Does viral interference affect spread of influenza?

A Linde (annika.linde@smi.se)[1], M Rotzén-Östlund[2], B Zweygberg-Wirgart[2], S Rubinova[1], M Brytting[3]
1. Department of Epidemiology, Swedish Institute for Infectious Disease Control, Solna, Sweden
2. Department of Clinical Microbiology, Karolinska University Hospital, Solna, Sweden
3. Department of Virology, Swedish Institute for Infectious Disease Control, Solna, Sweden

This article was published on 8 October 2009.
Citation style for this article: Linde A, Rotzén-Östlund M, Zweygberg-Wirgart B, Rubinova S, Brytting M. Does viral interference affect spread of influenza?. Euro Surveill. 2009;14(40):pii=19354. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19354

This short communication hypothesises that rhinovirus epidemics occurring after start of school may interfere with the spread of influenza during the period when warm and humid climate decreases the influenza spread by aerosol. Limited laboratory data supporting this hypothesis are included in the article, but the report is written mainly to stimulate interest and research concerning the possibility that viral interaction may affect influenza epidemiology.

Modelling and prediction of the spread of influenza are important for rational decisions on how to handle epidemics and pandemics. Apart from immunity in the population, both climate and social behaviour seem to be important factors affecting the spread. Holiday time usually interrupts the spread [1]. In dry and cold weather the aerosol transmission of influenza is more efficient since the virus becomes stabilised by hardening of the lipid membrane, remains airborne for longer time and is spread to longer distances [2-3]. In warm and moist weather, droplet and possibly contact spread and inoculation by contaminated hands seem to become more important [4].

However, these factors do not explain all characteristics of the spread of the pandemic influenza A(H1N1) virus during 2009. In Sweden, and some other European countries, the spread increased after the end of the holidays, but after four weeks of increasing activity the spread suddenly declined, despite similar weather conditions and social behaviour (Figure 1) [5]. Limitation by herd immunity induced by the spread that actually took place is possible, but not very likely, as the reported number of infections and of influenza-like disease in total was rather low. Also, the experience from the United States and the United Kingdom, with considerable, though patchy, spread of the virus during late spring and summer, despite a climate unfavourable to influenza, makes it likely that the virus would have managed to reach a substantial peak in Sweden in early October, unless other factors than the weather affected the spread.

All cases of influenza were made reportable in Sweden on 13 May 2009. Samples were taken from all suspected cases until 16 July, when the strategy was changed from containment to mitigation. Figure 1 shows the number of laboratory-confirmed cases reported in Sweden according to the law. Influenza diagnoses reported from all Swedish laboratories during the past three seasons are included for comparison.

Since the number of samples sent for influenza analysis was increasing until week 36 [5] while the proportion of samples positive for pandemic H1N1 influenza was already decreasing (Table 1), we hypothesised that some other virus infection may have interfered with the spread of the influenza pandemic.

Laboratories in Sweden conducting extended viral diagnosis on samples sent for influenza examination were asked what viruses they found in the influenza-negative samples, and the answer was unanimous: rhinoviruses dominated, with sporadic findings of other respiratory viruses, such as enteroviruses and adenoviruses. We retrieved all data from one of the dominant laboratories, the microbiological laboratory at Karolinska University Hospital. All respiratory samples received are analysed by PCR for influenzavirus A and B, including pandemic influenza A(H1N1) virus, as well as for respiratory syncytial virus (RSV). Tests for a further thirteen viral pathogens are done if extended diagnoses is requested by the doctor submitting the sample [6]. The number of samples analysed between weeks 32 and 39 2009 at Karolinska University Hospital, as well as the results of the analyses, are shown in Tables 1 and 2. Extended PCR was only requested for samples that were negative for RSV and influenza. As shown in Figure 2, there was an increase in the proportion and number of rhinovirus diagnoses roughly in parallel with the decrease of influenza diagnoses.

A simple but likely explanation for the sudden interruption of the spread of influenza could thus be the increase in the spread of above all rhinoviruses. It is well known that a major rhinovirus epidemic always occurs soon after school has started [7]. The virus is spread mainly by contaminated hands [8], and has not been reported to be climate-dependent. Thus the spread of rhinoviruses may have had an advantage over influenza due to the mild and moist climate. Once a rhinovirus infection has become established, infected cells start producing interferon and other cytokines, similar to those produced by influenza [9]. This immune reaction causes the cells to enter an antiviral state. Though double infections occur, they are probably not common enough to maintain high level spread of both rhino and influenza viruses in the population.

Figure 1

Laboratory-confirmed cases of seasonal influenza since 2006-7 and of pandemic versus seasonal influenza in 2009, Sweden

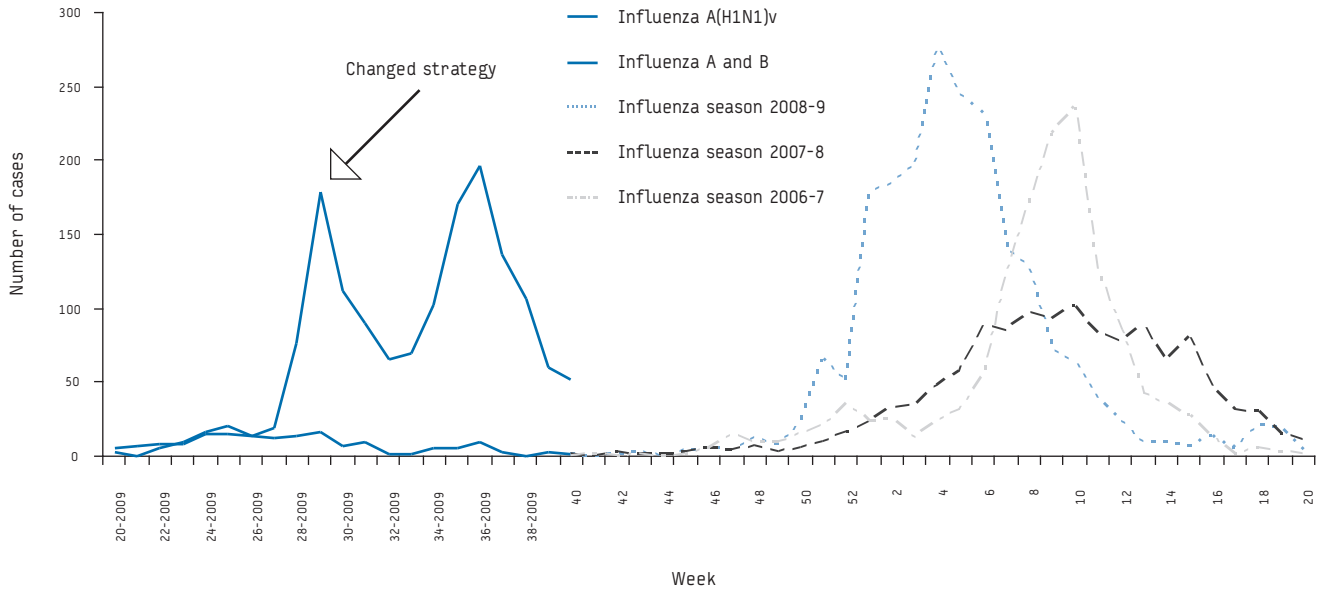

Table 1

Number of samples examined with PCR for pandemic influenza A(H1N1) and number and proportion of positives*, Karolinska University Hospital, Stockholm, August-September 2009 (n=2,994)

Week no. (2009)	32	33	34	35	36	37	38	39
Pandemic influenza A(H1N1)-positives, no. (%)	10 (7%)	16 (11%)	38 (14%)	85 (19%)	61 (8%)	33 (5%)	24 (7%)	9 (3%)
Total no. examined	**146**	**150**	**277**	**440**	**754**	**616**	**351**	**260**

* Respiratory syncytial virus and seasonal influenza were also included in the examinations, with one positive each during the whole period.

Table 2

Number of samples examined for 13 viruses*, Karolinska University Hospital, Stockholm, August-September 2009 (n=401)**

Week	32	33	34	35	36	37	38	39
Rhinovirus, no. (%)	2 (6%)	2 (5%)	7 (19%)	6 (11%)	18 (25%)	16 (27%)	14 (27%)	9 (16%)
Picornaviruses not subtyped, no. (%)	0	2 (5%)	0	1 (2%)	4 (6%)	2 (3%)	1 (2%)	2 (4%)
11 other viruses, no. (%)	1 (3%)	0	4 (11%)	4 (8%)	1 (1%)	1 (2%)	0	1 (2%)
Total no. examined**	**35**	**38**	**36**	**53**	**71**	**60**	**51**	**57**

*Rhinovirus , bocavirus , andenovirus, four types of human coronavirus, metapneumovirus, parainfluenzavirus types 1-3, non-subtyped picornaviruses, enteroviruses. Positive results for rhinovirus and non-subtyped picornaviruses, which could be rhinoviruses, are presented separately as numbers and percentages, the other viruses are summarised.
**A subset of samples from Table 1, which had tested negative for pandemic influenza A(H1N1), seasonal influenza and respiratory syncytial virus.

Influenza surveillance with sentinel reporting normally does not start until week 40, and respiratory sampling for viral diagnostics is usually scarce during early autumn. For week 40, most Swedish sentinel doctors usually report zero cases of influenza-like illness (ILI), and we do not know whether we the early autumn rhinovirus peak would have been reported as ILI in previous years even if reporting had been in place then. The reason for the large number of rhinovirus infections diagnosed in 2009 was most likely that people who got respiratory tract infections, who would not normally have visited a doctor, did so due to the fear of the pandemic influenza.

In conclusion, we hypothesise that a rhinovirus epidemic that occurred after the end of the summer holidays may have interfered with the spread of pandemic influenza during a period with warm and humid climate that decreases spread of influenza by aerosol. Although the laboratory data supporting this hypothesis are limited, it may stimulate research into the possibility that the interaction between different circulating viruses may affect influenza epidemiology.

We therefore suggest the following:

1. The epidemiology of influenza should be related to that of other respiratory viruses for improved understanding of the true epidemiological situation.
2. Surveillance of respiratory infections should be conducted throughout the year to create reliable baselines for ILI and acute respiratory infections, which are useful when a pandemic virus occurs that does not follow the usual pattern of spread.

References

1. Cauchemez S, Ferguson NM, Wachtel C, Tegnell A, Saour G, Duncan B, et al. Closure of schools during an influenza pandemic. The Lancet Infectious Diseases. 2009;9(8):473-81.
2. Polozov IV, Bezrukov L, Gawrisch K, Zimmerberg J. Progressive ordering with decreasing temperature of the phospholipids of influenza virus. Nat Chem Biol. 2008;4(4):248-55.
3. Lowen AC, Mubareka S, Steel J, Palese P. Influenza virus transmission is dependent on relative humidity and temperature. PLoS Pathog. 2007;3(10):1470-6.
4. Lowen AC, Steel J, Mubareka S, Palese P. High temperature (30 degrees C) blocks aerosol but not contact transmission of influenza virus. J Virol. 2008;82(11):5650-2.
5. Swedish Institute for Infectious Disease Control (Smittskyddsinstitutet). [Influenza reports. The season 2009-2010]. [Accessed 8 October 2009]. Swedish. Available from: http://www.smittskyddsinstitutet.se/publikationer/smis-nyhetsbrev/influensarapporter/sasongen-20092010/
6. Tiveljung-Lindell A, Rotzen-Ostlund M, Gupta S, Ullstrand R, Grillner L, Zweygberg-Wirgart B, et al. Development and implementation of a molecular diagnostic platform for daily rapid detection of 15 respiratory viruses. J Med Virol. 2009;81(1):167-75.
7. Monto AS. The seasonality of rhinovirus infections and its implications for clinical recognition. Clin Ther. 2002;24(12):1987-97.
8. Winther B, McCue K, Ashe K, Rubino JR, Hendley JO. Environmental contamination with rhinovirus and transfer to fingers of healthy individuals by daily life activity. J Med Virol. 2007;79(10):1606-10.
9. Khaitov MR, Laza-Stanca V, Edwards MR, Walton RP, Rohde G, Contoli M, et al. Respiratory virus induction of alpha-, beta- and lambda-interferons in bronchial epithelial cells and peripheral blood mononuclear cells. Allergy. 2009;64(3):375-86.

Figure 2

Proportion of samples examined at Karolinska University Hospital, Stockholm, containing pandemic influenza A(H1N1) and rhinoviruses, August-September 2009