Comparison of characteristics of outpatients with 2009 H1N1 pandemic and seasonal influenza

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**Comparison of characteristics of outpatients with
2009 H1N1 pandemic and seasonal influenza**

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Abstract

Background The latest influenza pandemic intensified the interest in this infection.

Objective We aimed to compare the characteristics of outpatients with seasonal and pandemic influenza.

Methods We retrospectively reviewed data regarding outpatients that sought medical advice from a network of physicians performing house-call visits at the area of Attica, Greece, that underwent a direct influenza test during the period of seasonal influenza (1/1/2009-1/5/2009), and 2009 H1N1 pandemic influenza period (17/5/2009-15/4/2010).

Results A total of 195 and 1317 patients had a direct influenza test during the seasonal and pandemic influenza period, respectively; 50.7% and 32% of these patients had a positive test result for influenza, respectively. Viral culture or polymerase chain reaction (PCR) were not implemented. Patients found positive for influenza during the pandemic period, compared to those evaluated during the seasonal period, were younger (mean age $\pm$ SD: 33 ± 17.2 vs 38.2 ± 19.2 , $p=0.008$), more likely to have no comorbidity (62.9% vs 45.5% , $p=0.002$), had milder clinical manifestations, and were treated with more antibiotics (38.3% vs 9.9% , $p<0.001$). However, patients found positive during the seasonal period were treated with more antivirals (oseltamivir: 69.1% vs 85.7% , $p=0.006$). No difference was observed regarding the need for immediate hospitalization. These findings were, consistent in the complementary analysis involving patients tested for influenza during the compared periods.

Conclusion Despite the methodological limitations, our findings suggest that patients with pandemic influenza were younger, had milder clinical manifestations, and were less likely to have any kind of comorbidity, compared to patients with seasonal influenza.

Keywords: influenza, oseltamivir, age distribution, diagnosis, primary care

What's known

The 2009 H1N1 pandemic influenza affected many people worldwide. However, there have been few reports comparing epidemiological, clinical, and treatment characteristics of outpatients with pandemic and seasonal influenza.

What's new

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61 Our analysis suggests that patients with pandemic influenza were younger, had milder
62 clinical manifestations, and were less likely to have any kind of comorbidity, compared
63 to patients with seasonal influenza.

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For Peer Review Only

Introduction

The recent influenza pandemic intensified the interest of health organizations, physicians, media, and the public in this infection. Specifically, issues regarding the epidemiological features, diagnosis and treatment of influenza underwent a re-evaluation under the perspective of the latest pandemic.

In particular, published reports have suggested that, younger age groups were predominantly affected by the 2009 H1N1 pandemic influenza,¹⁻³ whereas, pregnant and obese patients constituted a considerable percentage among more severely afflicted 2009 H1N1 pandemic influenza cases (including hospitalized and cases admitted in the intensive care unit), as well as among fatalities.²⁻⁴ With regard to influenza diagnosis, published evidence suggests that the use of direct influenza tests during seasonal influenza periods has been associated with reduced unnecessary antibiotic prescriptions, hospitalizations and laboratory tests.⁵⁻⁷ However, the experience of their use during the pandemic period was rather disappointing, as the sensitivities reported in studies evaluating its application in various clinical settings were considered suboptimal.⁸⁻¹⁰ The issue of influenza treatment was also re-evaluated during the pandemic period. Many reports pointed out the benefit of early administration of antiviral treatment to pandemic cases.¹¹⁻¹³ However, reports on the emergence of pandemic viral strains resistant to oseltamivir had also appeared in the literature.¹⁴

The aim of this study was to compare the epidemiological, clinical and treatment characteristics of outpatients that sought medical advice from a network of physicians performing house call visits in the area of Attica, Greece, and had a positive direct influenza test, during the 2009 H1N1 pandemic period, as well as the preceding seasonal (2008-2009) influenza period. Secondly, in a complementary analysis, we aimed to compare the above-mentioned characteristics of all the patients that underwent a direct influenza test in this specific clinical setting, at the respective influenza periods.

Methods

Patient population

We considered as eligible for inclusion patients that sought medical advice from a network of physicians performing house-call visits at the area of Attica, Greece, who underwent a direct influenza test either during the latest period of seasonal influenza (1/1/2009-1/5/2009), or during the period of 2009 H1N1 pandemic influenza

(17/5/2009-15/4/2010). Since the 1st confirmed case of 2009 H1N1 pandemic influenza in Greece was reported at the 16th of May 2009, we excluded the period 1/5/2009-15/5/2009 from our analysis. The direct test was performed at the discretion of the physician performing the house-call visit. The diagnosis was also at the discretion of the physician. Specifically, it was based on the patient’s clinical manifestations, along with epidemiological aspects (if any). **Diagnostic methods including viral culture and/or PCR were not implemented in our study.**

The direct influenza test used during both the evaluated periods was the “Influ A&B Uni-Strip – Dry Swabs (C-1512)” test, manufactured by Coris BioConcept (<http://www.corisbio.com>).¹⁵ The “Influ A&B Uni-Strip – Dry Swabs (C-1512)” test consists of two sides sensitized with a monoclonal antibody specific for Influenza A and B and thus allows detection of both influenza A and B, respectively.

A subset of the patients in the 1st study period were included in a recent publication focusing on the impact that the introduction of the direct influenza had on the decision making, particularly the prescribing pattern, of the network of SOS Doctors.⁷

Data collection

We retrospectively reviewed the electronic databases of the SOS-Doctors network. We retrieved data regarding the patient’s demographic characteristics, types of comorbidity, signs/symptoms that the patients complained for, types of diagnosis, treatment prescribed, as well as the need for immediate hospitalization.

Data analysis

Our primary analysis referred to the comparison regarding the demographic characteristics, types of comorbidity, symptoms, diagnosis, as well as the need for immediate hospitalization were performed between the subgroups of the patients that had a positive direct test for influenza during the evaluated influenza periods. In addition, in a complementary analysis we compared the above-mentioned features for the sub-groups of all the patients that were tested for influenza during the seasonal and pandemic period, respectively. The chi square test was used for all the evaluated dichotomous variables, whereas the Student's t-test or its non-parametric analogue, the Mann-Whitney U test, were used when appropriate for all the evaluated continuous variables. A p-value<0.05 was considered as indicative of statistical significance. The

Open Epi software was used to perform the comparisons regarding the outcomes expresses as dichotomous variables,¹⁶ whereas the SPSS Software was used for the continuous variables.

Results

Primary analysis: (patients with a positive direct influenza test result during seasonal vs pandemic influenza period)

A total of 99 and 424 patients had a positive test for influenza during the seasonal and pandemic influenza period respectively, constituting the 50.7% and 32% of the patients tested for influenza during the respective evaluated influenza periods. No difference was found regarding sex between the compared groups. Patients found positive during the pandemic period were younger compared to patients that were found positive during the seasonal influenza period [mean age $\pm$ standard deviation (SD): 38.2 ± 19.2 vs 33 ± 17.2 , $p=0.008$]. Additionally, pediatric patients constituted a significantly higher percentage among patients with a positive test during the pandemic (23%) period, compared to those with a positive test during the seasonal period (13%). Moreover, patients that did not have any type of comorbidity constituted a significantly higher percentage among patients with a positive test during the pandemic (62%) period, compared to those with a positive test during the seasonal period (45%). No difference was observed in the comparisons regarding the other evaluated types of comorbidity (detailed data are presented in Table 1).

Regarding the signs and symptoms for which the evaluated patients complained for, febrile episodes, cough, rigor, nasal congestion/discharge, headache, and myalgia/arthritis were reported significantly more frequently from patients that were found positive during the seasonal period, whereas the patients that were found positive during the pandemic period complained significantly more frequently for sore throat. No differences were observed in the remaining comparisons (Table 1).

With regard to treatment characteristics, antivirals (oseltamivir), anticongestants, and anti-asthmatic agents were prescribed significantly more frequently to patients found positive during the seasonal period, whereas antibiotics were prescribed significantly more frequently to patients that were found positive during the pandemic period. Specific data regarding the remaining comparisons of treatment characteristics are

presented in Table 1. Finally, no difference was observed between the compared groups regarding the need for immediate hospitalization.

Secondary analysis: (patients that underwent a direct influenza test during seasonal vs pandemic influenza period)

A total of 195 and 1317 patients underwent a direct influenza test during the seasonal and pandemic influenza period, respectively. No difference was found regarding sex between the compared groups. Patients tested during the pandemic period were younger compared to patients that were tested during the seasonal influenza period (mean age $\pm$ SD: 41.1 ± 20.6 vs 36.7 ± 19.5 , $p=0.02$). Moreover, pediatric patients were encountered significantly more frequently in the pandemic (17%) versus the seasonal period (8%). Detailed data regarding comorbidity were not available for a considerable percentage of the evaluated patients. In this regard, we were precluded from comparing the types of comorbidity between patients that were tested for influenza during the pandemic and the preceding seasonal influenza period.

Febrile episodes, cough, rigor, nasal congestion/discharge, headache, and myalgia/arthritis were reported significantly more frequently from patients that were tested during the seasonal influenza period compared to those tested during the pandemic influenza period. On the other hand, patients tested during the pandemic period complained for sore throat significantly more frequently compared to those tested during the seasonal influenza period. No differences were observed regarding the evaluated signs and symptoms between the compared groups (Table 2).

Influenza diagnosis was significantly more frequent in patients tested during seasonal influenza period (50.8%), compared to those tested during the pandemic period (32.2%), whereas the diagnoses of viral infection, pharyngitis/pharyngotonsillitis, and acute bronchitis were significantly more frequent in patients tested during the pandemic period. No differences were observed regarding the remaining evaluated diagnoses. Detailed data are presented in Table 2. Furthermore, antivirals (oseltamivir), anticongestants, and anti-asthmatics were prescribe significantly more frequently to patients tested during seasonal influenza period, whereas antibiotics were prescribed significantly more frequently to patients tested during the pandemic period. No differences were observed regarding other treatment characteristics (Table 2). No

difference was also observed between the compared groups regarding the need for immediate hospitalization.

Discussion

According to our findings, patients with a positive direct test for influenza during the 2009 pandemic period were younger and had milder clinical manifestations (as inferred by the signs and symptoms that the patients complained for) compared to those that had a positive test during the seasonal influenza period. Otherwise healthy and pediatric patients were represented by significantly higher percentages among patients found positive for influenza during the pandemic versus the seasonal period. Regarding treatment, antivirals, particularly oseltamivir, were prescribed significantly more frequently to patients found positive for influenza during the seasonal period, whereas antibiotics were prescribed significantly more frequently to patients found positive for influenza during the seasonal period. The above findings were consistent in the complementary analysis regarding the patients that underwent a direct influenza test during the respective influenza periods.

Our findings regarding the age distribution of patients with pandemic and seasonal influenza are in accordance with another recently published study that focused on the comparison of the epidemiological characteristics of outpatients, as well as inpatients with seasonal and 2009 H1N1 pandemic influenza. Specifically, this study suggested that patients with pandemic influenza were younger compared to patients with seasonal influenza. On the other hand, symptoms including cough, myalgias/arthralgias, and pleuritic chest pain were more frequently encountered among patients with pandemic versus seasonal influenza.¹⁷ Yet, in our study, cough and myalgia were more common among seasonal compared to pandemic cases. Another study also reported that hospitalized patients with pandemic influenza were younger compared to hospitalized patients with seasonal influenza.¹⁸

In addition, with regard to patients' comorbidity, no difference was observed between patients with seasonal and pandemic influenza, with the exception of pregnancy,¹⁷ in the first of the above-mentioned studies, whereas the other study noted that hospitalized patients with pandemic influenza were less likely to be immunocompromised as opposed to patients with seasonal influenza.¹⁸ In our study, otherwise healthy patients were encountered more frequently among patients with a positive test result during the

239 pandemic period, compared to those found positive during the seasonal influenza
240 period. This observation may reflect the high transmissibility rate of the 2009 H1N1
241 pandemic influenza virus.¹⁹ Another possible explanation may be the fact that younger
242 patients were encountered more frequently among patients with a positive test for
243 pandemic influenza compared to seasonal. Young individuals are more likely to have
244 less comorbidity compared to elderly. Preliminary reports had also suggested that
245 patients with specific types of comorbidity (obese, morbidly obese, pregnant patients)
246 constituted considerable proportions of the confirmed influenza cases and more severely
247 afflicted influenza cases.^{2,3} Yet, we observed no differences regarding any of the
248 evaluated types of comorbidity between pandemic and seasonal influenza cases. The
249 retrospective methodology of our study may potentially account for this observation.
250 Specifically, comorbidity data may have been less likely to be recorded, as opposed to
251 data regarding clinical symptoms and treatment.

252
253 Based on the evaluation of the reported clinical signs and symptoms, the patients tested
254 and those with a positive direct test for influenza during the seasonal influenza period,
255 had more severe clinical manifestations compared to patients evaluated during the
256 pandemic period. Indeed, most of the pandemic influenza cases, apart from those with
257 considerable comorbidity that were considered to predispose for more severe disease
258 (including obesity and pregnancy), were cases of mild severity.^{20,21,22} On the contrary,
259 patients tested, as well as those with a positive test complained significantly more
260 frequently for sore throat compared to the respective evaluated patients during the
261 seasonal period. Published evidence suggests that sore throat was one of the symptoms
262 that differentiated the clinical manifestations of seasonal and pandemic influenza
263 infection. Specifically, a recently published large prospective study suggested that the
264 odds of patients that had sore throat to develop pandemic compared to seasonal
265 influenza were 1.4 times as high, relatively to when they didn't have these symptoms.²⁰

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267 In our complementary analysis, patients with a positive test constituted a significantly
268 higher percentage among patients tested during the seasonal versus the pandemic
269 influenza period. Many factors may possibly account for this specific observation.
270 Firstly, it should be mentioned that the performance of direct influenza test during the
271 recent influenza pandemic has been questioned. Specifically, the reported sensitivities
272 of such tests were considered as rather low.^{8,9} According to the manufacturer's product
273 information, the sensitivity and specificity of the direct influenza test used in our

study,(namely Influenza A&B Uni-Strip – Dry Swabs (C-1512), for the detection of seasonal influenza A were considerably high (77% and 100%, respectively, compared with real time-PCR), and the sensitivity and specificity for the detection of seasonal influenza B were 97% and 100% (compared with time-resolved fluoroimmunoassay).¹⁵

However, the available published evidence regarding the diagnostic performance of this specific direct test for pandemic influenza is conflicting. Specifically, the reported specificity of this test is excellent (100%), whereas sensitivity is low (31.7%).²³

With regard to treatment characteristics, significantly more antiviral agents were prescribed to patients found positive for influenza during the seasonal compared to the pandemic influenza period. Indeed, an evaluation of preliminary evidence regarding treatment strategies used for cases of pandemic influenza suggested that a considerable percentage of the evaluated patients (85.0%) received antibiotic treatment.¹² However, one should consider the considerable proportion of missing treatment data during the interpretation of the respective findings. Another speculation that may be attempted is the fact that the potential of the emergence of a pandemic influenza strain resistant to the contemporary commercially available antiviral agents may have possibly made physicians reluctant to prescribe these drugs. Indeed, reports on the emergence of pandemic strains resistant to oseltamivir had appeared in the literature during the pandemic period.²⁴⁻²⁶ On the other hand, considering the alarmingly high rates of antibiotic resistance reported for respiratory pathogens,²⁷⁻²⁹ a more conservative therapeutic approach with regard to antibiotic treatment to patients with evidence of viral infections, including influenza, may eventually confer considerable benefit from an individual-patient care, as well from a public health perspective.

Specific limitations must be taken into consideration before the extrapolation of the findings of our study. Firstly, our findings refer to a specific clinical setting and to a patient population with specific characteristics. Previously published experience has suggested that patients older than 60 years old constitute a considerable percentage (up to 50%) of the target patient population of this specific network of physicians.³⁰ Selection bias may have also possibly influenced our findings, as the number of patients in the pandemic group by far exceeds the number of the patients in the seasonal group. However, this observation may be considered as expected, given the high demand of relevant medical services during the pandemic period. The intrinsic limitations of a retrospective study design may have also potentially influenced our findings. Finally,

influenza diagnosis was based on the results of a direct influenza test, whereas no other confirmatory methods like viral culture or polymerase chain reaction (PCR) were available in this specific primary-care clinical setting. The rather low sensitivities and specificities of rapid influenza tests used in various clinical settings during the latest influenza pandemic should also be considered in the interpretation of the findings of our study.

In conclusion, our findings suggest that patients with a positive direct test result during the pandemic influenza period were younger, had milder clinical manifestations, and were less likely to have any type of comorbidity compared to patients with a positive test result during the evaluated seasonal influenza period. Despite the intrinsic limitations of the retrospective study, our study provides useful comparative data regarding the epidemiological, clinical, as well as treatment characteristics of a considerable number of outpatients evaluated in a primary care setting during the latest pandemic influenza, as well as the preceding seasonal influenza period.

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Table 1. Characteristics and outcomes of the patients with a positive direct test for influenza.

	Patients with a positive test during the seasonal influenza period (N=99)	Patients with a positive test during the pandemic H1N1 influenza period (N=424)	P value
Demographic characteristics			
Sex [females]	45 (45.5)	202 (47.6)	0.77
Age (Mean ± SD, years)	38.2 ± 19.2	33 ± 17.2	0.008*
Pediatric patients (<18 years)	13 (13.1)	96 (22.6)	0.044
	n/N (%)		
Comorbidity			
Number of evaluated patients	99/99 (100)	393/424 (92.6)	
None	45 (45.5)	247 (62.9)	0.002
Malignancies	2 (2.0)	9 (2.3)	>0.999
Cardiovascular diseases	12 (12.1)	47 (12.0)	0.89
Tuberculosis	1 (1.0)	2 (0.5)	0.98
COPD	2 (2.0)	4 (1.0)	0.69
Renal insufficiency	0	5 (1.3)	0.64
Asthma	1 (1.0)	21 (5.3)	0.08
Allergy	0	4 (1.0)	0.81
Diabetes mellitus	2 (2.0)	8 (2.0)	>0.999
Lipid disorders	4 (4.0)	3 (0.8)	0.07
Thyroid disorders	5 (5.1)	18 (4.6)	0.95
Autoimmune diseases	0	3 (0.8)	>0.999
Multiple sclerosis	0	1 (0.3)	>0.999
Myoskeletal diseases	2 (2.0)	8 (2.0)	>0.999
Inflammatory bowel diseases	0	1 (0.3)	>0.999
Gastroesophageal reflux disease	1 (1.0)	2 (0.5)	0.98
Sideropenic anemia	1 (1.0)	2 (0.5)	0.98
Splenectomy	0	1 (0.3)	>0.999
Signs/symptoms			
Number of evaluated patients	91/99 (92)	392/424 (92.4)	
Febrile episode	91 (100)	364 (92.8)	0.017
Sore throat	16 (17.6)	128 (32.7)	0.007
Cough	81 (89.0)	301 (76.8)	0.015
Rigor	15 (16.5)	32 (8.2)	0.027
Nasal congestion/discharge	80 (87.9)	176 (44.9)	<0.001
Headache	29 (31.8)	44 (11.2)	<0.001
Otalgia	0	4 (1.0)	0.86
Fatigue/body aches	17 (18.7)	56 (14.3)	0.37
Myalgia/arthralgia	48 (52.7)	119 (30.4)	<0.001
Dyspnea/tachypnea	1 (1.1)	20 (5.1)	0.14
Thoracic pain	0	2 (0.5)	>0.999
Nausea/vomiting	4 (4.4)	24 (6.1)	0.73
Diarrhea/abdominal pain	0	8 (2.0)	0.37
Dizziness/loss of consciousness	1 (1.1)	4 (1.0)	>0.999
Treatment			
Number of evaluated patients	91/99 (92)	324/424 (76.4)	
Antivirals (oseltamivir)	78 (85.7)	224 (69.1)	0.006
Analgesics	10 (11.0)	29 (9.0)	0.7
Anti-cough drugs	16 (17.6)	42 (13.0)	0.34
Antibiotics	9 (9.9)	124 (38.3)	<0.001
Anticongestants	19 (20.9)	16 (4.9)	<0.001
Antihistamines	12 (13.2)	24 (7.4)	0.13
NSAIDs	2 (2.2)	11 (3.4)	0.86

Corticosteroids	1 (1.1)	1 (0.3)	0.78
Corticosteroids + β 2 agonist	5 (5.5)	15 (4.6)	0.91
Anti-asthmatics	15 (16.5)	12 (3.7)	<0.001
Other*	11 (12.1)	11 (3.4)	0.003
Hospitalization			
<i>Number of evaluated patients</i>	99/99 (100)	424/424 (100)	
Yes	1/99 (1.0)	10/424 (2.4)	0.65

Abbreviations: SD: standard deviation, COPD: chronic obstructive pulmonary disease, NR: not-reported, NA: non-applicable.

*p value: Sig. (2-tailed) for Student's t-test.

*Including: anti-emetics, gastro-protective agents, B-blockers, oral antiseptics, probiotics, antifungals.

*The denominators refer to the respective numbers of the tested pediatric patients.

Table 2. Characteristics and outcomes of the tested patients.

	Patients tested during the seasonal influenza period (N=195)	Patients tested during the pandemic H1N1 influenza period (N=1317)	P value
Demographic characteristics			
Sex [females]	91 (46.7)	640 (48.6)	0.67
Age (Mean, ± SD, years)	41.1 ± 20.6	36.7 ± 19.5	0.02^{‡‡}
Pediatric patients (<18 years)	16 (8.2)	219 (16.6)	0.003
n/N (%)			
Signs/symptoms			
<i>Number of evaluated patients</i>	182/195 (93.3)	1213/1317 (92.1)	
Febrile episode	180 (98.9)	1047 (86.3)	<0.001
Sore throat	35 (19.2)	395 (32.6)	<0.001
Cough	144 (79.1)	790 (65.1)	<0.001
Rigor	24 (13.2)	76 (6.3)	0.001
Nasal congestion/discharge	133 (73.1)	326 (26.9)	<0.001
Headache	54 (29.7)	128 (10.6)	<0.001
Otalgia	1 (0.5)	7 (0.6)	>0.999
Asthmatic crisis	0	1 (0.08)	>0.999
Fatigue/body aches	40 (22.0)	206 (17.0)	0.12
Myalgia/arthritis	101 (55.5)	310 (25.6)	<0.001
Dyspnea/tachypnea	4 (2.2)	43 (3.5)	0.49
Thoracic pain	1 (0.5)	6 (0.5)	>0.999
Nausea/vomiting	16 (8.8)	77 (6.3)	0.28
Diarrhea/abdominal pain	2 (1.1)	30 (2.5)	0.38
Dizziness/loss of consciousness	1 (0.5)	11 (0.9)	>0.999
Treatment			
<i>Number of evaluated patients</i>	164/195 (84.1)	839/1317 (63.7)	
Antivirals (oseltamivir)	80 (48.8)	240 (28.6)	<0.001
Analgesics	29 (17.7)	107 (12.8)	0.12
Anti-cough drugs	42 (25.6)	175 (20.9)	0.21
Antibiotics	52 (31.7)	464 (55.3)	<0.001
Anticongestants	32 (19.5)	69 (8.2)	<0.001
Antihistamines	21 (12.8)	67 (8.0)	0.06
NSAIDs	10 (6.1)	43 (5.1)	0.75
Corticosteroids	2 (1.2)	2 (0.2)	0.25
Corticosteroids + β2 agonist	7 (4.3)	42 (5.0)	0.84
Anti-asthmatics	29 (17.7)	74 (8.8)	0.001
Other*	28 (17.1)	93 (11.1)	0.043
Hospitalization			
<i>Number of evaluated patients</i>	195/195 (100)	1317/1317 (100)	
Yes	4 (2.1)	19 (1.4)	0.39

Abbreviations: SD: standard deviation, NR: not-reported, NA: non-applicable.

*P value: Asymp. Sig. (2-tailed) for Mann-Whitney U test.

‡Including: anti-emetics, gastroprotective agents, B-blockers, oral antiseptics, probiotics, antifungals