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Influenza and humidity — Why a bit more damp may be good for you!

Jane A. Metz, Adam Finn*

Bristol Childrens Vaccine Centre, University of Bristol and Bristol Royal Hospital for Children, Level 6, UHB Education and Research Centre, Upper Maudlin St., Bristol BS2 8AE, UK

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Summary Influenza viruses cause much winter-time morbidity and death in temperate regions. We still do not understand why 'flu is more common in winter. Since the 1960s, investigators have studied the role of relative humidity and temperature on viral survival, transmission and infection rates but results have demonstrated only inconclusive trends. Over the past few years however, a series of exciting studies have instead focussed on absolute humidity and demonstrated highly significant correlations with viral survival and transmission rates in both laboratory and epidemiological models. Here we review the evidence for a causal association between absolute humidity and 'flu transmission and outline how this could lead to a new approach to curbing this and perhaps other viral epidemics in the winter months.

Influenza

Influenza viruses are among the most common causes of human respiratory infections and cause high morbidity and mortality. In a typical endemic season, influenza results in approximately 200,000 hospitalizations and 36,000 deaths in the United States alone.[1] Globally, influenza A virus (IAV) is estimated to cause 3—5 million cases of severe influenza illness annually resulting in 250,000—500,000 deaths.[2] Influenza A viruses have mutation rates ranging from approximately 1×10^{-3} to 8×10^{-3} substitutions per site per year.[1] Gradual antigenic drift of surface antigens is the main driver of seasonal epidemics.[3] In contrast, influenza pandemics occur when a novel virus jumps to humans from an avian or mammalian host.[4] Creating enduring immune protection, either naturally or through vaccination to these evolutionarily dynamic viruses is therefore challenging. Furthermore, there has been limited success with achieving good coverage of annual 'flu vaccination programmes, although this is improving in some countries.[2,5] Alternative or adjunctive approaches to curbing the transmission of influenza are therefore of potential interest and importance.

* Corresponding author. Tel.: +44 1173420172.
E-mail addresses: janemetz@gmail.com (J.A. Metz), Adam.Finn@bristol.ac.uk (A. Finn).

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Influenza transmission

There are four main suspected transmission modes for influenza A, described in a review paper by Brankston et al.[6] and summarised below:

a) Direct contact: physical contact between infectious individual and a susceptible person.
b) Indirect contact: via inanimate objects (fomites) such as door handles, utensils etc.
c) Droplet: via large droplets ($\geq$5 μm diameter) generated and propelled through the air by coughing and sneezing into the upper respiratory tract of the susceptible recipient.
d) Airborne: via aerosolization in air borne virus-containing droplet nuclei ($<$5 μm diameter) resulting from evaporation of larger droplets or dust or cellular material. Suspended in the air for long periods and dispersed by air currents, droplet nuclei may be inhaled by susceptible hosts.

The relative importance of each transmission mode continues to be debated with a growing consensus that the main modes of influenza transmission are the droplet and both direct and indirect contact routes.[6]

The seasonality of influenza

In temperate regions of the world, influenza epidemics are more common in the winter.[7]

There are three main competing but not mutually exclusive hypotheses which seek to explain this[8]:

1) Reduced host immunocompetence, for example due to reduction in vitamin D levels and melatonin in the winter.[9–11]
2) Changes in host behaviours such as increased contact between individuals in indoor spaces, for example at the start of and during a school term.[12]
3) Changes in environmental conditions such as air humidity and temperature. These might affect infection rates either through effects on the host (for example the integrity or function of the upper respiratory mucosa) or on the infecting agent by changing virus viability or efficiency of transmission.[8]

The evidence for the first two hypotheses has already received some research attention and it appears possible that both have some effect on influenza transmission. However they do not appear fully to explain the seasonality observed. The focus of this paper will be around how humidity may influence 'flu epidemics.

Relative and absolute humidity

When we consider humidity we generally think in terms of relative humidity (RH); this is the amount of water vapour present in air, expressed as a percentage of the amount needed for saturation at the same temperature. RH affects how hot we feel at a given temperature by altering the effectiveness of sweating as a cooling mechanism. In high RH, sweat does not easily evaporate because the air is already nearly completely saturated with water. Heat is therefore not lost, leading to continued but ineffective sweating. At cloud level, RH also determines whether it will rain.

Absolute humidity (AH), also known as vapour pressure, and measured in millibars (mb), is the total water content of the air; it can be calculated by dividing the mass of water vapour by the mass of dry air in a volume of air at a given temperature. Crucially, the hotter the air, the more water it can contain so that much higher AH is achievable in warm conditions than in cold. When it is cold, the air often feels humid: the RH is high, but the amount of water in the air — the AH — is low, as cold air cannot carry much water.

Low absolute humidity and increased rates of influenza transmission in animals

Several attempts have been made to evaluate the effects of changing environmental factors including temperature and RH on the transmission of 'flu in laboratory animals.[13,14]

Lowen et al. used guinea pigs as their influenza transmission model to investigate how different temperature and RH conditions affected rates of transmission. Guinea pigs are reported to be good models for influenza transmission.[15] These authors showed a relatively weak inverse association between RH and viral transmission.[14,16]

There had not been any studies of the effect of AH on influenza virus transmission (IVT) until Shaman and Kohn used the data published by Lowen et al. to recalculate AH from the RH and temperature values and model its effect on IVT and influenza virus survival (IVS). Based on the observation that there a strong seasonal cycle in AH, both outdoor and indoor, with lowest values during the colder winter months in temperate regions, they hypothesised that AH was more likely to affect viral survival and transmission than RH which is often high in the winter. Using linear regression to plot temperature, RH and AH against IVT they demonstrated that AH had a highly significant inverse relationship ($p = 0.00027$) with viral transmission; i.e. the lower the AH, the more viral transmission occurred. The statistical significance of this was much greater than for RH and IVT as well as temperature and IVT (see Fig. 1).[17] To date, there are no trials investigating the effect of humidity on the rates of influenza transmission in humans.

Relationship between influenza virus survival and absolute humidity

Like transmission, IVS has been investigated at different levels of RH and temperatures, once again showing correlation trends of borderline significance.[18] A similar reanalysis, substituting RH with AH values, produced a clearer, nonlinear relationship between IVS and AH (Fig. 2).[17] The authors discuss the fact that a more comprehensive series of laboratory investigations at various AH levels are needed in order to validate and explore further the relationship between IVT and AH and whether this is also non-linear. The

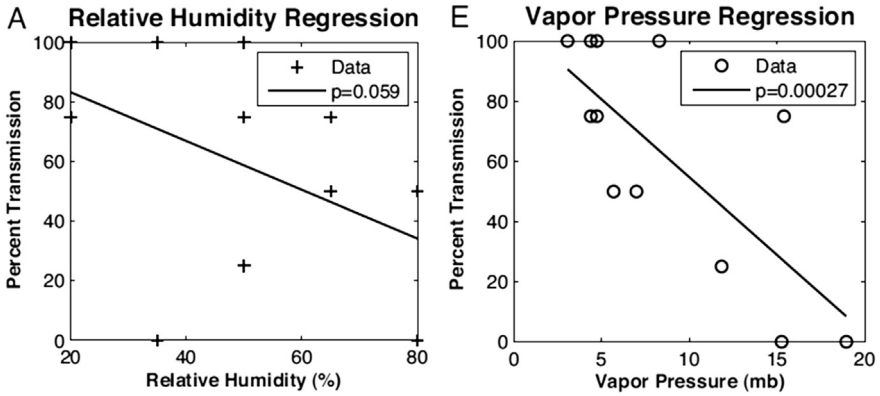

Figure 1 Comparison of the relationship between influenza virus transmission and relative (left — A) and absolute (right — E) humidity. Reproduced with kind permission from Shaman et al.[17]

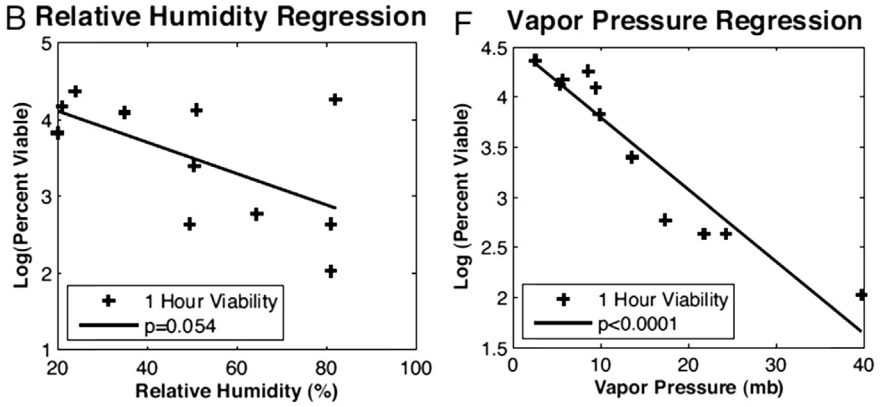

Figure 2 Comparison of the relationship between influenza virus viability and relative (left — B) and absolute (right — F) humidity *in vitro*. Reproduced with kind permission from Shaman et al.[17]

mechanisms by which AH affects IVS and IVT are not fully understood. One hypothesis is that AH could affect size distribution of expelled particles thereby affecting survival and transmission potential.[17] However, lower RH levels have also been shown to increase IVS on fomites[19]; the effects of AH on fomites needs exploration and more broadly the possibility that influenza and perhaps other viruses simply remain viable for longer in drier conditions.

Supporting epidemiological data: changes in absolute humidity predict the onset of seasonal influenza epidemics

To investigate whether laboratory-based findings implicating AH as a significant driver of seasonal influenza transmission are supported by epidemiological data, Shaman et al. studied the correlation between the onset of influenza epidemics and AH in the United States. First, they correlated the spatial and temporal variation of epidemic influenza onset from 1972 to 2002 (this equates to 1000 different 'flu epidemics in 48 contiguous states) with the concurrently recorded AH data for these regions. The onset date of wintertime influenza was defined as the date at which wintertime observed excess pneumonia and influenza mortality (P&IM) had been at or above a prescribed threshold level for 2 continuous weeks. They examined AH conditions prior to and following these onset dates in order to work out whether the onset of wintertime influenza occurred when AH was above or below typical daily local AH averaged over 31 years (referred to as anomalous AH). They demonstrated that negative (i.e. low) anomalous AH values were typically observed 4 weeks prior to the onset of an influenza epidemic. They found a small (55—60%), but highly statistically significant ($p < 0.0005$) association between atypically low local daily AH and the onset of wintertime influenza. This was statistically stronger than for RH, temperature or sunshine. There were apparent regional differences in the strength of association of low AH and onset of 'flu, the strongest association being in the eastern states US although even in the western states (some of which did not reach statistical significance), AH was typically low in the weeks prior to the onset of epidemic influenza.

Shaman et al. then went on to examine whether an AH-driven population-level model of influenza transmission would reproduce the observed seasonal patterns of P&IM. For this, they used five states (Arizona, Florida, Illinois, New York and Washington) which they described as representing the main different climates within the US. They also incorporated three different disease states into the model — the susceptible, the infected and the recovered (SIR) — and in

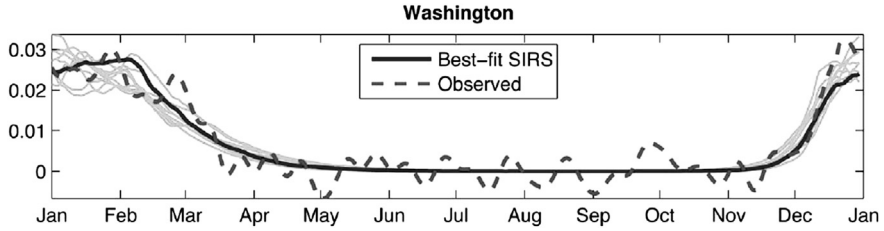

Figure 3 Graphical representation demonstrating the proximity between the observed 31-year mean daily excess pneumonia and influenza mortality rate (dashed black line) and the best-fit SIRS model simulations (solid black line = best fit, finer grey lines show the next 9 best simulations) which were calculated using mean daily absolute humidity conditions within Washington state. Reproduced with kind permission from Shaman et al.[4]

order to account for waning immunity, they defined a rate by which immune individuals went back to being susceptible. Observed mean daily AH conditions within each state were then used to modulate the basic reproductive number of the influenza virus — i.e. the transmission rate within the fully susceptible population. After running multiple simulations for each state, the mean annual cycle of daily infections were compared with the average observed P&IM rates (see Fig. 3). There were also numerous other considerations built into the model. They demonstrated that the model could accurately predict spatial and temporal variations in epidemic influenza. These data were cross-validated by performing 31 year (1972—2002) SIR simulations for each of the 48 states. These demonstrated good simulations of observed P&IM for the majority of states although the more sparsely populated Western states performed less well. Using the school calendar and more specifically school closure dates to modulate the basic reproductive number of the influenza virus, the model could generate a winter seasonal cycle of influenza but not the observed excess P&IM as seen using AH alone.[4]

Feasible ways of altering indoor humidity

Given the evidence summarised above that lower AH increases IVS and IVT, indoor AH and the potential to change it within public spaces has become a topic of interest. Koep et al. have investigated AH fluctuations in two Minnesota schools during two successive winters. Using automated sensors they compared outdoor and indoor AH, and the latter in different rooms and between the two schools. They also assessed how AH changes with the presence and absence of school pupils. They found large variations in indoor AH which were strongly associated with outdoor AH.[20] For reasons discussed above, in temperate regions, outdoor AH is low in the colder winter months. Indoor AH is presumably low too because dry cold air is piped indoors and warmed up but not humidified.[4]

AH also rose significantly during school time, most likely due to expiration of water vapour by the people in the rooms and evaporation of sweat. During school breaks such as weekends and holidays, household humidifiers were used to assess the feasibility of raising classroom AH levels. Humidifiers could almost double a single room's AH within about four hours, increasing the mean humidity from 4.89 mb up to 8.97 mb.

Using findings derived from laboratory influenza virus survival experiments, Koep et al. also made predictions of IVS at different levels of AH, calculating a maximum projected viral survival of 75% at one hour at an AH of 2.67 mb, the value falling to only 45% at an AH of 9.45 mb. They concluded that "modest and achievable changes in indoor AH are likely to have a substantial effect on 1-hour influenza virus survival".[20]

Could these data support a future cluster-randomised controlled trial evaluating, for example, whether classroom or GP surgery or hospital waiting room humidification reduces rates of influenza transmission? One would need to attend to numerous practical considerations such as adequate insulation of humidified rooms to avoid problems with condensation and appropriate regulations of levels of humidification. A potential hazard of increasing AH, for example, might be encouragement of fungal growth which, aside from causing damage to buildings, could pose a health risk to immunocompromised patients particularly in the healthcare setting.

Nevertheless it would also be interesting to consider further potential benefits of reducing influenza transmission rates upon other epidemics, for example invasive meningococcal disease, pneumococcal pneumonia and invasive group A streptococcal infections which may be secondary to 'flu[21—23] and to establish whether transmission of other respiratory viruses could also be reduced in this way.

Summary

In this paper, we have reviewed an emerging hypothesis and some early supporting evidence that low AH is a key causal factor in winter-time influenza peaks in temperate climates. Epidemiological data support this hypothesis as influenza-associated morbidity and mortality peaks 2—3 weeks following falls in AH. Mathematical modelling of *in vitro* experiments investigating influenza virus survival at different levels of AH have shown improved survival of the influenza virus at lower AH levels. Re-analysis of experiments using a guinea pig model have demonstrated an increase in influenza A infection rates at lower AH levels. There are data to suggest that outdoor AH levels affect humidity levels inside and that simple humidifiers may be adequate to raise AH to levels associated with a significant reduction in influenza virus survival.

Further research into the effects of increasing AH on IVT in humans appears to be warranted. The prospect of reducing influenza-associated morbidity and mortality by

increasing the AH in nurseries, classrooms, hospitals, homes for the elderly and general public spaces is an exciting and novel potential strategy for disarming 'flu.

Conflicts of interest

Neither author has any conflicts of interest relevant to the material in this paper. AF has previously undertaken research and consultancy related to influenza vaccines and antivirals, income relating to which was paid to his employers.

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