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Projected Population Benefit of Increased Effectiveness and Coverage of Influenza Vaccination on Influenza Burden — United States

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Abstract

Background—Vaccination is the best way to prevent influenza; however, greater benefit could be achieved. To help guide research and policy agendas, we aimed to quantify the magnitude of influenza disease that would be prevented through targeted increases in vaccine effectiveness (VE) or coverage.

Methods—For three influenza seasons (2011–12, 2015–16, and 2017–18) we used a mathematical model to estimate the number of prevented influenza-associated illnesses, medically-attended illnesses, and hospitalizations across five age groups. Compared with estimates of prevented illness during each season, given observed VE and coverage, we explored the number of additional outcomes that would be prevented from a 5% absolute increase in VE or coverage or achieving 60% VE or 70% coverage.

Results—During the 2017–18 season, compared with the burden already prevented by influenza vaccination, a 5% absolute VE increase would prevent an additional 1,050,000 illnesses and 25,000 hospitalizations (76% among those aged ≥65 years) while achieving 60% VE would prevent an additional 190,000 hospitalizations. A 5% coverage increase would result in 785,000 fewer illnesses (56% among those aged 18–64 years) and 11,000 fewer hospitalizations; reaching 70% would prevent an additional 39,000 hospitalizations.

Conclusions—Small, attainable improvements in effectiveness or coverage of influenza vaccine could lead to substantial additional reductions in influenza burden in the U.S. Improvements in VE would have the greatest impact in reducing hospitalizations in adults aged ≥65 years and coverage improvements would have the largest benefit in reducing illnesses in adults aged 18–49 years.

Summary:

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Mathematical modeling demonstrated how increases in influenza vaccine effectiveness or coverage during influenza seasons of varying severity would result in substantial reductions to influenza-associated illnesses, medically-attended illnesses, and hospitalizations in the United States.

Keywords

influenza; immunization; burden; mathematical model

Background

The Centers for Disease Control and Prevention (CDC) recommends that all people aged 6 months and older receive annual influenza vaccination as the primary strategy to prevent influenza virus infection and its complications [1]. However, in any given season, the overall protective benefit of influenza vaccines in the population depends on vaccine effectiveness (VE) and the proportion of people vaccinated.

A meta-analysis of randomized controlled trials (RCT) among adults aged 18–64 years found a pooled influenza vaccine efficacy of 59% [2]. However, VE varies by virus type, age group, season, and factors such as co-morbid conditions [3]. For example, in a meta-analysis comparing VE by virus subtype and lineage, the pooled VE varied for influenza A(H1N1)pdm09 (61%), influenza B (54%) and influenza A(H3N2) (33%) viruses [4]. In recent years, there have been some incremental improvements in VE and newly available vaccine formulations, yet significantly improving the efficacy of influenza vaccines is a long-term goal that requires investments in advancing new technologies and methodologies.

Alternatively, increasing influenza vaccination coverage would also provide greater population protection against influenza but likely does not require new vaccine products, and thus could be a focus for the near-term. Coverage among non-institutionalized persons aged ≥6 months has remained between 41–47% since the 2009 pandemic [5], well below the Healthy People 2020 target of 70% coverage for the general population [6]. Annual coverage in some age groups does approach this target, however; for example, during 2015–16 71% of adults aged ≥65 years and 67% of children aged 6–23 months received influenza vaccine [5]. Common reasons reported for non-vaccination against influenza include low perceived risk, concerns about safety of the vaccine, and lack of perceived benefit, possibly stemming from concerns about low VE [7].

To inform and target research and policy agendas to improve the effect of influenza vaccination in the United States, we used a mathematical model to estimate the number of additional influenza-associated illnesses that could be prevented by increasing VE or vaccination coverage [8].

Methods

Influenza Burden

Since the effect of influenza vaccination on the population depends on the amount of influenza that occurred during that season, we applied a mathematical model to data from three seasons representing a range of severity [9]: low severity (2011–12, influenza A(H3N2)-predominant), moderate severity (2015–16, influenza A(H1N1)-predominant), and high severity (2017–18, influenza A(H3N2)-predominant). For each included season, we used previously described methods to estimate influenza burden (illness episodes, medical visits, and hospitalizations; Supplemental Table 1) and outcomes prevented at observed levels of VE and coverage (Supplemental Table 2) [8, 10]. Briefly, we used age-specific (6 months–4 years, 5–17, 18–49, 50–64, and ≥65 years) rates of laboratory-confirmed influenza-associated hospitalizations from routine, annual surveillance (Influenza Hospitalization Surveillance Network, FluSurv-NET), adjusted for the probability that a hospitalization due to influenza is detected (accounting for influenza testing frequency and test sensitivity) [11]. From hospitalization rates, we applied age-group specific multipliers for the number of illness episodes per hospitalization to estimate the rate of symptomatic illnesses and multiplied by the proportion of people who reported seeking care for influenza-like illness to estimate the rate of influenza-associated medical visits [12, 13]. We then applied estimated rates to the U.S. population to calculate influenza-associated burden [14].

Vaccine Effectiveness

Estimates of adjusted influenza VE against all influenza virus types for the included seasons and age groups were obtained from the United States Influenza Vaccine Effectiveness Network [3]. Overall VE varied from 38% in the high severity season (2017–18) to 47% and 48% during the low (2011–2012) and moderate severity seasons (2015–16), respectively. VE varied by age groups within seasons (Supplemental Table 1) [15–17].

Vaccine Coverage

We obtained monthly influenza vaccination coverage estimates for the included seasons, by age group, from the National Immunization Survey – Flu (for children aged 6 months-17 years) and Behavioral Risk Factor Surveillance Survey (for adults aged ≥18 years) [5]. Overall coverage ranged from 41% during the low and high severity seasons to 45% during the moderate severity season, with additional variation by age group (Supplemental Table 1). To account for possible inaccurate recall of vaccination status and nonresponse bias in coverage surveys, we assumed the provided standard error was equal to half of the 95% confidence interval.

Analytic Methods

First, we applied a previously described compartmental model, stratified by age group, to influenza burden, VE and vaccination coverage estimates to calculate numbers of influenza-associated outcomes that would have occurred in the absence of vaccination and numbers prevented at observed levels of VE and coverage for each season [8]. Second, to estimate the additional burden that would be prevented with increases in either VE or vaccination coverage, we used the estimated risk of outcomes in the absence of vaccination and applied higher VE or coverage values, by age group, under four scenarios: (1 & 2) 5% absolute increases in VE or vaccination coverage during a specified season, (3) 60% VE in each season or (4) 70% vaccination coverage in each season — meeting the Healthy People 2020 target [6]. We used 60% VE as a target based on the results from a meta-analysis of RCTs among healthy adults [2]. We calculated additional outcomes prevented under the four scenarios by subtracting the estimated burden expected with improvements in vaccination coverage or VE from the estimates of burden using the VE and coverage observed during the season (Supplemental Table 2) [10]. We assumed no additional benefit in scenarios when vaccine target goals were surpassed. Lastly, we explored the additional number of hospitalizations that would be prevented through simultaneous 5% absolute increases in both VE and coverage versus independent 5% absolute increases.

We used 5,000 Monte Carlo simulations to construct 95% credible intervals (Cr I; 2.5% and 97.5% values) around the point estimates of the additional prevented burden. For simulations, we sampled model inputs using distributional assumptions listed in Supplemental Table 3. We truncated the lower bound of the 95% credible interval at zero because we assumed that increasing VE or coverage could not result in higher influenza burden in the population.

We rounded estimates for symptomatic illnesses and medically-attended illnesses to 3 significant figures, and hospitalization estimates to 2 significant figures. All analyses were conducted in R version 3.5.0 [18].

Results

Increase VE by 5 Percentage Points

The benefits of an absolute 5 percentage point increase in vaccine effectiveness (VE) varied by season severity (Figure 1). In the low severity season (2011–12), 5% increases in VE across all ages would prevent an additional 228,000 (95% Cr I: 209,000–299,000) illnesses, 112,000 (95% Cr I: 102,000–147,000) medically-attended illnesses, and 4,900 (95% Cr I: 4,000–7,700) hospitalizations (Figure 1 and Supplemental Tables 4–6). In the high severity season an additional 1,050,000 (981,000–1,170,000) illnesses, 526,000 (95% Cr I: 486,000–589,000) medically-attended illnesses, and 25,000 (95% Cr I: 22,000–30,000) hospitalizations would be prevented.

In the high severity season, increasing VE by 5% among adults 50–64 years would result in the greatest numbers of additional illnesses prevented (Figure 1). For adults aged ≥65 years, an increase of 5% in VE would translate to 19,000 more influenza-associated hospitalizations prevented in the high severity season.

Increase Vaccination Coverage by 5 Percentage Points

The absolute additional reduction in influenza-associated disease from a 5% increase in vaccination coverage varied by season and disease burden level (Figure 1). A 5% increase in coverage would prevent an additional 252,000 (95% Cr I: 185,000–368,000) illnesses, 117,000 (95% Cr I: 85,900–173,000) medically-attended illnesses, and 3,900 (95% Cr I:

1,400–8,300) hospitalizations in the low severity season and 785,000 (95% Cr I: 583,000–999,000) illnesses, 381,000 (95% Cr I: 287,000–489,000) medically-attended illnesses, and 11,000 (4,300–20,000) hospitalizations in the high severity season (Figure 1 and Supplemental Tables 4–6).

In most scenarios, the 5–64 years age groups would see larger reductions in illnesses from a 5% increase in coverage compared with young children and older adults (Figure 1A). During the moderate severity season, a 5% increase in coverage among persons aged 18–49 years would prevent an additional 270,000 illnesses, which was greater than any other age group. For illnesses and medically-attended illnesses, in general, age groups <65 years would see a larger absolute reduction from incremental improvements in coverage compared with adults ≥65 years (Figure 1A and 1B, Supplemental Tables 4 and 5). For hospitalizations though, during all seasons, adults aged ≥65 years would see the largest absolute reduction from increased coverage (Figure 1C, Supplemental Table 6).

Overall, compared to a 5% increase in coverage, a 5% increase in VE would prevent more influenza, primarily because VE was lower than coverage in most age groups. Due to this relationship, improvements in VE or VC amplify the benefit of the other; age groups with higher VE benefit most from increases in VC and age groups with higher VC benefit most from increases in VE. In adults aged 18–49 years, the VE was consistently higher than coverage; and, thus, a 5% increase in coverage would prevent more influenza than a 5% VE improvement.

60% Vaccine Effectiveness

In Figure 2, by age group, we show the gap between observed VE (panel A) during each season and a VE of 60% as well as the gap between observed and target vaccination coverage (70%) (panel B; Supplemental Tables 4–6).

The gap between the observed and 60% VE was greatest during the 2017–18 season where overall VE was 38% (Figure 2A). In that year, assuming 60% VE, 5,730,000 (95% Cr I: 4,530,000–7,240,000) illnesses, 2,750,000 (95% Cr I: 2,140,000–3,500,000) medically-attended illnesses, and 190,000 (95% Cr I: 120,000–260,000) more hospitalizations would be prevented. Note that during the high severity season, VE in children 6 months–4 years was 68%, surpassing the 60% target.

For adults aged ≥65 years, if VE had been 60% (instead of 17%) during the high severity season, an additional 1,810,000 illness episodes, 1,010,000 medically-attended illnesses, and 160,000 hospitalizations would be prevented, assuming that coverage remained unchanged at 59% (Figure 2A).

For adults aged 50–64 years who had lower VE estimates during the seasons we included, the gap between observed VE and 60% VE was greater in the moderate severity season than in the low severity season. The additional illnesses prevented by meeting 60% VE during the moderate severity season totaled 1,170,000 compared to 59,800 during the low severity season. In children aged 5–17 years, the gap between observed VE and 60% VE was higher during the high severity season and lower during the low severity season; and improving VE to 60% would result in 1,200,000 additional illnesses prevented in the high severity season and 121,000 in the low severity season.

70% Vaccination Coverage

During the high severity season, 70% influenza vaccination coverage would prevent an additional 3,840,000 (95% Cr I: 2,640,000–5,090,000) illnesses, 1,610,000 (95% Cr I: 1,100,000–2,160,000) medically-attended illnesses, and 39,000 (95% Cr I: 20,000–64,000) hospitalizations.

Coverage was consistently lower in the 18–49 year age group compared with other age groups. Assuming 70% coverage during the high severity season, 1,850,000 more illnesses, 683,000 more medically-attended illnesses, and 10,000 more hospitalizations would be prevented in this age group, assuming that VE remained unchanged at 33%. In the high severity year, coverage was higher in those aged ≥65 years (59%) compared with the 18–49 year age group (27%); however, adults ≥65 years have the highest burden of influenza-associated hospitalizations and, thus, closing the smaller coverage gap in those aged ≥65 years would prevent more hospitalizations than closing the larger coverage gap in those 18–49 years.

Simultaneous Increases in VE and Vaccination Coverage

Models suggested greater than additive benefit of simultaneously increasing VE and coverage by 5%. During the high severity season, 5% increases in both VE and coverage would prevent an additional 38,000 hospitalizations compared to the 25,000 and 11,000 prevented through independently increasing VE and coverage, respectively, although the difference was not statistically significant. Similarly, in the low severity season, simultaneous 5% increases in VE and VC would prevent an additional 9,300 hospitalizations compared to the 3,900 and 4,900 prevented through independent VE and VC increases.

Discussion

Each season influenza vaccination prevents millions of influenza-associated illnesses in the U.S [8]; however, further improvements in the effectiveness or coverage would result in substantial additional reductions for all age groups across a range of seasons. In the three seasons of wide-ranging severity modeled, improvements in VE would prevent the greatest number of hospitalizations in those aged ≥65 years whereas improvements in coverage would substantially reduce illnesses and medically-attended illnesses in those ≤65 years, particularly in higher severity seasons.

People aged ≥65 years tend to be the most highly vaccinated against influenza in the U.S. and also have the highest burden of influenza hospitalizations. Thus, even small absolute increases in VE in this age group would be more beneficial in reducing severe disease than increasing coverage. There are several influenza vaccines available for older adults that are designed to be more immunogenic [19, 20], or are alternatives to traditional egg-based vaccines [21, 22]; increasing use of these vaccines may increase the benefit of vaccination and reduce the population burden of influenza. For example, if we applied the reported 10% relative VE of cell-cultured versus egg-based vaccines [22] or 24% relative VE of high-dose versus standard dose vaccines [19] for our included seasons, this would translate, depending on the season, to a 6–8% or 14–20% absolute increase, respectively, over the VE observed in those ≥65 years. These ranges of improved VE are all higher than the 5% increase we explored.

For groups with lower vaccination coverage, such as adults aged 18–64 years, our models demonstrated that increasing coverage in working-age adults would be particularly beneficial for reducing the absolute burden of influenza illnesses, even with current vaccines. This is similar to findings from another modeling study, which incorporated indirect benefits of vaccination (i.e. reduced disease transmission) and found that targeted vaccination of adults aged 30–39 years and children aged 5–19 years, even with 10%–45% VE, resulted in the greatest reduction in disease burden [23]. Working age adults generally have the lowest influenza coverage in the U.S. but tend to have higher VE than other age groups [3–5]. For example, in the moderate severity season, among people aged 18–49 years, our analysis showed that increasing coverage by only 5% would prevent hundreds of thousands more illnesses and increasing coverage to 70% would prevent 3,780,000 total illnesses. Moreover, focusing vaccination efforts on working-aged adults also has economic benefits, as one study estimated that this age group experiences an average of 8 million productive days lost and high indirect costs due to influenza [24]. To help increase influenza coverage, vaccination could be offered in a variety of non-traditional settings (e.g. workplaces or schools) and be combined with targeted messaging that emphasizes the risk, the productivity and economic costs of influenza, as well as the and safety of influenza vaccination [25–27]. Improved confidence in the protective efficacy of influenza vaccines could also contribute to uptake in this age group [7, 28, 29].

Having a highly effective vaccine or meeting coverage targets for most age groups would lead to substantially larger reductions in disease burden compared to 5% increases in VE or coverage. The VE and coverage benchmarks in our models are achievable. Annual coverage in some populations already approaches or surpasses the 70% coverage target, including children 6 months–4 years and people aged ≥65 years [25]. While recent estimates of VE against illnesses due to influenza A(H1N1)pdm09 and B viruses have been close to 60% [4], many recent influenza seasons in the U.S. have been influenza A(H3N2)-predominant. Achieving a VE against influenza A(H3N2) viruses that is closer to VE against A(H1N1)pdm09 or B viruses, would help us prevent many more illnesses.

The relative magnitude of our estimates of benefit, from independent VE or coverage improvements, are small when compared with total burden of influenza-associated disease. For example, in the high severity season there were 950,000 hospitalizations in those aged ≥6 months.

With independent improvements in either VE or coverage we would prevent only 1–20% of hospitalizations that would have occurred in the absence of vaccination. However, investing in improvements to both VE and coverage would more dramatically increase the benefit of influenza vaccination, because VE and coverage have a synergistic relationship in reducing influenza disease burden, where improvements in one can amplify the benefit of the other.

Our modelling approach has limitations. First, we have likely underestimated the population benefit of influenza vaccination as our model does not include possible indirect protection that may come from decreased exposure to infected persons, though it remains unclear to what degree influenza vaccine reduces transmission currently and how that would be affected by improvements in coverage or effectiveness we consider in this analysis. VE estimates are measured against medical visits but are applied to hospitalizations; however, recent analyses suggest that VE against influenza-associated hospitalization may be similar to effectiveness against outpatient medically-attended illness [31]. Limitations in methods to estimate VE, coverage, and influenza burden inputs have been discussed in the literature and also affect the model outputs [11, 17, 25]. Coverage for children <9 years is based on receipt of one or more doses, which may not represent a fully vaccinated child if they needed two doses of influenza vaccine to be fully vaccinated [25]. Lastly, we do not include other aspects of influenza such as economic costs or differences in quality of life due to illness.

Conclusion

Annual influenza vaccination is the primary public health strategy to protect against influenza disease but currently available vaccines are not as effective as they could be and coverage remains below national targets. Our results quantify the possible additional illnesses, medically-attended illnesses, and hospitalizations that would be prevented by increased coverage and more effective vaccines. Improvements in VE would have the greatest impact in reducing hospitalizations in adults aged ≥65 years who have high coverage and hospitalization rates whereas coverage improvements would have the largest benefit in reducing illnesses in adults 18–49 years. By continuing to invest in and develop improved influenza vaccines and to promote higher coverage, we can achieve substantial reductions to influenza disease burden.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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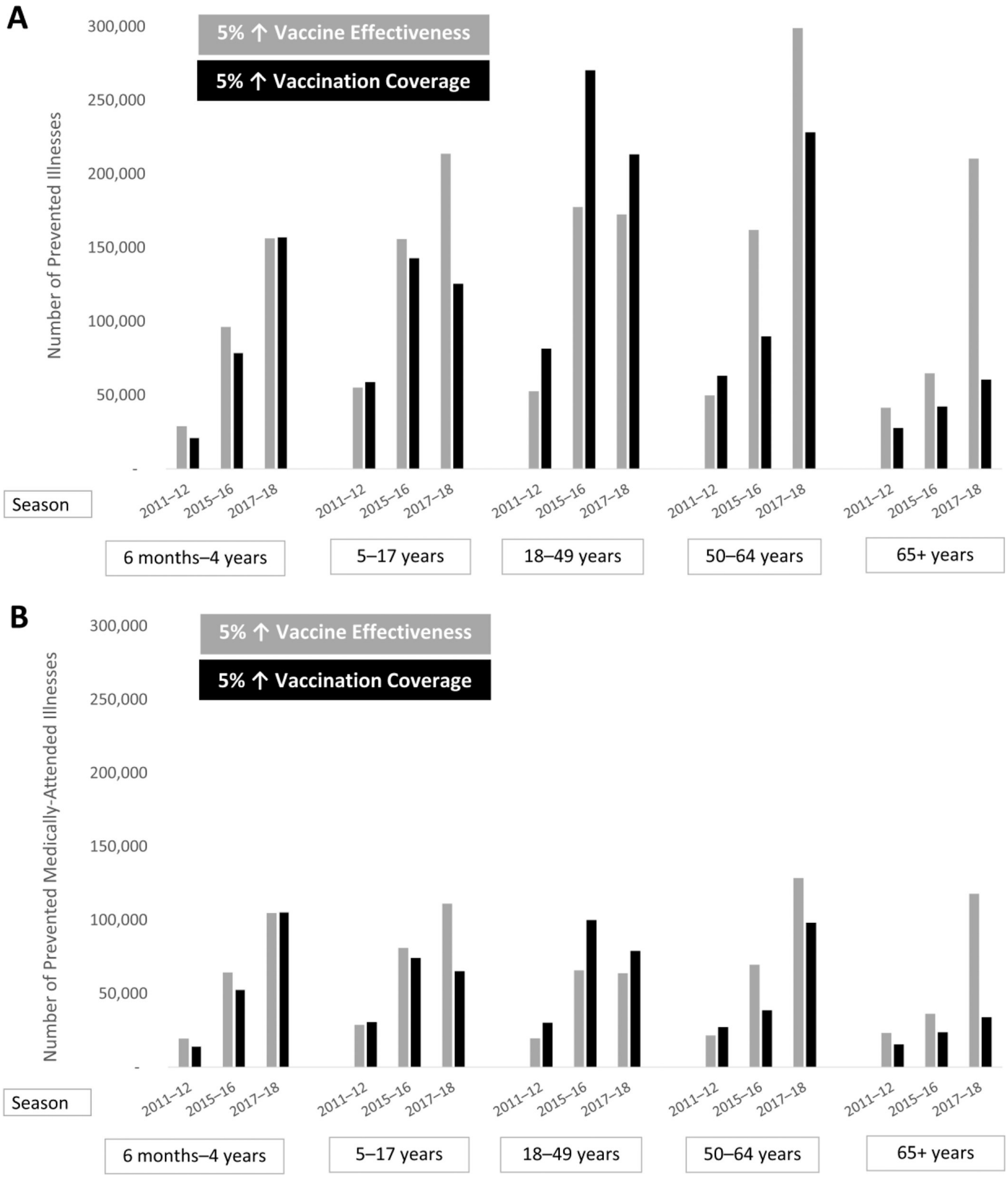

A
5% ↑ Vaccine Effectiveness
5% ↑ Vaccination Coverage
Number of Prevented Illnesses
300,000
250,000
200,000
150,000
100,000
50,000
-
Season
2011–12
2015–16
2017–18
6 months–4 years
5–17 years
18–49 years
50–64 years
65+ years
B
Number of Prevented Medically-Attended Illnesses

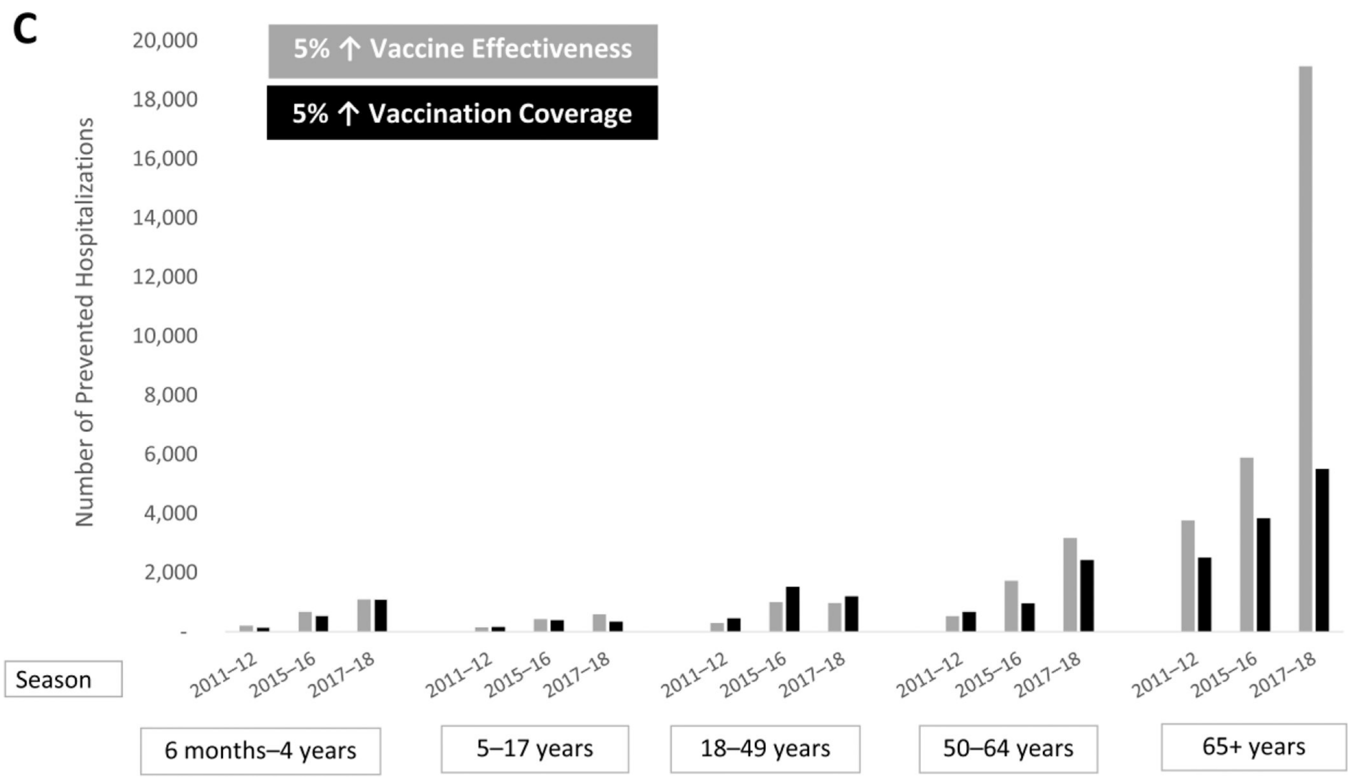
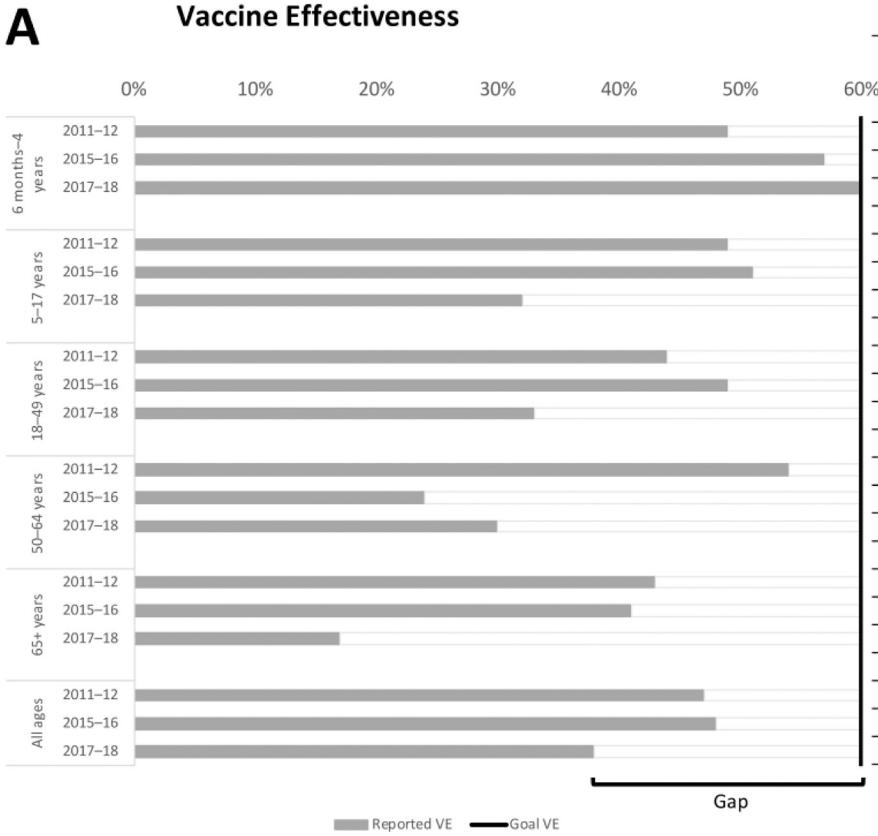


Figure 1:

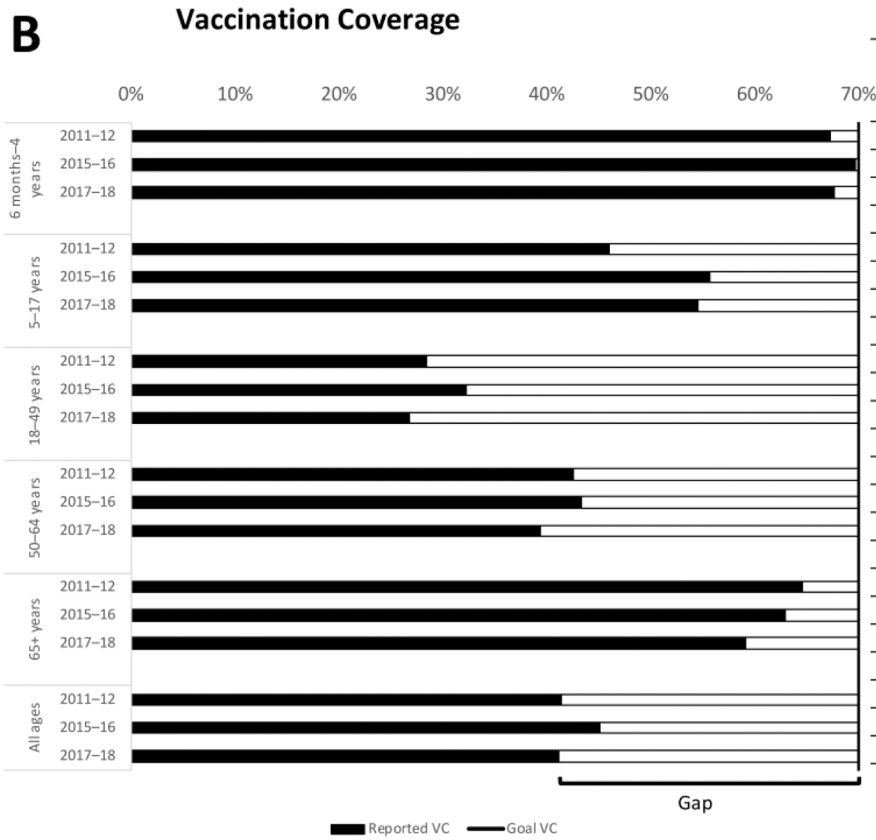
Additional number of illnesses (A), medically-attended illnesses (B), and hospitalizations (C) prevented by incremental increases in influenza vaccine effectiveness or vaccination coverage.

A



Additional Prevented Burden

Age group	Season	Illnesses	Medically-Attended Illnesses	Hospitalizations
6 months–4 years	2011–12	63,500	42,500	440
	2015–16	57,700	38,700	400
	2017–18	60% Target Surpassed		
5–17 years	2011–12	121,000	63,100	330
	2015–16	281,000	146,000	770
	2017–18	1,200,000	622,000	3,300
18–49 years	2011–12	168,000	62,300	950
	2015–16	391,000	145,000	2,200
	2017–18	932,000	345,000	5,200
50–64 years	2011–12	59,800	25,700	630
	2015–16	1,170,000	501,000	12,000
	2017–18	1,790,000	772,000	19,000
65+ years	2011–12	141,000	78,900	13,000
	2015–16	246,000	138,000	22,000
	2017–18	1,810,000	1,010,000	160,000
All ages	2011–12	554,000	272,000	15,000
	2015–16	2,140,000	968,000	38,000
	2017–18	5,730,000	2,750,000	190,000



Additional Prevented Burden

Age group	Season	Illnesses	Medically-Attended Illnesses	Hospitalizations
6 months–4 years	2011–12	11,800	7,890	82
	2015–16	4,720	3,160	33
	2017–18	75,500	50,600	530
5–17 years	2011–12	283,000	147,000	780
	2015–16	408,000	212,000	1,100
	2017–18	389,000	202,000	1,100
18–49 years	2011–12	678,000	251,000	3,800
	2015–16	2,040,000	756,000	11,000
	2017–18	1,850,000	683,000	10,000
50–64 years	2011–12	346,000	149,000	3,700
	2015–16	479,000	206,000	5,100
	2017–18	1,400,000	603,000	15,000
65+ years	2011–12	29,800	16,700	2,700
	2015–16	59,900	33,600	5,400
	2017–18	132,000	73,900	12,000
All ages	2011–12	1,350,000	572,000	11,000
	2015–16	3,000,000	1,210,000	23,000
	2017–18	3,840,000	1,610,000	39,000

Figure 2:

Additional prevented burden due to achieving 60% vaccine effectiveness (A) or 70% vaccination coverage target (B).