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CLINICAL FEATURES AND EPIDEMIOLOGICAL CHARACTERIZATION OF PANDEMIC INFLUENZA A/H1N1PDM09 IN CÔTE D'IVOIRE

Konan Kouassi Yannick*[1,2], Kadjo Adjé Hervé Albéric Junior[2], Kouassi Konan Adjoua Rose Marie Clémence[2,3], Kouakou Bertin[2], DOSSO Brétin-Mireille[2] and N'Guetta Assanvo Simon-Pierre[1]

[1]Félix Houphouët Boigny University, Abidjan (Côte d'Ivoire), 22 BP 582 Abidjan 22.
[2]Institut Pasteur of Côte d'Ivoire Abidjan (Côte d'Ivoire), 01 BP 490 Abidjan 01.
[3]Université Nangui Abrogoua, Abidjan (Côte d'Ivoire), 02 BP 801 Abidjan 02.

***Corresponding Author: Konan Kouassi Yannick**
Félix Houphouët Boigny University, Abidjan (Côte d'Ivoire), 22 BP 582 Abidjan 22.

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ABSTRACT

Background: Pandemic influenza A/H1N1Pdm09 viruses are among the most diagnosed and isolated influenza viruses worldwide. Their movement is widely documented but factors influencing this movement still poorly described. Côte d'Ivoire is at risk of influenza epidemics because of the precarious of he's health system and the poverty of he's population. The objective of this study is to describe the demographic factors and the characteristics of the risk factors associated with the movement of pandemic influenza A/H1N1Pdm09 in Côte d'Ivoire. **Methods:** Diagnosis of A/H1N1Pdm09 was performed by polymerase chain reaction targeting the hemagglutinin (HA) gene using SuperScript III Platinum® One-Step qRT-PCR System Amplification Kit (Invitrogen, USA) and primer Fw: AACTACTACTGGACTCTRCTKGAA, Rw: CCATTGGTGCATTTGAGKTGATG and probe : FAM-TGAYCCAAAGCCTCTACTCAGTGCGAAAGC-BHQ-1. RT-PCR was performed on 16,348 nasopharyngeal specimens collected from 2010 to 2017. Samples were collected from nine monitoring sites. Microsoft Excel and R 3.0.1 software were used for data analysis. **Results:** A proportion of 9.16 % of 16,348 samples tested were positive for influenza A over the entire study period and 57.41 % were A/H1N1Pdm09. A/H1N1Pdm09 was significantly distributed over the entire study period, within years and over all seasons. The average age of persons with A/H1N1Pdm09 was 12.47 and the most infected age group was 6 to 15, who were 3.04 times more likely to be infected than persons over 65 years of age. Malnutrition is the risk factor most associated with A/H1N1Pdm09 infections at a rate of 34.38%. **Conclusion:** Epidemiology of pandemic influenza in Côte d'Ivoire is characterized by an almost continuous movement of these viruses. It has a more pronounced impact among people aged 6 to 15 years and is a major health problem for those suffering from malnutrition and chronic pneumonia.

KEYWORDS: Influenza A/H1N1Pdm09, Demographic characterization, risk factor, Côte d'Ivoire.

INTRODUCTION

Influenza viruses are respiratory pathogens found worldwide and are responsible for a high burden of disease. Influenza viruses are subdivided into three serotypes A, B and C.[1,2,3] Serotypes A viruses, from which the last pandemic strain of 2009/2010 emerged, have a large gene pool,[4] thus refining their pandemic potential. They are the main type of influenza virus and are an interest in public health policies.[5-7] They are the only ones causing major influenza epidemics and pandemics worldwide.[8,9] Influenza epidemics each year represent a considerable burden for people around the world.[3] It is estimated that they cause between 250 000 and 500 000 deaths per year.[10] Each year, nearly 6 % of adults and 20 % of children worldwide are infected.[11] Although influenza infection is generally limited to the upper respiratory tract,[12] difficulties can occur in people with risk factors such as congenital heart disease, pneumonia, diabetes, HIV/AIDS, etc.[13] Under these conditions influenza can reach the lower respiratory tract and cause fatal pneumonia. Most of the immune compromised patients who die by influenza have pneumonia.[14] The factors that determine the movement of influenza viruses are still poorly understood. However, studies indicate winter and spring circulation in cold and temperate zones. In tropical and subtropical areas this circulation seems to be superimposed on periods of heavy precipitation according to several studies.[15-18] In areas of great poverty, such as in South Asia, Latin America and sub-Saharan Africa, the emergence of a new influenza strain would have serious consequences, especially for people with risk factors. Characterization of factors determining influenza viruses' circulation would help to better manage

influenza epidemics and/or pandemics, particularly for populations at risk and those with risk factors. In Côte d'Ivoire, since the beginning of influenza monitoring,[19] and the occurrence of the A/H1N1Pdm09 virus, several works have been carried out on the epidemiological aspects but few have focused on the characterization of risk factors associated with this virus. The objective of this study is to describe the demographic factors and the characteristics of the risk factors associated with the movement of pandemic influenza A/H1N1Pdm09 viruses in Côte d'Ivoire.

MATERIALS AND METHODS

Samples collection

Samples were obtained through the human influenza monitoring sites in Côte d'Ivoire. This monitoring is based on the national health programme approved by the Ministry of Health and supported by WHO and the Centre for Disease Control and Prevention (CDC) of Atlanta. This sites' network is composed by nine monitoring sites, from which five are located in the countryside and four in Abidjan (figure 1). The choice of these sites of monitoring was done according to several factors. In particular, (i) coverage of all climatic zones and major geographical regions of the country, (ii) the proximity of the largest health centres and (iii) density of the populations. Samples were taken from nasopharyngeal secretions obtained by swabbing, inserted in VTM at +4 °C and then taken to the laboratory.

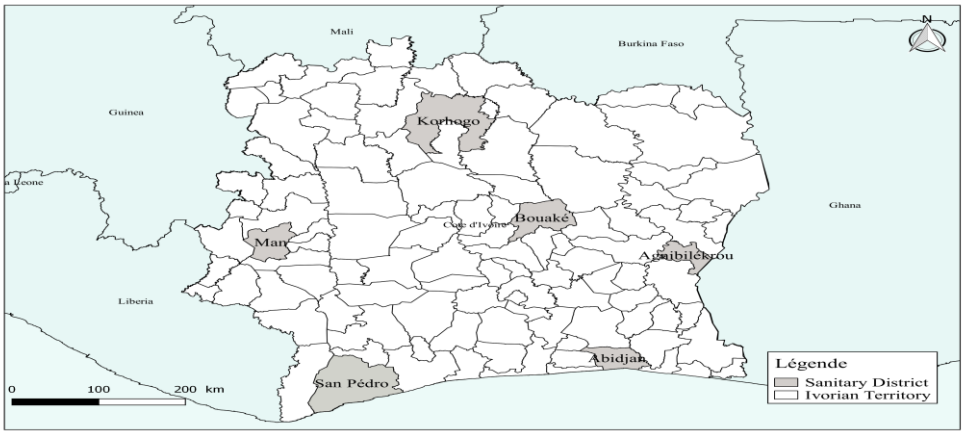

Figure 1: Sampling sites.

Patients were classified into two sex; man and woman and five ages groups defined according to immune system development stage, puberty, school age, etc. Group 1 (G1): 0 - 5 years, G2: 6 - 15 years, G3: 16 - 30 years, G4: 31 - 65 years and G5: +65 years.

Viral RNA Extraction and molecular diagnosis

RNA extractions were performed using the Qiagen RNA Extraction Kit (QIAAMP® Viral RNA, Valencia, CA, USA). Diagnosis of A/H1N1Pdm09 viruses was performed by polymerase chain reaction targeting the hemagglutinin (HA) gene using the SuperScript III Platinum® One-Step qRT-PCR System Amplification Kit (Invitrogen, USA) and primer
Fw: AACTACTACTGGACTCTRCTKGAA,
Rw: CCATTGGTGCATTTGAGKTGATG and
probe : FAM-TGAYCCAAAGCCTCTACTCAGTGCGAAAGC-BHQ-1.

Statistical analysis

Statistical analyses were performed using R software (3.0.1). The means of the cumulative monthly distribution for the eight years of study of pandemic influenza A/H1N1Pdm09 were compared by the analysis of variance test for one parameter (ANOVA 1) at the 5% level. In the event of a significant difference in the distribution of influenza A/H1N1Pdm09, the post-ANOVA test was used to determine the months of high virus circulation over the cumulative eight years. The comparison of the monthly distribution per year of pandemic influenza (A/H1N1Pdm09) was performed using the non-parametric tests of Kruskal Wallis and Mann Wekney since this distribution does not follow a normal distribution and has no variance equality. The distribution of viruses in age groups, by sex and clinical parameters was compared using the Chi2 test at the 5% level. The infection risk assessment for different age groups was done by analysis of the odds ratio and confidence intervals obtained using the statistical analysis tool of Aly-Abbara. Microsoft Windows Excel spreadsheet and R studio software were used to generate the graphs.

RESULTS

Côte d'Ivoire is a country in West Africa with a population of about 25 million of people. Influenza and other respiratory viruses monitoring is conducted by the national health system through nine monitoring sites and a WHO National Influenza Centre (NIC), distributed in the four major geographical regions. Four of the nine monitoring sites as well as the NIC are located in

Abidjan, the economic capital which has more than 20% of the country's population.

Molecular diagnosis and viral isolation

A total of 16,348 samples were analysed from 2010 to 2017. From the 1,498 (9.16%) specimens diagnosed positive for influenza A, 860 (57.41%) belonged to serotype A/H1N1pdm09. Figure 2 shows the number of A/H1N1Pdm09 positive versus influenza A positive. Thus, over the 8-year period, A/H1N1Pdm09 is the most representative serotype of influenza A infections.

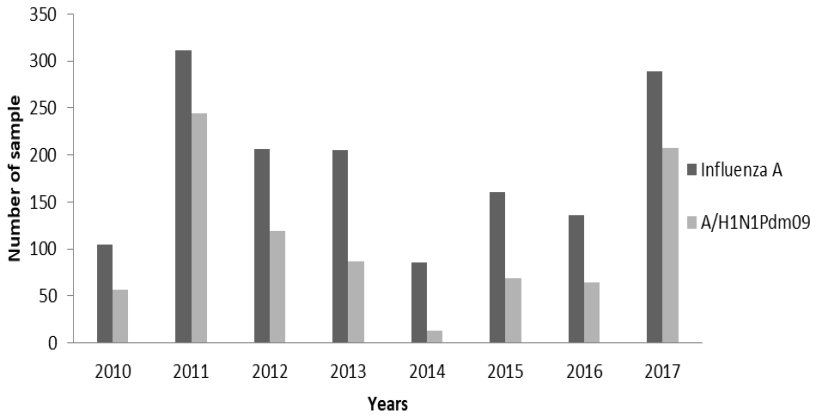

Figure 2: Positives A/H1N1pdm09 per year from 2010 to 2017 out of influenza A cases.

A/H1N1Pdm09 was significantly distributed over the cumulative 12 months during the period (8 years) of the experiment (P-Value = 0.008). The most impacted month was November followed by January, May, August and September. The cumulative distribution of the virus in the remaining months was relatively low. Overall, all the seasons were affected with at least one peak in each season. In terms of year, analysis by the non-parametric Kruskal Wallis test followed by the Mann Wekney test revealed a significant distribution of A/H1N1Pdm09 over the entire period of the study (P-Value = 0.001) and within each year (P-Value =0.002; 0.01; 0.047; 0.033; 0.0004; 0.005; 0.0006 and 0.0004782 respectively) (Table I).

Table I: Significativity of A/H1N1Pdm09 distribution over the entire study period and within each year.

Years	2010	2011	2012	2013	2014	2015	2016	2017
P-Value	0.002	0.01	0.04	0.03	0.0004	0.005	0.0006	0.0004
	0.001							

Also, in terms of years, epidemic peaks were recorded during June and July in 2011, February and March in 012 and November and December in 2011 and 2017 (Figure 3).

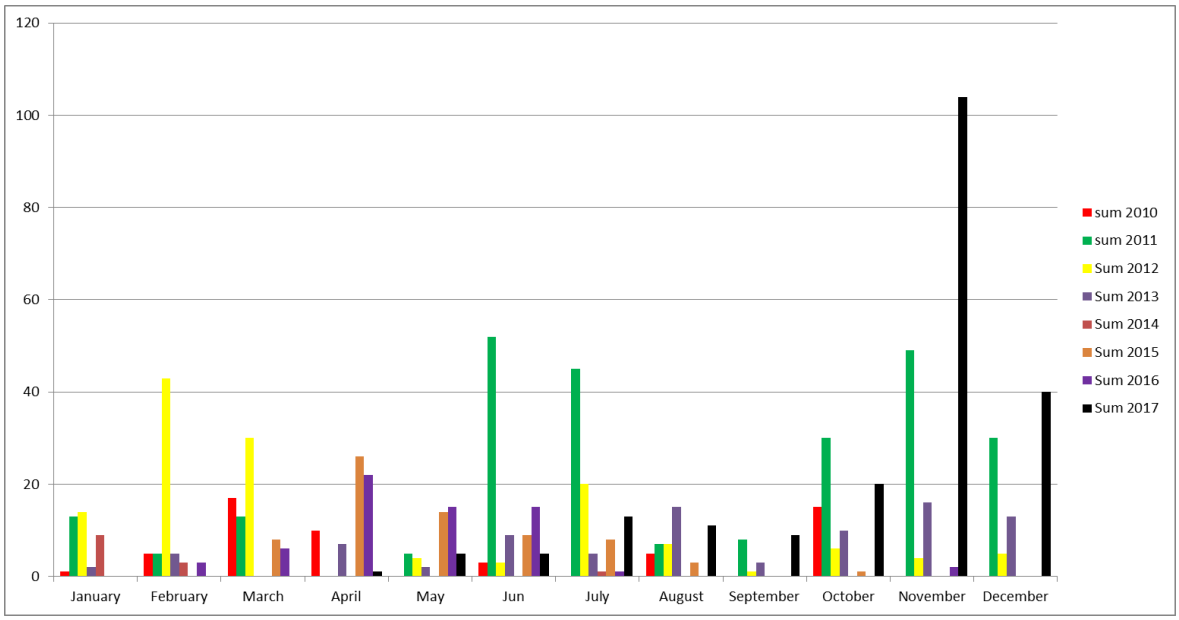

Figure 3: Distribution of pandemic influenza cases due to the A/H1N1Pdm09 virus per month in Côte d'Ivoire from 2010 to 2017.

The years 2011, 2012 and 2017 were the years most affected by the pandemic influenza A/H1N1Pdm09 virus (Figure 4).

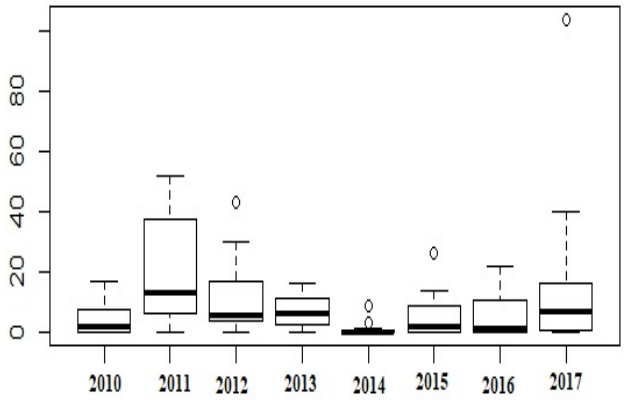

Figure 4: Significance of the distribution of the A/H1N 1Pdm09 virus from 2010 to 2017.

Demographic and clinical characterization of A/H1N1Pdm09 infected patients

The mean age of infected patients was 12.47 years old with lower and upper limits of 1 month and 91 years respectively. All genders (male and female) were infected, with 51.67% of males. All age groups were infected with the highest rate of positivity in the 6 to 15 year old group (7.79%) followed by the 16 to 30-year-old group (7.22%). The lowest rate of infection was recorded in the over-65 age group (2.46%) followed by the 31-65 age group (Table II). Thirty-two (3.72%) patients infected with Pandemic H1N1 influenza had the following risk factors: asthma (12.5%), immune deficiency (3.12%), immune-associated diabetes (3.12%), hypertension (3.12%), obesity (6.25%), malnutrition (34.38%), chronic lung disease (21.88%), chronic lung disease associated with malnutrition (12.5%), and other unspecified risk factors (3.12%) (Figure 5).

Table II: Distribution of A/H1N1Pdm09 virus by age group.

Age group	Patients infected by A/H1N1Pdm09 virus	Patients not infected by A/H1N1Pdm09 virus	Total	P-Value
0 – 5 (G1)	516	9092	9608	< 0.001
6 – 15 (G2)	97	1265	1362	
16 – 30 (G3)	107	1785	1892	
31 – 65 (G4)	132	2992	3124	
> 65 (G5)	08	354	362	
Total	860	15 488	16 348	

Distribution of pandemic H1N1 influenza in populations in Côte d'Ivoire is highly correlated with the age of patients (P-Value < 0.001). The age group most infected by the virus is between 6 and 15 years old and the least affected is the elderly (> 65 years old) (Table III).

Table III: Evaluation of the risk of infection by A/H1N1Pdm09 virus by age group with 65 years old as reference class.

	Positive Inf A/H1N1pdm09	Negative Inf A/H1N1pdm09	Odds Ratio	Confidence interval
0 – 5 (G1)	516	9092	2.25	1.11 – 4.56
6 – 15 (G2)	97	1265	3.04	1.46 – 6.32
16 – 30 (G3)	107	1785	2.38	1.15 – 4.93
31 – 65 (G4)	132	2992	1.75	0.85- 3.61
> 65 (G5)	08	317	Reference	

All age groups outside the adult age group from 31 to 65 years have a risk factor of being infected with the A/H1N1Pdm09 virus twice as high as that of the over-65 age group.

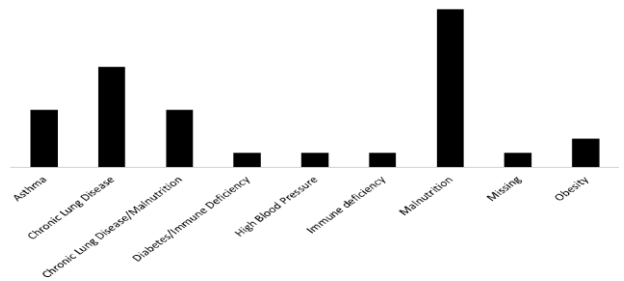

Figure 5: A/H1N1Pdm09 virus distribution by risk factors.

Malnourished people, those suffering from chronic pneumopathy and asthma are more at risk of A/H1N1Pdm09 virus infections in Côte d'Ivoire compared to people with other risk factors. People suffering from immune deficiencies, diabetes and high blood pressure were less infected than the one mentioned above.

DISCUSSION

The prevalence of Influenza A/H1N1Pdm09 in Côte d'Ivoire during the period of 2010 to 2017 is 5.26%. This low prevalence could be explained by the type of influenza monitoring in Côte d'Ivoire, which is "sentinel monitoring" and not systematic in all health centres. In addition, the monitoring sites are essentially public

healthcare centres. This makes it impossible to count patients from other healthcare centres. A/H1N1Pdm09 infections represent 57.41% of total Influenza A infections. This high proportion indicates the place that this virus occupies in influenza-like illness (ILI). This proportion is confirmed by several studies around the world, sach as Rajatonirina et al. (2012) in Madagascar and Koul *et al.* (2013) in Kashmir.[20,21]

The results of this study show that the A/H1N1pdm09 viruses circulate over the years among Ivorian populations and are responsible for a significant proportion of acute respiratory infections (ARI). The pandemic influenza virus is distributed over all seasons with November, January, May, August and September being the most affected months. These results can be explained by an important movement of the population in Côte d'Ivoire during these periods; end of year celebrations, Easter, school vacations and back to school, as it was the case in mainland China.[22] Initial work in tropical areas indicated the circulation of influenza throughout the year as found in this study.[23]

Outbreak peaks of A/H1N1Pdm09 were observed in June-July (2011), February-March (2012) and November-December (2011 and 2017). These results may be due to the rainfall during these periods. In Côte d'Ivoire, July and November are covered respectively by the long and short rainy seasons.[24,25] In previous studies conducted in Côte d'Ivoire, these two epidemic peaks have been identified at the same periods.[19,26,27] Several studies around the work have indicated that influenza transmission peaks during the seasons of heavy rainfall.[17,28,29] In Vietnam India and 15 African countries, previous research indicated that the movement of influenza and other respiratory viruses experiences two key peaks.[30-32] In tropical areas, it overlaps with periods of low temperature, mainly during the rainy seasons. Similarly, over the tropics in Hong Kong, two epidemic peaks have also been observed, one in winter/spring covering the period of November and the other in summer covering the period of July.[33] The correlation of influenza infection cases with variations in rainfall has been demonstrated in Senegal,[34] Honduras and several countries in the tropics.[35-37]

2011 was the year of high activity of the pandemic influenza virus after it has appeared in 2009 and 2014 the year of low activity. If the circumstances of the high activity of the pandemic influenza virus in 2011 remain unexplained for the time being, however the low activity of A/H1N1Pdm09 in 2014 would be due to the consequences of the strong awareness campaign of the Ivorian populations during the sanitary crisis of the Ebola disease which affected West Africa.[38-40] Hygiene measures, particularly hand washing, would have contributed greatly to the low rate of influenza infection in 2014.

The high rate of A/H1N1Pdm09 infection was observed in the 6 to 15 year-old age group. This age group includes the average school age in Côte d'Ivoire (6 and 12 years).[41] Indeed, the promiscuity in the classrooms and the lack of hygiene generally observed would favour transmission. The study by Broor et al (2012) conducted in Delhi (India) showed similar results. Indeed, their work showed that the A/H1N1pdm09 infection reached its peak (29.3%) in the 5 to 18– year – old age group. The progressive acquisition of herd immunity could explain the progressive decrease of the infection rate beyond the age of 15 years old.

The low rate of infection observed beyond the age of 65 years old could be explained by the small size (2.5%) of this fringe of the population due to life expectancy in Côte d'Ivoire being around 45 years old. Contrary to our results, a study in temperate and cold countries indicates that people over 65 years of age are at risk.[43]

People in the 6-15 age group are three times (3.04) more likely to be infected compared to those over 65 years old of age. Among people with risk factors (asthma, obesity, heart and lung disease, etc.), malnourished people (81.26%) are the most vulnerable to A/H1N1Pdm09 infections. The results obtained during this experiment are consistent with several studies conducted in various regions. These studies reported that people suffering from these risk factors were people at risk of influenza infections but also susceptible to developing forms of complications that could even lead to death.[44]

CONCLUSION

Epidemiology of influenza A/H1N1Pdm09 in Côte d'Ivoire is characterized by an almost continuous circulation of these viruses. It has a more pronounced impact among people aged six to fifteen years old and is a major health problem for those suffering from malnutrition and chronic pneumonia. The main factor influencing the circulation of influenza viruses in Côte d'Ivoire is the movement of populations mainly for end-of-year celebrations, during the periods surrounding school holidays.

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