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Report

The possible roles of solar ultraviolet-B radiation and vitamin D in reducing case-fatality rates from the 1918–1919 influenza pandemic in the United States

William B. Grant[1,*] and Edward Giovannucci[2]

[1]Sunlight, Nutrition and Health Research Center (SUNARC); San Francisco, CA USA; [2]Departments of Nutrition and Epidemiology; Harvard School of Public Health; and Department of Medicine; Brigham and Women's Hospital; Boston, MA USA

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Deaths during the 1918–1919 influenza pandemic have been linked to both the influenza virus and secondary bacterial lung infections. Case fatality rates and percentage of influenza cases complicated by pneumonia were available from survey data for twelve United States locations in the 1918–1919 pandemic. This study analyzes case fatality rates and cases complicated by pneumonia with respect to estimated summertime and wintertime solar ultraviolet-B (UVB) doses as indicators of population mean vitamin D status. Substantial correlations were found for associations of July UVB dose with case fatality rates ($r = -0.72$, $p = 0.009$) and rates of pneumonia as a complication of influenza ($r = -0.77$, $p = 0.005$). Similar results were found for wintertime UVB. Vitamin D upregulates production of human cathelicidin, LL-37, which has both antimicrobial and antiendotoxin activities. Vitamin D also reduces the production of proinflammatory cytokines, which could also explain some of the benefit of vitamin D since H1N1 infection gives rise to a cytokine storm. The potential role of vitamin D status in reducing secondary bacterial infections and loss of life in pandemic influence requires further evaluation.

Introduction

In the twentieth century, there were three influenza pandemics, in 1918, 1957 and 1968, caused by H1N1 (Spanish flu), H2N2 (Asian flu) and H3N2 (Hong Kong flu), respectively.[1] The 1918–1919 pandemic was different from the subsequent ones as it was the only one caused by an H1N1 virus, and is the only one considered in this work.

"In 1918, there was one distinct peak of excess death in young adults aged between 20 and 40 years old; leukopenia and hemorrhage were prominent features. Acute pulmonary edema and hemorrhagic pneumonia contributed to rapidly lethal outcome in young adults. Autopsies disclosed multiple-organ involvement, including pericarditis, myocarditis, hepatitis and splenomegaly. These findings are, in part, consistent with clinical manifestations of human infection with avian influenza A H5N1 virus, in which reactive hemophagocytic syndrome was a characteristic pathologic finding that accounted for pancytopenia, abnormal liver function and multiple organ failure."[1]

The influenza pandemic of 1918–1919 claimed many lives. While the influenza virus played an important role, there is evidence that the primary influenza infection was not necessarily the proximate cause of death. For example, the median time to death was 7–10 days, and a substantial proportion of deaths occurred greater than 2 weeks after onset of the initial symptoms.[2] The delay in death has been attributed to the influenza infection allowing bacteria to colonize the lower respiratory system and produce lethal pneumonias.[2,3] Bacterial pneumonia also was noted as a serious complication of influenza during 1957–8 influenza pandemic,[4] and antibacterial approaches have previously been proposed for reduction of the case-fatality rate during influenza pandemics.[5,6]

Vaccines are the first line of defence against epidemic influenza. However, successful treatment or prophylaxis of complicating bacterial pneumonias may be important, since a presently unknown or poorly characterized virus might cause a pandemic before an effective vaccine becomes universal.[2,5,6] Several months to a year are typically needed to develop and universally administer an effective vaccine for a new strain of influenza.[7]

While vaccines are absolutely essential for control of influenza, they are not always effective in eliminating influenza cases, and the associated risk of secondary respiratory infections, especially among older adults. It has been estimated that a recent influenza vaccine produced only a 27% reduction in hospital admissions for acute respiratory infections, such as pneumonia.[8] Other epidemiological approaches, such as limiting travel and case containment, could be part of an overall plan to limit the intensity of an

*Correspondence to: William B. Grant; Sunlight, Nutrition and Health Research Center (SUNARC); P.O. Box 641603; San Francisco, CA 94164-1603 USA; Tel.: 415.409.1980; Email: wbgrant@infionline.net

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influenza pandemic.[9] However such concepts are rarely implemented successfully. Targeted layered containment has also been proposed for limiting pandemic influenza cases in the US.[10] Such epidemiological measures would have serious economic impacts.

Since the fatal complications of influenza are due in part to secondary bacterial infection,[2-4] the degree of immunity to the most common bacterial agents of pneumonia may be important. Exposure to solar ultraviolet-B (UVB) starts a multi-step process, starting with biosynthesis of vitamin D and its metabolites, followed by upregulation of human cathelicidin (LL-37), by 1,25-dihydroxyvitamin D.[11] There are several recent reviews of the effects of cathelicidin against bacterial infections such as Mycobacterium tuberculosis.[11-16] Cathelicidin appears to be effective in fighting septicaemia, in part due to its antiendotoxin effects.[12]

The known benefit of cathelicidin is mainly limited to bacterial or mycoplasmal infections. Cannell et al. hypothesized that the annual seasonality of influenza was largely due to low solar UVB irradiation and vitamin D biosynthesis in winter and early spring.[17] A post hoc analysis of self-reported incidence of acute respiratory illnesses during a randomized controlled trial of vitamin D for another purpose supported this hypothesis.[18] Cannell et al. later extended their hypothesis.[19] Regional solar UVB irradiance is also inversely associated with incidence rates of respiratory syncytial virus (RSV) infection.[20] It is thought that the higher incidence rates of RSV in darker-skinned infants may be due to lower vitamin D production in them and their mothers.[21] Vitamin D receptor polymorphisms were found correlated with acute lower respiratory tract infection, primarily bronchiolitis, in Canada.[22] Vitamin D is also thought to reduce the risk of respiratory infections that may lead to development of asthma.[23]

There are several aspects to incidence and death from influenza including adaptive and innate immune response, exposure to the influenza virus, season and development of complications from other respiratory diseases. We analyzed data from the US during the 1918–1919 influenza pandemic to determine whether solar UVB irradiance and vitamin D status might have played a role in the development of pneumonia and in influenza-pneumonia case fatality rates.[24]

Results

The rates in each city, latitude and UVB irradiance are shown in Table 1. The lowest case-fatality rates occurred in the area with the highest solar UVB irradiance and lowest latitude, San Antonio TX, while the highest rates were in New London CT, which had the lowest UVB irradiance and highest latitude. The lowest rates of pneumonia as a complication of influenza were in Spartanburg, SC and San Antonio, the two areas at the lowest latitudes. The correlation between case-fatality rates for influenza and cases complicated by pneumonia was r = 0.78 (p = 0.005).

The results for case fatality rates (CFR) with respect to solar UVB are given in Table 2. Summer UVB irradiance had a slightly higher correlation coefficient than latitude with CFR. The results for influenza complicated by pneumonia are also given in Table 2. The correlation coefficients were slightly higher than those for case fatality rates. In the regression model, UVB accounted for 46% of

Table 1 **Cities included in the 1918–1919 influenza pandemic study, case-fatality rates and percentage of cases who developed pneumonia[24]**

City and state	No. of influenza cases	No. of pneumonia cases	Influenza case-fatality rate (deaths per 100 cases)	Pneumonia complications* (%)	July UVB dose (kJ/m^2)	Latitude (° N)
New London, CT	1466	136	3.14	9.3	4.7	40.6
Charles County, MD	6546	-	2.25	-	5.3	38.5
San Francisco, CA	4021	321	2.24	8.0	6.5	37.6
Baltimore, MD	8199	599	2.10	7.3	5.0	39.3
Minor MD towns	5060	322	1.66	6.4	5.1	39.2
Des Moines, IA	1353	138	1.63	10.2	4.8	41.6
Macon, GA	1681	103	1.49	6.1	7.5	32.8
Louisville, KY	1797	111	1.39	6.2	6.0	38.1
Augusta, GA	1405	63	1.28	4.5	7.3	33.5
Little Rock, AR	3565	159	1.09	4.5	7.1	34.8
Spartanburg, SC	1126	35	0.89	3.1	7.0	35.0
San Antonio, TX	6701	303	0.78	4.5	8.2	31.6
Total	42,920	2290				

*Incidence of pneumonia in influenza cases.

Table 2 **Association between UVB irradiance and case-fatality rate of influenza or rate of pneumonia as a complication of influenza with respect to UVB indices, linear regressions (from table 25 in Britten[24])**

Outcome	UVB indicator	r, adjusted r^2, p
Case-fatality rate	July UVB	-0.72, 0.46, 0.009
	Latitude	0.68, 0.42, 0.014
Pneumonia as a complication of influenza	July UVB	-0.77, 0.55, 0.005
	Latitude	0.81, 0.62, 0.003

the variation in case-fatality rates of pneumonia and 55% of the variation in rates of pneumonia as a complication of influenza.

Discussion

There was an inverse association between UVB irradiance and case-fatality rate of influenza and rate of pneumonia as a complication of influenza in the US. Both UVB indices gave similar results. According to data in Britten,[24] the 1918 influenza pandemic reached eastern US cities in September, and San Francisco in October. Peak mortality rates extended from late October to early December. Based on serum 25(OH)D measurements of 45-year old British adults, levels would be intermediate between summer and wintertime values.

There is other evidence for a role of vitamin D reducing the risk of pneumonia. For example, pneumonia deaths in England and Wales in the period 1988–92 had a peak-trough ratio of 2.7 with the peak in December and January and trough in July-September.[31] In Ethiopia, there was a 13-fold higher prevalence of rickets among children with pneumonia than among controls [odds ratio: 13.37 (95% CI 8.08–24.22), $p < 0.001$] in Ethiopia.[32] Low serum 25(OH)D (<22.5 nmol/L) was associated with higher risk of lower respiratory tract infection (odds ratio: 0.09; 95% CI 0.03–0.24; $p < 0.001$) in India.[33]

From inspection of the incidence and mortality rates from the 1918–1919 influenza pandemic at the total population level, it is not possible to draw conclusions about vitamin D with respect to pandemic influenza incidence.

As discussed above, the established role of vitamin D in upregulating production of catheliciden, an endogenous anti-bacterial peptide, may be a potential explanation of the association we observed. An additional potential mechanism may be the role of vitamin D in the reduction of pro-inflammatory cytokines. One of the important observations of deaths during the 1918–19 influenza pandemic was that the death rate was high for young adults.[34] This is different than for seasonal influenza, during which mortality rates are higher for the elderly and infants. The reason for this difference seems to be that those in their 20s and 30s have a more robust immune system which can mount a stronger attack on microbial infections. From recent studies, it has been determined that both H1N1 and H5N1 viruses induce a T-helper 1 (Th1) type cytokine response to viral infection of macrophages.[35] These cytokines are proinflammatory and include IL-6 and TNFα.[35] Nuclear factor kappaB (NFκB) is also an important risk factor.[36] Influenza A (H5N1) viruses induce production of proinflammatory cytokines at a greater rate than do H1N1 viruses.[37,38] 1,25-dihydroxyvitamin D [1,25(OH)2D] reduces the production of Th1 cells, thus shifting the Th1/Th2 balance towards Th2, which is less inflammatory.[39-41] 1,25(OH)D has also been found to reduce the production of NFκB[42] and TNFα.[43] Infection of macrophages also induces a toll like receptor induction of human cathelicidin, LL-37,[44] which is effective in combating bacterial infections such tuberculosis[44] and others.[45] Thus, an additional mechanism whereby vitamin D could reduce the severity and likeliness of death from H1N1 and H5N1 viral infections is reduced production of proinflammatory cytokines and NFκB. However, suppressing proinflammatory cytokines did not reduce the risk of death for mice infected with H5N1 viruses.[46,47] These results may not apply to the H1N1 virus in humans because mice have different immune responses than humans.

One strength of this study is that solar UVB was the primary source of vitamin D since in 1919, vitamin D had not yet been isolated or identified. The main limitation of this study is that other confounding factors were not evaluated. For example, differences in medical treatment or defensive measures[48] in the twelve cities were not considered. Also, differences in ethnic background and skin pigmentation were not considered. The fraction of African-Americans varied between locations. This was a study of aggregates rather than individual subjects. Findings that apply to aggregates may not apply to individuals. Another limitation is that data presented in Britten[24] were available for only twelve cities. While the sampling was made under specific instructions and careful supervision "in 10 or more districts so situated geographically as to give, presumably, a fair sample of the general population of the city," the method of selecting the districts would probably not meet today's standards for random sampling. A further limitation is that the fraction of the population surveyed varied from 0.039 in San Francisco to 1.00 in Charles County, MD, while the number of people surveyed in each region varied from 4,123 in Augusta, GA to 18,682 in San Francisco. Also, as the country was at war then, the total populations of each region had some additional uncertainty.

Data and Methods

The approach taken in this work to investigate the role of innate immune response is to examine case fatality rates for those who contracted the H1N1 influenza virus. The body can have both innate and adaptive immune responses; for respiratory infections, the adaptive response is based on either prior exposure to the same or similar virus, while the innate response is based on other immune parameters such as T cell subsets and immunoglobulin concentrations[25] and LL-37. It is assumed that those who developed H1N1 influenza had weaknesses in both the adaptive and innate immune systems but that the strength of the innate immune system is more important for survival.

A study was found that reported data for influenza and pneumonia case fatality rates for twelve cities in nine US states;[24] the proportion of influenza cases complicated by pneumonia was determined for eleven cities. The data reported (Table 1) are from special surveys by the US Public Health Service. These surveys were conducted in ten cities "varying in population from 22,500 to 680,000 and certain small towns of Maryland and one rural county of Maryland." The locations were chosen to be widely scattered, and generally in "localities in which the Public Health Service was at the time maintaining established organizations prepared to collect the requisite data reliably and efficiently." The surveys "were made as soon as possible after the subsidence of the autumn (1918) wave of the epidemic in each locality" and generally, started around December 2, 1918 and completed by the end of December. However, second surveys were also conducted in Baltimore and San Francisco to check for recrudescence which had

taken place in the interval. The Louisville canvass was made before the epidemic had run its full course. "In the case of Spartanburg, SC some time after the completion of the canvass in the city itself, an additional survey was made of adjacent mill villages. These villages had a disproportionately large population of one selected class—mill workers—and for this reason the Spartanburg data are not altogether comparable with those collected in other localities." The population canvassed ranged from 4,123 in Augusta to 33,316 in Baltimore and represented 3.9% (San Francisco) to more than 30% of the total population. There were 42,920 cases of influenza and 2,290 cases of pneumonia in Table 1.[24]

"In making inquiry as to the type or nature of illness, the enumerators were instructed to ask which members of a family had 'influenza', 'flu', 'grippe', 'pneumonia' or 'colds' since September 1, 1918. Persons who were said to have been only 'feeling badly' or as having a 'cold' were recorded as 'doubtful' cases. If, however, the illness lasted not less than three days and was of such severity as to confine the patient to bed for the whole of one day, the case was classed as 'influenza', unless otherwise diagnosed by the attending physician."

Solar UVB indices. Summertime UVB irradiance for the US was estimated using data from the NASA Total Ozone Mapping Spectrometer.[26] This index has been used successfully in ecologic studies of cancer mortality rates in the US.[27,28] Winter UVB irradiance was estimated using a cosine law that estimates solar irradiance based on season and latitude, which are the determinants of solar zenith angle. Solar zenith angle is the most important determinant of solar irradiance in winter. This index has been found correlated with risk of multiple sclerosis,[29] for which the Epstein-Barr virus is a risk factor and vitamin D a risk reduction factor,[30] likely in part through combating the virus through induction of LL-37.

Statistical analysis. Multiple linear regression was used to assess the independent contributions of UVB irradiance and latitude to case-fatality rates of pneumonia. All analyses were performed using SPSS Grad Pack 13.0 (SPSS Inc., Chicago, IL).

Summary and Conclusion

More research on this topic is needed. There is no question that vaccine development and distribution is the most important and reliable strategy for control of influenza epidemics and their resulting mortality. On a far less well-established level of certainty it should be determined whether higher serum 25(OH)D levels might be associated with lower incidence of bacterial pneumonia complicating influenza, particularly in older adults. Providing vitamin D supplements or fortifying commonly consumed foods with higher amounts of vitamin D should be evaluated further as a possibly useful component of a comprehensive, vaccine-centered, program to reduce influenza mortality rates, both in pandemics and seasonal influenza, especially in the elderly.

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