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An economic model assessing the value of microneedle patch delivery of the seasonal influenza vaccine

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Abstract

Background—New vaccine technologies may improve the acceptability, delivery (potentially enabling self-administration), and product efficacy of influenza vaccines. One such technology is the microneedle patch (MNP), a skin delivery technology currently in development. Although MNPs hold promise in preclinical studies, their potential economic and epidemiologic impacts have not yet been evaluated.

Methods—We utilized a Susceptible-Exposed-Infectious-Recovered (SEIR) transmission model linked to an economic influenza outcomes model to assess the economic value of introducing the MNP into the current influenza vaccine market in the United States from the third-party payer and societal perspectives. We also explored the impact of different vaccination settings, self-administration, the MNP price, vaccine efficacy, compliance, and MNP market share. Outcomes included costs, quality-adjusted life years (QALYs), cases, and incremental cost-effectiveness ratios (ICERs; cost/QALY).

Results—With healthcare provider administration, MNP introduction would be cost-effective (ICERs \$23,347/QALY) at all MNP price points (\$9.50–\$30) and market shares (10%–60%) assessed, except when compliance and efficacy were assumed to be the same as existing vaccines and the MNP occupied a 10% market share. If MNP self-administration were available (assuming

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Conflict of Interest

Bruce Y. Lee, Sarah M. Bartsch, Kristina M. Zapf, Kathleen Marinan, Angela R. Wateska, Mercy Mvundura, Courtney Jarrahan, Bill Snyder, Savitha Swaminathan, Erica Jacoby, and Darin Zehrung have no conflicts of interest to report. James J. Norman and Mark R. Prausnitz are inventors on patents and Mark R. Prausnitz has a significant financial interest in a company that is developing a microneedle-based product for influenza vaccination (Micron Biomedical). This potential conflict of interest has been disclosed and is overseen by Georgia Tech and Emory University.

the same efficacy as current technologies), MNP compliance or its efficacy would need to increase by 3% in order to be cost-effective (ICERs \$1,401/QALY), assuming a 2% reduction in administration success with unsupervised self-administration. Under these conditions, MNP introduction would be cost-effective for all price points and market shares assessed.

Conclusions—When healthcare providers administered the MNP, its introduction was cost-effective or dominant (i.e., less costly and more effective) in the majority of scenarios assessed. If self-administration were available, MNP introduction would be cost-effective if it increased compliance enough to overcome any decrease in self-administration success or if the MNP presentation afforded an increase in efficacy over current delivery methods for influenza vaccines.

Keywords

Microneedle patch; influenza; influenza vaccination; economics; cost-effectiveness

INTRODUCTION

In the United States (US), annual influenza epidemics cost an estimated \$87.1 billion (direct medical costs and indirect costs due to absenteeism and premature death), of which direct medical costs account for \$10.4 billion (based on the 2003 population).[1] Although the United States Centers for Disease Control and Prevention recommends that all persons six months and older receive annual influenza vaccinations, coverage rates demonstrate that many persons continue to not get vaccinated.[2] Reasons for forgoing vaccination include the belief that it is not necessary or effective, concern about side effects, cost, inconvenience/lack of time, and fear of needles.[3-9] New delivery technologies could address some of these reasons. Microneedle patches (MNPs), a delivery technology under development, consist of an array of micron-sized, solid-coated, or dissolvable needles on a patch backing that allows for cutaneous administration of vaccines or drugs.[10] Preclinical studies demonstrate that MNP delivery of influenza vaccine can lead to longer-lasting and more-robust antibody response, suggesting the possibility of improved efficacy.[10-13] The potential ease of use and safety of MNP vaccines may enable them to be administered with less or potentially no supervision by healthcare providers.

While MNPs have the potential to improve acceptability and increase the efficiency of delivery, clinical efficacy, and vaccination coverage, their potential economic and epidemiologic impact have not yet been quantified. Such assessments could help developers to better understand how much MNPs would need to increase compliance and coverage to make them more cost-effective than existing technologies before reaching the market. Conducting economic evaluations while the technology is still under development could help inform product attributes, better facilitating MNP adoption and use.[14] Therefore, we developed a compartment model linked to a Monte Carlo simulation to evaluate the potential economic and epidemiologic value of adding MNPs to the existing delivery technologies in the US influenza vaccine market under various scenarios (compared to the current vaccination market). Appendix 1 contains a description of the different delivery technologies. We evaluated the economic and epidemiologic value from the third-party payer and societal perspectives, as recommended by the US Panel on Cost-Effectiveness in Health and Medicine.[15]

METHODS

Utilizing Microsoft Excel (Microsoft Corporation, Redmond, WA) with the Crystal Ball add-in (Oracle Corporation, Redwood Shore, CA) we developed a susceptible-exposed-infectious-recovered (SEIR) influenza transmission compartment model representing the entire US population over one influenza season linked with a simulated decision tree cohort economic model. The population (311,591,917 based on 2011 census data[16]) consisted of three age groups: children (ages 0–17), adults (ages 18–64), and elderly (ages 65 and over). Figure 1 outlines the model; Table 1 provides the input parameters and values and their original sources. Parameter estimates came from published review articles or systematic reviews and/or nationally representative databases when available; other estimates came from an extensive literature search. Distributions were created to account for variability and key parameters were varied in sensitivity analysis.

Influenza transmission model

Our model included all parameters and influenza outcomes necessary to model its transmission (Table 1). The SEIR transmission model consisted of four mutually exclusive health states: susceptible (S: not infected with influenza but able to become infected), exposed (E: infected with influenza but not yet able to transmit to others), infectious (I: infected and able to transmit to others), and recovered (R: immune and cannot become infected, either from vaccination or recovery from illness). Each person was represented in one of these states. The model assumed equal mixing and proceeded in discrete, one-day (t) time steps (i.e., cycle length of one day) through the course of an influenza season. Each day, the following equation governed the number of susceptible individuals who become exposed (i.e., transition from S to E):

$$S \text{ to } E_{\text{day } t} = \beta * S * I$$

where β (beta) is equal to the reproductive rate (R_0 , the average number of secondary cases generated by one infectious influenza case) divided by the duration of the infectious period and the number of individuals in the population. S and I are the number of susceptible and infectious persons, respectively, on day t. R_0 was set to 1.2.[17]

Each day, exposed individuals became infectious (i.e., moved from the E to I compartment) at a rate of 1/duration of incubation period. Infectious individuals recovered (i.e., moved from the I to R compartment) at a rate of 1/duration of the infectious period. Vaccination could move susceptible individuals to recovered (i.e., from the S to R compartment) based on the vaccine efficacy and likelihood of successful administration. To ensure strain-matching did not outweigh vaccine presentation (e.g., a high efficacy value for adults and a low value for children for the same vaccine), we used one baseline vaccine efficacy distribution (Table 1) and adjusted the value drawn for age and vaccine presentation. These adjustment factors (Table 1) were chosen to closely represent the efficacy of each vaccine presentation in each age group.[18-20]

Economic model

We adapted our previously published influenza models[21-28] to translate infectious cases into health and cost outcomes from the third-party payer and societal perspectives. Our economic model included all the necessary clinical probabilities and cost outcomes (Table 1). Each infectious influenza case from the SEIR model had a probability of being symptomatic. Each symptomatic case had age-specific probabilities of seeking ambulatory care, being hospitalized, or dying from influenza. These outcomes accrued associated age-specific costs and/or health effects, quality-adjusted life-years (QALYs), depending on the analysis (performed both cost and cost-effectiveness analyses).

The baseline scenario reflected the current US vaccine market (in which the MNP is not commercially available) and people are vaccinated using one of the existing technologies (Appendix 1). The market shares of each vaccine (2011–2012 influenza season) determined the proportion of the population that received the intramuscular (multi-dose vial and prefilled syringe), intradermal, and intranasal vaccines, taking into account the age eligibility for each vaccine presentation. Other scenarios introduced the MNP into the market and assumed a proportional reduction in the market shares of existing technologies.

Each microsimulation consisted of 1,000 probabilistic trials drawing values for each parameter from the distributions in Table 1. For each scenario, the incremental cost-effectiveness ratio (ICER), our primary outcome, was calculated as:

$$ICER = [COST_{MNP \text{ Introduction}} - Cost_{Baseline}] / [Effectiveness_{MNP \text{ Introduction}} - Effectiveness_{Baseline}]$$

where effectiveness was measured in QALYs. A person's QALY value was based on their age-stratified healthy QALY value attenuated by their influenza-related outcome's utility weight for the duration of that outcome. People who survived accrued discounted lifetime QALY values for the remainder of their life expectancy. ICER values US \$50,000/QALY were considered cost-effective.[29]

The third-party payer perspective included all direct vaccination costs (vaccine, administration, and waste disposal) and influenza treatment costs (ambulatory care visit and hospitalization). Administration costs included clinical labor (estimated as the product of healthcare worker time to administer vaccine and their personnel wage per minute), nonclinical labor, and overhead costs. These administration costs varied by vaccination setting. Thus, total third-party payer costs were calculated as the sum of the direct costs of vaccination for those who were vaccinated and the treatment costs for those who developed influenza-like symptoms and sought treatment among the entire population (both the vaccinated and unvaccinated). The societal perspective included the direct and indirect costs (costs associated with productivity losses due to absenteeism and mortality). Including productivity losses allowed us to capture the full effects of influenza illness. Productivity losses due to absenteeism assumed an eight-hour work day and the median hourly wage for all occupations for each work day missed, while mortality resulted in the net present value of a person's remaining lifetime earnings based on his/her life expectancy.[30-31] A 3%

discount rate, which accounts for inflation, converted all costs and future QALYs into 2013 values.[32]

In addition to the ICER, model outcomes included: vaccination costs, influenza-related direct medical costs, influenza-related productivity losses, total costs, number of persons vaccinated, number of influenza cases, and number of QALYs accrued.

Vaccination scenarios

Table 2 shows the four scenarios evaluated and the proportion of persons vaccinated in each vaccination setting. Currently, influenza vaccination occurs in either traditional or group settings. Traditional settings included both medical and nonmedical settings (e.g., doctor's offices, pharmacies, walk-in clinics, etc.) wherein a medical provider (nurse or pharmacist depending on location) administers the vaccine on an individual basis. In group settings, a healthcare worker (i.e., nurse) visited workplaces or schools to vaccinate a group of people. In addition to these supervised settings, we assumed that the MNP could be self-administered in an unsupervised setting (e.g., home) if regulation allowed for self-administration. When utilizing the MNP in group settings, we assumed that one nurse could supervise up to 10 vaccinees (and either administer the patch or supervise the self-administration of the patch, depending on the scenario). In the unsupervised setting, we assumed the vaccine was obtained from a pharmacy (behind-the-counter [BTC]).

Sensitivity analyses

In addition to examining the impact of vaccination settings (Table 2), one-way and multi-way sensitivity analyses varied the MNP cost [\$9.50 (the same as the prefilled syringe), \$15, \$20, and \$30]; MNP market share (10% to 60%); compliance with the MNP (0%, 3%, 5%, 10%, and 15% increases); and patch efficacy (0%, 3%, 5%, and 10% increases). (The baseline MNP compliance rate was the same as the current vaccines and, since clinical efficacy data is not available for this technology, the baseline MNP efficacy was assumed to be the same as the intramuscular vaccine.) Additionally, we varied the administration success of the BTC MNP (95% and 98%) to account for those who might purchase and fail to use the vaccine or fail to apply it correctly. The choice of variables for the sensitivity analysis included key MNP characteristics that have yet to be determined but can be optimized during product development (efficacy and administration success) and during marketing (price), and variables that can capture the range for potential response of consumers and the market when the product is available for use (compliance and market share). We also varied the discount rate to 5%. As mentioned above, probabilistic sensitivity analyses (i.e., Monte Carlo simulation) were performed for each simulation.

RESULTS

Baseline

The influenza season follows the standard influenza epidemic curves[33]; the epidemic curves generated result with a peak occurring in December, resulting in 13,007,923 influenza cases (95% confidence interval [CI]: 11,161,151–15,062,097). Without the MNP, approximately 146 million vaccinations (95% CI: 143–149 million) are delivered annually,

costing \$6.1 billion (95% CI: \$5.1–\$7.1 billion). Approximately 13 million influenza cases occur (95% CI: 11–15 million), costing \$1.4 billion (95% CI: \$1.0–\$1.8 billion) and \$11.3 billion (95% CI: \$7.0–\$17.0 billion) to third-party payers and society, respectively.

Provider administration of MNP

Assuming the same efficacy and compliance as the current technologies, MNP introduction would be cost-effective (ICERs \$23,347/QALY) at all MNP price points (\$9.50–\$30) and market shares 20% explored, when administered by a healthcare provider. MNP introduction would be economically dominant (i.e., less costly and more effective) compared to the baseline when the MNP price was US\$9.50 and market share 30% (due to reduced waste disposal and total vaccine costs). Vaccination costs would total \$5.9 billion (95% CI: \$4.9–\$7.0 billion) with a \$9.50 MNP at a 30% market share. The number of influenza cases would be similar to the baseline, as incremental differences would not be significant.

Increases in MNP efficacy of 3% allowed for MNP introduction to be cost-effective at market shares 10%–60% for all price points \$15, and dominant at the \$9.50 price point. Efficacy increases up to 10% resulted in ICERs \$822/QALY (MNP price \$30 and market shares 10%) and allowed for higher price points (up to \$20) to become dominant from the societal perspective. Table 3 shows how MNP efficacy would affect the number of cases averted as well as incremental costs (i.e., cost gain or loss compared to baseline) at a 30% MNP market share. Appendix 2 shows acceptability curves for 0% and 5% efficacy increases, showing the probability that a \$20 MNP introduced at a 30% market share is cost-effective for various willingness-to-pay (WTP) thresholds. MNP introduction was always cost-effective (100% of the time) with an efficacy increase of 5% for WTP \$500.

Table 4 shows how increasing compliance with the MNP would affect the number of persons vaccinated as well as incremental influenza vaccination and treatment costs (\$9.50 and \$20 MNPs). While vaccination costs increased with compliance, as more persons were vaccinated, the \$9.50 MNP still afforded total cost savings with compliance increases 5%. For all compliance increases, influenza treatment costs were lower than the baseline as the total number of influenza cases decreased compared to the current vaccination market. However, total costs also increased as more persons were vaccinated. (Appendix 2 provides acceptability curves for 0% and 5% compliance increases.) Tables 3 and 4 can be used to determine the impact that efficacy and compliance would have on productivity by subtracting the third-party payer costs from societal costs. For example, a 5% increase in compliance would save \$260 million in productivity losses compared to the current market (Table 4).

If the MNP presentation could increase both efficacy and compliance, the benefits of its introduction would be substantial; increasing both efficacy and compliance by 3%, MNP introduction would avert ~402,000 influenza cases (assuming a 30% market share) and would save third-party payers \$102 million and society \$416 million (assuming a \$9.50 MNP price).

Provider or self-administration of MNP: option 1

In this scenario, 72.7% of MNP vaccinees receive the patch BTC.[34] Vaccination costs would total \$5.7 billion (95% CI: \$4.7–\$6.8 billion) with a \$9.50 patch price at a 30% market share (less than the baseline and provider administration scenarios). However, while MNP vaccination may result in lower administration costs, we assumed a slightly lower administration success for BTC (98%); thus, if the MNP efficacy were the same as existing vaccines, MNP vaccination would result in fewer effectively vaccinated people and an increased number of influenza cases and treatment costs. The number of additional influenza cases could vary from ~37,000–162,000 (10%–60% MNP market share, respectively); however, this would not be significant unless the MNP held 40% market share. Raising the MNP price to \$20 would eliminate cost savings for the MNP, making its introduction more costly and less effective (i.e., dominated) than the baseline.

If unsupervised MNP self-administration were less effective than provider administration (98% vs. 100%), the MNP would prevent more influenza cases (assuming MNP efficacy is the same as current vaccines) only if its availability made persons 3% more likely to be vaccinated. These compliance increases would result in fewer influenza cases (and their associated treatment costs), which would not only offset but also overcome the increased vaccination costs from more persons being vaccinated. Compliance increases 3% resulted in ICERs \$1,401/QALY for MNP prices \$30 and market shares of 10%–60%. MNP introduction would be dominant at price points \$15 for compliance increases up to 15% (Table 4).

Increasing the MNP efficacy 3% over that of existing vaccines made all MNP scenarios cost-effective (\$916/QALY) or dominant (\$15 and \$20 MNP from third-party payer and societal perspectives, respectively). Table 3 shows results for higher efficacy increases and Appendix 2 gives acceptability curves. Increasing efficacy and compliance by 3% would generate ICERs \$394/QALY for MNP price points \$20 and would be dominant at price points \$15 for all market shares 10%–60%. Again, the difference between the third-party payer and societal costs in Tables 3 and 4 reflect the impact on productivity.

If BTC-administration success was 95%, the number of influenza cases would increase significantly (~235,000 additional cases, 30% market share) with MNP vaccination compared to the baseline. Under these conditions, the MNP would need to afford a 5% efficacy increase or a 5% compliance increase in order to be cost-effective and overcome the assumed 95% BTC-administration success.

Provider or self-administration of MNP: option 2

If 36.4% of MNP vaccinees receive the patch BTC, and if its efficacy and compliance were the same as the existing vaccines, MNP vaccination would lead to ~20,000–63,000 additional influenza cases (10%–60% market share) due to the assumed lower BTC-administration success (98%). However, these increases are not significant. MNP scenarios would not be cost-effective if MNP efficacy and compliance were the same as existing vaccines and would be dominated (i.e., more costly and less effective) by the current market at prices \$15 with market shares 20% and prices \$20 with market shares 30%.

Assuming the same efficacy as existing vaccines, MNP compliance would need to increase by 3% in order to prevent additional influenza cases. Compliance increases up to 15% resulted in ICERs \$974/QALY and would be dominant at a \$9.50 MNP price for all market shares 10% (Table 4). Increasing MNP compliance would increase cost-effectiveness.

MNP efficacy increases as little as 3% would allow MNP scenarios to be cost-effective (ICERs \$778/QALYs) at all price points \$30 and market shares 10%–60% and would be dominant if \$15 (results not shown). Even a \$20 MNP would generate cost savings to society (Table 3). Increasing both compliance and efficacy by 3% would generate ICERs \$402/QALY for price points \$30 and all market shares 10%.

Assuming a 95% BTC-administration success rate would increase the number of influenza cases and their related costs. The MNP would need to increase efficacy or compliance by 3% in order to overcome the reduced BTC-administration success rate and be cost-effective (ICERs \$2,201/QALY) for MNP prices of \$15–\$30 and dominant at a \$9.50 price.

DISCUSSION

An innovative, less-invasive vaccine presentation such as the MNP has many potential advantages including increased efficacy and compliance; it may also enable new vaccination settings. While self-administration and other new administration settings may help to increase compliance and lower costs, the potential for lower vaccination success rates must also be considered. However, if higher compliance or efficacy could be obtained with the MNP, the impact of a lower success rate may be mitigated. Therefore, determining the thresholds at which the MNP remains cost-effective can be helpful in guiding the development and ultimate pricing of the MNP technology leading up to market introduction and use. This analysis helps highlight the potential importance of new delivery technologies, especially when vaccination coverage is well below target. We found that the MNPs could save as much as \$950 million to third-party payers and \$2.6 billion to society over an influenza season, depending on the scenario and assumptions used. For comparison, pneumococcal vaccination (with PCV7) saved \$480 million (2006 USD) over a six-year period (2000–2006) in direct healthcare costs;[35] while MMR vaccination of infants in the US was estimated to save third-party payers \$3.5 billion and society \$7.6 billion (in 2001 USD).[36] Varying the discount rate did not change our findings.

Currently, there are high rates of influenza vaccination in places that offer weekend or off-clinic hours, such as pharmacies and retail clinics.[37-38] If the MNP could be given in an even wider range of settings or self-administered (if policy allowed), it could potentially capture a greater portion of the population that feels they do not have the time to get vaccinated or are concerned about missing work to get vaccinated, thus increasing compliance and coverage. A usability and acceptability study of MNPs showed that if self-administration was offered, the intent to vaccinate increased from 44% to 65%. [34] Self-administration could also reduce administration costs. As with all self-administered healthcare products, self-administration success must be demonstrated during the development process, and there may be concerns about reduced adherence and vaccination success when obtained BTC. However, other self-administered vaccines, such as the oral

typhoid vaccine, have resulted in high rates of adherence to administration instructions and correct use of vaccine storage.[39-40] Any potential decrease in administration success (and consequent increase in influenza cases and costs) should be weighed carefully against the benefits of improved coverage and decreased administration costs that self-administration might enable.

Our analysis could help inform the development or modification of a target product profile (TPP) for the class of MNP technologies. While developers and manufacturers may focus on the maximization of certain vaccine characteristics (e.g., cost, efficacy) as well as ideal target populations and market segments and share, the thresholds for efficacy, price, vaccination settings, and market share established in our analysis could help inform decision-making and technology development. Vaccine price is important, as it can have a considerable impact on the vaccine's adoption.[41] Having a thorough and robust TPP during the development stage can help ensure a vaccine's success before it reaches the market.[14]

Limitations

All models are simplifications of real life and cannot represent every influenza event or outcome. Our model's parameters come from studies of varying quality and do not include actual observed data related to MNP vaccination. Estimates will be improved when data from MNP clinical trials become available. We assumed equal mixing and that influenza cases were evenly distributed across all age groups; however, in reality the burden may be higher in one or more age groups. Additionally, we assumed persons were vaccinated evenly over the course of the vaccination season. To be conservative, we also assumed standard care for influenza and included only the common complications; we excluded rare or unusual complications and potential side effects from vaccination, such as Guillain-Barre, as this outcome is not expected to differ between the different vaccine presentations. Additionally, we did not evaluate MNP introduction from the government perspective. In the US, a large portion of the government perspective for healthcare is the Centers for Medicare and Medicaid Services (CMS), and thus is a third-party payer. Our results may not be generalizable outside the US and in places not having a comparable health system.

Conclusion

Although a less-invasive influenza vaccine technology such as the MNP has many potential advantages, its economic value will depend on price and, if self-administered, the percentage of persons who successfully administer the MNP. With self-administration, there is a trade-off between lower administration costs and a potential reduction in administration success. This could be offset if the MNP technology afforded higher efficacy or compliance than current technologies. When MNPs were administered only by healthcare providers, MNP introduction proved cost-effective (even dominant at a US\$9.50 price point) under all scenarios tested, except when MNPs with a similar efficacy and compliance as existing vaccines held a 10% market share. If self-administration were available and MNPs had the same efficacy as existing vaccines, compliance would need to increase by 3% to be cost-effective. If efficacy increased by 3%, MNP vaccination would be cost-effective or dominant for all price points \$30 for all administration settings explored.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

MNP	microneedle patch
QALY	quality-adjusted life years
ICER	incremental cost-effectiveness ratio
SEIR	Susceptible-Exposed-Infectious-Recovered
BTC	behind-the-counter
WTP	willingness-to-Pay

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Highlights

- Microneedle patches (MNPs) may bring potential advantages over existing vaccine technologies.
- We evaluated their potential economic and epidemiologic impacts in various vaccination settings.
- Administered by healthcare providers, MNPs would be cost-effective under most conditions tested.
- Self-administration may have a reduced administration success and fewer effective vaccinations.
- Efficacy or compliance increases could offset reduced self-administration success.

Figure 1. Model overview: A) variables impacted by vaccine presentation; B) flow of persons through model.

Table 1

Transmission and economic model input parameters, values, and sources.

Parameter	Distribution Type	Estimate	Modeled Range	Source
Transmission Model Parameters				
Vaccine compliance				
<5 years	Beta	0.63	0.5097 – 0.7409	[42]
5-17 years	Beta	0.451	0.4152 – 0.4855	
18-49 years	Beta	0.358	0.3272 – 0.3911	
50-64 years	Beta	0.510	0.4752 – 0.5470	
65 years	Beta	0.707	0.6741 – 0.7438	
Daily vaccine uptake rate				
<5 years	Point Estimate	0.31		A
5-17 years	Point Estimate	0.22		
18-49 years	Point Estimate	0.18		
50-64 years	Point Estimate	0.25		
65 years	Point Estimate	0.35		
Market shares by vaccine presentation				
Multi-dose vial	Point Estimate	0.7787		B
Prefilled syringe	Point Estimate	0.11075		
Intradermal	Point Estimate	0.00675		
Intranasal [†]	Point Estimate	0.10375		
Baseline vaccine efficacy (18-64 years old; injectable vaccines)	Triangular	0.6162	0.5435 – 0.6852	[19]
Vaccine efficacy adjustment factors				
17 years (injectable vaccines)	Point Estimate	0.06		[43]
17 years (intranasal vaccine)	Point Estimate	0.24		
18-64 years (intranasal vaccine)	Point Estimate	–0.15		
65 years (injectable vaccines)	Point Estimate	–0.06		
Incubation period	Triangular	2.27	1 – 4	
Viral shedding (infectious period)	Triangular	4.8	4.17 – 5.43	[44]
Economic Model Parameters				
Costs (2013, USD)				
Ambulatory care visit				
<1 year	Point Estimate	78.46		[45]
1-17 years	Point Estimate	83.91		[45]
18-64 years	Point Estimate	105.59		[45]
65 years	Point Estimate	96.26		[46]
Hospitalization				
<1 year	Gamma	4,347.67	3,024.18 -	
1-17 years	Gamma	6,303.52	3,821.43 – 9,596.68	

Parameter	Distribution Type	Estimate	Modeled Range	Source
18-44 years	Gamma	10,832.81	9,213.34 – 12,617.24	[47]
45-64 years	Gamma	11,713.68	10,323.93 – 13,324.61	
65 years	Gamma	9,787.11	8,370.63 – 11,342.36	
Multi-dose vial vaccine	Point Estimate	8.54		[48]
Prefilled syringe vaccine	Point Estimate	9.50		[48]
Intradermal vaccine	Point Estimate	16.44		[49]
Intranasal vaccine	Point Estimate	21.32		[50]
Vaccine disposal				
Intradermal and intramuscular vaccines	Uniform		0.12 – 0.34	[51]
Microneedle, not dissolvable	Point Estimate	0.0015		C
Vaccine supplies				
Multi-dose vial	Point Estimate	0.91		
Prefilled syringe	Point Estimate	0.49		[48]
Intranasal	Point Estimate	0.12		
Intradermal	Point Estimate	0.49		D
Microneedle *	Point Estimate	0.12		E
Resource Use				
Pharmacist hourly wage	Triangular	57.00	31.29 – 82.03	[52]
Registered nurse hourly wage	Triangular	31.84	15.03 – 58.02	[52]
All occupations hourly wage	Triangular	16.87	1.88 – 58.24	[52]
Nonclinical labor cost				
Medical settings (<1 to 17 years)	Triangular	9.79	5.53 – 19.65	[53]
Medical settings (18 years)	Triangular	9.02	2.20 – 36.32	[54]
Group self-administration settings (all ages)	Triangular	9.02	2.20 – 36.32	[54]
Overhead cost				
Medical settings (<1 to 17 years)	Triangular	12.83	7.87 – 21.63	[53]
Medical settings (18 years)	Triangular	13.70	11.72 – 14.11	[54]
Group self-administration settings (all ages)	Triangular	6.23	5.34 – 6.42	[54]
Vaccine administration time (minutes) in medical setting (18 years)				
Multi-dose vial	Point Estimate	5.105		[48]
Prefilled syringe	Point Estimate	4.488		[48]
Intranasal	Point Estimate	5		[55]
Microneedle	Point Estimate	5		E
Vaccine administration time (minutes) in medical setting (17 years)				
Multi-dose vial	Point Estimate	3.105		[48]
Prefilled syringe	Point Estimate	2.488		[48]
Intranasal	Point Estimate	3		[55]
Microneedle	Point Estimate	3		E
Vaccine administration time (minutes) in group self-administration settings (all ages)				

Parameter	Distribution Type	Estimate	Modeled Range	Source
Multi-dose vial	Point Estimate	11.105		[48]
Prefilled syringe	Point Estimate	10.488		[48]
Intranasal	Point Estimate	11		[55]
Microneedle	Point Estimate	11		<i>E</i>
Probabilities				
Symptomatic influenza	Triangular	0.6652	0.5591 – 0.7677	[44]
Ambulatory care visit given influenza				
<5 years	Beta	0.455	0.1451 – 0.7912	
5-17 years	Beta	0.318	0.1279 – 0.5586	[56]
18-64 years	Beta	0.314	0.2716 – 0.3523	
65 years	Beta	0.620	0.5183 – 0.7173	
Hospitalization given influenza				
<5 years	Beta	0.0141	0.0028 – 0.0383	
5-17 years	Beta	0.0006	0.0002 – 0.0013	
18-49 years	Beta	0.0042	0.0012 – 0.0095	[56]
50-64 years	Beta	0.0193	0.0038 – 0.0521	
65 years	Beta	0.0416	0.0085 – 0.1142	
Mortality given influenza				
<5 years	Beta	0.00004	0.0000213 – 0.0000627	
5-17 years	Beta	0.00001	0.0000095 – 0.0000112	[56]
18-49 years	Beta	0.000089	0.000028 – 0.000190	
50-64 years	Beta	0.00133	0.000367 – 0.003038	
65 years	Beta	0.0117	0.00229 – 0.03182	
Durations (days)				
Microneedle patch wear time (minutes)	Point Estimate	10		<i>B</i>
Influenza symptoms	Point Estimate	7		<i>B</i>
Work absenteeism	Triangular	3.2	1.5 – 4.9	[57]
School absenteeism	Point Estimate	2.54		[58]
Clinic visit (hours)	Point Estimate	4		<i>B</i>
Hospitalization				
<1 year	Gamma	2.8	2.45 – 3.19	
1-17 years	Gamma	3.1	2.53 – 3.93	[47]
18-44 years	Gamma	4.4	4.04 – 4.79	
45-64 years	Gamma	5	4.66 – 5.41	
65 years	Gamma	4.8	4.45 – 5.18	
Utilities				
Healthy QALYs 1-17 years	Point Estimate	1		
Healthy QALYs 18-64 years	Point Estimate	0.92		[59]

Parameter	Distribution Type	Estimate	Modeled Range	Source
Healthy QALYs 65 years	Point Estimate	0.84		
Influenza no hospitalization [^]	Point Estimate	0.659		[21, 60-68]
Influenza with hospitalization [^]	Point Estimate	0.514		[21, 66, 69]

* Except for the unsupervised setting, which assumed no supplies.

[†] For elderly, this was evenly distributed over the other presentations.

[^] Values are the average across multiple studies.

A) Unpublished data from Pittsburgh, PA: 2011 influenza season (University of Pittsburgh).

B) Assumption.

C) Calculated by assuming same relationship between cost and volume of prefilled syringe.

D) Assumed same as prefilled syringe.

E) Assumed same as intranasal.

Table 2

Proportion of children, adults, and elderly vaccinated in each vaccination setting for the simulated scenarios.

Microneedle Patch (MNP) introduction scenario	Vaccination setting		
	Traditional [‡]	Group	BTC
Baseline scenario (current market with no MNP) [‡]			
Children	95.3	4.7	0
Adults	74.4	25.6	0
Elderly	94.4	5.6	0
Provider administration only [‡]			
Children	95.3	4.7	0
Adults	74.4	25.6	0
Elderly	94.4	5.6	0
Provider and self-administration: option 1 [*]			
Children	26.0	1.3	72.7
Adults	15.9	11.4	72.7
Elderly	25.8	1.5	72.7
Provider and self-administration: option 2 [^]			
Children	60.6	3.0	36.4
Adults	41.8	21.8	36.4
Elderly	60.0	3.6	36.4

[‡] 91% of children, 57% of adults, and 67% of elderly are vaccinated in medical vs. nonmedical settings. [42, 70]

[‡] Uses group setting vaccination reported for the 2011-2012 influenza season.[42]

^{*} BTC administration based on preferences reported by Norman et. al, for unsupervised self-administration of the MNP.[34]

[^] Halves the rate of BTC MNP administration.

Table 3

Effect of MNP efficacy on the mean number of cases averted and mean (95% confidence interval) incremental cost (USD, millions) between scenarios including the MNP and the current baseline from the third-party payer and societal perspectives when the MNP holds 30% of the market.

Increase in efficacy	\$9.50 MNP				\$20 MNP				\$30 MNP			
	0%	5%	10%	0%	5%	10%	0%	5%	10%	0%	5%	10%
Provider administration of MNP												
Cases averted	8,612 (-95,781 to 113,006) [†]	338,043 (235,009 to 441,076)	653,066 (549,353 to 765,780)	11,744 (-94,411 to 117,898) [†]	336,157 (229,411 to 442,902)	653,025 (547,843 to 758,206)	11,108 (-95,195 to 117,412) [†]	339,995 (235,387 to 444,604)	651,688 (548,152 to 755,223)	11,108 (-95,195 to 117,412) [†]	339,995 (235,387 to 444,604)	651,688 (548,152 to 755,223)
Incremental cost third-party	-115 (-173 to -56)	-150 (-208 to -91)	-183 (-243 to -123)	345 (286 to 404)	310 (251 to 369)	276 (216 to 336)	778 (719 to 837)	747 (-689 to 806) [†]	712 (653 to 771)	778 (719 to 837)	747 (-689 to 806) [†]	712 (653 to 771)
Incremental cost societal	-121 (-414 to 172) [†]	-410 (-689 to -132)	-690 (-960 to -420)	336 (58 to 613)	48 (-228 to 325) [†]	-234 (-511 to 43) [†]	770 (478 to 1,061)	487 (203 to 772)	210 (-69 to 489) [†]	770 (478 to 1,061)	487 (203 to 772)	210 (-69 to 489) [†]
ICER [^]	Dominant	Dominant	Dominant	5,804	182	84	13,692	434	216	13,692	434	216
Provider or self-administration of MNP: option 1 *												
Cases averted	-89,012 (-191,195 to 13,171) [†]	244,471 (140,680 to 348,262)	561,822 (454,226 to 669,418)	-86,168 (-192,772 to 20,437) [†]	242,289 (137,417 to 347,162)	561,543 (460,392 to 662,695)	-85,588 (-191,365 to 20,190) [†]	243,948 (137,655 to 350,242)	563,071 (459,871 to 666,272)	-85,588 (-191,365 to 20,190) [†]	243,948 (137,655 to 350,242)	563,071 (459,871 to 666,272)
Incremental cost third-party	-352 (-411 to -292)	-383 (-443 to -322)	-409 (-470 to -348)	87 (28 to 146)	82 (20 to 144)	50 (-11 to 111) [†]	538 (478 to 597)	518 (456 to 580)	488 (428 to 548)	538 (478 to 597)	518 (456 to 580)	488 (428 to 548)
Incremental cost societal	-283 (-566 to -1)	-568 (-834 to -303)	-846 (-1,123 to -568)	153 (-127 to 434) [†]	-104 (-385 to 177) [†]	-388 (-668 to -108)	605 (312 to 897)	331 (48 to 614)	50 (-226 to 324) [†]	605 (312 to 897)	331 (48 to 614)	50 (-226 to 324) [†]
ICER [^]	Less costly but less effective	Dominant	Dominant	Dominated	67	18	Dominated	420	171	Dominated	420	171
Provider or self-administration of MNP: option 2 *												
Cases averted	-38,889 (-145,884 to 68,106) [†]	290,786 (182,965 to 398,608)	607,555 (508,154 to 706,957)	-38,685 (-145,364 to 67,994) [†]	290,750 (184,845 to 396,654)	607,364 (504,184 to 710,545)	-38,852 (-141,181 to 63,478) [†]	293,430 (188,164 to 398,697)	607,865 (501,458 to 714,272)	-38,852 (-141,181 to 63,478) [†]	293,430 (188,164 to 398,697)	607,865 (501,458 to 714,272)
Incremental cost third-party	-240 (-299 to -180)	-266 (-327 to -205)	-308 (-369 to -247)	219 (159 to 279)	185 (126 to 245)	152 (93 to 211)	650 (592 to 709)	622 (562 to 682)	588 (528 to 647)	650 (592 to 709)	622 (562 to 682)	588 (528 to 647)
Incremental cost societal	-210 (-491 to 71) [†]	-492 (-776 to -208)	-780 (-1,063 to -497)	250 (-36 to 535) [†]	-44 (-328 to 240) [†]	-321 (-607 to -36)	680 (391 to 969)	393 (103 to 684)	120 (-155 to 394) [†]	680 (391 to 969)	393 (103 to 684)	120 (-155 to 394) [†]
ICER [^]	Less costly but less effective	Dominant	Dominant	Dominated	126	50	Dominated	419	191	Dominated	419	191

Note: MNP is microneedle patch; Negative cases averted are additional cases with MNP vaccination; negative costs are savings; costs are in millions.

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Incremental cost-effectiveness ratio (ICER) calculated using mean values from the third-party payer perspective; dominant, adding MNP is less costly and more effective than current vaccination market;
ICERs \$50,000/QALY considered cost-effective; dominated, adding MNP is more costly and less effective than the current vaccination market.

* 98% BTC administration success.

† Difference is not significant

Table 4

The impact of MNP compliance on the additional number of vaccinations (in millions) and vaccination costs (USD, millions) for a \$9.50 and \$20 MNP. And the effect on the number of cases averted and influenza-related costs (USD, millions) from the third-party payer and societal perspectives when the MNP holds 30% of the market. All values are mean (95% confidence interval) difference between MNP scenario and baseline.

	Increase in compliance			
	0%	5%	10%	15%
Provider administration of MNP				
Additional vaccinations	0.0 (-0.2 to 0.1) [†]	2.2 (2.0 to 2.4)	4.4 (4.2 to 4.5)	6.6 (6.4 to 6.7)
Incremental vaccination cost for a \$9.50 MNP	-114 (-170 to -58)	-25 (-81 to 32) [†]	62 (8 to 116)	152 (97 to 206)
Incremental vaccination cost for a \$20 MNP	345 (291 to 402)	442 (387 to 498)	538 (480 to 595)	630 (575 to 686)
Cases averted	8,612 (-95,781 to 113,006) [†]	336,111 (233,881 to 438,341)	652,847 (549,090 to 765,605)	955,391 (854,563 to 1,056,219)
Incremental influenza cost third-party	-1 (-25 to 23)	-36 (-58 to -13)	-70 (-93 to -47)	-102 (-124 to -80)
Incremental influenza cost societal	-7 (-296 to 282)	-296 (-557 to -30)	-573 (-842 to -304)	-830 (-1,088 to -572)
ICER [^] for a \$9.50 MNP	Dominant	Dominant	Dominant	10
ICER [^] for a \$20 MNP	5,804	237	141	110
Provider or self-administration of MNP: option 1 *				
Additional vaccinations	0.0 (-0.2 to 0.1) [†]	2.2 (2.0 to 2.4)	4.4 (4.2 to 4.5)	6.6 (6.4 to 6.7)
Incremental vaccination cost for a \$9.50 MNP	-361 (-416 to -305)	-218 (-327 to -213)	-198 (-254 to -143)	-101 (-157 to -45)
Incremental vaccination cost for a \$20 MNP	78 (23 to 133)	194 (136 to 251)	288 (231 to 345)	357 (299 to 414)
Cases averted	-89,012 (-191,195 to 13,171) [†]	244,762 (138,816 to 350,708)	560,108 (454,952 to 665,294)	858,435 (759,657 to 957,213)
Incremental influenza cost third-party	10 (-13.9 to 32.9) [†]	-26 (-49 to -3)	-59 (-82 to -36)	-91 (-113 to -70)
Incremental influenza cost societal	78 (-201 to 357) [†]	-212 (-471 to 47)	-489 (-742 to -236)	-760 (-1,034 to -487)
ICER [^] for a \$9.50 MNP	Less costly but less effective	Dominant	Dominant	Dominant
ICER [^] for a \$20 MNP	Dominated	135	81	61
Provider or self-administration of MNP: option 2 *				
Additional vaccinations	0.0 (-0.2 to 0.1) [†]	2.2 (2.0 to 2.4)	4.4 (4.2 to 4.5)	6.6 (6.4 to 6.7)
Incremental vaccination cost for a \$9.50 MNP	-244 (-299 to -189)	-155 (-210 to -99)	-74 (-129 to -19)	15 (-40 to 71)
Incremental vaccination cost for a \$20 MNP	215 (159 to 2701)	315 (260 to 369)	395 (340 to 450)	498 (442 to 553)
Cases averted	-38,889 (-145,884 to 68,106) [†]	288,207 (189,391 to 387,022)	608,228 (502,929 to 713,527)	909,523 (808,765 to 1,010,292)

	Increase in compliance			
	0%	5%	10%	15%
Incremental influenza cost third-party	4 (-19 to 27) [†]	-31 (-53 to -8)	-64 (-86 to -42)	-96 (-119 to -74)
Incremental influenza cost societal	34 (-241 to 309) [†]	-257 (-553 to 39)	-530 (-815 to -245)	-800 (-1,064 to -536)
ICER [^] for a \$9.50 MNP	Less costly but less effective	Dominant	Dominant	Dominant
ICER [^] for a \$20 MNP	Dominated	305	108	87

Note: MNP is microneedle patch; Negative cases averted are additional cases with MNP vaccination; negative costs are savings; costs and additional vaccinations are in millions.

[^] Incremental cost-effectiveness ratio (ICER) calculated using mean values from the third-party payer perspective, calculated from mean differences; dominant, adding MNP is less costly and more effective than current vaccination market; ICERs \$50,000/QALY considered cost-effective; dominated, adding MNP is more costly and less effective than the current vaccination market.

* 98% BTC administration success.

[†] Difference is not significant.