

# Using clinical criteria on seasonal and pandemic influenza: what to look for?

Paulo Gonçalves<sup>1</sup>, Eleonora Paixão<sup>2</sup>, Ausenda Machado<sup>2</sup>, Rita Cordeiro<sup>1</sup>, Baltazar Nunes<sup>2</sup>, Pedro Pechirra<sup>1</sup>, Raquel Guiomar<sup>1</sup>

<sup>1</sup>National Influenza Reference Laboratory, Department of Infectious Diseases; <sup>2</sup>Department of Epidemiology National Institute of Health Dr. Ricardo Jorge, Lisbon, Portugal

## Background

The reliability of clinical criteria on the diagnosis of Influenza has been a question which has generated much debate in the scientific community. In Portugal, Influenza-Like Illness cases have been notified to the National Influenza Reference Laboratory, in the context of the National Influenza Surveillance Programme, by two sentinel networks, one of general medical practitioners (the "Médicos-Sentinelas" Network) and another of emergency rooms of hospitals and health centres, using clinical criteria adapted from the International Classification of Health Problems in Primary Care. With the emergence of a novel Influenza A(H1N1) virus circulating in humans, the clinical definition of an Influenza case was reformulated to accommodate the clinical features observed at that time. But how clinically different was the new variant A(H1N1) infection when compared to the seasonal Influenza? In this study we propose to evaluate the signs and symptoms present in Influenza cases diagnosed in Portugal during a seasonal Influenza winter with those reported during the recent A(H1N1)2009 pandemic. Also, we intend to evaluate the clinical criteria used for the notification of Influenza cases during these two periods.

## Materials and Methods

### Cases and variables studied

Influenza-Like Illness (ILI) cases were diagnosed for Influenza at the National Influenza Reference Laboratory in the context of the National Influenza Surveillance Programme during the 2008/2009 influenza winter season and the 2009/2010 pandemic period. Clinical information collected from those cases included the presence of signs and symptoms related with ILI as defined by the International Classification on Health Problems in Primary Care and on the case definition introduced by the European Commission Decision 202/253/EC (signs/symptoms analysed: sudden onset of symptoms, presence of fever, weakness, headache, myalgia, cough, sore throat, respiratory difficulty, chills and contact with an ILI patient). The odds ratio (OR) of being positive for Influenza for each sign/symptom was calculated, independently and using multivariable logistic regression with all the signs/symptoms. Results were compared with the clinical definition of Influenza used during both periods.

### Surveillance period

This study includes Influenza cases diagnosed during the 2008/2009 and 2009/2010 Influenza seasons, collected in the context of the National Influenza Surveillance Programme. Usually, the Surveillance Programme is reactivated on September of one year (week 40) and follows through May of the following year (week 20). However, during the period of this study and facing a situation where two influenza seasons of different characteristics occurred, one seasonal and another pandemic, it was decided to consider the 2008/2009 Influenza winter season from week 40/2008 to week 16/2009, and the 2009/2010 pandemic season from week 17/2009 to week 20/2010. This particular division was decided considering that the first Influenza case attributed to Influenza A(H1N1)2009 infection was observed on week 17/2009.

## Results

### Influenza Activity

Based on the ILI incidence rates calculated each week, the influenza activity in both seasons was described as high. The epidemic period of the 2008/2009 season lasted for 8 consecutive weeks, from week 49/2008 through 4/2009, with a maximum of 165.8 cases per 100 000 inhabitants in week 52/2008 (Fig 1). The epidemic period for the pandemic season was one week shorter than that of the previous winter but occurred much earlier, from week 44/2009 through week 50/2009, with a maximum of 136.4 cases per 100 000 inhabitants in week 46/2009.

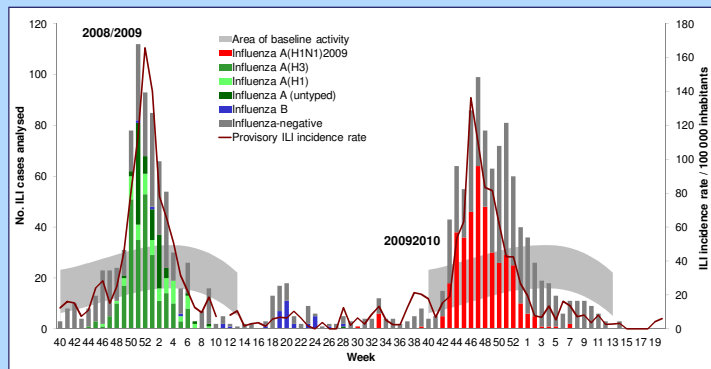


Fig 1. Influenza activity during 2008/2009 and 2009/2010, results of the National Influenza Surveillance Programme. Weekly incidence rates per 100 000 inhabitants and the results for the ILI cases tested for influenza are presented.

The presence of Influenza viruses was determined in 411 (55%) of 747 ILI cases analysed during 2008/2009, the majority of which of the A(H3) subtype (61.1%). AH1, AH3 and B influenza viruses circulating in Portugal during the 2008/2009 season were replaced by the new Influenza A(H1N1)2009 virus during the pandemic season. 430 (40.2%) out of 1070 specimens tested positive for Influenza, 92.8% of which of the new A(H1N1)2009 subtype.

### Symptoms and signs of seasonal and pandemic Influenza

Table I shows the independent odd ratios for the association of each symptom/sign considered for the clinical definition of Influenza and a confirmed Influenza case. It can be observed that for the 2008/2009 winter season, when seasonal Influenza viruses were in circulation, particularly Influenza A(H3), fever, cough, chills and contact with another ILI patient were statistically significant. Adjusting for all the significant signs/symptoms, the multivariable logistic regression reveals cough (OR 10.7, CI95% 5.2-22.0), fever (OR 5.1, CI95% 3.2-8.2) and contact with another patient (OR 1.4, CI95% 1.0-1.9) to be statistically significant.

Table I. Association between the presence of the symptoms/signs considered for clinical definition of Influenza and a confirmed Influenza case

Symptom/sign	2008/2009			2009/2010		
	% positive	Odds ratio	IC95%	% positive	Odds ratio	IC95%
Sudden onset	83.6	1.2	(0.8; 1.8)	92.9	0.7	(0.8; 1.8)
Fever	93.4	4.7	(2.9; 7.6)	96.9	4.9	(2.7; 9.0)
Weakness/prostration	78.3	1.2	(0.8; 1.7)	71.5	0.8	(0.6; 1.0)
Headache	-	-	-	75.6	0.9	(0.6; 1.2)
Myalgia	93.2	1.6	(0.9; 2.7)	77.5	0.9	(0.6; 1.2)
Cough	98.0	5.9	(2.7; 12.8)	92.0	3.9	(2.6; 5.8)
Sore throat	85.3	1.0	(0.7; 1.5)	77.0	1.0	(0.6; 1.2)
Respiratory difficulty	-	-	-	12.6	0.6	(0.4; 1.0)
Chills	93.4	2.0	(1.2; 3.4)	66.9	0.9	(0.6; 1.1)
Contact with another ILI patient	55.3	1.3	(1.0; 1.8)	48.8	2.0	(1.5; 2.7)

For the pandemic season, the symptoms/signs with an elevated risk of being associated with a confirmed Influenza case were fever, cough and contact with another ILI patient, all of which statistically significant, analysed independently (Table I) or by multivariable logistic regression analysis (cough; OR 3.4, CI95% 2.2-5.3; fever; OR 4.9, CI95% 2.6-9.2; contact with another patient; OR 1.9, CI95% 1.3-2.7). An interesting result was obtained for the sudden onset of symptoms. The independent analysis revealed low risk of this symptom being associated with a confirmed influenza case, although not statically significant. The multivariate regression analysis confirmed this low association (OR 0.5, CI95% 0.2-1.0).

## Comments

It is well beyond discussion that Influenza is associated with a broad range of clinical signs and symptoms which make confirmation of the infection, based on clinical criteria alone, virtually impossible. However, laboratory testing of all suspected cases, particularly during an epidemic/pandemic, is not feasible. Therefore, a clinical definition of case is extremely important and must consider several aspects: if, on one hand, a very strict definition will lead to less cases being analysed and an increase in the percentage of positive results, milder infections may not be identified; on the other hand, a less strict definition, although leading to a greater number of isolates, will also cause an increase in the number of laboratory tests and an increase in the number of negative results, that is, infections caused by other agents. These considerations will have an important role, for example, in the evaluation of prevention and control measures and in the determination of the influenza activity, in the context of National Influenza Surveillance Programs. Within this framework, it is important to determine guidelines upon which a clearer and more appropriate clinical definition of Influenza can be based. The question that needs to be answered is: which indicators, that is, which signs and symptoms have a higher association with Influenza infection?

Seasonal Influenza had been defined according the ICHPPC, which included the presence of several symptoms and signs. The most recent Portuguese data continues to agree with that definition, as almost all symptoms/signs considered show a high risk of being associated with a confirmed Influenza case, particularly fever, cough and contact with another ILI patient. Similar results had already been obtained from past Influenza seasons. Initial evidences that the new Influenza pandemic variant A(H1N1)2009 could cause a clinically different infection, and fears that the disease would present a more severe profile than seasonal influenza, prompted the ECDC to adopt a new definition of case, assuming the sudden onset of symptoms as a criteria for Influenza. Data collected in our country through the National Influenza Surveillance Programme does not seem to agree with this. In fact, the presence of this sign seems to be associated with a reduced risk of having Influenza. However, fever, cough and contact with another ILI case reveal a statistically significant high risk of being associated with a confirmed Influenza case. Finally, the data suggests that both seasons were similar in terms of the clinical presentation of Influenza. We hope that this information, generated through the Portuguese National Influenza Surveillance Programme may contribute, in the future, to a more accurate clinical diagnosis of Influenza.