

## **A review of the 1918 herald pandemic wave**

Importance for contemporary pandemic response strategies

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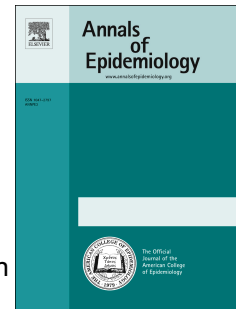
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# Accepted Manuscript

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## **A Review of Herald Pandemic Waves in 1918: Importance for Contemporary Pandemic Response Strategies**

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**Abstract/Summary**

Mounting epidemiological evidence supports the occurrence of a mild herald pandemic wave in the spring and summer of 1918 in North America and Europe, several months before the devastating autumn outbreak that killed an estimated 2% of the global population [1]. These epidemiological findings corroborate the anecdotal observations of contemporary clinicians who reported widespread influenza outbreaks in Spring and Summer 1918, with sporadic occurrence of unusually severe clinical manifestations in young adults. Initially seen as controversial, these findings were eventually confirmed by retrospective identification of influenza specimens collected from US soldiers who died from acute respiratory infections in May-August 1918. Other studies found that having an episode of influenza illness during the spring herald wave was highly protective in the severe autumn wave. Here we conduct a systematic review of the clinical, epidemiological and virological evidence supporting the global occurrence of mild herald waves of the 1918 pandemic and place these historic observations in the context of pandemic preparedness. Taken together, historic experience with the 1918 and subsequent pandemics shows that increased severity in second and later pandemic waves may be the rule rather than the exception. Thus, a sustained pandemic response in the first years following a future pandemic is critical; conversely, multi-wave pandemic patterns allow for more time to roll out vaccines and antivirals.

## Introduction

While describing and analyzing historic events is important in its own right, identifying patterns and drawing lessons from historic pandemics can inform planning for and response to future pandemics. Over the last decade, epidemiologists, demographers, medical historians, and virologists have spent considerable efforts studying the 1918 “Spanish” influenza pandemic, the most devastating pandemic in modern history. A key question has been whether the unusual outbreaks of influenza-like illness during February-August of 1918 in many regions of the world could be considered as an early manifestation of the pandemic – a “harbinger” of the devastating 1918 autumn pandemic mortality wave. This hypothesis has been investigated by uncovering, reviewing, and analyzing century-old morbidity and mortality data using modern analytical methods. Such data originated from nearly forgotten mortality and morbidity reports available from surveillance systems established in the US and Europe 100 years ago (see for example [1-5]) and from labor-intensive compilation of church records, grave yards, and individual death certificates (e.g. [5-10]).

To distinguish the impact of the 1918 pandemic virus from that of seasonal influenza or other respiratory pathogens, epidemiologists have relied on the unique “signature” mortality age pattern associated with the lethal autumn 1918 wave, characterized by an atypical and dramatic increase in mortality risk in young adults, consistently observed across many studied locations [1, 2, 4-6, 9, 11-15]. High disease transmissibility is a complementary epidemiological telltale sign of pandemic virus activity, as prior population immunity is low for a new pandemic strain, compared to that for seasonal viruses circulating globally and annually. Here we review and synthesize historical observations, epidemiological data, and modern virological findings

speaking to the phenomenon of a herald wave of the 1918 pandemic in the Americas, Europe, Asia and Pacific regions. We highlight remaining gaps in our understanding of the beginnings of the 1918 pandemic, discuss the public health response to the 2009 pandemic in the context of what is known about the 1918 pandemic, and make recommendations for pandemic preparedness going forward.

### **Contemporary clinical descriptions, 1918**

Many physicians reported detailed clinical observations during the great pandemic which were carefully collated in a book by E. Jordan [16]. The clinical description of the most severe cases during the autumn 1918 wave included heliotrope cyanosis, sudden death and acute respiratory distress in otherwise healthy young adults [17]. Less well remembered are the clinical descriptions of unseasonal influenza outbreaks in the spring and summer of 1918, characterized by brief febrile respiratory illnesses and high infectivity. A small subset of cases, however, presented a graver and unusual clinical picture that included severe respiratory distress and death [18, 19], and “a fulminating pneumonia with wet hemorrhagic lungs fatal in 24 to 48 hours” [20]. One clinician was so startled by autopsy findings from the spring of 1918 he suggested that it should be considered “as a new disease.” [16]. Such evidence of heliotrope cyanosis in young adults is a clinical signature of 1918 pandemic influenza.

There was no doubt for contemporary physicians that the fall wave was a resurgence of the summer influenza epidemic; an editorial of the British Medical Journal on 2 Nov 1918 make a strong argument for the same pathogen causing the summer and fall epidemics [21].

### **Characterization of the 1918 pandemic signature age patterns**

Seasonal influenza epidemics are characterized by most deaths occurring among the elderly. In contrast, pandemics are (to various degrees) characterized by a shift of deaths towards younger ages [1, 2, 22, 23]. Contemporary reports from the US and Europe noted that older adults were relatively spared during the severe autumn 1918 wave. In contrast, young adults aged 20-40 years suffered unusually and were at highest absolute risk of death (Figure 1) [16, 24]. A full understanding of this signature age pattern of this pandemic remains elusive. The most plausible hypotheses at this stage involve a “recycling” phenomenon, so that elderly were protected in the 1918 pandemic season by prior immunity from exposure to an antigenically similar virus in childhood, combined with aberrant immune pathology specific to young adults, leading to dysregulated immune responses (cytokine storm) and elevated mortality risk in this age group [1, 5, 25-27].

This unusual 1918 signature age pattern is so unique that it can be used to “fingerprint” the pandemic. In a 2005 pioneer study, Olson et al. [1] used time series data from New York City to demonstrate that young adults were at pronounced increased risk of death while persons over 45 years of age had no measurable excess mortality over typical winter levels (Figure 1). Here, 93% of influenza-related deaths occurred in people under 45 years old during autumn and winter 1918-1919, up from 25-34% in typical pre-pandemic seasons [1]. Another study set in a uniquely detailed and comprehensive surveillance system in Copenhagen confirmed these age patterns (Figure 1) [2].

A similar pandemic signature age pattern was associated with respiratory outbreaks occurring in the spring-summer of 1918 in many settings, including New York City, the state of Arizona,

Copenhagen, and central Mexico – the so-called herald wave of the pandemic [1, 2, 6, 9].

Thus, the age signature could be used to distinguish pandemic influenza from seasonal influenza.

### **A mild herald pandemic wave in spring-summer 1918.**

The generally mild character of the respiratory outbreaks in summer 1918 in the UK is well described in the Great Britain Ministry of Health Report on the 1918-1919 influenza pandemic [28]. Several articles appeared in the summer of 1918 in the British Medical Journal that make reference to widespread epidemics across European countries with clear influenza manifestations [18, 19].

The epidemic became known as “Spanish influenza,” partly because it was so widespread in Spain in May 1918 and partly because Spain was not at war so it did not censor newspaper articles referring to the disease[29]. The term “Influenza Pandemic” was first used in the 13 July 1918 issue of BMJ [18]. In Switzerland in July, the epidemic was so virulent that military intelligence officers rejected medical diagnoses of “Spanish grippe” and warned it may be bubonic plague [30]. Vaughan noted that influenza disease had “developed a greatly heightened virulence toward the end of August [31].”

It was not a subtle change; in Norway, for example, the first wave caused far more illnesses than the autumn 1918 wave, and in Denmark physician-attended cases of respiratory diseases in summer 1918 exceeded that of any influenza epidemic in the previous decade [2] (Figure 2). But in this setting there was no concomitant spike in mortality, so that the influenza case-fatality rate was ~6 fold lower in the summer wave than in the fall 1918 [2].



Unfortunately, the identification of herald pandemic waves must often rely on historic mortality statistics without availability of morbidity data (only Scandinavia had solid Sentinel surveillance of morbidity at the time). And because of their mild nature, early waves are easily missed in mortality data [1, 2, 32].

### **Evidence from remote populations in the Americas.**

In addition to reports from Europe and US, “herald” pandemic waves of mild nature have been recently documented in Latin America in spring and summer 1918 (e.g., Mexico City [6], Toluca, Mexico [6], and Lima, Peru [11]). In contrast, the absence of an early wave in some areas of Colombia [4] has been explained by a late introduction of the pandemic virus or that any mild outbreak was not recorded and could not be seen in mortality records.

In contrast to the substantial mortality protection observed among seniors in the US and Europe [1, 2, 13], the data recently reconstructed for a few Latin American settings [4, 6] indicates that older populations did in fact experience high mortality rates in autumn 1918 in this region (Figure 1). This phenomenon may be explained lack of exposure to influenza in Latin America 50 years before the 1918 pandemic, as long-distance travel by train and boat was much less developed in Latin America in the 19<sup>th</sup> century than in US and European cities [6, 33].

The hypothesis of protective immunity in seniors varying with population connectivity in the 19<sup>th</sup> Century is also in line with evidence of entire aboriginal populations in Alaska and remote Pacific islands being decimated by the 1918 pandemic [33, 34], and by findings of dramatically higher mortality risk in indigenous populations than in those of European descent [35]. Long-term epidemiological time series from Iceland have shown that remoteness can

affect the probability of introduction and local dissemination of influenza viruses, particularly in weakly connected populations [36]. Thus, the absence of senior sparing in remote settings in our view supports the “recycling” hypothesis (i.e., exposure to influenza viruses during childhood may confer significant lifetime protection to similar viruses[27, 37]). In contrast, extreme pandemic mortality risk in young adults was consistently observed in all populations studied [6].

### **Evidence from US army camps**

A map of the putative timing and location of herald waves reported in the US is shown in Figure 3. In the US military, the first reports of respiratory disease outbreaks associated with unusual young adult mortality occurred in early March 1918 in Camp Funston, Kansas, and the disease spread to other US training camps during the following months [32]. Although the case fatality rate was relatively low at 1.3% in March 1918, ~4-fold lower than during the main autumn wave ([32]), some influenza patients would develop acute pneumonic symptoms and die within 4 hours, resembling the clinical accounts of fulminant disease in the fall 1918 wave [20]. The military population demographic was particularly homogeneous and tightly concentrated among young male adults aged 18-40 years. Hence it was not possible to identify the etiology of these army camp outbreaks using the “signature age shift” pattern of elderly sparing, so it cannot be ruled out that these outbreaks were caused by seasonal influenza or other respiratory viruses [32]. Nonetheless, the existence of a summer pandemic wave has been recently confirmed from study of viral RNA in soldiers who died in US Army camps as early as May 1918 [38].

### **Evidence of cross-protection between spring and autumn 1918 waves**

Data from military and civilian populations in the US, UK and Australia provide a strong piece of epidemiological evidence in the form of clinical protection between successive pandemic waves. Based on data on the reported occurrence of repeated respiratory illnesses in spring and fall 1918, we have previously estimated that the spring wave provided 35%–94% protection against clinical influenza illness in the fall and 56%–89% protection against death [32]. In the Australian army, Shanks et al found a 61% (43-73%) protective effect of 1918 spring/summer respiratory illness against mortality in the autumn wave [39]. This level of protection compares favorably to that afforded by modern vaccines, suggesting that the pathogens circulating in the two waves were similar enough to convey protective immunity [32] and thus, were likely antigenically related. Furthermore, mathematical transmission models indicate that cross-protective immunity played a key role in generating multi-wave pandemic patterns in 1918 [40, 41]. In other words, settings that experienced a mild summer wave were likely protected in the severe autumn wave – perhaps in part explaining why Scandinavia was not as dramatically affected as other settings[15].

### **High transmissibility in the summer wave is only consistent with pandemic influenza**

Seasonal influenza is far less transmissible than pandemic influenza due to partial immunity in the population from repeated exposure to past viruses, and the reproduction number  $R$  (number of secondary cases per index case) is typically around 1.1-1.3 [42, 43]. Therefore, a high  $R$  in the spring wave would strongly point to pandemic activity.

Only a few studies have estimated the basic reproduction number associated with the pandemic in spring and summer 1918, when the population was largely susceptible (except for

older adults in some regions) [2, 3, 44, 45]. R estimates have ranged between 2.0 and 4.8 during the summer wave for Scandinavian cities [2, 3], decreasing to seasonal influenza level (1.2-1.5) in the autumn wave [2], consistent with build-up of population immunity.

For most other settings, insufficient data were available to contrast the transmissibility of the first two pandemic waves. For example, a seminal study provided a robust R estimate for the autumn wave based on mortality in multiple US Cities but could not measure the spring wave due to lack of morbidity data [46].

Overall, whenever available, R estimates for the spring-summer wave in 1918 are similar or higher to those of other pandemics of this century in 1957, 1968 and 2009 -- and substantially higher than those for seasonal influenza [2, 4, 44, 46, 47] [42] [48-55]. Thus, these R estimates add to the epidemiological evidence that the herald wave was caused by a pandemic virus, while reduction of influenza transmissibility in the 2<sup>nd</sup> wave supports circulation of a related virus in both waves.

### **Timing and Global Spread of the herald pandemic wave**

Remarkably, in the era before air travel, the 1918 pandemic autumn wave circumvented the globe in just a few months during October-December 1918. What is less clear is whether the spring-summer herald wave took a similar global journey but went unreported in many locales as it was not severe. In Table 1 we review available evidence of the presence of a 1<sup>st</sup> wave in various countries. Estimating the timing of the spring-summer wave is hampered by the fact that global boat travel and WW1 troop movements were frequent at this time, and that a cross-Atlantic crossing took only about a week, consistent with rapid transcontinental spread[56].

Furthermore, we cannot rule out the possibility of earlier seeding of the virus before Mar-Apr 1918. In particular, the apparent mild nature of the herald wave requires morbidity data and this complicates efforts to identify them and characterize the earliest patterns of spread of influenza pandemics. Some early efforts to unravel the pattern of pandemic spread including those by Vaughan who compiled rough estimates of the earliest recorded dates of increased influenza incidence around the world from a variety of sources [31]. Correspondingly, Kansas, Missouri, Illinois, Ohio, and Michigan observed increases in influenza transmission in early March 1918, followed by Georgia and South Carolina in mid and late March, and a peak in 30 of the largest US cities in April according to a report by Collins et al. [57]. Only a handful of epidemiological studies have relied on epidemiological signature features (such as age patterns) to ascertain the presence and timing of herald pandemic waves (reviewed in Table 1; see also map in Figure 4).

In the US, such epidemiological evidence supports pandemic activity in New York City in February 1918 [1] and in Kentucky [5], Arizona[9], Missouri [10] and military training camps throughout the country in March-April 1918 [32]. Influenza incidence increased in France in April 1918, likely due to military troop arrivals from the US, with peak activity in hospitalization and death during May-July 1918 [31].

By May 1918, influenza had reached Central Mexico as evidenced by elevated excess respiratory death rates among young adults. An early wave of influenza transmission in May 1918 is also evident from a detailed analysis of mortality records from remote Newfoundland, an island located off the eastern coast of mainland Canada [8]. At the same time, influenza was spreading in a number of European settings including Scotland, Spain, and Greece according to Vaughan (Table II in [31]). By June, influenza activity was widespread in England & Wales,

Switzerland, Germany, Austria and Norway. The analysis of detailed morbidity or mortality data indicates that influenza had peaked by July 1918 in England & Wales, Denmark, Sweden, Norway, Poland, and Switzerland [31] (Figure 4B).

In the Southern Hemisphere, there is evidence of mild pandemic activity in Lima, Peru during the winter months of July-September 1918 with mortality peaking in August 1918 [11]. Similarly, the southern city of Concepcion in Chile appears to have exhibited a mild pandemic wave during July-September 1918 as deemed by significant elevation in respiratory mortality rates particularly among individuals <20 years, relative to baseline mortality periods [12].

In Asia, evidence from the Australian army supports the existence of a mild and limited yet protective spring/summer wave [39]. Excess all-cause mortality rates data supports an early wave of transmission in Singapore in July 1918 [58], but not in Taiwan or Japan [13, 59]. Judging from the complex evidence from Australia [39], it is entirely possible that modest herald waves would have been missed in Asian settings where only mortality but not morbidity data were available. There is unfortunately a scarcity of quantitative 1918 pandemic reports from less wealthy countries in Asia and Africa, settings where most global 1918 pandemic deaths are thought to have occurred [15].

Overall, our review of historical epidemiological evidence supports widespread occurrence of herald waves in the Northern Hemisphere, and less frequent occurrence (or more delay in the arrival of the pandemic virus) in Southern Hemisphere. The available evidence was patchy in many locations however, particularly in the Southern Hemisphere and in civilian communities (most notably, Africa). Further, more data may be uncovered in already sampled locations, supporting earlier pandemic onsets than the currently available evidence. Of note, the available information was sometimes localized to a single city and generalized to a large

country for mapping purposes, potentially masking heterogeneity (eg, Brazil, Figure 4). We note substantial geographic heterogeneity in first wave onset in the US population (range February -July) and in Peru (Lima experienced a herald wave while Iquitos did not, Table 1), and so we would expect to see heterogeneity in other large countries.

### **Putting the pieces together**

Epidemiological evidence supports the occurrence of a relatively mild pandemic wave in spring and summer 1918 featuring the unusual “signature” age mortality pattern seen in the autumn wave, high transmission potential consistent with an emerging pandemic virus, and similar to the autumn wave virus as it conferred substantial protection. Taken together, this is compelling epidemiological evidence that the herald wave was widespread, particularly in the Northern Hemisphere, and either caused by the 1918 pandemic virus, or a closely related precursor that had not yet achieved the unique severity of the 1918 autumn wave [2].

This epidemiological evidence for herald waves was recently much strengthened by the identification of the A/H1N1 pandemic virus in autopsy specimens from US soldiers who died of influenza-like-illness during May-August 1918 [38]. The hemagglutinin protein sequence collected from these spring and summer casualties was nearly identical to that of the virus isolated from autumn victims [38]. However, assembly and analysis of the entire summer-wave virus genome is needed to identify putative genetic differences between viruses circulating in the spring and fall of 1918, that may explain the dramatic increase in case fatality by fall 1918. Alternatively, the increased lethality in autumn could be due to respiratory bacterial pathogens in the colder (autumn) months of the year [60, 61]. A much anticipated phylogenetic comparison of herald and fall wave influenza virus isolates could help identify

specific mutations associated with increased virulence, or in the absence of such mutations strengthen the bacterial co-infections hypothesis, although the world-wide simultaneous increase in influenza severity makes this explanation less likely. Epidemiological studies are also particularly useful to identify locations with pandemic excess mortality elevation in summer 1918 (Oslo, Norway in mid-July, for example). Archeovirologists could focus exploration of archival specimens and autopsies in these locations and test for the presence of influenza, potentially increasing the sample size of specimens from herald wave victims.

In the most recent influenza A/H1N1pdm pandemic in 2009, the summer wave was mild [62, 63] albeit with an alarming 1918-like “signature” age pattern of elevated young adult mortality and elderly sparing. A global study of 2009 pandemic mortality demonstrated considerable heterogeneity in timing and magnitude of first waves [64]. And several countries reported severe recrudescent pandemic waves in the second [65] and third winter [66] of pandemic virus circulation.

Early pandemic waves of mild nature may in fact be the rule rather than exceptions associated with the 1918 and 2009 pandemic. Most deaths related to the A/H3N2 Hong-Kong pandemic occurred in the second winter of circulation in Europe, 1969-70 [47, 67]. The historic precedence of mild herald waves of pandemic influenza, and the recrudescence of pandemic waves of varying severity over multiple years, supports a vigorous public health response, even when first wave data indicates a mild disease. Careful monitoring of changes in case fatality rate associated with pandemic influenza infection is warranted in the months and years following the emergence of a new virus.



Embracing the knowledge that a pandemic can cause a mild herald wave and delayed mortality impact is critical for contemporary pandemic preparedness. Meanwhile, on the upside such a pattern is good news as it allows more ample time for vaccine development and roll-out of control measures. More than ever, looking to the past for clues about the severity of future pandemic events is key to shaping pandemic responses. As the WHO is revising pandemic preparedness guidelines to embrace the concepts of “severity” or “seriousness” of emerging threats, it will be important to keep in mind the complicating fact that initially mild pandemic waves may be followed by lethal waves several months later.

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## Tables

**Table 1.** Timing of pandemic waves of the 1918-1919 influenza pandemic as evidenced by quantitative studies across different locations around the world. Locations are organized by continent (America, Europe, Asia).

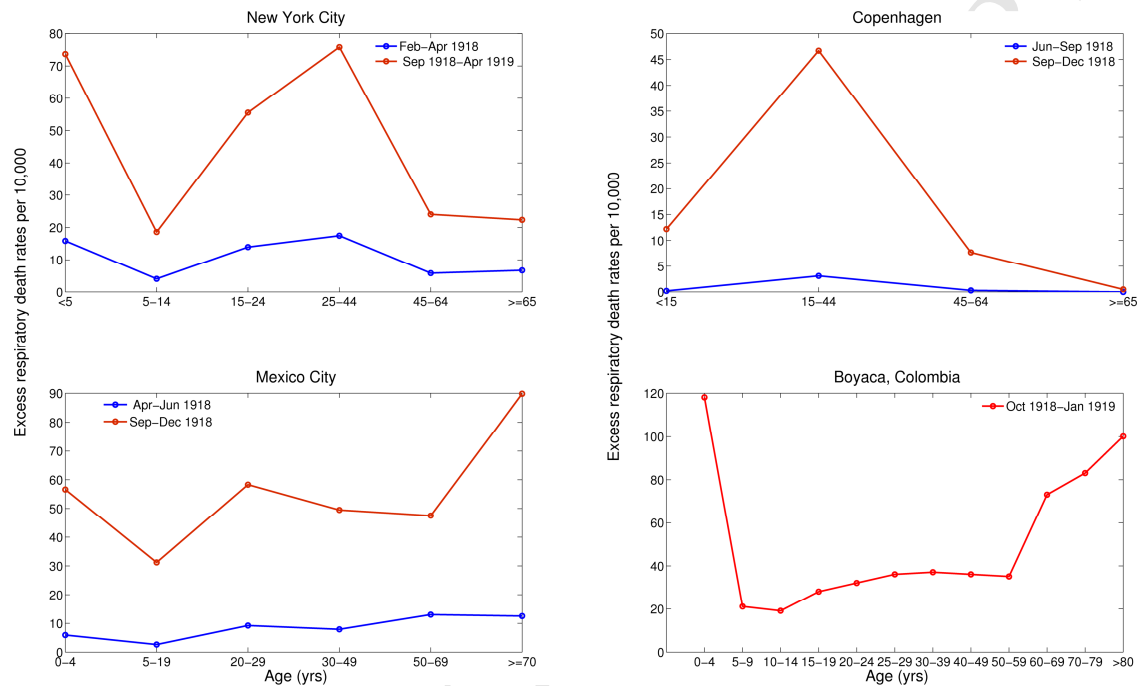
Location	Herald wave in 1918 (period)	Peak pandemic mortality	Data type	Source
New York, USA	Feb-Apr	Oct-Nov-1918	Age-specific P&I mortality	[1]
Kentucky, USA	Apr	Oct-Dec 1918	Age-specific respiratory mortality	[5]
Arizona, USA	Apr	Oct-Dec 1918	Age-specific respiratory mortality	[9]
Saint Joseph, Missouri	Feb-May	Oct-Dec 1919	Age-specific respiratory mortality	[10]
Mexico City and Toluca, Mexico	May	Nov-1918	Age-specific respiratory mortality	[6]
Boyacá, Colombia	No wave	Nov-1918	Age-specific respiratory mortality	[4]
Florianapolis, Brazil	No wave	Nov-Dec 1918	Age-specific respiratory mortality	[68]
Newfoundland, Canada	May-July	Oct-Nov 1918	Age-specific respiratory mortality	[8]
Lima, Peru	Jul-Sep	Nov 1918	Respiratory mortality	[11]
Iquitos, Peru	No wave	Nov 1918	Respiratory mortality	[11]
Concepcion, Chile	Jul-Sep	Aug 1919	Age-specific respiratory mortality	[12]
Copenhagen, Denmark	June-July	Oct-1918	ILI cases; Age-specific mortality	[2]
Paris, France	No wave	Oct-1918	Age-specific respiratory mortality	[69]
Basque country, Spain	June	Oct-1918	Age-specific respiratory mortality	[70]
Florence, Italy	May-Jul	Oct-Nov 1918	Age-specific hospitalizations, deaths	[45]
Göteborg and Stockholm, Sweden	June-July	Oct-1918	ILI cases and P&I mortality	[2]
Oslo, Norway	June-July	Oct-1918	ILI cases and P&I mortality	[2]
England and Wales	May-Jul	Nov-1918	Influenza-related mortality	[71]
Wrocław, Poland	Jul	Oct-Dec 1918	Influenza-related mortality	[72]
Geneva, Switzerland	Jul	Oct-Nov 1918	Influenza-related hospitalizations	[73]
Madrid, Spain	May	Oct-1918	Age-specific respiratory mortality	[69]
Taiwan	No wave	Nov-1918	All-cause mortality	[15, 59]

Singapore	Jul	Oct-1918	All-cause mortality	[15, 58]
Australian army in Europe	Spring/summer	Nov-1918	Case-control study demonstrating protective effect of spring-summer illness in autumn wave (no direct demonstrated of spring-summer mortality elevation)	[39]

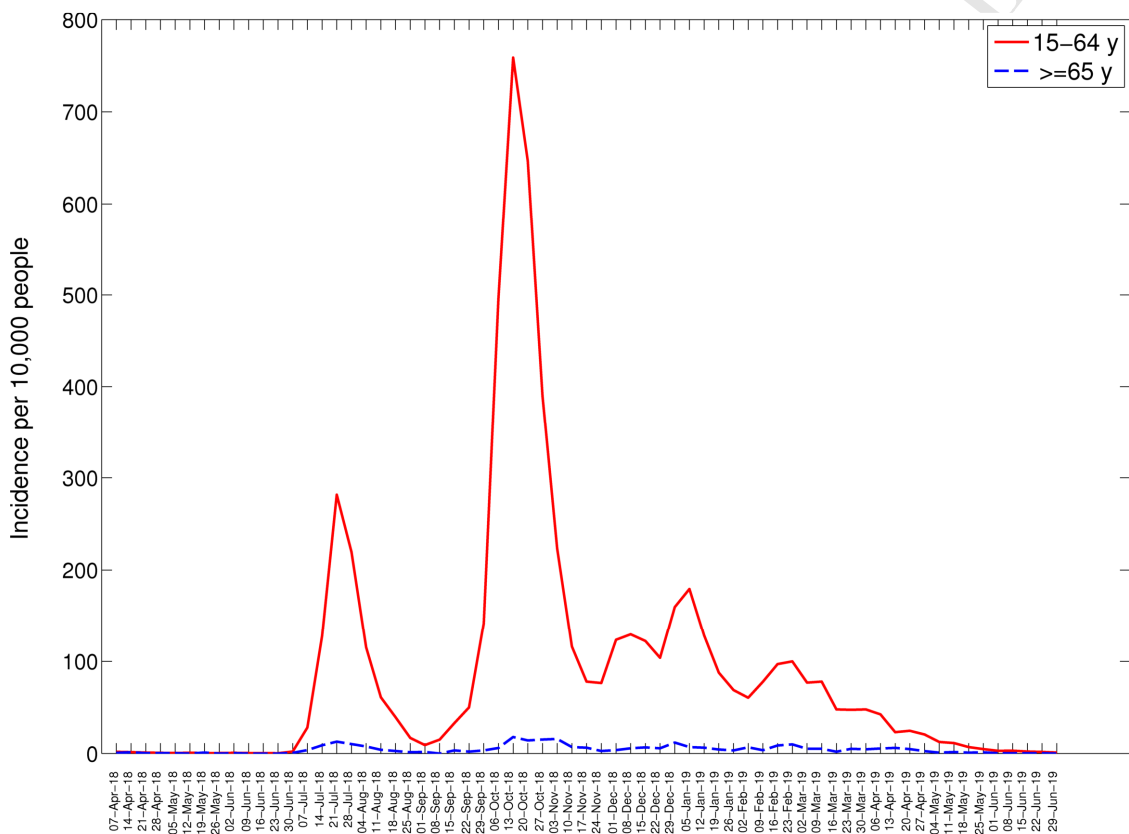


## Figures

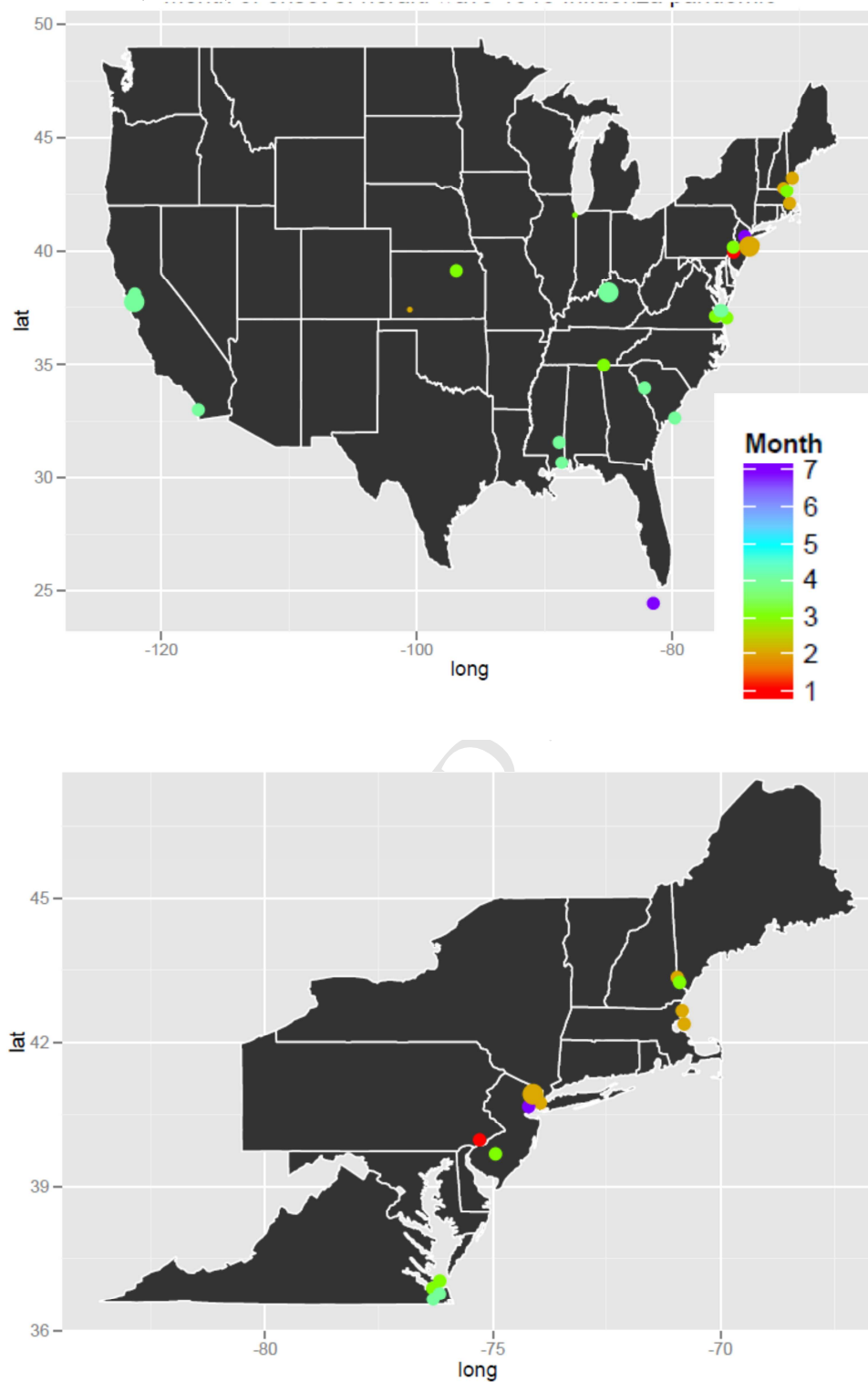
**Figure 1.** Age-specific excess-death rates per 10,000 population associated with the 1918–19 pandemic waves in New York City (based on all-cause deaths), Copenhagen (P&I deaths), Mexico City (P&I deaths), and Boyacá, Colombia (P&I deaths).



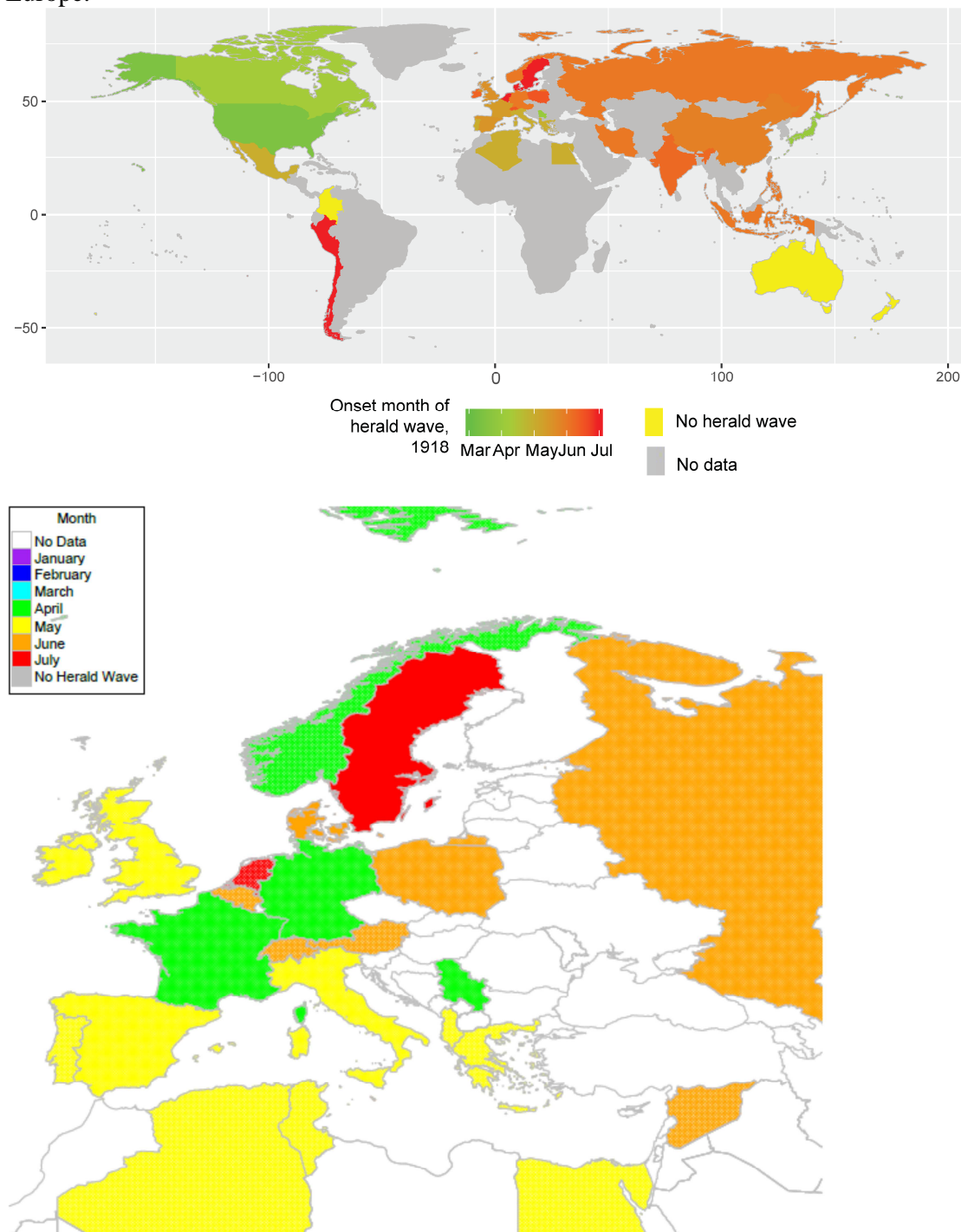
**Figure 2.** Weekly incidence per 10,000 people among individuals aged 15-64 years and  $\geq 65$  years for reported patient visits for influenza-like-illness for the 1918-1919 influenza pandemic to a weekly surveillance system “Ugelisterne” that was in place in Copenhagen, Denmark. The summer wave was far more intense than any epidemic during the last decade, and even more pronounced in Oslo [2].



**Figure 3.** Map of timing of herald pandemic 1918 wave occurrence in the US (top) and East Coast (bottom).



**Figure 4.** Map of timing of herald pandemic 1918 waves, based on epidemiological and virological evidence. Estimates are based on the month of onset of pandemic virus circulation, aggregated at the country level. If the month of onset was reported to occur later than September 1918, it was not considered a herald wave. Top: World. Bottom: Europe.



Footnote: While the data suggests the first wave was more widespread in the Northern hemisphere, it is possible that some true first waves were overlooked due to the lack of efforts to look for it. Further herald waves were generally mild and thus morbidity data or age-specific time series analysis are required to demonstrate occurrence of a first wave. A severe outbreak of influenza-like illness occurring during Jan-Aug 1918 would not be sufficient evidence of a first wave, as it could be due to a host of other viruses causing respiratory illnesses.