COMMENTARY
Seasonality – still confusing

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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 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 ≥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 cor-
relating with overall population immunity, might
be an explanation, although exceedingly complex to
ponder.

Other recent studies also have been confusing, re-
quiring additional explanations to account for data
that do not fit with the hypotheses. The elegant in-
vestigation by Lowen et al. [2] of aerosol transmission
in guinea pigs, for example, documented that influ-
enza 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 re-
egions 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 sensi-
tivity 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 high-
est 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 sys-
tematic 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 tem-
peratures 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 de-
creased 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 cli-
matic 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 per-
haps 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 exter-
nal 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 approxi-
mately 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 inci-
dence 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


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