 doi:10.20944/preprints202202.0153.v1

Article

Trends in Excess Winter Mortality (EWM) From 1900/01 to 2019/20—Evidence for a Complex System of Multiple Long-Term Trends

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Abstract: Trends in excess winter mortality (EWM) were investigated from the winter of 1900/01 to 2019/20. During the 1918-1919 Spanish flu epidemic a maximum EWM of 100% was observed in both Denmark and the USA. During the Spanish flu epidemic in the USA 70% of excess winter deaths were coded to influenza. EWM steadily declined from the Spanish flu peak to a minimum around the 1960's to 1980's. There is evidence that this decline was accompanied by a shift in deaths away from the winter, and that the EWM calculation shifted from a maximum around April to June in the early 1900's to around March since 1967. EWM has a good correlation with the number of estimated influenza deaths, but in this context influenza pandemics after the Spanish flu only had an EWM equivalent to that for seasonal influenza. Using data from 1980 onward the effect of influenza vaccination on EWM was examined using a large international data set. No effect of increasing influenza vaccination could be discerned; however, there are multiple competing forces influencing EWM which will obscure any underlying trend, e.g, increasing age at death, multimorbidity, dementia, polypharmacy, diabetes, and obesity – all of which either interfere with vaccine effectiveness or are risk factors for influenza death. After adjusting the trend in EWM in the USA, influenza vaccination can be seen to be masking higher winter deaths among a high morbidity US population. Winter deaths are clearly the outcome of a very complex biological system of competing long-term trends.

Keywords: winter mortality; trends; season; estimated influenza mortality; pandemic influenza; aging

Definitions

Total winter deaths (TWD) = total deaths during the 4 winter months, December to March. This total is calculated as a rolling total to detect winter deaths in the Southern hemisphere, near the equator and in those years when influenza outbreaks occur earlier or later than December/March.

Excess winter deaths (EWD) = total deaths during the 4 winter months minus half the deaths in the 8 non-winter months. As a rolling calculation.

Excess winter mortality (EWM) = total deaths during the 4 winter months divided by half the total deaths during the 8 non-winter months. As a rolling calculation.

Both TWD and EWD need to be adjusted for growth in deaths over time. EWM does not need such an adjustment. For example, between Jan-07 and Dec-19 deaths in the USA grew by 0.14% per month which makes a negligible impact on the EWM calculation.

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1. Introduction

A previous study in IJERPH investigated the use of excess winter mortality (EWM) as a forensic tool [1]. The magnitude of EWM was shown to be greatly influenced by respiratory deaths and by a mix of other factors such as access to health care, relative wealth, home insulation (indoor temperature), and age at death [1,2]. All these factors are changing over time. Can EWM shed light upon other issues?

There has been considerable debate around exactly how many influenza deaths have occurred during various pandemics. The difficulty is that such deaths must be estimated and that different estimation methods give widely different answers [3-9]. Deaths due to influenza are a subset of EWM, and the high dependence of EWM on respiratory deaths [1,2] suggest that EWM may be able to shed additional insight into this issue.

Indeed, to the present there have been only a few studies on the long-term trends in EWM or investigation into other trends which may lie hidden in the EWM value.

This study seeks to conduct such analysis to see if EWM can be also used to detect the net effects of influenza vaccination or whether other trends could be confounding the association.

In this study EWM is calculated as the average deaths in the four 'winter' months (usually December to March in the temperate parts of the northern hemisphere) versus the average deaths in the previous eight 'non-winter' months (usually April to November) [1]. To further generalize the applicability of this method the calculation is performed as a rolling calculation, i.e, move forward one month and re-calculate. This allows EWM to be more accurately determined in winters with an early or late influenza outbreak, and for countries in the southern hemisphere or nearer to the equator [1]. This is a simple method which can be widely applied across multiple world countries but gives answers comparable to more complex methods such as Serfling, etc [10]. Even Serfling and other models make assumptions regarding the shape of the winter baseline. In EWM deaths are total all-cause mortality, which avoids ambiguity in the assignment of cause of death, and influenza deaths are a subset of EWM – although a key contributor to EWM, i.e, estimated influenza deaths cannot exceed excess winter deaths [1].

2. Materials and Methods

2.1. Monthly deaths

Monthly deaths are available from 1960 onward for European Union countries via Eurostat [11], and wider data for many world countries is available from 1980 onward via the United Nations [12]. Data for the USA from 1900 to 2004 was provided by Peter Doshi as part of his study on influenza mortality trends [13]. Missing monthly data for the five years 1905 to 1909 in the US time series was reconstructed from annual totals using typical summer month totals either side of these years as a baseline. Only one of these years shows high EWM. This was supplemented by monthly US data from 2005 onward [14]. Data for Denmark from 1901 onwards was obtained from Stats Denmark [15]. Additional data from 1960 onward was obtained from Stats Singapore [16] and Stats Estonia [17]. Deaths in Puerto Rico are excluded from the total for the USA from 2018 onward, and the full time series for Puerto Rico is reported separately.

2.2. Adjusting EWM for differences between countries

All countries are referenced to the USA by adjusting all EWM values such that the median EWM for each country is equal to the median of the USA.

In the USA since the 1960's, EWM reached a minimum of 4.8% in the winter of 1973/74 and a maximum of 21% in the winter of 1975/76 and 22% in 1998/99. Given that all EWM values in this study have been adjusted to USA-equivalent EWM, individual country values below 5% have been adjusted to 5% while values above 22% have been adjusted to 20%. This prevents undue effects from outlying values which can arise in some of the smaller countries. In practice trimming makes little difference to the slope of the trends (below).

2.3. Influenza doses per 1,000 population

Influenza dose distribution per 1,000 population from the winter of 1980/81 to 2013/14 was from a series of publications by the MIV Study Group [18-25]. Additional doses distributed for the USA was from the CDC [26] divided by population [27]. A variety of northern hemisphere countries were chosen to reflect a range of low to high vaccination, i.e, former Soviet countries (lowest) to Japan/USA (highest). To accurately quantify the intercept at zero vaccination special emphasis was given to countries with very low vaccination levels. For the Netherlands and Finland, the doses of vaccine were extrapolated back to the winter of 1970/71, and the data for the USA was extended to 2019/20 given vaccine doses available from the US CDC [26,27]. The list of countries with ranges in doses distributed is given in Table S1 in the Supplementary Material.

2.4. Influenza vaccination rates, aged 65+

Influenza vaccination rates in those aged 65+ in the USA up to 2001/02 was from the study of Simonsen et al [28], while more recent data was from the US CDC [29-32]. Data for 60 countries was from the OECD [33], European countries were from the study of Spruijt et al [34], and other sources including the WHO Immunization Data Portal [35-49]. Since elderly vaccination rates are only widely available from 2000 onward a method based on a correlation between doses distributed (Section 2.3 above) and proportion elderly vaccinated in the overlapping period 2000 to 2013 was used to extrapolate backwards before 2000 based on doses distributed. In this method the nominal proportion elderly vaccinated calculated from the regression (above) was matched to the available trend from 2000 onward by adjusting the calculated value (from doses distributed) up or down to match the available trend in actual proportion elderly vaccinated. See Figure A1 in the Appendix. This allowed an extended time series from 1988/89 onward. The list of countries with range in proportion elderly vaccinated is given in Table S2 in the supplementary material.

2.5. Data Manipulation

Microsoft Excel was used to manipulate the data and produce the charts. Regression was performed using the Excel 'add trendline' function.

3. Results

3.1. Long-term Trends in EWM

To show a wider historic picture from 1900 to date, Figure 1 shows EWM for the USA and Denmark over the past 120 years. Several important observations can be made from Figure 1, namely:

1. Both countries show 100% EWM during the 2018/19 winter of the Spanish flu epidemic, i.e, EWM is directly influenced by, and sensitive to, influenza activity and virulence.
2. While the EWM calculation for Denmark and the USA during the Spanish flu both shows a maximum for the 4–months ending January 1919, the USA shows maximum monthly deaths in October 1918, while maximum deaths in Denmark occurred in November 1918. In terms of the timing for higher Spanish flu deaths Denmark tends to be right skewed while the USA is left skewed. This demonstrates the need for a rolling EWM calculation rather than a static one.
3. In addition, EWM shows more complex trends in both Denmark and the USA, with a localized maximum around 1906–1907 (1900/01 to 1911/12) and a wider maximum centered around the time of the Spanish flu (1911/12 to 1930/31) – by coincidence Spanish flu occurred at a time of high baseline EWM. It should be noted that the emergence of Spanish flu precursor strains appears to have started somewhere around 1911 [50], and

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EWM appears to have correctly identified the timing of re-assortments culminating in the maximum at 1918 [50].

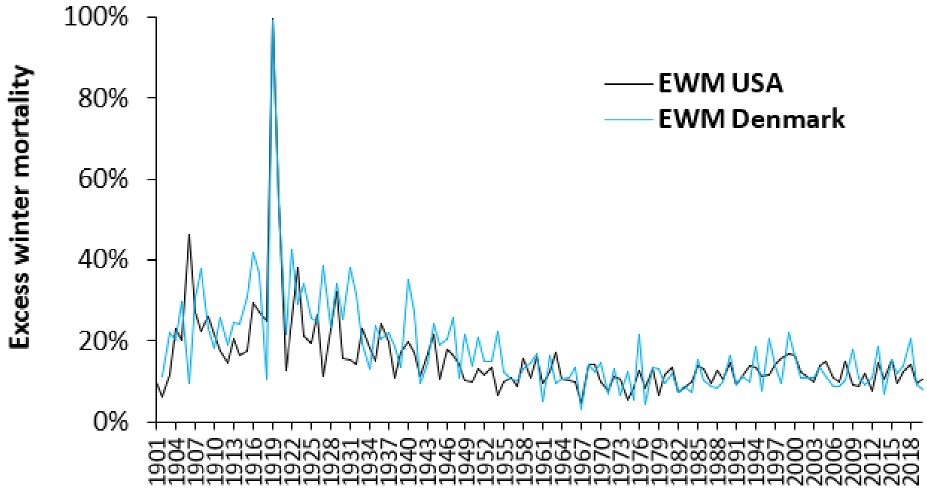

Figure 1. Excess winter mortality (EWM) over the past 120 years in Denmark and the USA.

4. After the Spanish flu, EWM then declined to reach a general minimum in the mid-1960's to 80's.
5. As an interesting observation there is no evidence that the subsequent flu pandemics of the 1957–58 Asian flu, 1968–69 Hong Kong flu, 1977–79 Russian flu, or the 2009 Swine flu gave rise to unusually high EWM.
6. There was another small peak for the three winters ending 2000 – none of which are pandemics.

Having established the long-term trends in EWM it is relevant to determine how the relative importance of winter may have changed over time.

3.2. Month in Which EWM Reaches a Maximum

Given the long-term trend to lower EWM in Figure 1 it is useful to see if the month in which the rolling EWM calculation reaches a maximum has changed over time.

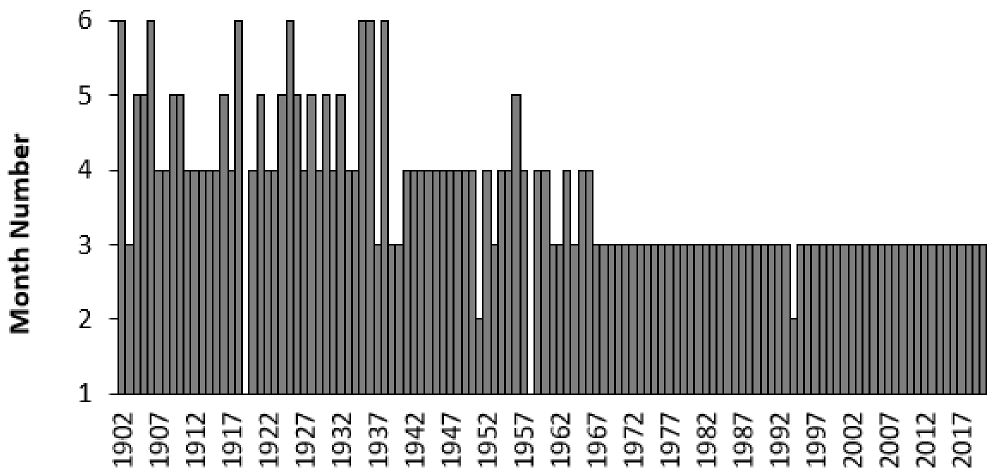

Figure 2. Month of the year at which the rolling EWM calculation reaches its maximum value in Denmark, month 1 = January, etc.

This is shown in Figure 2 with data from Denmark where the rolling EWM reached a maximum between April to June up to 1935 (autumn excess mortality), then switches to between March and April up to 1966, and beyond that predominantly occurs in March. Two exceptions occur in the winter of 1918/19 and 1957/58 where the maximum EWM occurs in January. The reasons for the seeming sudden transitions remains unknown.

Data for the USA shows a similar transition from April in the early 1900's to March in the late 1960's (data not shown). The transition is more muted than for Denmark because the USA lies further south than Denmark and has a far wider range in latitude.

As an additional observation, using the data on influenza deaths coded to ICD J10 and J11 from the study of Doshi [13] in the USA, reported "influenza" deaths appear to peak across 3 months in the early 1900's moving to 2 months in more recent years (data not shown). A transition appears to occur around the winter of 1967/68 (as also in Figure 2). Additional trends relating to influenza seasonality may lie concealed in the time trends.

3.3. Winter Deaths are Higher Before the 1970's

Figure 1 suggests that winter deaths were higher relative to summer deaths in the early 1900's. This is explored for Denmark in Figure 3 where the deaths in each month have been adjusted to equal days per month, and then to the 1995 equivalent number of maximum annual deaths. The Y-axis is truncated at 8,400. Deaths per month merge over time with June and July showing the least change. The seven months June to December show an increase over time, while the five months January to May reduce over time. February, November, and December are the most volatile.

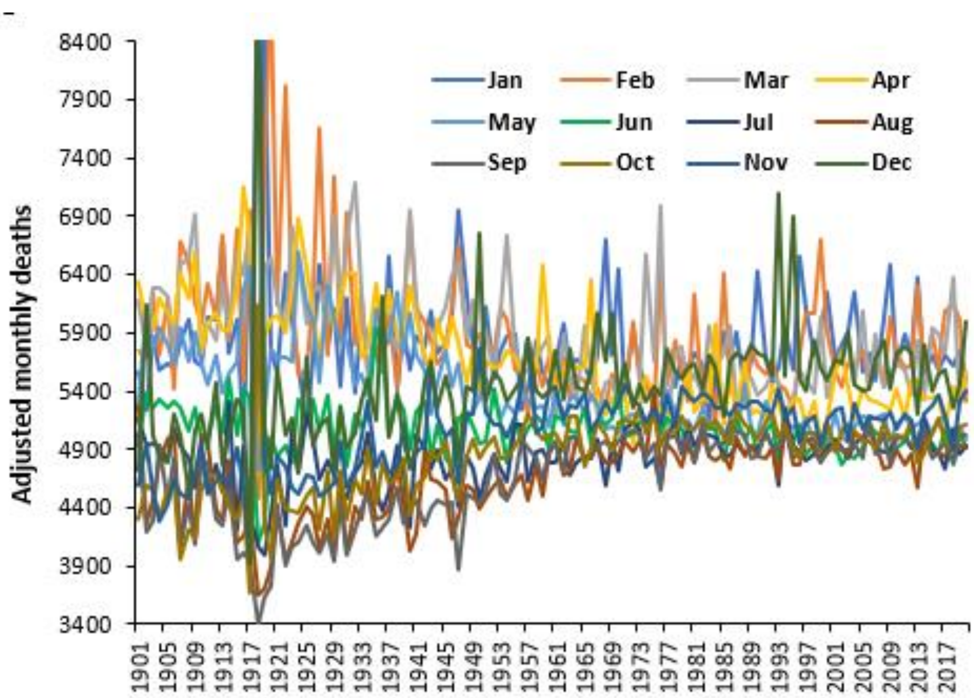

Figure 3. Trend in adjusted monthly deaths in Denmark. Monthly deaths adjusted to give an annual total equal to the maximum achieved in 1995.

Not only have monthly deaths converged but relative volatility may have shifted over time. Hence relative to the period around the time of the Spanish flu deaths have been shifted out of the (moveable) "winter/spring" (January to May) into the "non-winter months". These trends seem to stabilize from the 1970's onward. This explains the reduction in EWM over time seen in Figure 1. Once again, complex trends lie behind the calculated EWM which are poorly understood.

However, it is pleasing to note that the definition of "winter" in the EWM calculation as covering 4 months is sufficiently wide to cover all the obscure trends since the 1900's.

3.4. Similar Trends are Seen in World Countries since the 1960's

It is useful to see if these trends are replicated wider than just Denmark and the USA and Figure 4 shows data for a wide selection of countries with local EWM converted to the USA-equivalent as per the median-EWM method in section 2.5.

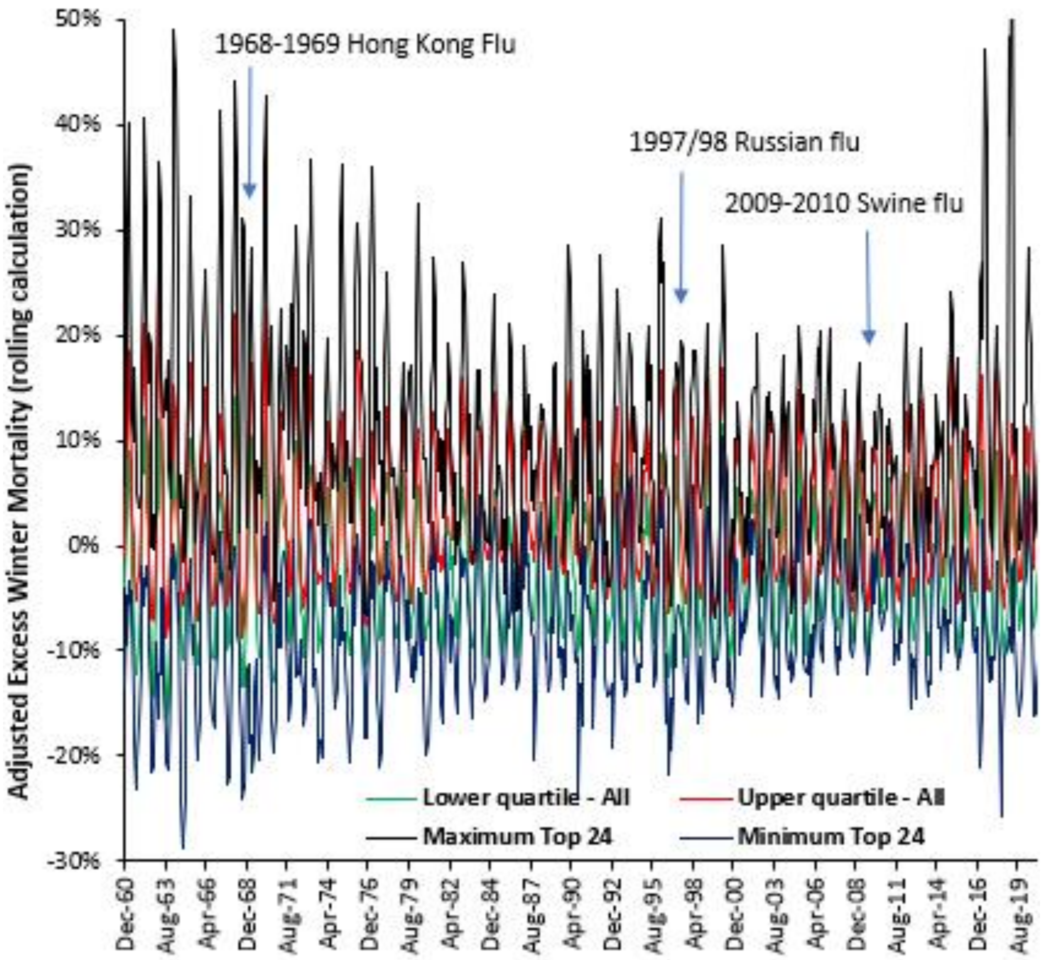

Figure 4. Trend in adjusted EWM for 112 countries, 1960 to 2020.

In Figure 4 the maximum and minimum rolling EWM is shown for the 24 countries with continuous data from 1960 onward, while the upper and lower quartile is shown for a far wider group of up to 112 countries for the years in which data is available. EWM data for countries in the southern hemisphere has been shifted forward by six months to give the northern hemisphere equivalent.

As can be seen there is no evidence for unusually high EWM during the three influenza pandemics occurring over this time frame. The early years of this chart pick up on the end of the downward trend seen in Figure 1. Considerable spatiotemporal variation can be seen in all years, although in general countries move up and down together. Hence the data in Figure 1 is more widely applicable than just Denmark and the USA.

Figure A2 (appendix) shows the proportion of excess winter deaths (EWD) due to "influenza" (ICD codes J10 to J11) in the USA from the winter of 1900/01 to 2003/04. Data is from the study of Doshi [13]. As can be seen this proportion reaches a maximum of 70% during the Spanish flu pandemic, but regularly goes as high as 50% up to the mid-1940's. More widespread availability of penicillin from 1945 onward could be one possible reason for the shift down after the mid-1940s. There are complex long-term undulations but no indication that the epidemic years after the Spanish flu have higher deaths than seasonal influenza. This will be covered further in Section 4.4.

3.5. EWM Correlates Well With Calculated Influenza Deaths

Given that influenza was the major winter pathogen over these years it is useful to see if EWM correlates with estimates of influenza deaths. Such a relationship is demonstrated in Figure 5 using data from Denmark where the FluMOMO European-wide methodology has been employed for the estimated influenza deaths. This is the most advanced methodology which uses weekly deaths after adjustment for the effect of cold temperature extremes. Three different methods are used with influenza-like-illness (ILI), etc, described in the study of Nielson et al [51]. The line for the Goldstein Index probably gives the most reliable estimate of influenza deaths. However, all three lines give good correlation and EWM explains > 85% (as R-squared) of the observed variation in estimated influenza deaths. As similar chart is available for data from Canada using data from the study of Schanzer et al [52] and is given in the Appendix as Figure A3.

It can therefore be concluded that in all influenza pandemics, other than the Spanish flu, influenza deaths are about the same as expected from seasonal influenza. See discussion regarding role of antigenic distance.

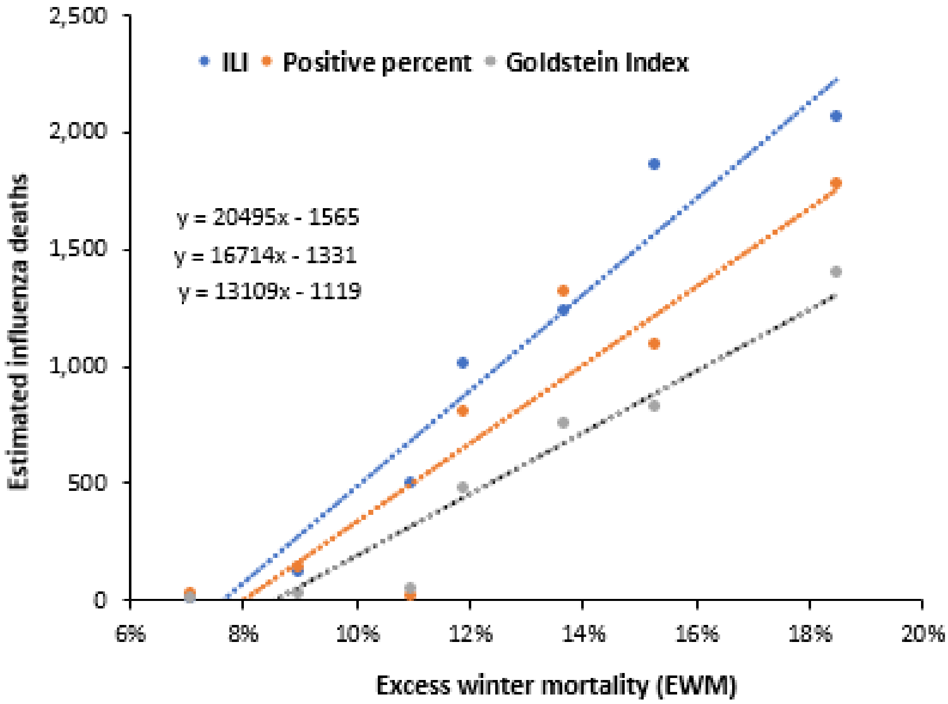

Figure 5. Three different methods for estimating influenza deaths in Denmark, 2010/11 to 2016/17. Influenza deaths are from the study of Nielson et al [51]. FluMOMO data was adjusted for excess deaths arising from periods of very cold weather. The Goldstein Index method is considered the most reliable method. R-squared for the 3-methods ranges from 0.851 (Positive percent), 0.9178 (Goldstein) to 0.9482 (ILI).

3.6. Is the effect of influenza vaccination detectable using EWM?

Given that influenza was the major winter pathogen over the period of this study it is interesting if rising international influenza vaccination levels are associated with any change in EWM over time. This issue was addressed in two ways. In the first EWM was plotted against influenza vaccine doses distributed per 1,000 population (see Figure A4 in the Appendix). Data was available from 1980 to 2013. A slight trend to higher EWM was seen, however, there was no statistical difference from the null hypothesis, namely, no change. A list of countries with associated data ranges is given in Table S1 in the Supplementary material.

In the second method EWM was plotted against proportion age 65+ vaccinated and this is shown in Figure 6.

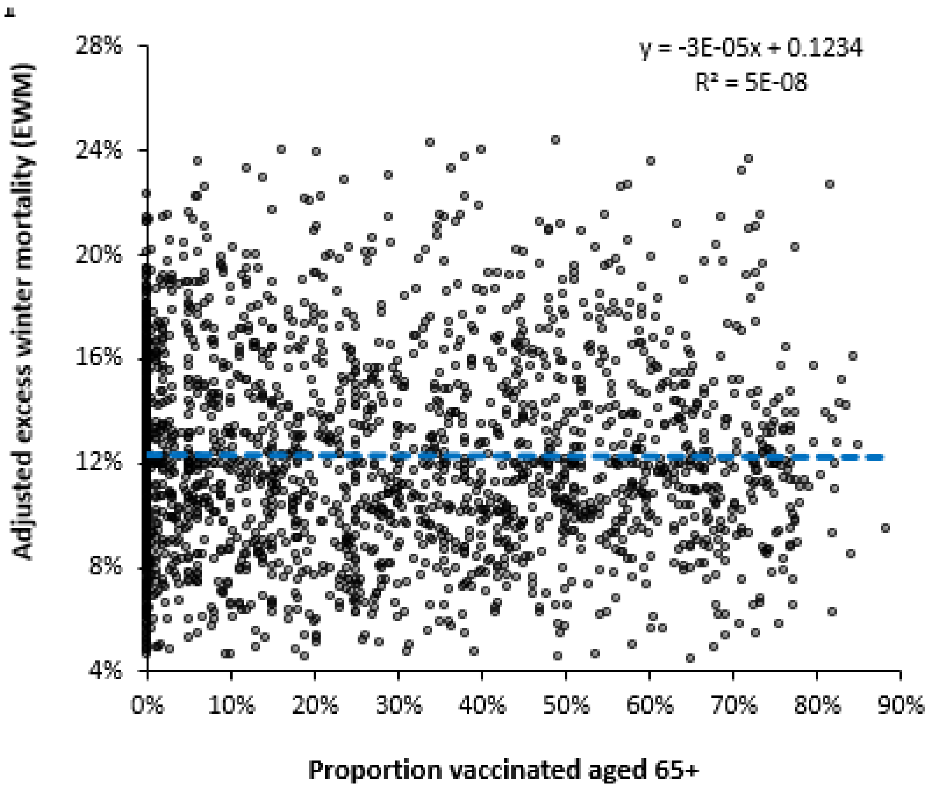

Figure 6. Adjusted EWM versus proportion aged 65+ vaccinated in 97 countries, 1988/89 to 2019/20.

Data was available from 1988 to 2019/20 for 97 countries. A slight negative slope was seen, however, there was no statistical difference to the null hypothesis. A list of countries with associated data ranges is given in Table S2 in the Supplementary material. In both Figures the R-squared is very low indicating that factors other than influenza vaccination control the observed variation.

During the period of the study there have been trends in multimorbidity, polypharmacy and obesity which are acting to oppose influenza vaccination and these and other trends are discussed in Section 4.5.

3.6. Is influenza vaccination masking a trend to poor health in the USA?

Figure 6 could be concealing a trend upward for EWM in some countries. Given the fact that the USA has among the highest levels of obesity, diabetes, and cancer in the developed world (see Section 4.5) we postulated that EWM may be trending upward over time in the US and that influenza vaccination may be masking the extent of this trend. This is illustrated in Figure 7 where the maximum possible effect of influenza vaccination has been estimated to be a 10% (percentage point) reduction in EWM for a 100% vaccinated population at 100% VE. However, in the USA the average VE for persons aged 65+ has only been 40% [53], and so the blue dots represent the likely maximum possible EWM in the absence of any vaccination.

As can be seen there is indeed a trend upward in EWM since the 1960's (0.02% per annum) and that this trend would be around 3-times higher (0.07% per annum) if there were no influenza vaccination. The two dotted lines are 5th order polynomial curve fits to show that the fundamental trends are probably far more complex, however, these lie around the approximate upward linear trends indicative of declining population health over time.

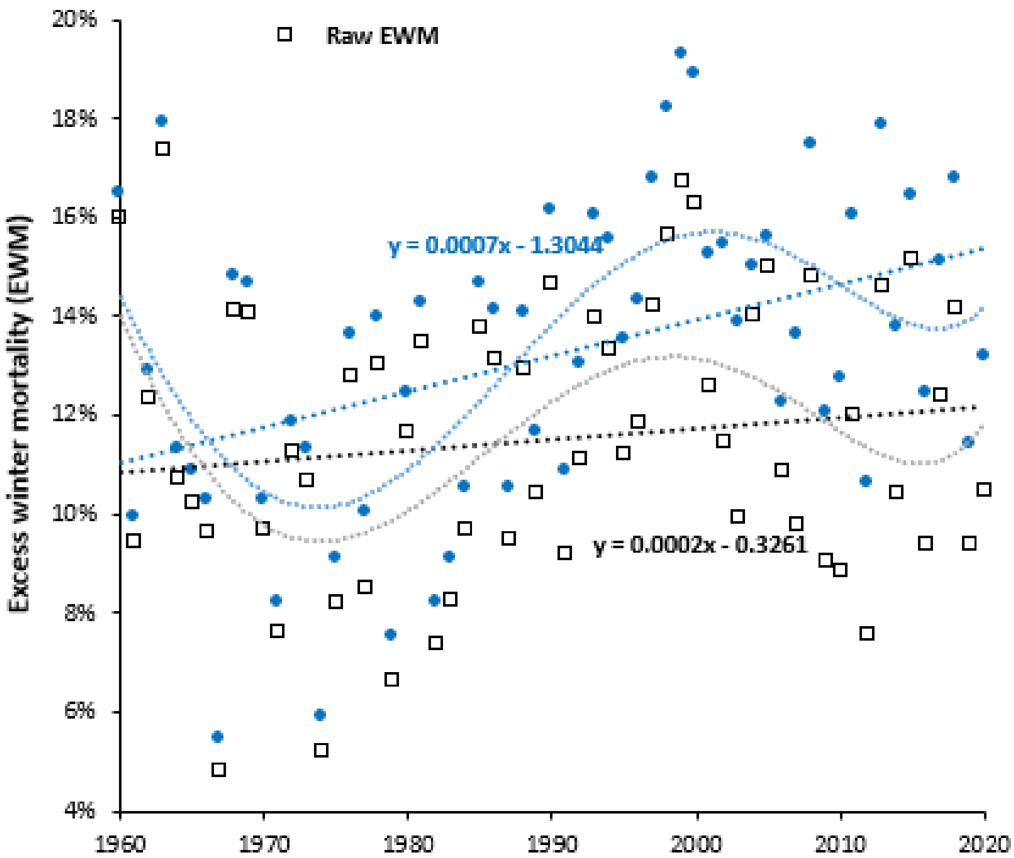

Figure 7. Trend in excess winter mortality (EWM) in the USA from 1960 to 2020, with and without correction for the effect of influenza vaccination. Vaccine effectiveness estimated at 40%, actual VE values for 2003/04 onward [53]. Percent elderly vaccinated increases from around 15% in the early 1960's [28] rising to 67% to 70% from 2001 onward [29-32].

The US population is seemingly paying a high price for the factors fueling obesity and related morbidities, which in terms of excess winter deaths is being masked by widespread influenza vaccination. Discussed in Section 4.5.

4. Discussion

4.1.. Long-term trends in EWM

This study has revealed that there are multiple complex biological long-term trends influencing EWM. Figure 1 shows evidence for long-term cycles with a minimum EWM in the early 1900's, a maximum around 1906 and then another minimum around 1911, and a further minimum around the mid-1960's. The work of Smith et al [50] has identified that Spanish flu precursor strains appear to have emerged somewhere around 1911, and EWM appears to have correctly identified the timing of re-assortments culminating in the maximum at 1918 [50].

Note that after the Spanish flu, EWM declines during the pre–antibiotic era. This decline is most likely to be due to improvements in sanitation, refuse collection, health literacy, improved nutrition, and other general improvements in public health, building standards [54,55], and finally the eradication of widespread respiratory tuberculosis via BCG vaccination after World War 2 [56]. Both countries then reach a broad minimum in EWM between the mid-1960's and 1970's.

A shift in deaths out of winter into summer was demonstrated in Denmark. A somewhat similar shift from 1968 to 2018 has been observed in Australia seemingly prompted by some very hot summers induced by global warming [57].

The curious trends in the timing and magnitude of winter deaths observed in Figures 2 and 3 are reflected in the timing of maximum EWM revealed by the rolling EWM calculation. While such trends are occurring, they seem to have reached an asymptote from 1967 onward. This at least removes one unknown confounding factor from the analysis conducted in Figures 6 and A3.

A reduction in the difference between summer and winter deaths has also been observed in older people in Sweden over the period 1860 to 1995 [58]. About 40% of increased life expectancy at age 60 could be attributed to the decrease in seasonality. The main part of the reduction in seasonality was observed to occur between 1870 to 1970, the latter date being somewhat close to the 1980 date in Denmark when the shift reached an asymptote. In 1860 most of the population lived in the country engaged in agriculture and forestry while by 1970 Sweden was a prosperous country with a highly developed welfare system with most of the population living in cities [58].

Every country will therefore have a different context in which such changes are occurring.

4.2. EWM is sensitive to influenza deaths

Figure 5 and A2 suggest that EWM is explaining >85% of the observed variation in estimated influenza deaths, and hence, there is every reason to believe that EWM has correctly identified the fact that influenza pandemics since the Spanish flu have not generated any excess deaths over and above that from seasonal influenza as seen in Figures 1 and 4.

Also note that somewhat paradoxically EWM is highest midway between the poles and the equator [1]. This is simply because countries near the equator experience minimal temperature variation and those nearest the poles are better prepared for winter, i.e, the issues are wider than just external winter temperature [1,2]. This has wider implications to the estimation of global influenza deaths both during pandemics and for seasonal influenza which are discussed in Sections 4.4 and 4.5.

4.3. The EWM adjustment factor

As a rule, EWM reaches a maximum at approximately midway between the equator and the poles (45^{o}) – for example, Spain, France, Croatia, Serbia, Romania, Ukraine, northern Italy, and the most northern US states (northern hemisphere), and New Zealand, and parts of Chile and Argentina (southern hemisphere) [1]. The USA has a generally low international value of EWM. One of the most prominent reasons is its sheer size and range in latitude (24 to 49 ^{o}N) which means that the spatiotemporal variability of EWM at the state level is moderated. The resulting variation in timing and magnitude leads to offsets creating the appearance of low EWM at national level. EWM adjustment is therefore required to bring other countries to a comparable value to that for the USA – as the country with the longest time series of both EWM and influenza vaccination.

The adjustment factors for the countries are a complex mix of geographic size (as for the USA), latitude, altitude, microclimate, housing standards, access to health care, population age structure, relative wealth and amount of fuel poverty for winter heating [1]. All of these combine to determine the median EWM for each country. The most obvious adjustment, namely using median EWM, has been used in this study.

It is acknowledged that the use of median EWM has limitations and Figure S2 shows long-term trends in EWM for 4 countries. The difference in the trends relative to the USA are unlikely to have a major impact on the scatter seen in Figures 6 and A4 since the available data for these Figures only started in the 1980's.

4.4. Evidence for seasonal levels of influenza deaths during subsequent pandemics

This anomaly between estimated pandemic deaths and recorded influenza deaths was first noted by Doshi [13]. Put simply, influenza deaths are a subset of EWM and reported 'higher' pandemic deaths may be an artefact of the methods used to estimate influenza deaths [3-9,59], or due to reporting bias where deaths during the pandemics are not compared to non–pandemic years.

It has been proposed that the very high mortality seen during the Spanish flu pandemic arose from previous exposure during the 1889–90 Asiatic flu pandemic. This led to a very high mortality peak at the exact age of 28 [59]. Original antigenic sin or antigenic imprinting during the earlier Asiatic flu then led to immune dysregulation during exposure to a highly dissimilar variant/clade during the Spanish flu [59].

This can work in the other direction, and two notable examples exist where pandemic influenza did not increase deaths due to antigenic imprinting. The 1977–79 Russian flu pandemic was antigenically similar to strains circulating in 1947 to 1956 [60,61], and antigenic imprinting created pre–existing immunity and low deaths, as demonstrated in Figures 1 and 4. The same holds for the 2009 Swine flu pandemic [62,63] in which there were very few elderly deaths due to childhood exposure to similar strains, as also seen in Figures 1 and 4.

The issue is not the 'pandemic' designation but antigenic distance from previous lifetime exposure [64-68]. As demonstrated in Figure 1, seemingly only the Spanish flu met the antigenic distance criteria. The problem seems to be one of selective reporting of pandemic deaths without comparison to other years, of which 2017/18 is but one example where influenzas type B were unusually high, there was a vaccine mismatch due to a shift in dominant clades [69], and consequently VE was generally low [70,71].

Regarding the issue of pandemic influenza deaths from Figure 1 it should be noted that other studies have commented upon the apparent absence of higher influenza deaths during pandemics compared to seasonal influenza [71] – Spanish flu excepted. It was proposed that the wider publicity surrounding pandemics may have led doctors to code more hospital admissions and deaths to influenza/pneumonia thereby artificially inflating the estimates of influenza deaths [71].

Some comment needs to be made regarding the study of Peter Doshi [13] which investigated trends in recorded influenza mortality (ICD codes J10 and J11). Doshi was fully aware that ICD codes J10/J11 underestimate total influenza mortality, however, his study used these codes as a common denominator to explore the trend over time, i.e, there is no a priori reason for doctors to record fewer J10/J11 as cause of death over time. Trends in recorded influenza deaths in his study and observed for EWM in Figure 1 of this study both decline over time, and do not show undue deaths during pandemics after the Spanish flu. This point was further emphasized in Figure A2.

Also note that EWM is highest midway between the poles and the equator and reaches an absolute minimum at the equator [1]. Countries nearest the poles are better prepared for winter [1], i.e, the issues are wider than just external winter temperature. (see Section 4.5).

International estimates of influenza deaths do not account for the role of latitude in moderating EWM and deaths, and overestimation of deaths is likely. Most of Africa is equatorial or sub-equatorial and will have a low EWM (although monthly data is absent for most of Africa and even annual deaths are estimated). As demonstrated in Figure 5 the method developed in FluMOMO using the Goldstein Index probably gives the most reliable basis. The method based on ILI is least reliable because ILI is caused by multiple pathogens and usually less than 35% of persons with ILI test positive for influenza [72-75]. The method currently used in the USA by the CDC appears to overestimate influenza deaths by around 30% (See Figure S1 in the Supplementary material [76-81]. The USA is so large and covers such a wide range in latitude that monthly or weekly deaths in each state can be converted to EWM or a FluMOMO equivalent. The FluMOMO algorithms are open source [7].

4.5. EWM and influenza vaccination – competing underlying trends

In 1945 the first inactivated influenza vaccine became available for public use [82]. Most advanced economies start to increase influenza vaccination during the 1980's [18-25]. According to the WHO by 2000 only 20 countries had policies for seasonal influenza vaccination, rising to 91 in 2010 and 124 in 2020 [83], hence, higher levels of vaccination in the elderly only generally occur beyond 2000. In 2000 elderly vaccination rates ranged up

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to 76% in the Netherlands (the majority below 65%), to a maximum of 86% in 2019 for South Korea (the majority below 70%) [12,83].

Influenza vaccination is known to reduce both hospitalization and death in the elderly [84] and should act to reduce EWM. Several studies have estimated that influenza vaccination should make a detectable effect upon EWM [28,85]. The fact that Figures 6 and A4 do not demonstrate any downward trend raises the question as to whether the effect of influenza vaccination is being counterbalanced by other trends. Figure 7 investigated this possibility using EWM data from the USA which is possibly the developed country with the worst morbidity trends. It was proposed that rising morbidity was causing EWM to rise by a maximum possible upper limit of 0.07% per annum (in the absence of influenza vaccination) and that increasing influenza vaccination over time led to the observed lower value of 0.02% per annum increase.

The issues around rising morbidity is explored in Table 1 where increases in multimorbidity, polypharmacy, obesity, Alzheimer's and dementia, and age at death will all contribute to pressure to increase EWM since the 1980's. Several factors contributing to lower EWM are also discussed.

Table 1. Factors increasing or decreasing EWM with time

Factors Increasing EWM with time	**Factors reducting EWM with time**
Multimorbidity – Levels of basic and complex multimorbidity have been increasing over time [86,87]. Multimorbidity is associated with diminished response to influenza vaccination [88] and risk of influenza mortality [89].	Home insulation – this is a major contributor to reductions in winter hospitalization and mortality in some countries [115-121]. The greatest benefit will occur in countries midway between the poles and equator which tend to have housing suited to summer rather than winter [1].
Polypharmacy – Polypharmacy in the Netherlands and USA had more than doubled in the interval 1999 to 2014 [90]. Certain pharmaceuticals and polypharmacy alter the immune response to influenza vaccination [91]. Polypharmacy has been found to be a risk factor for hospitalization, and death from COVID-19 [92] and for pneumonia admissions for nursing home residents [93,94].	Increased access to health care (critical care, antibiotics, antivirals, etc) and wider public health measures [1,2] - this will mainly apply to the less developed countries.
Obesity – has been increasing over time [87]. It creates systemic inflammation, reduces B-cell function [95,96], generates auto-immune antibodies during infection [97], and interferes with influenza vaccination efficiency [98,99].	Reduced smoking prevalence – smoking prevalence is declining in the developed world [121]. Smoking leads to inflammation and is a risk factor in influenza mortality [123,124].
Alzheimers and dementia – Incidence increases exponentially with age [100] and are a significant risk factor for influenza mortality [101].	Improvements in influenza vaccine technology such as cell versus egg grown vaccines [125,126].
Diabetes – Incidence increases with age [102] and is a significant risk factor in influenza mortality [103]. In the USA persons aged 65+ experienced the greatest increase in the incidence of diabetes since 1988 [102]. However,	Influenza vaccination in the elderly – increased vaccination will lead to lower influenza deaths [84], especially in years with a high VE.

Factors Increasing EWM with time	Factors reducting EWM with time
mortality is reduced by influenza vaccination [104,105].	
Cancer – Cancer incidence increases with age [106] with incidence especially high in the US [106]. Cancer survivors are at far higher risk of influenza mortality [107]. Mortality is reduced by influenza vaccination [108]	Global warming – winter temperatures should be more mild leading to lower EWM with time. Although this will be moderated by long-term adaption such that the temperature for minimum mortality is very close to the most frequently experienced temperature [127].
Air pollution (especially in large cities with population growth) – Air pollution is well recognized for its ability to increase systemic inflammation [109], alter aspects of immune function [110], increase incidence of ILI [111], and increase the proportion of persons infected with influenza [112]. It also interferes with influenza vaccination efficiency and is a risk factor for influenza mortality [113]. In children, air pollution has an adverse effect on lung function which is moderated by influenza vaccination [114].	
Longeivity or increasing age at death – EWM increases with age at death, however, difficult to assess over many decades as chronological age is not a good measure of biological or epigenetic age [1]. Chronological age will also be serving as a proxy for the above factors.	

Age at death is probably the greatest contributor to higher EWM [1] and in England and Wales the proportion of persons dying at age 65+ has risen since 1980 from 82% to 88% (in 2019) in females and from 71% to 82% in males [128]. Age will also be serving as a proxy for many of the morbidity issues. Since 1980 average age at death over the age of 65 has risen from 76 to 81 in males and 80 to 85 in females [128]. Age will be intertwined with multimorbidity, polypharmacy, etc.

These forces are opposed by improvements in home insulation, reduced smoking prevalence, improvements in influenza technology and more widespread influenza vaccination in the elderly.

There have not been any studies looking at how all the factors may (synergistically) combine to change EWM over time, and thereby diminish the ability of influenza vaccination to reduce EWM. All these trends will be country specific, and it is suggested that the analysis in Figures 6 and A4 be repeated for each country to disentangle the multiple trends.

The role of temperature is more problematic. The temperature for minimum deaths in each location is very close to the most frequent temperature experienced in that location [127]. Deaths respond far more to extreme temperature events [129]. Hence, it has been noted that although deaths increase as it gets colder, temperature alone only explains a small amount of the variation in EWM between years [130]. There are complex interactions between air pollution (PM10), temperature and influenza on all–cause, respiratory, and cardiovascular mortality [131]. Each of these variables operates both alone (PM10 mainly affects cardiovascular, and influenza affects mainly respiratory) and in combination with additional specific interactions between influenza–PM10 for cardiovascular mortality and between influenza–temperature upon all–cause mortality. The

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relationships are complex and will mostly affect those living in large cities – which usually make a major contribution to total deaths and hence the whole country value of EWM.

Once again, the complex relationships between temperature/air pollution/influenza will be country specific.

Indoor temperature is a known major factor in EWM [115-121], which suggests that it is not influenza per se, but influenza infection exaggerated by poorly maintained indoor temperature which is a contributory factor in deaths. It is extremely difficult to disentangle the two.

4.6. Strengths and Limitations

The major strengths of this study are that very long-term trends have been investigated using a method which can be applied to readily available monthly international data. Apart from the Spanish flu pandemic the absence of higher pandemic influenza deaths has been established from multiple perspectives. The ability of influenza vaccination to reduce EWM was investigated with two large data sets, however, these lacked information on the relative effects of the opposing forces. The role of competing trends was highlighted, but quantifying these trends was beyond the scope of the study.

The method based on median EWM to adjust all countries to the US equivalent could potentially suffer from country-specific trends in EWM which are different from those in the US. It is also possible that additional complexity between countries lies at annual level.

6. Conclusions

EWM is a simple but powerful way of investigating the role of multiple and complex trends over time. 'Winter' has seemingly moved from the four months ending April/May in the early 1900's to ending March in more recent times. Deaths have seemingly been shifted out of winter as time has progressed, but in the two developed countries studied this had seemingly reached an asymptote by the mid-1960's. Higher influenza deaths during pandemics (except the Spanish flu) have been discounted on multiple fronts, and the role for antigenic distance was highlighted. The seeming lack of effect against EWM due to rising influenza vaccination has raised the possibility that increasing age at death and increasing aspects of elderly morbidity are acting to obscure any trend. The exact contribution of the opposing trends needs to be quantified.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Table S1: Summary of data relating to each country included in the influenza vaccine doses distributed analysis.; Table S2: Summary of data relating to each country (n=98) included in the proportion elderly vaccinated study. Figure S1**:** US CDC estimated flu deaths (adjusted for growth in deaths over time) versus EWM. Figure S2: Trend in EWM for Denmark, Iceland, Singapore, and Sweden over the 60-year period 1960 to 2020.

Author Contributions: Conceptualization, RJ; methodology, RJ; validation, RJ; formal analysis, RJ; investigation, RJ; data curation, RJ; writing—original draft preparation, RJ.; writing—review and editing, AP.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable

Data Availability Statement: All data is publicly available. Data compiled for this study is available on request from Dr Rodney Jones, email: hcaf_rod@yahoo.co.uk

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

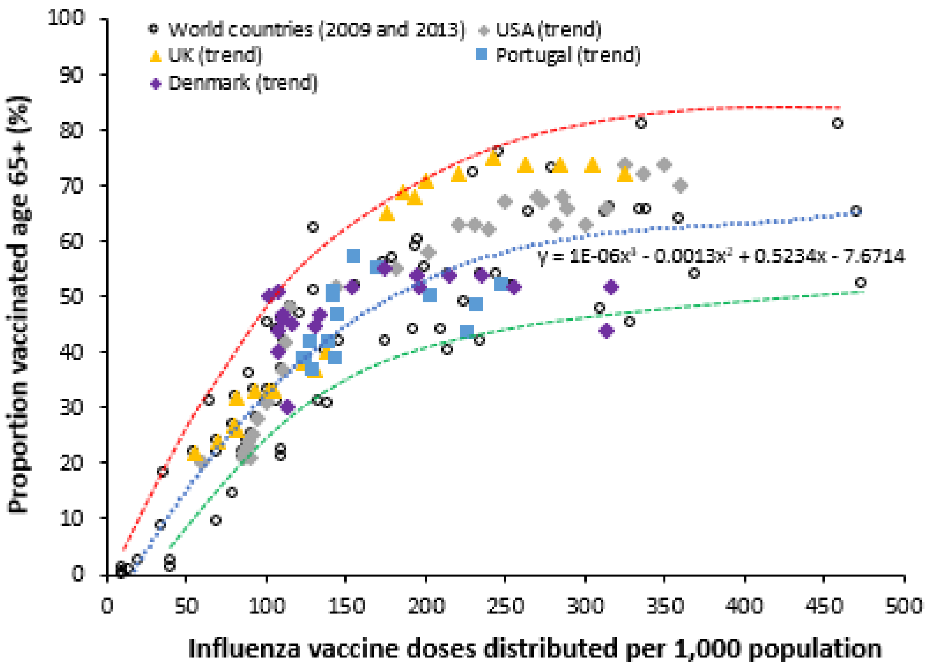

Figure A1. Relationship between influenza doses distributed and proportion vaccinated in various countries (2009-2013) and the time trend for 4 countries (2000 onward). Red and green dashed lines are the upper and lower limit. The blue dotted line is the line of best fit using a third order polynomial. Before 2000 the bulk of countries lie below 150 doses per 1,000 population.

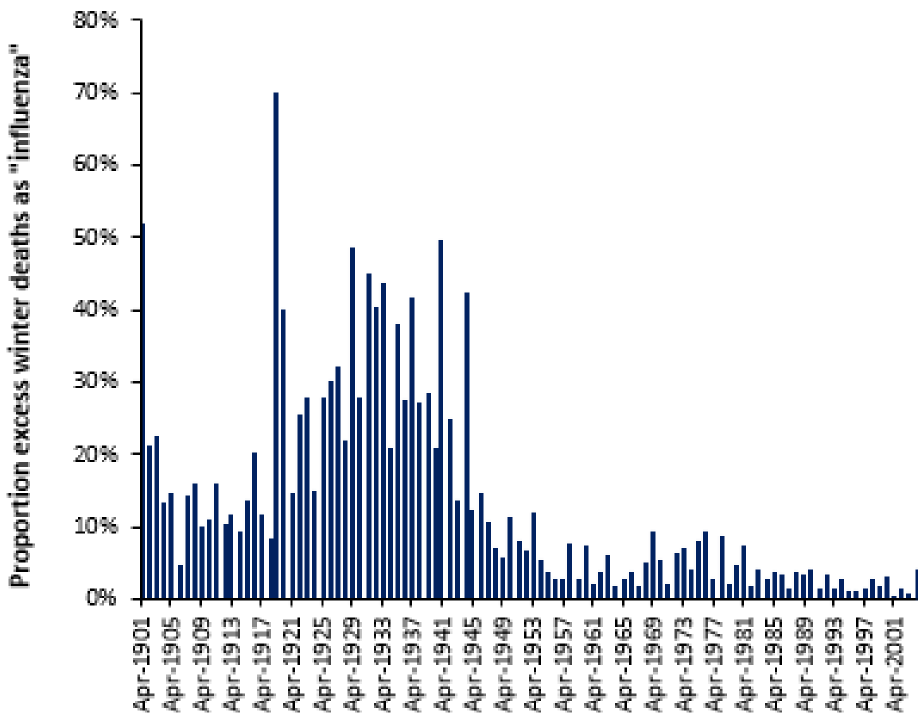

Figure A2. Proportion of excess winter deaths (EWD) recorded as "influenza" (ICD codes J10 and J11). Data is from the study of Doshi [13]. Coding practice seem to have changed from 1977 onward and the proportion after this date has been multiplied by 1.8 to compensate.

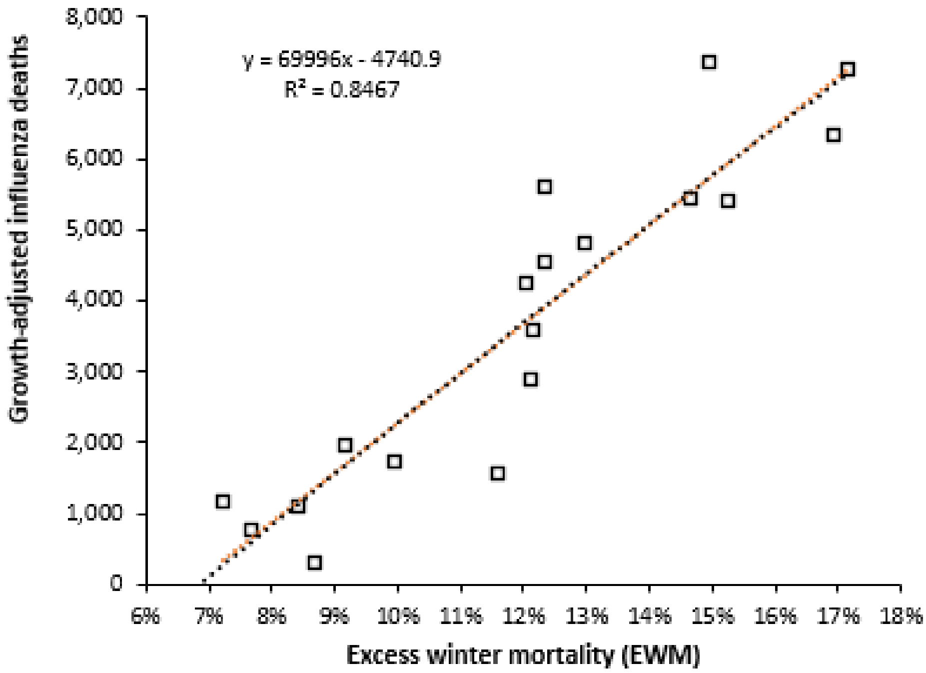

Figure A3. Relationship between estimated influenza deaths in Canada versus EWM, 1992-2009. Data is from the study of Schanzer et al [50]. From 1992 to 2009 there was around 19% growth in deaths. Each year has been adjusted for underlying growth using a polynomial curve fit.

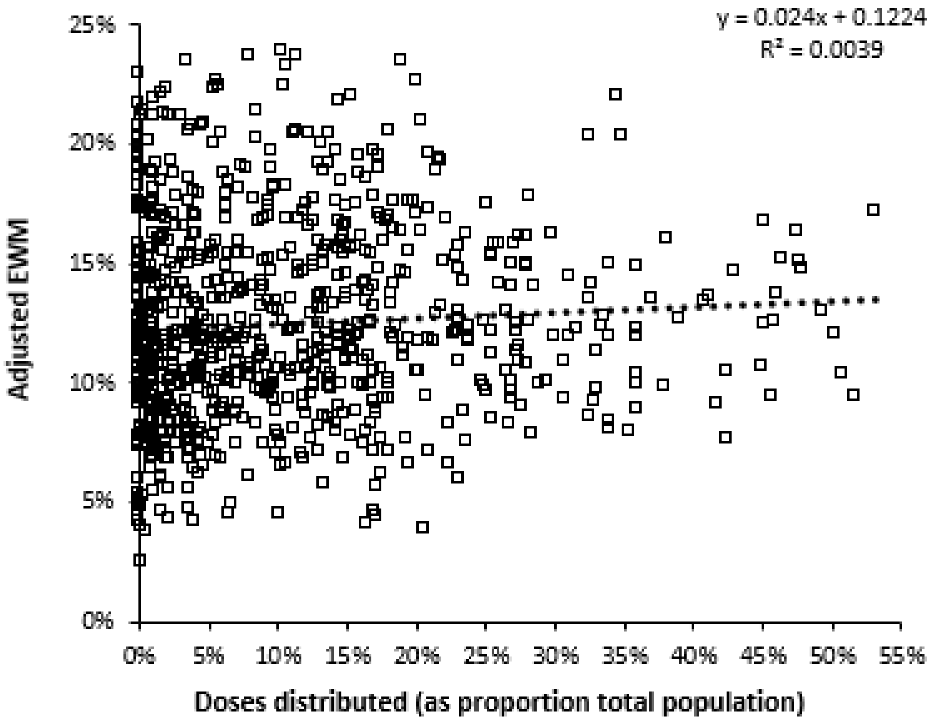

Figure A4. Relationship between influenza doses distributed and adjusted EWM over the winters 1980/81 to 2013/14 (before trimming of high/low values). Trimming of high/low values makes little difference (data not shown). Before 2013/14 the bulk of countries lie below 200 doses per 1,000 population (20% vaccinated). Dividing the data into three groups of high/medium/low vaccination (17% increments of proportion vaccinated) gives overlapping confidence intervals, and the null hypothesis cannot be excluded. i.e, the slope is zero (data not shown) or no effect can be discerned.

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Supplementary Material

Table S1. Summary of data relating to each country included in the influenza vaccine doses distributed analysis. The column "10% achieved" gives the winter at which 10% population vaccination coverage was achieved.

Country	Latitude	EWM adjustment	Data (n) up to 2013/14	Vaccination Range	Vaccination 10% achieved
Singapore	1.3	1.650	34	0%-10%	2009/10
Hong Kong	22.3	0.656	33	1%-15%	2003/04
South Korea	36.1	1.463	23	5%-41%	1996/97
Japan	36.3	0.668	33	0%-51%	2000/01
USA(!)	38.0	1.000	40	6%-53%	1988/89
Turkey	39.1	0.981	4	3%-4%	No
Portugal	39.6	0.443	34	1%-25%	1994/95
Greece	39.7	1.150	14	12%-32%	2000/01
Armenia	40.3	0.471	22	0%	No
Spain	40.4	0.590	34	5%-34%	1988/89
Macedonia	41.4	0.826	21	0%-1%	No
Kyrgyzstan	41.5	1.600	8	0%	No
Uzbekistan	41.8	0.979	7	0%-1%	No
Italy	42.5	0.746	24	15%-34%	1984/85
Montenegro	42.8	0.993	9	0%-7%	No
Bosnia and Herzegovina	43.7	0.939	10	0%-4%	No
San Marino	43.9	0.453	26	0%-15%	2004/05
France	46.6	1.080	34	9%-36%	1988/89
Switzerland	46.8	0.900	34	5%-22%	1998/99
Austria	47.6	0.996	34	1%-17%	1999/00
Kazakhstan	48.1	1.520	21	2%-4%	No
Ukraine	48.4	1.060	30	0%-2%	No
Luxembourg	49.6	0.924	12	15%-48%	2004/05
Belgium	50.6	0.854	34	5%-27%	1993/94
Germany	51.9	1.200	34	6%-35%	1997/98
Poland	52.1	1.040	34	1%-10%	2001/02
Netherlands(α)	52.3	1.070	44	3%-46%	1994/95
Ireland	53.2	0.738	22	3%-31%	2002/03
UK	54.6	0.760	26	2%-33%	1995/96
Canada	56.1	1.090	34	4%-38%	1990/91
Denmark	56.1	1.100	32	0%-26%	1998/99
Latvia	56.9	1.095	25	1%-14%	2005/06
Estonia	59.4	1.120	34	1%-7%	No
Sweden	62.7	0.990	34	0%-21%	2001/02
Finland(α)	64.3	1.240	44	2%-34%	1995/96

Country	Latitude	EWM adjustment	Data (n) up to 2013/14	Vaccination	
				Range	10% achieved
Iceland	64.9	0.935	34	1%-28%	1986/87
Norway	66.8	1.020	34	1%-16%	1995/96

(!) Data for USA extended to 2019/20 due to doses data available from US CDC. (α) Low vaccination at the beginning of the time series enables extrapolation back in time using an assumed linear trend.

Table S2. Summary of data relating to each country (n=98) included in the proportion elderly vaccinated study.

Country	EWM Adjustment	Median EWM	Data (n=)	Age 65+ vaccinated (%)		
				Minimum	Maximum	Median
Albania	0.44	31.2%	13	0%	14%	6%
Armenia	0.47	24.6%	15	0%	2%	0%
Australia	0.72	16.6%	32	12%	79%	58%
Austria	0.87	13.8%	33	0%	49%	21%
Azerbaijan	0.79	14.9%	21	0%	0%	0%
Bahamas	0.99	12.1%	22	0%	27%	0%
Barbados	0.87	13.8%	6	0%	40%	8%
Belarus	1.38	9.4%	18	5%	76%	23%
Belgium	0.72	15.4%	33	15%	65%	57%
Bermuda	0.62	19.6%	17	0%	12%	0%
Bosnia and Herzegovina	0.97	12.4%	10	0%	0%	0%
Bulgaria	0.71	17.6%	20	2%	20%	8%
Canada	1.03	11.6%	33	25%	71%	60%
Chile	0.57	21.2%	32	3%	68%	18%
Costa Rica	1.54	8.2%	26	0%	50%	15%
Croatia	0.78	16.0%	31	0%	43%	23%
Cuba	1.22	9.7%	26	0%	99%	28%
Cyprus	0.52	22.0%	18	23%	49%	33%
Czechia	1.08	11.4%	28	0%	24%	17%
Denmark	1.08	11.1%	33	4%	52%	20%
Egypt	0.90	13.4%	25	0%	1%	0%
El Salvador	1.20	10.0%	23	0%	42%	12%
England	0.68	17.6%	33	12%	75%	71%
Estonia	1.10	10.9%	32	0%	20%	2%
Finland	1.12	10.7%	33	4%	52%	40%
France	0.87	13.7%	33	39%	67%	52%
Georgia	0.63	18.9%	16	0%	0%	0%
Germany	1.00	12.0%	33	13%	63%	38%
Greece	1.04	11.0%	20	20%	59%	49%
Greenland	0.66	18.1%	28	0%	0%	0%
Guadeloupe	1.18	10.1%	6	0%	18%	9%
Guam	0.79	15.3%	11	0%	0%	0%
Guatemala	2.42	5.0%	9	1%	15%	9%
Hong Kong SAR	0.67	20.2%	33	0%	44%	5%
Hungary	1.03	11.7%	32	13%	39%	27%
Iceland	1.01	11.5%	31	35%	49%	43%
Ireland	0.75	15.8%	20	38%	70%	59%
Israel	0.57	21.4%	27	43%	66%	49%

Country	EWM Adjustment	Median EWM	Data (n=)	Age 65+ vaccinated (%)		
				Minimum	Maximum	Median
Italy	0.75	16.0%	29	40%	68%	52%
Japan	0.64	18.9%	33	0%	57%	48%
Kazakhstan	1.54	7.6%	18	1%	15%	3%
Kosovo	0.80	15.0%	9	0%	0%	0%
Kuwait	0.75	17.0%	28	0%	23%	4%
Kyrgyzstan	1.76	6.8%	13	0%	7%	1%
Latvia	1.01	12.1%	31	0%	15%	3%
Lebanon	0.63	18.9%	20	5%	35%	15%
Liechtenstein	0.47	25.6%	32	20%	30%	27%
Lithuania	0.95	12.7%	26	0%	25%	9%
Luxembourg	0.93	13.0%	30	15%	54%	40%
Macao SAR	0.57	21.0%	31	9%	36%	25%
Malaysia	2.13	5.6%	24	0%	1%	0%
Maldives	0.89	13.6%	24	0%	6%	0%
Malta	0.37	34.0%	30	20%	57%	46%
Martinique	1.43	9.0%	11	0%	6%	0%
Mauritius	0.86	13.9%	26	0%	51%	14%
Mexico	0.74	15.9%	27	1%	88%	51%
Mongolia	1.16	10.4%	15	0%	15%	0%
Montenegro	0.89	13.5%	14	14%	31%	17%
Netherlands	0.89	13.4%	32	25%	84%	70%
New Caledonia	0.83	14.6%	23	7%	35%	21%
New Zealand	0.67	18.4%	33	9%	69%	58%
North Macedonia	0.83	14.7%	22	0%	12%	4%
Northern Ireland	0.71	17.0%	31	12%	78%	72%
Norway	0.96	12.4%	33	15%	44%	31%
Philippines	1.77	6.8%	16	0%	9%	2%
Poland	1.09	11.7%	33	0%	32%	8%
Portugal	0.44	27.4%	33	0%	65%	42%
Puerto Rico	1.18	10.2%	22	0%	37%	8%
Qatar	0.88	13.2%	23	0%	59%	5%
Republic of Moldova	0.66	18.3%	20	0%	5%	3%
Reunion	1.03	12.5%	10	0%	0%	0%
Romania	0.71	17.3%	32	0%	29%	15%
Russian Federation	1.79	6.7%	23	1%	69%	14%
Saint Lucia	0.78	15.3%	4	0%	0%	0%
Saint Vincent & Grenadines	0.73	16.1%	17	0%	20%	0%
Scotland	0.81	14.8%	30	12%	77%	72%
Serbia	0.95	12.7%	19	0%	15%	9%
Singapore	1.56	7.4%	31	2%	21%	8%

Country	EWM Adjustment	Median EWM	Data (n=)	Age 65+ vaccinated (%)		
				Minimum	Maximum	Median
Slovakia	1.32	9.1%	29	0%	38%	14%
Slovenia	0.83	14.2%	32	0%	35%	13%
South Africa	0.95	12.6%	18	0%	17%	3%
South Korea	1.46	8.2%	27	9%	86%	73%
Spain	0.60	20.0%	33	37%	70%	58%
Sri Lanka	1.12	10.7%	13	0%	0%	0%
Suriname	1.31	9.1%	16	0%	0%	0%
Sweden	0.94	12.7%	33	13%	66%	44%
Switzerland	0.82	14.6%	32	14%	61%	36%
Trinidad and Tobago	1.44	9.6%	17	0%	25%	2%
Turkey	0.82	14.6%	21	1%	13%	6%
Ukraine	1.10	11.5%	27	0%	70%	0%
United Kingdom	1.00	12.0%	33	12%	75%	71%
Uruguay	0.42	30.5%	18	0%	70%	0%
US Virgin Islands	0.86	15.0%	7	0%	16%	2%
USA	1.00	12.0%	33	36%	71%	65%
Uzbekistan	1.30	9.2%	12	0%	13%	0%
Venezuela	1.59	8.0%	13	0%	50%	15%
Wales	0.74	16.1%	20	9%	69%	60%

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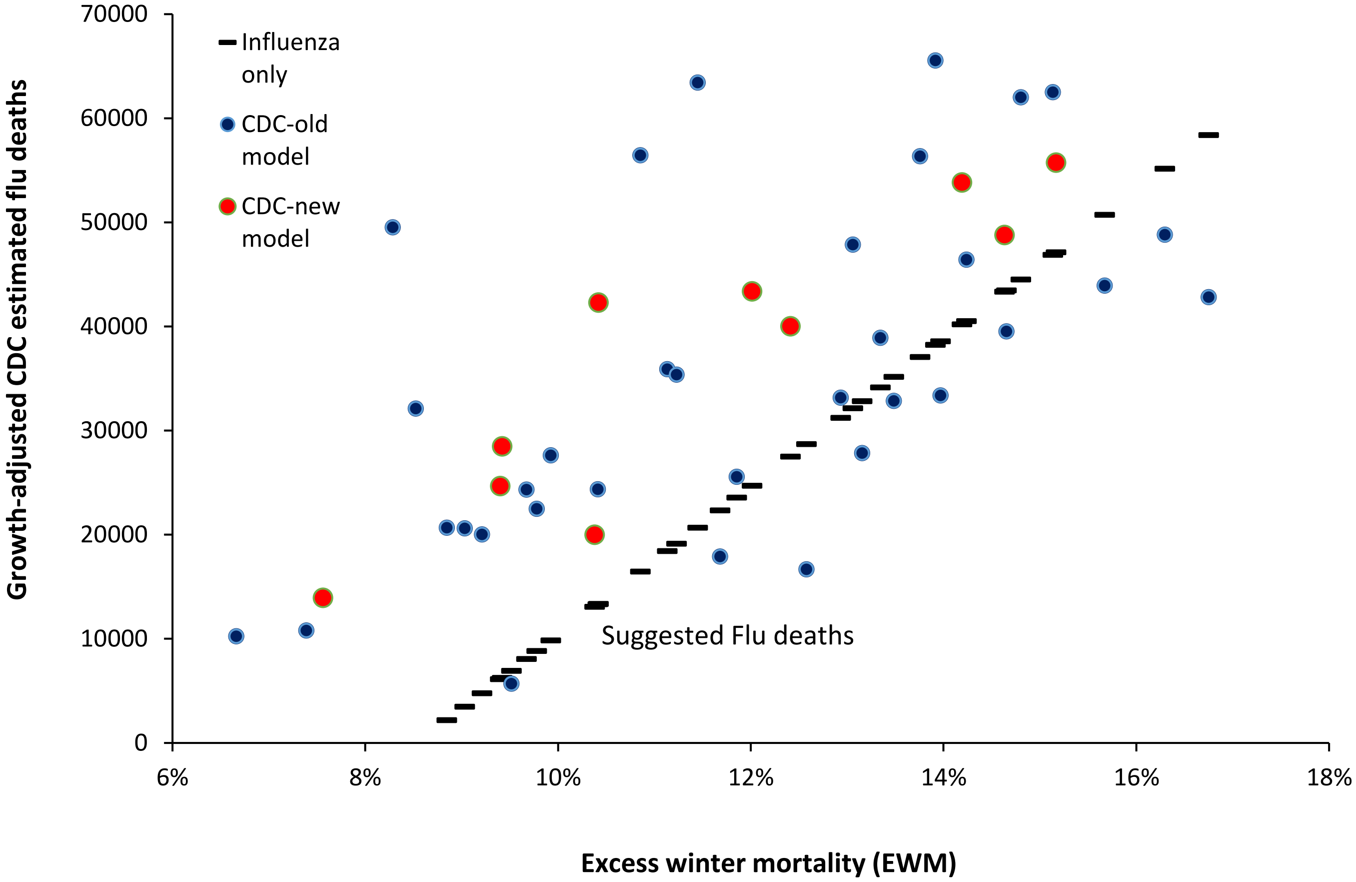
Figure S1: US CDC estimated flu deaths (adjusted for growth in deaths over time) versus EWM



Footnote: CDC estimated flu deaths were first adjusted for the growth in total deaths over time. Data is from [77-81]. The underlying trend in total deaths was determined from a series of polynomial curve fits giving an adjustment factor for each year taking flu deaths to the 2020 equivalent. Over time the CDC has used two models to estimate flu deaths (old model covers 1976/77 to 2006/07, while the new model is from 2007/08 onward) of which the most recent model gives higher estimated flu deaths [77-81]. Data from the earlier model was adjusted up to the more recent model by plotting both sets of data against EWM and using the difference between the regression lines as the adjustment factor. The line for suggested flu deaths is in line with Figures 5 and A3. Note the far higher scatter in the CDC results, with an R-squared of only 0.4368. The R-squared for the old model is 0.448 while that for the new model is 0.8403. This scatter arises because the CDC uses a limited sample of hospitals from which admissions and other surveillance data are used to estimate flu deaths. As a result, there are multiple sampling issues, hidden assumptions, and adjustment factor issues. While the new CDC model has a higher R-squared, the CDC models are less reliable than may be expected and lead to over-estimated influenza deaths.

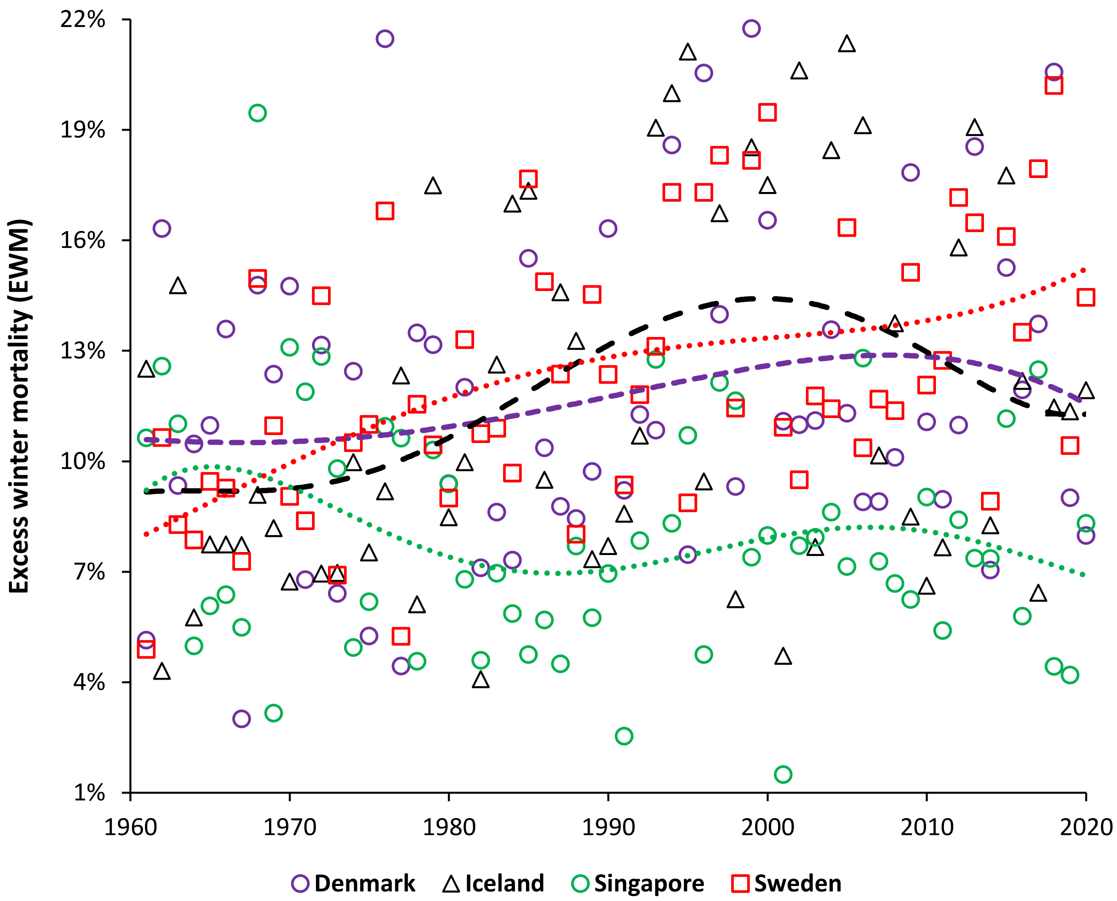
On average the CDC model overestimates flu deaths by around 30% and in the high years (mainly for the old model) gives flu deaths which are incompatible with excess winter deaths (EWD).

After adjusting all years for the growth in total deaths in the USA over the period 1957/58 to 2019/20 there was a median of 1.047 million winter deaths (interquartile range 1.027 – 1.063 million), a median excess winter deaths of 108,500 (IQR 89,800 – 130,700), and a median estimated winter influenza deaths of 30,000 (IQR 20,000 – 43,000). Estimated influenza deaths as a proportion of excess winter deaths had a median of 28% (IQR 20% - 36%). The proportion influenza deaths reached a maximum of 50% of excess winter deaths in the winter of 2001/02, which was not a pandemic year. Hence within these ranges there is ample opportunity for the estimated influenza deaths to "steal" from otherwise unrelated reported cause of death in persons who would otherwise have died in that year.

For the USA, EWM reached a minimum in 2011/12 of 7.6% and the US CDC noted that this winter set a record for the lowest and shortest peak in ILI [79]. Outpatient visits, inpatient admissions and deaths were at baseline levels, i.e, 2011/12 represents the lowest possible influenza year. Other than 3 high years between 1997/98 to 1999/00 (14.2%, 15.7%, 16.8% EWM), EWM reached a maximum of 15.2% during the winter of 2014/15 and 14.2% in 2017/18. Both later years saw high influenza outpatient visits, hospitalizations, and deaths [72,73]. Hence EWM is correctly detecting the severity of each influenza season. The CDC estimated 12,000 influenza deaths in 2011/12 and 52,000 in 2017/18 [79,81].

 doi:10.20944/preprints202202.0153.v1

Figure S2. Trend in EWM for Denmark, Iceland, Singapore, and Sweden over the 60-year period 1960 to 2020



Footnote: The trend for each country is estimated using a 4th or 5th order polynomial. Singapore (closest to the equator) seems to have a slight downward trend while Sweden appears to have the highest trend upward. During the period 1992 to 2010 obesity among Singaporeans aged 60 – 69 was static [132]. Singapore has traditionally been a low influenza vaccination country and vaccination of the elderly has only increased very recently. The trends are dominated by very high year-to-year volatility which is reflected in the high volatility in Figure 6. Since this study ran from 1980 onward it is considered that adjustment for the underlying trends relative to the USA would make only a small impact on the observed volatility in Figure 6. The non-linear trends are consistent with the overall observation of this paper that long-term trends in EWM are regulated by very complex factors and their potential interactions.