Influenza Related Mortality in Populations That Fail to Reach Herd Immunity

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Influenza related mortality in populations that fail to reach herd immunity

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Abstract

Background

Vaccines remain an important public health tool to prevent morbidity and mortality. For influenza, this requires an annual vaccination strategy due to the need to reformulate the vaccine to target circulating strains. The annual success of such vaccine efforts on the annual mortality rates is important to understand and the focus of this study.

Methods

Data on vaccination rates and mortality associated with Influenza was obtained from the CDC Morbidity and Mortality Weekly Reports and STATS of the States. In addition, data searches were performed using the CDC WONDER database, local and county health reports, the World Health Organization, and United States census reports.

Results

Annual vaccination efforts have had minimal impact on the number of influenza related deaths for those over the age of 65. Additionally, herd immunity has not been achieved in any year at the state and national levels. A closer examination of the 2017 influenza season found that the most populous states had the highest mortality burden. However, there was no correlation in local population density and an increase in influenza mortality.

Conclusion

Deaths associated with Influenza circulating in largely populated states are going to occur where susceptible people are regardless of whether they live in rural counties or densely populated cities. Overall, we propose that to prevent annual deaths related to seasonal influenza, herd immunity must be reached in the most populous states. Targeted vaccination of only the susceptible populations is not enough to protect them from mortality associated with influenza.

Key Words: Influenza; Vaccine; Herd Immunity; Respiratory Infection; Viral Infection; Public Health

Background

Each year a new formulation of influenza vaccine is released to the public and each year the public responds by either getting vaccinated or not. Getting vaccinated to protect yourself from influenza and its complications such as bacteria super infections is important. It is equally important that the population reaches herd immunity to protect individuals who are at risk for severe disease and death. Influenza is a unique virus whose replication and gene reassortment make annual vaccine formulations necessary and requires a reset of herd immunity each year.

Herd immunity is the fraction of a population that is immune to a disease that is needed to protect the un-immune or susceptible – those that are vaccinated but due to comorbidities remain susceptible to severe infection. Each disease has its own pathogenicity and infectivity. To date, Measles is the most contagious disease known, and a vaccine coverage rate of 95-98% is required to prevent endemic spread of the disease in the population ¹. For influenza, it is believed that 80% vaccine coverage in those under 65 and 90% vaccine coverage for those over 65 are required to establish herd immunity ². The current herd immunity threshold for SARS-CoV-2 is under debate and will likely fall somewhere between other respiratory infections such as Measles and influenza ³.

The immune response to influenza is focused on the virus envelope surface glycoproteins hemagglutinin (HA) and neuraminidase (NA). However, these primary immunogens have high mutation rates which is the reason for the annual reformulation of the vaccine ⁴. The subtypes of influenza A virus that circulate in humans are A(H1N1) and A(H3N2) ⁵. Influenza has the ability

to undergo a sudden major change resulting in a strain that most people have little to no immunity. Such an antigenic shift contributed to the 1918 influenza pandemic ⁶.

Several additional factors have a major role in overall influenza vaccine success. First, there is variability in the success of each annual influenza vaccine and how well it matches circulating strains ⁷. Therefore, if a novel strain develops during a flu season that strain may not be included in the annual vaccine. Second, over the past several decades there have been an increase in vaccine hesitancy that has resulted in a reduction in vaccination rates in general ⁸. This is reflected in the annual influenza vaccination rates. It is well known that influenza vaccine rates fall below public health targets of 70% which is also below the estimates of herd immunity ⁹. There are numerous publications on ways to try and increase vaccine uptake ^{10,11}.

A vaccine is a public health resource, and with any resource its use must be optimized to have the greatest impact. Therefore, we propose that achievement of herd immunity against influenza in high-risk populations and within populations with the most transmission will result in a decrease in mortality. Here we analyzed influenza data from 1980 to 2019 to determine whether the use of the influenza vaccine had an impact on annual deaths associated with influenza.

Methods

Data Sources

Estimated number of annual influenza-associated deaths with underlying pneumonia and influenza causes by age group and prominent influenza subtypes were retrieved from the CDC Morbidity and Mortality Weekly Report (MMWR) ¹²⁻¹⁵. Estimated influenza vaccination

coverage among adults and children was obtained on the CDC MMWR publications ⁹ and recommendations for composition of influenza vaccines by the World Health Organization ¹⁶. Antigenic character of the influenza virus and identification of subtyping percentages from 2004-2011 were collected from the CDC weekly archives ¹⁷. Estimated vaccine effectiveness between 2004-2019 was obtained through the CDC publications ¹⁸. 2017 national influenza data was found on the CDC data finder site ¹²

Population data was obtained from the US census¹⁹. State data were obtained from searching the CDC WONDER database ¹⁵. County data was obtained from the county public health publications ²⁰⁻²⁴.

Statistical analysis

Prism software was used for all analysis. Mean differences between data points were determined by 1-way ANOVA and analysis between groups using the student t test.

Results

The CDC published a comparison of the top ten morbidity and mortality categories in the year 1980 and the year 2016 ¹². Influenza was included on both lists. Analyzing the data there were no significant differences in the percentage or total deaths associated with influenza in any age group (Supplemental Figure 1a and 1b). There was no significant difference in the number of deaths in each category analyzed (Supplemental Table 1). There was however, a 10-fold increase in the number of influenza vaccine doses administered ²⁵. Due to this finding, an analysis of

influenza vaccine usage and the effect influenza virus had on mortality across multiple years was performed.

The influenza vaccine changes each year based on the circulating strains of the virus (Table 1) ¹⁶. On average, the overall population of the United States is increased by 1% each year (Figure 1a) ^{19 26}. To achieve influenza vaccine herd immunity, it is estimated that at least 80% of the population and 90% of persons in high-risk groups such as individuals over 65 must be vaccinated. Based on the population in the United States, we estimated the number of doses necessary to achieve the 80% threshold (Figure 1b) and amount of vaccine available each year from 1980 to 2019 (Figure 1c) ²⁵. In addition, the percentage of individuals vaccinated in three different age categories between 1980 and 2019 never reach herd immunity (Figure 1d) ^{13,14,27}. Influenza mortality burden is found in those in the high-risk group of over the age of 65 (Figure 2a) ²⁸. Further, within this age group there is a significant increase in deaths related to influenza and other respiratory comorbidities as compared to influenza and pneumonia related deaths (Figure 2b) ²⁸. Therefore, within the high-risk group and at every time point tested, those suffering from other respiratory diseases had the highest influenza related annual mortality rate.

We examined data from the 2017 influenza season. During this season no state reached the 80% herd immunity threshold (Figure 3a) ²⁹. The most burdened states with influenza related mortality were the most populous states: California, Texas, New York and Florida (Figure 3b and Figure 3c) ³⁰. This demonstrates that the influenza virus is most burdensome in the most populous states and that herd immunity in these states has not been reached.

Finally, we closely examined different counties within Texas and California to determine if there was a pattern of mortality within the more densely populated regions (Table 2)^{15,20-24}. We found that in general, the higher the population, the more mortality burden. However, not every populated region was the same. For example, Los Angeles County has an 11-fold higher population than San Francisco County, but the death rate is orders of magnitude less. Houston, Texas in Harris County has over twice as many residents as Bexar County near San Antonio, yet Bexar County suffered far more deaths than Houston. Overall vaccine rates across all counties in Texas and California regardless of population size was similar. Both Bexar and Harris counties have a similar population of persons over the age of 65.

Discussion

The success of the influenza vaccine has been under investigation for decades since a significant portion of public health resources are focused on the annual influenza vaccine formulation³¹⁻³⁷. In addition, it is well known that herd immunity for influenza is 80% of the general population and 90% of persons over the age of 65 being vaccinated. However, due to vaccine usage and vaccine production herd immunity has not been achieved (Figure 1c and 1d). Additionally, the current trend in COVID-19 vaccine hesitancy is similar to annual influenza vaccine hesitancy and uptake³⁸. There is a great need to increase vaccine usage for highly contagious respiratory virus infections.

Since the same strain of influenza may circulate over many seasons (Table 1), annual influenza vaccination can provide protection over several years. However, due to the high recombination rate of influenza virus, a single vaccine cannot yet cause lifelong immunity.

Therefore, carry over protection by similar circulating flu viruses from year to year will not result in a fixed herd immunity. Achieving herd immunity each year is needed until a more universal approach is developed. As the United States population grows each year, the amount of influenza vaccine doses available and administered will also need to increase in order to reach the 80% and 90% herd immunity thresholds for the general population and persons over 65 population respectively. Despite the nearly ten-fold increase in influenza vaccine use within the United States since 1980, there is very little change in the overall number of influenza and pneumonia related deaths (Supplemental figure 1A and 1B). While care must be taken in comparing data from year to year, this does suggest a very clear pattern: that a highly contagious respiratory virus infection will spread through a population and infect susceptible individuals and we propose this is due to a lack of achieving herd immunity. The success of Measles vaccination and the benchmark set for annual influenza vaccination should both be used as an example for SARS-CoV-2 vaccination efforts.

Not surprisingly, data shows a pattern of the highest influenza related morbidity in the United States to be in the most densely populated states (Figure 3). Although, the concentration of deaths within these states does not correlate with the most populous cities (Table 2). This suggests that once influenza is circulating within a populous state, susceptible persons are at risk regardless of if they are in a large or small community. Overall, this emphasizes how contagious and transmissible of a viral infection influenza is, and the need to reach herd immunity to protect those at most risk for severe disease.

The estimated number of annual Influenza associated deaths by age group shows that

individuals over 65 with underlying respiratory and circulatory causes have a predisposition towards flu related death (Figure 2). The death rate in these patients closely follows overall deaths. The death rate for those older than 65 is higher in those with underlying respiratory infection than those individuals over 65 with a pneumonia super-infection (Figure 2). This stands out because a respiratory virus infection allows for bacteria to move in, and this leads to a super infection. This data demonstrates that influenza is a real threat for those that are over 65 and have underlying respiratory comorbidities.

Conclusions

In conclusion, vaccines can protect individuals from severe disease and death associated with respiratory virus infections such as Measles, influenza and SARS-CoV-2. However, at the population level, protection of susceptible populations can be achieved by reaching herd immunity. For influenza the susceptible population for annual influenza are those over the age of 65 and with lung comorbidities. The vaccination of the US population has not achieved herd immunity and therefore a level of influenza related mortality occurs each year. While it should be a public health goal and the public's overall interest to get the annual influenza vaccine, this is of utmost importance for the larger states that carry the most influenza mortality burden.

List of abbreviations

HA – influenza hemagglutinin

NA - influenza neuraminidase

MMWR – morbidity and mortality weekly report

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Consent for publication: Not applicable

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Authors' contributions: Mary Premenko-Lanier designed and oversaw the student's involvement in the project and assisted in all aspects of the study from data collection to the writing and submission of the manuscript. Both Liliya and Jared equally contributed to data gathering, generation of figures and tables and in the writing of the manuscript.

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SUPPLEMENTAL TABLE 1: INFLUENZA AND PNEUMONIA DEATHS IN 1980 COMPARED TO 2016

	1980	2016	<u>Δ</u>
Overall	54,619	51,537	-3082
Male	27,574	25,011	-2,563
Female	27,045	26,526	-519
White	48,369	43,429	-4,940
Black	6,648	7,731	+1,083
American Indian	257	377	+120

Table 1. The strain of influenza virus included in the annual influenza vaccine compared to its year in circulation

VACCINE YEAR ¹	H3N2 STRAIN	H3N2 CIRCULATION	H1N1 STRAIN	H1N1 CIRCULATION	INFLUENZA B	INFLUENZA B CIRCULATION
2004	Fujian	2002	New Caledonia	1999	Shanghai	2002
2005	California	2004	New Caledonia	1999	Shanghai	2002
2006	Wisconsin	2005	New Caledonia	1999	Malaysia	2004
2007	Wisconsin	2005	Solomon Islands	2006	Malaysia	2004
2008	Brisbane	2007	Brisbane	2007	Florida	2006
2009	Brisbane	2007	Brisbane	2007	Brisbane	2008
2010	Perth	2009	California	2009	Brisbane	2008
2011	Perth	2009	California	2009	Brisbane	2008
2012	Victoria	2011	California	2009	Wisconsin	2010
2013	Victoria	2011	California	2009	Massachusetts	2012
2014	Texas	2012	California	2009	Massachusetts	2012
2015	Switzerland	2013	California	2009	Phuket	2013
2016	Hong Kong	2014	California	2009	Brisbane	2008
2017	Hong Kong	2014	Michigan	2015	Brisbane	2008
2018	Singapore	2016	Michigan	2015	Colorado	2017
2019	Kansas	2017	Brisbane	2018	Colorado	2017

1. Vaccine year refers to the annual influenza vaccine that includes influenza A H3N2 and H1N1 and influenza B

Table 2. Mortality caused by influenza during the 2017-2018 season in California and Texas counties.

	County	Population	Number of deaths	% population deaths	% vaccinated
California	Los Angeles	10000000	278	0.00278	38
	San Francisco	864000	141	0.01631944	41
	Sacramento	1530000	20	0.00130719	44
	San Diego	3321000	343	0.01032821	41
	San Luis Obispo	282000	49	0.01737589	48
	Yolo county	218000	8	0.00366972	50
Texas	Harris County (Houston)	4658000	4	8.5874E-05	44
	Dallas	2620000	1	3.8168E-05	51
	Bexar County (San Antonio)	1957000	800	0.0408789	38
	Travis County (Austin)	1228000	49	0.00399023	49

Figure Legends

Supplemental Figure 1. The total number of influenza related deaths in 1980 compared to

2016. A. the % of influenza related deaths and, B. the total number of influenza related deaths in each age group were analyzed. No significant differences were found between groups, one-way ANOVA.

Figure 1. A failure to reach herd immunity in the US population from 1980 to 2019. A. the total population in the United States from 1980 through 2019 (left y axis) and the annual % population change (right y axis). B. The number of individuals required to be vaccinated to achieve herd immunity for each year (red) as compared to the US annual population (blue). C. The number of influenza vaccine doses produced in the US by year (green) as compared to the number needed for herd immunity in the US (red) and D. the percentage of vaccinated individuals in the US according to high risk (those over 65, green), or under 65 (blue and red). The target for the high-risk individuals is 90% (dotted line).

Figure 2. Estimated Number of Annual Influenza Associated Deaths. Morbidity and Mortality Weekly Reports (MMWR) data was analyzed. A. The number of influenza related deaths overall (red line) and in individuals over the age of 65 (blue line) or under the age of 65 (green line) by year in the United States, 1976-77 influenza season through 2006-07 influenza seasons. B. The number of influenza related deaths in those over the age of 65 overall (red line) or with either an underlying non-pneumonia respiratory or circulatory conditions (blue) or deaths associated with underlying pneumonia (black).

Figure 3. Greatest influenza related deaths during 2017 were concentrated in the most populated states. A. The population in 2017 of each US State. B. the percent vaccinated in each US State during 2017 and C. the number of deaths related to influenza during the 2017 influenza season.

Supplemental Figure 1

Figure 1.

Figure 2.

Figure 3.