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Adult outpatient experience of the 2009 H1N1 pandemic: Clinical course, pathogens, and evaluation of case definitions

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Summary *Objectives:* The aim was to describe causative agents and clinical characteristics in adult outpatients with upper airway symptoms during the 2009 H1N1 pandemic and to evaluate case definitions that are used in clinical practice.
Methods: From August through December 2009, 964 symptomatic adult outpatients were included. RT-PCR was used to detect the following pathogens: *influenza A* (*H1N1*) and *B*, *parainfluenza 1–4*, *adenovirus*, *respiratory syncytial virus*, *human rhinovirus*, *human metapneumovirus*, *human coronavirus* (*OC43*, *229E*, *NL63*), *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *Legionella* species. The Dutch GHOR, American CDC and WHO, and British HPA case definitions were evaluated.
Results: A respiratory pathogen was detected in 41% of tested patient samples; *influenza A* (*H1N1*) and *human rhinovirus* were both detected in 16%. Clinical presentation of *influenza* cases was significantly more serious when compared to *rhinovirus* or negative-tested cases. Test characteristics were almost similar for all 4 case definitions, with an average sensitivity of 66%, specificity of 70%, positive predictive value of 34% and negative predictive value of 90%.
Conclusions: Influenza A (*H1N1*) and *human rhinovirus* were the major pathogens responsible for respiratory disease. The 2009 H1N1 pandemic in Amsterdam followed a mild course. Test characteristics of 4 different clinical case definitions seemed comparable but rather useless.

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Introduction

In April 2009, officials at the Centers for Disease Control and Prevention (CDC) confirmed two cases of swine *influenza* in children living in neighboring counties in California, after several cases had already been reported in Mexico.[1,2] This event led to the proclamation of a serious global health threat caused by a new *influenza A* (*H1N1*) virus.[3,4] Several surveillance studies have shown a moderate severity of the pandemic, with an overall relatively mild illness in those infected with the virus.[5–7] Nevertheless, the virus spread globally and almost all countries had reported cases, with more than 17,700 deaths among those that were laboratory confirmed.[8] The actual impact of the pandemic, however, is not really known because the number of laboratory-confirmed infected cases is undoubtedly a significant underestimation of the true number of infected cases.

Acute respiratory tract infections are the most common illnesses in all individuals over the world.[9] Whereas *influenza* has always been an important causative agent in this regard, *rhinoviruses* have generally been associated with the greatest number of illnesses.[10] However, *influenza* viruses produce more severe symptoms and, when there is a major *influenza* outbreak, they may be identified at a greater frequency when compared to other common causative viral agents.[11] Interactions between viruses causing respiratory infections are known to cause an interference between successive outbreaks in the community.[12–14] It has been postulated that, during the 2009 H1N1 pandemic, the interaction between novel *influenza A* (*H1N1*) virus and *rhinoviruses* has caused a delay in the circulation of *respiratory syncytial viruses* in France.[15]

Molecular methods, and in particular the development of polymerase-chain-reaction (PCR) technology, has proved invaluable in our understanding of the epidemiology of *influenza* and other respiratory viruses and has enabled rapid and sensitive diagnostic tests influencing patient management.[16] Clinicians have always been identifying patients with *influenza*-like illness mainly based on clinical findings, despite them not being particularly useful for confirming or excluding a true diagnosis of *influenza*.[17] Studies evaluating several clinical case definitions have demonstrated moderate sensitivity, poor specificity and extremely divergent predictive values, with positive predictive values ranging from 27% to 87% and negative predictive values ranging from 39% to 91%.[18,19] Of all signs and symptoms, a pooled analysis of eight double-blind, placebo-controlled studies showed both cough and fever to be most predictive of *influenza* infection in patients with *influenza*-like illness.[20]

The aim of this study is to describe clinical characteristics of adults with flu-like symptoms visiting an *influenza* outpatient clinic in Amsterdam during the 2009 H1N1 pandemic. Furthermore, we aim to provide an overview of the distribution and possible mutual interferences of different viral agents causing respiratory infections in our outpatient population. Another secondary objective is to evaluate the practical usefulness of several existing clinical case definitions attempting to predict *influenza* virus infection by comparing their predictive values.

Patients and methods

Study design and population

The data that have been collected were studied in order to provide an epidemiological overview of the causative viral respiratory pathogens and general characterization of the 2009 flu pandemic in a population of adults. All adults aged $\geq$18 years presenting with any flu-like signs and symptoms at the Slotervaart Hospital from August 12, 2009 until December 31, 2009, were included for our analysis. Patients could be referred by their general practitioner or other (para-) medical, but so-called 'self-referred' patients were also welcome to sign-up for a consultation, and those were included in our analysis as well. The Slotervaart Hospital is a general, 410-bed, teaching hospital that provides basic care for the Western region of Amsterdam, serving a low- to middle-income urban population of about 140,000 inhabitants; the population consists for 49% of ethnic minorities, most of them from Moroccan and Turkish origin. Ethical approval and informed consent were not required since this study solely describes findings resulting from regular patient care in our hospital.

Laboratory confirmation of infection

Influenza virus RNA was amplified and detected by real-time one-step reverse-transcriptase-polymerase-chain-reaction (RT-PCR) performed on oropharyngeal aspirates.[16] A generic PCR (directed against the matrix gene) was used to detect *influenza* virus type *A* or *B* and an H1N1-specific PCR was applied to the H1 gene. Next to *influenza*, the presence of the following pathogens was also detected by RT-PCR: *parainfluenza-1*, *parainfluenza-2*, *parainfluenza-3*, *parainfluenza-4*, *adenovirus*, *respiratory syncytial virus* (*RSV*), *human rhinovirus*, *human metapneumovirus*, *human coronavirus OC43*, *human coronavirus 229E*, *human coronavirus NL63*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *Legionella* species.

Clinical presentation and case definitions

Upon presentation at our hospital, every patient with any flu-like signs or symptoms was submitted to a structured patient history and physical examination by one of our internal medicine residents. An oropharyngeal swab sample was collected by a trained nurse for diagnostic purposes. When indicated, additional laboratory and imaging tests were performed to exclude *influenza*-related complications or any suspected differential diagnoses.

Test results with regard to presence or absence of *influenza* virus RNA were mostly available within 24 h. Adults with suspected *influenza* infection according to the case definition that was used in our hospital (GHOR — Dutch organization of Medical Assistance for Accidents and Disasters — website www.ghor.nl), were always given the strict advice to stay at home until the definitive *influenza* test results were known. If the test turned out positive, the advised period to stay at home was extended until at least five days after the onset of complaints; if the test turned out negative, the strict staying-at-home advice was undone.

Table 1 describes 4 *influenza* case definitions that are applied worldwide. The national GHOR case definition has been used in our clinical practice, aiding in our prediction of a clinical diagnosis and the initiation of proper medical management. The remaining case definitions have been used for analytical purposes in order to compare associated predictive values between different definitions.

Medical management

Treatment with the antiviral drug oseltamivir was started in suspected *influenza* cases conform national guidelines (www.rivm.nl/en). Oseltamivir was prescribed only in high-risk patients (age $\geq$60 years, pregnancy in 3rd trimester or suffering from a specified chronic medical condition) and in patients with a complicated course. If the clinical suspicion was confirmed by a positive test result, patients were supposed to finish the five-day course with the antiviral; in case of a negative test result the use of oseltamivir was immediately discontinued. Antibiotics were prescribed at the discretion of the responsible physician. Hospitalization would follow in case of a complicated course and/or instability of the patient's medical condition.

Statistical analysis

Statistical analysis was performed using the SPSS software package (version 18.0, SPSS Inc. Chicago, Illinois). Continuous variables were summarized as means and for categorical variables percentages of adults in each group were calculated. Demographic and clinical characteristics were compared between groups using a Student's *t*-test or non-parametric test for continuous variables and Chi-square or Fisher's exact test for categorical variables, as appropriate. Stepwise logistic regression analysis was performed in order to determine which independent variables contributed significantly to the prediction of the outcome variable. In general, a *p*-value of less than 0.05 was considered statistically significant.

Results

Study population

From August 12, 2009 until December 31, 2009, a total of 964 adults visited the *influenza* outpatient clinic of our hospital. The overall mean age was 36 years and 43% were male. General characteristics as well as the presence of certain risk groups and way of referral are summarized for patients with and without any detected respiratory pathogens in Table 2.

RT-PCR *influenza* and other pathogens

Fig. 1 demonstrates detected respiratory pathogens in oropharyngeal samples collected from all 964 adult patients, given as absolute numbers per month and percentage overall distribution. Major responsible pathogens causative of respiratory disease were *influenza A* (*H1N1*) and *human rhinovirus*, both overall contributing in 16% of the patient samples that had been tested. Diagnosis of infection with *influenza A* (*H1N1*) virus peaked in October (corresponding prevalence 30%). *Human rhinovirus* infection showed its peak in August and September (average corresponding prevalence 20%). Furthermore, in December *RSV* prevalence reached 7%, equaling the *influenza A* (*H1N1*) prevalence in that month. Of particular last note is that infections with *influenza B* and *Legionella* species were not seen at all.

Two concurrent pathogens were demonstrated in 18 individuals of which 5 suffered from at least one comorbid condition. The following double infections were seen: *influenza A* (*H1N1*) with *human rhinovirus* ($n = 8$); *influenza A* (*H1N1*) with *parainfluenza virus* ($n = 2$); *influenza A* (*H1N1*) with *adenovirus* ($n = 2$); *influenza A* (*H1N1*) with *human metapneumovirus* ($n = 1$); *influenza A* (*H1N1*) with *human coronavirus* ($n = 1$); *parainfluenza virus* with *C. pneumoniae* ($n = 1$); *RSV with human rhinovirus* ($n = 1$); *human rhinovirus* with *human metapneumovirus* ($n = 1$); and *human rhinovirus* with *human coronavirus* ($n = 1$).

Table 1 Clinical case definitions for *influenza* diagnosis.

Abbreviation	Explanation/country of origin	Definition
GHOR	Medical Assistance for Accidents and Disasters *The Netherlands*	Fever $\geq$38.5 °C and two or more acute-onset 'flu' complaints: cough, rhinorrhea, sore throat, headache, myalgia, malaise, chills
WHO	World Health Organization *International United Nations system*	Fever >38 °C, and cough or sore throat (*in the absence of other diagnoses*)
CDC	Centers for Disease Control and Prevention *United States*	Fever >100 °F (>37.8 °C), and cough or sore throat
HPA	Health Protection Agency *United Kingdom*	Fever $\geq$38° C and two or more of following: cough, sore throat, rhinorrhea, limb or joint pain, headache, vomiting or diarrhea; or severe and/or live-threatening illness suggestive of an infectious process

Table 2 General characteristics of symptomatic adults visiting an *influenza* outpatient clinic during the 2009 H1N1 pandemic.

		Any confirmed pathogen	No confirmed pathogen
Number of adults		379	585
Age (mean, range)		34 (18–78)	38 (18–88)
Sex	Male	43%	43%
	Female	57%	57%
Risk groups	Airway disorder	13%	12%
	Cardiological disorder	3%	5%
	Diabetes mellitus	4%	3%
	Immunocompromised	3%	3%
	Pregnancy 3rd trimester	3%	2%
	Age ≥60 years	3%	7%
Referral	General practitioner (GP)	35%	28%
	Self-referral	54%	55%
	Referral by (para-) medical other than GP	11%	17%

Clinical presentation and case definitions

Clinical characteristics of patients with the two most frequently detected pathogens (i.e. *influenza A* (*H1N1*) and *human rhinovirus*) and of those without any detected pathogens are summarized in Table 3. *Influenza A* (*H1N1*)-positive patients, compared with patients in whom we did not detect any pathogen, reported more fever ≥38.5 °C (65% versus 32%; $p < 0.001$), showed significantly worse vital parameters, and suffered more from most general flu complaints. In patients with RT-PCR confirmed *human rhinovirus* infection, less statistically significant differences, when compared again with patients in whom we did not detect any pathogen, were seen. When comparing *influenza A* (*H1N1*) cases with *human rhinovirus* cases, a history of fever ≥38.5 °C was reported more frequently by H1N1-positive cases (65% versus 34%; $p < 0.001$) and those patients suffered more cough, less rhinorrea, more myalgia and more subjective chills than those infected with *rhinovirus*.

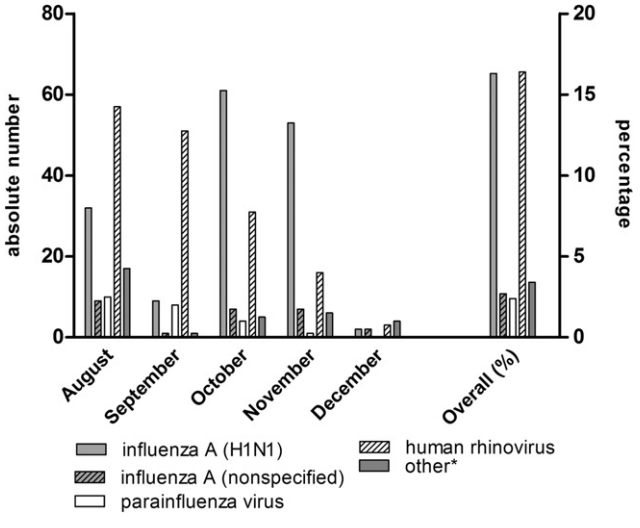

Figure 1 Detected respiratory pathogens in 964 symptomatic adult outpatients during the 2009 H1N1 pandemic. *Other includes: *adenovirus*, *respiratory syncytial virus*, *human metapneumovirus*, *human coronavirus*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.

Table 1 explains the *influenza* case definitions that were used for this study. In general, no statistically significant and relevant differences between the different criteria sets were demonstrated for each individual performance characteristic. Fig. 2 therefore shows the performance characteristics (i.e. sensitivity, specificity, positive predictive value and negative predictive value) of only the GHOR case definition, which was used in our outpatient practice. Overall performance characteristics are shown, as well as performance characteristics in August–September (period of relatively low incidence of pandemic flu) and October–November (period of relatively high incidence of pandemic flu), and also for patients with and without having been referred by their general practitioner (GP). Overall, sensitivity and specificity were 64% and 71%, respectively; the positive predictive value was 35% and the negative predictive value 89%.

Statistically significant differences in positive and negative predictive values were seen within all criteria sets when comparing the period August–September with the period October–November. With regard to the GHOR case definition, positive predictive value increased from 17% to 53% and negative predictive value decreased from 94% to 81%. Additional statistically significant differences were seen within criteria sets when comparing patients that had been referred by their GP with patients who visited the outpatient clinic without having been referred by their GP. For all criteria sets sensitivity was significantly higher for GP referrals than self-referrals (80% versus 51% in Fig. 2). Specificity for the GHOR case definition showed a borderline significant lower value of 62% among GP referrals (compared with 73% among self-referrals); for the other case definitions the lower specificity that was demonstrated among GP referrals did reach true statistical significance ($p < 0.05$).

Finally, besides fever and cough, stepwise logistic regression analysis did not result in the discovery of any additional

Table 3 Clinical characteristics.

		Influenza A (H1N1)	*Human Rhinovirus*		None
Number of adults		157	158		585
Age (mean, range)		32 (18–67)***	36 (18–78)	##	38 (18–88)
Sex	Male	46%	41%		43%
	Female	54%	59%		57%
History of fever $\geq$ 38,5		65%***	34%	###	32%
Highest temperature by history	(Mean $\pm$ SD)	39.0 ± 0.61*	38.8 ± 0.59	#	38.8 ± 0.74
Vital parameters (mean $\pm$ SD)	Temperature (tympanic)	37.6 ± 0.97***	37.1 ± 0.61	###	37.0 ± 0.61
	Heart rate	92 ± 17.1***	80 ± 14.5	###	81 ± 14.7
	Systolic blood pressure	120 ± 17.1***	123 ± 17.3		127 ± 19.0
	Diastolic blood pressure	73 ± 11.0***	76 ± 11.1**	#	79 ± 11.8
	Peripheral O_2 saturation	98 ± 1.3**	99 ± 1.4	##	99 ± 1.2
General flu-complaints	Cough	97%***	88%***	##	72%
	Rhinorrea	70%***	82%***	#	52%
	Sore throat	74%	83%**		68%
	Headache	83%*	76%		74%
	Myalgia	81%***	68%	##	66%
	Malaise	90%**	87%*		79%
	Subjective chills	80%***	59%	###	58%
Complicated flu-complaints	Subjective dyspnea	42%	42%		39%
	Productive cough	59%***	54%**		39%
	Chest pain	34%***	23%		20%
	Otalgia	27%	26%		23%
Chest radiograph	Performed	4%	4%		3%
	Abnormal result	0%	0%		1%
Laboratory investigation	Performed	4%*	2%		1%
	Abnormal result	2%	1%		1%
Influenza-like illness (GHOR)		68%***	33%	###	27%
Oseltamivir prescription (initiated)		14%***	6%	###	6%
Antibiotics prescription		5%	5%		4%

***$p < 0.001$, **$p < 0.01$, *$p < 0.05$: Statistical significance level of difference between group of individuals with detected virus (*influenza A (H1N1)* or *human rhinovirus*) and group of individuals with none detected.
###$p < 0.001$, ##$p < 0.01$, #$p < 0.05$: Statistical significance level of difference between group of individuals with detected *influenza A (H1N1)* virus and *human rhinovirus*.

statistically significant and clinically relevant predictor variables.

Medical management

Oseltamivir therapy was initiated according to national guidelines in 23 patients (13%) with confirmed *influenza A* infection (either H1N1 subtype or non-specified) and in 38 patients (5%) without confirmed *influenza A* infection. Treatment with oseltamivir was discontinued (mostly within 24 h) in all of the 38 *influenza A* negative patients. Antibiotics were prescribed on average in 4% of all patients visiting the outpatient clinic; no statistically significant difference in antibiotics prescription rate was demonstrated between groups based on RT-PCR result. Hospitalization for complicated infection was seen in 7 adult patients. Four patients had to be hospitalized because of a complicated course of infection with the pandemic H1N1-virus; for two of these patients, admission to the intensive care unit was required because of respiratory insufficiency and the need for mechanical ventilation. The other three adults were hospitalized for other diagnoses than viral respiratory infection: bronchial carcinoma, colonic peridiverticulitis and community acquired bacterial pneumonia. No *influenza*-related deaths occurred during the entire study period.

Discussion

This observational study describes interesting epidemiological findings in a population of 964 symptomatic adults visiting an *influenza* outpatient clinic during the 2009 H1N1 pandemic from August 12 until December 31, 2009. *Influenza A* (*H1N1*) and *human rhinovirus* were the major pathogens responsible for respiratory disease among our patients, both having been detected in 16% of the tested throat swab samples. Overall, any respiratory viral pathogen was detected in 41% of tested patient samples. Infections with *influenza B* and *Legionella* species were not observed at all. Double infections were seen in 18 patients. These findings are reasonably comparable to a published report describing prevalence rates of respiratory viruses that were identified annually from 1967–1981 in Tecumseh, Michigan.[10,11] In contrast, due to the pandemic nature of the *influenza A* outbreak last year, we observed a much higher number of cases with a confirmed *influenza A*

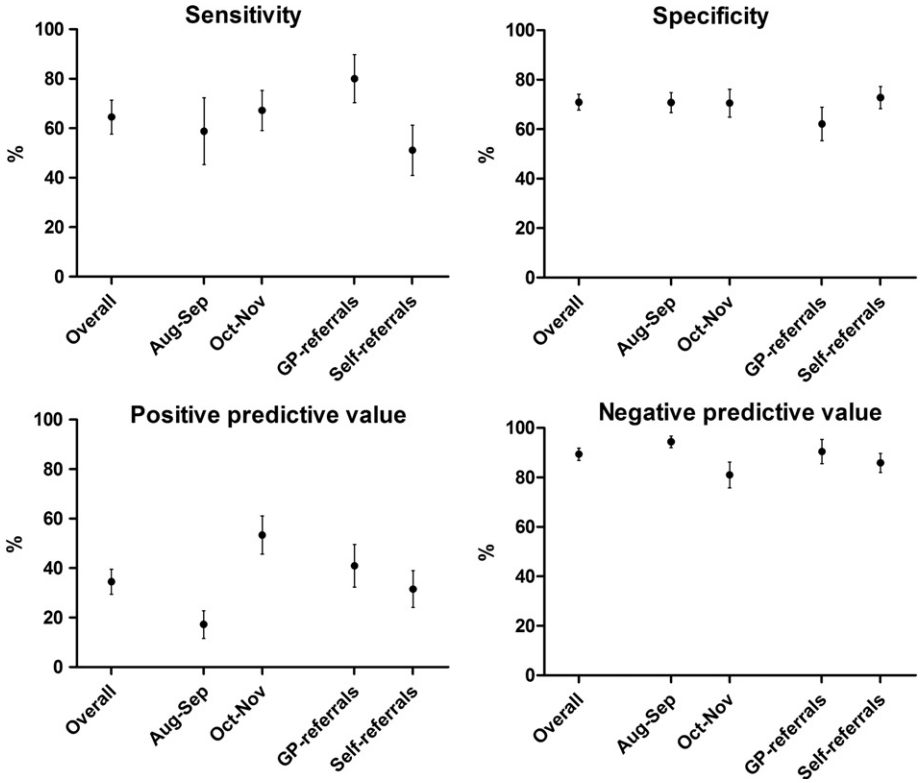

Figure 2 Performance characteristics (including 95% confidence intervals) of GHOR *influenza* case definition.

diagnosis than from previous *influenza* seasons that were observed in the Tecumseh studies. The incidence of confirmed H1N1-positive cases over the course of time, however, does correspond fairly well with numbers reported during the past 2009 H1N1 pandemic by sentinel stations for *influenza* surveillance in the Netherlands and Europe.[21,22]

During the course of the pandemic, different pathogens were dominating the etiologic picture of upper airway infection at different periods. In August and September, *human rhinovirus* infection peaked among symptomatic patients, with a corresponding 20% of throat swab samples having tested positive in those months. Novel swine-origin *influenza A* (*H1N1*) virus infection encountered its highest peak prevalence of 30% in the month October. *RSV*, a less frequently seen viral cause of airway disease in adults, did reach a 7% prevalence rate in December. The consecutive outbreaks of *human rhinovirus*, *influenza A* (*H1N1*) and *RSV* followed its usual pattern. Unlike postulations from French investigators, the interaction between the pandemic flu and *rhinoviruses*, did not cause a delay in the circulation of *respiratory syncytial viruses* in our population.[15]

Clinical features of the 157 cases of 2009 pandemic *influenza A* (*H1N1*) were different from cases that had not been diagnosed with any respiratory viral infection. A history of fever was reported twice as much by the H1N1-positive cases. Most flu-signs and -symptoms were reported significantly more often and vital parameters were slightly, but significantly worse than in the cases in which no respiratory virus could be demonstrated. When comparing the H1N1-positive cases with patients with *human rhinovirus* infection, less statistically significant differences were seen, but on average the 'flu' patient could be regarded as being sicker than the 'common cold' patient. Our study is the first to compare clinical features of patients in an outpatient setting in relation to different pathogens that have been detected during the 2009 H1N1 pandemic. A Chinese observational study described clinical features of 426 persons infected with the 2009 pandemic *influenza A* (*H1N1*) virus, using thermal scanners installed at airports and ports of entry to China to include travelers and subsequently their close contacts.[6] Furthermore, a report from the United States summarized clinical findings from hospitalized patients only with 2009 H1N1 *influenza* infection.[23]

In the Netherlands, with a population size of approximately 16.5 million people, the pandemic followed a relatively mild course. Until the end of December 2009, a total of 2156 hospitalizations of cases with laboratory confirmed *influenza A* (*H1N1*) were reported of which 10% required intensive care, and in total 53 patients had died. In our population, the low number of H1N1-related hospitalizations, and the fact that only two adults had to be admitted to the ICU because of respiratory insufficiency, all confirmed the mild course of the pandemic. An important finding from our study is that treatment with oseltamivir could be discontinued in 38 of 61 patients after the test results had become available and turned negative for *influenza* virus. These adults, had they not been tested by a throat swab and RT-PCR, would have been treated for an unnecessarily long time with the antiviral drug and, although clinically probably not very serious, subjected to an unnecessary risk of adverse effects.[24]

Four different case definitions for *influenza*-like illness were evaluated. The corresponding criteria sets were derived from the World Health Organization (WHO), the United States Centers for Disease Control and Prevention (CDC), the United Kingdom Health Protecting Agency (HPA), and the Dutch organization of Medical Assistance for Accidents and Disasters (GHOR). Overall, performance characteristics were rather poor and similar for the different criteria sets. Positive predictive value increased and negative predictive value decreased when comparing the lower-prevalence period August—September with the higher-prevalence period October—November. This finding is not surprising since the predictive value is determined by the prevalence of disease in the population being tested.[25] Further statistically significant differences were seen within criteria sets when comparing patients that had been referred by their GP with patients that visited the outpatient clinic without having been referred. For all criteria sets, sensitivity was significantly higher for GP referrals than self-referrals, and specificity was significantly lower. This could be explained by some kind of selection bias, i.e. general practitioners referring those patients who were more ill and therefore might meet case definition criteria more easily.

In the daily practice of our *influenza* outpatient clinic, we needed a case definition with a high sensitivity, since missing *influenza* infection might have had important consequences with regard to uncontrolled spread of the virus and the risk for a complicated course of the infection if treatment would not have been initiated. Unfortunately, neither the GHOR case definition that has been used by us, nor the other case definitions that were studied, have been very helpful in that regard. Even though a maximum positive predictive value of 53%, which was seen in October and November at the peak of the epidemic, is still rather useless when wishing to confirm the diagnosis being sought, a maximum negative predictive value of 90% (among patients that had been referred by their GP) might be of quite some value to our practicing clinicians, who also want to be confident that a negative case definition rules out infection with *influenza* virus. In a report evaluating clinical case definitions in France during the 1995—1996 *influenza* epidemic, 12 case definitions were associated with positive predictive values of 27%—40% and negative predictive values of 80%—91%.[19] These findings are comparable to findings from our population.

Limitations of this observational study should be mentioned. First, a selection bias of so-called 'worried well', mostly self-referred, patients is very likely to have influenced our results. National surveillances, however, have demonstrated comparable low rates of hospitalization and ICU admission. Another limitation is that we restricted the RT-PCR analyses to 8 viral and 3 'bacterial' pathogens. Although we have been detecting the most common pathogens during a normal *influenza* season, we might have missed some notable causative bacterial organisms like *Streptococcus pneumoniae* and *Haemophilus influenzae*. Sputum and blood samples have been collected from few adults for bacterial cultures in our microbiology laboratory; none did result in the detection of any bacterial pathogens.

In conclusion, from August through December 2009, *influenza A* (*H1N1*) and *human rhinovirus* were the major pathogens responsible for respiratory disease in a population of 964 symptomatic adult outpatients. The clinical presentation of *influenza* cases was significantly more serious when compared to *rhinovirus* cases or cases that tested negative for any respiratory pathogen. Overall, viewed from an outpatient setting, we can conclude that the 2009 H1N1 pandemic in Amsterdam followed a mild course. Test characteristics of 4 different clinical case definitions seemed comparable but rather useless, with the exception of a relatively high negative predictive value that might be of value in clinical practice when ruling out a diagnosis of *influenza* infection is of importance to the practicing clinician.

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Conflict of interest

None.

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