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Original Article

The potential economic value of a 'universal' (multi-year) influenza vaccine

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Background Limitations of the current annual influenza vaccine have led to ongoing efforts to develop a 'universal' influenza vaccine, i.e., one that targets a ubiquitous portion of the influenza virus so that the coverage of a single vaccination can persist for multiple years.

Objectives To estimate the economic value of a 'universal' influenza vaccine compared to the standard annual influenza vaccine, starting vaccination in the pediatric population (2–18 year olds), over the course of their lifetime.

Patient/Methods Monte Carlo decision analytic computer simulation model.

Results Universal vaccine dominates (i.e., less costly and more effective) the annual vaccine when the universal vaccine cost ≤$100/dose and efficacy ≥75% for both the 5- and 10-year duration. The universal vaccine is also dominant when efficacy is ≥50% and protects for 10 years. A $200 universal vaccine was only cost-effective when ≥75% efficacious for a 5-year duration when annual compliance was 25% and for a 10-year duration for all annual compliance rates. A universal vaccine is not cost-effective when it cost $200 and when its efficacy is ≤50%. The cost-effectiveness of the universal vaccine increases with the duration of protection.

Conclusions Although development of a universal vaccine requires surmounting scientific hurdles, our results delineate the circumstances under which such a vaccine would be a cost-effective alternative to the annual influenza vaccine.

Keywords Cost-effectiveness, economics, influenza vaccine, pediatrics, universal vaccine.

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Background

The following limitations of the current annual influenza vaccine have led to ongoing efforts to develop a 'universal' influenza vaccine, i.e., one that targets a ubiquitous portion of the influenza virus so that the coverage of a single vaccination can persist for multiple years:

- Annual vaccine administration: Administering influenza vaccine to the same patients each year incurs substantial costs and efforts. Persons must miss work. Maintaining influenza vaccination clinics and sites requires personnel time.
- Annual vaccine manufacturing: Every year influenza vaccine manufacturers must allocate significant resources to produce influenza vaccines. Owing to varying viral strains every season and the limited production period, the timing and preparation of vaccine development might cause unnecessary delays.
- Patient compliance: Even when a person is recommended to be vaccinated, he or she may miss getting immunized certain years. According to the National Health Interview Survey and National Immunization Survey of United States for seasons 2005–2006, 2006–2007, and 2007–2008 and National Immunization Survey, influenza vaccination coverage levels ranged 31·8–32·2% for ages 6–23 months, 26·4–40·3% for ages 2–4 years, and 12·4–21·1% for ages 5–17 years.[1] Estimation from the Behavioral Risk Factor Surveillance System (BRFSS) for influenza season 2008–2009 was 26·0–38·7% for ages 2–4 year olds and 18·4–23·4% for ages 5–17 year olds.[2]
- Changing influenza strains: Each year, different influenza strains emerge as the dominant circulating strains. Although each year, scientists attempt to predict these strains, their predictions are not always accurate.[3] Mutations may cause major antigenic drift every 2–5 years.[4]

- Emergence of novel influenza strain: As the 2009 influenza pandemic demonstrated, the annual vaccine may not cover new emergent strains.

Better understanding of the potential economic value of a 'universal' vaccine can help guide investment and development for policy makers, manufacturers, insurance companies, investors, scientists, and other decision makers. Forecasting the impact of a vaccine early in its development when changes can still be made can increase the chances of a vaccine's success.[5]

Objectives

We developed a computational model to estimate the potential economic value of a 'universal' influenza vaccine compared to the standard annual influenza vaccine in the pediatric population (ages 2–18 years), one of the Advisory Committee on Immunization Practices (ACIP) recommended high-risk groups.[6]

Patients/methods

Model structure

Figure 1 presents the general structure of the Markov decision analytic computer simulation model constructed using TreeAge Pro 2009 (TreeAge Software, Williamstown, MA, USA). The model represents the decision from the societal perspective of whether a child (age 2–18 years old) should begin receiving a hypothetical universal influenza vaccine or the standard annual influenza vaccine. The universal vaccine would have a certain duration of protection, therefore necessitating a periodic booster, and is assumed to be a single immunization. Each year the individual is scheduled to receive a vaccine, the individual had a probability of complying. Additionally, we looked at the effects of vaccinating high-risk children. For these scenarios, we assumed individuals were at high-risk throughout their lifetime and had a twofold risk of hospitalization and mortality.

The time horizon for the model is the child's lifetime. The model has a cycle length of 1 year. The Markov states are mutually exclusive; an individual can only be in one state in a given year. Each year, an individual had a probability of becoming infected with influenza. Vaccination attenuates this probability by the vaccine-related efficacy. Each time an individual is vaccinated, he or she has a probability of developing vaccine side effects.[7] Individuals who contract influenza have probabilities of developing symptoms or remaining asymptomatic. Symptomatic individuals then have a probability of visiting an outpatient setting and a probability of requiring hospitalization. Each individual with influenza has a probability of surviving or dying from influenza. Those who die from influenza or other unrelated causes enter the death state. The model

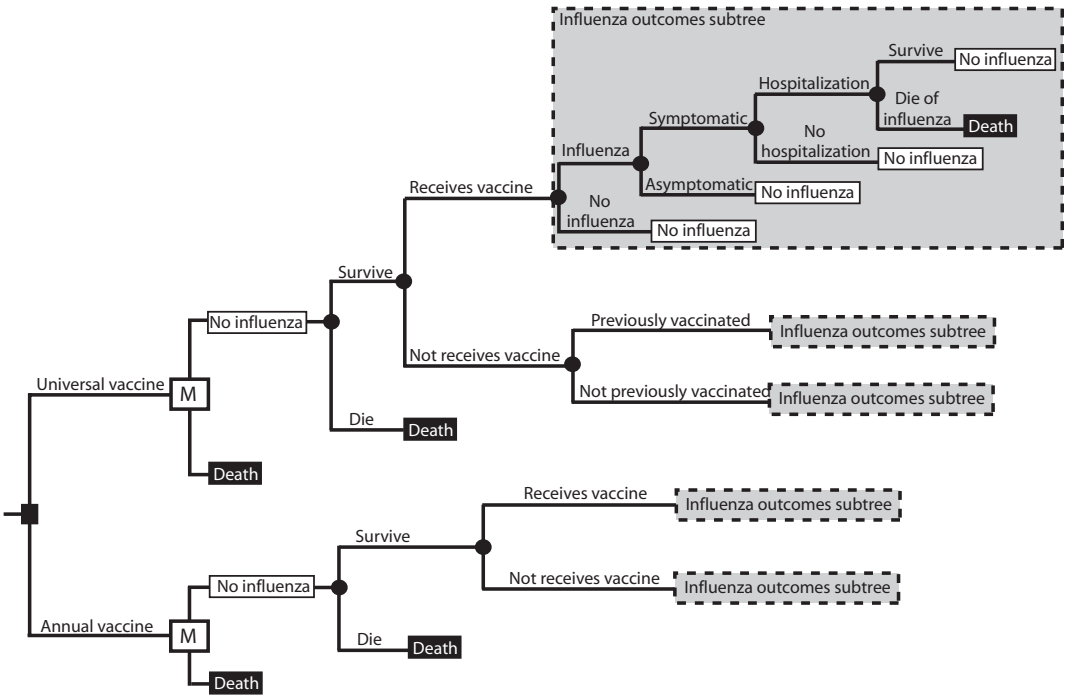

Figure 1. Model structure state diagram.

concludes its run when an individual enters this state, otherwise known as the absorptive state.

Each simulation run sends 1000 individuals 1000 times through the model for a total of 1 000 000 trials of an individual's lifetime. For each simulation, the following equation calculates the incremental cost-effectiveness ratio (ICER) of the 'universal' vaccine versus the annual vaccine:

$$\frac{\text{Cost}_{\text{utilizing universal vaccine}} - \text{Cost}_{\text{utilizing annual vaccine}}}{\text{Effectiveness}_{\text{utilizing universal vaccine}} - \text{Effectiveness}_{\text{utilizing annual vaccine}}}$$

where effectiveness is expressed in quality-adjusted life-years (QALYs). ICER values <$50 000 per QALY identified the strategy as cost-effective.[8,9] The model was from the societal perspective, and therefore accounted for both direct (i.e., outpatient and hospitalization costs) and indirect costs (i.e., cost of productivity losses owing to missed work, e.g., parent losses for child care, and influenza-attributable mortality of expected lifetime earnings).

Budget impact analysis

We also calculated the potential economic value of a universal influenza vaccine from the societal perspective for the U.S. pediatric population. The U.S. Census Bureau estimate in July 2009 was used to provide the age-stratified population: 21·3 million (under 5 years), 20·6 million (5–9 years), 20·0 million (10–14 years), and 21·5 million (15–19 years).[10]

Data inputs

Table 1 lists the probabilities, costs, durations, and utilities used in the model along with their corresponding distributions and sources. Costs of annual vaccination are based on the average whole sale price and administration cost.[11] Mortality values are from the CDC National Vital Statistics Reports of Number of Deaths and Death Rates, by Age, Race, and Sex: United States 2007.[12] A 3% discount rate converted costs and QALYs from other years into 2010 values.[13] Death resulted in a QALY loss based on the QALY-adjusted life expectancy of the person's age.[14] Each influenza episode resulted in age-adjusted QALY decrements for the duration of the condition.[8]

Sensitivity analyses

Sensitivity analyses systematically varied the cost of the universal vaccine ($100 and $200), universal vaccine efficacy (range: 50–75%), probability of influenza infection being symptomatic (50% or 67%), initial age of the individual (range: 2–18 years), annual vaccine compliance (25%, 50%, 75%, and 100%), and the duration of universal vaccine protection (5 or 10 years).[15,16] Probabilistic sensitivity analyses simultaneously varied the values of each parameter across the ranges listed in Table 1.

Results

Cost-effectiveness analysis when universal protection duration is 5 years

Table 2 shows how the ICER of universal vaccination compares to annual vaccination varying with differing universal vaccine efficacy, cost, and annual vaccine compliance when the duration of universal vaccine protection is 5 years. Universal vaccine is the dominant strategy (i.e., saves costs and provides health benefits) when vaccine cost is ≤$100/dose and vaccine efficacy is ≥75% for all scenarios tested. The annual vaccine dominates the $100 universal vaccine, only when the universal is 50% efficacious and annual compliance is 100%. When increasing the cost to $200/dose, universal vaccine is cost-effective only when annual compliance is ≤25% and universal vaccine efficacy ≥75% for both symptomatic rates. A $200 universal vaccine with an efficacy ≤50% was not cost-effective for any annual compliance rate. For high-risk children, a $100 universal vaccine dominated the annual vaccine or had ICER values ≥$185 060/QALY for all probabilities of annual compliance.

Budget impact analysis when universal protection duration is 5 years

Switching from the annual vaccine to the universal vaccine can yield cost savings from the societal perspective. A $100/dose universal vaccine with a vaccine efficacy ≥75% will provide cost savings per pediatric patient vaccinated: $1–$104 (younger than 5 years), $5–$102 (5–9 years), $6–$96 (10–14 years), and $168–$266 (15–18 years). Therefore, switching the entire pediatric population to universal vaccination could generate cost savings of $15 million–$2·2 billion for those below 5 years, $101 million–$2·1 billion for 5–9 years, $121 million–$1·9 billion for 10–14 years, and $3·6 billion–$5·7 billion for 15–18 years over their lifetimes. Increasing the proportion of developing symptomatic influenza from 50% to 67% will provide more cost savings.

Cost-effectiveness analysis when universal protection duration is 10 years

Table 3 demonstrates the ICER when duration of protection by the universal vaccine increases from 5 to 10 years. The universal vaccine is optimal (i.e., economically dominant) compared to annual vaccine when its efficacy ≥50% and cost ≤$100/dose for all annual compliance and symptomatic rates explored.

Figure 2 shows acceptability curves for the universal and annual vaccine when the universal protects for 10 years and costs $100. The universal vaccine consistently has a higher probability of being cost-effective, even with an increasing willingness to pay. A $200/dose universal

Table 1. Data inputs

Description (units)	Distribution Type	Mean	Standard deviation or range	Source
Costs ($US)				
Annual vaccine	Point estimate	20	–	11,35
Influenza treatment				
Outpatient visit				
Pediatric outpatient visit	Point estimate	74·90	–	36
Adult outpatient visit	Triangular	104·77	69·14–140·39	37
Elderly outpatient visit	Triangular	155·92	118·39–193·44	37
Hospitalization				
Age 1–4	Gamma	5992	515	38
Age 5–9	Gamma	5761	561	38
Age 10–14	Gamma	8735	1231	38
Age 15–17	Gamma	6559	816	38
Age 18–44	Gamma	6506	461	38
Age 45–64	Gamma	7580	759	38
Age 65–84	Gamma	7568	234	38
Age 85 and Over	Gamma	7698	240	38
General death	Triangular	6921	5191–9025	39
Treatment of vaccine side effects	Triangular	0·79	0·70–3·93	11
Median hourly wage	Point estimate	15·57	–	35
Durations				
Work hours per day	Point estimate	8	–	Assumption
Absenteeism from influenza (days)	Uniform	3·2	1·5–4·9	40
Time being sick from the flu	Uniform	6	5–7	41,42
Time after having vaccine side effects	Uniform	0·75	0·5–1	43
Utilities (QALYs)				
One year of life				
Age 0–17	Point estimate	1	–	8
Age 18–64	Point estimate	0·92	–	8
Age 65 and Over	Point estimate	0·84	–	8
Influenza with no hospitalization	Triangular	0·65	0·49–0·81	44,45
Influenza with hospitalization	Triangular	0·50	0·38–0·63	44,46
Vaccine side effects	Triangular	0·95	0·71–1·00	46
Probabilities				
Clinical outcomes without vaccination				
Influenza throughout the year	Triangular	0·125	0·05–0·2	7
Outpatient visit given influenza				
Age 0–4	Beta	0·455	0·098	47
Age 5–17	Beta	0·318	0·061	47
Age 18–64	Beta	0·313	0·014	47
Age 65 and over	Beta	0·620	0·027	47
Age 0–4 (high-risk)	Beta	0·910	0·250	47
Age 5–17 (high-risk)	Beta	0·635	0·167	47
Age 18–64 (high-risk)	Beta	0·625	0·118	47
Age 65 and over (high-risk)	Beta	0·850	0·093	47
Hospitalization given influenza				
Age 0–4	Beta	0·0141	0·0047	47
Age 5–17	Beta	0·0006	0·0002	47
Age 18–49	Beta	0·0042	0·0014	47
Age 50–64	Beta	0·0193	0·0064	47
Age 65 and over	Beta	0·0421	0·0140	47
Mortality given influenza				
Age 0–4	Beta	0·00004	0·00001	47
Age 5–17	Point estimate	0·00001		47
Age 18–49	Beta	0·00009	0·00003	47
Age 50–64	Beta	0·00134	0·00045	47
Age 65 and over	Beta	0·01170	0·00390	47
Vaccine efficacy	Triangular	0·45	0·56–0·68	7
Vaccine side effects	Point estimate	0·03	–	48

Table 2. Cost, effectiveness, and incremental cost-effectiveness ratio (ICER; cost per QALY) of switching from annual to universal vaccine when universal vaccine provides 5 years of protection (50% symptomatic influenza rate)

Annual vaccine compliance	Vaccination strategy	Cost	Effectiveness	ICER
Vaccine cost $100				
Vaccine efficacy 75%				
100%	Universal	1580–2120	25·52–28·29	Universal dominates
	Annual	1684–2385	25·52–28·29	
75%	Universal	1579–2118	25·53–28·29	Universal dominates
	Annual	1649–2560	25·52–28·29	
50%	Universal	1579–2120	25·52–28·29	Universal dominates
	Annual	1616–2320	25·52–28·28	
25%	Universal	1577–2118	25·53–28·29	Universal dominates
	Annual	1578–2286	25·52–28·28	
Vaccine efficacy 50%				
100%	Universal	1775–2473	25·52–28·29	Annual dominates
	Annual	1685–2387	25·52–28·30	
75%	Universal	1777–2474	25·53–28·29	**39 482**–52 197
	Annual	1650–2351	25·53–28·29	
50%	Universal	1775–2475	25·53–28·29	**31 544**–74 353
	Annual	1612–2320	25·53–28·29	
25%	Universal	1775–2474	25·53–28·29	**33 987–49 354**
	Annual	1579–2282	25·52–28·29	
Vaccine cost $200				
Vaccine efficacy 75%				
100%	Universal	2019–2718	25·52–28·30	77 108–124 575
	Annual	1684–2384	25·53–28·29	
75%	Universal	2214–2893	25·52–28·29	171 099–319 601
	Annual	1648–2353	25·52–28·28	
50%	Universal	2020–2717	25·53–28·29	79 422–81 349
	Annual	1614–2317	25·52–28·29	
25%	Universal	2018–2718	25·53–28·30	**33 562–47 763**
	Annual	1579–2288	25·52–28·28	
Vaccine efficacy 50%				
100%	Universal	2411–3072	25·53–28·29	Annual dominates
	Annual	1682–2387	25·53–28·29	
75%	Universal	2411–3071	25·53–28·29	Annual dominates–495 957
	Annual	1650–2353	25·52–28·29	
50%	Universal	2413–3073	25·52–28·29	257 930–806 958
	Annual	1614–2560	25·52–28·29	
25%	Universal	2412–2284	25·53–28·29	144 542–172 231
	Annual	1580–3073	25·52–28·29	

Bold ICER values are cost-effective.

vaccine is cost-effective only when its efficacy is ≥75%. At an efficacy of 50%, a $200 universal vaccine is not cost-effective compared to the annual vaccine. Figure 2B shows the curves for this change in cost.

Budget impact analysis when universal protection duration is 10 years

Increasing the duration of universal protection to 10 years further augments the potential cost savings to society. A $100/dose universal vaccine with ≥75% efficacy can provide cost savings of $295–$398 per pediatric patient (ages below 5 years), $284–$388 (5–9 years), $274–$377 (10–14 years), and $261–$364 (15–18 years) vaccinated. Therefore, switching the entire pediatric population to universal vaccination could generate cost savings of $6·2 billion–$8·5 billion for those below 5 years, $5·9 billion–$8·0 billion for 5–9 years, $5·5 billion–$7·5billion for 10–14 years, and $5·6 billion–$7·8 billion for 15–18 years over their lifetimes. As before, increasing the probability of being symptomatic will provide even more cost savings.

Table 3. Cost, effectiveness, and incremental cost-effectiveness ratio (ICER) of switching from annual to universal vaccine when universal vaccine provides 10 years of protection (50% symptomatic influenza rate)

Annual vaccine compliance	Vaccination strategy	Cost	Effectiveness	ICER
Vaccine cost $100				
Vaccine efficacy 75%				
100%	Universal	1287–2021	25·53–28·29	Universal dominates
	Annual	1685–2385	25·52–28·29	
75%	Universal	1286–2021	25·52–28·29	Universal dominates
	Annual	1648–2353	25·52–28·29	
50%	Universal	1286–2019	25·53–28·29	Universal dominates
	Annual	1613–2319	25·52–28·29	
25%	Universal	1286–2022	25·53–28·29	Universal dominates
	Annual	1581–2283	25·52–28·29	
Vaccine efficacy 50%				
100%	Universal	1483–2197	25·53–28·29	Universal dominates
	Annual	1685–2386	25·52–28·29	
75%	Universal	1485–2201	25·53–28·29	Universal dominates
	Annual	1649–2351	25·53–28·29	
50%	Universal	1482–2200	25·52–28·29	Universal dominates
	Annual	1615–2316	25·52–28·29	
25%	Universal	1484–2200	25·52–28·29	Universal dominates
	Annual	1579–2282	25·52–28·29	
Vaccine cost $200				
Vaccine efficacy 75%				
100%	Universal	1630–2347	25·53–28·29	**9180–45 456**
	Annual	1683–2386	25·53–28·29	
75%	Universal	1649–2348	25·52–28·29	**1285–31 956**
	Annual	1629–2354	25·53–28·29	
50%	Universal	1615–2348	25·52–28·29	**4222–4755**
	Annual	1616–2378	25·52–28·29	
25%	Universal	1629–2346	25·53–28·30	**5194–5970**
	Annual	1580–2285	25·52–28·29	
Vaccine efficacy 50%				
100%	Universal	1829–2526	25·53–28·29	Annual dominates
	Annual	1684–2384	25·53–28·29	
75%	Universal	1827–2530	25·52–28·29	Annual dominates
	Annual	1651–2350	25·52–28·29	
50%	Universal	1827–2527	25·52–28·29	69 797–380 364
	Annual	1613–2322	25·52–28·29	
25%	Universal	1827–2527	25·53–28·29	59 443–74 421
	Annual	1580–2286	25·52–28·28	

Bold ICER values are cost-effective.

Discussion

Our results suggest that a universal vaccine could provide substantial economic value by overcoming the annual vaccine's current drawbacks. This favors investment in universal vaccine development, helps establish efficacy and duration of protection targets for developers, and prepares policy makers for reimbursement questions. Addressing these issues early in a vaccine's development when changes are easier to make could help avoid considerable problems in the future.[5]

In many ways, our study underestimates the potential value of a universal vaccine. Not only is compliance with the annual vaccine far <100%, but many children also do not get vaccinated until later into the influenza season, i.e., after October or even November. Previous studies have demonstrated the value of annual influenza vaccine drops the later in the season the vaccine is administered, because the longer the patient remains unvaccinated, the more susceptible they are to being infected.[17,18] Moreover, our model did not account for how the universal vaccine may prevent the vaccinated individual from transmitting the

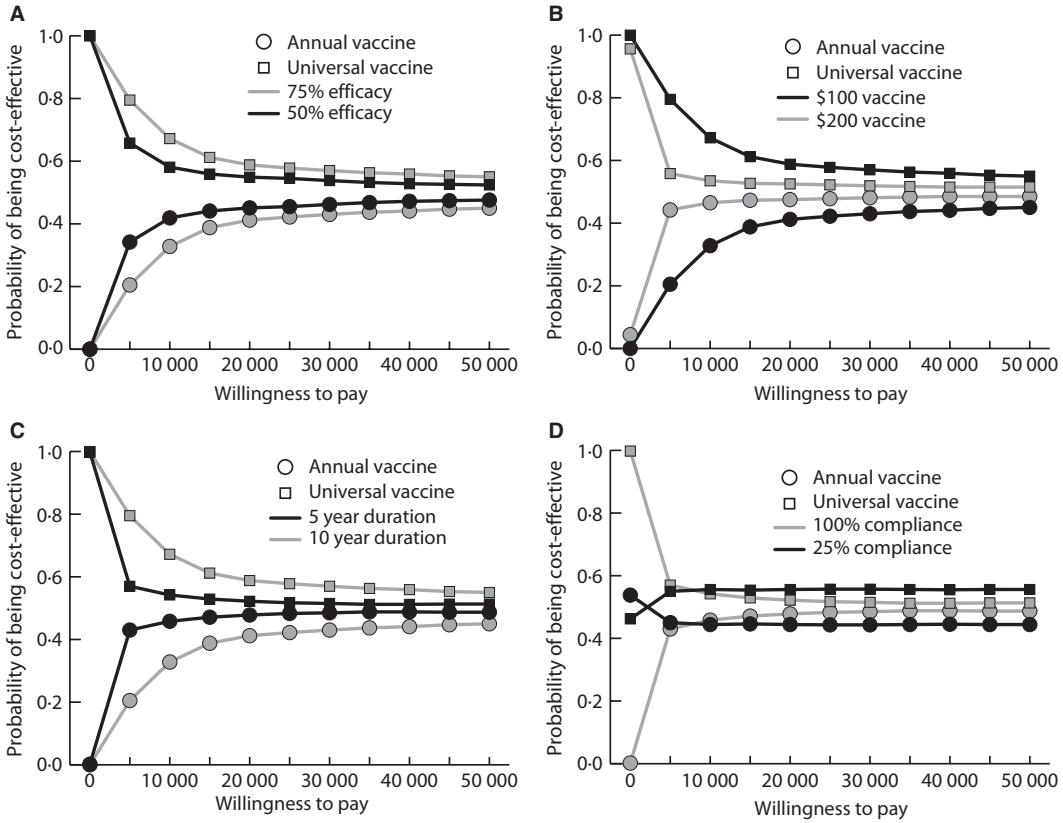

Figure 2. Acceptability curves (A) varying the efficacy of universal vaccine, (B) varying the cost of universal vaccine, (C) varying the duration of universal vaccine protection, (D) varying annual vaccine compliance.

influenza virus to others. Unvaccinated individuals are not only more susceptible to infection but may shed more virus when infected compared to vaccinated individuals. Our model focuses on the individual and does not consider influenza transmission and herd immunity. If the universal vaccine results in a greater proportion of the population protected, then it could more substantially reduce transmission than the standard annual vaccine and therefore would be more cost-effective. Finally, in our model, individuals are healthy children without comorbidities that may worsen influenza outcomes.

The 2009 influenza pandemic identifies another possible benefit of the universal vaccine. A universal vaccine that provides protection against novel strains may circumvent the need to develop a specific vaccine against an emerging pandemic strain. As computer simulation studies have suggested, timely and effective vaccination of the population may be the most important mitigation intervention.[17–20]

Bringing a universal vaccine to market requires surmounting numerous hurdles. First, the vaccine must contain an appropriate antigen common to all possible circulating influenza viruses. Second, the antigen should be stable and not prone to mutation. Third, the antigen must not occur in other common human tissues. Fourth, the antigen needs to generate an adequate immune response. Fifth, the vaccine must remain effective and not wane for the duration of vaccine coverage.

Du and colleagues describe the possible approaches in developing a universal influenza vaccine which focus on the conserved sequences of M2e, HA (HA1, HA2), NP, and epitopes from different influenza viral proteins.[21] These sequences occur across many known subtypes of influenza virus making them ideal universal vaccine targets. Some candidates use a combination of these conserved epitopes from different viral proteins, potentially offering further cross-protection across varying subtypes.[21] Other candidates focus on the sequences of major structural proteins of the virus surface, ectodomain of matrix protein 2.[22,23] Scientists have also targeted human antibodies that could cross-react with and neutralize several different hemagglutinin viral subtypes.[24–27] Several candidate 'universal' influenza vaccines are currently at different stages of development based on these targets. Five companies, Acambis Inc. (Cambridge, UK), Cytos Biotechnology (Schlieren, Switzerland), Merck & Co Inc. (Whitehouse Station, NJ, USA), and VaxInnate Corp. (Cranbury, NJ, USA) have reported promising preli-

minary Phase 1 clinical study results.[3,28] BiondVax's (Ness Ziona, Israel) Mulitmeric-001 Universal Flu Vaccine successfully navigated through Phase I/II trials and will enter Phase II trials in 2010.[29,30] BiondVax is currently recruiting patients 55–75 years old for its next study.[31]

A recently published article reports significant human B cell responses toward the 2009 pandemic H1N1 influenza.[32] Most of the neutralizing antibodies induced by the virus are able to cross-react against epitopes in the hemagglutinin head and stalk of various influenza strains. Tested antibodies show broad protection against H1N1 and H5N1 influenza strains with abundant stalk-reactive antibodies in H1N1 patients. Such universal vaccine may have a stronger cross-protection to divergent virus subtypes, reduced production time and cost. This advantage may serve as an important direction in the development of a universal influenza vaccine.

Another study provides evidence that a universal vaccine which covers all influenza strains is achievable. This novel influenza vaccine is able to reactivate and induce T-cell responses (CD8+ and CD4+) toward NP and M1 proteins of the virus that is common in all influenza type A strains.[33] It proves to be safe and well tolerated with less local side effects. Extensive protection against seasonal and pandemic influenza is promising. According to researchers, introduction of such a vaccine would provide protection for at least 5–10 years.[34]

Limitations

In addition to the limitations identified earlier, all models are simplifications of real life. A model cannot represent all possible influenza outcomes and the heterogeneity that exist among the patient population. Rather than make decisions, a model provides information for decision makers such as public health officials, scientists, insurance companies, investors, manufacturers, and clinicians. Models are designed to elucidate relationships, raise questions, and approximate orders of magnitude instead of providing exact answers. Although our model does not explicitly represent natural immunity from infection, which may persist for several years, especially when occurring in children, the various outcome probabilities (e.g., risk of influenza) did draw from studies where natural immunity was present.

Conclusion

Limitations of the current annual influenza vaccine have led to ongoing efforts to develop a 'universal' influenza vaccine, i.e., one that targets a conserved portion of the influenza virus so that the coverage of a single vaccination can persist for multiple years. Our results suggest that a universal vaccine could provide substantial economic value by overcoming the annual vaccine's current drawbacks. This favors investment in universal vaccine development, helps establish efficacy and duration of protection targets for developers, and prepares policy makers for reimbursement questions. Addressing these issues early in a vaccine's development when changes are easier to make could help avoid considerable problems in the future. Although development of a universal vaccine requires surmounting scientific hurdles, our results delineated the circumstances under which such a vaccine would be a cost-effective alternative to the annual influenza vaccine.

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