Estimating The Impact of Public Health Interventions on COVID Mortality in The United States Using Reductions in Influenza Mortality as an Indicator Of Non-Pharmaceutical Infection Control

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Abstract

Background

Non-pharmaceutical interventions (NPIs) for control of COVID include a range of methods from masks to closures of schools and businesses with the efficacy of any individual strategy contingent on which other NPIs are employed and the extent of compliance with those strategies. In the case of a public health intervention, one typically looks at historical data for comparison, but, because COVID is a new disease, we have no such data. However, we do have extensive historical data for influenza, a respiratory disease with similar modes of transmission. Influenza incidence and mortality dropped dramatically during the COVID pandemic, almost certainly because of these NPIs. The extent of that drop provides an indirect measure of the efficacy of COVID NPIs in stopping the transmission of respiratory infections.

This study evaluates the association of influenza mortality reduction (IMR) during the pandemic with age-adjusted COVID mortality among US states, adjusting for mortality prior to the introduction of NPIs and vaccination rates, while taking into account the impact of population density on NPI effectiveness.

Results

A simple linear model with pre-intervention COVID mortality, IMR, vaccination rate, and population density explained 70% of the state-to-state variability in age adjusted COVID mortality. The resulting model suggests that NPIs prevented 831,000 COVID related deaths in the United States over the course of the pandemic.

Conclusions

These results provide strong evidence that IMR is an accurate indicator of the efficacy of NPIs in controlling transmission of respiratory infections, including COVID. This analysis suggests that NPIs together with vaccination prevented an estimated 2.15 million COVID related deaths and full intervention could have prevented over 700,000 more.

Background

Since the outset of the COVID pandemic, non-pharmaceutical interventions (NPIs) to protect public health have come under heavy criticism for their impact on everything from the economy¹ to mental health^{2–4} to education^{5,6}. Furthermore, almost every intervention has, at some point, been declared ineffective, including masking,^{7,8} routine testing,⁹ school closures,¹⁰ and business "lockdowns".^{11,12}

Meta-analyses of studies of the efficacy of individual NPIs have tended to find beneficial effects^{13–15} with a few prominent exceptions.^{7,8} Closures of businesses and schools, limits on social gathering, travel restrictions, social distancing rules, masking mandates, and other NPI's act in concert to reduce the transmission of respiratory infections. Some protect the individual from the infection in the community, some protect the community from the infected individual, and some do both. Also, the effectiveness of NPI's depends on compliance, which is difficult to quantify. How, then, do we evaluate the overall impact of these interventions on the transmission of COVID?

In an ideal natural experiment, we would have two isolated regions experiencing epidemic conditions that are identical in every way except for fully quantified and controlled differences in NPIs. Alternatively, we might have historical data for a particular disease and could examine changes in incidence and mortality after interventions were imposed. No such natural experiment occurred and, because COVID is a new human disease, we have no historical data. All of this makes the aggregate impact of NPI's on COVID difficult to assess directly.

However, the impact of these NPIs was not limited to COVID. Interventions designed to stop one respiratory pathogen will stop others as well. Therefore, the extent to which these NPIs halted the spread of respiratory pathogens with similar patterns of airborne transmission may provide a surrogate for the efficacy of NPIs for COVID. By far the best characterized of these diseases is influenza.

The marked seasonal patterns of influenza incidence and mortality have been measured for decades. As a result, the expected influenza mortality and the variability in that mortality are well established. Multiple studies have noted the dramatic, global decline in influenza incidence and mortality ^{16–18} during the COVID pandemic and suggested an association with NPIs. In the United States, influenza mortality rates for the first two complete flu seasons (2020-22) were 80% below historic rates,¹⁹ as can be seen in Figure 1. The sharpness of this decline and the fact that flu mortality rose back to pre-pandemic levels once precautions were lifted in 2022-23 makes it unlikely that the drop was due to any change in the prevalent virus or treatment options. Influenza vaccination rates did rise 7% above historical averages during the pandemic,²⁰ probably due to concurrent vaccination with COVID, but this cannot explain an 80% drop in influenza mortality.

It appears that something changed during the pandemic that resulted in a dramatic drop in respiratory disease transmission. By far the most likely explanation of this is COVID NPI's. That suggests that the extent to which influenza mortality decreased from expected levels represents a drop in respiratory disease transmission and may provide an indicator of the effectiveness of COVID NPI's.

The current study explores the association between the influenza mortality reduction (IMR) and COVID mortality at the state level. Other factors considered in the analysis were COVID mortality during the first month of the pandemic and vaccination rates. Because the effectiveness of NPIs can be influenced by population density, it was also included in the model as an interaction term.

Results

As listed in Table 1, state-level influenza mortality rates were an average of 78% lower during the two full flu seasons of the pandemic, 2020-21 and 2021-22, as compared to the three full flu seasons prior to the pandemic, 2016-17, 2017-18, and 2018-19. The decrease in mortality ranged from 49% (North Dakota) to 94% (Washington). This radical difference in influenza mortality during the pandemic at the state level is highly unlikely to reflect simple seasonal variation in the flu strain or vaccine effectiveness (p<<0.0001 by simple ANOVA).

COVID mortality had a strong negative correlation with IMR and vaccination rates (p<0.001). As shown in Figure 1, IMR explains almost a third of the variability in COVID mortality. IMR is also strongly correlated with vaccination rates (Table 2).

Multiple linear regression model results are provided in Table 3. Model 1, with only four predictor variables, IMR, COVID mortality, vaccination rates, and population density, predicts COVID mortality at the state level with an r^2 to 0.66. Introducing an interaction term for IMR and population density in Model 2 improves the adjusted model r^2 to 0.70. This interaction had a positive coefficient, suggesting the rate of reduction in COVID mortality associated with IMR was diminished in more densely populated states. Also, introducing the interaction to the model converted the direction of the effect of population density on COVID mortality from positive to negative. The close fit of the model to actual age-adjusted state COVID mortality rates can be seen in Figure 2.

The predictive power of these models allows us to explore two key counterfactuals, the zerointervention case and the full intervention case. Analysis of the zero-intervention case provides an estimate of how many more COVID deaths would have occurred without NPI's or vaccines. The full intervention case suggests how many additional lives might have been saved if NPIs had been fully implemented and vaccination rates had reached 100%.

The results of the counterfactual models are provided in Table 4. With IMR set to zero, COVID deaths rise by 824,000. Note that Model 1 was used for this case because the interaction term is meaningless in this case. With vaccine rates set to zero, COVID deaths rise by 1,326,000 using Model 2. (Note that using Model 1 results in a higher estimate of lives saved but was presumed to be less accurate.) If neither vaccines nor NPI's were available, the model estimates 2.15 million additional deaths would have occurred. If, instead, IMR and vaccination rates were raised to 100%, an additional 158,000 and 588,000 additional lives respectively might have been saved for each individual intervention and the two combined would have saved 735,000 lives. Note that, in both the non-intervention and full intervention cases, the individual estimates do not precisely add to the total because of the effect of the interaction term.

Discussion

The current study provides strong evidence that NPIs played a key role in limiting the impact of the pandemic. The final model estimates that NPIs and vaccinations prevented 830,000 and 1.3 million COVID deaths respectively.

It is conceivable that decreased influenza mortality was the result of a decrease in ascertainment rather than reduced transmission. Some have even suggested that COVID deaths are actually influenza deaths,²¹ but several observations allow us to dismiss these possibilities. First, failure to diagnose a fatal case of the flu correctly, even during the pandemic, seems unlikely given the well-established surveillance system and diagnostic tools for influenza. Second, the sharp drop in influenza incidence during the pandemic was observed in data from the Seattle Flu Study, which was an active surveillance program that demonstrated pandemic-related decreases for a broad range of respiratory infections.^{22,23} All respiratory infections dropped sharply including influenza, respiratory syncytial virus, and non-COVID corona viruses. Finally, if flu deaths were being misdiagnosed as COVID, we would expect the reduction in influenza mortality to have a strong positive correlation with COVID mortality rates, not the strong negative correlation observed in these data.

It is notable that the regression coefficient for population density changes sign when interaction with IMR is included in the model. This may reflect the fact that population density is a twoedged sword with respect to COVID mortality, inferring a higher transmission risk but providing better access to life-saving medical care. Also of note is the negative association between the pre-intervention COVID mortality and total COVID mortality. This may reflect greater compliance with interventions in the states hardest hit at the outset of the pandemic.

One key advantage in using state IMR as a measure of NPI efficacy is that a region can serve as its own control. Comparing influenza mortality during the pandemic to historical mortality rates of influenza incidence and mortality with those that prevailed during periods when COVID NPIs largely eliminates the effect of time invariant confounders.

The ability of this relatively simple model to explain over 70% of the variability in state COVID mortality provides compelling evidence that IMR is useful indicator for the effectiveness of NPIs against COVID and that the factors included in the model were the primary drivers of COVID mortality. Although IMR appears to be an excellent indicator of the effect of NPIs, it does not provide any insight into exactly which interventions were effective. Understanding the contribution of various NPI's to IMR will be critical to refining management strategies for future epidemics of respiratory infectious disease.

It appears that NPI's, as indicated by IMR, prevented 824,000 COVID related deaths and vaccines prevented another 1,326,000, suggesting that COVID would have killed 3.3 million Americans without interventions. This is consistent with the controversial early estimates from the Imperial College of London,²⁴ although that relatively simple model assumed a far more rapid spread of the disease. The model further suggests that, raising both IMR and vaccination rates to 100% would have reduced the US COVID deaths by 65%.

Methods

Weekly counts of influenza deaths for the period from 2016 through 2023 were abstracted from the CDC FluView System²⁵ for each state. Average annual influenza mortality rates for each state were calculated for the pre-COVID period 2016 through 2019 and for the two flu seasons during the pandemic, 2020-21 and 2021-22. The decrease in average flu season mortality for each state during the pandemic as compared to average mortality rates prior to the pandemic were calculated for each state to determine the Influenza Transmission Control.

State specific, weekly COVID mortality data were obtained from the CDC COVID Data Tracker and used to calculate mortality rates for March of 2020 to determine initial COVID mortality rates.²⁶ Vaccination rates at the end of 2023 were obtained from the same site with vaccination defined as receipt of two initial doses.²⁶ Age adjusted COVID mortality was determined based

on data fron NCHS.²⁷ Population density for 2020 was obtained from the United States Census Bureau.²⁸

All statistical analyses were conducted using the STATA statistical package.

The counterfactual cases were evaluated by entering 0% (for the zero-intervention case) or 100% (for the full intervention case) into the model for each state, determining the difference from the actual mortality rates, multiplying by the state population, and summing the results. Two different models were used, one which included a term for the interaction between IMR and population density and one with no interaction term. The model with no interaction term was used to consider the cases when the NPI indicator, IMR, was set to 0%.

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State	Pre-Covid Influenza Mortality	2020-2022 Influenza Mortality	Infection Mortality Reduction	Vaccination Rate (2023)	Population Density (Per mi²)	3/2022 Covid Mortality	Age- Adjusted Covid
Alabama		<u>Rate</u>	71.0%	520/	00	0.52	
Alaoka	2.33	0.77	60.6%	5270	1	3.50	253
Alaska	2.75	0.95	77 80/	6494	62	0.35	255
Arizona	2.33	0.51	77.070	560/	59	0.33	295
California	4.09	0.88	//./70	7494	254	0.80	275
Calarada	2.31	0.28	00.070	7470	234 56	0.07	273
Colorado	3.13	0.80	/ 5.470	/270	30	0.43	205
Deleware	3.39	0.40	88.2%	82%	/45	0.75	295
Elavida	2.97	0.54	8/./70 66.40/	/270	308	2.33	297
Florida	1.88	0.67	60.4%	09% 560/	402	0.12	299
	1.38	0.37	07.470	2070 910/	180	1.24	5/1
	3.07	0.35	8/.0%	81%0 5(0/	227	1.84	100
	4.34	0.87	//.2%	30% 70%	22	1.34	313
	2.80	0.35	80.3%	/0%	231	0.21	289
Indiana	5.76	0.69	80.3%	5/%	189	0.38	384
Iowa	5.38	1.00	/9.8%	03%	57	0.82	298
Kansas	5.25	1.07	/9.0%	64% 50%	30	0.90	321
Kentucky	4.52	0.80	81.5%	59%	114	0.58	420
Louisiana	2.52	0.60	/5./%	55%	108	0.58	3/8
Maine	5.16	0.68	85.6%	82%	44	1.89	180
Maryland	2.03	0.37	83.0%	/8%	636	0.43	286
Massachusetts	3.27	0.79	/5.3%	82%	901	0.38	270
Michigan	3.18	0.65	79.3%	62%	178	0.26	333
Minnesota	3.68	0.61	82.4%	/1%	12	0.46	246
Mississippi	2.77	1.17	57.3%	53%	63	0.90	486
Missouri	4.55	0.78	81.5%	58%	90	0.43	343
Montana	4.86	1.06	76.7%	58%	8	2.33	324
Nebraska	4.77	1.16	72.9%	65%	26	1.33	272
Nevada	1.62	0.53	69.1%	63%	28	0.82	403
New Hampshire	4.04	0.82	77.1%	70%	154	1.88	189
New jersey	1.94	0.25	86.9%	/8%	1263	0.28	367
New Mexico	2.79	0.76	74.7%	74%	18	1.25	385
New York	1.64	0.35	78.2%	/9%	429	0.13	370
North Carolina	3.47	0.44	86.7%	65%	215	0.24	308
North Dakota	3.32	1.66	49.0%	57%	11	3.36	3/7
Ohio	3.46	0.49	85.1%	60%	289	0.22	380
Oklahoma	4.51	1.57	64.1%	59%	58	0.65	447
Oregon	5.55	0.34	92.8%	71%	44	0.62	190
Pennsylvania	3.44	0.73	77.5%	72%	291	0.20	342
Rhode Island	4.78	0.50	88.4%	86%	1061	2.40	324
South Carolina	3.54	0.61	82.1%	59%	170	0.49	369
South Dakota	5.29	1.69	64.6%	65%	12	2.87	351
Tennessee	3.31	1.16	65.8%	56%	168	0.37	420
Texas	2.15	0.67	68.7%	62%	112	0.09	412
Utah	2.07	0.50	74.8%	66%	40	0.77	231
Vermont	5.41	0.46	90.7%	84%	70	4.07	114
Virginia	2.36	0.47	79.1%	75%	219	0.30	262
Washington	4.61	0.26	93.6%	75%	116	0.34	190
West Virginia	5.07	1.30	73.1%	59%	75	1.49	377
Wisconsin	3.91	0.52	85.8%	67%	109	0.45	260
Wyoming	3.48	0.77	75.0%	52%	6	4.51	302
Average	3.50	0.72	78%	67%	207	1.05	317

Table 1. Vaccination, population density, influenza and COVID mortality rates (deaths/100,000).

	COVID	Initial		Vaccination	Population
	mortality	COVID	NPI-S	Rate	Density
COVID mortality	1.00				
Initial COVID	-0.29	1.00			
IMR	-0.53	-0.18	1.00		
Vaccination Rate	-0.63	0.02	0.55	1.00	
Population Density	-0.01	-0.18	0.34	0.57	1.00

Table 2. Pairwise correlations for model variables.

Table 3. Multiple linear regression results for US state, age adjusted COVID mortality rates as a function of Influenza Mortality Reduction (IMR), vaccination rate (at least 2 doses), COVID mortality in the first month of the pandemic, and population density. Model 2 introduces a term for the interaction between IMR and population density.

	State Characteristics	Coef.	95% C.I.		P > t
Model 1	Vaccination Rate	-534.68	-731	-339	0.00000
$r^2 = 0.66$	Initial COVID Mortality	-27.95	-42	-14	0.00000
	Influenza Mortality Reduction	-466.22	-669	-264	0.00000
	Population Density	-0.789	-1.49	-0.0927	0.028
	Constant	1044.35	898.29	1190.41	0.00000
Model 2	Vaccination Rate	-587.7	-792.2	-383.2	0.00000
$r^2 = 0.70$	Initial COVID Mortality	-19.8	-32.8	-6.7	0.004
	Influenza Mortality Reduction	-314.5	-492.7	-136.4	0.001
	Population Density	0.133	0.0715	0.195	0.00000
	IMR x Population Density	946	812	1080	0.00000
	Constant	-587.7	-792.2	-383.2	0.00000

Table 4. Model estimates of lives saved by actual interventions and potential lives saved by full interventions. Mortality data in model based on values when US COVID mortality was 1.1 million. Model 2 was used in all cases except with NPI=0 when Model 1 with no interaction term was used (see text for discussion). The results with Model 1 for the zero-vaccine case were included for comparison, but the combined case uses the lower number.

	Estimated COVID Deaths with specified Intervention set to zero	Estimated Lives Saved by Actual Intervention	Estimated COVID Deaths with Full Intervention	Estimate of additional Lives Saved with full intervention
NPI	1,923,132	823,530	941,259	158,342
Vaccine (Model 1)	2,425,358	1,325,756	NA	NA
Vaccine (Model 2)	2,298,515	1,198,913	511,262	588,340
Both	3,251,175	2,151,574	364,456	735,145



Figure 1. CDC estimates of deaths from influenza for past 13 flu seasons. Note that the CDC did not provide an estimate for the 2020-2021 season because the mortality rates were too low for their estimation procedures, which seek to account for unreported cases, so the number provided is the actual count.



Figure 2. Actual age adjusted COVID mortality as compared to model estimates for US states.