Why Infants Rarely Die of COVID-19 and Morbidity and Mortality Rates Vary by Location: Pneumococcal and Hib Vaccinations as Possible Means to Mitigate Future Pandemics

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ABSTRACT

Two conundrums have puzzled COVID-19 investigators: 1) morbidity and mortality is rare among Infants and young children and 2) rates of morbidity and mortality exhibit very large variances across nations, locals and even within cities. These differences correlate with rates of *Haemophilus influenzae* type B (Hib) and pneumococcal vaccination, which are almost universal among infants and vary widely by geography among adults and the elderly. The higher the rate of vaccination, the lower the COVID-19 morbidity and mortality. Vaccination rates with other vaccines, including BCG and poliovirus, do not correlate with COVID-19 risks. Notably, both Hib and pneumoccoci are common co-infections with influenza and coronaviruses and are associated with more severe disease and risk of death. Whether the vaccines simply protect against COVID-19 complications, directly protect against COVID-19 infection by inducing cross-reactive immunity, or are markers for some other types of protection such as availability of better healthcare, is not yet known. What is known is that improving coverage rates of Hib and pneumococcal vaccination has significantly lowered severe morbidity and mortality in influenza epidemics and might have similar efficacy for mitigating coronavirus outbreaks. If infants and children are valid indicators, the beneficial effects might be very significant.

PROBLEM AND HYPOTHESIS

Why do infants and young children rarely develop serious COVID-19 infections and almost never die of it? Why are there huge differences in the incidence of severe COVID-19 cases and deaths from one nation to another? I hypothesize that the controlling factor is the rate of vaccination against *Haemophilus influenzae* type B and pneumococcal infections by *Streptococcus pneumoniae*, which are the most common causes of lower respiratory tract infections and fatalities following viral infections such as influenza and coronaviruses (Ieven, et al., 2018; Root-Bernstein, et al., 2013; Morens, et al., 2008; McNamee and Harmsen, 2006; Brundage, 2006).

EVIDENCE FOR THE HYPOTHESIS

Various types of existing evidence support the hypothesis. First, infants and young children rarely develop serious COVID-19 infections and almost never die of it (CDC COVID-19 Response Team, 2020; Porcheddu, et al., 2020). Few factors clearly differentiate this age group from others in terms of decreased disease risk except for near universal vaccination, across most of the developed world, for both streptococcal and *Hemophilus influenzae* infections, usually by the second year of life (see TABLE 1 for data and references).

Second, individuals at high risk for streptococcal and haemophilus infections are exactly the groups of people at high risk of severe COVID-19 infections and complications. The risks for invasive pneumococcal disease (IPD) in adults are, "chronic cardiovascular, pulmonary, liver and kidney diseases, diabetes mellitus, neurological disorders and defects in immune defenses. Compared with healthy

adults, individuals with chronic heart and lung diseases and diabetes mellitus have a three- to six-fold increased risk of IPD, and those who are severely immunocompromised have a 23-48-fold increased risk. Adults who have asthma or who smoke tobacco are also at increased risk for IPD" (Fedson, et al., 2011). The same risks attend *Hemophilus influenzae* type B (Hib) infection (Nix, et al., 2012).

Third, as in the previous SARS-CoV outbreaks, (Zahariadis, et al., 2006), COVID-19 mortality and serious morbidity is highly associated with pneumococcal and haemophilus co-infections, as well as other, secondary infections (Xia, et al., 2020; Wang, et al., 2020). Such patients invariably have severe eosinopenia (Li, et al., 2020; Zhang, et al., 2020), which is an accurate indicator of systemic bacterial infection (Lavoignet, et al., 2019). Below 15/mm3, eosinopenia can differentiate bacterial from viral infection with reasonable accuracy (Debray, et al., 2019). Unfortunately, despite the well-known fact that viral infections of the lungs predispose to bacterial super-infection (Fainstein, et al., 1980; George, et al., 1983), physicians often fail to test for such co-infections (Ljungström, et al., 2017) or do so using inappropriate tests using sputum or nasal discharge rather than lung aspiration or biopsy.

Fourth, it follows logically from the hypothesis that national rates of vaccination against streptococcal and Hib infections should correlate inversely with risk of severe COVID-19 disease and fatality. As TABLE 1 and FIGURE 1 demonstrate, pneumococcal vaccinations generally do.

Country	Cases of COVID-19 per million (8 April 2020)	Deaths from COVID-19 per million people (as of 29 March 2020	PPV23 or PCV13 Streptococcal vaccine coverage rate among adults (%) over 65	PPV23 or PCV13 Streptococcal vaccine coverage rate among high risk adults 18-59	PCV13 Streptococcal vaccine coverage in infants <2	Hib in infants	Influenza vaccine coverage rate (%) among adults over 60	Influenza vaccine coverage rate (%) among adults 18-59	BCG 2010-2018 + [WHO]	Polio vacc. (IPV) +[WHO]	DTP vacc. +[WHO]	Measles vacc. (MCV) +[WHO]
Spain	3125	310	25 - 41	3	61*	94+	60^	27.6^	0	97+	93+	94+
Italy	2260	202	20 - 31	23	49 (range 22 - 94)*	94+	60^		0	95	95+	89+
Belgium	2040	186	29		94+	97+	63^	35 – 44^	0	99+	98+	85+
France	1627	154	35		71* - 92+	95+	63^		44 - 0	96	96+	83+
Netherlands	1209	132	0.5 - 3		93+ - 94	93+	79^		0	93	93+	83+
Switzerland	2650	100	2.1 **		88*	95+	39>		0	97+	96+	89+
UK	825	90	34 - 53	15	92+	94+	82 - 85	63 – 64^	0	94	94+	88+
Sweden	842	69	36		97+	97+	49^		26	97	97+	95+
Ireland	1142	42	33		94+	94+	62^	23^	80 - 0	94	94+	89+
US	1236	40	61.3 - 70	24.5	83 – 92+	92+	63 - 68	37.1 - 45.3	0	96+	94+	97+
Portugal	1314	38	10		97 - 98+	99+	68 >	30.5	21	99+	99+	96+
Austria	1433	30	50 #		62	85+			0	92+	85+	84+
Germany	1317	25	50.9		79* - 85	92+	41 – 50^	8.8	0	98+	96+	93+
Canada	496	10	37	17	81+	91+	64	32	0	87+	91+	87+
Greece	188	8	30 - 34	20	87*- 96+	99		19^	91 - 0	99+	99+	83+
S. Korea	203	4	57.3 – 62.4	29.7	64 – 97+	98+	74	57	98	98+	98+	97+
Australia	240	2	70 - 80	33.9	91 – 95+	94+	78.5 - 81.7	40 - 49.2	0	96	95+	93+
Japan	34	0.8	74		99+	99+	27	19.2 - 39.5	99	99+	99+	93+
New Zealand	245	0.2			96+	92+		73	2	95+	93+	90+

TABLE 1: Cases and deaths from COVID-19 per million population for countries (as of 6 April 2020), selected for availability of the range of required data, compared with vaccination rates with pneumococcal vaccines within various age groups (see text for vaccine descriptions); vaccination with Hemophilus influenzae *type B vaccine (Hib); and influenza vaccine. Data are arranged by COVID-19 death rate. Some data were not available from sufficient countries to permit useful comparisons, including infant influenza vaccination rates and Hib vaccination rates in groups other than infants and so these data are not included. Note that data from China have been excluded because serious concerns have been reported about the data available at this time; vaccination rate data were often lacking as well. DTP is diphtheria-tetanus-pertussis vaccine; BCG is Bacillus Calmette-Guerin (tuberculosis) vaccine; vacc. Is short for vaccine. SOURCES: * Gervaix, et al., 2014; ^ Mereckiene, 2017; + WHO, 2020; > Blank, et al., 2018; # estimated from accumulated yearly vaccinations.   Austria (Richter, et al., 2019); France (Contou, et al., 2020); Germany (Theidel, et al., 2013; Pletz, et al., 2016); Greece (Maraki, et al., 2018); US (FluVaxView; Wateska, et al., 2020; Zhang, et al., 2018; Sings, 2017; Williams, et al., 2016); UK (Tolman, et al., 2016); Australia (Hull, et al., 2019; Yang, et al., 2019; Dyda, et al., 2016); Japan (Naito, et al., 2020; Takeda, et al., 2019; Shibata, et al., 2019; Kajikawa, et al., 2019; Kumar, et al., 2014); S. Korea (Song, et al., 2013; Yang, et al., 2015; Kim, et al., 2016; Park, et al., 2019; Yang, et al., 2020); Italy (Giammanco, et al., 2018; Baldo, et al., 2016; Tozzi, et al., 2014; Fedson, 2011); Spain (Ciruela, et al., 2018; Arencibia Jiménez, et al., 2014; Fedson, 2011); Canada (Kaplan, et al., 2019; Farmanara, et al., 2018); Portugal (Kislaya, et al., 2019); Netherlands (Vestjens, et al., 2019); Switzerland ** NB no current data available(Büla, et al., 1996).*

TABLE 1 supports the idea that Hib vaccination may have a protective effect particularly among children to whom it is almost universally administered [WHO] (TABLE 1). Vaccination with Hib is, conversely, almost completely absent in adults of any age in any country, potentially leaving adults, especially the elderly in whom immunity is fading, at risk. Notably, while most adults between 18 and 65 carry limited natural immunity to Hib, 90% are carriers of the bacteria and thus a risk to the elderly and immune-compromised (Nix, 2012). Fortunately, adults in regions with high rates of Hib vaccination are indirectly protected by significant levels of herd immunity (Cohen, et al., 2010). However, it must be noted that Hib vaccine inoculation rates are five to twelve percent lower in some immigrant populations in London than the average (Tiley, et al., 2018) and even lower among African Americans in many cities particularly hard-hit by COVID-19 such as Detroit, Michigan, (MDHHS, 2020) and New Orleans, Louisiana (Louisiana, 2020) as compared with state and national averages. One can assume that similar disparities related to socio-economic, ethnic and racial factors exist in other populations as well, putting some groups at higher risk of *H. influenzae* complications. Anti-vaccination groups will also be at unusual risk.

The story for pneumococcal vaccines is more complicated since several types have been used over the past two decades and older versions with incomplete serotype coverage are still used in some populations. The 23-valent polysaccharide pneumococcal vaccine (PPV23) protects against the 23 most common serotypes of pneumococci, as compared with the 13-valent pneumococcal conjugate vaccine (PCV13) or earlier versions that protected against either 7 or 10 serotypes (PCV7 and PCV10). TABLE 1 demonstrates that pneumococcal vaccination rates are significantly lower than Hib vaccination rates among children and that they vary widely by nationality among adults. Thus, according to the hypothesis, pneumococcal vaccination rates should be a better measure of COVID-19 risk of infection and rate of death.

Indeed, a good inverse correlation exists between combined rates of *childhood-plus-adult* pneumococcal vaccination with PPV23 or PCV13 and lower rates of COVID-19-associated cases (TABLE 1, TABLE 2, FIGURE 1). In other words, pneumococcal vaccination lowers the risk of COVID-19 infection. Thus, those nations with the lowest per capita cases (and often deaths as well) from COVID-19, such as Australia, Canada, Korea and Japan, are those that have the highest *combined* rates of pneumococcal vaccination (using the PPV23) in *both* infants *and* over-64 adult coverage (60-70%). Conversely, the coverage rate for adults 65 and over in most European countries ranged between 20% and 30% and is associated with much higher rates of infection and death from COVID-19. More specifically in Italy, the cumulative coverage rates ranged from 26.3% to 31% and was about 23% in adults 18 to 64 with underlying risk conditions (Alicino, et al., 2014). A weaker inverse correlation exist between combined childhood-plus-adult pneumococcal vaccination and COVID-19 rates of death suggesting that individuals not protected against pneumococci are at higher risk death. It is clear that the combined rates of childhood-plus-adult pneumococcal vaccination is a much better predictor of protection against COVID-19-associated morbidity and mortality than either childhood or adult vaccination alone (FIGURE 1; TABLE 2). Unfortunately, data on pneumooccocal vaccination rates among at-risk adults 18-64 was too spotty to be included in the statistical analyses but one would expect that higher rates of such vaccination among such at-risk groups would add an even greater predictive quality to the analysis.
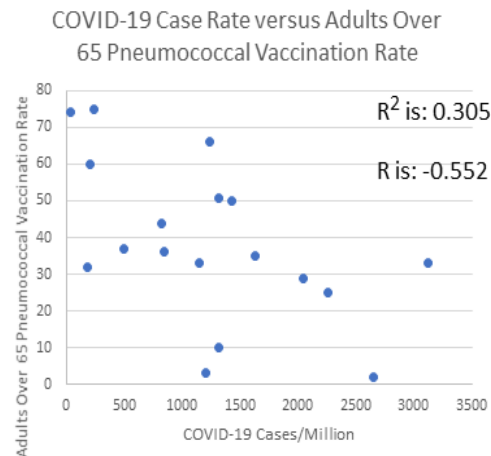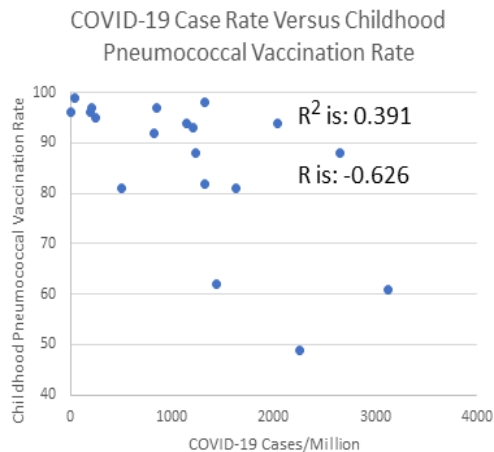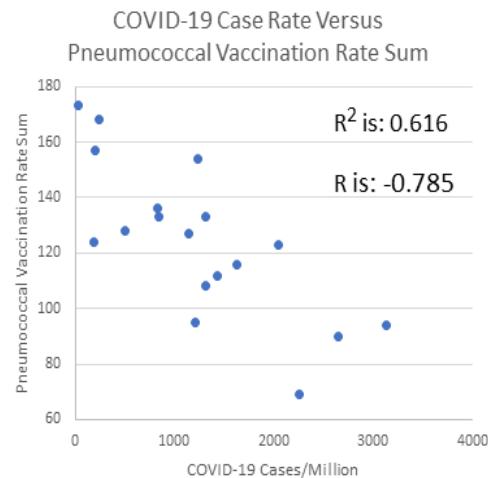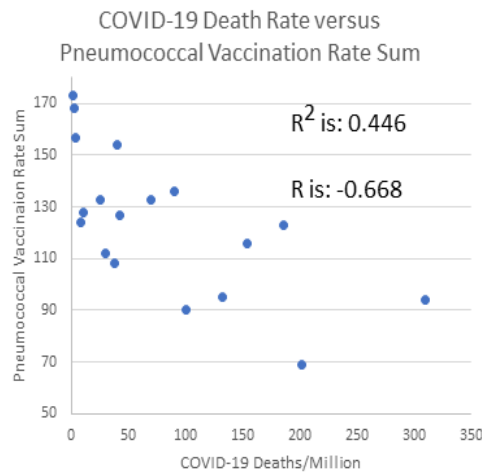
*FIGURE 1: Scatter plots for the pneumococcal vaccination data from TABLE 1 compared with COVID-19 rates of cases and deaths. There is a significant inverse correlation between the sum of childhood and adults-65-and-over pneumococcal vaccination rates and **case rates** of COVID-19 infection. This sum correlates more poorly with COVID-19 death rates. Childhood pneumococcal vaccination rates alone and adult vaccination rates alone have even poorer correlations with case rates. The correlations are even worse between COVID-19 **death rates** and the separate vaccination rates (TABLE 2) suggesting that the main effect that pneumococcal vaccination has is in prevention of COVID-19 infection. The lower correlations with death rates may be a consequence of people who die of COVID-19 being more likely to have been unvaccinated. Correlation coefficients were calculated using (Agrimetsoft, 2019).*

	COVID-19 CASE Rate	COVID-19 CASE Rate		COVID-19 DEATH Rate	COVID-19 DEATH Rate
Vaccination	Correlation Coefficient R^2	Pearson's Correlation Coefficient, R	Vaccination	Correlation Coefficient R^2	Pearson's Correlation Coefficient, R
Sum Adult + Infant Pneumococcal	0.616	-0.785	Sum Adult + Infant Pneumococcal	0.446	-0.668
Pneumococcal Infants	0.391	-0.626	Pneumococcal Infants	0.326	-0.571
Pneumococcal Adults >64	0.305	-0.552	Pneumococcal Adults >64	0.273	-0.523
Hib Infants	0.029	-0.019	Hib Infants	0.000	-0.171
BCG	0.196	-0.443	BCG	0.135	-0.367
Influenza Adults 18-59	0.107	-0.328	Influenza Adults 18-59	0.066	0.256
Influenza Adults >59	0.021	-0.161	Influenza Adults >59	0.001	-0.026
Polio (IPV)	0.033	0.181	Polio (IPV)	0.022	0.148
DTP	0.016	-0.125	DTP	0.000	-0.010
Measles (MCV)	0.000	0.006	Measles (MCV)	0.014	-0.100

TABLE 2: Correlation coefficients (R2) and Pearson's correlation coefficient (R) for vaccination rates for the nations in TABLE 1 as a function of COVID-19 rates of death per million or rates of diagnosed cases

per million. R2 and R calculated using Agrimetsoft (2019). Hib is Haemophilus influenzae type B vaccine; BCG is Bacillus Calmette-Guerin (tuberculosis) vaccine; IPV is inactivated polio virus vaccine; DTP is diphtheria-tetanus-pertussis vaccine; MCV is measle-containing vaccines.

TABLE 2 demonstrates the lack of correlation between COVID-19 rates of death and rates of cases as a function of Influenza, Hib, inactivated vaccination rates (the latter possibly being an artifact due to almost universal childhood vaccination). A similar absence of correlations was found for measles containing vaccines such as measles-mumps-rubella and for diphtheria-pertussis-tetanus vaccine as well as meningococcal vaccine (data not shown) using World Health Organization data [WHO]. More importantly, a recent manuscript claims that a very significant inverse correlation exists between a nation having a BCG vaccination policy and risk of COVID-19 morbidity or mortality (Miller, et al., 2020) and that study has already led to several nations beginning clinical trials to test the efficacy of BCG vaccine to prevent COVID-19 infection. This study contradicts that finding. Five of the nations for whom data is presented in TABLE 1 have had BCG vaccination during the period 2010 to the present but these nations are randomly distributed among the COVID-19 morbidity and mortality data. More importantly, most of the nations in TABLE 1 have never had BCG vaccination, yet their COVID-19 morbidity and mortality risks range from the highest in the world (e.g., Spain and Italy) to the lowest (e.g., New Zealand and Australia). Thus, something other than BCG vaccination must mediate this two-orders-of-magnitude difference in risks. Equally importantly, China has had mandatory BCG vaccination for children for decades with rates of compliance over 99% (WHO), yet China was not protected against the emergence of COVID-19. Moreover, the hypothesis that BCG can protect against COVID-19 is completely incompatible with the fact that morbidity among children is very low and mortality almost non-existent across *all* nations, including all of those used in this study, regardless of BCG vaccination policy. Whatever the factor is that mediates COVID-19 risk of infection and death, it is not BCG. Similarly, it has been reported that clinical trials have begun utilizing inactivated polio vaccine to prevent or treat COVID-19 infection. The data in TABLE 2 once again argues against it having any effect.

Another factor that needs to taken into account but which is not included in the analyses presented here is herd immunity. The data presented in TABLE 1 suggest that countries with high COVID-19 death rates tend to have low *childhood* vaccination rates for pneumococci. Hib and pneumococcal vaccines are strong determinants of herd immunity protecting at-risk adults and the elderly from pneumonia risk (Lexau, et al., 2005; Isaacman, et al., 2008; Pletz, et al., 2016; Richter, et al., 2019; Wiese, et al., 2019). In a few countries, high levels of infant vaccination with PCV-13 seem to balance out low levels of adult vaccination, as exemplified by the case of the Netherlands and Switzerland (TABLE 1). However, not all nations have adopted PCV-13 or have only done so recently and incompletely. Thus, childhood vaccination rates against pneumococcal infections correlate poorly with COVID-19 deaths per capita in individual regions of Italy. Baldo, et al. (2016) documented the probable reason for this lack of correlation: Italy has, until very recently, relied on the PCV-7 pneumococcal vaccine, which protects against only seven pneumococcal serotypes, rather than PCV-13, resulting in selection for pneumococcal serotypes in Italy to non-vaccinated types and a documented loss of herd immunity for the elderly. Similarly, many regions in Spain not only have very low rates of adult and childhood vaccination but have relied on PCV7 or PCV10 for both groups, again limiting herd immunity against many serotypes (Arencibia Jiménez, et al., 2014; Ciruela, 2018). Belgium also saw a reemergence of pneumonia deaths involving previously herd-immunized strains of *S. pneumonia* after recently

switching from PCV13 to PCV7 (Desmet, et al., 2018). Thus, Italy, Spain and Belgium may have lacked the protection against COVID-19 infection hypothesized here.

To reiterate, the best predictor of protection afforded by pneumococcal vaccination, or lack thereof, documented in TABLES 1 and 2 and FIGURE 1 is a combination of infant, at-risk-adults 18-64, and 65-and-over adult vaccination rates. This tri-partite coverage effect is more clearly illustrated in TABLE 3, which compares rates of COVID-19 cases and deaths per million population in states of the United States with rates of pneumococcal vaccination across all three age groups. States with high rates of COVID-19 infections and deaths average 5% fewer vaccinations *in each age group* compared with states with the lowest rates of COVID-19 infections and deaths. Assuming that the lower vaccination rate in each age group increases the risk for the next older age group because of lowered herd immunity, it follows that high-infection-rate states have a cumulative dearth of vaccinations of three times that 5% average, or 15% percent overall as compared with low-infection states. The impact on decreased herd immunity might be even greater than that. In extreme cases, such as New York City – the epicenter of infections and deaths in the United States – and Washington, D. C. (the District of Columbia), which has a very large minority population, the cumulative deficit in vaccinations is in the range of 25%, or an average deficit of about 8% in each age group (TABLE 3). Similar deficits can be found in other cities where COVID-19 infections and deaths are unusually high, such as Detroit, Michigan (20 deaths /100,000 people as of 4 April 2020). There, the coverage rates in infants are 57.2% for Hib and 72.4% for PCV13 as compared with the statewide rates of 74% and 82.6%, the latter being very similar to the national averages. Only 31.8% of adults in Detroit 65 and over received PPV23 as compared with a statewide average of 51.6% and a national average of over 60% (MDHHS, 2020). New Orleans, Louisiana has the highest per capita rate of COVID-19 deaths in the United States (36/100,000 as of 4 April 2020) and low rates of infant vaccination (60-68% coverage of both Hib and PVC-13 in infants) (Louisiana, 2020) similar to those of Italy and Spain. New York City, the next most COVID-19-affected city, also has unusually low infant and adult vaccination rates (see TABLE 3). Thus, there is once again a good inverse correlation between combined rates of pneumococcal and Hib vaccination and risk of COVID-19 infection and death at the level of individual states and cities.

STATE	COVID-13 CASES (PER MILLION)	COVID-13 DEATHS (PER MILLION)	PCV-13 VACCINE COVERAGE CHILDHOOD (%) 2017	PNEUMO-COCCAL VACCINE COVERAGE 18-64 AT RISK (%) 2017	PNEUMO-COCCAL VACCINE COVERAGE >65 (%) 2006	SUM OF VACC %	DIFF. FROM LOW IMPACT STATES
NEW YORK	75,983 (3799)	1714 (86)	74.2 (NYC)	34.0 (NYC)	65.9	174.1	-24.0
LOUISIANA	5237 (1140)	239 (50)	79.1	36.2	68.6	183.9	-14.2
NEW JERSEY	18,696 (2100)	267 (30)	80.1	32.0	67.6	179.7	-18.4
WASHINGTON	5482 (730)	225 (30)	84.7	41.6	67.9	194.2	-3.9

MICHIGAN	7615 (762)	259 (26)	82.9	36.8	66.9	186.6	-11.5
CONNECTICUT	3128 (869)	69 (19)	89	32.3	73.1	194.4	-3.7
DISTRICT OF COLUMBIA	495 (825)	9 (15)	88.5	30.2	54.9	173.6	-24.5
NEVADA	1278 (430)	26 (9)	83.9	31.2	59.0	174.1	-24.0
AVERAGES			82.8	34.3	65.5	182.6	-15.5
MAINE	344 (264)	7 (5)	82.2	43.1	72.2	197.5	
OREGON	690 (164)	18 (4.3)	83.3	42.5	71.1	196.8	
WISCONSIN	1351 (233)	25 (4)	87.9	40.5	74.3	202.7	
KENTUCKY	59 (131)	17 (4)	92.4	38.0	64.3	194.7	
MINNESOTA	629 (112)	12 (2)	79.6	33.8	78.3	191.7	
IOWA	497 (166)	7 (2)	88.8	38.1	74.1	206.0	
NEBRASKA	177 (90)	3 (1.5)	89.5	38.3	75.8	203.6	
SOUTH DAKOTA	108 (120)	1 (1)	82.5	37.2	76.9	196.6	
AVERAGES			86.3	39.0	72.8	198.1	

TABLE 3: COVID-19 infections and deaths per million people in selected states and the District of Columbia (Washington, D. C.) in the United States as of 6 April 2020 compared with rates of pneumococcal vaccination among infants, at-risk individuals 18-64, and adults 65 years of age or older. The top group are states with the highest rates of COVID-19 infection and death; the lower group are those with the lowest rates of COVID-19 infection and death. The right-hand columns sum the rates of vaccination across all age groups in order to give a rough numerical summary of that state's overall vaccination rate across all three age groups, assuming that the overall herd immunity protection afforded by vaccination is a function of vaccination in all three groups. The differences between the high-death-rate states and the low-death-rate groups are provided. Sources: Worldometer, 31 March 2020; Centers for Disease Control, 2006; 2017a; 2017b.

Such local variations appear to mediate COVID-19 risks at local levels worldwide. As noted above for Hib vaccination and inherent in the data in TABLE 3, the international data provided in the TABLE 1 mask significant variations in vaccination rates for pneumococci by socio-economic background, ethnicity, religion (Fry, et al., 2001), and mask local or regional variations (TABLE 2). For example, infant vaccination rates for Hib and pneumococci are significantly lower among African Americans (Jones, et

al., 2010) and impoverished inner-city families than among Caucasian Americans with median or higher incomes in the United States (Hill, et al., 2017; Lu, et al., 2015). Pneumococcal vaccination rates among adults over 65 varied from 18% to 91%. with the same factors nationally (McLaughlin, et al., 2019) and within neighborhoods in individual cities such as Chicago (Hughes, et al., 2018), Logically, the hypothesis proposed here predicts that medically marginalized communities should have greater susceptibility to coronavirus deaths due to lower rates of pneumococcal and Hib vaccination in both infants and adults so that those with the least ability to afford such devastating disease will be most impacted putting not only them, but everyone, at additional risk of severe infection during influenza and coronavirus pandemics.

LIMITATIONS OF THE HYPOTHESIS

The hypothesis that Hib and pneumococcal vaccination rates mediate COVID-19 severity and mortality is based on correlation and should not be taken as proof of causation. The correlation may be due to other factors that these vaccinations are themselves correlated with such as better access to healthcare in general, better nutrition, and so forth. The hypothesis also leaves out many obvious factors that would have to be taken into account in any complete understanding of the pandemic. One is other super-infections that have been associated with COVID-19 such as *Mycoplasma pneumoniae* (Fan, et al., 2020) and various viral, fungal and yeast infections (Wang, et al., 2020). Vaccination against pneumococci and haemophilus should not be considered a complete prophylactic against severe disease or death and it may be necessary to revive development of vaccines against *M. pneumoniae* (Linchevski, et al., 2009), which would protect against one of the most common coinfection of influenza and coronaviruses (Zahariadis, et al., 2006; Liu, et al., 2019). Other factors missing from this account include those defining rates and modes of disease transmission such as population density, frequency and number of interpersonal contacts, the proportion of elderly individuals in a population, availability of testing and timely medical treatment, etc. Thus, the hypothesis should not be over-interpreted as being meant to explain all aspects of COVID-19 risk but in the more limited context of why such large disparities exist in these risks among certain populations by age or geographical location.

TESTS OF THE HYPOTHESIS

This hypothesis is testable in multiple ways.

 First, it should be possible to determine from patient records whether those with serious or fatal cases of COVID-19 are unusually *unlikely* to have had Strep or Hib vaccinations compared with age-matched controls who either had mild cases or did not become infected. The correlation between lack of vaccination and severity of COVID-19 disease is unlikely to be perfect, however, since vaccinations become increasingly ineffective with age and often do not protect the elderly as well as younger people (Westerink, et al., 2012; Papadatou and Spoulou, 2016).

Second, vaccination of high-risk populations such as nursing home and retirement community residents, everyone over the age of 50, and all health-care workers, with Strep and Hib vaccines should significantly lower their risk of serious or fatal COVID-19 infections as it did previously did for influenza-related deaths (Mahamat, et al., 2013; Yang, et al., 2019). Younger individuals may also benefit from these vaccinations in a time of constant threat of influenza and coronavirus pandemics although this recommendation currently runs counter to the guidelines in the US and most European nations (reviewed in Sing, 2017). However, because current vaccination procedures for elderly adults are only

partially effective and antibiotics often fail to cure pre-existing pneumococcal (Fedson, et al., 2011) and Hib (Nix, et al., 2012) infections at time of hospitalization, precautionary vaccination should be taken seriously for everyone. Moreover, vaccination strategies for the elderly should be modified to include a combination of PCV13 and PPV23 in properly timed doses to improve immunity (Westerink, et al., 2012; Papadatou and Spoulou, 2016).

Third, epidemiological studies should demonstrate that COVID-19 has preferentially affected national regions, neighborhoods and groups of people such as anti-vaccine advocates with the lowest rates of pneumococcal and Hib vaccination.

Fourth, several possible mechanisms should be explored as explanations for the correlation between higher Hib and pneumococcal vaccination rates and lower COVID-19 morbidity and mortality: A) Hib and/or pneumococcal vaccines directly protect against COVID-19 infection by means of inducing cross-reactive antibodies; B) Hib and/or pneumococcal vaccination prevents secondary infection following COVID-19 exposure thereby lowering the risk of severe or fatal complications and keeping COVID-19 symptoms minimal; C) vaccination rates are a stand-in for other factors that more directly control COVID-19 risks.

Fifth, test every hospitalized coronavirus patient for eosinopenia and those with severe eosinopenia for the presence of streptococci, haemophilus and *M. pneumoniae* infections using high-sensitivity tests. Combined viral-bacterial infections are particularly difficult to diagnose because of a tendency to test only for the expected pathogen (in this case COVID-19) and also because one infection may mask the other (Kumar, et al., 2018; Zahariadis, et al., 2006). Additionally, viral-bacterial co-infections often synergize so that levels of infection that may seem inconsequential may become deadly. For example, Shope demonstrated with regard to swine flu that a combination of the influenza virus with *H. influenzae* was 100% fatal at doses of the individual microbes that caused no mortality and, in most experimental animals, no morbidity either (Shope, 1931). Pathologists, who are unfortunately in short supply in most countries, will be needed to carry out autopsies looking for such combined infections in deceased individuals.

Sixth, set up animal models such as those invented by Shope (1931) to explore the effects of combined COVID-19-pneumococcal or COVID-19-Hib infections and the effectiveness of vaccines against pneumococci and Hib in preventing the transmission of severe COVID-19 infections.. On a positive note, Shope demonstrated that vaccination with *either one* of the causative agents protected against mortality from their combination (Shope, 1931). Not only do Shope's experiments provide a model for setting up COVID-19 animal models to test this hypothesis, they also suggest that the type of protection hypothesized here has been demonstrated to exist for the combination of Hib with influenza.

RISKS

A caveat is in order: it is not clear at this time whether healthcare providers and other people at high risk of contracting coronavirus should be vaccinated with strep and/or Hib *vaccines while at risk for exposure to the virus*. Vaccinating on top of an existing coronavirus infection could lead to complications (Westall and Root-Bernstein, 1986). On the other hand, there is some evidence that combining *H. influenzae* antigens with influenza vaccines leads to a heightened vaccine response (e.g., Gönczi, 1987; Root-Bernstein, et al., 2013), a possibly beneficial phenomenon.

And a warning: It follows from the hypothesis that one of the most serious risks presented by the present COVID-19 pandemic is that, in some regions such as Italy and Iran, or in some high-density locations such as New York City, Detroit and New Orleans during Mardi Gras, the virus has become conjoined to a synergistic bacterial pandemic so that seriously ill individuals will transmit both infections concomitantly. As Shope (1931) demonstrated in the case of swine-flu-plus-*H.-influenzae*, such a combination is likely to be far more infectious and fatal, than the individual infections would be, even among healthy people. This effect may explain the extreme risks associated with healthcare providers tending to COVID-19 infected individuals and why some young people are unexpectedly dying. Indeed, concurrent infections between influenza virus and *H. influenzae* or streptococci characterized the great Flu Pandemic of 1918-19 and several subsequent influenza pandemics (Root-Bernstein, et al., 2013; Morens, et al., 2008; McNamee and Harmsen, 2006; Brundage, 2006). Breaking the chain of concurrent infections by means of vaccination against bacteria may therefore be an essential component of any attempt to control the coronavirus pandemic.

CONCLUSION

If Hib and pneumococcal vaccinations either indirectly or directly lower COVID-19 morbidity and mortality, then should be possible to mitigate significantly the impact of any future influenza or coronavirus pandemic by investing as soon as possible in mass pneumococcal and Hib vaccination programs worldwide, especially for populations in which the vaccination rate is currently low (Brundage, 2006; Root-Bernstein, et al., 2013). If the resistance of infants and children to COVID-19 is due to these vaccinations, then the protection they provide is very significant. And notably, this vaccination strategy has already proven to be effective in mitigating influenza-associated complications and deaths (Mahamat, et al., 2013; Yang, et al., 2019) so that it will certainly have benefits in terms of decreasing morbidity and mortality associated with yearly influenza epidemics.

Because the more broadly vaccinations are implemented, the stronger both individual immunity and herd immunity becomes, the greater the benefits for everyone. Indeed, every study that has been done of the economic impact of pneumococcal and Hib vaccination programs has shown that for every billion dollars invested in vaccination, several billions are saved in critical care costs for elderly and at-risk patients (Wateska, et al., 2020; Richter, et al., 2019; Zhang, et al., 2018; Ciruela, et al., 2018; Baldo, et al., 2016; Arencibia Jiménez, et al., 2014; Isaacman, et al., 2008). Actual savings may be significantly greater since these economic studies have not included the benefits that may accrue from protection against the global economic devastation that a coronavirus or influenza pandemic can cause by shutting down businesses and harming trade.

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CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest.

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