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# Does Virus Interference Account for the Multiple Epidemic Waves that are Characteristic of the 1918 Spanish Influenza and other Influenza Pandemics?

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## Abstract

In 2009 several European countries, including Norway, experienced a delay in the spread of the new pandemic influenza A (H1N1) pdm09 virus after its initial emergence in spring and summer. In the present communication it is discussed whether this delay was shaped by virus interference with other respiratory viruses, in particular rhinoviruses, and thereby the forming of epidemic waves. Albeit a mere hypothesis at the moment virus interference may give a reasonable explanation to why outbreaks with the 1918 Spanish influenza and other influenza pandemics, in contrast to seasonal influenza, tend to occur in several subsequent epidemic waves. According to the evolution theories it is unlikely that epidemic viruses should circulate independent of each other.

**Keywords:** Virus interference; 1918 Spanish influenza; Pandemic influenza; Epidemic waves

## Introduction

A novel strain of influenza A (H1N1) virus, presently known as influenza A (H1N1) pdm09 virus, was first identified in Mexico and the United States in April 2009. A rapid spread across the world was observed, and on June 11, 2009 World Health Organization declared the first pandemic influenza outbreak in the 21st century.

In Norway the first cases with influenza A (H1N1) pdm09 virus infection were diagnosed in May 2009. However, during the following months there was a remarkable slow development of the pandemic with only scattered influenza virus detections. In the middle of October a sharp increase in influenza virus detections was observed with culmination in the beginning of November (week 45).

Sweden and France experienced similar delays in the epidemiological development of the new pandemic influenza virus. Concomitant with this delay, they all observed an increase in rhinovirus detections, and it was hypothesized that interference with rhinoviruses could have affected the spread of the new pandemic influenza A virus [1-4]. Studies from Germany did partly support this observation [5].

Virus interference refers to that infections with one virus may have impact on the spread of other viruses. In the present communication we will discuss whether rhinoviruses could have inhibited and thereby delayed the epidemic development of the new pandemic influenza virus. Fluctuations in this inhibition activity may in turn form the opportunities for the shaping of epidemic waves.

### Influenza virus seasonality and virus interference

In temperate regions in the Northern Hemisphere influenza epidemics usually show marked wintertime seasonality, with circulation detected over a two to three months period between November and March [6]. On the other hand, pandemic influenza outbreaks may have a more unpredictable occurrence, often with several epidemic waves. As an illustration to this, the first wave of the 1918 Spanish influenza pandemic reached Norway in June 1918 and had receded by August, followed by a much larger main wave peaking in October-November [7]. As already mentioned, for the new A (H1N1) pdm09 virus, the first cases observed in May 2009 were followed by a minor wave during the summer weeks and a decline in late summer. In both instances, the second wave did not take place until autumn/early winter. Thus, in Norway the timing of the pandemic waves of the 1918 Spanish influenza virus and the new influenza A (H1N1) pdm09 virus was apparently almost identical.

Like many other respiratory viruses, influenza virus is enveloped with an outer lipid membrane that surrounds the virus capsid. This lipid membrane is fragile and will easily be damaged if the external conditions are unfavorable. Studies have shown that in cold weather this lipid membrane will be stabilized by hardening [8]. This may, at least partly, explain why influenza and other enveloped respiratory viruses such as respiratory syncytial virus (RSV) and parainfluenza viruses usually have their main activity during the winter months. On the other hand, respiratory viruses like rhinoviruses lack this vulnerable lipid membrane. Under weather conditions less favorable to enveloped viruses, rhinoviruses will therefore have clear advantages over influenza virus and other complex built respiratory viruses [2]. This is also in agreement with observations from the United States that found rhinoviruses to be the most frequently isolated respiratory virus during summer-time [9].

The rhinoviruses may have found their ecological niches in late spring and late summer/early autumn and autumn, and thus, if the interference hypothesis is correct, be able to exist with limited competition from other epidemic respiratory viruses, and the interference effect will be obscured. What will happen if a new virus, which has not found its place in the hierarchy and occurs across these seasonal boundaries, suddenly appears in the population? Under this scenario it is quite likely that the interference phenomenon will be brought into operation and become visible as a delayed epidemiological development of the intruder [2]. In this context an

Australian study by Greer et al. should be mentioned [10]. They observed that co-infection with rhinoviruses and other respiratory viruses were less common than expected, indicating that rhinovirus infection may for a while render the host less likely to be infected with other viruses.

It should also be mentioned that if virus interference really exists, it is not expected to be restricted to only pandemic influenza and rhinoviruses, but pandemic influenza may form temporary constellations where the interference forces are more heavily manifested.

Is it reasonable to believe that some small and humble rhinoviruses are able to inhibit and partially stop the epidemiological development of a new pandemic influenza virus? The rhinoviruses may in this context have another advantage, namely their great immunological diversity. More than 100 different rhinovirus serotypes which provide no mutual serological cross protection have been identified. As a consequence of this, most people experience several rhinovirus infections each year, whilst several years may pass between recurring infections of other respiratory viruses like influenza.

In Norway vaccine against the new pandemic influenza A (H1N1) pdm09 virus was not available before the middle of October 2009 (week 42) [11], whilst the pandemic culminated in week 45, thus vaccination came too late to have a role in suppressing the autumn wave. In theory antiviral treatment and prophylaxis without doctor`s prescriptions could have contributed to the observed decrease in influenza virus identifications during summer and early autumn but this is not considered likely. School holidays and general public health and hygiene measures due to heightened public awareness did not hold back the rhinovirus summer outbreak and thus are not likely to have been the deciding factor for limiting the spread of the influenza virus. These viewpoints are also in agreement with observations from Sweden [1].

The almost identical temporal timing of the 1918 Spanish influenza pandemic and the influenza A (H1N1) pdm09 pandemic does also argue against that school holydays were the main reason for the decreased influenza summer spread in 2009 as well as in 1918.

Apart from rhinoviruses, the incidence of other respiratory viruses, including seasonal influenza viruses, and other picornaviruses like enterovirus and parechovirus was low during the summer 2009. The enteroviruses which were sero- or genotyped did belong to virus types that we were familiar with.

## The virus interference hypothesis-an old idea

Interference between outbreaks of infection with RSV and influenza virus was first suggested by Glezen and Denny [12]. They observed that RSV outbreaks seemed to be interrupted by the onset of influenza virus infections. This finding was supported by Norwegian observations which showed that RSV and influenza virus outbreaks usually did not reach their epidemiological peaks during the same period [13]. Later studies have supported these findings [14,15]. It should, however, be mentioned that these observations are not unambiguous [16].

It may seem strange to talk about virus interference in the development of outbreaks with epidemic viruses. However, it is well known that if one subsequently infects the same cell cultures with two different viruses, this will result in virus interference which will be exhibited as a reduced susceptibility of the cells for the last added virus. It was studies on this phenomenon that led Isaacs and Lindenmann to the discovery of interferon [17], a discovery that was rewarded with the Nobel Prize in medicine.

It is unlikely that the virus interference phenomena observable at the level of individual cells are not operating at organism level, i.e. *in vivo* [14]. In addition to interferon, it is possible that other broadly reactive responses of the innate immune system may also contribute.

The immune system will, for a while after a virus infection, leave the cells in an "antiviral state" with reduced susceptibility to other competing viruses [1]. It is therefore unlikely that epidemic viruses, i.e. viruses that occur in distinct outbreaks during which they infect a considerable proportion of the population, should circulate freely and independently of each other. If so, it would be contrary to current biological, ecological and evolutionary understanding of the considerable interdependence of living entities that occupy the same environment. Rather, two questions should be posed: Is the actual virus in such a position that the interference forces are expressed, and are our monitoring systems sufficiently suited to detect this phenomenon?

Several factors may play a role in both influenza seasonality and the propensity of pandemic influenza viruses to occur in subsequent waves. This topic is discussed in some recent review articles [6,18,19]. Their conclusions are that, although thoroughly investigated, these entities are not well understood. It may be that a better understanding of this complexity could be achieved if the virus interference aspect is taken into account

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