ELECTRONIC SUPPLEMENTARY MATERIAL

Epidemiologic Module Inputs

Table S1 Contact matrix

		Infectious (j)								
	Age (y)	0–3	4–6	7–9	10–19	20–34	35–49	50–64	65–69	≥70
Susceptible (i)	0–3	0.98	1.36	1.55	0.87	1.07	0.64	0.12	0.07	0.06
	4–6	0.54	1.00	1.23	0.74	0.49	0.43	0.06	0.04	0.03
	7–9	0.44	0.99	1.26	0.78	0.33	0.40	0.05	0.03	0.03
	10–19	1.02	2.52	3.27	2.72	1.59	2.28	0.55	0.30	0.19
	20–34	0.91	0.93	0.95	1.02	3.51	3.22	1.33	0.80	0.38
	35–49	0.50	0.92	1.14	1.42	3.15	3.59	1.32	0.79	0.40
	50–64	0.17	0.25	0.29	0.63	2.52	2.54	1.69	1.17	0.54
	65–69	0.05	0.06	0.07	0.14	0.58	0.58	0.42	0.50	0.23
	≥70	0.06	0.09	0.10	0.11	0.52	0.55	0.37	0.40	0.92

Source: Del Valle et al. [1], adapted to match the age structure of the model

Table S2 Population distribution

Age range (y)	%	Population
0–3	4.59	14,077,000
4–6	3.97	12,188,400
7–9	3.99	12,249,600
10–19	13.64	41,844,000
20–34	20.57	63,097,000
35–49	20.05	61,510,000
50–64	19.67	60,343,000
65–69	4.43	13,599,000
70+	9.10	27,907,000
Total	**100.00**	**306,815,000**

Source: 2012 US Current Population Survey [2]

Table S3 US influenza virologic surveillance						
Season	**% Type B**	**% Yamagata**	**% Victoria**	**% Type A**	**% H1N1**	**% H3N2**
1999–2000	0.4	100.0	0.0	99.6	3.2	96.8
2000–2001 (high/low match scenarios)	**46.4**	**100.0**	**0.0**	**53.6**	**96.9**	**3.1**
2001–2002	12.5	22.8	77.2	87.5	1.9	98.1
2002–2003	42.6	0.4	99.6	57.4	74.9	25.1
2003–2004	1.0	93.0	7.0	99.0	0.0	100.0
2004–2005	24.6	74.4	25.6	75.4	0.3	99.7
2005–2006	19.1	21.9	78.1	80.9	7.6	92.4
2006–2007	20.8	23.5	76.5	79.2	62.3	37.7
2007–2008	29.0	97.7	2.3	71.0	26.2	73.8
2008–2009	33.5	16.6	83.4	66.5	89.2	10.8
2009–2010	1.2	11.6	88.4	98.8	95.0	5.0
2010–2011	26.2	5.8	94.2	73.8	38.0	62.0
2011–2012	18.3	48.3	51.7	81.7	27.0	73.0
2012–2013	29.6	63.8	36.2	70.4	5.6	94.4
2013–2014	14.7	93.0	7.0	85.3	87.7	12.3
Average match scenario	**21.3**	**10.3**	**11.0**	**78.7**	**30.4**	**48.3**

Source: Centers for Disease Control and Prevention (CDC) [3–5], Reed et al. [6], and Epperson et al. [7]

Table S4 US influenza vaccine coverage 2013–14 season

Age cohort (y)	% vaccinated
0–3	72.2
4–6	63.4
7–9	61.0
10–19	49.3
20–34	32.3
35–49	32.3
50–64	45.3
65–69	65.0
70+	65.0

Source: Centers for Disease Control and Prevention (CDC) [8]

Table S5 Probability of successful vaccination when vaccinated

Age (y)	aTIV ≥65; QIV <65				QIV				TIV			
	Estimate	SD of estimate	Low	High	Estimate	SD of estimate	Low	High	Estimate	SD of estimate	Low	High
Low match season												
0–3	0.40	0.05	0.30	0.51	0.40	0.05	0.30	0.51	0.25	0.04	0.18	0.33
4–6	0.40	0.05	0.30	0.51	0.40	0.05	0.30	0.51	0.25	0.04	0.18	0.33
7–9	0.65	0.06	0.52	0.77	0.65	0.06	0.52	0.77	0.56	0.05	0.47	0.65
10–19	0.65	0.06	0.52	0.77	0.65	0.06	0.52	0.77	0.56	0.05	0.47	0.65
20–34	0.65	0.06	0.52	0.77	0.65	0.06	0.52	0.77	0.56	0.05	0.47	0.65
35–49	0.65	0.06	0.52	0.77	0.65	0.06	0.52	0.77	0.56	0.05	0.47	0.65
50–64	0.60	0.06	0.48	0.72	0.60	0.06	0.48	0.72	0.50	0.05	0.41	0.59
65–69	0.44	0.09	0.27	0.62	0.40	0.09	0.23	0.58	0.25	0.07	0.13	0.39
70+	0.44	0.09	0.27	0.62	0.40	0.09	0.23	0.58	0.25	0.07	0.13	0.39
Average match season												
0–3	0.40	0.08	0.26	0.55	0.40	0.08	0.26	0.55	0.37	0.07	0.23	0.51
4–6	0.40	0.08	0.26	0.55	0.40	0.08	0.26	0.55	0.37	0.07	0.23	0.51
7–9	0.65	0.09	0.47	0.81	0.65	0.09	0.47	0.81	0.63	0.09	0.45	0.79

10–19	0.65	0.09	0.47	0.81	0.65	0.09	0.47	0.81	0.63	0.09	0.45	0.79
20–34	0.65	0.09	0.47	0.81	0.65	0.09	0.47	0.81	0.63	0.09	0.45	0.79
35–49	0.65	0.09	0.47	0.81	0.65	0.09	0.47	0.81	0.63	0.09	0.45	0.79
50–64	0.60	0.09	0.42	0.77	0.60	0.09	0.42	0.77	0.58	0.09	0.40	0.74
65–69	0.52	0.09	0.34	0.71	0.40	0.13	0.16	0.66	0.37	0.12	0.15	0.62
70+	0.52	0.09	0.34	0.71	0.40	0.13	0.16	0.66	0.37	0.12	0.15	0.62
High match season												
0–3	0.40	0.05	0.30	0.51	0.40	0.05	0.30	0.51	0.40	0.04	0.32	0.48
4–6	0.40	0.05	0.30	0.51	0.40	0.05	0.30	0.51	0.40	0.04	0.32	0.48
7–9	0.65	0.06	0.52	0.77	0.65	0.06	0.52	0.77	0.65	0.05	0.56	0.74
10–19	0.65	0.06	0.52	0.77	0.65	0.06	0.52	0.77	0.65	0.05	0.56	0.74
20–34	0.65	0.06	0.52	0.77	0.65	0.06	0.52	0.77	0.65	0.05	0.56	0.74
35–49	0.65	0.06	0.52	0.77	0.65	0.06	0.52	0.77	0.65	0.05	0.56	0.74
50–64	0.60	0.06	0.48	0.72	0.60	0.06	0.48	0.72	0.60	0.05	0.51	0.69
65–69	0.55	0.09	0.37	0.72	0.40	0.09	0.23	0.58	0.40	0.07	0.27	0.54
70+	0.55	0.09	0.37	0.72	0.40	0.09	0.23	0.58	0.40	0.07	0.27	0.54

Weighted average of age-stratified strain-specific efficacies (assumed to be the same across all matched strains for purposes of this analysis). Determined in conjunction with Beckmann Bio [9] based on meta-analysis (references available separately) [10–12]. aTIV viral effectiveness >65 y based on reduction in hospitalization observed in LIVE study [13]. Beta distribution applied for probabilistic variations *aTIV* adjuvanted TIV, *QIV* quadrivalent influenza vaccine, *SD* standard deviation, *TIV* trivalent influenza vaccine

Table S6 US influenza attack rates and conditional probabilities (Pr) of morbidity and mortality

Age (y)	Gross attack rate	Pr (outpatient/ influenza)	Pr (hospital/ influenza)	Pr (death/ influenza)
0–4	0.203	0.47866	0.0141	0.00004
5–17	0.102	0.351602	0.0006	0.00001
18–49	0.066	0.359488	0.0042	0.00009
50–64	0.066	0.42735	0.0193	0.00134
65+	0.09	0.7224	0.0421	0.0117

Source: Molinari et al. [14]

Calibration of the Model

The model was calibrated to fit a cumulative influenza incidence with observed historical US-specific data based on age-stratified trivalent influenza vaccine (TIV) vaccination rates averaging 45.8% (using the population distribution as described above) across the entire population estimated by the Centers for Disease Control and Prevention (CDC) for the 2013–2014 season [15] (**Table S4**), and age-stratified TIV vaccine effectiveness of 56.2% in an average match season based on literature sources [9–12] (**Table S5**). The proportion of the population with immunity at baseline was assumed as 67% [16]. The relative transmissibility factor σ was adjusted using Excel's goal-seek functionality (maximum 10,000 iterations, maximum change 0.00001) to produce cumulative influenza incidence in low (2.8%) (2000–2001 season [6]), average (8.4%) [14], and high (15.0%) (near high-end of CDC's estimated annual incidence range of 5–20% [17]) intensity influenza seasons (i.e. three calibrations) (**Table S7**).

The Excel goal-seek function was also used to ensure that the number of influenza cases by age cohort matched those obtained using age-stratified gross attack rates from Molinari et al. [14] in an average intensity, average match season. Adjusted age-stratified susceptibility factors φ_i were applied to all scenarios (**Table S4**).

Age-stratified conditional probabilities of hospitalization and death due to influenza and complications (pneumonia, bronchitis, other respiratory illness, cardiovascular disease) were adjusted to match the conditional probabilities suggested by Molinari et al. [14], and were applied to all scenarios (**Table S9** [14, 18–22]). Because of lack of specificity of the Molinari estimates, conditional probabilities of hospitalization and death for each complication were assumed to be the same.

Transmissibility factors σ and the corresponding R_e values, calculated by calibrating the model to observed incidence of influenza in the United States, were as follows: (1) low intensity season = 0.54 (2.8% influenza incidence in the population) corresponding to R_e = 0.97; (2) average season = 0.73 (8.4% incidence) corresponding to R_e = 1.30; (3) high intensity

= 0.94 (15.0% incidence) corresponding to R_e =1.70. The R_e range is consistent with estimates in the literature [23, 24] (**Table S7**).

Table S7 Relative transmissibility σ calibrated to incidence of influenza

Scenario	Relative transmissibility (σ)	Effective reproduction parameter (Re)	Incidence (%)	Source
Low intensity	0.54	0.97	2.8	Reed et al. [6]: 2000–2001 season
Average intensity	0.73	1.30	8.4	Molinari et al. [14]
High intensity	0.94	1.70	15.0	CDC [17]

Table S8 Age–stratified susceptibility

Age cohort	Susceptibility (a_i)
0–3	10.92
4–6	6.80
7–9	6.67
10–19	1.33
20–34	0.68
35–49	0.67
50–64	0.98
65–69	5.58
70+	4.99

Source: Calibrated to age-stratified gross attack rates in Molinari et al. [14], defined as average intensity, average match season then applied to all scenarios

Sensitivity Analysis

Within each scenario, we conducted a probabilistic sensitivity analysis across 1000 simulation runs by varying duration of infection, vaccine efficacy, conditional probabilities of complications, hospitalization and death, as well as impacts on life-years and quality-adjusted life-years (QALYs). Variation in the intensity (severity) of the influenza season was investigated using deterministic scenarios based on influenza incidence. The impact of vaccine match on outcomes was investigated in low, average, and high match scenarios using virology surveillance data from within which vaccine efficacy was probabilistically varied using a beta distribution.

The WAIFW (Who Acquired Infection From Whom) Matrix

The WAIFW matrix β is a product of the relative transmissibility parameter σ obtained via calibration, the contact matrix γ_{ij}, the susceptibility vector φ_i by age cohort i obtained via calibration, and the force of infection vector ζ_j by age cohort j assumed to be 1 in the model due to lack of specification.

$$\beta = (\beta_{ij}) = \sigma \cdot \gamma_{ij} \cdot \varphi_i \cdot \xi_j$$

An effective reproduction parameter, R_e, is calculated as the dominant eigenvalue of the next-generation matrix K according to Diekmann et al. [25]:

$$K = (k_{ij}) = \frac{\sigma \cdot \gamma_{ij} \cdot N_j}{N \cdot \upsilon}$$

where N_j / N is the proportion of the population in age cohort j and 1/υ is the duration of infection [23, 26, 27]. The challenges of measuring the reproduction parameter R (whether basic or effective) are well documented [28, 29].

Since our relative transmissibility parameter σ is a function of the cumulative incidence in a population which is partially immune due to previously acquired protection and vaccination in the current season, our estimate is not of the basic reproduction R_0, which is relevant for a fully susceptible population, but rather an effective reproduction parameter R_e. Where the contact and recovery rates do not vary with time as in this model, R_0 is linearly related to R_e according to the inverse of the proportion of the population that is susceptible [16].

$$R_0 = \frac{N}{S} R_e$$

Based on the model's assumptions that (a) 67% of the population is immune at baseline [16], (b) the immunization rate is 45.8% [15], and (c) an average match with TIV effectiveness of 56.2%, 24.5% of the total population is susceptible and hence R_0 = 1/24.5% x R_e = 4.08 x R_e. Therefore, R_0 in our simulations is 3.96, 5.30, and 6.94 in the low, average, and high intensity seasons, respectively.

Notes on the Calibration of Outcome Probabilities

To match the overall age-stratified conditional probabilities of hospitalization due to influenza in Molinari et al. [14], the conditional probabilities of hospitalization due to individual complications in the population ≥65 years are >1. The discrepancy is a complication of the model and highlights the difficulty in estimating burden for a disease that is rarely confirmed with laboratory tests. The conditional probabilities of the individual complications due to influenza were sourced from the UK study of Meier et al. [20] for cases without antivirals, and a relative risk estimate was applied to Meier's data using the meta-analysis of Kaiser et al. [21] for cases with antivirals. The implication is that (1) estimates derived from Meier et al. [20] and Kaiser et al. [21] for individual influenza-related complications in the elderly in the United States are conservative, or (2) Molinari et al. [14] overestimates this burden.

Meier et al. (Meier et al. [20] estimated probabilities of influenza and complications in the primary care setting using the UK-based General Practice Research database, while Molinari et al. [14] used data from the National Center for Health Statistics and the National Hospitalization Discharge Survey to estimate excess rates of hospitalization and death due to influenza based on seasonality. We believe the Molinari estimates are more appropriate calibration targets for the present study because the data were empirically fitted to US epidemiology with a commonly accepted and validated regression model as utilized by the CDC. The implication is that our model is conservative in its estimation of complications and related impacts on direct non-hospital costs, indirect costs, life-years, and QALYs.

Outcomes Module Inputs

Table S9 Outcome probabilities

Variable	Estimate	Low	High	Distribution	Source
Probability of influenza symptoms given infection					
All ages	0.5	0.25	0.75	Beta	Carrat et al. [18]
Probability of medical consultation if symptomatic					
0–3	0.479	0.266	0.696	Beta	
4–6	0.394	0.224	0.578	Beta	
7–9	0.352	0.205	0.514	Beta	
10–19	0.353	0.216	0.504	Beta	
20–34	0.359	0.270	0.455	Beta	Molinari et al. [14]
35–49	0.359	0.270	0.455	Beta	
50–64	0.416	0.285	0.553	Beta	
65–69	0.722	0.578	0.847	Beta	
70+	0.722	0.578	0.847	Beta	
Probability of antivirals prescribed if medical consultation					
0–3	0.277	0.257	0.298	Beta	
4–6	0.304	0.282	0.327	Beta	
7–9	0.333	0.309	0.357	Beta	
10–19	0.362	0.336	0.389	Beta	
20–34	0.425	0.394	0.456	Beta	Linder et al. [19]
35–49	0.523	0.485	0.561	Beta	
50–64	0.619	0.573	0.664	Beta	
65–69	0.679	0.628	0.727	Beta	
70+	0.706	0.654	0.757	Beta	

Complications					
Probability of pneumonia if prescribed antivirals					
0–3	0.00200	0.00083	0.00368	Beta	Meier et al. [20]; Kaiser et al. [21]
4–6	0.00200	0.00083	0.00368	Beta	
7–9	0.00200	0.00083	0.00368	Beta	
10–19	0.00036	0.00007	0.00088	Beta	
20–34	0.00043	0.00014	0.00087	Beta	
35–49	0.00043	0.00014	0.00087	Beta	
50–64	0.00071	0.00019	0.00158	Beta	
65+	0.00879	0.00679	0.01104	Beta	
Probability of pneumonia if not prescribed antivirals					
0–9	0.00200	0.00139	0.00272	Beta	Meier et al. [20]
10–19	0.00250	0.00205	0.00299	Beta	
20–64	0.00300	0.00261	0.00342	Beta	
65+	0.01157	0.01004	0.01320	Beta	
Probability of pneumonia if no medical consultation					
0–9	0.00200	0.00139	0.00272	Beta	Meier et al. [20]
10–19	0.00250	0.00205	0.00299	Beta	
20–64	0.00300	0.00261	0.00342	Beta	
65+	0.01157	0.01004	0.01320	Beta	
Probability of bronchitis if prescribed antivirals					
0–9	0.00600	0.00377	0.00873	Beta	Meier et al. [20]; Kaiser et al. [21]
10–19	0.00454	0.00318	0.00613	Beta	
20–49	0.00671	0.00534	0.00823	Beta	
50–64	0.01224	0.00948	0.01534	Beta	
65+	0.02003	0.01801	0.02215	Beta	

Probability of bronchitis if not prescribed antivirals					
0–9	0.00700	0.00581	0.00830	Beta	Meier et al. [20]
10–19	0.00900	0.00813	0.00991	Beta	
20–49	0.01100	0.01024	0.01179	Beta	
50–64	0.01900	0.01694	0.02117	Beta	
65+	0.03014	0.02766	0.03272	Beta	
Probability of bronchitis if no medical consultation					
0–9	0.00700	0.00581	0.00830	Beta	Meier et al. [20]
10–19	0.00900	0.00813	0.00991	Beta	
20–49	0.01100	0.01024	0.01179	Beta	
50–64	0.01900	0.01694	0.02117	Beta	
65+	0.03014	0.02766	0.03272	Beta	
Probability of other respiratory illness if prescribed antivirals					
0–9	0.08200	0.073	0.091	Beta	Meier et al. [20]; Kaiser et al. [21]
10–19	0.01725	0.015	0.020	Beta	
20–64	0.01400	0.012	0.016	Beta	
65+	0.01961	0.018	0.022	Beta	
Probability of other respiratory illness if not prescribed antivirals					
0–9	0.08600	0.082	0.090	Beta	Meier et al. [20]
10–19	0.06850	0.066	0.071	Beta	
20–49	0.05100	0.049	0.053	Beta	
50–64	0.04500	0.042	0.048	Beta	
65+	0.04575	0.043	0.049	Beta	
Probability of other respiratory illness if no medical consultation					
0–9	0.08600	0.082	0.090	Beta	Meier et al. [20]
10–19	0.06850	0.066	0.071	Beta	
20–49	0.05100	0.049	0.053	Beta	
50–64	0.04500	0.042	0.048	Beta	

65+	0.04575	0.043	0.049	Beta	
Probability of CVD if prescribed antivirals					
0–9	0.00000	0.00000	0.00000	Beta	
10–19	0.00035	0.00007	0.00087	Beta	
20–49	0.00070	0.00031	0.00124	Beta	Meier et al. [20]
50–64	0.00400	0.00250	0.00585	Beta	
65+	0.00387	0.00301	0.00485	Beta	
Probability of CVD if not prescribed antivirals					
0–9	0.00000	0.00000	0.00000	Beta	
10–19	0.00005	0.00001	0.00014	Beta	
20–49	0.00010	0.00004	0.00019	Beta	Meier et al. [20]
50–64	0.00040	0.00015	0.00076	Beta	
65+	0.00387	0.00301	0.00485	Beta	
Probability of CVD if no medical consultation					
0–9	0.00000	0.00000	0.00000	Beta	
10–19	0.00005	0.00001	0.00014	Beta	Meier et al. [20]
20–64	0.00010	0.00004	0.00019	Beta	
65+	0.00387	0.00301	0.00485	Beta	
Probability of otitis media if prescribed antivirals					
0–9	0.04100	0.03485	0.04763	Beta	
10–19	0.02450	0.02122	0.02801	Beta	
20–49	0.00800	0.00650	0.00966	Beta	Meier et al. [20]
50–64	0.00300	0.00172	0.00462	Beta	
65+	0.00200	0.00139	0.00271	Beta	
Probability of otitis media if not prescribed antivirals					
0–9	0.04000	0.037	0.043	Beta	
10–19	0.02350	0.022	0.025	Beta	Meier et al. [20]
20–49	0.00700	0.006	0.008	Beta	

50–64	0.00300	0.002	0.004	Beta	
65+	0.00200	0.001	0.003	Beta	
Probability of otitis media if no medical consultation					
0–9	0.04000	0.037	0.043	Beta	
10–19	0.02350	0.022	0.025	Beta	
20–49	0.00700	0.006	0.008	Beta	Meier et al. [20]
50–64	0.00300	0.002	0.004	Beta	
65+	0.00200	0.001	0.003	Beta	
Hospitalization due to complications: all causes					
0–3	0.2989	0.2420	0.3591	Beta	
4–6	0.1081	0.0878	0.1301	Beta	
7–9	0.0127	0.0103	0.0153	Beta	
10–19	0.0363	0.0295	0.0438	Beta	
20–34	0.1436	0.1166	0.1729	Beta	Calibrated to fit total hospitalizations by age cohort based on Molinari et al. [14]
35–49	0.1474	0.1197	0.1775	Beta	
50–64	0.6653	0.5293	0.7887	Beta	
65–69	1.1663	1.1663	1.1663	Beta	
70+	1.1791	1.1791	1.1791	Beta	
Case fatality of complications in hospital: all causes					
0–3	0.0008	0.0007	0.0010	Beta	
4–6	0.0004	0.0003	0.0005	Beta	
7–9	0.0002	0.0002	0.0003	Beta	
10–19	0.0007	0.0006	0.0008	Beta	
20–34	0.0030	0.0024	0.0036	Beta	Calibrated to fit total deaths by age cohort based on Molinari et al. [14]
35–49	0.0031	0.0025	0.0037	Beta	
50–64	0.0458	0.0372	0.0552	Beta	
65–69	0.3288	0.2660	0.3948	Beta	
70+	0.3328	0.2693	0.3996	Beta	

Case fatality of complications outside of hospital					
Pneumonia					
0–3	0.0014	0.0012	0.0015	Beta	Myles et al. [22]
4–6	0.0007	0.0006	0.0008	Beta	Assumed case fatality is higher than hospitalized patients; observed 18.5% 30-day mortality from pneumonia in general practice, which is higher than the 30-day mortality of 8–15% reported in hospital-based studies. Standard deviation as for hospital
7–9	0.0003	0.0003	0.0004	Beta	
10–19	0.0011	0.0010	0.0013	Beta	
20–34	0.0048	0.0043	0.0054	Beta	
35–49	0.0050	0.0044	0.0056	Beta	
50–64	0.0737	0.0650	0.0829	Beta	
65–69	0.5290	0.4643	0.5931	Beta	
70+	0.5354	0.4700	0.6003	Beta	
Bronchitis, other respiratory illness, CVD					Assumed same as hospitalized patients
Otitis media					
All	0	0	0	Not applicable	Assumed no case fatality

CVD cardiovascular disease

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