Epidemiol. Infect. (2012), **140**, 87–90. © Cambridge University Press 2011
doi:10.1017/S0950268811001695

COMMENTARY
Seasonality – still confusing

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(*Accepted 3 August 2011; first published online 12 September 2011*)

Annual peaks in incidence are almost universal features of infectious disease epidemiology, yet a consistent explanation for this phenomenon remains elusive. The article by Murray and colleagues [1] adds rigorously collected and analysed data and proposes household crowding as an explanation, but there are internal inconsistencies in this study as there are throughout the infectious disease seasonality literature. What exists are models that explain only a subset of the data, or proposed drivers for seasonality that correlate with the seasonal variation for one pathogen in one geographical area, but break down for the same pathogen in another location, or correlate well for several years and then fail to do so consistently over time. And yet a regular annual variation in the incidence of acute respiratory infections is among the most undeniable patterns in infectious disease epidemiology, almost begging for a simple explanation.

The study by Murray and colleagues begins by acknowledging a contradiction. The authors note that a recent laboratory study identified cold, dry air as more conducive to the aerosol transmission of influenza viruses in guinea pigs [2], but that such an explanation could not be the reason for the seasonal increase in Bangladesh, because that peak occurs during the hottest, wettest time of the year. They go on to describe an elegant study exploring the hypothesis that household crowding during the rainy season is the explanation. Indeed, during a single 3-month period respiratory infections were significantly more likely to be associated with rainy days than were control periods. Their explanation that people were crowded indoors during the rains, increasing the transmission of influenza and other respiratory viruses, appears to have been substantiated by a stronger association for homes with >3 inhabitants.

The strengths of this study are substantial, including the well-defined population, consistent surveillance, and laboratory testing that gives the investigators the uncommon ability to look at pathogen-specific incidence over time. The study adds hard data and rigorous methods to what has been a largely speculative explanation for many years – that people crowd together indoors during rainy periods in tropical countries and this increases the transmission of infectious diseases. Like many well-designed studies, this one raises as many new questions as it answers. If rain driving families indoors is what leads to the increase in the incidence of respiratory infections, then why does the incidence drop before the rainy season peaks? Indeed, during the rainiest time of the year, when rains occur daily, the incidence of respiratory infections dropped off to its seasonal trough level. The authors speculate that population immunity may have been sufficient to bring the annual epidemic to an end. Although this explanation seems sensible at face value, the fact is that in most influenza seasons only 5–20% of the population is infected. Transmission models indicate that a much higher proportion would need to have immunity before spread is significantly limited [3–7], although precisely what level of immunity would be needed is not clear. Moreover, if crowding is what increases transmission, then why did the odds of respiratory infection actually decrease in houses with $\geqslant 5$ persons? Perhaps it is

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true that this anomaly can be explained if the more crowded households had older children, who were more likely to have been exposed to influenza viruses previously, thus paradoxically reducing the risk of infection in those households with the most crowding. Changes in household immunity, not necessarily correlating with overall population immunity, might be an explanation, although exceedingly complex to ponder.

Other recent studies also have been confusing, requiring additional explanations to account for data that do not fit with the hypotheses. The elegant investigation by Lowen *et al*. [2] of aerosol transmission in guinea pigs, for example, documented that influenza viruses were transmitted more effectively in this model when the air was cool and dry, fitting nicely with seasonal patterns observed in temperate zones but in direct contrast with the observed seasonal pattern in Bangladesh and other tropical regions. The authors speculate that transmission in temperate zones is by airborne routes, whereas in tropical regions influenza is transmitted by direct contact. In a 2010 study, Steel *et al*. [8] used the guinea pig model to investigate the transmission characteristics of the 2009 pandemic influenza virus, observing that this virus was transmitted substantially during the winter and spring, rather than the winter transmission of seasonal H3N2 viruses. However, the transmission characteristics of the new virus in this model were the same as seasonal viruses, indicating that viral sensitivity to temperature and humidity were not likely explanations for the very different seasonal pattern of the new virus. Shaman *et al*. [9] in 2010 concluded, based on modelling of influenza patterns, that low absolute (not relative) humidity correlated best with influenza virus epidemiology in temperate regions, but they did not explain how the peaks in tropical regions could be occurring during periods with highest absolute humidity [9].

Recent support for vitamin D deficiency as a cause for the increased incidence of influenza and some other respiratory infections in winter has come from some studies [10, 11], but not others [12, 13]. A systematic review of randomized trials of vitamin D for prevention of infectious diseases concluded that more rigorously designed trials are needed [14].

The current state of understanding of influenza seasonality is summarized in a comprehensive review by Tamerius and colleagues [15]. Influenza viruses are transmitted more efficiently as aerosols in cold temperatures but transmission by close contact is not impacted by temperature. Low absolute humidity increases virus survival on surfaces and in aerosols under experimental conditions but does not correlate with peak influenza rates in tropical zones. Peaks in incidence often but not invariably correlate with rains in the tropics. Rainy days were associated with decreased contact among schoolchildren in Germany but higher rates of influenza in Bangladesh. In mice selenium, vitamin C, vitamin D, and vitamin E may all influence the severity of influenza. Confusing! Tamerius *et al*. conclude: 'The central questions in influenza seasonality remain unresolved'.

As I see it, infectious disease seasonality looks like a biological rhythm. The reliable sinusoidal seasonal variation that persists through a wide range of climatic and epidemiological settings is entirely typical. The term biological rhythm should not be confused with 'biorhythm'. According to Wikipedia, the notion of biorhythms 'has no more predictive power than chance, and is now considered a classic example of pseudoscience'. Biological rhythms, on the other hand, are the focus of a well-established field of biology called chronobiology. Biological rhythms are intrinsically rhythmic phenomena of living organisms that include daily rhythms (body temperature, sleep–wake cycle), as well as monthly (menstrual cycle), and annual (reproductive capacity in many mammals, loss of leaves in deciduous trees, and perhaps seasonal variation in infectious diseases) [16–18]. A central aspect of biological rhythms is that they are internally driven – maintained by a biological clock within the organism itself. In the absence of all external signals (as has been done for volunteer subjects kept in constant light with no time cues), the rhythms 'free-run', meaning that they persist with approximately the same timing as when there are external cues (hence the term 'circadian', meaning approximately a day). External cues help to set the timing of the clock (these are known as *zeitgeibers*), but are neither necessary nor sufficient to drive the rhythm [16]. For seasonal rhythms the external cue is usually day length, presumably because it is a strong and reliable signal of season. As with seasonal viral infections that are precisely timed in temperate latitudes [19, 20], but variable and less predictable in the tropics [21, 22], seasonal biological rhythms, such as reproductive physiology in mammals, are strongly and precisely timed in temperate latitudes, but follow variable and less predictable patterns in the tropics [23–25].

If the seasonal variation in infectious disease incidence is fundamentally a biological rhythm, searches

for a consistent external driver (temperature, humidity, crowding, vitamin D), will continue to produce apparently confusing and contradictory results. Certainly, many seasonally varying phenomena (and there are innumerable such phenomena, ranging from temperature and humidity to indoor crowding and the Christmas shopping season) will be found to correlate strongly and significantly with seasonal variation in infectious diseases. But the correlations will not hold up in different settings, and modifying these *zeitgebers* will produce only modest and inconsistent changes in the underlying rhythm. In populations living in temperate parts of the earth, seasonal rhythms will be strong and consistently timed. In the tropics, the underlying rhythms will still be present, but may be timed to different and weaker signals, or may free run, leading to seasonal rhythms in sub-populations that differ across geographical areas, or that shift every few years.

Factors that influence transmission, such as absolute humidity for airborne pathogens or physical proximity for those transmitted directly, may be important influences on rates of disease even if they are not what fundamentally drive the rhythmic behaviour. As one example, the violation of seasonality that is consistently observed in the first year after a novel influenza virus appears may be related to the population-wide susceptibility to the new pathogen before the seasonal rhythm settles in to the predictable pattern.

Much of the available information on respiratory pathogen seasonality in tropical countries has been accumulated in just the past 3 years. As more well designed studies explore the various hypotheses for infectious disease seasonality in different settings around the world, the accumulated evidence, even if confusing and contradictory on the surface, should soon lend itself to a coherent explanatory model.

DECLARATION OF INTEREST

None.

REFERENCES

1. **Murray E, *et al.*** Rainfall, household crowding, and acute respiratory infections in the tropics. *Epidemiology and Infection*. Published online: 4 March 2011. doi:10.1017/S0950268811000252.
2. **Lowen AC, *et al.*** Influenza virus transmission is dependent on relative humidity and temperature. *PLoS Pathogens* 2007; **3**: 1470–1476.
3. **Cannell JJ, *et al.*** On the epidemiology of influenza. *Virology Journal* 2008; **5**: 29.
4. **Mathews JD, *et al.*** Understanding influenza transmission, immunity and pandemic threats. *Influenza and Other Respiratory Viruses* 2009; **3**: 143–149.
5. **Chowell G, Miller MA, Viboud C.** Seasonal influenza in the United States, France, and Australia: transmission and prospects for control. *Epidemiology and Infection* 2008; **136**: 852–864.
6. **Russell CA, *et al.*** Influenza vaccine strain selection and recent studies on the global migration of seasonal influenza viruses. *Vaccine* 2008; **26** (Suppl. 4): D31–34.
7. **Hope-Simpson R, Golubev D.** A new concept of the epidemic process of influenza A virus. *Epidemiology and Infection* 1987; **99**: 5–54.
8. **Steel J, Palese P, Lowen AC.** Transmission of a 2009 pandemic influenza virus shows similar sensitivity to temperature and humidity as an H3N2 seasonal strain. *Journal of Virology* 2011; **85**: 1400–1402.
9. **Shaman J, *et al.*** Absolute humidity and the seasonal onset of influenza in the continental United States. *PLoS Biology* 2010; **8**: e1000316.
10. **Sabetta JR, *et al.*** Serum 25-hydroxyvitamin d and the incidence of acute viral respiratory tract infections in healthy adults. *PLoS One* 2010; **5**: e11088.
11. **Urashima M, *et al.*** Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *American Journal of Clinical Nutrition* 2010; **91**: 1255–1260.
12. **Li-Ng M, *et al.*** A randomized controlled trial of vitamin D3 supplementation for the prevention of symptomatic upper respiratory tract infections. *Epidemiology and Infection* 2009; **137**: 1396–1404.
13. **Laaksi I, *et al.*** Vitamin D supplementation for the prevention of acute respiratory tract infection: a randomized, double-blinded trial among young Finnish men. *Journal of Infectious Diseases* 2010; **202**: 809–814.
14. **Yamshchikov AV, *et al.*** Vitamin D for treatment and prevention of infectious diseases: a systematic review of randomized controlled trials. *Endocrine Practice* 2009; **15**: 438–449.
15. **Tamerius J, *et al.*** Global influenza seasonality: reconciling patterns across temperate and tropical regions. *Environmental Health Perspectives* 2011; **119**: 439–445.
16. **Schulz P, Steimer T.** Neurobiology of circadian systems. *CNS Drugs* 2009; **23** (Suppl. 2): 3–13.
17. **Foster RG, Roenneberg T.** Human responses to the geophysical daily, annual and lunar cycles. *Current Biology* 2008; **18**: R784–R794.
18. **Roden LC, Ingle RA.** Lights, rhythms, infection: the role of light and the circadian clock in determining the outcome of plant-pathogen interactions. *Plant Cell* 2009; **21**: 2546–2552.
19. **Noah ND.** Cyclical patterns and predictability in infection. *Epidemiology and Infection* 1989; **102**: 175–190.

20. **Dowell SF.** Seasonal variation in host susceptibility and cycles of certain infectious diseases. *Emerging Infectious Diseases* 2001; **7**: 369–374.
21. **Paccaud M.** World trends in poliomyelitis morbidity and mortality, 1951–1975. *World Health Statistics Quarterly* 1979; **32**: 198–224.
22. **Cox NJ, Subbarao K.** Global epidemiology of influenza: past and present. *Annual Review of Medicine* 2000; **51**: 407–421.
23. **Fatet A, Pellicer-Rubio MT, Leboeuf B.** Reproductive cycle of goats. *Animal Reproductive Science* 2011; **124**: 211–219.
24. **Reiter RJ.** The melatonin rhythm: both a clock and a calendar. *Experientia* 1993; **49**: 654–664.
25. **Heideman PD, Bronson FH.** Sensitivity of Syrian hamsters (*Mesocricetus auratus*) to amplitudes and rates of photoperiodic change typical of the tropics. *Journal of Biological Rhythms* 1993; **8**: 325–337.