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The seasonality of pandemic and non-pandemic influenzas: the roles of solar radiation and vitamin D

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SUMMARY

Objectives: Seasonal variations in ultraviolet B (UVB) radiation cause seasonal variations in vitamin D status. This may influence immune responses and play a role in the seasonality of influenza.
Methods: Pandemic and non-pandemic influenzas in Sweden, Norway, the USA, Singapore, and Japan were studied. Weekly/monthly influenza incidence and death rates were evaluated in view of monthly UVB fluences.
Results: Non-pandemic influenzas mostly occur in the winter season in temperate regions. UVB calculations show that at high latitudes very little, if any, vitamin D is produced in the skin during the winter. Even at 26°N (Okinawa) there is about four times more UVB during the summer than during the winter. In tropical regions there are two minor peaks in vitamin D photosynthesis, and practically no seasonality of influenza. Pandemics may start with a wave in an arbitrary season, while secondary waves often occur the following winter. Thus, it appears that a low vitamin D status may play a significant role in most influenzas.
Conclusions: In temperate latitudes even pandemic influenzas often show a clear seasonality. The data support the hypothesis that high fluences of UVB radiation (vitamin D level), as occur in the summer, act in a protective manner with respect to influenza.

1. Introduction

Nearly all human diseases related to respiratory pathogens exhibit seasonal variations.[1,2] However, the reasons for this seasonality are still not known. Among the tested hypotheses are: seasonality of low temperatures, absolute humidity (aerosol transmission), or of dry air, crowding together indoors during the winter, travel patterns, vacations, seasonality of ultraviolet (UV) radiation from the sun that might kill pathogens, circannual rhythms of hormones, such as the 'dark hormone' melatonin, etc.[1,3–8] Another founded hypothesis is that seasonal variations in UVB radiation and consequently vitamin D photosynthesis, causing seasonal variations in vitamin D status,[9,10] which plays a role in the immune response to infections, may be responsible for the influenza seasonality.[9–15] Additionally, the question of whether it is the host or the virus/bacterium that exhibits seasonality arises. However, there are exceptions from seasonality, notably for pandemic influenzas, which often occur outside the winter influenza seasons. Furthermore, in equatorial regions the seasonal pattern is weak.[2,16]

In the present work we have compared the seasonality of cases and deaths caused by both pandemic and non-pandemic influenzas with doses of UVB radiation (vitamin D photosynthesis). Influenza may cause death either directly (due to a primary complication caused by the influenza virus) or indirectly (due to secondary non-influenza complications either pulmonary or non-pulmonary in nature).[17,18] Recent studies have indicated that the majority of deaths in previous influenza pandemics have been a result of secondary bacterial pneumonias.[18–21] In this paper all deaths related to influenza are referred to as 'influenza deaths' without further specification.

2. Materials and methods

2.1. Influenza cases and deaths

Data from various sources were used in the present study (Figures 1–6). The numbers of weekly Russian influenza cases in Sweden (Figure 1) are from the publication by Skog et al.[22] The monthly death cases from influenza in Norway during 1980–1999

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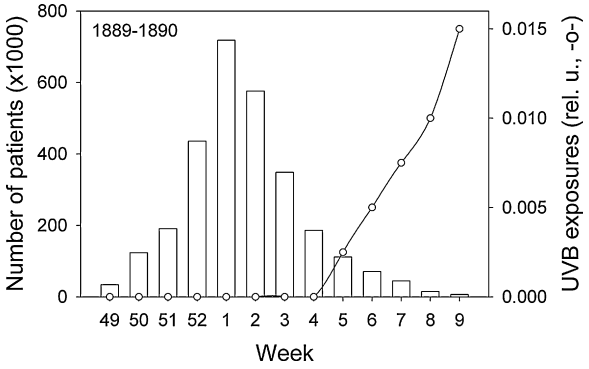

Figure 1. Numbers of infected persons (□) per Thiessen area in Sweden for each week from 1889 to 1890 during the Russian flu, obtained from Skog et al.[22] Weekly photosynthesis of vitamin D (—○—) for a relevant latitude (Oslo, 60°N) was calculated by use of the vitamin D action spectrum, UV measurements, and radiative transfer calculations (see Materials and methods).

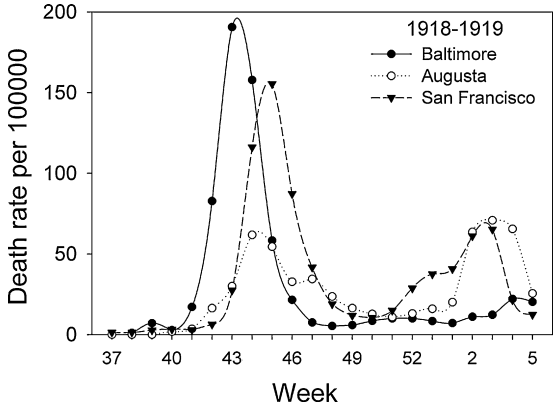

Figure 3. Weekly Spanish influenza death rates in Baltimore (39°N), Augusta (33°N), and San Francisco (37°N) from 1918 to 1919, taken from Britten.[23]

(Figure 2) are from the publication by Moan et al.[14] The weekly death rates of the Spanish flu in some American cities (Figure 3) were obtained from the work of Britten.[23] Monthly death rates from 10 non-pandemic and two pandemic influenza seasons in the USA during 1941–1976 (Figure 4) are from the publication by Doshi.[24] The pattern of monthly influenza cases in Okinawa from 2001 to 2007 (Figure 6) are from Suzuki et al.,[25] while the data for Singapore from 1990 to 1994 (Figure 5) are from the publication by Chew et al.[26]

2.2. Solar exposure and seasonal vitamin D synthesis in human skin

The main factors influencing UV irradiance at ground level are solar zenith angle (variable with season, latitude, and time of day), cloud and snow cover, aerosols, and the thickness of the ozone layer.[27] In this study, global solar UV irradiances were calculated using a radiative transfer model.[28,29] Daily total ozone amounts used in this model were measured by the Total Ozone Mapping Spectrometer (TOMS) onboard the Earth Probe satellite. The daily cloud cover used in our model was derived from reflectivity measurements by TOMS. The errors in ozone derived from TOMS instruments onboard several satellites are generally less than 2%.[30,31] Not included in our calculations were atmospheric aerosols, which may potentially have an impact on the solar irradiance reaching the earth's surface.[32–34]

The calculated monthly UV exposures were based on the satellite measurements in the period 1997–2004. A cylinder geometry of the human body was used. The arguments for such a choice have been presented previously.[35,36]

Results are presented as vitamin D-forming UV doses. The efficiency spectrum for vitamin D production gives the relative effectiveness of solar radiation at different wavelengths in converting 7-dehydrocholesterol (7-DHC) to previtamin D. An efficiency spectrum is calculated by multiplying the intensity of the solar radiation (wavelength by wavelength) with the action spectrum for vitamin D production for the corresponding

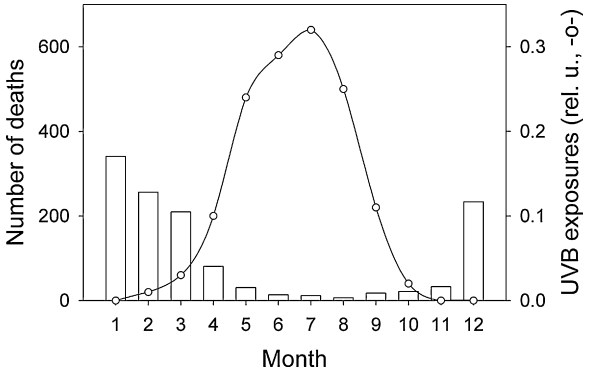

Figure 2. The monthly influenza deaths (□) from 1980 to 1999 in Norway, extracted from Moan et al.[14] Monthly photosynthesis of vitamin D (—○—) for Oslo (60°N) was calculated by use of the vitamin D action spectrum, UV measurements, and radiative transfer calculations (see Materials and methods).

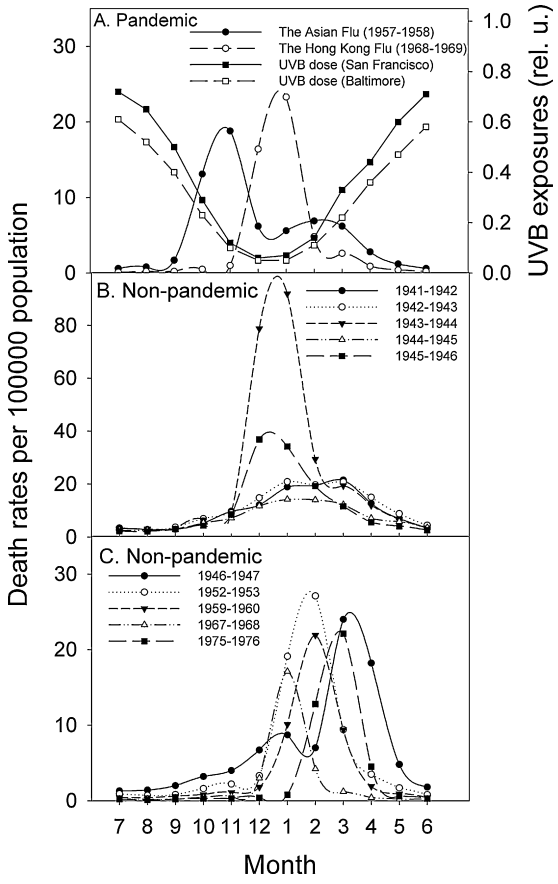

Figure 4. The monthly death rates from two pandemic (A) and 10 non-pandemic (B and C) influenza seasons in the USA during 1941–1976; data from Doshi.[24] Monthly photosynthesis of vitamin D for San Francisco (37°N) and Baltimore (39°N) was calculated by use of the vitamin D action spectrum, UV measurements, and radiative transfer calculations (see Materials and methods).

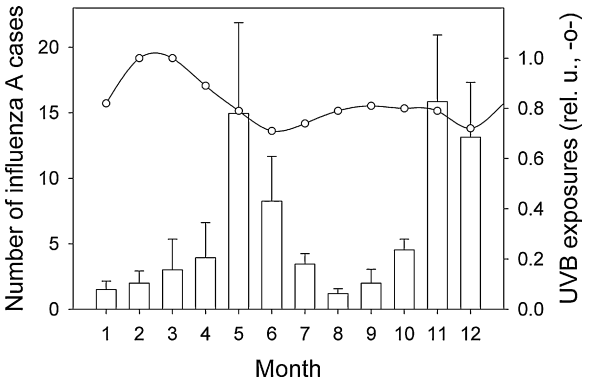

Figure 5. The pattern of mean monthly influenza A cases (□) from 1990 to 1994 in Singapore; data from Chew et al.[26] Monthly photosynthesis of vitamin D (—○—) for Singapore (1°N) was calculated by use of the vitamin D action spectrum, UV measurements, and radiative transfer calculations (see Materials and methods).

wavelength. The vitamin D action spectrum was taken from the publication of Galkin and Terentskaya,[37] and is similar to that measured by MacLaughlin et al. in ex vivo skin specimens.[38] This action spectrum is being used by a large number of investigators, but is not ideal.

3. Results and discussion

3.1. Pandemic and non-pandemic influenzas

There are three types of influenza virus: influenza A virus, influenza B virus, and influenza C virus.[39] Influenza A viruses are the most important because they generally cause severe secondary diseases and often cause seasonal epidemics and pandemics.[40,41] Influenza B is less common than influenza A, but can periodically cause large epidemics, although not pandemics.[40] Influenza C virus is less common than influenza A and B, and diseases caused by this species are generally much milder; it is not thought to cause epidemics.[40,42] Influenzas mainly attack weaker persons in a population, such as children, the elderly, and the immune incompetent.[39]

The best known and documented influenza pandemics are the Russian flu (1889–1890, about 1 million deaths), the Spanish flu (1918–1919, about 50 million deaths worldwide), the Asian flu (1957–1958, about 2 million deaths worldwide), and the Hong Kong flu (1968–1969 about 0.7 million deaths worldwide).[43,44] In

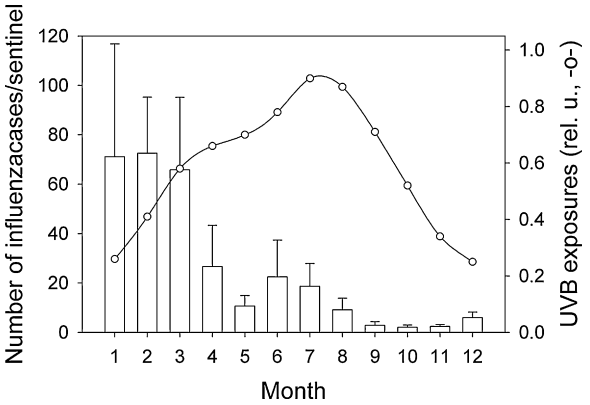

Figure 6. The mean number of monthly influenza cases (□) from 2001 to 2007 in Okinawa, adapted from Suzuki et al.[25] Monthly photosynthesis of vitamin D (—○—) for Okinawa (26°N) was calculated by use of the vitamin D action spectrum, UV measurements, and radiative transfer calculations (see Materials and methods).

April 2009, a novel H1N1 influenza A virus, the so-called pandemic H1N1/09 virus (swine influenza, Mexican flu, North American flu) was identified in Mexico.[45–47] The virus has since spread throughout the world and has caused an influenza pandemic, but it has not exhibited unusually high pathogenecity.[21] The full impact of the current pandemic is not yet clear.[47,48] According to the World Health Organization (WHO), more than 209 countries have reported laboratory confirmed cases of pandemic influenza H1N1 2009, and there have been at least 14 142 deaths.[49]

The spread of Russian pandemic influenza, caused by the influenza A virus subtype H2N2, was extremely rapid. The Russian flu was first detected in Bokara (Central Asia) in May 1889, quickly reached St Petersburg in October, and 6 weeks later was registered in the UK.[22,44,50] In mid-December 1889 the flu was reported in North America and in North and South Africa; in February 1890 it was reported in Latin America and in Asia and in March in New Zealand, Australia, and East Africa.[43,51] In Sweden, Russian flu occurred in the winter, with maximal numbers of infected persons between mid-December 1889 and late January 1890 (Figure 1),[22] almost coinciding in time with the seasonal (non-pandemic) influenza deaths in Norway (Figure 2).[14] We can conclude that in temperate latitudes even pandemic influenzas may appear with a clear winter seasonality of incidence and mortality.

The Spanish flu, caused by influenza A virus subtype H1N1, is sometimes referred to as 'the mother of all pandemics', because since 1919 almost all influenza A pandemics have been caused by descendants of this virus.[52] It is still uncertain whether the first wave of the Spanish flu occurred in Europe or in America.[44,53–55] The first wave of the pandemic in European countries was in the spring and summer of 1918. It was highly contagious, but caused few deaths.[56] The second and largest peak was the most serious and occurred in October 1918.[56] The third, most long-lasting pandemic wave started in February 1919.[56] Influenza-related mortality rates were high, ranging from 0.2 to 11 deaths per 1000 inhabitants in European countries.[56]

In the USA, the first wave of the Spanish flu occurred in March 1918.[52,55,57] The second lethal wave peaked in the autumn of 1918, and was responsible for most of the deaths, just as in Europe. However, in Europe, only one autumn wave was seen in most cities, whereas many of the USA cities had two peaks of mortality, spaced by only a few weeks (Figure 3).[58] The second wave probably spread from the east coast to the west coast, because the highest death rates were registered on October 19 in Baltimore (39°N, 76°W), on October 26 in Augusta (33°N, 81°W), and on November 5 in San Francisco (37°N, 122°W) (Figure 3).[23] The third wave came in the classical influenza season (Figure 3).[23] In Baltimore the winter wave was weak and came later, while in the other cities it came in mid-January (Figure 3), i.e., when the vitamin D photosynthesis rate is at its minimum (Figure 4A). One possible mechanism explaining the differences in death rates between the summer, autumn and winter waves of the Spanish flu could be related to serum vitamin D levels and pre-existing heterosubtypic immunity, probably induced by prior exposure to different subtypes of influenza.[59]

However, this pattern of three waves was not universal: Australia, for example, due to the partial success of a maritime quarantine that delayed the outbreak until early in 1919, experienced a single, longer wave of influenza activity.[60–62] The Spanish flu came in two waves in Singapore (1°N), a tropical island city-state: in June–July and in October–November 1918,[63,64] i.e., later than the first wave in Europe and in the USA.

Arguments for the role of UVB and vitamin D in Spanish flu in the USA have been reviewed previously.[15] The lowest pneumonia and influenza mortality rates were seen in the areas with the highest solar UVB irradiance and lowest latitudes (these being good indicators for high levels of vitamin D), while the highest

rates were in the areas with the lowest UVB irradiance and highest latitudes (indicators of low vitamin D levels).[15]

The Asian pandemic influenza originated in the southwest of China in February 1957 (i.e., in the influenza season).[2] It reached Hong Kong in April, and then spread rapidly to Singapore, Taiwan, and Japan. The causative agent, an influenza A H2N2 virus, was first isolated in Japan in May 1957. This virus was found in June 1957 in the UK and in July 1957 in the USA, but the peak of influenza incidence and mortality occurred in October 1957.[2,54,65] This first wave of disease in North America and in Europe was followed by a second wave in January–February 1958, again in the influenza season.[2,54,65]

The Hong Kong influenza A virus subtype H3N2 was first isolated in Hong Kong in July 1968, and in September it was registered in Japan, the USA, England and Wales; it was registered in France in January 1969.[66] Despite the rapid and extensive spread of this virus, its impact was not the same in all geographical regions: in North America, the majority of influenza-related deaths occurred during the first pandemic season ((1968/1969), while in Europe most deaths occurred during the second pandemic season (1969/1970). The highest rates of influenza cases and mortality were observed during the winter in all studied countries (the USA, Canada, England and Wales, France, Japan, and Australia).[66,67]

Thus, these two pandemics, the Asian flu and the Hong Kong flu, followed an almost classical trend with high winter death rates, similar to non-pandemic seasonal influenzas in the USA (Figure 4, B and C).[24] Both of these pandemics occurred in Singapore, which has almost no incidence variations in seasonal influenzas (see below).[64,68] The Asian influenza pandemic in Singapore started in May 1957 (earlier than in the USA, Figure 4A), and the Hong Kong influenza pandemic first occurred in August–early September 1968 (also earlier than in the USA, Figure 4A).[64]

All seasonal influenzas in the period from 1941 to 1976 in the USA followed a similar winter trend, with the exceptions of the 1946–1947 and the 1975–1976 waves, which came late, peaking in March–April (Figure 4, B and C).[24] However, these waves also came before the vitamin D levels start to increase after the winter (Figure 4A).

3.2. Seasonal variations in vitamin D photosynthesis and non-pandemics

The monthly variations in vitamin D photosynthesis in human skin in some selected countries were calculated using the action spectrum of Galkin and Terentskaya[37] and assuming cylinder geometry.[35,36] As shown in our earlier studies of the Nordic countries,[69] the vitamin D level is maximal about a month after the time of maximal rate of synthesis, which occurs close to midsummer. This is due to the fact that the vitamin D level here is determined as the concentration of 25-hydroxyvitamin D in serum, and that the formation of this metabolite from previtamin D, via vitamin D (mainly in the liver), takes around one week.[70] Above 37° latitude, very low UVB fluences reach the ground during the months of November through February.[71] Therefore, very little, if any, vitamin D is produced in the skin during the winter. In fact, the lowest vitamin D levels are found in February–March.[71]

Seasonal variations in vitamin D photosynthesis decrease as the equator is approached (Figure 5). In fact, as the curve for Singapore (1°N) shows (Figure 5), there are two minor maxima per year, located almost symmetrically around the midsummer minimum. The reasons why the symmetry is not complete are the slight ozone asymmetry and changes in cloud cover, which were both taken into account when we calculated the curves in Figure 5. November and December are the months of the rainy season in Singapore. In this city there is almost no seasonality of influenza,[26,64,72] as might be expected from the small seasonal variation in vitamin D photosynthesis (Figure 5). However, a small seasonal variation in influenza has been observed, with small peaks in June and December–January.[26,64,72] It appears that the influenza waves start during periods of low vitamin D photosynthesis. These peaks may be related to humidity, or possibly to contamination from seasonal influenzas in the southern and northern hemisphere, and to the seasonal variation in vitamin D photosynthesis (Figure 5).

For the subtropical region, influenza data are available for Okinawa (26°N) and Taiwan (23°N).[25,73] In both of these places there is a regular, major outbreak of influenza in the winter and a minor outbreak in the summer. This pattern is also characteristic of influenza circulation in other subtropical areas.[74] In these places there is significant vitamin D photosynthesis throughout the year, but it should be noted that the winter rate is only a fourth of the summer rate (Figure 6).

In the USA, non-pandemics of influenza typically start during the fall or winter months, but the peak of activity occurs in January–March (Figure 4), just as we have found for Norway (Figure 2). In both countries, very few cases are registered in the summer time. Seasonal variations in immune system responses have been reported in humans[75] and such variations may be responsible for the increased incidence of infectious diseases during winter and for the seasonality of non-pandemic influenza. Vitamin D modulates the immune system, essentially strengthening it, in several ways, as reviewed elsewhere.[76–80]

Norway is located between 60 and 70°N, while the center of population gravity of the USA is located between 35 and 45°N. The seasonal variations in vitamin D photosynthesis are larger for Norway than for the USA (Figures 2 and 4). Thus, in the USA, as in Norway, the numbers of deaths are small in the season when vitamin D status is best.

3.3. Mechanisms behind seasonality

Being the main source of vitamin D, UVB radiation may affect influenza via the immune system. It was demonstrated in two independent studies[81,82] that children who were regularly exposed to artificial UVB radiation had around two times lower incidence rates of upper respiratory tract infections, influenza, and sore throat than non-exposed children, and the phagocytic activity of macrophages increased significantly in all exposed subjects in a dose-dependent manner.

The impact of rurality on morbidity and mortality from the 1918 pandemic influenza in England, Wales, New Zealand, and Japan was investigated.[83–85] The influenza morbidity in villages was higher than or similar to that in towns and cities, while the mortality appeared to be lowest in villages, revealing significant differences compared to all cities and towns. The differences in mortality rates between urban and rural regions may be related to many factors, including differences in vitamin D status. People living in rural areas have significantly higher vitamin D levels compared to those living in urban areas.[86,87]

3.4. Seasonal variations in host immunity or in pathogen virulence

An argument for the seasonal effect on the host are that outbreaks of genetically similar strains occur simultaneously at similar latitudes across different continents.[1] There seems to be, in many cases, a continuous presence of pathogens throughout the year.[88] Circadian variations of hormones, like melatonin, change with the season.[88,89] This may lead to a seasonal variation in immunity.[89] Thus, mice exhibit circadian variations of susceptibility to pathogens, with the highest susceptibility in the morning.[90]

The same virus strain appears to be present in the hosts over longer periods, two years or more, but leading to manifest disease

only under favorable conditions, mainly related to host immune weakening.[88] One might expect variations in the immune system to play a major role. The preventive effect of vitamin D supplementation against influenza has also been demonstrated in intervention studies.[11] Furthermore, Ginde et al.[91] found that serum levels of vitamin D were inversely associated with upper respiratory tract infections.

UV radiation interacts with the immune system in several ways, as already mentioned. We believe that the main mechanism involves vitamin D photosynthesis in the skin.

3.5. The influence of vitamin D on the immune response

Vitamin D plays an important immunomodulatory function in primates. Deficiency has been linked with several autoimmune diseases, the development of cancer, and an increased risk of infection.[92–96] Better knowledge of the mechanisms through which vitamin D regulates immune responses is essential for understanding how it may prevent or reduce the impact of an influenza pandemic in humans. Calcitriol, the metabolically active form of vitamin D, influences host immunity in two different important ways: generally it suppresses adaptive immunity, particularly Th1 cellular immune responses, while it stimulates innate non-specific immunity.[97]

Vitamin D strengthens innate non-specific immunity in several different ways. It up-regulates the expression of antimicrobial proteins (AMPs) like cathelicidins or β-defensins.[98,99] The synthesis of LL-37 antimicrobial peptide (the only human member of the cathelicidin family, an important component of innate defense) in human macrophages is one of the best known mechanisms involving vitamin D.[98] In addition to its antimicrobial properties, it is also effective against viruses, including influenza virus.[100–102] Moreover, vitamin D induces the production of NF-κB transcription factor inhibitor – IκBα.[103] The inhibition of NF-κB signaling may impair influenza virus infection. Nimmerjahn et al.[104] showed that human cells with low NF-κB activity were resistant to influenza virus infection.

Other non-specific components of innate immunity regulated by calcitriol are Toll-like receptors (TLRs) that recognize structurally conserved molecules derived from microorganisms such as bacteria, viruses, and fungi, and activate immune responses once an antigen is recognized.[105] TLR signaling is strictly linked with vitamin D. Influenza A is a single-stranded (ss)RNA virus. (ss)RNA is a TLR7/8 ligand.[106,107] Furthermore, it can induce expression of the gene coding for the LL-37 peptide.[102]

While vitamin D may strengthen innate, non-specific immune responses and possibly reduce the risk of influenza virus infection, attenuation of adaptive immune responses might be linked with decreased mortality.[9] Calcitriol down-regulates secretion of proinflammatory cytokines and up-regulates the release of anti-inflammatory cytokines, hence influences the Th1/Th2 balance.[108,109] Moreover, it suppresses antigen presentation by antigen presenting cells (APC) like dendritic cells (DCs) and macrophages.[110,111] The mortality caused by the highly pathogenic influenza A virus strains appears to be related to the release of pro-inflammatory mediators.[112] Thus, the attenuation of the Th1 immune response by vitamin D might be beneficial for infected patients.

3.6. Use of vitamin D supplementation to prevent influenza

Solar radiation contributes significantly to vitamin D status. In temperate regions vitamin D levels are higher in late summer than in late winter, when the solar radiation contains too little UVB to synthesize enough vitamin D in human skin. Cannell et al.[9,10] hypothesized that wintertime vitamin D insufficiency may explain seasonal variation in influenza. Two preliminary studies support this hypothesis.[11,113] A randomized controlled trial of bone loss in postmenopausal, black women found that women given vitamin D (800 IU/day) were three times less likely to report cold and flu symptoms than controls given a placebo.[11] The intake of high doses of vitamin D (2000 IU/day) for 1 year efficiently protected women against the 'typical' winter colds and influenza, since only one patient reported these symptoms.[11] Another randomized, double-blind, placebo-controlled trial, comparing vitamin D supplements with placebo in schoolchildren, found that intake of vitamin D (1200 IU/day) during winter and early spring can reduce the incidence of seasonal influenza A by a factor of around two, while this is not true for influenza B.[113]

4. Conclusions

Non-pandemic influenzas usually arrive in winter/early spring, while the initial wave of pandemic influenzas may occur in any season, but with secondary waves in midwinter. Seasonal waves of all influenzas are small at low latitudes. It seems likely that seasonal variations in the incidence and death rates of both pandemic and non-pandemic influenza are related to seasonal variations in vitamin D status. An argument against this hypothesis might be that influenza death rates start to increase almost 2 months after the vitamin D levels have reached their minimum. Similarly, the death rates start to decrease several months before vitamin D levels start to increase significantly. This is likely to be related to the generation of immunity.

Conflict of interest

We have no personal or financial conflict of interest to declare and have not entered into any agreement that could interfere with our access to the data on the research, or upon our ability to analyze the data independently, to prepare this manuscript, and to publish it.

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