Multidisciplinary Insights into Health Care Financial Risk and Hospital Surge Capacity, Part 3:

Outbreaks of a New Type or Kind of Disease Create Unique Risk Patterns and Confounds Traditional Trend Analysis

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Suggested citation: Jones R. Multidisciplinary insights into health care financial risk and hospital surge capacity, Part 3: Outbreaks of a new type or kind of disease create unique risk patterns and confounds traditional trend analysis. **Journal of Health Care Finance**, Winter 2021; http://www.healthfinancejournal.com/~junland/index.php/johcf/index

Abstract

Public health agencies have promoted a single pathogen view of infection which simplifies the message about vaccination. However, research over the past 20 years shows a far more complex set of interactions between multiple pathogens, the nose/throat microbiota, the gut microbiota, immune function, and ageing. Influenza vaccination is effective at reducing General Practitioner (GP) visits for influenza like illness (ILI), for reducing health care staff sickness absence, and in reducing hospital admission due to influenza.

The narrative regarding influenza mortality has been overly simplified and the levels of reported deaths are more correctly due to interactions between a mix of pathogens. There is no such thing as a single pathogen winter. There is mixed evidence that influenza vaccination protects against death from influenza. Influenza vaccination does not seem to diminish excess winter mortality (EWM) – with EWM being the complex outcome of the mix of pathogens interacting with metrological variables. In those likely to die in the next year, while influenza vaccination may protect against death from influenza per se, this merely creates space for another pathogen to trigger final demise. The central problem is that there is no 100% accurate method to determine who is in the last year of life. For this reason, all elderly should be vaccinated. The ratio of male to female deaths and admissions appears to be an indicator of which mix of pathogens predominate each winter.

Amid all the conflicting trends there is room for the action of a new type or kind of infectious disease. This new disease may be triggered by the novel action of a common pathogen or may be the outcome of the multiple interactions between pathogens throughout each year. While outbreaks of this new disease can occur throughout the year they seem to occur more commonly at the interface between winter and spring. These outbreaks cause deaths and medical admissions to suddenly shift to a higher level, stay at the higher level for most commonly 12 months but shorter and longer periods also occur, deaths then shift back to the usual levels while medical admissions seem to sustain a more lingering effect. The combined interaction of the mix of winter infections plus outbreaks of the new disease generate a complex set of cost and capacity challenges. This complex set of challenges is completely ignored in the funding formulas used to distribute resources between different populations.

Issues of population density discussed in Parts 1 and 2 are highly relevant. Steady state thinking and silo mentality is a hindrance when seeking to fully understand issues of financial risk and capacity surges. Part 4 investigates why deaths are serving as a wider proxy for morbidity and how the number of deaths can be used as a tool to determine the optimum size for insurers, HMOs, healthcare commissioners to achieve minimum volatility in costs.

Key Points

- Public health agencies have promoted a simple message about influenza mortality to maintain adherence to seasonal influenza vaccination
- Evidence for a more complex 'story' has been emerging from 1996 onward
- The ratio of female to male deaths each winter shows high variation and looks likely to reflect a complex mix of cold and the exact proportions of pathogens at work each winter
- Influenza and other respiratory pathogens all interact in complex ways including inhibition, co-operation and worsened clinical outcomes
- Respiratory Syncytial Virus (RSV) mortality in the elderly is equal or greater than from influenza
- Amid the ambiguity surrounding winter mortality there is considerable scope for outbreaks of a new type or kind of disease which may be triggered by a single common pathogen or may be the outcome of more complex interactions between pathogens
- Details of these new outbreaks are presented for the USA and the UK
- The net result is that cost and capacity trends are far more complex than have hitherto been appreciated
- Financial and capacity planning will need to employ far more sophisticated methodologies such as wavelet analysis, Fourier transforms, ARIMAs, etc along with the recognition that it is nearness to death rather than age *per se* which is driving the marginal changes in cost and capacity surges

Influenza Key Points

- The very fact that a large proportion of the target population for influenza vaccination have entered the transition called "the last year of life", implies that while influenza vaccination may prevent death from influenza, death will then occur due to another pathogen
- This will, of itself, diminish the vaccine effectiveness rate, which never achieves 100% and much less than this is the elderly. One of many complicating factors
- If the influenza(s) mutate (called antigenic drift) in the interval between vaccine formulation and vaccination, it is possible to get negative vaccine effectiveness, i.e., the unvaccinated can fare better than the vaccinated – fortunately, this does not happen every year and so vaccination is still considered to have a positive balance between risks and rewards
- Likewise, allergic reactions to vaccination are more common than appreciated – once again not serious enough to advise against vaccination
- As always, the population is vaccinated to the point where there is economic benefit
- Vaccination is effective at diminishing GP visits for influenza like illness, and for diminishing respiratory hospital admissions – the effectiveness at diminishing (ultimate) death is less clear – which goes back to the last year of life paradigm
- To avoid the anti-vaxxers seizing on this as 'evidence' that vaccination does not work or is too dangerous Public Health agencies may have been forced to present a simplified public message which glosses over key issues
- Influenza(s) operate in a complex interacting pool of infectious agents, which itself interacts with the nose/throat microbiota and with the gut microbiota
- Simultaneous vaccination against influenza(s) and other common winter pathogens would yield a far greater benefit
- Year-to-year volatility in the outcomes of this infectious cocktail (which now includes COVID-19) is remarkably high, hence the observed cost and capacity surges

Introduction

In the anonymous English poem "Who killed cock robin?" the reader is guided to reach the conclusion that multiple conspirators were involved in the robin's death. Parts 1 and 2 of this series have introduced the biological and medical concepts behind higher-than-expected volatility (risk) in hospital capacity and health care costs which are regulated by inflammatory signals (Jones 2020a,b).

The key points so far in the series are:

1.   Very few people look at volatility because they tend to look at averages and trends in the average.
2.   Population density both should (from common sense) and does (from theory and practice) affect disease transmission.
3.   Air pollution is a central factor since it is associated with population density and promotes chronic inflammation.
4.   Illness and disease is far more multi-pathogen than realised.
5.   Infection in the young may cause discomfort, however, in the elderly can lead to hospitalization and death.

Unusual behaviour in Part 2 regarding length of stay and the gender ratio of admissions tends to invoke cognitive dissonance, i.e., we think we know how healthcare trends behave, and such issues are a threat to this belief system. The evidence is then rationalised away. This is especially true in health policy where the policy maker seeks to simplify the 'how things behave' such that they 'believe' that the push and pull of policy will work in the real world. This can lead to cherry picking of the evidence with consequent policy-based evidence rather than evidence-based policy (Marmot 2004). Indeed, the process of setting health insurance premiums and calculating hospital capacity may be overly simplistic.

This 3rd part of the series is about how outbreaks of a new type or kind of disease may be acting as a confounding factor in the analysis of health trends. This is based on 30 years of research by this author. It has been my experience that Public Health Agencies typically seek to promote influenza as the cause for anomalies in the trends (Jones 2013a, Newton et al 2015), and so we must first commence with an understanding of the principles of influenza spread and resulting morbidity and mortality. Is influenza acting in splendid isolation or are more nuanced forces at work?

Having investigated the more complex issues behind influenza outbreaks and the interactions between pathogens we can then turn to anomalous trends in both deaths and medical admissions and how these may be affecting both capacity pressures and costs.

However, before investigating these matters it is important to re-emphasize the role of nearness to death (NTD) rather than age as a risk factor. This is an important component in forecasting health care costs, setting health insurance premiums and in hospital capacity planning.

Nearness to death (NTD) and age

The literature is full of studies seemingly linking age and risk from a wide variety of factors. Part 2 in this series sought to emphasize the role of nearness to death (NTD) rather than age *per se* in health care admissions, bed occupancy and costs (Jones 2020b). Chronological and biological/physiological age are not the same (Burkle et al 2015). In England & Wales in 1963 the most common age to die was 74 in males and 82 in females. By 2018 this had risen to 86 in males (+12 years) and 88 in females (+6 years). For

deaths at or above the most common age, in 1963 some 38% of males died age 74+, while in 2018 around 28% died 86+. In females 28% died age 82+, but in 2018 some 37% died age 88+ (ONS 2020). The shape of the age profile for NTD is changing with time which will have a knock-on effect against admission rates in various age bands.

Applying rates of hospital admission by age band from 1963 to 2018 would give nonsensical answers (Jones 2021a) simply because the 1963 data set contains far more persons in the last year of life in the age band 74+. In fact, for many years the highest age band in the English Hospital Episode Statistics (HES) aggregated data was age 75+.

Omission of NTD acts to spuriously overestimate the importance of age in health care utilisation (Rabbit et al 2008, Wettstein et al 2019). Persons of identical age therefore experience different risk of dying depending on where they live (Dwyer-Lindgren et al 2016, Boulieri and Blangiardo 2020). Age alone is therefore an unreliable predictor of future resource needs. Unsurprisingly six trajectories of disability have been identified during the last year of life with the course of disability closely tracking the prevalence of hospital admission (Gill et al 2015).

As an example, lower and upper respiratory tract mortality is extremely high in sub-Saharan Africa (GBD collaborators 2017, Shi et al 2020). Abject poverty, contaminated water, malnutrition, and the near absence of health care for many means that despite a relatively young age, some of the population has entered that period of rapid decline called the last year of life. In the West, serious drug and alcohol abuse plus poverty create the same situation.

Hence the repeated observation that highest rates of acute hospital usage occur in the last year of life, almost irrespective of the age at death, and that acute admission especially escalates during the last six months of life. Indeed, the risk of dying within one year for persons hospitalized for any reason is at least 8-times higher (increasing with *younger* age) than in the age-matched non-hospitalized population (Hohn et al 2018). Persons in the last year of life are consistently over-prescribed medications of which 25% are considered 'futile' (Curtin et al 2018).

Frailty is a key measure of nearness to death (Finkel et al 2019), along with the onset of exhaustion (Hajek et al 2018) and is therefore associated with increasing falls and fall related injuries, emergency department revisits and hospitalisations (Travis et al 2001, Shankar et al 2020). Loss of independence is another measure and persons with a higher number of limitations in the activities of daily living (ADLs) have a shorter life expectancy, lower active life expectancy and disability-free life expectancy (Jia and Lubetkin 2020). Pneumonia is highly prevalent in the last months of life (Travis et al 2001). A Frail-safe score gave good prediction of death withing 6 months of admission in the elderly (Lewis et al 2020).

In almost all Western countries there was a baby boom toward the end of World War II which implies that while the birth rate is currently declining, all the baby boomers are about to die in increasing numbers (Office for National Statistics 2018). As it were, NTD has become the new (although old) hot topic in healthcare cost and capacity planning. However, in most western countries there are only around 8 to 11 deaths per 1,000 population (World Bank 2020). Within each country this is highly location specific, however, hospital admissions among those not in the last year of life outweigh those who are. Multi-compartment models using both age and NTD are therefore required (Jones 2021b). An example of such multi-compartment models can be found in the study of prescription costs in Ireland (Moore et al 2017).

Influenza epidemiology revisited

This section is not seeking to dispute the fact that various influenza(s) are serious pathogens which causes considerable morbidity and mortality. Rather it seeks to establish the epidemiological basis of seasonal infectious outbreaks and epidemics, of which influenza(s) are an important part. Far greater detail is given in Appendix 1. They key issue is to elucidate the possible effects on costs.

Not all influenza(s) are the same

Influenzas come in a multiplicity of strains and subtypes (called clades). The influenza A virus protein PB1-F2 has been linked to the pathogenesis of both primary viral and secondary bacterial infections. The study of Alymova et al (2011) gives relevant insight. They observed that Influenza A viruses have historically expressed full-length PB1-F2 proteins with either proinflammatory (e.g., influenza A/Hong Kong/1/1968) or noninflammatory (e.g., influenza A/Wuhan/359/1995) properties. PB1-F2-derived peptides containing the proinflammatory motif caused significant morbidity, mortality, pulmonary inflammation, and increased bacterial infection with *Streptococcus pneumoniae* in mice, manifesting as increased acute lung injury and the presence of proinflammatory cytokines and inflammatory cells in the lungs. Infections of mice with an otherwise isogenic virus engineered to contain this proinflammatory sequence in PB1-F2 demonstrated increased morbidity resulting from primary viral infections and enhanced development of secondary bacterial pneumonia.

The presence of the PB1-F2 noninflammatory (P62, H75, Q79, and S82) sequence in the wild-type virus mediated an antibacterial effect. These suggest that loss of the inflammatory PB1-F2 phenotype that supports bacterial superinfection during adaptation of H3N2 viruses to humans, coupled with acquisition of antibacterial activity, contributes to the relatively diminished frequency of severe infections seen with seasonal H3N2 influenza viruses in recent decades compared to their first two decades of circulation (Alymova et al 2011).

This study nicely takes us back to the central role of inflammation discussed in Part 2. Inflammation is a two-edged sword. In the lung, recruitment of immune effectors is essential to eliminate bacteria and virus-infected cells, but inflammatory cytokines drive changes in the lung conducive to increased pathogen replication. Excessive accumulation of inflammatory cells also hinders lung function, possibly causing death of the host. These changes are highly likely to be age dependent (Aguilera and Lenz 2020).

Inflammation is also a key trigger for dormant pathogens to reactivate. This is especially true for the immune modifying virus cytomegalovirus (CMV). Inflammatory triggers and/or immune suppression make this a serious pathogen to those with immune therapy, infected with other immune modifying pathogens and for those in a weakened state such as burns victims or those in intensive care (Jones 2013b,c, 2014a,b, 2015a,b). CMV plus elevated inflammation is therefore associated with higher mortality (Simanek et al 2011), i.e., pathogens do not operate in splendid isolation.

Influenzas typically need to have a new mutation to be highly virulent. For example, the winter of 1977/78 was atypically mild for a new epidemic strain; the influenza mortality rate was <5 out of 100,000, less than typical seasonal influenza infections of 6 per 100,000. In addition, the 1977 strain appeared to affect only those 26 years of age and younger. There was a simple explanation: the virus was not novel. The 1977 strain was virtually identical to an H1N1 influenza strain that was prevalent in the 1950s but had since dropped out of circulation (Rozo and Gronval 2015).

Table 1: Studies demonstrating considerable interaction between respiratory pathogens and how immunity is maintained

Type of study	Date	Findings	Comments	Authors
Mortality in England and Wales, 1975 to 1990	1996	Over 15 winters the estimated mortality from RSV was 60–80 % greater than due to influenza.	Deaths correlated strongly with influenza A and B reports, temperature, and interactions between aggregated URTI and temperature, and RSV outbreaks and temperature.	Nicholson 1996
Multivariate time-series methodology to examine the impact of RSV and influenza on hospital admissions for bronchiolitis, pneumonia, and COPD.	2006	COPD and pneumonia are not influenced by RSV (P=0·2999 and 0·7725), but RSV does influence bronchiolitis (P=0·0001). Influenza was found to influence COPD, pneumonia, and bronchiolitis (P<0·0001).	Seemingly Respiratory Syncytial Virus (RSV) and influenza can interact via bronchiolitis (which can be misdiagnosed).	Upshur et al 2006
Acute-phase respiratory specimens for VIRAP diagnosis protocol during spring 2006 peak infection season processed in parallel by analysis with Genaco molecular diagnostic panels.	2008	A total of 1,742 specimens were examined for 21 relevant pathogens.	Multiple infections are frequent and indicate complex interactions between pathogens. Statistically relevant association patterns (both positive and negative) were observed. Some interactions are substantiated by prior reports; however, several specific patterns have not been reported previously. There is clinical evidence supporting a hypothesis that these coinfections are medically relevant and that effective treatment for severe respiratory tract infections will increasingly require diagnosis of all involved pathogens, as opposed to single-pathogen reporting.	Brunstein et al 2008
Review of deviations in influenza seasonality	2012	Investigated issues of terminology of both seasonality and influenza illness in terms of past and present-day studies	Seasonal patterns emerge from the interaction of individual factors behaving as coupled resonators. These concepts seem applicable to the complex interactions between winter pathogens and their host as discussed in this table and reflected in the Excess Winter Mortality variances reported here.	Moorthy et al 2012
Nonsocomal Clostridium difficile infection (CDI) following influenza and pneumonia.	2013	CDI infection peaks following the peak in influenza and pneumonia.	Peak pneumonia prevalence preceded peak CDI incidence by 9 weeks (CI 4.6 - 13.7). A 1% increase in pneumonia prevalence was associated with a cumulative effect of 11.3% over a 6-month lag period (relative risk = 1.113, CI: 1.07 - 1.15).	Brown et al 2013

Type of study	Date	Findings	Comments	Authors
In vivo and in vitro studies.	2014	Coinfection with Respiratory syncytial virus (RSV) and *S. Streptococcus pneumoniae* is associated with severe and often fatal pneumonia.	Following incubation with RSV or purified G protein, pneumococci demonstrated a significant increase in the inflammatory response and bacterial adherence to human ciliated epithelial cultures and markedly increased virulence in a pneumonia model in mice.	Smith et al 2014
Community and hospital-based surveillance, 2003 through 2009 in San Luis Potosí State, México. Alternating patterns of Respiratory Syncytial Virus (RSV) and influenza.	2015	The data analyzed consists of community-based and hospital-based Acute Respiratory Infections (ARI) consultations.	The model was able to capture the two main cyclic behavior observed in data: the annual one driven by yearly climatic variability which is exploited by RSV (since the power of its signal is stronger that of influenza) and a second biannual one, exploited by influenza. These two cyclic behaviors are the root of the superinfection (ecological) mechanism for coexistence of both populations.	Velasco-Hernández et al 2015
Review	2016	Pathogen interactions in the mucous layer of the respiratory tract are complex.	Current understanding of respiratory mucus and its interactions with the respiratory pathogens Pseudomonas aeruginosa, respiratory syncytial virus and influenza viruses, with particular focus on influenza virus transmissibility and host-range specificity. The authors propose that respiratory mucus represents an understudied host-restriction factor for influenza virus.	Zanin et al 2016
Patients with COPD aged 40–85 years underwent sputum sampling for detection of bacteria and viruses.	2017	Acute exacerbation of COPD etiology varies with season. Rises in incidence in winter may be driven by increased pathogen presence as well as an interaction between airway infection and effects of viral infection.	The most common bacterial species were non-typeable *Haemophilus influenzae* (NTHi) and *Moraxella catarrhalis*, most common virus was rhinovirus. Logistic regression analyses (culture bacterial detection) showed significant OR for Acute Exacerbation COPD occurrence when *M. catarrhalis* was detected regardless of season (5.09 (95% CI 2.76 to 9.41)). When NTHi was detected, the increased risk of exacerbation was greater in high season (October–March, OR 3.04 (1.80 to 5.13)) than low season (OR 1.22 (0.68 to 2.22)). Bacterial and viral coinfection was more frequent at exacerbation (24.9%) than stable state (8.6%). A significant interaction was detected between NTHi and rhinovirus presence and exacerbation risk (OR 5.18 (1.92 to 13.99); p=0.031).	Wilkinson et al 2017

Type of study	Date	Findings	Comments	Authors
Modelling of interaction between influenza and other pathogens	2018	Models demonstrate potential outcomes from co-infection and competition	Excellent review of studies identifying interactions between influenza and other pathogens.	Opatowski et al 2018
Data for 44,230 cases of respiratory illness tested for 11 respiratory viruses	2019	Strong statistical support for the existence of interactions among respiratory viruses.	Computer simulations showed that very short-lived interferences may explain why common cold infections are less frequent during flu seasons.	Nickbakhsh et al 2019
In vitro and in vivo studies	2019	Literature review plus in vitro and in vivo studies in a mouse model	Direct interaction between influenza on the lung surface upon Gram-positive, *S. pneumoniae* and *S. aureus*, and Gram-negative, *Moraxella catarrhalis* and non-typeable *Haemophilus influenzae*, bacterial colonizers and respiratory tract pathogens.	Rowe et al 2019.
Vaccination of mice and studies using Madin–Darby Canine Kidney (MDCK) monolayers	2019	Influenza immunity is enhanced by co-vaccination with influenza and pneumococcal vaccines	Mucosal co-administration of γ-Flu and γ-PN similarly augments influenza-specific immunity, particularly tissue-resident memory cell responses in the lung. In vitro analysis revealed that *S. pneumoniae* directly interacts with both γ-Flu and with live IAV, facilitating increased uptake by macrophages as well as increased infection of epithelial cells by IAV. These provide explanation for the synergistic pathogenicity of IAV and *S. pneumoniae*, and the prospect to develop better vaccine strategies for both pathogens.	David et al 2019
Role of the nose/throat microbiome on susceptibility to influenza infection	2019	Different bacterial community types were determined by swabs followed by PCR characterisation.	Five bacterial community types were identified. The group 4 was associated with a 70% lower risk of influenza infection. Two oligotypes, *Alloprevotella sp.* and *Prevotella histicola / sp. / veroralis / fusca / scopos / melaninogenica*, were positively associated with enhanced influenza virus infection. One oligotype, *Bacteroides vulgatus* was negatively associated with influenza virus infection.	Lee et al 2019
Retrospective clinical study	2020	Effect of prior infection with influenza on subsequent infection with COVID-19, and effect of coinfection with influenza and COVID-19 on ventilator use and mortality	The risk of testing positive for COVID-19 was *68% lower* among influenza positive cases. The coinfected had a risk of death 5.9-times higher than among those with neither suggesting possible synergistic effects. The odds of ventilator use or death and ICU admission or death was greatest among coinfection patients showing strong evidence of an interaction effect compared to the viruses acting independently.	Stowe et al 2020

Type of study	Date	Findings	Comments	Authors
Competition between COVID-19 and other pathogens	2020	Preliminary findings	COVID-19 looks to have displaced influenza via competition. Rates of certain notifiable infectious diseases look to have dramatically reduced during the COVID-19 outbreak. Competition between viruses or by-product of infection control?	WHO 2020c, Jones 2020d
Regulation of the inflammatory response in the lung				
Population study investigating role of elevated inflammation marker CRP on susceptibility to infection	2016	Individuals with high CRP at baseline were excluded in this prospective general population cohort and cross-sectional general population study	Those with CRP >3 mg/L at baseline had 1.2- and 1.7- times increased risk of infectious disease, compared with individuals with CRP <1 mg/L. Individuals in the highest CRP tertile (compared with the lowest) had an increased risk of bacterial diseases (hazard ratio 1.7, CI 1.6-1.8), but not viral, mycosis, and parasitic diseases. The increased risk was mainly carried by pneumonia, sepsis, and particularly gram-negative infections. None of the CRP genetic combinations examined conferred an increased risk of infectious disease.	Zacho et al 2016
Review and results from a mouse study	2020	The tightly regulated interplay between the gut microbiota and the host enables the establishment and persistence of immune homeostasis	Sublethal infection with influenza alters the activity of gut microbiota, partly from reduced food intake. Fecal transfer shows that influenza-conditioned microbiota compromises lung defenses against pneumococcal infection. Reduced production of acetate affects the bactericidal activity of alveolar macrophages. Mice colonized with the IAV-conditioned microbiota display reduced bacterial loads after acetate treatment. In influenza infection, acetate supplementation reduces local and systemic bacterial loads via a FFAR2-dependent mechanism. This reduces lung pathology and improved survival of double-infected mice. Pharmacological activation FFAR2 during influenza reduces bacterial superinfection. Changes in the gut microbiota following COVID-19 infection have also been observed (Zuo et al 2020).	Sencio et al 2020
Review of interaction between lung microbiota and lung epithelium	2020	The molecular and cellular mechanisms shaping immunity in the lung.	Loss of epithelial integrity after exposure to infection results in inflammation in susceptible individuals and lung disease. This seemingly explains why the elderly more susceptible to respiratory infections and subsequent adverse inflammation.	Invernizzi et al 2020

A study in Spain of confirmed influenza hospital admissions (2010 to 2017) showed that of 8,985 patients those with influenza A(H1N1)pdm09 virus were significantly younger, more frequently had class III obesity, and had a higher risk for pneumonia or acute respiratory distress syndrome than patients infected with influenza A(H3N2) or B. Hospitalized patients with influenza A(H1N1)pdm09 also had a higher risk for intensive care unit admission and/or death, after adjusting for other factors (Delgado-Sanez et al 2020).

It is also known that influenza(s) kill people in three different ways. Based on autopsy studies it is estimated about one-third of people who die from flu-related causes die because the virus overwhelms the immune system; another third die from the immune response to secondary bacterial infections which take advantage of a taxed immune system, usually in the lungs; and the remaining third die due to the failure of one or more other organs induced by inflammation (Jabr F 2017). Refer to the study relating to PB1F2 inflammatory and noninflammatory proteins above. Such dysregulated inflammation is also a characteristic of severe COVID-19 disease (Gong et al 2020).

Other common fatal respiratory infections

While influenza causes a significant mortality burden there are other pathogens with the same or greater mortality. Respiratory Syncytial Virus (RSV) is a serious pathogen in the young and elderly. In one study of infants with severe lower respiratory tract infection (LRTI) some 66% were infected with RSV. Some 6% experienced respiratory failure or died with RSV. RSV LRTI accounted for 57% of fatal LRTI in infants (Geoghegan et al 2017).

Acute respiratory infection (ARI), including pneumonia, constitutes a substantial disease burden in older adults ≥65 years. The Global Burden of Disease (GBS), Injuries, and Risk Factors Study 2015 estimated that lower respiratory infections have caused around 1.2 million deaths and 13.5 million disability-adjusted life-years in older adults. RSV is one of the important viral pathogens identified in older adults with ARI and is increasingly recognized as a cause of illness in high-risk adults, including those with chronic lung and heart disease. RSV infection occurs in 3%–7% of healthy older adults and in 4%–10% of high-risk adults. The hospitalization rate for RSV-ARI increases with age (Shi et al 2020).

The Global Burden of Disease study 2015 estimated that for lower respiratory tract infections in older adults for every 100 influenza deaths there were 72 RSV deaths and 770 pneumococcal pneumonia deaths (GBD collaborators 2017).

Influenza(s) cannot act in isolation

The simple message given to the public to date regarding influenza is misleading. Table 1 gives an overview of studies conducted ***since 1996*** which show that influenza(s) act in cooperation with other pathogens, the nose/throat microbiota, and the digestive microbiota. To say that influenza (alone) has killed someone is misleading. The poem "Who killed cock robin?" is a good allegory to this fact.

Especially note the 2008 study of Brunstein et al (2008) which detailed previously unknown interactions between pathogens. The order in which a person is infected by different pathogens is also highlighted in Table 1. Another example is varying clinical severity due to the order of infection with Dengue and Zika viruses, and indeed with a different serotype of the same virus (Katzelnick et al 2020). Prior infection with tuberculosis increased influenza mortality in the 1918 pandemic (Noymer and Garenne 2000). This is called heterologous immunity and is far wider than just dengue and Zika (Kim and Shin 2019).

In conclusion, influenza(s) cannot and does not operate in splendid isolation, and indeed, neither does any other pathogen. A silo mentality focus on influenza is creating misleading expectations regarding the efficacy of influenza vaccination to tackle a far more complex problem. See Appendix 1 for wider discussion.

Influenza(s), other infections, and spatial granularity

The messages about influenza can give the impression that influenza is more universal than it ever could be. All infectious outbreaks show considerable spatiotemporal granularity (Balkan et al 2009, Fry et al 2015, Chanlekha et al 2010, Elson et al 2020). Influenza is no exception (Skog et al 2014, Yang et al 2016, Charu et al 2017, Pei et al 2018). Spatiotemporal granularity means that the infection is worse in some areas than others, and that timing differences are also present. Granularity arises from the sum of chance events in the human introduction of different strains of influenza(s) and other pathogens into different communities and regions (Li et al 2020).

Figure 1: COVID-19 and spatial granularity. Calculated excess mortality in US states during a 12-month period ending June 2020 when COVID-19 was circulating compared to the same period ending June 2019 (National Centre for Health Statistics 2020).
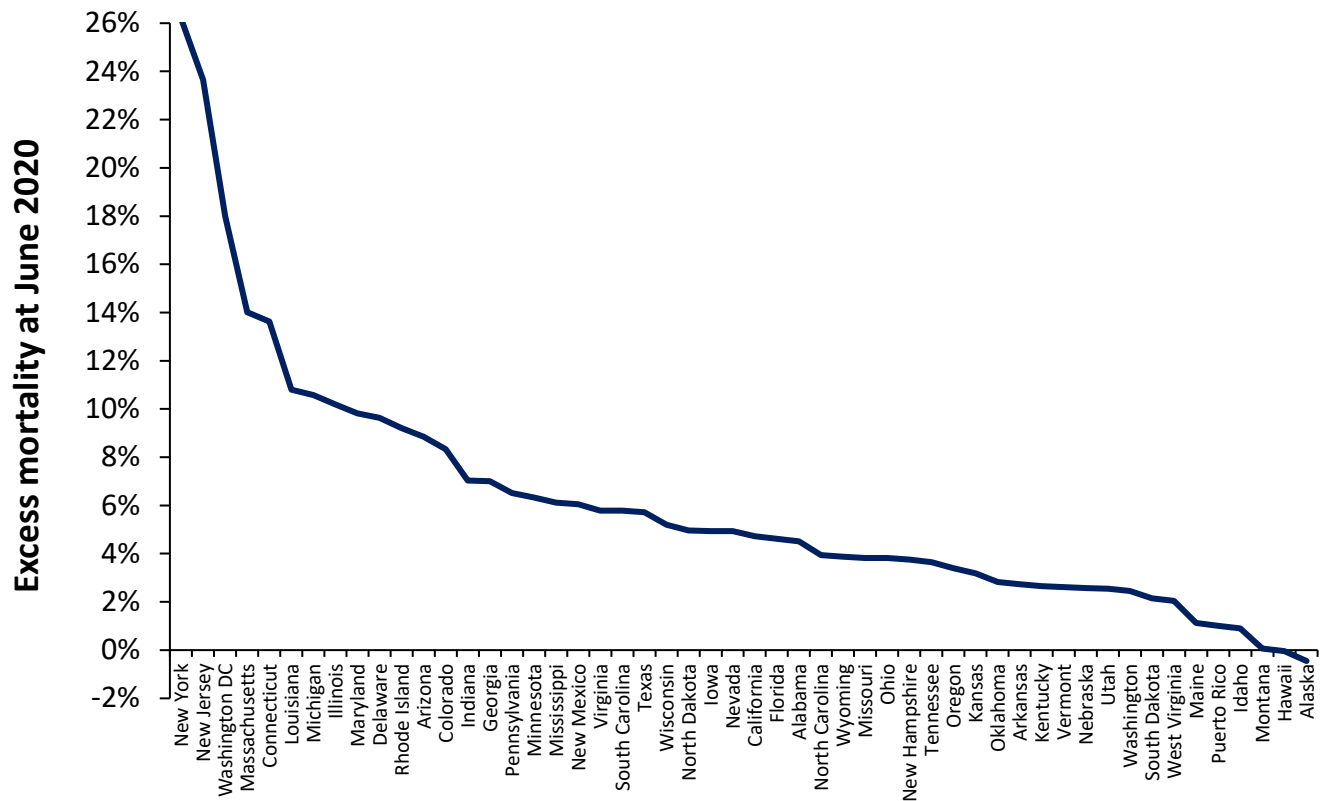
In a study of mortality risk due to heat and cold the highest risk groups were female sex, age 75+, and cities with higher urbanization rates (Chen et al 2018). All three and especially the latter confirms the observations made in Parts 1 and 2 of this series regarding transmission of infectious agents at high population density. Issues regarding cold are discussed in more detail in the section dealing with Excess Winter Mortality.

Table 1: Maximum value of the rolling EWM calculation in US states, and the month and year when this occurred. Winter 2007/08 to 2019/20 (National Centre for Health Statistics 2020)

When	EWM	State	When	EWM	State
Mar-08	15.1%	Michigan	Jan-15	15.3%	Alaska
Mar-08	15.6%	West Virginia	Feb-15	15.4%	New Hampshire
Mar-08	15.9%	Wisconsin	Mar-15	14.8%	Tennessee
Mar-08	16.2%	Connecticut	Mar-15	15.2%	USA
Mar-08	16.6%	Minnesota	Mar-15	15.9%	South Carolina
Mar-08	17.1%	Nevada	Mar-15	16.4%	Georgia
Mar-08	17.2%	Indiana	Mar-15	16.5%	Virginia
Mar-08	17.2%	Illinois	Mar-15	17.0%	Kentucky
Mar-08	17.5%	Ohio	Mar-15	17.1%	Alabama
Mar-08	17.7%	Arkansas	Mar-15	17.2%	Maryland
Mar-08	18.7%	Kansas	Mar-15	17.4%	North Carolina
Mar-08	18.8%	North Dakota	Mar-15	18.9%	Nebraska
Mar-08	18.9%	Oklahoma	Mar-15	18.9%	Delaware
Mar-08	19.4%	South Dakota	Mar-15	19.3%	Rhode Island
Mar-08	19.6%	New Mexico	Apr-15	15.6%	Vermont
Mar-08	19.7%	Iowa	Apr-15	19.6%	Massachusetts
Mar-08	22.3%	Missouri	Mar-17	12.9%	Idaho
Apr-08	15.6%	Colorado	Mar-17	14.9%	Montana
Mar-09	12.3%	Hawaii	Mar-17	15.1%	Oregon
Jan-13	14.6%	Wyoming	Mar-17	18.3%	Washington
Mar-13	13.6%	Utah	Jan-18	14.6%	Louisiana
Mar-13	17.7%	Pennsylvania	Mar-18	12.1%	Florida
Mar-13	21.2%	Maine	Mar-18	16.0%	Mississippi
			Mar-18	16.6%	Texas
			Mar-18	17.4%	Arizona
			Mar-18	18.7%	California
			Jan-20	17.6%	Washington DC
			Mar-20	17.1%	New Jersey
			Mar-20	20.4%	New York

Figure 1 gives an example of spatiotemporal granularity in the spread of COVID-19 across the USA. Spatiotemporal spread was studied in detail in Part 1 using direct counts of COVID-19 attributed deaths. Figure 1 avoids the issues surrounding missed COVID-19 diagnosis in the early parts of the epidemic and the ambiguity of assigning the direct cause of death. It does this by looking at excess all-cause mortality. Hence the figure of 26% excess mortality for New York is the number of deaths in July 2019 to June 2020 (with COVID-19 present) compared with the number of deaths in July 2018 to June 2019 (without COVID-19). Alaska shows a slight negative excess mortality which may be due to small number uncertainty. One standard deviation of Poisson variation for Alaska is ± 0.4%. States to the far right of Figure 1 are those identified in Part 1 where COVID-19 infection was low by June of 2020 and contained only sporadic instances of COVID-19 reported deaths at county level.

Table 1 also addresses the issue of spatiotemporal granularity by looking at the date of the highest value of the rolling Excess Winter Mortality (EWM) calculation in each US state. EWM is described in more detail in the next section. Two clear clusters are evident in the winter of 2007/08 and that of 2014/15. Even within those clusters the EWM calculation reached its peak mainly in the four months ending March 2008 but in April 2008 in Colorado. But across January, February, March and April in 2015. January dates also appear in the winters of 2012/13 2017/18 and 2019/20.

Table 2: Maximum value of the rolling EWM calculation in Scottish and Northern Ireland local government areas, and the month and year when this occurred. Winter 2001/02 to 2019/20

When	EWM	Location	When	EWM	Location
Feb-03	60%	Orkney Islands	Mar-16	34%	East Dunbartonshire
Jan-04	37%	Ards	Feb-17	35%	Limavady
Jan-04	68%	Moyle	Feb-17	40%	Craigavon
Mar-05	30%	Midlothian	Mar-17	25%	Highland
Apr-06	55%	Shetland Islands	Mar-17	46%	Antrim
Apr-07	38%	Castlereagh	Mar-17	47%	Coleraine
Feb-09	43%	Fermanagh	Mar-17	55%	Omagh
Mar-09	39%	Clackmannanshire	Jan-18	28%	East Lothian
Mar-10	38%	Newry & Mourne	Jan-18	30%	North Lanarkshire
Apr-10	31%	Down	Jan-18	32%	North Ayrshire
Mar-12	38%	Armagh	Jan-18	34%	Argyll and Bute
Mar-13	60%	Banbridge	Jan-18	35%	West Lothian
Apr-13	49%	Ballymena	Jan-18	35%	Eilean Siar
Jan-15	33%	Derry	Jan-18	46%	Stirling
Feb-15	61%	Ballymoney	Feb-18	28%	Edinburgh City
Mar-15	24%	Glasgow City	Feb-18	31%	Renfrewshire
Mar-15	**27%**	**Scotland**	Feb-18	34%	East Ayrshire
Mar-15	28%	Aberdeenshire	Feb-18	47%	Newtownabbey
Mar-15	31%	South Lanarkshire	**Mar-18**	**28%**	**Northern Ireland**
Mar-15	33%	East Renfrewshire	Mar-18	28%	Belfast
Mar-15	34%	Dundee City	Mar-18	29%	Angus
Mar-15	37%	Perth and Kinross	Mar-18	30%	Dumfries + Galloway
Mar-15	39%	Moray	Mar-18	33%	Falkirk
Mar-15	40%	Lisburn	Mar-18	35%	South Ayrshire
Apr-15	26%	Fife	Mar-18	36%	Aberdeen City
Apr-15	32%	Inverclyde	Mar-18	39%	West Dunbartonshire
Apr-15	53%	Carrickfergus	Mar-18	39%	Scottish Borders
Apr-15	87%	Cookstown	Mar-18	44%	North Down
			Mar-18	47%	Larne
			Apr-18	39%	Dungannon
			Apr-18	54%	Magherafelt
			Mar-19	57%	Strabane

The cluster in the winter of 2007/08 is due to an influenza outbreak and an extraordinarily strong La Nina event which mainly affected the West (Pacific) coast of the US with temperature and precipitation anomalies (L'Heureux 2008). Higher than usual deaths were reported by the CDC and influenza activity peaked in February. The CDC also reported that "the majority (66%) of influenza A (H1N1) viruses were

similar to the vaccine strain. However, 77% of influenza A (H3N2) and 98% of B viruses sent to CDC for further testing were not optimally matched to the 2007-2008 influenza vaccine strains" (CDC 2008). This poor matching between the vaccine and the circulating A (H3N2) and B strains probably accounted for the higher than usual deaths. See Appendix 1 for a wider discussion of influenza vaccine effectiveness.

The cluster in 2015 is far more nuanced and appears to involve an unusually synchronised outbreak of the proposed new type or kind of disease. The winter of 2014/15 also involved unusually high temperatures on the US west (Pacific) coast and unusually low temperatures on the East (Atlantic) coast (Freedman 2015). The 20.4% EWM for New York in March-20 is probably contaminated with unrecognized COVID-19 deaths.

By way of international comparison, Table 2 gives similar analysis for local government areas (LGA) in Scotland and Northern Ireland. As can be seen there is no cluster for the winter of 2007/08, however, there is a common cluster for the winter of 2014/15, plus a large cluster in the winter of 2017/18. The total for Scotland falls in the winter 2014/15 cluster while that for Northern Ireland in 2017/18. As in the US the maximum for the rolling EWM calculation can fall between January to April with the 2017/18 cluster having an unusually large number of January and February occurrences (mostly from Scotland). Due to larger Poisson randomness associated with smaller numbers the maximum EWM in Scotland and Northern Ireland LGAs can be higher than for the larger US states. Although the UK is well recognised for its above average values of EWM – reasons unknown. Appendix 2 discusses the winter of 2014/15 in more detail.

From a financial and capacity risk perspective, the spatiotemporal effects of infectious outbreaks should be clear. Given the unknown implications of many infectious events one could imagine the situation where hospital managers in Alaska, Hawaii and Montana (Figure 1) are muttering, "what is wrong with the rest of you, there are no cost and capacity issues here". Not so amusing as it sounds since NHS managers in the UK are consistently blamed for all unexplained increases in cost and capacity variances as illustrated in Table 2.

Hence, when outbreaks of a potential new type or kind of disease are discussed, evidence of spatiotemporal granularity must be consistent with that known to be associated with infectious outbreaks in general.

Gender differences in deaths

One study has demonstrated that the pattern of gender differences (male:female) for influenza and other acute upper respiratory infections from 1998/99 to 2002/03 varied from 1.05:1 to 2.0:1 between English local authorities (SEPHO 2005). This ratio seemed to increase from South (Cornwall and Devon) to North. Location seems to play a role.

Figure 2 explores the trend in the proportion of total deaths and the percentage point difference between the genders for respiratory conditions (mainly infectious) plus infectious agents using ICD-10 chapters A, B and J. As can be seen there is an initial trend upward for these conditions as a proportion of total deaths (all-cause mortality), although the gender gap (dashed line) peaked in 2005. In 2012, the revised version of ICD-10 was implemented which shifted some deaths into Dementia as a primary cause although this did not seem to make a huge change in the trends. Subtle shifts in the gender ratio are occurring over time.

Figure 2: Proportion of total deaths due to respiratory conditions plus infections (ICD-10 chapters A, B, J) for male and females and the percentage point difference between the two
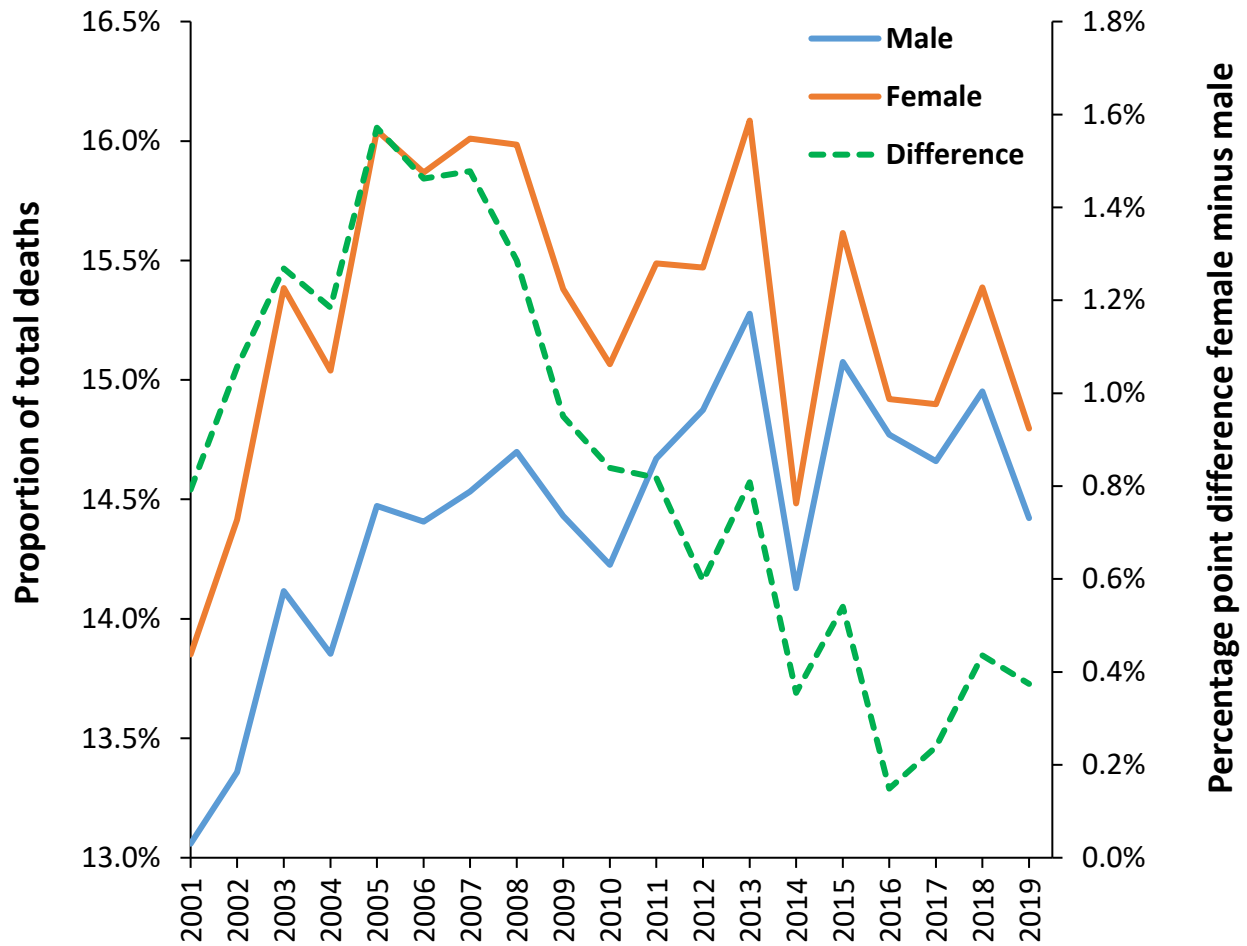
The reader may wonder why there is no age standardized analysis in this series. The simple answer is that health care costs and capacity arise from the absolute numbers of admissions and deaths, not from age standardized rates. A role for Excess Winter Mortality (EWM) will now be explored.

Excess Winter Mortality (EWM)

Given the fact that deaths from a variety of conditions (especially cardiovascular and respiratory) peak in the winter (Rau et al 2018) it is useful to use a measure called Excess Winter Mortality (EWM) to study the combined effects of infectious agents in combination with associated metrological conditions. There are known metabolic and hormonal differences in the response to cold between men and women (Mengel et al 2020) and the neuroendocrine and immune response in men is greater than in women (Solianik et al 2014). The higher immune response in men gives a possible clue to the generally higher female EWM.

The EWM calculation usually compares the four winter months (December to March) with the eight non-winter months. I have modified the EWM calculation to give a rolling calculation (Jones 2020c) which allows a more flexible calculation of when the peak in EWM occurred and an evaluation of the shape of

the rolling EWM curve. Figure A1.1 (Appendix 1) shows the maximum EWM in England and Wales for each winter from 1949/50 to 2019/20. The EWM calculation in 2019/20 ceased at March-20 to avoid contamination with the COVID-19 outbreak in April of that year.

The 1962/63 peak in England & Wales (Appendix 1, Figure A1.1) is illustrative of the somewhat unusual conditions in that winter. Snow covered most of the UK for over two months from just before Christmas through to 4th March, and temperatures remained more than 5 C below average (Homewood 2014). This was at a time when thermal housing standards in the UK were low and most homes were heated by coal fires, leading to pollution (Scott et al 1964).

Figure 3: A variable year to year gender gap in the EWM in England and Wales
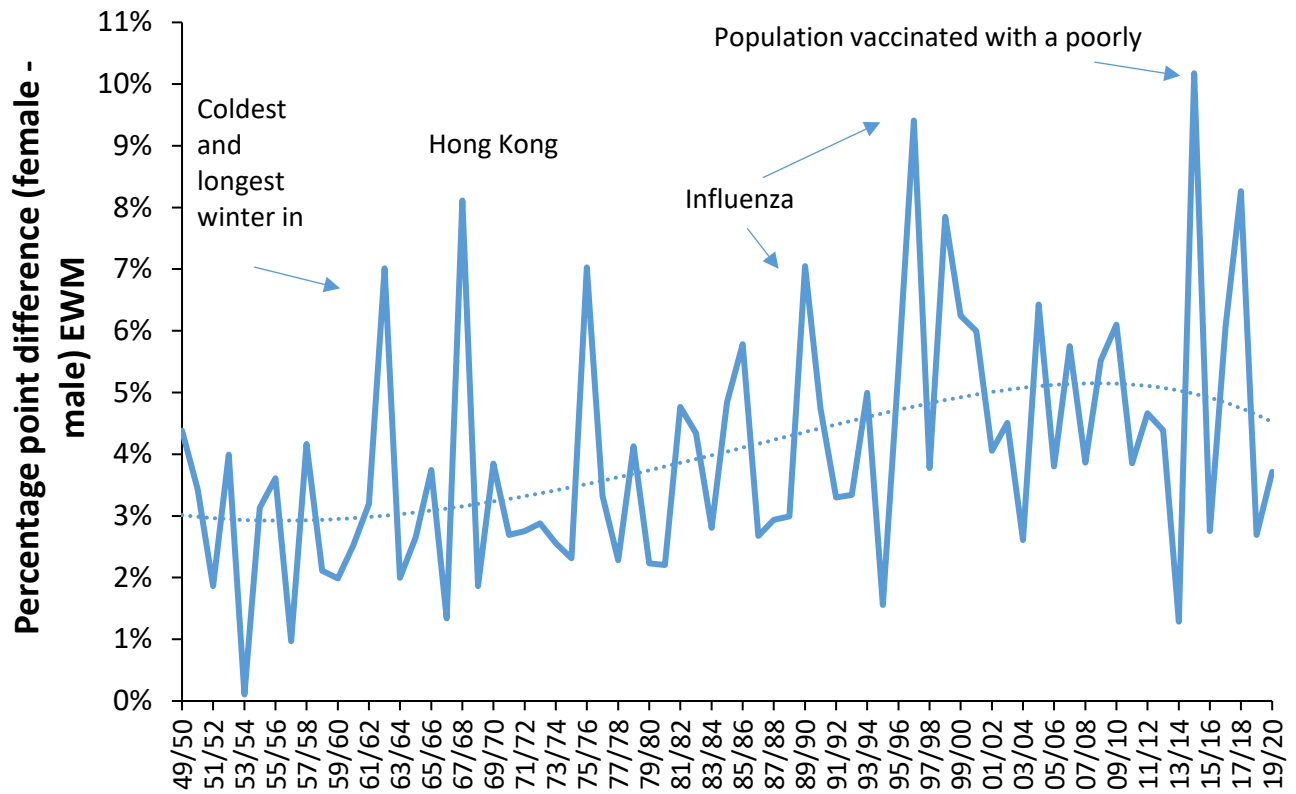
Figure 3 explores this gap between male and female deaths in greater detail. As can be seen the gap between male and female EWM is highly variable. Known influenza years are associated with higher female deaths. The reason for the underlying trend (dotted line) is unknown. Equally mysterious are the winters when the gap between male and female is exceptionally low, i.e., 1953/54, 1994/95 and 2013/14.

The fact that the 1962/63 peak is not far higher is largely because low temperature is generally not as great a source of excess deaths compared to high temperatures (Ekamper et al 2009), however, the prolonged duration of cold would have meant that many elderly people would have died from pneumonia. There were 10.1% excess female deaths aged 75+ compared to 5.4% excess male deaths (authors calculation). Part 2 has already given evidence for similar volatility in different specialties and conditions. A general excess of female EWM has also been noted in New Zealand (Davie et al 2007).

Bacterial and viral pneumonia in English hospital admissions were tested for a relationship with the difference between female and male EWM. This was done using the English Hospital Statistics (HES) data tabulations. Prior to 2008/09 insufficient data was coded to enable differentiation, however, Figure 3 shows a potential relationship between viral pneumonia (which includes influenza) and the year-to-year change in the difference between female and male EWM. As can be seen a change to higher excess female EWM is associated with a change to a higher proportion of female admissions.

Figure 4: Relationship between the year-on-year change in the gender ratio associated with EWM and the gender ratio associated with viral lung infection
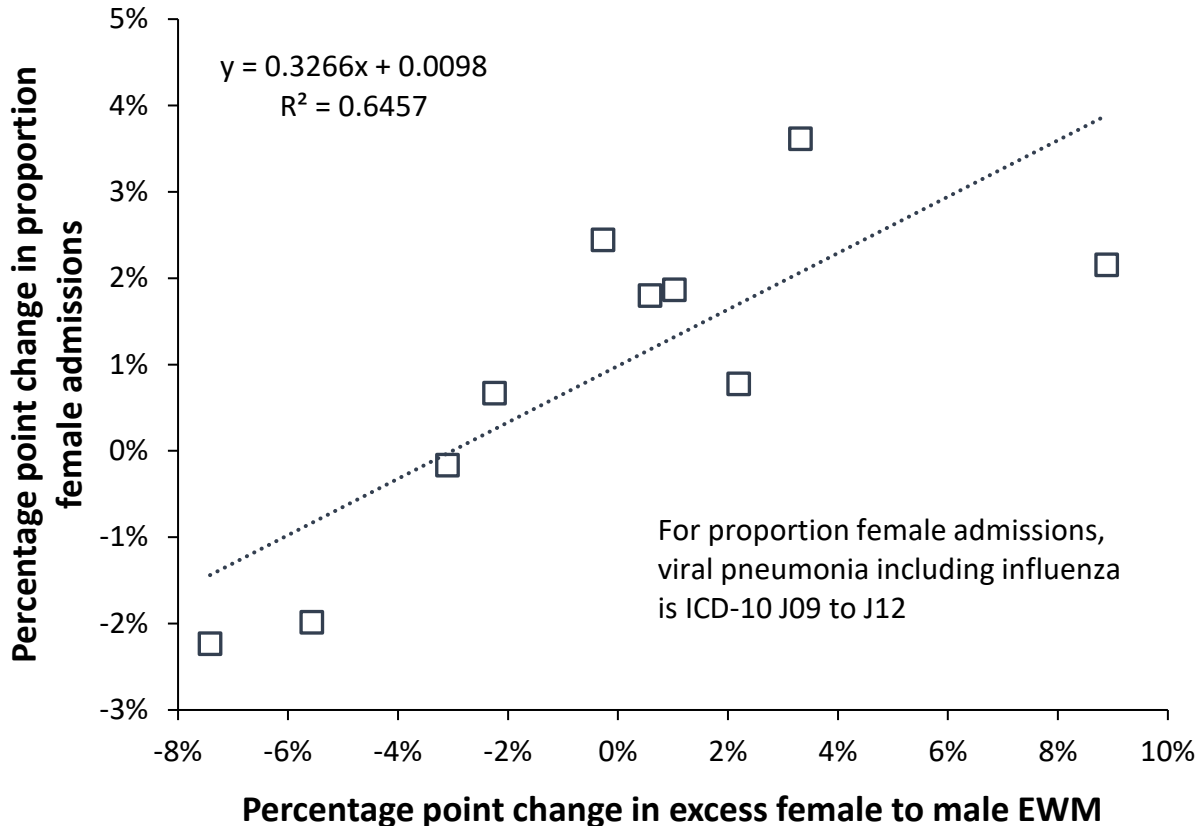
The gender ratio for deaths (as EWM) is more sensitive than the change in proportion female admissions. Attempting to force the regression through the origin gives a parallel line below the trend shown in Figure 4.

By way of contrast, bacterial pneumonia shows no correlation. Both bacterial and viral pneumonia admissions do however show a slight trend upward in the gender ratio over time which adds around 0.5% per annum to the proportion female viral pneumonia ratio (49.5% rising to 54.5%, 2008/09 to 2019/20), and around 0.2% per annum to that for bacterial pneumonia (44.5% rising to 47%).

It is therefore proposed that the gap between male and female EWM is a complex mix of temperature and viral infections (Influenza, RSV, etc). This confirms the importance of the trends in gender ratio for admissions reported in Part 2.

Regional variation in EWM

If a series of largely undocumented infectious events were to be travelling throughout the UK, then there should be regional patterns behind the rolling EWM calculation (Figure 5).

Figure 5: The UK value and the standard deviation (STDEV) for a rolling weekly EWM calculation (17 vs 35 weeks) for the nine regions of England, plus Northern Ireland, Scotland, and Wales
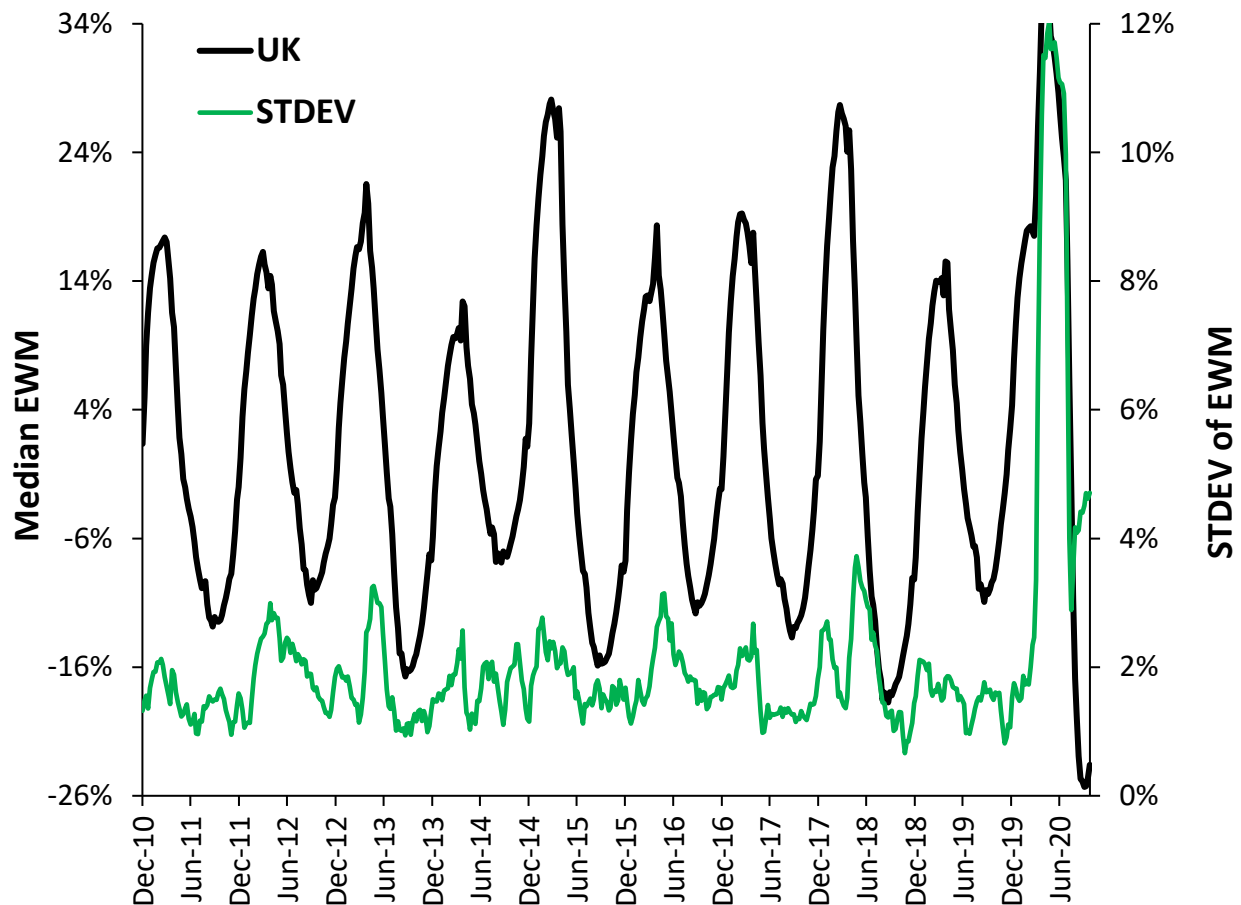
On this occasion, weekly data has been used to construct a rolling 17-week versus 35-week EWM calculation. A each point the EWM for the UK is calculated as is the associated standard deviation across the regions. The nine English regions are roughly similar size to the other three countries in the Union. London is a single region. Especially note that the outbreak of COVID-19 at around the week ending 20th March sets a precedent for how an infectious outbreak may affect the shape of the EWM line plus alter the STDEV across the regions. The spread of COVID-19 was highly regional depending on the number of large cities in each region and associated population density. Hence, the shape of a usual EWM pattern is significantly interrupted at the week ending 3rd April as the epidemic sweeps across the UK. The large STDEV between regions illustrates both the timing and magnitude of local outbreaks (spatiotemporal granularity) across each region. After the peak of the COVID-19 epidemic the EWM calculation shows a compensating dip since thousands of deaths had been moved forward in time. A compensating dip is also

seen after the winters of 2014/15 and 2017/18. The dip after the winters of 2013/14 and 2018/19 is less than usual as fewer deaths have occurred over the winter and then occur in the following summer. The inflection in the STDEV line in Figure 5 on the 14th of August reflects the point when local infections and deaths begin to rise again after a national lockdown was relaxed. Given this basis, then note the shape and size of various other infectious events, some of which can occur in the summer months. The point of minimum STDEV between the regions (0.66%) occurs at the 17-week period ending 23rd November 2018. Prior to COVID-19 the point of maximum STDEV (3.72%) occurs on 1st June 2018. To suggest that influenza is the sole cause of all this diversity is a serious exaggeration.

Note that influenza activity and mortality drop to a 100 year low in early 2000 (WHO 2020, Jones 2020), counterintuitively the proportion of total deaths due to lung disease and other infections and the excess of female deaths then climbs to a maximum.

Having established the principle that winter mortality is far more nuanced that just influenza, and that amid all the uncertainty around influenza mortality, there is room for alternate explanations for some of the mortality. We can now discuss if any evidence exists for outbreaks of a new type or kind of infectious disease.

A new type or kind of infectious outbreak

In the early 1990's I commenced working at the Royal Berkshire and Battle Hospitals NHS Trust as Assistant Director of Information. All was going well until precisely in the middle of March 1993 medical admissions at the hospital suddenly shifted up by 15%. The West Berkshire Health Authority accused the hospital of admitting more patients to get more income. This was entirely untrue; in fact, nothing had changed other than the sudden appearance of medical patients. Appendix 3 discusses if these shift-up events are as sudden as seemingly implied by this paragraph. The simple answer is no.

What the hospital or the Health Authority did not know was that a similar happening had swept across the entire UK. Doctors were mystified and wrote letter to the editor of the British Medical Journal as they attempted to grapple with possible reasons. I was asked to investigate and started to notice curious male/female differences and even diagnosis and age specificity. I concluded that the only explanation was a new type or kind of infectious disease. These sudden changes in medical admissions and deaths have continued at regular intervals since 1993 and have been covered by ongoing reviews (Jones 2010a-c, 2013a-c, 2014, 2015a-c, 2016a-d, 2017, Jones and Goldeck 2014).

The key features of each outbreak are:

1. A simultaneous jump in both deaths and volume of total medical admissions.
2. The jump in deaths lags that for admissions by around one to two months, i.e., illness precedes ultimate death.
3. However, some medical conditions are unaffected, and others decrease
4. Males and females appear to act as separate compartments and can initiate shift-up either before or after each other.
5. Attendances at the emergency department jump.
6. Sickness absence among NHS workers jumps.
7. The gender ratio at birth shows a wobble some nine months after the event.
8. General practitioner referrals for an outpatient appointment also jump.
9. NHS finances suddenly shift into overspend.

The order of events seems to be, first the female foetus is spontaneously aborted leading to a higher male gender ratio at birth, medical admissions increase, staff sickness absence increases and finally deaths increase.

Alas, since no one has an explanation these events just get ignored (cognitive dissonance), even though they show all the spatiotemporal patterns expected of an infectious event and occur more widely around the world including the USA. Politicians in the UK seem to take the view that this is just another example that the NHS is inefficient, and therefore needs more policy intervention to correct these perceived problems. A full list of studies is available via the link in the suggested reading at the end of this study.

Having establish that something of a highly peculiar nature keeps occurring I will now demonstrate how these events disturb the trends in deaths. The effect on hospital admissions has been characterised in several detailed studies (see suggested reading at the end of the study). This section will commence by a demonstration of curious shifts in the profile of EWM.

Figure 6 takes the rolling EWM calculation and applies it to a time series of daily deaths in England and Wales between 1989 and 2000. Data was obtained from the Office of National Statistics by special request. This period has been chosen simply because it represents a period over which deaths were relatively constant, and beyond 2000 deaths experience a decline due mainly to improvements in life expectancy.

Figure 6: A rolling EWM calculation (122 days versus 243 days) using daily deaths in England and Wales, 1989 to 2000
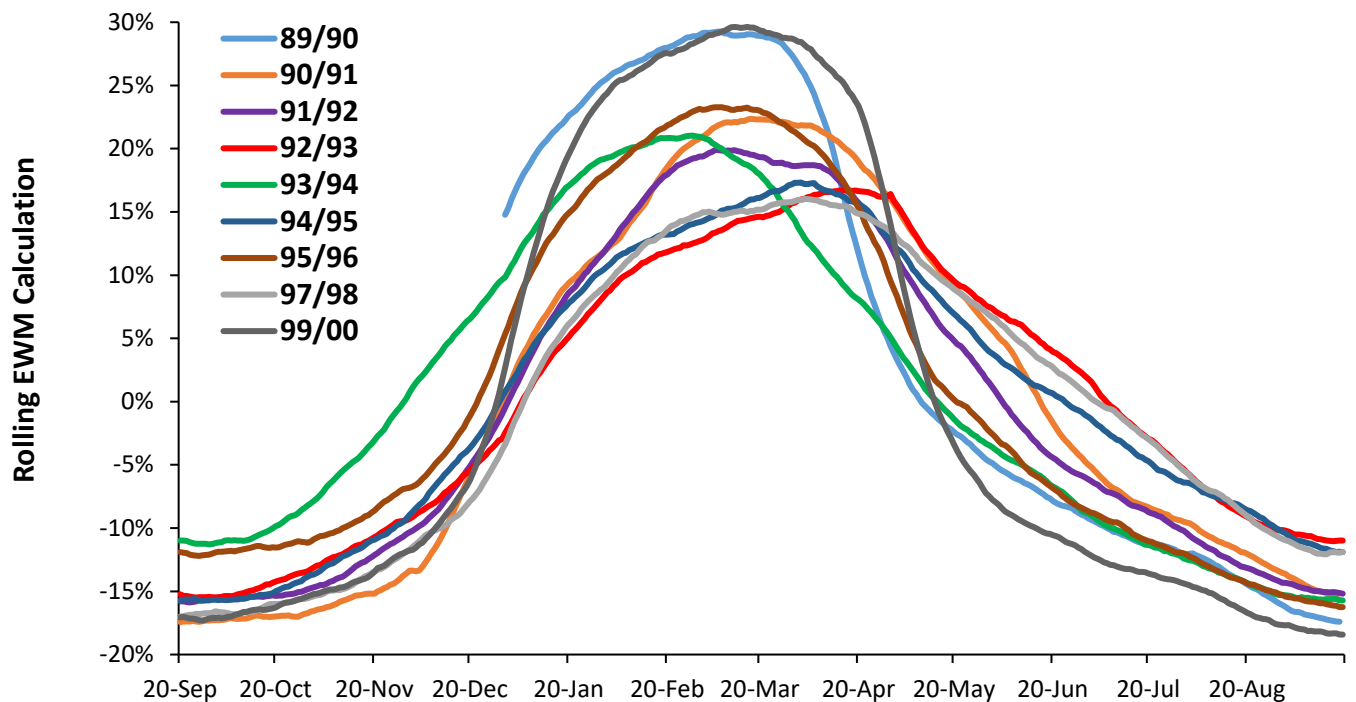

Rather than four months versus eight months the daily calculation uses 122 days versus 243 days. The shape of the resulting pattern is roughly similar but on some years the peak is wider than others, while differences in the shape (skewing) around the maximum can also be discerned. As can be seen in Figure

6, the point of excess mortality is variable and occurs at the 122 days ending in late February for 1993/94 through to April for 1992/93. The Office for National Statistics have concluded that EWM is not strongly related to average winter temperature (ONS ???) which leaves the timing and extent of infectious outbreaks to explain the observed variability. Clearly, influenza will be involved in some of the higher peaks, however, as pointed out earlier even influenza does not act in splendid isolation.

The 1998/99 and 1999/00 patterns represent the last large influenza outbreaks at the close of the 20th Century (Whiting et al 1999). The shape across the girth is narrow. The 1989/90 profile was due to another large influenza outbreak which commenced earlier than the winter of 1999/00.

Especially note the 1992/93 and 1993/94 patterns. The 1992/93 pattern is reasonably average up to the beginning of March 1993 when the curve is suddenly pushed upward and to the right. This corresponds to the large increase in medical admissions observed at the hospital in Berkshire in mid-March of 1993. What could have caused this unique pattern? Appendix 3 gives an example of how a 5% shift-up in deaths will affect EWM depending on the time the shift-up commences and that a shift-up can indeed push the maximum EWM to the right.

Figure 7: Month in which deaths underwent shift-up during spread of a new type or kind of disease among US states in 20913 and 2014
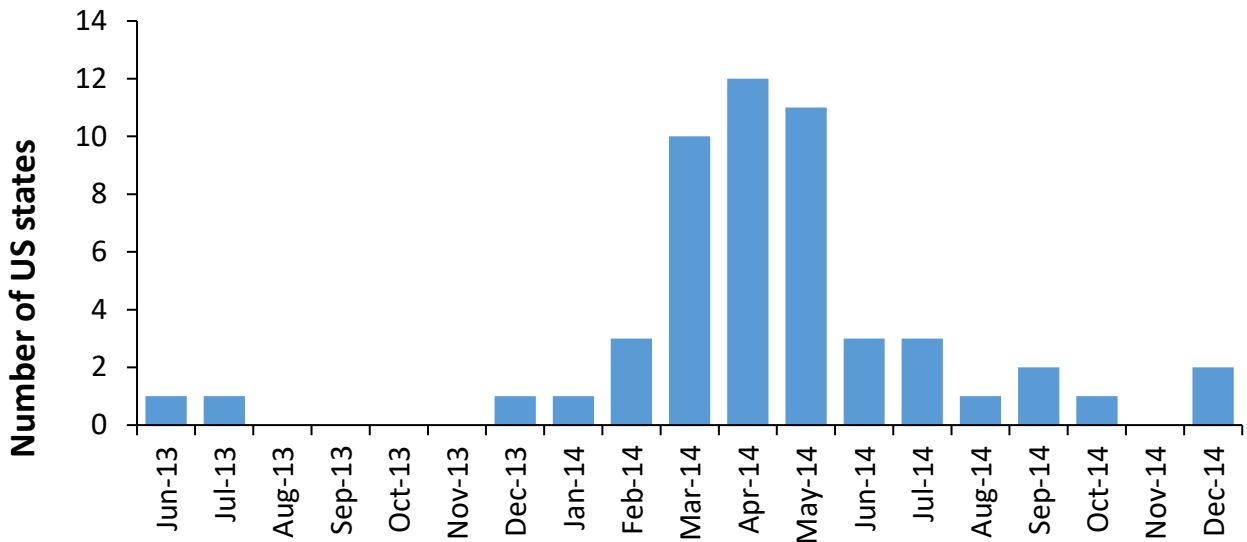
Spread of the new disease among US states in 2014

The spread of a potential new disease will now be illustrated using monthly data from the USA for an outbreak in 2014 and data from the UK for an outbreak in 2019 prior to the arrival of COVID-19. Recall that the new disease causes a sudden shift-up in both admissions and deaths which endures over time.

This shift-up is best characterised using a rolling 12-month total of deaths where a sudden (step-like) shift-up in the level of deaths shows up as a ramp in the rolling 12-month total. An influenza (spike) event does not create a ramp in the rolling 12-month total but instead creates a tabletop shaped feature. Figure 7 determines at which month this sudden shift-up in deaths occurs for US states. As can be seen there is

sporadic initiation in four states prior to February 2014. Some 33 states initiate this novel outbreak during March to May and the remainder initiate through to December of 2014.

Figure 8: Effect of size (as number of deaths) on the apparent magnitude of the shift-up in deaths during the 2013-2014 spread of the new type or kind of disease
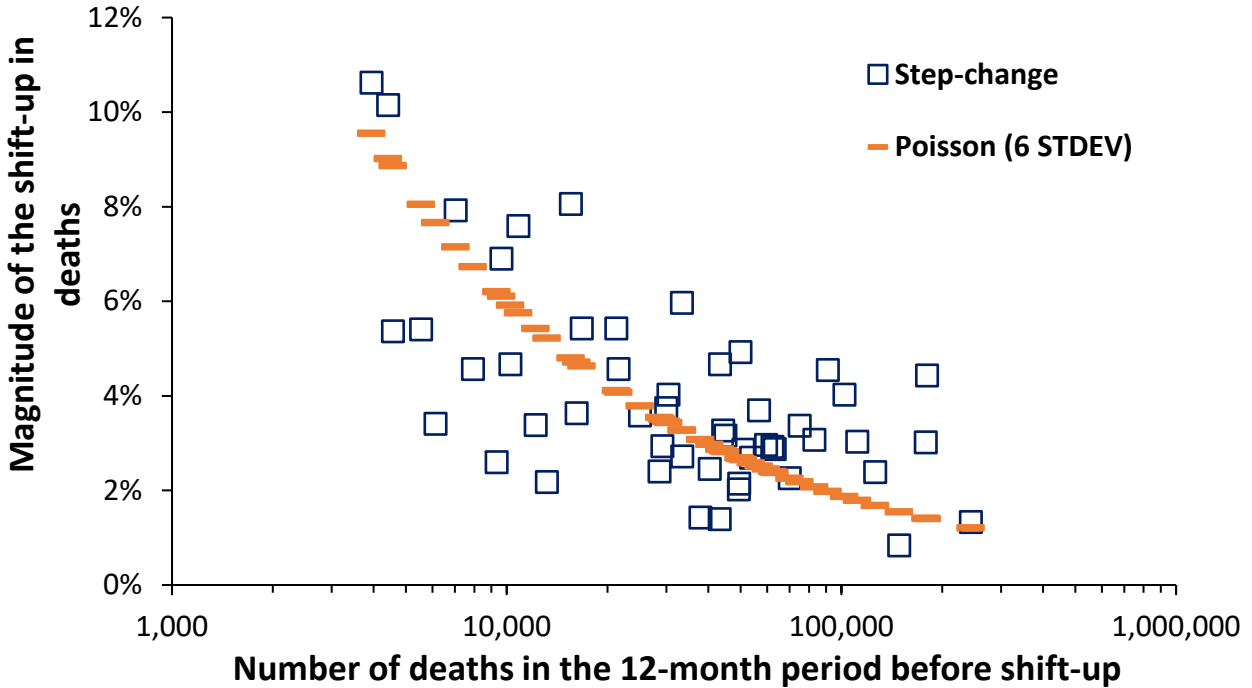

Figure 9: Effect of initiation date of the shift-up in deaths on the size-adjusted magnitude of the shift-up. All states adjusted to the same size as Hawaii (roughly 10,000 deaths)
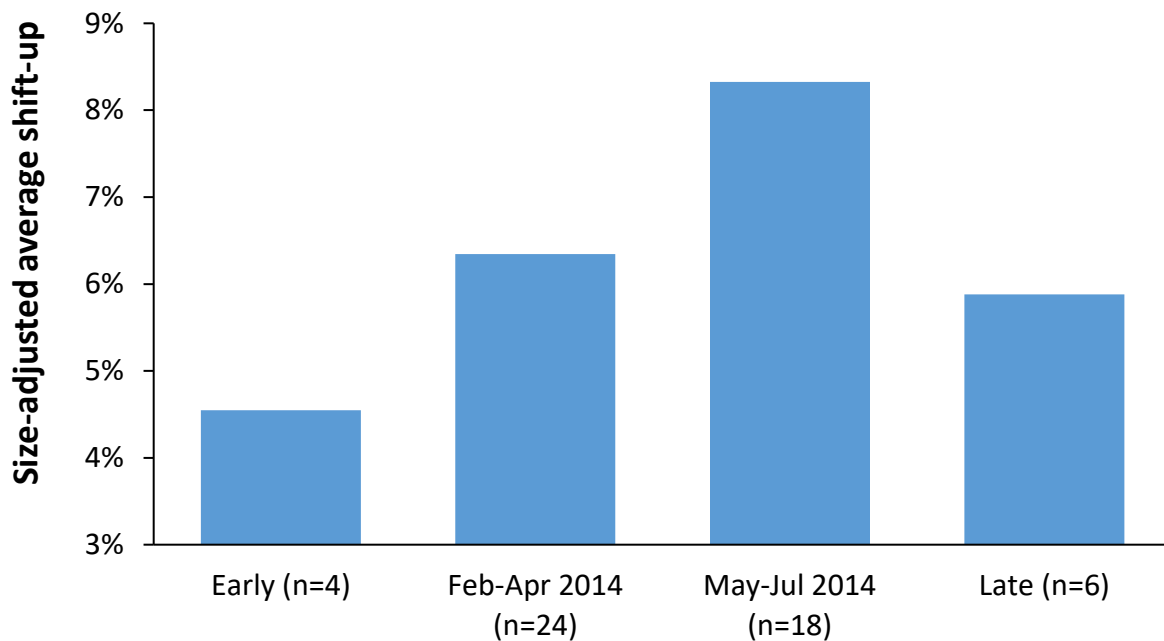
Figure 8 shows the effect of size (as total deaths per state) on the apparent magnitude of the step-like sudden shift to higher deaths. In the smaller states the shift is highest since spread of the agent will mostly

occur in the capital city. Larger states have multiple large cities or multiple suburbs which blunts the apparent maximum due to spatiotemporal effects. The line showing 6-times the standard deviation from Poisson chance is designed to assure that whatever has happened cannot occur from chance.

Lastly, Figure 9 shows that the magnitude of the sudden shift may increase to a maximum for initiation between May to July. All states were adjusted to the same size as Hawaii using the Poisson relationship. The key point in this section is high spatiotemporal granularity as expected from an infectious outbreak.

Spread of the new disease in the UK during 2019

As has been previously discussed a rolling 12-month total is an excellent method for detecting unexpected Shift-up and Shift-down hidden in a data series. Such sudden shifts are often concealed by both the statistical scatter in the smaller monthly numbers and the seasonal patterns. The rolling 12-month total removes most of the underlying seasonal pattern and greatly diminishes the scatter associated with the smaller monthly numbers.

Figure 10 shows a typical shift-down and shift-up pattern for the Vale of Glamorgan in Wales. Even at 1,300 deaths ± 1 standard deviation is around ± 36, hence the scatter around the trend lines. The slope of the lines measures the magnitude of shift-down (-9.0 per month) and shift-up (+11.9 per month). Shift-up commences in month 15 (August 2019). COVID-19 excess deaths commence in April 2019.

Figure 10: Example of shift-down followed by shift-up using a rolling 12-month total in the Vale of Glamorgan, Wales

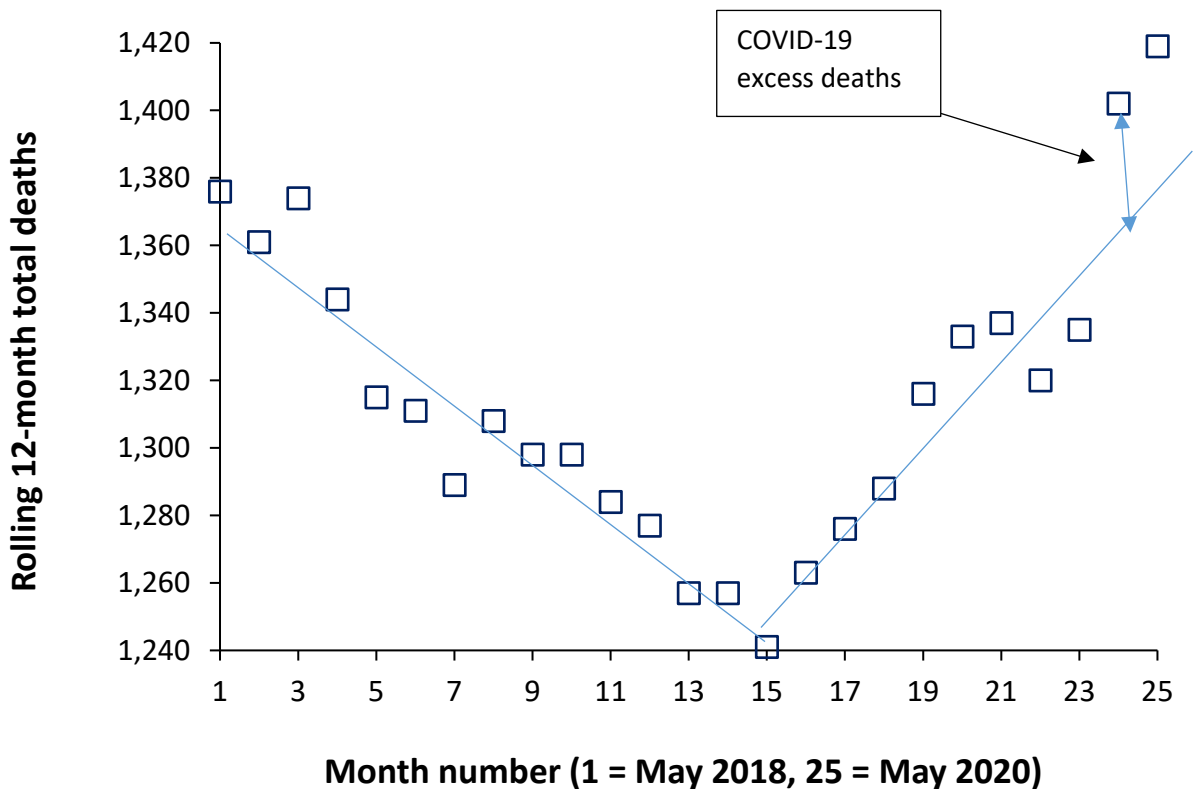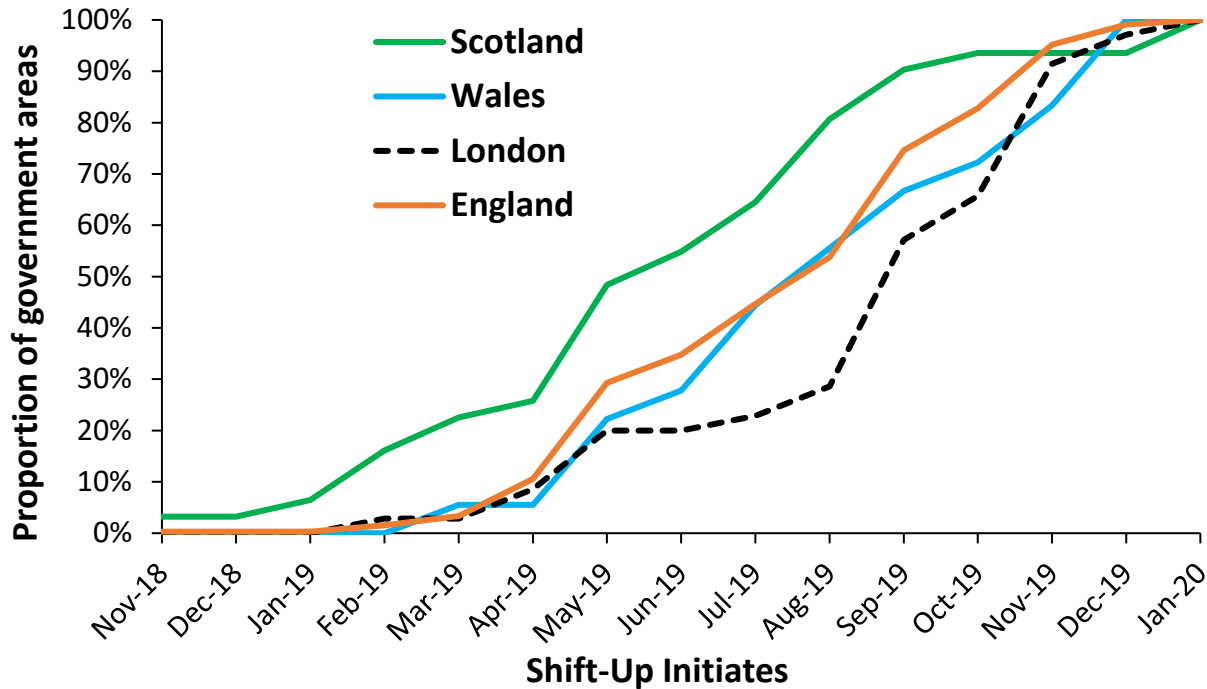**Month number (1 = May 2018, 25 = May 2020)**

Figure 11: Timing for Shift-up (where it occurs) in different areas (local authority, county, STP Footprint and Region/Country) during 2019

The exact magnitude of COVID-19 excess deaths is relative to the shift-up trend line and has a degree of uncertainty. Due to the spread of COVID-19 throughout the UK excess deaths commence in March in larger cities and then in April in other local authorities such as Vale of Glamorgan, and to an almost negligible extent in some locations.

It is important to demonstrate that shift-up shows typical infectious spread and the timing of Shift-up across the UK during late 2018 and 2019 is demonstrated in Figure 11.

As can be seen, Shift-up commences first in Scotland with half of local authorities having commenced Shift-up by May-19, next comes England and Wales with half of local authorities commencing by Aug-19 and then London with half by Sep-19. London catches up with the rest of the UK with a late rush of initiation in October and November.

Clearly the Vale of Glamorgan (Fig. 10) is a simple example where the bulk of the population experienced Shift-up at roughly the same time, however, in larger areas with multiple population loci and/or distinct social groups shift-up can occur at different times leading to a bi-phasic time response.

As with all infectious events, both COVID-19 and the 2019 shift-up preceding COVID-19 show differences in magnitude across the UK. See Appendix 3 for a wider discussion.

The key point is that shift-up and shift-down are very real and have the potential to significantly influence the calculation of 'excess' deaths.

It should be noted that overall, some 16% of areas were in shift-down prior to COVID-19, of this average 10% in Scotland, 15% in Outer London, 21% in Inner London and 23% in Wales.

Finally, Figure 12 investigates the possibility that shift-up and shift-down influence the magnitude of the ensuing COVID-19 outbreak.

Figure 12: Excess deaths (all-cause mortality) during COVID-19 in areas either experiencing shift-up or shift-down at the time of the COVID-19 outbreak
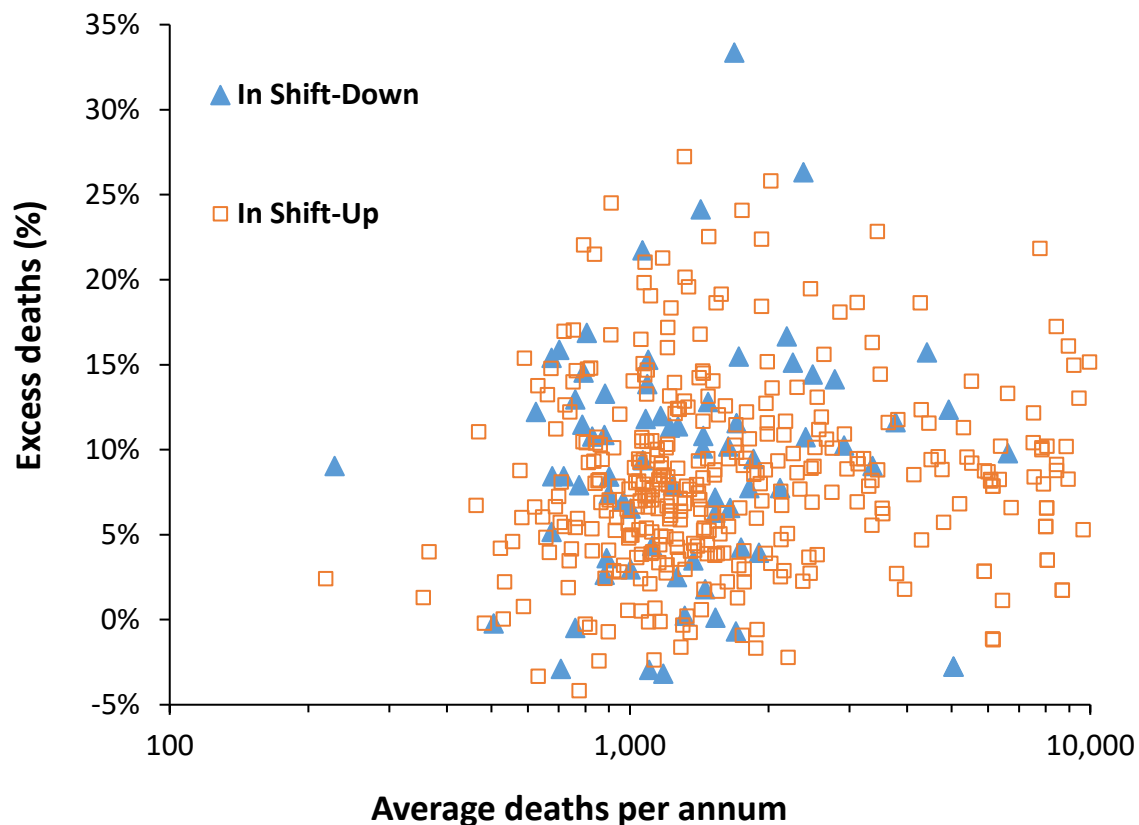
Clearly this is a complex issue which depends on original exposure to COVID-19 and rate of spread, however, there is tentative evidence to suggest that it is possibly shift-down which results in highest COVID-19 mortality with a median of 9.5% excess deaths compared to 7.9% for the shift-up group. These are clearly preliminary results. The original hypothesis that shift-up and shift-down involves some subtle form of immune shift may still apply.

Cost implications of infectious outbreaks

In the USA, the estimated average annual total economic burden of influenza to the healthcare system and society was $11.2 billion ($6.3-$25.3 billion). Direct medical costs were estimated to be $3.2 billion ($1.5-$11.7 billion) and indirect costs $8.0 billion ($4.8-$13.6 billion). This is around $34 per person per year or $4,600 per all-cause death (Putri et al 2018).

Average cost per influenza admission in Canada was $14 612 CAD, including $133 for medical care prior to admission, $14 031 during initial hospital stay, and $447 post-discharge, including readmission within 30 days. Some 14% of patients were admitted to intensive care (Ng et al 2018).

Cancer patients with a concomitant diagnosis of influenza (0.4% of cancer-related hospitalizations) had a 30% higher mortality rate, 0.7-day higher average length of stay, a higher incidence of complications including pneumonia, neutropenia, sepsis and acute kidney injury. Older age, no insurance (an indicator of low income), more comorbidities, lung cancer and haematological malignancy were independently associated with higher mortality (Li et al 2020).

The economic burden of the entire infectious spectrum will be many times higher than this. A study into the inpatient costs associated with outbreaks of the new type or kind of disease in England gave around £700 million (around £840 million in 2020 costs) extra costs during each outbreak (Jones 2012). This cost is around £16 or £1,70 per all-cause death. The cost will include those associated with higher EWM during the outbreaks.

Discussion

It is often the 'experts' who are the last to accept the shift to a new paradigm (Greenwood 2019). Indeed as 'everybody knows' hospital LOS is a measure of efficiency/inefficiency and staff sickness absence rates are the responsibility of the employer. Among government agencies and politicians in the UK there is a presupposition that periods of poor financial or operational performance are the direct result of poor management or the inability to manage demand.

This study has sought to give a biological and medical basis for winter mortality as the combined interaction between existing (persistent) pathogens, the nose/throat microbiome, the gut microbiome, and the prevailing mix of winter pathogens. Influenza is an important winter pathogen, but its effects cannot be separated completely from the complex set of interactions between pathogens and from the effects of heterologous immunity, i.e., the unexpected effects arising from the order in which infections are acquired. Indeed, vaccination itself becomes part of the sequence of heterologous immunity.

Irrespective of these issues, the confusion arising from multiple influenza(s), vaccine effectiveness and actual influenza mortality has almost certainly deflected attention away from the curious behaviour of deaths which is seen around the world.

Outbreaks of the new disease only serve to increase the resulting cost and capacity uncertainty in health care. Both the financial and acute hospital sector need to be aware that cost and capacity planning is less certain than probably assumed. The issues surrounding the Health Insurance Underwriting Cycle raised in Part 1 are a testament to this uncertainty.

All uncertainty implies a safety margin. In finance this implies a surplus to cover for times of higher-than-expected costs while in hospital capacity this implies flexible design to enable beds to be bought onstream as need requires.

Further research

The rolling 12-month total method has its limitations. The key is to use tools such as Fourier transforms, wavelet analysis, autoregressive integrated moving average (ARIMA) models, etc which look for the

variety of hidden patterns lying in the cost, admission, and bed occupancy data. ARIMA models have the advantage in that they anticipate that shift-up and down behaviour is part of the time series.

Wider implications

This study has far wider implications to those countries which use a funding formula to allocate health care budgets to different states, health authorities or clinical commissioning groups (CCG). See Part 4 for further discussion. Such formula has the implicit assumption that financial risk is not area dependant. This series has amply demonstrated that this is entirely untrue. For whatever reason some areas, i.e., large cities, experience higher infectious volatility which is further modified by metrological variables such as humidity and temperature. Both factors affect the survival and infectious capacity of respiratory pathogens. Clearly non-respiratory pathogens are also involved; however, winter is a time of high volatility.

Conclusions

There is no doubt that the silo mentality of Public Health Agencies has led to undue focus on influenza. We need to broaden our view of how infection works to craft a wholistic view of immune function and the wider role of the biome in both the nose/throat and digestive system. The health services can take wider steps to mitigate the intrinsic high volatility in costs and capacity challenges. In both cases targeted government policy is required.

Data Sources and methods

Data sources

Monthly deaths in US states were obtained from the National Centre for Health Statistics (2020). HES inpatient admissions in England 1998/99 to 2019/20 were obtained from NHS Digital (2020a). NHS staff sickness rates was also from NHS Digital (2020b).

Monthly deaths in Scotland were from National Records of Scotland (2020), and for Northern Ireland were by request from the Northern Ireland Statistics and Research Agency. Weekly deaths were from the office of national Statistics (2020), National records of Scotland (2020) and Northern Ireland Statistics and Research Agency (2020).

Weekly Influenza-like-illness rates and deaths in England and Wales were from the Office for National Statistics (2019).

Methods

Excess Winter Mortality (EWM) was calculated as a rolling percentage difference of eight months versus four months. Hence percentage difference between average deaths September to December versus average deaths January to August. Move forward one month and recalculate. The maximum for the rolling EWM calculation usually occurs in the four months ending March, however this calculation can peak between the four months ending February to the four months ending April. The maximum was chosen for each winter. The standard deviation (STDEV) of EWM was adjusted for local authority size by plotting the STDEV versus average deaths (2001 to 2020) and a power law line of best fit calculated. STDEV was adjusted to the equivalent of 1,000 deaths per annum.

The year-to-year difference in total deaths was calculated by constructing a rolling 12-month total of deaths commencing the 12-months ending December 2001. This was compared to the 12-months ending December 2002 as the absolute value of the difference calculated as a standard deviation equivalent assuming Poisson statistics for whole numbers. Hence difference divided by the square root of the average deaths in year n and n+1. Move forward one month and recalculate. This transformation is required to adjust for the effect of size. The standard deviation of the transformed differences was then calculated. Analysis of monthly sickness absence rates in NHS Regions was conducted in the same manner.

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Further Reading
Further studies relating to factors affecting financial and operational risk in healthcare, and studies on outbreaks of the new disease can be found at http://www.hcaf.biz/2010/Publications_Full.pdf

References

Aguilera E, Lenz L. Inflammation as a modulator of host susceptibility to pulmonary Influenza, Pneumococcal, and co-Infections. Front Immunol 2020; https://doi.org/10.3389/fimmu.2020.00105
Ainslie K, Shi M, Haber M, Orenstein W. On the bias of estimates of influenza vaccine effectiveness from test-negative studies. Vaccine. 2017; 35(52): 7297-7301. doi: 10.1016/j.vaccine.2017.10.107.
Ainslie K, Shi M, Haber M, Orenstein W. A dynamic model for evaluation of the bias of Influenza vaccine effectiveness estimates from observational studies. Am J Epidemiol. 2019; 188(2): 451-460. doi:10.1093/aje/kwy240
Ainslie K, Haber M, Orenstein W. Bias of influenza vaccine effectiveness estimates from test-negative studies conducted during an influenza pandemic. Vaccine 2019; 37(14): 1987-1993. https://doi.org/10.1016/j.vaccine.2019.02.036.
Alymova I, Green A, van de Velde N, et al. Immunopathogenic and antibacterial effects of H3N2 Influenza A virus PB1-F2 map to amino acid residues 62, 75, 79, and 82. J Virology 2011; 85(23): 12324-12333. doi: 10.1128/JVI.05872-11
Anderson ML, Dobkin C, Gorry D. The effect of influenza vaccination for the elderly on hospitalization and mortality: An observational study with a regression discontinuity design. Ann Intern Med. 2020; 172(7):445-452. doi: 10.7326/M19-3075
Aranow C. Vitamin D and the immune system. J Investig Med 2011; 59(6): 881-6. doi: 10.231/JIM.0b013e31821b8755.
Baggerly C, Cuomo R, French C, et al. Sunlight and vitamin D: necessary for public health. J Amer Coll Nutrit 2015; 34(4): 1-7.
Balcan D, Colizza V, Gonçalves B, et al. Multiscale mobility networks and the spatial spreading of infectious diseases. PNAS 2009; 106 (51): 21484-21489; doi: 10.1073/pnas.0906910106

Boulieri A, Blangiardo M. Spatio-temporal model to estimate life expectancy and to detect unusual trends at the local authority level in England. BMJ Open 2020; 10: e036855. Doi: 10.1136/bmjopen-2020-036855

Brown K, Daneman N, Arora P, et al. The co-seasonality of pneumonia and influenza with Clostridium difficile infection in the United States, 1993–2008, American Journal of Epidemiology 2013; 178(1): 118-125. https://doi.org/10.1093/aje/kws463

Brunstein J, Cline C, McKinney S, Thomas E. Evidence from multiplex molecular assays for complex multipathogen interactions in acute respiratory infections. J Clinical Microbiology 2008; 46(1) 97-102; doi: 10.1128/JCM.01117-07

Brunnström H, Englund E. Cause of death in patients with dementia disorders. Eur J Neurol. 2009; 16(4): 488-492. doi: 10.1111/j.1468-1331.2008.02503.x.

Bürkle A, Moreno-Villanueva M, Bernhard J, et al. MARK-AGE biomarkers of ageing. Mechanisms of Ageing and Development 2015; 151: 2-12. https://doi.org/10.1016/j.mad.2015.03.006.

Butler A, Layton J, Krueger W, et al. Assessing residual bias in estimating influenza vaccine effectiveness: Comparison of high-dose versus standard-dose vaccines. Med Care 2019; 57(1):73-78. doi: 10.1097/MLR.0000000000001018.

CDC. Summary of the 2007-2008 influenza season. 26 June 2008. https://www.cdc.gov/flu/pastseasons/0708season.htm

CDC. CDC Seasonal flu vaccine effectiveness studies. 2020. CDC Seasonal Flu Vaccine Effectiveness Studies | CDC

Cannell J, Zasloff M, Garland C, et al. On the epidemiology of influenza. Virol J. 2008; 5: 29. doi: 10.1186/1743-422X-5-29.

Carrat F, Lavenu A, Cauchemez S, Deleger S. Repeated influenza vaccination of healthy children and adults: borrow now, pay later? Epidemiology and Infection 2006; 134(1): 63–70.

Castilla J, Guevara M, Martínez-Baz I, et al. Enhanced estimates of the influenza vaccination effect in preventing mortality: A prospective cohort study. Medicine (Baltimore). 2015; 94(30): e1240. doi:10.1097/MD.0000000000001240

Chanlekha, H., Kawazoe A, Collier N. A framework for enhancing spatial and temporal granularity in report-based health surveillance systems. BMC Med Inform Decis Mak 2010; **10,** 1. https://doi.org/10.1186/1472-6947-10-1

Charu V, Zeger S, Gog J, Bjørnstad ON, Kissler S, et al. Human mobility and the spatial transmission of influenza in the United States. PLOS Computational Biology 2017; 13(2): e1005382. https://doi.org/10.1371/journal.pcbi.1005382

Chen R, Yin P, Wang L, Liu C, Niu Y, Wang W. et al. Association between ambient temperature and mortality risk and burden: time series study in 272 main Chinese cities. BMJ 2018; 363: k4306. http://dx.doi.org/10.1136/bmj.k4306

Cheng Y, Cao X, Cao Z, Xu C, Sun L, Gao Y, Wang Y, Li S, Wu C, Li X, Wang Y, Leng SX. Effects of influenza vaccination on the risk of cardiovascular and respiratory diseases and all-cause mortality. Ageing Res Rev. 2020 Sep;62:101124. doi: 10.1016/j.arr.2020.101124

Clothier H, Crawford N, Russell M, Buttery J. Allergic adverse events following 2015 seasonal influenza vaccine, Victoria, Australia. Euro Surveill 2017; ;22(20): 30535. doi: 10.2807/1560-7917.ES.2017.22.20.30535.

Curtin D, O'Mahony D, Gallagher P. Drug consumption and futile medication prescribing in the last year of life: an observational study. Age and Ageing 2018; 47(5): 749-753.

David, S.C., Norton, T., Tyllis, T. et al. Direct interaction of whole-inactivated influenza A and pneumococcal vaccines enhances influenza-specific immunity. Nat Microbiol **4,** 1316–1327 (2019). https://doi.org/10.1038/s41564-019-0443-4

Davie, G.S., Baker, M.G., Hales, S. et al. Trends and determinants of excess winter mortality in New Zealand: 1980 to 2000. BMC Public Health **7,** 263 (2007). https://doi.org/10.1186/1471-2458-7-263

Dedman D, Joseph C, Zambon M, Fleming D, Watson J. Influenza surveillance in England and Wales: October 1996 to June 1997. Commun Dis Rep CDR Rev. 1997;7(13): R212-9.

Delgado-Sanz C, Mazagatos-Ateca C, Oliva J, et al. Illness severity in hospitalized influenza patients by virus type and subtype, Spain, 2010–2017. Emerging Infectious Diseases. 2020;26(2):220-228. doi:10.3201/eid2602.181732.

Denly L. The effect of sex on responses to influenza vaccines. Human Vaccines & Immunotherapeutics 2020; 109, 1-7.

De Smedt T, Merrall E, Macina D, et al. Bias due to differential and non-differential disease- and exposure misclassification in studies of vaccine effectiveness. PLoS One. 2018; 13(6): e0199180. doi: 10.1371/journal.pone.0199180.

Doshi P. Trends in recorded influenza mortality: United States, 1900–2004. Amer J Public Health 2008; 98, 939_945, **https://doi.org/10.2105/AJPH.2007.119933**

Doshi P. Influenza: marketing vaccine by marketing disease BMJ 2013; 346 :f3037 doi: https://doi.org/10.1136/bmj.f3037

Durán A, González A, Delgado L, Mosquera J, Valero N. Serum level of C-reactive protein is not a parameter to determine the difference between viral and atypical bacterial infections. J Med Virol. 2016 Feb;88(2):351-5. doi: 10.1002/jmv.24341.

Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs R, et al. US county-level trends in mortality rates for major causes of death, 1980-2014. JAMA 2016; 316(22): 2385-2401. Doi: 10.1001/jama.2016.13645

Ekamper P, van Poppel F, van Duin C, Garssen J. 150 Years of temperature-related excess mortality in the Netherlands. Demographic Research 2009; 21: 385-426.

Elson R, Davies T, Jenkins C, et al. Application of kernel smoothing to estimate the spatio-temporal variation in risk of STEC O157 in England. Spatial and Spatio-temporal Epidemiology 2020; 32: 100305. https://doi.org/10.1016/j.sste.2019.100305.

Finkel D, Sternäng O, Jylhävä J, et al. Functional aging index complements frailty in prediction of Entry Into care and mortality. J Gerontol A Biol Sci Med Sci. 2019 Nov 13;74(12):1980-1986. doi: e0.1093/gerona/glz155.

Fireman B, Lee J, Lewis N, et al. Influenza Vaccination and Mortality: Differentiating vaccine effects from bias. American Journal of Epidemiology 2009; 170(5): 650-656. https://doi.org/10.1093/aje/kwp173

Freedman A. The winter of 2014-15 was the season that divided America. MashableUK, 9 March 2015. https://mashable.com/2015/03/08/winter-split-us-warm-west-frigid-east/?europe=true (accessed 19 November 2020)

Fry H, Bull M, Leach S, Hayward AC. Spatial methods for infectious disease outbreak investigations: systematic literature review. Euro Surveill 2015;20(39):pii=30026. doi: http://dx.doi.org/10.2807/1560-7917.ES.2015.20.39.30026

GBD Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory tract infections in 195 countries: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Infect Dis 2017; 17(11): 1133-1161.

Gaksch M, Jorde R, Grimnes G, et al. Vitamin D and mortality: Individual participant data meta-analysis of standardized 25-hydroxyvitamin D in 26916 individuals from a European consortium. PLoS One 2017; 12(2): e0170791. doi: 10.1371/journal.pone.0170791.

Geoghegan S, Erviti A, Caballero MT, et al. Mortality due to Respiratory Syncytial Virus. Burden and risk factors. Am J Respir Crit Care Med. 2017 Jan 1;195(1):96-103. doi: 10.1164/rccm.201603-0658OC.

Gill T, Gahbauer E, Han L, Allore H. The role of intervening hospital admissions on trajectories of disability in the last year of life: prospective cohort study of older people BMJ 2015; 350: h2361

Goncalves-Mendes N, Talvas J, Dualé C, et al. Impact of vitamin D supplementation on influenza vaccine response and immune functions in deficient elderly persons: A randomized placebo-controlled trial. Front Immunology 2019; 10: 65. https://www.frontiersin.org/article/10.3389/fimmu.2019.00065

Gong J, Dong H, Xia Q, et al. Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19: a retrospective study. BMC Infect Dis **20,** 963 (2020). https://doi.org/10.1186/s12879-020-05681-5

Grant W, Lahore H, McDonnell S, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients. 2020 Apr 2;12(4):988. doi: 10.3390/nu12040988. PMID: 32252338; PMCID: PMC7231123.

Greenwood V. Do the deaths of top scientists make way for new growth? UNDARK, 11 June 2019. https://undark.org/2019/11/06/top-scientists-dying/

Hajek A, Bock J, Saum K, et al. Frailty and healthcare costs-longitudinal results of a prospective cohort study. Age Ageing. 218 Mar 1;47(2):233-241. doi: 10.1093/ageing/afx157.

Herbinger K-H, Hanus I, Schunk M, et al. Elevated values of C-Reactive Protein induced by imported infectious diseases: A controlled cross-sectional study of 11,079 diseased German travellers returning from the tropics and subtropics. Am J Trop Med Hyg 2016; 95(4): 938-944. Doi: 10.4269/ajtmh.16-0387

Homewood P. The winter of 1962/63. December 1 2014. https://notalotofpeopleknowthat.wordpress.com/2014/12/01/the-winter-of-196263/ (accessed 12 November 2020)

Höhn A, Larsen L, Schneider D, et al. Sex differences in the 1-year risk of dying following all-cause and cause-specific hospital admission after age 50 in comparison with a general and non-hospitalised population: a register-based cohort study of the Danish population. BMJ Open. 2018; 17;8(7):e021813. doi: 10.1136/bmjopen-2018-021813.

Howse K. Dementia as a cause of death, 23 November 2016. https://www.ageing.ox.ac.uk/blog/2016-Howse-Dementia-as-a-cause-of-death#:~:text=If%20more%20people%20are%20being%20recognised%20as%20dying,the%20software%20that%20is%20used%20for%20automated%20coding.

Invernizzi R, Lloyd C, Molyneaux P. Respiratory microbiome and epithelial interactions shape immunity in the lungs. Immunology 2020; 160: 171-182. https://doi.org/10.1111/imm.13195

Jabr F. How does the flu actually kill people? Scientific American 2017; https://www.scientificamerican.com/article/how-does-the-flu-actually-kill-people/ (accessed 23 October 2020)

Jacobs J, Archer B, Baker M, et al. Searching for sharp drops in the incidence of pandemic A/H1N1 influenza by single year of age. PLoS One 2012; 7(8): e42328. doi:10.1371/journal.pone.0042328

Jackson L, Jackson M, Nelson J, et al. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. Int J Epidemiology 2006; 35(2):337-344. https://doi.org/10.1093/ije/dyi274

Jia H, Lubetkin E. Life expectancy and active life expectancy by disability status in older U.S. adults. PLOS ONE 2020; 15(9): e0238890. Doi: 10.1371/journal.pone.0238890.

Jones R. Unexpected, periodic and permanent increase in medical inpatient care: man-made or new disease. Medical Hypotheses 2010a; 74: 978-83. doi: http://dx. doi.org/10.1016/j.mehy.2010.01.011

Jones R. Can time-related patterns in diagnosis for hospital admission help identify common root causes for disease expression. Medical Hypotheses 2010b; 75: 148-154. doi: http://dx. doi.org/10.1016/j.mehy.2010.02.009

Jones R. The case for recurring outbreaks of a new type of infectious disease across all parts of the United Kingdom. Medical Hypotheses 2010c; 75: 452-457. doi: http://dx. doi.org/10.1016/j.mehy.2010.04.023

Jones R. Time to re-evaluate financial risk in GP commissioning. Brit J Healthc Manage 2012; 18(1): 39-48.

Jones R. Analysing excess winter mortality: 2012/13. Brit J Healthc Manage 2013a; 19(12): 601-605.

Jones R. Could cytomegalovirus be causing widespread outbreaks of chronic poor health? In Hypotheses in Clinical Medicine, 2013b; pp 37-79, Eds M. Shoja, et al. New York: Nova Science Publishers Inc. Available from: http://www.hcaf.biz/2013/CMV_Read.pdf

Jones R. Widespread outbreaks of a subtle condition leading to hospitalization and death. Epidemiology: Open access 2013c; 4(3): 137. doi: 10.4172/2161-1165.1000137

Jones R. A Study of an unexplained and large increase in respiratory deaths in England and Wales: Is the pattern of diagnoses consistent with the potential involvement of cytomegalovirus? BJMMR 2014; 4(33): 5179-5192. doi: 10.9734/BJMMR/2014/11382

Jones R, Goldeck D. Unexpected and unexplained increase in death due to neurological disorders in 2012 in England and Wales: Is cytomegalovirus implicated? Medical Hypotheses 2014; 83(1): 25-31. http://dx.doi.org/10.1016/j.mehy.2014.04.016

Jones R. An unexpected increase in adult appendicitis in England (2000/01 to 2012/13): Could cytomegalovirus (CMV) be a risk factor? BJMMR 2015a; 5(5): 579-603. doi: 10.9734/BJMMR/2015/13302

Jones R. Roles for cytomegalovirus in infection, inflammation and autoimmunity. In Infection and Autoimmunity, 2nd Edition, Eds: N Rose, et al. Elsevier: Amsterdam. 2015b; Chapter 18, pp 319-357. doi:10.1016/B978-0-444-63269-2.00068-4

Jones R. A previously uncharacterized infectious-like event leading to spatial spread of deaths across England and Wales: Characteristics of the most recent event and a time series for past events. BJMMR 2015c; 5(11): 1361-1380. doi: 10.9734/BJMMR/2015/14285

Jones R. Are emergency admissions contagious? BJHCM 2015d; 21(5): 227-235. http://www.hcaf.biz/2015/Double_Epidemic.pdf

Jones R. Recurring outbreaks of an infection apparently targeting immune function, and consequent unprecedented growth in medical admission and costs in the United Kingdom: A review. Brit J Med and Medical Research 2015e; 6(8): 735-770. doi: 10.9734/BJMMR/2015/14845

Jones R. A presumed infectious event in England and Wales during 2014 and 2015 leading to higher deaths in those with neurological and other disorders. Journal of Neuroinfectious Diseases 2016a; 7(1): 1000213 doi: 10.4172/2314-7326.1000213

Jones R. The unprecedented growth in medical admissions in the UK: the ageing population or a possible infectious/immune aetiology? Epidemiology: Open Access 2016b; 6(1): 1000219 http://dx.doi.org/10.4172/2161-1165.1000219

Jones R. Rising emergency admissions in the UK and the elephant in the room. Epidemiology: Open Access 2016;c 6(4): 1000261. doi: 10.4172/2161-1165.1000261

Jones R. Is cytomegalovirus involved in recurring periods of higher than expected death and medical admissions, occurring as clustered outbreaks in the northern and southern hemispheres? BJMMR 2016d; 11(2): 1-31. doi: 10.9734/BJMMR/2016/20062

Jones R. International outbreaks of a novel type of infectious immune impairment: A call to action. Досягнення біології та медицини (Achievements of Biology and Medicine - transl) 2017a; 29(1): 75-81. http://files.odmu.edu.ua/biomed/2017/01/d171_75.pdf

Jones R. Year-to-year variation in deaths in English Output Areas (OA), and the interaction between a presumed infectious agent and influenza in 2015. SMU Medical Journal 2017b; 4(2): 37-69. http://smu.edu.in/content/dam/manipal/smu/smims/Volume4No2July2017/SMU%20Med%20J%20(July%202017)%20-%204.pdf

Jones R. The calendar year fallacy: The danger of reliance on calendar year data in end-of-life capacity and financial planning. Int J Health Planning and Management 2019; 334(4): e1533-e1543. https://doi.org/10.1002/hpm.2838

Jones R. Multidisciplinary insights into health care financial risk and hospital surge capacity, Part 1: Nearness to death, infectious outbreaks, and COVID-19. Journal of Health Care Finance.2021a; In press.

Jones R. Insights into health care financial risk and hospital surge capacity, Part 2: High population density is associated with enhanced year-to-year volatility in many aspects of poor health including health care worker sickness absence. Journal of Health Care Finance 2021b; in press

Jones R. Excess winter mortality (EWM) and stalling international improvements in life expectancy and mortality rates. Brit J Healthc Manage 2020c; 26(12); https://doi.org/10.12968/bjhc.2020.0020

Jones R. How many extra deaths have really occurred in the UK due to the COVID-19 outbreak? XXIII.COVID-19 infection shows massive spatiotemporal granularity. Healthcare Analysis and Forecasting 15 December 2020d. doi: 10.13140/RG.2.2.14874.88006

Jones R. Were the hospital bed reductions proposed by English Clinical Commissioning Groups (CCGs) in the Sustainability and Transformation Plans (STPs) achievable? Insights from a new model to compare international bed numbers. Intl J Health Plan Mgmt 2021a; https://doi.org/10.1002/hpm.3094

Jones R. Does the ageing population correctly predict the need for medical beds over the next 40 years? Brit J Healthc Manage 2021b; in press.

Jorgensen P, Mereckiene J, Cotter S, et al. How close are countries of the WHO European Region to achieving the goal of vaccinating 75% of key risk groups against influenza? Results from national surveys on seasonal influenza vaccination programmes, 2008/2009 to 2014/2015. Vaccine. 2018; 36(4): 442-452. doi: 10.1016/j.vaccine.2017.12.019.

Juzeniene A, Ma L-W, Kwitniewski M, et al. The seasonality of pandemic and non-pandemic influenzas: the roles of solar radiation and vitamin D. Int J Infect Dis 2010; 14(12): e1099-e1105. https://doi.org/10.1016/j.ijid.2010.09.002.

Katzelnick L, Narvaez C, Arguello S, et al. Zika virus infection enhances future risk of severe dengue disease. Science 2020; 369(6507);1123-1128. doi: 10.1126/science.abb6143

Kim T, Shin E. The activation of bystander CD8+ T cells and their roles in viral infection. Exp Mol Med 2019; 51, 1–9. https://doi.org/10.1038/s12276-019-0316-1

Lee KH, Gordon A, Shedden K, Kuan G, Ng S, Balmaseda A, et al. The respiratory microbiome and susceptibility to influenza virus infection. PLoS ONE 2019; 14(1): e0207898. https://doi.org/10.1371/journal.pone.0207898

Lee WJ, Chen LK, Tang GJ, Lan TY. The impact of influenza vaccination on hospitalizations and mortality among frail older people. J Am Med Dir Assoc. 2014 Apr;15(4):256-60. doi: 10.1016/j.jamda.2013.12.003

Lewis S, Evans L, Rainer T, Hewitt J. Screening for frailty in older emergency patients and association with outcome. Geriatrics 2020; 5: 20.

L'Heureux M. An overview of the 2007- 08 La Niña and boreal wintertime variability. Science and Technology Infusion Climate Bulletin. NOAA's National Weather Service 33rd NOAA Annual Climate Diagnostics and Prediction Workshop Lincoln, NE, 20-24 October 2008.

Li J, Zhang D, Sun Z, Bai C, Zhao L. Influenza in hospitalised patients with malignancy: a propensity score matching analysis. ESMO Open. 2020 Oct;5(5):e000968. doi: 10.1136/esmoopen-2020-000968.

Li L, Wong J, Wu P, et al. Heterogeneity in estimates of the impact of influenza on population mortality: A systematic review. Amer J Epidemiology 2018; 187(2): 378–388. https://doi.org/10.1093/aje/kwx270

Li, X., Chan, K.K.Y., Xu, B. et al. Spatial, temporal and genetic dynamics characteristics of Influenza B viruses in China, 1973–2018. Virol. Sin. 2020; 35, 14–20. https://doi.org/10.1007/s12250-019-00161-w

Lipsitch M, Jha A, Simonsen L. Observational studies and the difficult quest for causality: lessons from vaccine effectiveness and impact studies. Int J Epidemiol. 2016 Dec 1;45(6):2060-2074. doi: 10.1093/ije/dyw124.

London School of Economics. Stalling of mortality in the United Kingdom and Europe: an analytical review of the evidence. 2019. http://www.lse.ac.uk/business-and-consultancy/consulting/consulting-reports/stalling-of-mortality-in-the-uk-and-europe (accessed 6 October 2020)

Longevity Science Panel. An analysis of mortality trends in developed countries, focusing on the recent slowdown in mortality improvement. 2020. https://www.longevitypanel.co.uk/_files/LSP2020_Report.pdf (accessed 6 October 2020)

Luan YY, Yao YM. The clinical significance and potential role of C-Reactive Protein in chronic inflammatory and neurodegenerative diseases. Front Immunol. 2018; 7(9):1302. doi: 10.3389/fimmu.2018.01302.

Marmot M. Evidence based policy or policy based evidence? BMJ 2004; 328 :906

Meehan M, Penckofer S. The Role of Vitamin D in the aging adult. J Aging Gerontol. 2014 2(2):60-71.

Met Office. Hot spell August 1990. http://www.metoffice.gov.uk/climate/uk/interesting/aug1990/

Mengel L, Seidl H, Brandl B, Tet al. Gender differences in the response to short-term cold exposure in young adults, The Journal of Clinical Endocrinology & Metabolism, 2020; 105(5): e1938–e1948. https://doi.org/10.1210/clinem/dgaa110

Mo Y, Zeng J, Xiao C, Zhang L, Wang L, Lu F, Johnson DW, Stålsby Lundborg C, Nitsch D, Liu X, Su G. Effectiveness and safety of pneumococcal vaccines used alone or combined with influenza vaccination in dialysis patients: A systematic review and meta-analysis. Vaccine. 2020 Nov 3;38(47):7422-7432. doi: 10.1016/j.vaccine.2020.09.080.

Moore PV, Bennett K, Normand C. Counting the time lived, the time left or illness? Age, proximity to death, morbidity and prescribing expenditures. Soc Sci Med. 2017; 184:1-14. doi: 10.1016/j.socscimed.2017.04.038.

Moorthy M, Castronovo D, Abraham A, et al. Deviations in influenza seasonality: odd coincidence or obscure consequence? Clin Microbiol Infect 2012; 18: 955-962.

Muscatello D, Amin J, MacIntyre C, et al. Inaccurate ascertainment of morbidity and mortality due to Influenza in administrative databases: A Population-based record linkage study. PLoS ONE 9(5): e98446. https://doi.org/10.1371/journal.pone.0098446

National Centre for Health Statistics. VSRR - State and National Provisional Counts for Live Births, Deaths, and Infant Deaths, 2020. https://data.cdc.gov/NCHS/VSRR-State-and-National-Provisional-Counts-for-Liv/hmz2-vwda (accessed 22November 2020)

National Records of Scotland. Monthly data on births and deaths registered in Scotland, Table 4: Council area, 2020. https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/general-publications/weekly-and-monthly-data-on-births-and-deaths/monthly-data-on-births-and-deaths-registered-in-scotland#: (accessed 3 November 2020)

National Records of Scotland. Weekly Data on Births and Deaths Registered in Scotland, 2020. Weekly Data on Births and Deaths Registered in Scotland | National Records of Scotland (nrscotland.gov.uk) (accessed 22 November 2020)

NHS Digital. Hospital admitted patient care activity, 2020a. https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity (Accessed 3 November 2020)

Newton J, Pebody R, Fitzpatrick J. Peak in deaths in 2015 is not a complete mystery. BMJ 2016; 352: i1582. Doi: 10.1136/bmj.i1582

Ng C, Ye L, Noorduyn S, Hux M, et al. Resource utilization and cost of influenza requiring hospitalization in Canadian adults: A study from the serious outcomes surveillance network of the Canadian Immunization Research Network. Influenza Other Respir Viruses. 2018; 12(2): 232-240. doi: 10.1111/irv.12521.

Nicoll A, Ciancio B, Lopez Chavarrias V, et al. Influenza-related deaths - available methods for estimating numbers and detecting patterns for seasonal and pandemic influenza in Europe. Eurosurveillance2012; 17, 20162. https://doi.org/10.2807/ese.17.18.20162-en

Nicholson K. Impact of influenza and respiratory syncytial virus on mortality in England and Wales from January 1975 to December 1990. Epidemiology and Infection 1996; 116(1): 51–63.

Nickbakhsh S, Mair C, Matthews L, et al. Virus–virus interactions impact the population dynamics of influenza and the common cold. PNAS 2019; 116(52): 27142-27150; doi: 10.1073/pnas.1911083116

Northern Ireland Statistics and Research Agency. Weekly deaths, 2020. Weekly Deaths | Northern Ireland Statistics and Research Agency (nisra.gov.uk) (Accessed 22 November 2020)

Noymer A, Garenne M. The 1918 influenza epidemic's effects on sex differentials in mortality in the United States. Population and Development Review. 2000; 26(3): 565-581. doi: 10.1111/j.1728-4457.2000.00565.x

OCSI. LSOAs, LEPs and lookups: A beginner's guide to statistical geographies. 2021. LSOAs, LEPs and lookups : A beginner's guide to statistical geographies - OCSI (accessed 18 January 2021)

OECD Data. Influenza vaccination rates (indicator); 2020. doi: 10.1787/e452582e-en (Accessed 12 November 2020)

Office for National Statistics. Provisional analysis of death registrations: 2015. 7 April 2016. Provisional analysis of death registrations - Office for National Statistics (accessed 22 November 2020)

Office for National Statistics. How do the post-World War baby boom generations compare? 6 March 2018. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/ageing/articles/howdothepostworldwarbabyboomgenerationscompare/2018-03-06 (accessed 17 November 2020)

Office for National Statistics. Excess winter mortality in England and Wales: 2018 to 2019 (provisional) and 2017 to 2018 (final). 27 November 2019. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/excesswintermortalityinenglandandwales/2018to2019provisionaland2017to2018final (accessed 17 November 2020)

Office for National Statistics. Deaths by single year of age tables, UK. 17 January 2020a. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummarytablesenglandandwalesdeathsbysingleyearofagetables (accessed 17 November 2020)

Office for National Statistics. Deaths registered weekly in England and Wales, provisional, 2020b. Deaths registered weekly in England and Wales, provisional - Office for National Statistics (ons.gov.uk) (Accessed 22 November 2020)

Office for National Statistics. Deaths registered monthly in England and Wales, 2020c. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/monthlyfiguresondeathsregisteredbyareaofusualresidence (accessed 3 November 2020)

Office for National statistics. 21st Century mortality dataset, England & Wales, 2001-2019. 1 July 2020d. Deaths registered in England and Wales – 21st century mortality - Office for National Statistics (ons.gov.uk) (accessed 24 November 2020)

Opatowski L, Baguelin M, Eggo R. Influenza interaction with cocirculating pathogens and its impact on surveillance, pathogenesis, and epidemic profile: A key role for mathematical modelling. PLoS Pathog 2018; 14(2): e1006770. https://doi.org/10.1371/journal.ppat.1006770

Pebody R, Warburton F, Andrews N, et al. Effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2014/15 end of season results. Euro Surveill. 2015;20(36):pii=30013. doi: http:// dx.doi.org/10.2807/1560-7917.ES.2015.20.36.30013

Pebody R, Green H, Warburton F, et al. Significant spike in excess mortality in England in winter 2014/15 – influenza the likely culprit. Epidemiology and Infection 2018; 146: 1106-1113.

Pei S, Kandula S, Yang W, Shaman J. Forecasting the spatial transmission of influenza in the United States. PNAS 2018; 115 (11) 2752-2757; doi: 10.1073/pnas.1708856115

Public Health England. Surveillance of influenza and other respiratory viruses in the United Kingdom: winter 2014 to 2015. May 2015. Surveillance of influenza and other respiratory viruses in the United Kingdom: winter 2014 to 2015 (publishing.service.gov.uk) (accessed 22 November 2010)

Public Health England. A review of recent trends in mortality in England. 2018. https://www.gov.uk/government/publications/recent-trends-in-mortality-in-england-review-and-data-packs (accessed 6 October 2020)

Public Health England. Pneumococcal Polysaccharide Vaccine (PPV) coverage report, England, April 2018 to March 2019. Health Protection Report Volume 13 Number 39, 1 November 2019. Pneumococcal Polysacchride Vaccine (PPV) coverage report, England, April 2018 to March 2019 (publishing.service.gov.uk) (accessed 17 January 2021)

Putri W, Muscatello D, Stockwell M, Newall A. Economic burden of seasonal influenza in the United States. Vaccine. 2018 Jun 22;36(27):3960-3966. doi: 10.1016/j.vaccine.2018.05.057.

Qin Y, Zhang Y, Wu P, et al. Influenza vaccine effectiveness in preventing hospitalization among Beijing residents in China, 2013–15. Vaccine 2016; 34(20): 2329-2333. https://doi.org/10.1016/j.vaccine.2016.03.068.

Rabbitt P, Lunn M, Wong D. Death, dropout, and longitudinal measurements of cognitive change in old age, *The Journals of Gerontology: Series B*, 2008; 63(5): P271-P278. https://doi.org/10.1093/geronb/63.5.P271

Rau R, Bohk-Ewald C, Muszyńska M, Vaupel J. Seasonality of causes of death. In: Visualizing Mortality Dynamics in the Lexis Diagram. The Springer Series on Demographic Methods and Population Analysis, 2018; 44: Springer, Cham. https://doi.org/10.1007/978-3-319-64820-0_9

Rezaei R, Aslani S, Marashi M, et al. Immunomodulatory effects of Vitamin D in influenza infection. Current Immunology Reviews 2018; 14(1): 40-49. doi : 10.2174/1573395513666171031162100

Rondy M, El Omeiri N, Thompson M, et al. Effectiveness of influenza vaccines in preventing severe influenza illness among adults: A systematic review and meta-analysis of test-negative design case-control studies. J Infect 2017; 75(5):381-394. doi:10.1016/j.jinf.2017.09.010

Rowe, H.M., Meliopoulos, V.A., Iverson, A. et al. Direct interactions with influenza promote bacterial adherence during respiratory infections. Nat Microbiol 2019; **4,** 1328–1336. https://doi.org/10.1038/s41564-019-0447-0

Rozo M, Gronvall G. The reemergent 1977 H1N1 strain and the gain-of-function debate. mBio 2015; 6(4): e01013-15. **doi:** 10.1128/mBio.01013-15

Scott J, Taylor L, Gore A, Shaddick C. Mortality in London in the winter of 1962-63. Medical Officer 1964; 111(23): 327-330.

Schanzer D, Langley J, Tam T. Co-morbidities associated with influenza-attributed mortality, 1994–2000, Canada. Vaccine 2008; 26(36):4697-4703. https://doi.org/10.1016/j.vaccine.2008.06.087.

Science Direct. Modifiable areal unit problem. Elsevier BV 2020. Modifiable Areal Unit Problem - an overview | ScienceDirect Topics

Sencio V, Barthelemy A, Tavares A, et al. Gut dysbiosis during influenza contributes to pulmonary pneumococcal superinfection through altered short-chain fatty acid production. Cell Reports 2020; 30(9): 2934-2947. https://doi.org/10.1016/j.celrep.2020.02.013.

Shankar K, Lin F, Epino H, et al. Emergency department falls: a longitudinal analysis of revisits and hospitalisations between patients who fall and patients who did not fall. BMJ Open 2020; 10: e041054. Doi: 10.1136/bmjopen-2020=041054

South East England Public Health Observatory (SEPHO). Influenza and other acute upper respiratory infections in England, 1998/9 to 2002/3. Unit of health Care Epidemiology, Oxford University 2005.

Simanek A, Dowd J, Pawelec G, et al. Seropositivity to cytomegalovirus, inflammation, all-cause and cardiovascular disease-related mortality in the United States. PLoS ONE 2011; 6(2): e16103. https://doi.org/10.1371/journal.pone.0016103

Smith C, Sandrini S, Datta S, et al. Respiratory Syncytial Virus increases the virulence of Streptococcus pneumoniae by binding to penicillin binding protein 1a. A new paradigm in respiratory infection. Amer J Resp and Crit Care Med 2014; 190(2): https://doi.org/10.1164/rccm.201311-2110OC

Smith C, Le Comber S, Rowe H, et al. Direct interactions with influenza promote bacterial adherence during respiratory infections. Nat Microbiol 2019; 4, 1328–1336. https://doi.org/10.1038/s41564-019-0447-0

Shi T, Denouel A, Tietjen A, et al. Global disease burden estimates of Respiratory Syncytial Virus–associated acute respiratory infection in older adults in 2015: A systematic review and meta-analysis, J Infectious Diseases, 2020; 222(S7), S577-S583. https://doi.org/10.1093/infdis/jiz059

Skog L, Linde A, Pairngren H, et al. Spatiotemporal characteristics of pandemic influenza. BMC Infect Dis 2014; 14: 378. http:///.biomedcentral.com/1471-2334/14/378

Skowronski D, Chambers C, Sabaiduc S, et al. A perfect storm: Impact of genomic variation and serial vaccination on low influenza vaccine effectiveness during the 2014-2015 season. Clin Infect Dis. 2016; 63(1): 221-3. doi: 10.1093/cid/ciw176.

Solianik R, Skurvydas A, Vitkauskienė A, Brazaitis M. Gender-specific cold responses induce a similar body-cooling rate but different neuroendocrine and immune responses. Cryobiology 2014; 69(1): 26-33. https://doi.org/10.1016/j.cryobiol.2014.04.015.

Stowe J, Tessier E, Zhao H, et al. Interactions between SARS-CoV-2 and Influenza and the impact of coinfection on disease severity: A test negative design. medRxiv September 18, 2020. doi: https://doi.org/10.1101/2020.09.18.20189647

Thompson W, Moore M, Weintraub E, et al. Estimating influenza-associated deaths in the United States. Amer J Public Health 2009; 99(S2): S225:S230.

Travis S, Loving G, McClanahan L, Bernard M. Hospitalization patterns and palliation in the last year of life among residents in long-term care. The Gerontologist 2001; 41(2): 153-160. https://doi.org/10.1093/geront/41.2.153

Upshur R, Moineddin R, Crighton E, Mamdani M. Interactions of viral pathogens on hospital admissions for pneumonia, croup and chronic obstructive pulmonary diseases: Results of a multivariate time-series analysis. Epidemiology and Infection 2006; 134(6), 1174-1178. doi:10.1017/S0950268806006236

van den Wijngaard C, van Asten L, Meijer A, et al. Detection of excess influenza severity: Associating respiratory hospitalization and mortality data with reports of Influenza-Like Illness by primary care physicians. Amer J Public Health 2010; 100, 2248-2254. https://doi.org/10.2105/AJPH.2009.168245

Velasco-Hernández J, Núñez-López M, Comas-García A, et al. Superinfection between Influenza and RSV alternating patterns in San Luis Potosí State, México. PLoS ONE 2015; 10(3): e0115674. https://doi.org/10.1371/journal.pone.0115674

Wettstein M, Spuling S, Cengia A. Trajectories of functional health and its association with information processing speed and subjective well-being: The role of age versus time to death. Psychol Aging 2020; 35(2):190-203. doi: 10.1037/pag0000418.

Wilkinson T, Aris E, Bourne S on behalf of the AERIS Study Group, et al. A prospective, observational cohort study of the seasonal dynamics of airway pathogens in the aetiology of exacerbations in COPD. Thorax 2017; 72: 919-927.

Williams T-I. GET FLUED UP: How many people die of flu every year? The Sun. 7 Oct 2020 https://www.thesun.co.uk/news/12797578/flu-how-many-people-die-year/

World Bank. Death rate, crude (per 1,000 people). 2020. https://data.worldbank.org/indicator/SP.DYN.CDRT.IN (accessed 20 November 2020)

World Health Organization. Deaths (#), Influenza. Updated 7 September 2020a. https://gateway.euro.who.int/en/indicators/hfamdb_405-deaths-influenza/visualizations/#id=30223&tab=graph (accessed 17 November 2020)

World Health Organization. RSV vaccine research and development. 2020b. WHO | RSV vaccine research and development

World Health Organization. Influenza update – 383. 2020c. WHO | Influenza update - 383 (accessed 9 January 2021)

Yang W, Olson D, Shaman J. Forecasting influenza outbreaks in boroughs and neighborhoods of New York City. PLoS Comput Biol. 2016; 12(11): e1005201. doi: 10.1371/journal.pcbi.1005201.

Yin M, Huang L, Zhang Y, et al. Effectiveness and safety of dual influenza and pneumococcal vaccination versus separate administration or no vaccination in older adults: a meta-analysis. Expert Rev Vaccines. 2018; 17(7): 653-663. doi: 10.1080/14760584.2018.1495077.

Whiting P, Joseph C, Zambon M, et al. Influenza activity in England and Wales: October 1998 to June 1999. Commun Dis Public Health 1999; 2(4): 273-279.

Zacho J, Benfield T, Tybjærg-Hansen A, Nordestgaard BG. Increased baseline C-Reactive Protein concentrations are associated with increased risk of infections: Results from 2 large Danish population cohorts. Clin Chem. 2016 Feb;62(2):335-42. doi: 10.1373/clinchem.2015.249680.

Zanin M, Baviskar P, Webster R, Webby R. The interaction between respiratory pathogens and mucus. Cell Host Microbe. 2016;19(2):159-68. doi: 10.1016/j.chom.2016.01.001.

Zhang YY, Tang XF, Du CH, et al. Comparison of dual influenza and pneumococcal polysaccharide vaccination with influenza vaccination alone for preventing pneumonia and reducing mortality among the elderly: A meta-analysis. Hum Vaccin Immunother. 2016;12(12): 3056-3064. doi: 10.1080/21645515.2016.1221552.

Zuo T, Zhang F, Lui G, et al. Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. Gastroenterology 2020; 159(3): 944-955. https://doi.org/10.1053/j.gastro.2020.05.048

**Appendix 1: Controversies in influenza mortality and vaccination**

As I was conducting the analysis supporting this part of the series, it became increasingly apparent that the simple messages given to the public were sometimes inconsistent with the data. I am not the first to reach this conclusion, and the seminal paper by Peter Doshi published in 2008 on "Trends in recorded influenza mortality" (Doshi 2008) gives a compelling summary of the evidence as does the paper by Cannell et al (2008) on the potential role of vitamin D on nine conundrums in influenza epidemiology. Peter Doshi has also suggested that a silo mentality focus on influenza has led to the situation that vaccination is being taken far beyond the point of economic benefit (Doshi 2013).

This section will attempt to give an overview of the controversies surrounding influenza mortality and vaccination.

Why did EWM decline to the mid-1990's and then stop declining?

Figure A1.1 gives the trend in EWM in England and Wales over the period 1950/51 to 2019/20. The EWM for 2019/20 is in March just before COVID-19 deaths started to rise in April-20. Clearly seen is a trend down through to the mid-1990's after which EWM reaches an asymptote – although it is possible that the asymptote was reached in the early 1980's. In New Zealand from 1980–2000 no decline in seasonal mortality was also observed (Davie et al 2007). My own analysis of data for Germany shows no decline in EWM after the winter of 1969/70.

Figure A1.1: Maximum winter EWM in England and Wales from the winter of 1950/51 to that of 2019/20
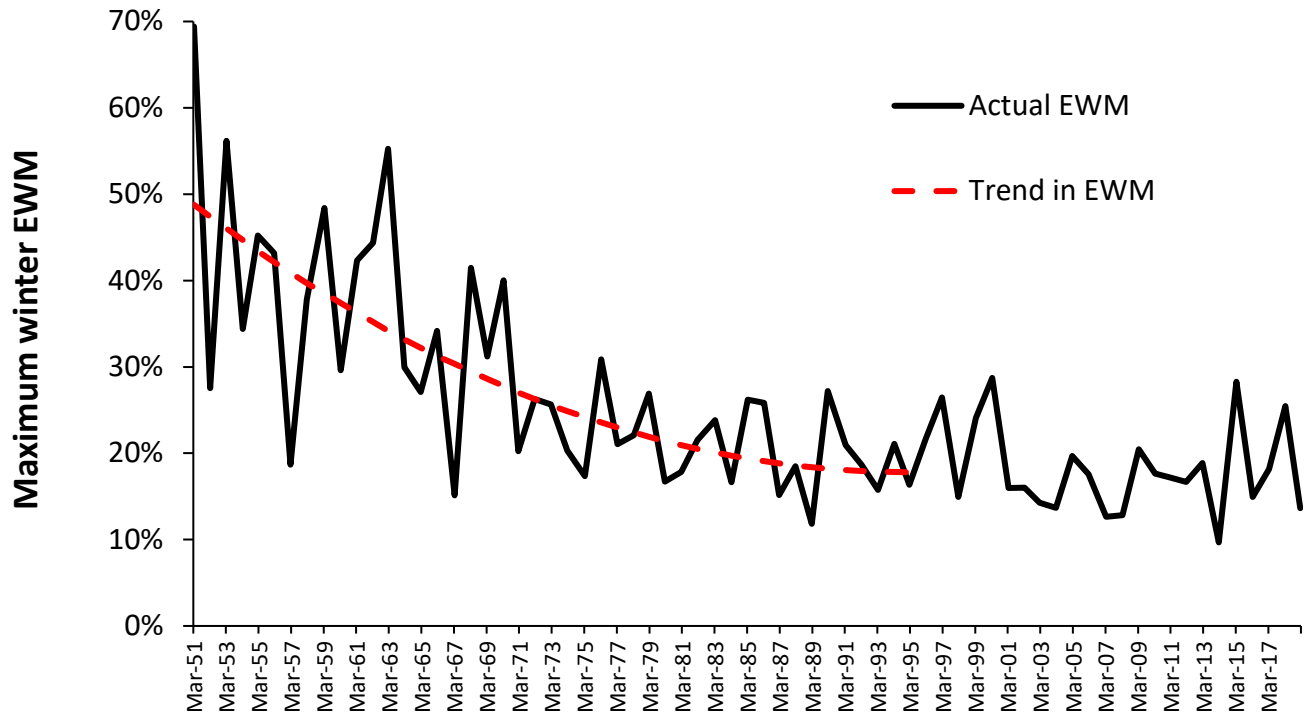
In theory, EWM should have continued to decline for three reasons:

1. Thermal insulation standards in housing have progressively improved over time
2. Global warming means that the winters have become progressively milder
3. Influenza vaccination rates have improved over this period

If influenza vaccination is as effective against influenza *mortality* as the public have been led to believe then EWM should have progressively fallen after the mid-1990's. A similar study in New Zealand between 1980 and 2000 showed that no decline in seasonal mortality was evident over the two decades (Davie et al 2007), i.e., the decline was not country specific.

In England and Wales EWM rises in a near linear manner with age above 74 years, with slightly higher slope in females. In males from an average of around 14% EWM at age below 75 to 29% age 90+ (in both England and Wales, and in females from around 15% age below 75 to 33% age 90+ in England to 37% in Wales (ONS 2020). Recall that age is also a proxy for the NTD effect. The ageing population would act to slightly elevate EWM over time, however, influenza vaccination has increased markedly since the mid-1990's and is around 75% for older people (Jorgensen et al 2018).

Interestingly, the study of Fireman et al (2009) could only demonstrate a 4.6% reduction in mortality among the vaccinated elderly (age 65+) over nine consecutive flu seasons. See section below regarding the different measures of vaccine effectiveness.

Uncertain estimates of influenza morbidity and mortality

An Australian study which used record linkage between multiple health care databases concluded "Among death registrations, hospital admissions and ED presentations with influenza recorded as a cause of illness, 15%, 28% and 1.4%, respectively, also had laboratory notified influenza. Time trends in counts of influenza recorded on the ED, admission and death databases reflected the trend in counts of virologically diagnosed influenza. A minority of the death, hospital admission and ED records for persons with a virologically diagnosed influenza infection identified influenza as a cause of illness. Few database records with influenza recorded as a cause had laboratory confirmation. The databases have limited value for estimating incidence of influenza outcomes but can be used for monitoring variation in incidence over time" (Muscatello et al 2014).

A Canadian study into the costs of influenza admissions conducted over a three-year period including 41 hospitals could only muster data for 2,943 laboratory confirmed admissions (Ng et al 2017). The problem is that laboratory confirmed influenza is not considered necessary except perhaps in the intensive care unit.

Counting and coding of influenza deaths in the UK have improved from 2018 onward. For example, the number of persons coded as having a confirmed *or possible* death from influenza (ICD-10 J09 to J12) in England & Wales have been low, hence in 2015 (331), 2016 (388), 2017 (297), 2018 (1,664), 2019 (1,290). This total includes J12 which covers viral pneumonia. These can be considered as lower respiratory tract attributable deaths (Office for National Statistics 2020d).

All Public Health Agencies must then estimate what they believe to be the deaths attributable to influenza.

As has been shown above, no one directly counts the number of influenza admissions or deaths and these must be inferred as 'influenza-associated' (Nicoll et al 2012). Clearly such inference is open to methodological problems and hidden bias (Schanzer et al 2008, Thompson et al 2009, Nicholl et al 2012). In their review of 103 estimates of influenza mortality Li et al (2018) concluded, "No 'average' estimate of excess mortality could reliably be made due to substantial variability of the estimates partly attributable to methodological differences in the studies".

To do this an estimate of lower respiratory tract infections (LRTI) incidence, hospitalizations and deaths are constructed of which a proportion is attributed to influenza (see GBD Influenza collaborators 2018). Hence for 2017, an estimated 145,000 (UI 99,000 – 200,000) LRTI influenza deaths occurred around the world. Mortality is highest among adults aged 70+. Around 11.5% (UI 10% - 12.9%) of LRTI admissions were estimated to be due to influenza. Hence in 2017 influenza accounted for roughly 0.3% of global deaths. Applied to England & Wales this gives around 1,300 deaths which is close to the figures in 2018 and 2019 (above) after counting and coding of influenza improved.

Public Health England estimate around 17,000 (Williams 2020) which is about 10-times higher (approximately 3% of deaths in England). One study showed that the highest years for potentially attributable influenza deaths in England were 2008/09 and 2014/15, with 26, 542 excess mortality for 2014/15 for those aged 65+ (Pebody et al 2018) – which was assumed to be 100% attributable to influenza. This study failed to mention the potential contribution from negative vaccine effectiveness specific to the 2014/15 season – see Appendix 2.

The real figure is probably somewhere in between the two extremes and closer to the more robust GBD Influenza collaborators (2018) estimate. Is Public Health England erring toward exaggerating influenza mortality to maintain public compliance with the remarkably high influenza vaccination rates in the UK (OECD Data 2020). Indeed, since the UK has the second highest influenza vaccination rate in the world (Korea has the highest), why so many estimated influenza deaths in England?

Issues around influenza vaccine effectiveness will now be discussed.

What does influenza vaccine effectiveness (VE) measure?

It is not widely appreciated that three different types of vaccine effectiveness measures exist:

1. Against rates of influenza like illness (ILI) determined by GP consultation rates (most common)
2. Against rates of hospital admission (less common)
3. Against deaths (least common)

As with all methods, different types of bias have been noted (Jackson et al 2006, Fireman et al 2009, Castilla et al 2015; Lipsitch et al 2016, Ainslie et al 2017, 2018, 2019, De Smedt et al 2018, Butler et al 2019). However, the key issue is whether the different methods of VE measure different aspects of the effects of vaccination in different groups of people. Hence caution is warranted when attempting to apply VE from GP consultation rates to VE for death.

As can be seen in Figure A1.2, the VE for #1 above varies greatly from year to year. Recall that the all-age VE is generally higher than VE in the 65+ age group. Potential bias is because persons who have died or been hospitalized are excluded as are persons who cannot afford a GP visit. See Appendix 2 for a detailed

examination of potential adverse consequences of negative VE in the 2014/15 winter upon mortality in the elderly.

Figure A1.2: Overall vaccine effectiveness (all-ages) against GP consultation for influenza like illness (ILI) in the USA (source CDC 2020)
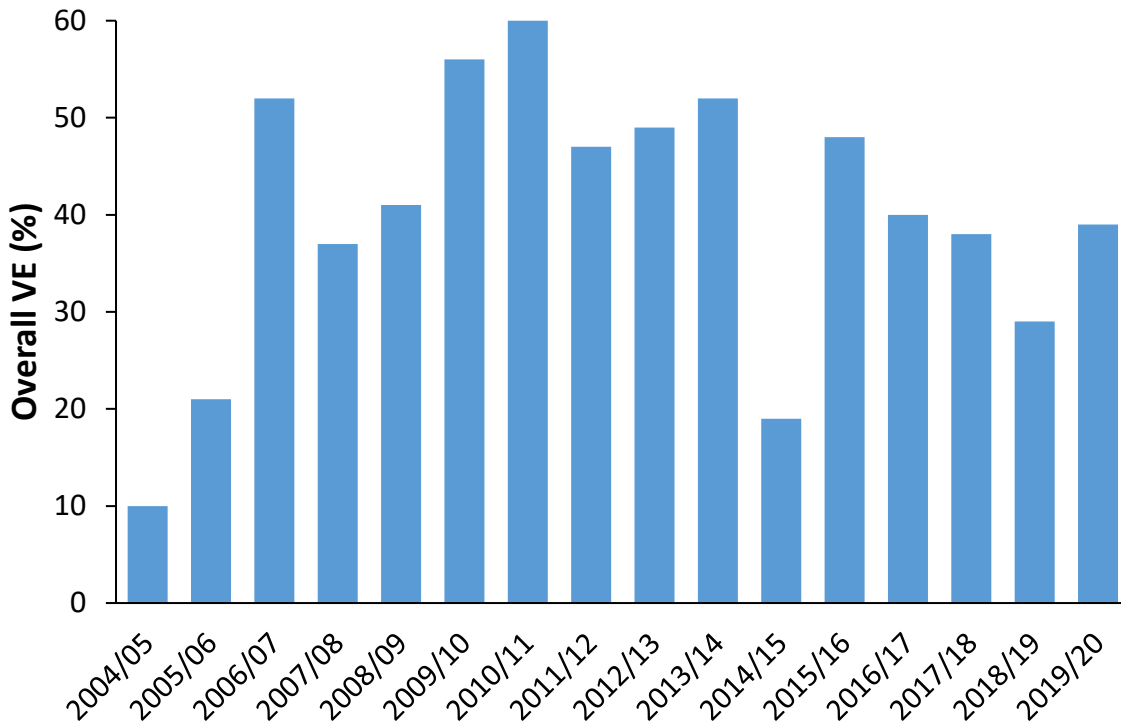
The common immune modifying virus, cytomegalovirus (CMV), is known to have profound effects on influenza vaccine effectiveness – especially in the elderly, but this is ignored as a confounding factor in most VE studies (Jones 2016d). This is especially relevant given that individuals not infected by this virus typically live longer.

A study of vaccination and prevention of hospitalization for the seasons 2010/11 to 2014/15 for those aged 65+ gave 37% VE overall. For influenza A(H3N2) VE was 43% in the years when there was a good antigenic match and 14% in the seasons when there was a poor antigenic match (Rondy et al 2017).

A recent study in the UK concluded that there was little evidence to suggest that influenza vaccination in the elderly reduced rates of hospitalization or death (Anderson et al 2020). However, a study in Taiwan of the frail elderly observed an 8% reduction in hospitalization and a 45% reduction in mortality (Lee et al 2014). A review of published studies by Cheng et al (2020) showed that "the pooled adjusted relative risks among influenza-vaccinated people relative to unvaccinated people were 0.74 (95 % confidence interval [CI] = 0.70-0.78) for cardiovascular diseases (63 studies), 0.82 (95 % CI = 0.75-0.91) for respiratory diseases (29 studies), and 0.57 (95 % CI = 0.51-0.63) for all-cause mortality (43 studies)".

Another study for community dwelling elderly (those least likely to be in the last year of life) for the influenza seasons 1990/91 to 1999/00 gave a pooled 27% reduction in the risk of hospital admissions for influenza or pneumonia and a 48% reduction in the risk of death (Nichol et al 2007). For hospitalization,

the exception was for 1993/94 when VE was zero, although VE for death for this winter was supposedly over 40%. The trend over time for VE for hospitalization and death likewise did not match. The protective effect against death reached between 60% to 70% for the 1996/97 season when only a 20% to 40% effect against admission was inferred. Something peculiar is happening in the VE estimates. The protective effect against mortality in these studies seems somewhat too good to be true.

Indeed, does apparent influenza VE vary with the mix of pathogens each winter, and a complex pecking order of competition between pathogens, as implied for COVID-19 against influenza?

Joint vaccination against pneumococcus and influenza

There is overwhelming evidence that joint vaccination against pneumococcus and influenza gives lower pneumonia rates and all-cause mortality than vaccination in one without the other. These results are applicable to both the elderly and patients undergoing dialysis, both of which are examples of a weakened immune response (Zhang et al 2016, Yin et al 2018, Mo et al 2020).

Rates of Pneumococcal Polysaccharide Vaccine (PPV) uptake in England are around 69% in those aged 65+ and 82% for those aged 85+ (Public Health England 2019).

Influenza vaccine adverse reactions and other risks

One modelling study has suggested that repeated vaccination of children increases the risk of influenza in old age by a factor of 2.4-times (Carrat et al 2005). The accuracy of this forecast will alas, not be known for another 50 years.

The state of Victoria in Australia monitors adverse reactions to influenza vaccination. In particular, the 2015 vaccination season (corresponding to 2015/16 in the Northern hemisphere) saw a doubling in the rate of allergy-related reactions from 12% in 2014 to 25% in 2015 (Clothier et al 2017). While the clinical severity of these reactions was judged to alter the vaccination program risk benefit, it does suggest that a surprising high proportion of people do suffer allergy (immune) reactions. In relation to the male/female differences noted in this series females are known to have higher proportions of adverse reactions to influenza vaccination (Denly 2020).

Periods when respiratory hospitalisation and death are far higher than levels of influenza-like-illness (ILI)

A study in the Netherlands between 1999 and 2005 identified that hospitalisation and deaths in the winter of 2003/04 was far higher than levels of ILI (van den Wijngaard et al 2010). Data from England and Wales is given in Figures A1.3a and A1.3b where there is extremely high scatter in the relationship between ILI rates and weekly deaths.

Note that 2009 was during the Swine-flu (A(H1N1)) epidemic where deaths in the elderly were extremely rare due to prior exposure to an antigenically similar strain circulating before 1957 (Jacobs et al 2012).

Given that most deaths occur in the age 75+ band it would seem sensible to report ILI rates broken down for children age 0-15, then age 16-74 and age 75+. There is little point in having a misleading statistic covering all ages.

Figure A1.3a: Relationship between weekly influenza-like-illness (ILI) rates and deaths per week (adjusted for the trend over time using a 2nd order polynomial), Wales 1999 to 2019
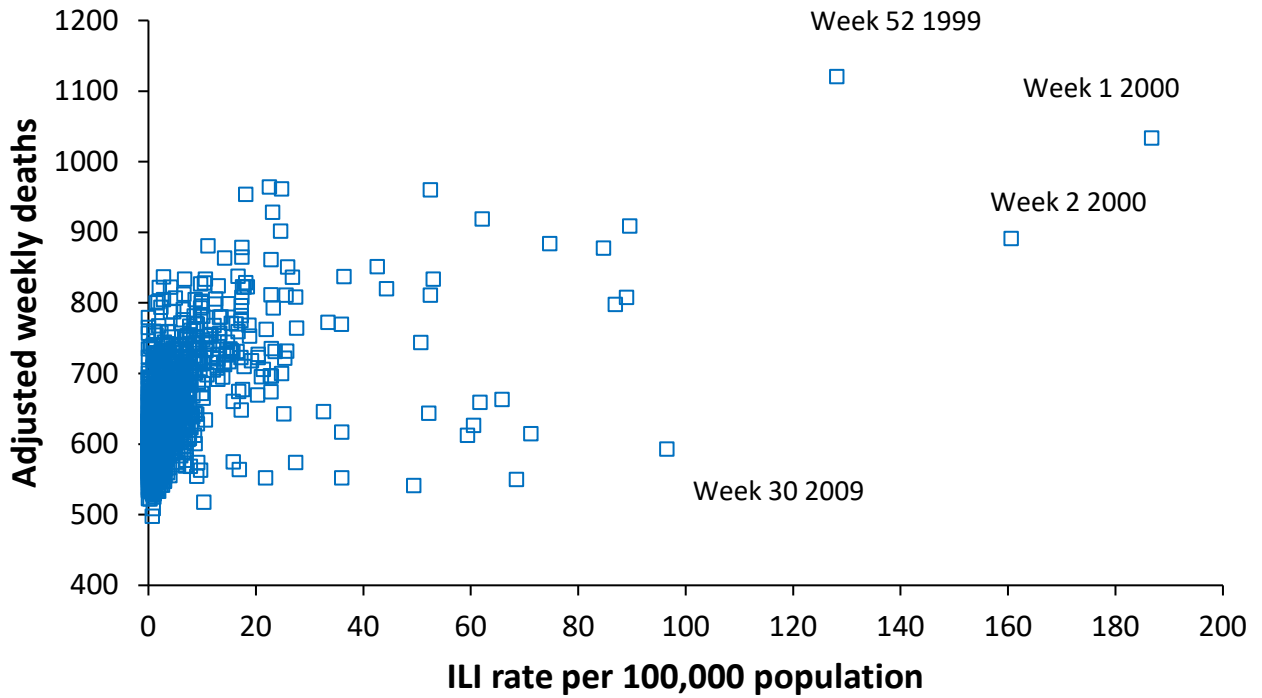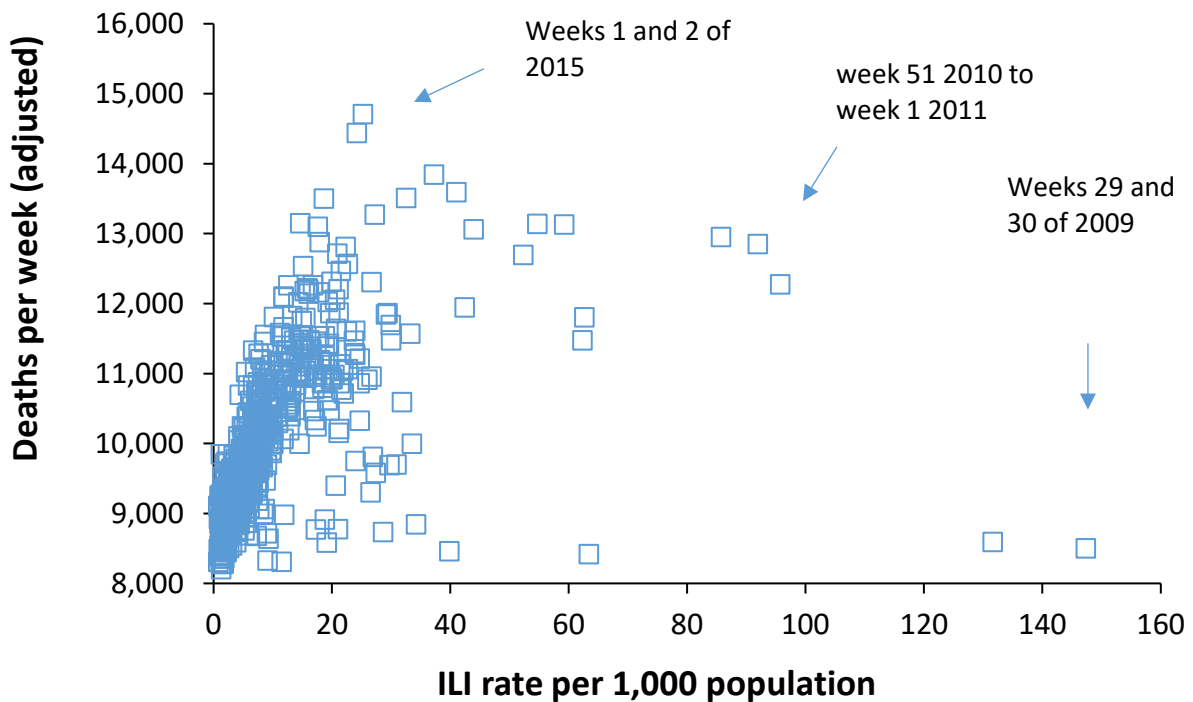

Figure A1.3b: Relationship between weekly influenza-like-illness (ILI) rates and deaths per week (adjusted for the trend over time using a 2nd order polynomial), England 2004 to 2019

Roles for Vitamin D

In temperate latitudes even pandemic influenzas often show a clear seasonality. The data support the hypothesis that high levels of UVB radiation (vitamin D level), as occur in the summer, act in a protective manner with respect to influenza (Juzeniene et al 2010). Cannell et al (2008) suggest that the role of vitamin D in immune regulation explains the nine conundrums seen in influenza epidemiology.

The immune protective and anti-inflammatory roles of vitamin D are widely recognised (Aranow 2011, Meehan and Penckofer 2014, Baggerly et al 2015). Vitamin D supplementation in deficient elderly persons promotes a higher TGFβ plasma level in response to influenza vaccination without improving antibody production. The Vit-D supplementation seems to direct the lymphocyte polarization toward a tolerogenic immune response as suggested by the lower Th1/Th2 ratio compared to controls (Goncalves-Mendes et al 2019). A tolerogenic immune response would be helpful in those instances of influenza-induced inflammatory damage.

The latest advice regarding COVID-19 is 10,000 IU/d of vitamin D_3 per day for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d. The goal should be to raise 25(OH)D concentrations above 40-60 ng/mL (100-150 nmol/L). For treatment of people who become infected with COVID-19, higher vitamin D_3 doses might be useful. Randomized controlled trials and large population studies should be conducted to evaluate these recommendations (Grant et al 2020).

Figure A1.4: Hazard ratio for death from cancer versus serum standardized Vitamin D concentration.
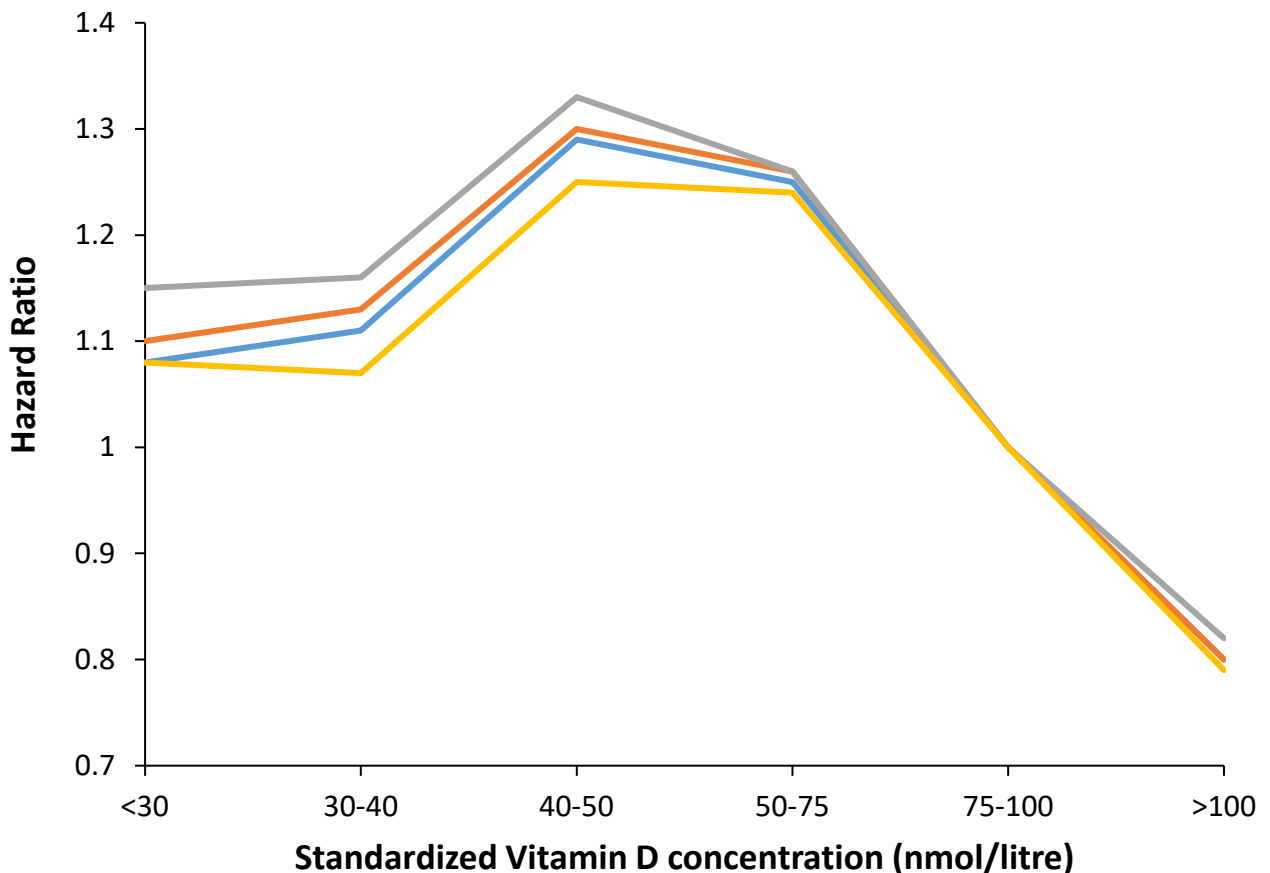
Rezaei et al (2018) concluded that their literature review suggested that treatment of influenza-infected individuals with Vitamin D supplements or cathelicidin-derived agents may provide appreciable protection against natural influenza infection. Moreover, Vitamin D given at appropriate doses may facilitate protection against seasonal flu.

Prudence suggests that all elderly persons, and especially those in nursing homes, should be given vitamin D supplements of an appropriately high dosage.

As an example of the unexpected potential benefits of high serum vitamin D levels the data of Gaksch et al (2017) relating to cancer mortality has been reanalysed in Figure A1.4. The four lines represent the models used to adjust for risk factors. As can be seen the risk of death initially rises and then approaches a minimum above 100 nmol/litre. This concentration is consistent for the advice regarding COVID-19 above. Note the high consistency between models above 50 nmol/litre. It remains unknown if this reduced risk for higher serum vitamin D is specific to certain cancers. Indeed, at which serum level is the minimum reached?

A recent study regarding the effect of Vitamin D supplementation fir three months in Vit-D deficient elderly persons yielded some interesting results. After influenza vaccination there was no benefit regarding antibody titres, however, lower plasma levels of TNFα and IL-6, and higher ones for TFGβ were observed three months after vaccination and the Th1/Th2 ratio was lower in the D group after 3 months of Vit-D supplementation. Supplementation seemed to direct the lymphocyte polarization toward a tolerogenic immune response. The authors concluded that "a deeper characterization of metabolic and molecular pathways of these observations will aid in the understanding of Vit-D's effects on cell-mediated immunity in aging" (Goncalves-Mendes et al 2019). Given the observed higher sensitivity of females to EWM a tolerogenic immune response may be beneficial to females. Further studies are required regarding gender-specific effects.

Conclusions

Influenza vaccination remains the single most effective defence against a serious pathogen. Influenza vaccination reduces GP visits for ILI, reduces sickness absence among health care workers and reduces hospitalization for influenza. However, the effect on mortality is less clear with some estimates being far too good to be true.

Our understanding of immune function is increasing and far more effective vaccines for the elderly will be developed. Despite a small percentage of adverse reactions (mostly minor) and occasional rapid mutations of the virus leading to negative vaccine effectiveness, vaccination against influenza is still recommended. Hopefully, vaccines for other winter pathogens will be developed soon. A vaccine against RSV remains a WHO priority area (WHO 2020b).

All-age influenza-like-illness (ILI) has little correlation with mortality which mainly occurs in the elderly. While the all-age ILI rate is a good measure for pressures on primary care, a separate ILI rate should be reported for those aged 65-84 and 85+ to allow the potential mortality consequences of each seasons infections to be inferred.

However, it is almost certain that current methods estimating deaths from influenza give an over-estimate due to lack of adjustment for RSV mortality in the elderly. This may affect the cost-effectiveness of

influenza vaccination in the elderly. The absence of a trend down in EWM since the early 1990's is problematic to the case for influenza vaccination as a means of protection against death in the elderly.

The apparent discrepancy between influenza vaccination and mortality reduction and overall trends in mortality and EWM may arise because in those who are in the last year of life influenza vaccination does confer benefit, however, this benefit is immediately lost when the person succumbs to another pathogen against which there is no current vaccine.

Given the major conclusion of this study that winter is a multi-pathogen event the observation that joint pneumococcal and influenza vaccination gives greater protection than influenza vaccination alone seems to indicate that vaccination against both is a priority.

Even if the WHO target of 75% vaccination in the over 65's is reached influenza and it's interactions with the winter pathogen pool will remain a source of highly variable cost and capacity pressures each winter. The costs associated with persons in the last year of life are unlikely to be significantly diminished by influenza vaccination, however, studies need to be initiated to determine if this is the case.

My own ongoing research in this area (in preparation) seems to indicate that rates of EWM do not seem to show any difference between countries with minimal influenza vaccination and those with the highest rates. Those with the highest influenza vaccination rates may even show slightly higher EWM. This could be interpreted to confirm the observation in Table 1 that winter is a highly multi-pathogen event and that the observed EWM is the outcome of complex interactions between pathogens including outbreaks of the new type or kind of disease.

Appendix 2: What happened in winter 2014/15?

A2.1 Background

This section will attempt to re-interpret an unexpected increase in total deaths in the Northern hemisphere in 2015 compared to 2014. The issues are multifactorial, and interpretation relies heavily on spatiotemporal granularity with multiple pathogens, hence, comparing two calendar years (2014 versus 2015) is subject to the calendar year fallacy (Jones 2019). The combined forces of the Office for National Statistics and Public Health England (ONS 2016) failed to adequately explain the cause(s) because they relied too heavily on calendar year comparison.

The year 2015 was also the year when many Western countries saw a trend to increased mortality rates and declining life expectancy (Public Health England 2018, London School of Economics 2019, Longevity Science Panel 2020). Hence understanding the multifactorial issues is far more important than just 2015.

The 2014/15 vaccine was identical to that used in 2013/14 when VE had been high. During 2014 the predominant strains of influenza underwent multiple mutations such that when the Southern hemisphere had been vaccinated for the winter of 2014 (middle of the year) the vaccine was already showing signs of being somewhat ineffective. VE for influenza A(H3N2) which was the predominant strain in Australia during the 2014 winter had dropped to 26% (Sullivan 2016). Between winter in the Southern hemisphere and the Northern hemisphere further antigenic drift occurred and the mix of strains infecting each country/region became more diverse.

By the time the Northern hemisphere were vaccinated for the 2014/15 season, low and even negative VE had emerged which in Beijing China had dropped to 27% for A(H3N2) and -32% for influenza B. Across all strain's vaccine effectiveness fell rapidly with age from +56% (age 6-17), to -13% (age 18-59) and -67% for age 60+ (Qin et al 2016). In Canada, VE for A(H3N2) was -16% overall (with -13% for clade-3C.2a and +52% for clade-3C.3b). VE for influenza B was 42%. However, for those vaccinated only in 2014/15 VE was 53%, but fell to -32% for those also vaccinated in 2013/14 and -54% for those vaccinated each year since 2012/13 (Skowronski et al 2016). In the UK, VE for Influenza A and A(H3N2) was around 30% (across all ages), while for influenza B VE was around 45% up to age 64 but was a massive -200% for age 65+ (Peabody et al 2015). The percentage uptake of vaccination varied considerably between regions, i.e., only 32% for children in Cumbria, 23% for health care workers in Northern Ireland, etc (PHE 2015).

However, levels of ILI were not unusually high and barely go above 50 per 100,000. Influenza hospital admissions peaked in week 2 of 2015 and were mainly A(H3N2). Compared to previous years ICU admissions were not high. GP and ED attendances for respiratory illness peak in week 52 of 2014 and week 1 of 2015. Acute respiratory outbreaks (mainly influenzas Type A) peak in week 2 of 2015 and are predominantly *in care homes*. RSV rates peaked in weeks 49 and 50 of 2014 and rates of acute bronchitis for those aged 75+ peaked at 7.2 per 1,000 in week 2 of 2015 and remain high through to week 16 when monitoring stopped. ***Influenza B levels only start to rise after week 4 of 2015 (important due to the massive negative VE for this strain). Parainfluenza rates increase above normal after week 4 in 2015*** and were still rising at week 15 when monitoring stopped (Public Health England 2015).

In England, a peak in all-cause mortality occurred mainly in January 2015 followed by a period of higher mortality such that deaths in 2015 had shown the highest jump over the previous year since 1968 (ONS 2016). Deaths went above the upper control limit from week 50 in 2014, peaked in week 2 and went back to upper limit at week 7 in 2015.Excess death did not go back to baseline till week 14 of 2015. Some 86% of the extra deaths occurred in the over 75's and those with Dementia were particularly affected. Dementia(s) are a key indicator of frailty and inability to communicate symptoms and this explains why dementia is recorded as the primary cause of death (Howse 2016). Those with dementia die ***with*** dementia but die ***from*** either respiratory infections (56%) or circulatory system failures – 33% (Brunnström and Englund 2009).

A2.2. An outbreak of the new kind or type of disease complicates analysis

An outbreak of the new disease had been spreading across the UK during 2014. As can be seen in Figure A2.1 from the shift-up initiates bars most of the outbreak occurred between May-14 and Sep-14 with one-third of areas initiating shift-up in June 2014. Some 90% of government areas were therefore in "shift-up" at the time of the January 2015 spike in deaths. Overlaid on Figure A2.1 is a second estimate derived from the rolling difference between successive 12-month periods, the from maximum difference bars. For example, a May-14 date implies that the rolling difference reaches a maximum for the difference between the 12-month total ending April-14 versus the 12-month total ending April-15 – this latter period commences at May-14.

The point of initiation for Wales and England is June-14, with Scotland and Northern Ireland in August-14. Local Authority and Regional areas cluster around these dates due to spatiotemporal spread of the agent across the UK. For example, in London around Dec-13 for Haringey, Aug-14 for Hackney and Dec-14 for Hammersmith & Fulham, etc. The difference between the two viewpoints in Figure A2.1 is that shift-up is due to a single cause whereas the maximum difference encompasses the combined effects of multiple pathogens during the winter months.

Figure A2.1: Spread of an outbreak of the new disease across UK government areas during 2014 (the shift-up initiates bars) and point at which the rolling difference between successive 12-month periods indicates a potential retrospective start date (the from maximum difference bars)
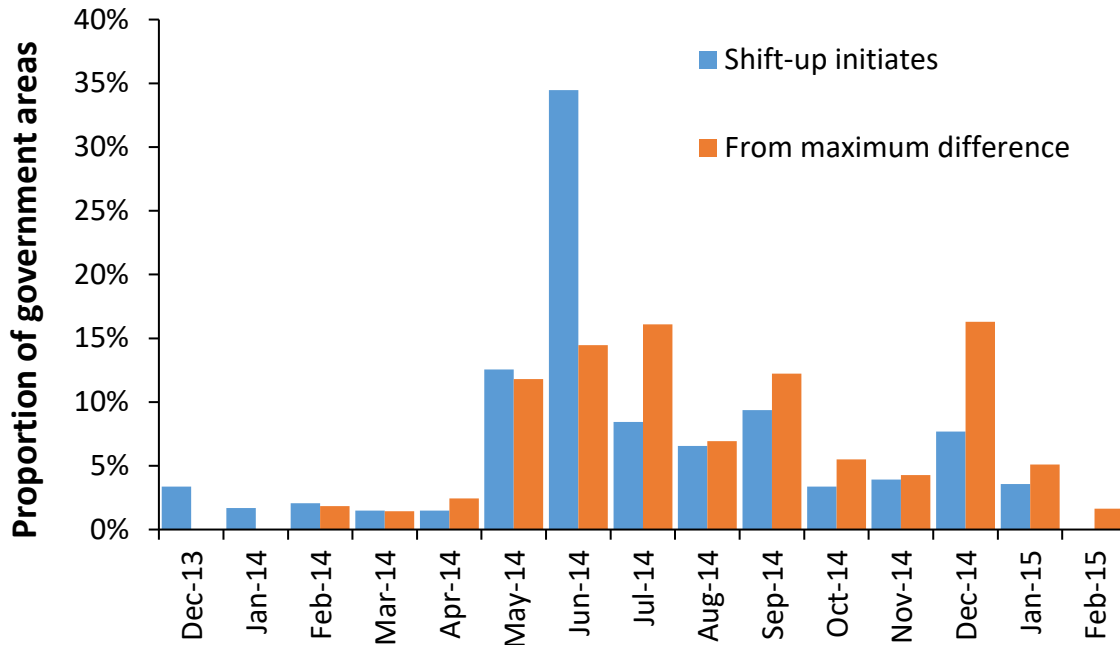

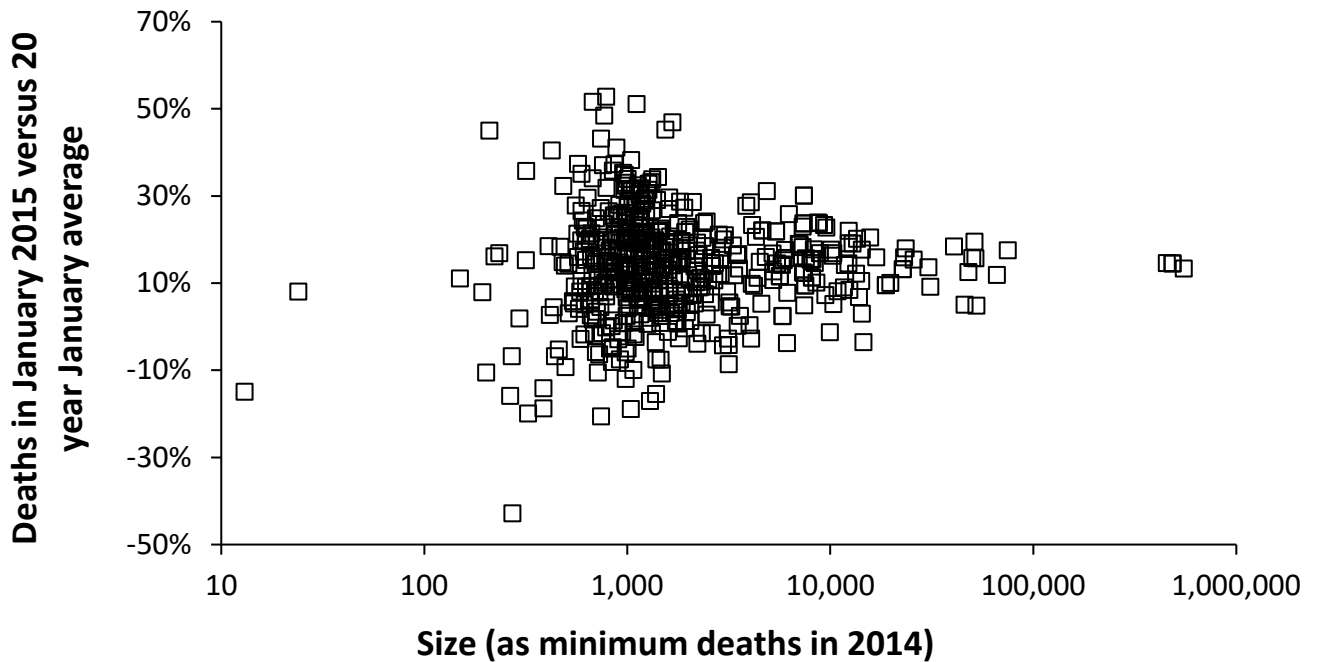**Figure A2.2: Deaths in January 2015 versus the 20-year average for UK local government areas**
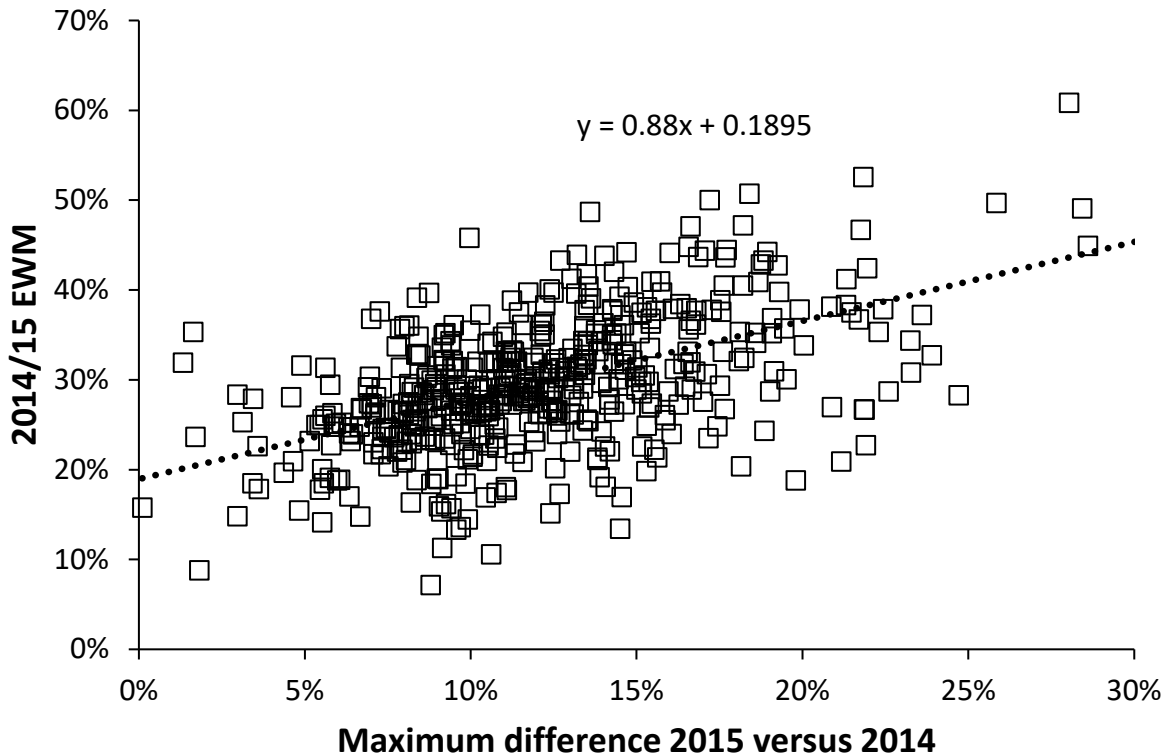
Figure A2.3: Relationship between maximum rolling difference between 12-month total deaths in 2015 versus 2014 and the 2014/15 EWM for UK local government areas


As can be seen in Figure A2.2, deaths across the UK peaked in January 2015 at approximately 13% higher than a 20-year average for January. However, at Regional level this varies from 5 to 20% and within London from -4% in inner London to 9% in Outer London. At 120,000 deaths per annum 1 standard deviation of Poisson variation is ± 1%, at 12,000 ± 3% while at 1,200 it is ± 10%, and chance variation fails to explain the far wider spread. This is consistent with the spatiotemporal granularity in infectious outbreaks.

As intimated in the ONS study (2016) deaths were elevated for several months after Jan-05 and this period of elevated deaths falls within the period used to calculate maximum EWM (maximum of the four-month rolling period ending December through to April). The relationship between the maximum rolling 12-month difference between 2015 and 2014 and the EWM is given in Figure A2.3.

As expected, data from the smallest local government areas lie furthest from the trend line where the data is densely populated. For those few local authorities with a small difference between the two years the EWM appears to reach a minimum of 19%. This is not far from the minimum EWM of 10% for England and Wales in the winter of 2013/14 (Figure A1.1 above).

Figure A2.4 shows the effect of time on the maximum increase in the rolling year-on-year difference in deaths and the resulting median value of EWM in UK local authorities. Note an October 2015 date for maximum EWM implies that initiation occurred in November 2014, etc. This is confirmed in Appendix 3.

Figure A2.4: Effect of the date at which the rolling year-on-year difference in deaths reaches its maximum value and the resulting median value of EWM in UK local authorities.

Month for maximum year-on-year change
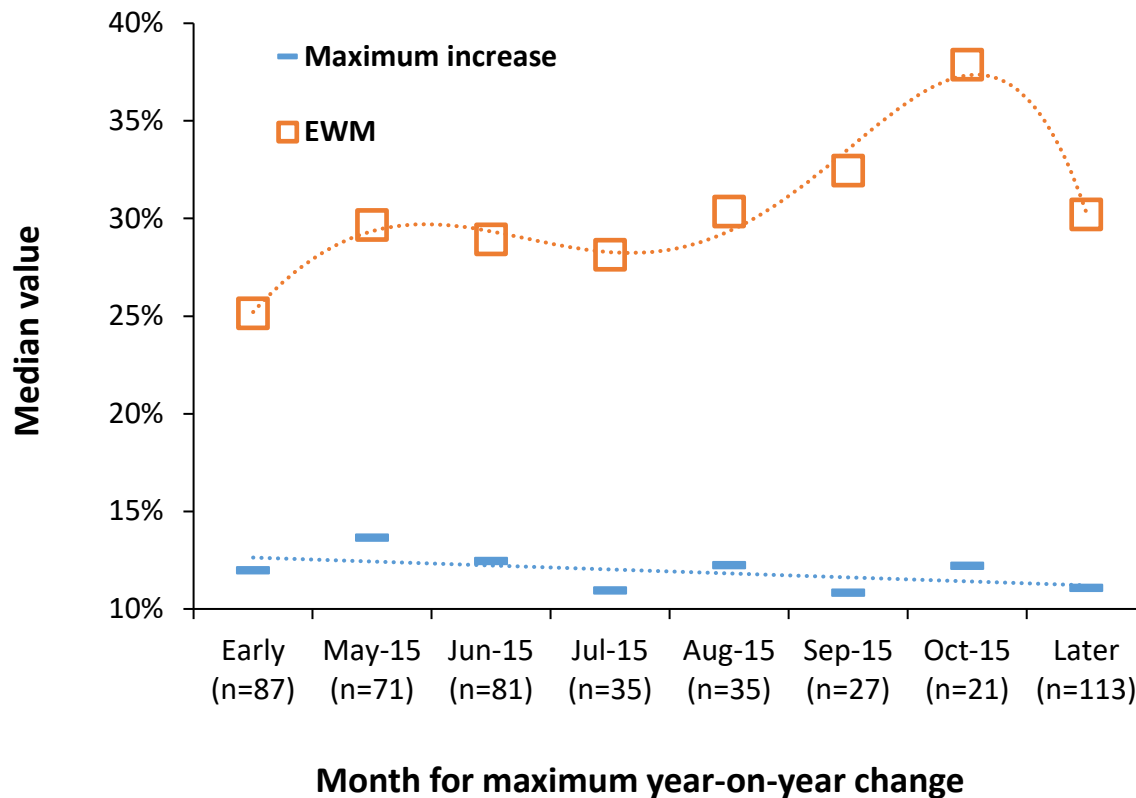
Hence the winter of 2014/15 was a complex mix of spread of the agent causing shift-up across the UK, vaccination with a poorly matched influenza vaccine (especially influenza B in the elderly) in late 2014 followed by a moderate influenza outbreak in late 2014 which will have interacted with the vaccinated population, continued higher deaths after the spike in January 2015. The early peak in deaths corresponds to the peak in RSV infections (recall that deaths will peak about 4 -6 weeks later). Continued higher deaths were probably due to rising levels of both influenza B (negative vaccine effectiveness in the elderly) and parainfluenza as noted in the PHE influenza report (PHE 2015). PHE does not report levels of dual infections although it will have access to such data. Spatiotemporal granularity was imposed on top of these changes giving a confusing view using national level data.

Deaths in 2015 do not drop back to normal levels in the rolling 52-week analysis and continue high through to 2018 when a large shift-down eventually emerges. See Appendix 3.

This confusing jumble of events is consistent with spatiotemporal granularity in the spread of multiple pathogens and ensuing interactions between pathogens and vaccination (positive and negative).

A2.3 Evidence for massive spatiotemporal granularity at small area level

Massive spatiotemporal granularity of the 2015 event in England and Wales has already been demonstrated at small area level (Jones 2017b). This analysis has been repeated at Lower Super Output Area Level (LSOA). A LSOA contains around 1,500 persons or approximately 650 households (OCSI 2021).

The analysis shows the difference in deaths between mid-2015 (July 2014 to June 2015) and mid-2014 (July 2013 to June 2014). Use of mid-year totals avoids the calendar year fallacy since all the excess deaths in the winter of 2014/14 occurred between December 2014 and June 2015.

Figure A2.5 Spatiotemporal small-area granularity of the 2015 increase in deaths in England and Wales
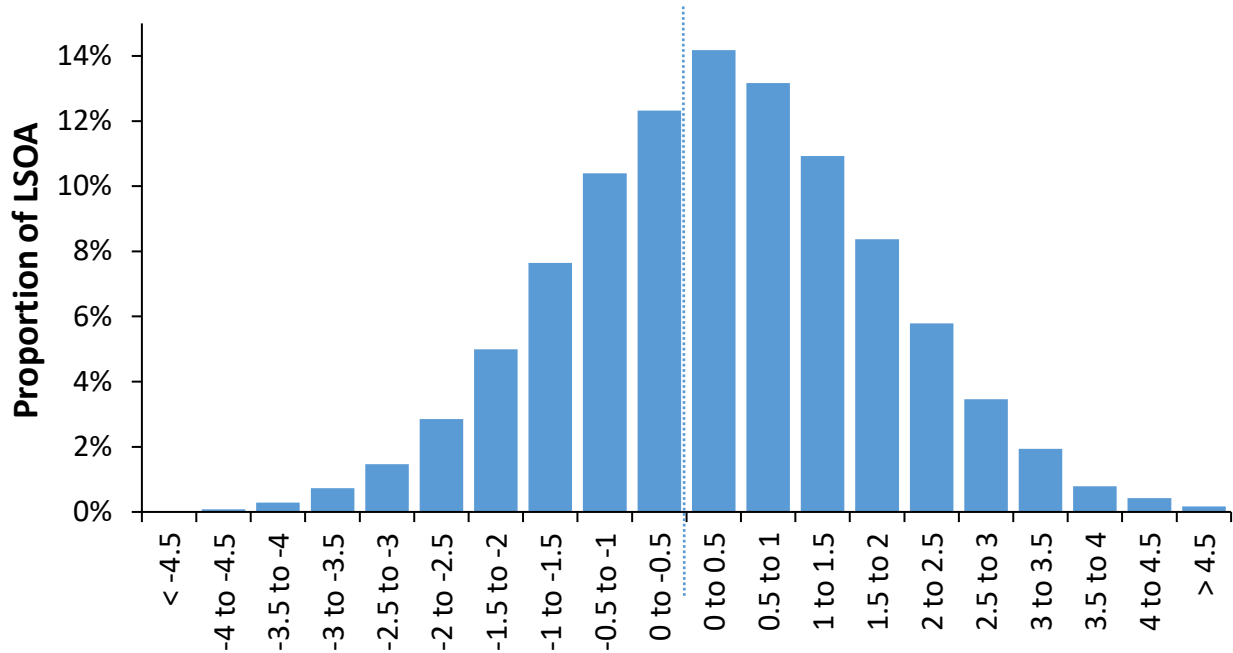
Difference in total deaths mid-2015 and mid-2014 as STDEV

The analysis gives the difference in deaths in each LSOA from 2014 to 2015 expressed as a standard deviation equivalent difference between the two. Hence deaths in 2015 minus deaths in 2014 divided by the square root of the average number of deaths in that LSOA.

Analysis shows that there is a slight increase in the difference between the two years due to population density, with lowest population density LSOA showing a 12% increase rising to a 16.3% increase above 4,000 persons per square Km. The least deprived LSOA had a 12% increase while the most deprived showed a 17% increase. Taking the most deprived 7% of LSOA and segregating by population density showed a 5% increase between the two years for less than 1,200 persons per square Km compared to an 11% increase for LSOA with >7,000 persons per square Km and 12%for more than 12,000 per square Km.

This is typical infectious spread which is highest in deprived areas with high population density, although population density may be more important than deprivation per se.

The distribution of differences is shown in Figure A2.5 with a skewed distribution consistent with higher deaths. However only 59% of LSOA showed higher deaths in 2015 and there are only 18% more LSOA at the right-hand side of the frequency distribution. Likewise, the two tails of the distribution show extreme deviation with a minority of LSOA showing a difference more than ± 4.5 standard deviation equivalent between the years.

How is the negative tail to be explained? The simple explanation is two-fold, namely:

1. Influenza and other winter pathogens show high spatiotemporal granularity and hence will be completely absent in some LSOA but concentrated in others. This was demonstrated for COVID-19 in Part 1 of this series.
2. On top pf the differences in #1 is the spatiotemporal differences in the outbreaks of the new type or kind of infectious disease resulting in a mix of LSOA which are in shift-down in 2015 and others are in shift-up. This was illustrated in Figure A2.1. Hence those LSOA without any outbreaks of winter pathogens but which went into shift-down can show significantly lower mortality in 2015.

Clearly all this is subject to Poisson variation, hence, the use of the frequency distribution in Figure A2.5. Based on pure Poisson randomness alone some 99.8% of outcomes should lie below + 3 standard deviation (only 97.7% in the distribution) and 97.7% below + 2 standard deviation (only 87.4% in the distribution). More importantly only 0.1% should be below - 3 standard deviation equivalent yet some 1.1% do so. Hence even in the presence of winter infections increasing deaths another force is at work acting to cause a large decrease in deaths in some locations.

I have encountered the same problem when attempting to interpret COVID-19 mortality in UK local government areas during 2020 and 2021. Both shift-up and shift-down are operating throughout the duration of the epidemic.

Hence, local authorities which show a shift-up in late 2018 to early 2019 have the potential to revert to shift-down in late 2019 to early 2020 and shift down then diminishes the COVID-19 deaths and resulting all-cause mortality is lower. See http://www.hcaf.biz/2020/Covid_Excess_Deaths.pdf

See next section for more detail regarding spatiotemporal granularity in outbreaks of the new type or kind of disease.

Appendix 3: Is the shift-up instantaneous and how outbreaks of the new type or kind of disease change the shape of the rolling EWM calculation

Firstly, we need to address the issue of whether shift-up is instantaneous as seemingly implied by my early observations during the 1993 outbreak. Two perspectives of the same outbreak are possible (see dual viewpoint studies of the 2012 outbreak in Berkshire as given in the list of further reading just before the reference section):

1. From the viewpoint of a hospital receiving medical patients affected by the new disease condition.
2. A population-based view where patients or deaths occur in a defined area whose boundaries may be somewhat arbitrary.

From the first perspective the outbreak will be moving through the hospital catchment area which is defined by usual patient flow determined by travel time, etc. It is assumed that the infection will disproportionately affect nursing home residents as demonstrated in the Berkshire study on the 2012 outbreak. Hence the hospital receives an initial rush of patients from throughout the catchment area.

Figure A3.1: Spread of a shift-down in 2018 followed by a shift-up in 2019 using a rolling 12-month total of deaths for the entire UK
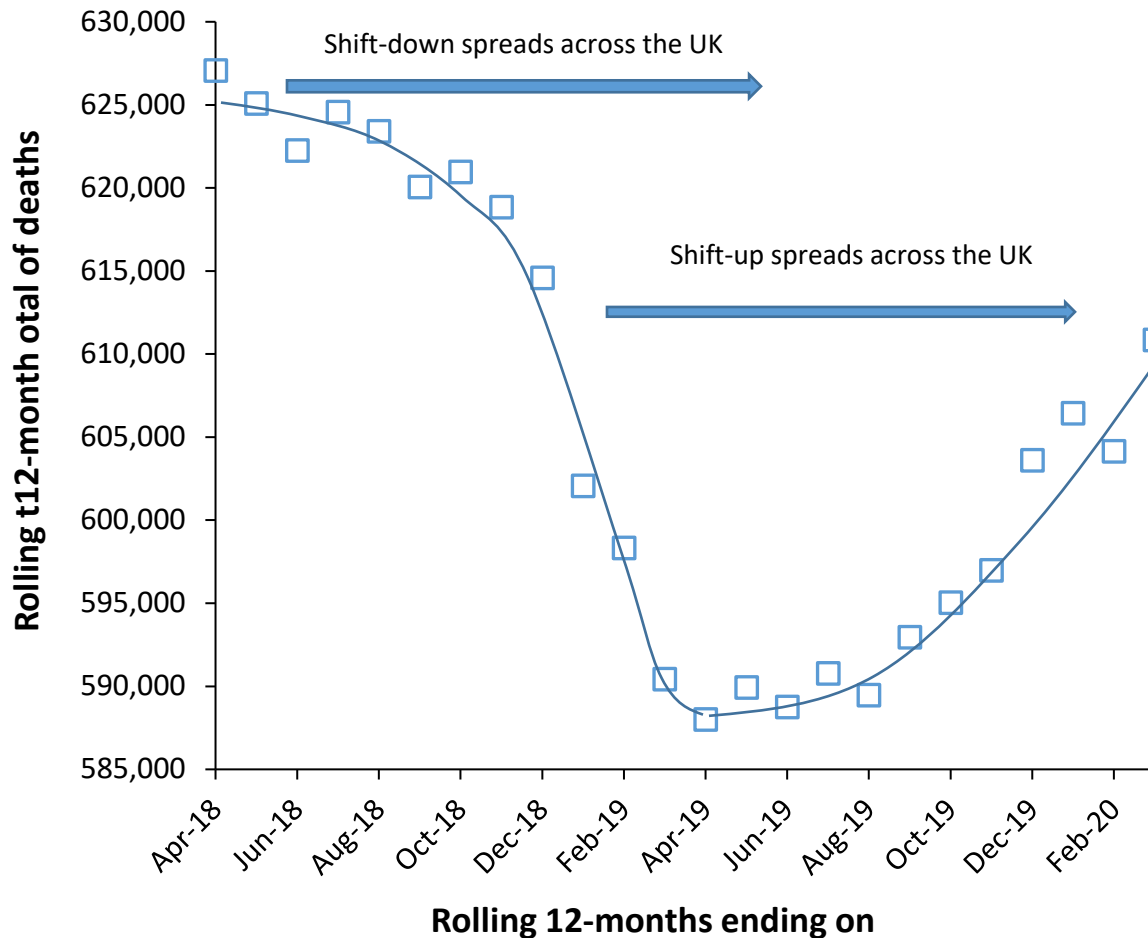

From the defined area perspective, the exact spatiotemporal characteristics will depend on the complexity of the population structure. Hence, using deaths in UK local government areas as an example the shape of the rolling 12-month total for deaths will often show evidence for an initial build up period when the agent is spreading through the various social networks within that defined area. At a gross level spread across the whole UK generates a pattern of shift-down and shift-up which is blunted. This is shown in Figure A3.1.

Detailed analysis shows that shift-down commences in a few local authority areas in late 2017, while shift-up likewise commences in a few local authorities in late 2018. An organisations perception of the outbreak therefore depends entirely upon the spatial area which it services. This behaviour is replicated at local authority level and it depends on the size of the local authority and the disposition of towns and cities within that area defined by its boundary. If you change the boundary a slightly different view emerges. This is called the modifiable areal unit problem (MAUP) (see Science Direct 2020). The MAUP effect explains why weighted population density was used in Parts 1 and 2 of this series.

Figure 3.1 also encompasses one of the limitations of the rolling 12-month total methodology. The shift-down on the left-hand side of Figure A3.1 is contaminated with the effect of an earlier influenza outbreak in the winter of 2016/17. The resulting spike in deaths enters the rolling 12-month total and drops out some 12-months later. However, like all influenza outbreaks not every health authority was equally

affected and Figure A3.2 shows a longer trend for the West Berkshire local authority in the South of England, located along the M4 corridor from London to Wales.

Figure A3.2: Rolling 12-month trend in total deaths in West Berkshire, England from Dec-01 to Sep-20
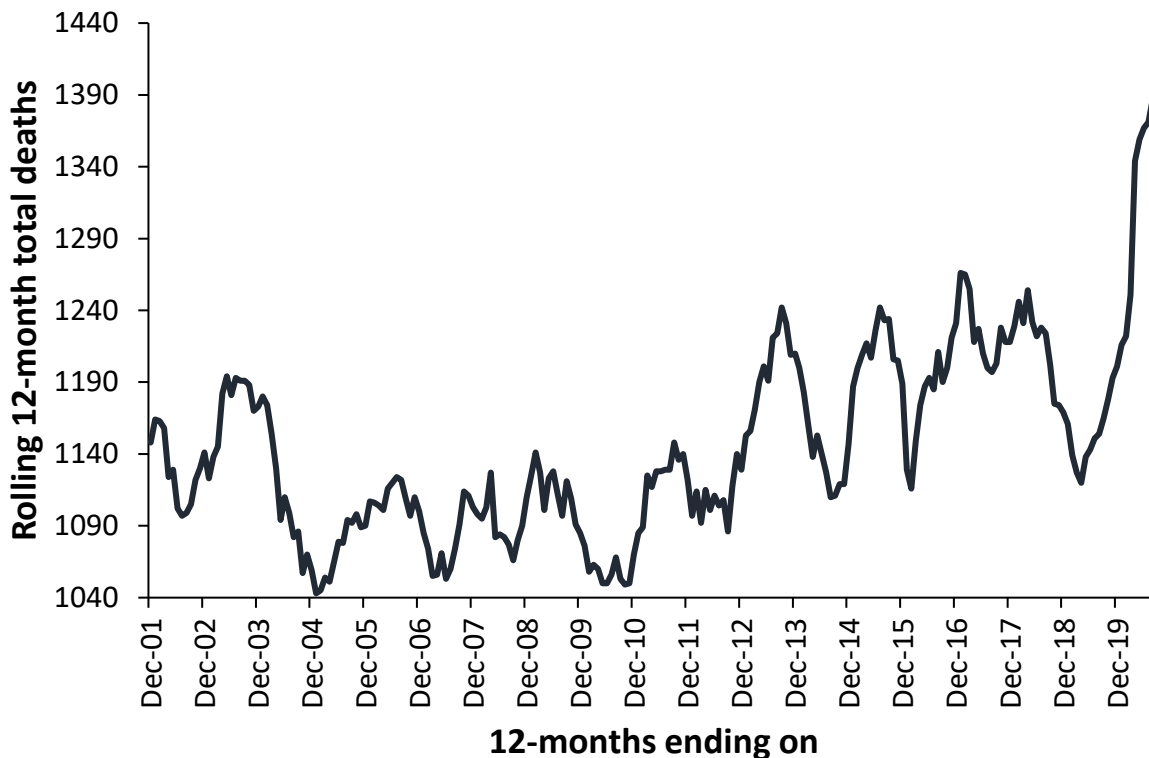
Working through the chart, Aug-02 shift-up occurs followed by influenza in late Feb-03. Shift-down is concealed by the influenza tabletop feature but finishes at Jan-05. Another shift-up immediately commences in Feb-05, immediately followed by influenza in Mar-05, etc. Sep-12 sees the start of a large shift-up with little influenza, shift-down follows and concludes at Sep-14, another shift-up commences Oct-14 followed by influenza in late December and Jan-15. This gives the typical shoulder in both shift-up and shift-down. Feb-16 sees an influenza event which obscures another shift-up starting in Apr-17. A shift-down concludes in April-19 followed by a large shift-up in May-19. The COVID-19 epidemic is then imposed-on top of shift-up from April-20 onward. While West Berkshire seems to have no gap between shift-down and shift-up this is not universally true and in some local authorities a gap of up to six months occurs. West Berkshire has a simple population structure and has a single urban area covering Newbury and nearby Thatcham. The rest of the local authority is agriculture. In this simple population structure shift up seems to have occurred within a one-month period. Hence there is a short warm-up period. Weekly data would be needed to demonstrate the finer detail.

Having established that shift-up is not in fact instantaneous – as would be expected from a genuine infectious outbreak – we can now turn to the issue of how shift-up modifies the EWM calculation.

Figure A3.3: Change in the value of the calculated maximum EWM using an artificial 5% shift-up in daily deaths from original 1990/91 data in England and Wales.

Date of introduction of 5% shift-up
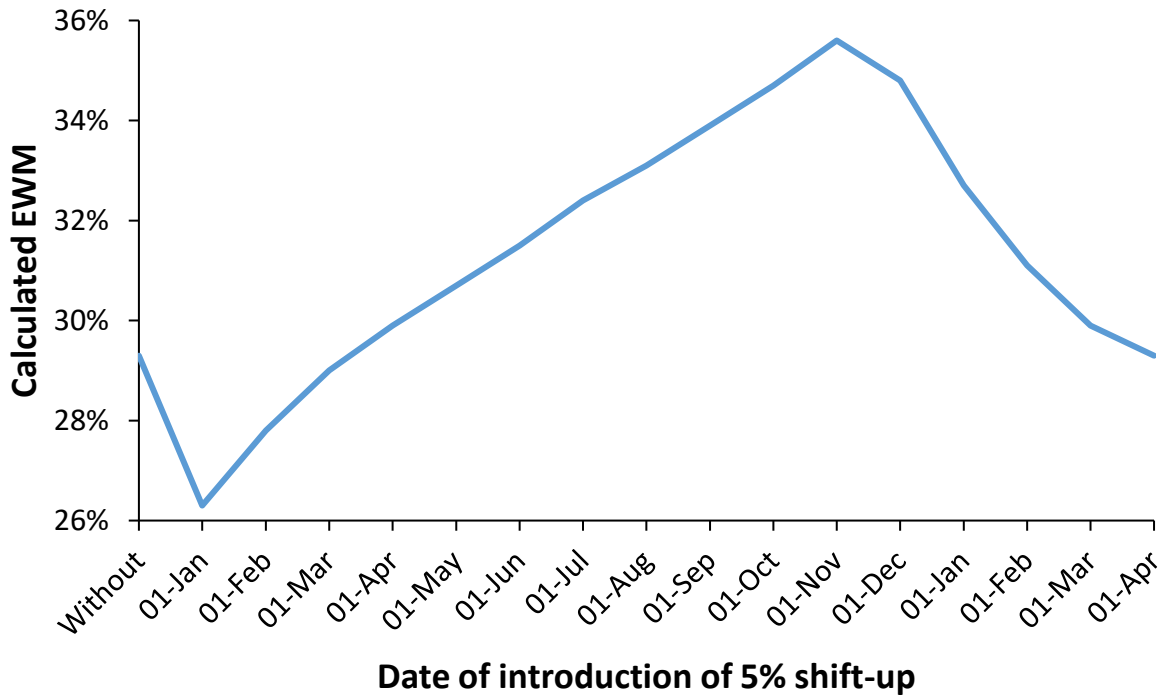
To achieve this, a 5% shift-up in deaths was introduced into daily deaths data in England and Wales for the winter of 1990/91. As can be seen in Figure A3.3 a hypothetical 5% shift-up in deaths early in 1990 at first led to a reduction in calculated EWM for the winter of 1990/91. EWM then increases up to a maximum for a shift commencing on the 1st of November 1990.

Using the original data, the EWM calculation reached a maximum on the 8th of March 1991. The point of Maximum EWM went back in time to around the 3rd of March for a shift introduced earlier in the year, after this it then moved later in the winter reaching a maximum on the 19th of March for a shift-up introduced on the 1st of January. These changes confirm the observations regarding the rolling EWM calculation in Figure 6 in the main text.

Clearly the exact effect of the shift-up will depend on how the agent causing shift-up interacts with other pathogens. From Figure 9 in the main text, we can deduce that more complex effects will be obtained if the magnitude of shift-up varies with time of year. The November date in Figure A3.3 also agrees with a November date for initiation of a shift-up (plus other winter effects) on the value of the maximum EWM shown in Figure A2.4 above.