# The El Niño–Southern Oscillation (ENSO)–pandemic Influenza connection: Coincident or causal?

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**We find that the four most recent human influenza pandemics (1918, 1957, 1968, and 2009), all of which were first identified in boreal spring or summer, were preceded by La Niña conditions in the equatorial Pacific. Changes in the phase of the El Niño–Southern Oscillation have been shown to alter the migration, stopover time, fitness, and interspecies mixing of migratory birds, and consequently, likely affect their mixing with domestic animals. We hypothesize that La Niña conditions bring divergent influenza subtypes together in some parts of the world and favor the reassortment of influenza through simultaneous multiple infection of individual hosts and the generation of novel pandemic strains. We propose approaches to test this hypothesis using influenza population genetics, virus prevalence in various host species, and avian migration patterns.**

The recurrent emergence of novel influenza subtypes, such as the recent 2009 A/H1N1 pandemic, poses a continued and considerable public health threat. At present, our ability to predict the development of a novel influenza pandemic is limited. Instead, surveillance and response are the principle means for identifying and controlling a new influenza pandemic after it has emerged.

Wild birds are thought to be the primary reservoir of influenza A viruses and facilitate the emergence of new pandemic lineages through the introduction of virus to domestic animals and humans (1, 2). Migratory birds, with their long travel distances and many stopovers, are thought to be particularly critical for the mixing and reassortment of influenza virus genomes (3).

The El Niño–Southern Oscillation (ENSO) has been shown to affect the health and behavior of migratory birds by altering bird biomass (4), flight and stopover patterns (5), time to molt (6), and population density (7). ENSO affects weather conditions, including temperatures, precipitation, wind speed, and direction, and storm tracking throughout the planet; however, these effects are not uniform but vary from region to region (8). The effect of ENSO on migratory birds is mediated through these regional shifts in weather and local ecosystem health. Thus, it is possible that a specific phase of ENSO produces a shuffling of migratory bird populations that, in certain regions, is conducive to the reassortment of influenza virus gene segments. Here, we explore this potential association through a comparison of ENSO conditions with the timing of the emergence of the last four human influenza pandemics.

## Results

The last four human influenza pandemics (1918, 1957, 1968, and 2009) are sufficiently well-documented to allow approximate dating of their first emergence. Emergence dates were established through examination of the peer-reviewed literature. We identified the earliest transmission or isolate of each pandemic as follows: March 1918 for the 1918–1920 pandemic (9); February 1957 for the 1957–1958 pandemic (10); July 1968 for the 1968–1969 pandemic (11); and March 2009 for the 2009–2010 pandemic (12).

All four pandemics first appeared in the human population within the first 7 mo of their initial calendar year. We, therefore, examined conditions in the equatorial Pacific during the prior fall and winter to determine whether one particular phase of ENSO was associated with novel human influenza pandemic emergences. We used seasonal (3 mo) average sea surface temperature (SST) anomalies from the Niño 3.0 region (5°S–5°N, 150°–90°W) and the Niño 3.4 region (5°S–5°N, 170°–120°W) as our measures of ENSO (13). These ENSO SST anomaly values were calculated for the fall and winter seasons preceding each pandemic emergence, and the mean of these four values was also determined to create a pandemic year average.

All four pandemics were preceded by below normal SSTs in the central equatorial Pacific consistent with the La Niña phase of ENSO (Fig. 1 and Table 1). SSTs in the equatorial Pacific are highly autocorrelated. The negative SST anomalies preceding pandemic influenza emergence occur consecutively during fall and winter for a span of 6 mo or more. ENSO itself is influenced by the seasonal cycle such that both El Niño and La Niña events tend to maximize during boreal winter.

For these four pandemic events, the average November to January (NDJ) Niño 3.0 SST anomaly was −0.730 K. Bootstrap resampling of NDJ Niño 3.0 SST anomalies for 4 arbitrary years shows that, by chance alone, an average SST anomaly of −0.730 K or less would occur only 6.9% of the time (two-sided $P = 0.069$). This finding is insensitive to the precise index of SSTs (i.e., Niño 3.0 or 3.4), the calendar months used, or the inclusion of the less well-documented 1889–1890 Russian pandemic. For instance, if we use October to December Niño 3.0 SST anomalies to include the 1889–1890 pandemic, which may have emerged in the late fall of 1889 (14), then the average Niño 3.0 SST anomaly for the last five pandemics is −0.746K ($P = 0.033$).

The findings are also insensitive to restriction of the time series used for bootstrapping. Specifically, if we recognize that 19th century SSTs in the equatorial Pacific are less-well constrained and only use the 1900–2010 period for random resampling, the statistical significance changes little (e.g., NDJ Niño 3.0 SST anomalies for the last four pandemics, $P = 0.068$). Fig. 2 presents distributed plots of NDJ SST anomalies preceding each of the last four pandemics.

## Discussion

An extensive literature exists documenting the effects of ENSO on infectious disease, including cholera (15, 16), malaria (17, 18), and dengue (19, 20). A few studies have examined the regional effects of ENSO on seasonal (epidemic) influenza for places such as France (21, 22), the United States (22–24), and Japan (25). These studies have looked for an ENSO influence on the timing, magnitude, or severity of epidemic influenza activity because of a change in local weather conditions rather than any induced change in virus genome structure. This study, however, has focused on pandemic influenza rather than epidemic influenza. The distinction between pandemic and epidemic influenza is critical,

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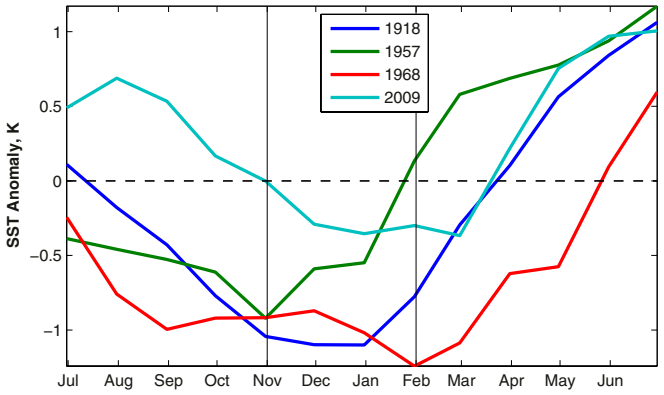


**Fig. 1.** Time series of Niño 3.0 SST anomalies in units of Kelvin from July of the year preceding the appearance of a novel pandemic influenza strain to July of the year during which the novel pandemic strain emerged. The dashed line shows the 0 K SST anomaly level. The vertical solid black lines demark the period of November through January.

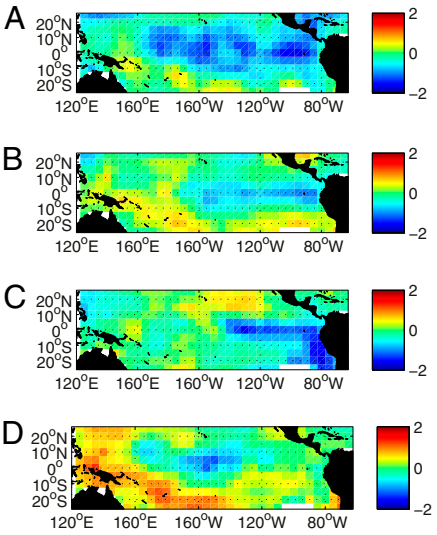


**Fig. 2.** Plots of NDJ SST anomalies for the NDJ period preceding each of the last four pandemics. (*A*) November 1917 to January 1918. (*B*) November 1956 to January 1957. (*C*) November 1967 to January 1968. (*D*) November 2008 to January 2009. SST anomalies are a statistically homogeneous concatenation of two SST reconstructions (13, 31).

because pandemics arise from viral reassortment, whereas epidemics generally do not. By focusing on pandemic influenza, we are, in essence, examining the effect of ENSO on viral reassortment.

Our findings indicate a possible association between the emergence of pandemic influenza and the phase of ENSO. Whether this ENSO–pandemic influenza association is causal or merely coincidental is unclear; however, the effect of ENSO on migratory bird health and behavior could be one means by which the large-scale environment alters the likelihood of influenza virus reassortment events and cross-over to human hosts. It has been suggested that the risk of pandemic influenza emergence may vary in time because of changes in the population genetics and ecology of influenza in reservoir species (26). Our findings here lead us to hypothesize that the likelihood of such emergence events is greater during La Niña events.

A recent paper by Mazzarella et al. (27), published while this paper was in initial review, has posited that influenza pandemics have been preceded by moderate to strong El Niño events rather than La Niña events. We disagree with these findings and conclusions. The work by Mazzarella et al. (27) includes five pandemic events that occurred before the 20th century, for which onset dating is uncertain, but excludes the best-documented and most recent 2009 pandemic from the analysis. Inclusion of all well-dated pandemics and only well-dated pandemics is needed so that conditions during the appropriate time period—before the emergence of the virus in humans—are used in analysis. By exploring conditions immediately preceding well-dated pandemic emergences, we account for virus reassortment before the initial recognition of human cases.

In addition, in the identification of El Niño events, the work by Mazzarella et al. (27) uses an ENSO reconstruction from the work by Quinn et al. (28) that is not based on the instrumental record of SSTs or atmospheric conditions and only identifies El Niño events (no La Niña events). This identification of El Niño events is based on historical inference (e.g., ship logs and travel times, changes in fishery productivity, destruction of agricultural crops, etc.). Although use of such a reconstruction makes sense for periods before the instrumental record (~1850), it is a less precise metric of ENSO phase and magnitude that, after 1850, has multiple discrepancies with instrumental records of ENSO (13, 29). For instance, the data in the work by Quinn et al. (28) incorrectly refers (tables 1 and 2 in ref. 28 and reproduced data in table 1 in ref. 27) to 1917 as a year with El Niño conditions, when in fact, conditions were strongly La Niña throughout the year and did not switch to the El Niño phase until June of 1918 after the March 1918 onset of the pandemic. From 1887 to 1891, similarly, 4 El Niño y are cited when, in fact, the instrumental record shows two strong La Niña and one strong El Niño (29). Admittedly, a strong phase of ENSO, either El Nino or La Niña, would disrupt bird migration, and in theory, any disruption might facilitate changes in wild bird migration, fitness, and mixing, which could favor influenza virus reassortment. However, the four most recent and best-dated pandemics all followed La Niña phase events.

Ultimately, omissions, errors in attribution, and errors in the ENSO reconstruction used (28) invalidate the findings and conclusions in the work by Mazzarella et al. (27). Specifically, the 2009 pandemic is omitted, the 1957 and 1968 pandemics do not follow El Niño events, which Mazzarella et al. (27) mistakenly claim, and conditions preceding the 1918 pandemic are incorrectly labeled El Niño in the dataset by Quinn et al. (28) used in the work by Mazzarella et al. (27). Furthermore, the work by Mazzarella et al. (27) uses data from before 1850 for which the dating of both pandemic emergence and ENSO are less precise. As a result of these problems in their analysis, the work by Mazzarella et al. (27) misses the association between La Niña phase events and subsequent pandemic emergence.

The most plausible biological explanation for the La Niña–pandemic influenza association identified here involves ENSO-mediated changes to bird migration (Table 2). The 1957 and 1968 pandemics are thought to have originated from the reassortment of avian influenza viruses; however, the 2009 pandemic is thought to have arisen from the reassortment of two swine influenza viruses (12). Our hypothesis would require avian infection and transport of one or more of these viruses to facilitate the final

**Table 1. NDJ averaged SST anomalies (in Kelvin) during the fall/winter preceding the initial emergence of the last four human influenza pandemics**

| Pandemic (first identification) | NDJ Niño 3.0 index | NDJ Niño 3.4 index |
|---|---|---|
| 1918–1920 (March 1918) | −1.081 | −1.030 |
| 1957–1958 (February 1957) | −0.687 | −0.596 |
| 1968–1969 (July 1968) | −0.936 | −0.535 |
| 2009–2010 (March 2009) | −0.216 | −0.627 |

Average SST anomalies are shown for the Niño 3.0 (5°S–5°N, 150°–90°W) and 3.4 (5°S–5°N, 170°–120°W) regions.

**Table 2. Potential mechanisms underpinning the ENSO–pandemic influenza association**

| | Potential mechanisms |
|---|---|
| 1 | Changes in bird number in SE Asia during La Niña |
| 2 | Changes in bird fitness/viral shedding in SE Asia during La Niña |
| 3 | Changes in bird stopover time in SE Asia during La Niña (more time in residence to mix with local population) |
| 4 | Changes in bird species composition in SE Asia during La Niña caused by migration changes that bring new virus segments to the region (testable by both bird species composition and virus diversity in bird-exploited waters) |
| 5 | Changes in water habitat type and abundance in SE Asia during La Niña that facilitate fecal–oral avian and swine infections, multiple infections, and reassortments |

These changes would likely differ from region to region. As an example, we focus on southeast Asia. SE, southeast.

reassortment in pigs. Such infection of birds with swine influenza has been documented (30).

Human influenza pandemics are fortunately rare, but this infrequency makes their analysis difficult. However, our hypothesis does make predictions that are testable, at least in principle, in ecological, epizootiological, and viral population genetic data (Table 2). In particular, study of influenza virus gene flow within migratory bird populations and changes to migratory bird health, migration, and mixing within domestic fauna in response to ENSO are needed to substantiate whether La Niña events portend increased pandemic risk.

Ecologically, one would expect increased opportunities for virus transmission among birds or between birds and swine during La Niña events by one or more of the mechanisms shown in Table 2. These opportunities would lead to an increase in the prevalence of influenza infection and shedding in key migratory bird species, measurable by viral sampling from these species. Alternatively, the effect could manifest purely through changes in local species composition. Finally, if the hypothesis is correct, one would expect an increase in the prevalence of novel reassortant viruses among migratory birds and/or swine during La Niña years, the downstream consequence of these ecological and transmission changes and the precursor to events that may lead to a pandemic.

The effect of ENSO on influenza dynamics is also likely heterogeneous in space. It remains to be determined whether particular geographies (e.g., Asian vs. European vs. North American flyways) and particular bird species, for which this ENSO-induced influenza virus introduction and reassortment sensitivity is strongest, exist. In addition, the movement of virus from ENSO-sensitive geographies must be considered. The likelihood of reassortment during La Niña may increase in one or more places; however, the new virus may emerge in the human population elsewhere because of transport by migratory birds.

## Methods

The statistical significance of the pandemic year average was evaluated using a bootstrapping procedure. For instance, to assess the significance of average NDJ Niño 3.0 SST anomalies preceding the four most recent pandemics, we averaged four randomly chosen NDJ periods from the 1856–2010 Niño 3.0 SST record 100,000 times to create a distribution of 4-y NDJ Niño 3.0 SST average values. Statistical significance was then assessed based on where the actual pandemic year average lay on this synthetic distribution.

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