.1570, Std 0.0027, Min 0)	[26]
Proportion high risk (ages 50–64)	Normal(Mean 0.3056, Std 0.0044, Min 0)	[26]
Proportion high risk (ages 65+)	Normal(Mean 0.4701, Std 0.0050, Min 0)	[26]
High-risk relative mortality (ages 0–19)	Triangular(Min 0.4, Mode 0.6, Max 21.9)/Triangular(Min 0.041, Mode 0.07, Max 0.30)	[17]
High-risk relative mortality (ages 20–64)	Uniform(Min 0.8, Max 24.9)/Triangular(Min 0.21, Mode 0.31, Max 0.41)	[17]
High-risk relative mortality (ages 65+)	Uniform(Min 23, Max 29.6)/Triangular(Min 2.3, Mode 3.51, Max 4.52)	[17]
High-risk relative hospitalization (ages 0–19)	Uniform(Min 6.0, Max 21.4)/Uniform(Min 0.57, Max 6.9)	[17]
High-risk relative hospitalization (ages 20–64)	Uniform(Min 6.9, Max 22.3)/Uniform(Min 1.5, Max 12.0)	[17]
High-risk relative hospitalization (ages 65+)	Uniform(Min 33.3, Max 68.4)/Uniform(Min 12.5, Max 15.8)	[17]
Vaccine efficacy against infection (ages 0.5–15)	Uniform(Min 0.54, Max 0.8)	[27,28]
Vaccine efficacy against infection (ages 16–64)	Uniform(Min 0.54, Max 0.7)	[27,28]
Vaccine efficacy against infection (ages 65+)	Uniform(Min 0.33, Max 0.66)	[27,28]
Vaccine efficacy against mortality	Uniform(Min 0.39, Max 0.54)	[16]
Vaccine efficacy against hospitalization	Uniform(Min 0.21, Max 0.73)	[16,27]

Std = standard deviation; Min = minimum; Max = maximum; Normal(Mean m, Std s, Min a) is the standard Normal(Mean m, Std s) random variable censored so that it has minimum a.

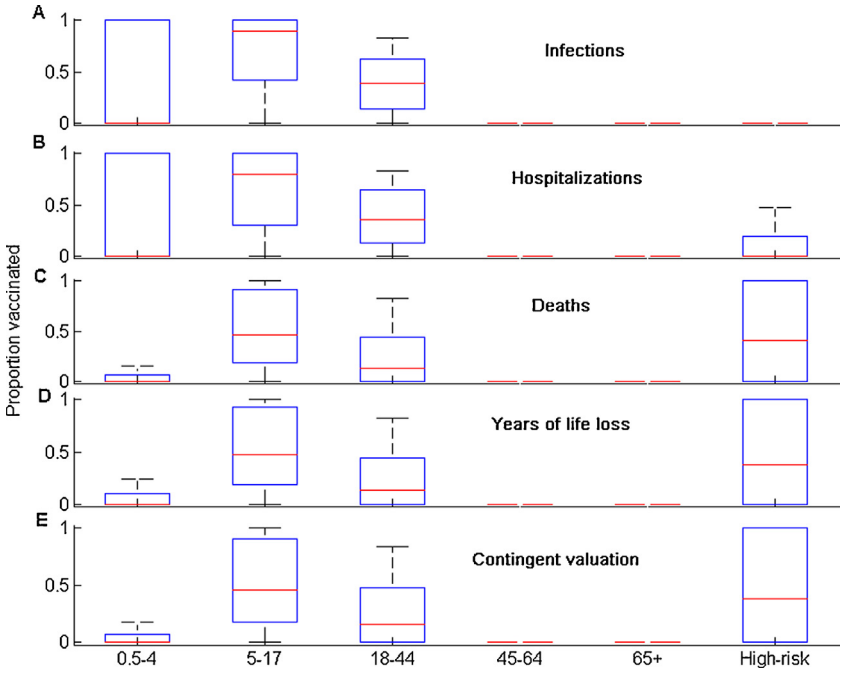

Fig. 1. The optimal allocation of 80 million vaccine doses for the five different outcome measures. The box-plot shows the median (red line), the interquartile range (blue box), and the minimum and maximum values (black bars) of the optimal proportion of individuals vaccinated for each group. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)