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Seasonality and selective trends in viral acute respiratory tract infections ☆

Patrick D. Shaw Stewart *

2 Marsh Cottages, Weston, Berkshire RG20 8JB, UK

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ABSTRACT

Influenza A and B, and many unrelated viruses including rhinovirus, RSV, adenovirus, metapneumovirus and coronavirus share the same seasonality, since these viral acute respiratory tract infections (vARIs) are much more common in winter than summer. Unfortunately, early investigations that used recycled "pedigree" virus strains seem to have led microbiologists to dismiss the common folk belief that vARIs often follow chilling. Today, incontrovertible evidence shows that ambient temperature dips and host chilling increase the incidence and severity of vARIs. This review considers four possible mechanisms, M1 - 4, that can explain this link: (M1) increased crowding in winter may enhance viral transmission; (M2) lower temperatures may increase the stability of virions outside the body; (M3) chilling may increase host susceptibility; (M4) lower temperatures or host chilling may activate dormant virions. There is little evidence for M1 or M2, which are incompatible with tropical observations. Epidemiological anomalies such as the repeated simultaneous arrival of vARIs over wide geographical areas, the rapid cessation of influenza epidemics, and the low attack rate of influenza within families are compatible with M4, but not M3 (in its simple form). M4 seems to be the main driver of seasonality, but M3 may also play an important role.

The seasonality of colds and 'flu'

When you have eliminated all which is impossible, then whatever remains, however improbable, must be the truth.

[A. Conan-Doyle, the Case-Book of Sherlock Holmes, 1927.]

The lack of a sound explanation for the seasonality of viral acute respiratory tract infections (vARIs) is a major problem for microbiology [1–4]. Other anomalous features of vARIs need to be explained too. For example, vARI epidemics often erupt very rapidly after ambient temperature drops. The increase may, however, be too rapid and too short-lived to be the result of increased transmission [5], as discussed below. Surveys also show that epidemics often occur simultaneously throughout wide geographical areas [5–7] (see Figs. 1 and 2). Moreover, influenza epidemics often cease very abruptly, even when many susceptible individuals remain in the population [7].

The viruses that cause vARIs include many unrelated families such as double-stranded DNA viruses (e.g. adenovirus), positive-sense single-stranded RNA viruses (e.g. coronavirus), negative-sense single-stranded RNA viruses (e.g. respiratory syncytial virus (RSV), influenza, measles, mumps and parainfluenza virus), and positive-sense single-stranded RNA viruses (e.g. hand foot and mouth virus, rhinovirus, rubella virus). They differ in their physical forms, with some having a lipid envelope (e.g. coronavirus, influenza, and parainfluenza viruses), which many others (e.g. adenovirus and rhinovirus) lack. Some are icosahedral (e.g. adenovirus. rhinovirus and Rubella virus) whereas many are spherical, filamentous or variable (e.g. RSV, influenza, and measles viruses). It is notable that the great majority of these diverse and often distantly-related strains share the same seasonality in temperate regions. For example, Hope-Simpson found in both 1954 and 1955 that the number of people suffering from "colds" in a sample of 380 volunteers was roughly 50 times greater in February than at the beginning of September [3] (Fig. 3). The common cold is caused by over 200 serologically-distinct strains [8]. It is clear that the great majority of these strains share the same seasonality in temperate regions, since colds in general show such strong seasonality. However, variations in the precise timing of the various respiratory viruses within the cold season have been reported, and it has been

Abbreviations: HEF, hemagglutinin-esterase-fusion protein; HFMD, hand, foot and mouth disease; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; *Ts* or *ts*, temperature-sensitive; vARI or vARIs, viral acute respiratory tract infection or infections.

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* Tel.: +44 (0) 1488 649090; fax: +44 (0) 1488 648975.
E-mail address: Patrick@douglas.co.uk

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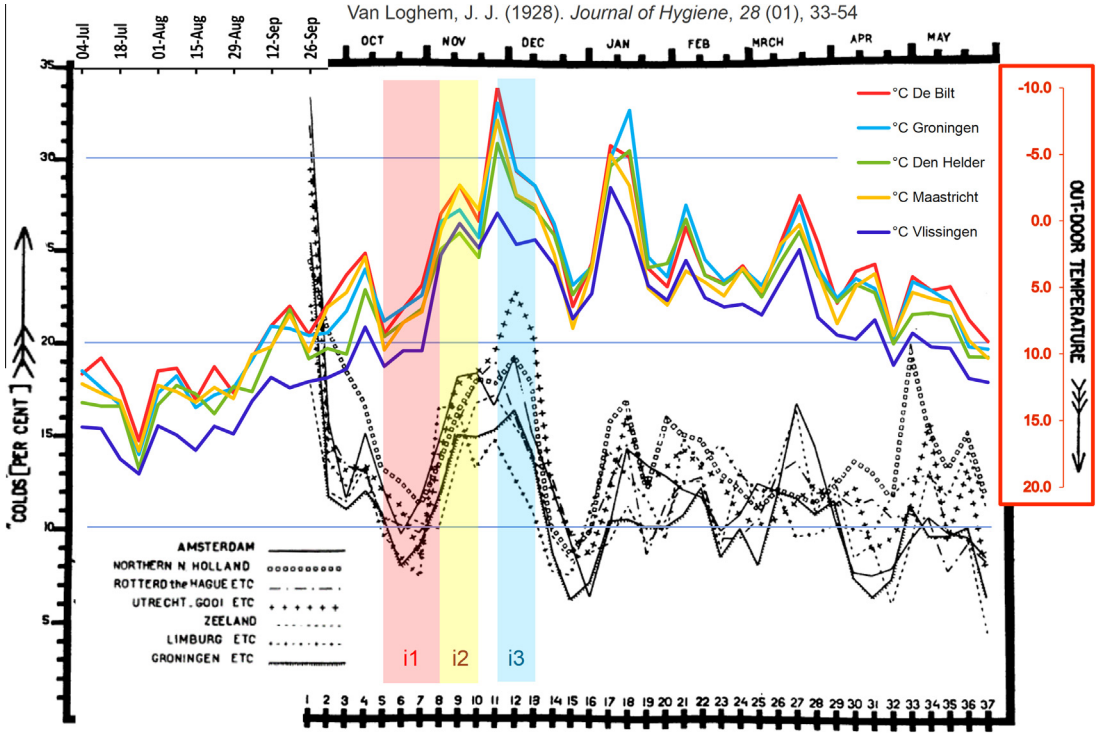

Fig. 1. Graph II from van Loghem's report [5] on the epidemiology of vARIs in the Netherlands in the winter of 1925/26, with ambient temperature superimposed. The graph shows the percentages of persons with colds in seven regions of the Netherlands for 37 weeks. The data was compiled from the reports of 6933 correspondents that were submitted by post each week. Amsterdam had the largest number of informants (1159) and Noord-Holland the fewest (581). I have added the daily minimum outdoor air temperature (also averaged over 7 days at weekly intervals) from five Dutch weather stations, with the temperature scale inverted (lowest temperatures at the top). Note that by far the highest rate of vARIs was at the beginning of the study (September 1925), and that vARIs in different regions are closely correlated with each other and with inverted temperature. These correlations are strongest in the first half of the cold season. Correspondents reported coryza, angina, laryngitis, bronchitis and "influenza". It is likely that a variety of viral "species" were present. See the main text for discussion of the events occurring during the intervals labeled i1, i2 and i3. ©1928, 2015. This figure was originally published in the Journal of Hygiene, 28(01), 33–54.

suggested that these variations might reflect fundamental differences in the mechanisms of replication or transmission of the viruses involved [4,9–11]. For example, rhinovirus is particularly prevalent in the autumn [12], while RSV and influenza usually cause outbreaks around the turn of the year [12]. Several comments can be made here: (1) very few vARIs have been found that consistently show the *opposite* seasonality, with more outbreaks in summer than in winter. For example, a study at a children's hospital in Mainz, Germany, that used modern diagnostic tests found that 7 out of 10 vARIs displayed normal seasonality, since these 7 showed significant inverse correlations with ambient temperature (p-value < 0.001) [4]. The remaining 3 were weakly inversely correlated with temperature. (A counter-example was reported by Hope-Simpson [13], although the tendency was weak: of the type 3 parainfluenza viruses isolated by him over 14 years, 66% were collected in the warm semester.) (2) Studies show that the reported variations in the timing of particular vARIs are in fact rather inconsistent. For example, RSV in children in Mainz peaked in spring in 2002 and 2006, but in the winters of the intervening years [4]. (3) It is possible that certain vARIs are more prevalent in, say, spring and autumn as a result of "interference" by other viral strains during winter. For example, the immune systems of hosts may frequently be activated by certain dominant viruses during the winter months, reducing the likelihood of subsequent infection by less active strains. The patterns of vARIs in the Mainz study suggest the existence of such interference (compare the relatively smooth curve of all respiratory illnesses in Fig. 1 in [4] with the irregular occurrences of the individual vARIs shown in Figs. 1 and 2 of that report).

These trends imply the existence of important mechanisms concerned with viral replication or transmission that are common to the majority of respiratory viruses, in spite of their widely-differing physical structures and biochemistry. It seems likely that an explanation of seasonality would have far-reaching practical and economic implications for treating and protecting humans and animals from vARIs.

Microbiologists have put forward many explanations of the seasonality of vARIs. Proposed explanations of influenza seasonality, for example, include factors that change host contact rates (school closures, ambient temperature and precipitation), factors that may influence virus survival outside the body (relative humidity, absolute humidity, solar radiation and temperature), and factors that may change the immunity of hosts (humidity, photoperiodicity, temperature, viral interference, as well as deficiency of selenium, vitamin C, vitamin D and vitamin E) [1]. (Factors that may change the behavior of viruses at the biochemical level are seldom considered.) The same or similar explanations have been put forward for other respiratory viruses [4,9–12,14–18]. However, these well-known explanations are very difficult to reconcile with a straightforward observation: the vARIs in question are present in many tropical regions at intermediate levels throughout the year – often at much higher levels than in the summer in temperate locations [1,2]. Moreover, surveys show that the viral "species" that commonly cause vARIs in the tropics are similar to those in other climates. For example, the four most frequently identified viruses in two large hospitals in a tropical location (Singapore, 1990–1994) were, in order of prevalence, RSV, parainfluenza, influenza A and adenovirus [10]. (Most samples came from hospitalized children.)