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

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SUMMARY

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 who sought medical advice from a network of physicians performing house-call visits at the area of Attica, Greece, and who 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 with those evaluated during the seasonal period, were younger (mean age ± 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 hospitalisation. 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 with patients with seasonal influenza.

What's known

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

What's new

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

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Disclosures
None.

Introduction

The recent influenza pandemic intensified the interest of health organisations, 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 hospitalised 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, hospitalisations 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 who 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 who underwent a direct influenza test in this specific clinical setting, at the respective influenza periods.

Methods

Patient population

We considered patients who sought medical advice from a network of physicians performing house-call visits at the area of Attica, Greece, and 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) as eligible for inclusion. As the first 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 sensitised 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 first 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 hospitalisation.

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 hospitalisation was performed between the subgroups of the patients who 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 who were tested for influenza during the seasonal and pandemic period, respectively. The $\chi^2$was used for all the evaluated dichotomous variables, whereas the Student's *t*-test or its non-parametric analogue, the Mann–Whitney *U*-test, was 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 expressed 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 gender between the compared groups. Patients found positive during the pandemic period were younger compared with patients who were found positive during the seasonal influenza period [mean age ± standard deviation (SD): 38.2 ± 19.2 vs. 33 ± 17.2, p = 0.008]. In addition, paediatric patients constituted a significantly higher percentage among patients with a positive test during the pandemic (23%) period, compared with those with a positive test during the seasonal period (13%). Moreover, patients who did not have any type of comorbidity constituted a significantly higher percentage among patients with a positive test during the pandemic (62%) period, compared with 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,

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*
Paediatric 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 anaemia	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*
Rigour	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
Diarrhoea/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 + β2 agonist	5 (5.5)	15 (4.6)	0.91

Table 1 (Continued)

	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
Anti-asthmatics	15 (16.5)	12 (3.7)	< 0.001*
Other†	11 (12.1)	11 (3.4)	0.003*
Hospitalisation			
Number of evaluated patients	99/99 (100)	424/424 (100)	
Yes	1/99 (1.0)	10/424 (2.4)	0.65

*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 paediatric patients. SD, standard deviation; COPD, chronic obstructive pulmonary disease; NR, not-reported; NA, non-applicable.

cough, rigour, nasal congestion/discharge, headache and myalgia/arthralgia were reported significantly and more frequently from patients who were found positive during the seasonal period, whereas the patients who were found positive during the pandemic period complained significantly and 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 and more frequently to patients found positive during the seasonal period, whereas antibiotics were prescribed significantly and more frequently to patients who 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 hospitalisation.

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 gender between the compared groups. Patients tested during the pandemic period were younger compared with patients who were tested during the seasonal influenza period (mean age ± SD: 41.1 ± 20.6 vs. 36.7 ± 19.5, p = 0.02). Moreover, paediatric patients were encountered significantly and more frequently in the pandemic (17%) vs. 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 who were tested for influenza during the pandemic and the preceding seasonal influenza period.

Febrile episodes, cough, rigour, nasal congestion/discharge, headache and myalgia/arthralgia were reported significantly and more frequently from patients who were tested during the seasonal influenza period compared with those tested during the pandemic influenza period. On the other hand, patients tested during the pandemic period complained for sore throat significantly and more frequently compared with 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 with 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 prescribed significantly and more frequently to patients tested during the seasonal influenza period, whereas antibiotics were prescribed significantly and 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 hospitalisation.

Discussion

According to our findings, patients with a positive direct test for influenza during the 2009 pandemic

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*
Paediatric patients (< 18 years)	16 (8.2)	219 (16.6)	0.003*
n/*N* (%)			
Signs/symptoms			
Number of evaluated patients	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*
Rigour	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/arthralgia	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
Diarrhoea/abdominal pain	2 (1.1)	30 (2.5)	0.38
Dizziness/loss of consciousness	1 (0.5)	11 (0.9)	> 0.999
Treatment			
Number of evaluated patients	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*
Hospitalisation			
Number of evaluated patients	195/195 (100)	1317/1317 (100)	
Yes	4 (2.1)	19 (1.4)	0.39

*p value: Asymp. Sig. (2-tailed) for Mann–Whitney *U*-test. †Including: anti-emetics, gastro-protective agents, B-blockers, oral antiseptics, probiotics, antifungals. SD, standard deviation; NR, not-reported; NA, non-applicable.

period were younger and had milder clinical manifestations (as inferred by the signs and symptoms that the patients complained for) compared with those who had a positive test during the seasonal influenza period. Otherwise, healthy and paediatric patients were represented by significantly higher percentages among patients found positive for influenza during the pandemic vs. 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 pandemic period. The above findings were consistent in the complementary analysis regarding the patients who 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 with 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 vs. seasonal influenza (17). Yet, in our study, cough and myalgia were more common among seasonal cases compared with pandemic cases. Another study also reported that hospitalised patients with pandemic influenza were younger compared with hospitalised 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 hospitalised 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 pandemic period, compared with those found positive during the seasonal influenza period. This observation may reflect the high transmissibility rate of the 2009 H1N1 pandemic influenza virus (19). Another possible explanation may be the fact that younger patients were encountered more frequently among patients with a positive test for pandemic influenza compared with seasonal influenza. Young individuals are more likely to have less comorbidity compared with elderly people. Preliminary reports had also suggested that patients with specific types of comorbidity (obese, morbidly obese, pregnant patients) constituted considerable proportions of the confirmed influenza cases and more severely afflicted influenza cases (2,3). Yet, we observed no differences regarding any of the evaluated types of comorbidity between pandemic and seasonal influenza cases. The retrospective methodology of our study may potentially account for this observation. Specifically, comorbidity data may have been less likely to be recorded, as opposed to data regarding clinical symptoms and treatment.

Based on the evaluation of the reported clinical signs and symptoms, the patients tested and those with a positive direct test for influenza during the seasonal influenza period had more severe clinical manifestations compared with patients evaluated during the pandemic period. Indeed, most of the pandemic influenza cases, apart from those with considerable comorbidity who were considered to predispose for more severe disease (including obesity and pregnancy), were cases of mild severity (20–22). On the contrary, patients tested, as well as those with a positive test complained significantly and more frequently for sore throat compared with the respective evaluated patients during the seasonal period. Published evidence suggests that sore throat was one of the symptoms that differentiated the clinical manifestations of seasonal and pandemic influenza infection. Specifically, a recently published large prospective study suggested that the odds of patients who had sore throat to develop pandemic influenza compared with seasonal influenza were 1.4 times as high, relatively to when they did not have these symptoms (20).

In our complementary analysis, patients with a positive test constituted a significantly higher percentage among patients tested during the seasonal influenza period vs. the pandemic influenza period. Many factors may possibly account for this specific observation. Firstly, it should be mentioned that the performance of direct influenza tests during the recent influenza pandemic has been questioned. Specifically, the reported sensitivities of such tests were considered as rather low (8,9). According to the manufacturer's product information, the sensitivity and specificity of the direct influenza test used in our study, (namely Influ 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 antibiotic agents were prescribed to patients found positive for influenza during the pandemic influenza period compared with the seasonal 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 emer-

gence 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 should 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 had suggested that patients older than 60 years 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 inherent 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 with patients with a positive test result during the evaluated seasonal influenza period. Despite the inherent 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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