Official Journal of the Brazilian Association of Infection Control and Hospital Epidemiology

Journal of INFECTION CONTROL

ISSN 2316-5324 | Ano IV . Volume 4 . Número 1 . 2015 . Jan./Mar.

> ACESSE AQUI A REVISTA ONLINE

ARTIGO ORIGINAL

Oseltamivir: what is the real meaning of the use in the treatment of Severe Acute Respiratory Infection?

Débora Cristina Haack Bassani,[1] Eliane Carlosso Krummenauer,[1,2] Janete Aparecida Machado,[1,2] Jéssica Chaves,[1] Lia Possuelo,[1] Patrícia Micheli Tabile,[1] Marcelo Carneiro.[1,2]

[1]School of Medicine, Department of Biology and Pharmaceutical Sciences, Universidade de Santa Cruz do Sul (Unisc), Santa Cruz do Sul, RS, Brazil.
[2]CCIH - Hospital Santa Cruz (HSC), Santa Cruz do Sul, RS, Brazil.

Recebido em: 07/07/2015
Aceito em: 10/04/2015
carneiromarcelo@yahoo.com.br

RESUMO

Introdução: Dentre os principais agentes etiológicos da infecção Respiratória Aguda Grave (IRAG) está o vírus Influenza A H1N1/2009 (IA/2009). O tratamento antiviral precoce (<48 horas) está indicado para tais casos. **Objetivo:** Analisar o perfil do paciente com IRAG, a fim de possibilitar um aprimoramento dos procedimentos de triagem nos casos suspeitos de IA/2009 e adequar o uso de antiviral. **Métodos:** Estudo descritivo realizado através das fichas de notificação governamental dos casos de IRAG, de 2012, preenchidas no Hospital Santa Cruz, Brasil. **Resultados:** Dos 64 casos de IRAG, 41 (64,1%) eram do sexo masculino. As faixas etárias mais atingidas foram de crianças menores de quatro anos (56,0%). Os quatro casos confirmados de IA/2009 foram em maiores de 50 anos. Ter uma comorbidade foi o fator mais prevalente (34,4%). Os sintomas mais comuns de IRAG foram tosse, febre e dispneia. O oseltamivir foi dispensado para 84,4% dos casos de IRAG e em 100% dos pacientes com IA/2009. **Conclusão:** Verificou-se que na maioria dos casos não houve confirmação da cepa pandêmica, o que ocasionou uma supervalorização do diagnóstico e indicação antiviral. Portanto, os resultados demonstram a falta de um teste rápido para otimizar a terapia.

Palavras-chave: *Síndrome Respiratória Aguda Grave; Vírus da Influenza A Subtipo H1N1; Oseltamivir.*

ABSTRACT

Introduction: One of the main etiological agents of Severe Acute Respiratory Infection is the Influenza A H1N1/2009 virus. Early antiviral treatment (<48 hours) is indicated for such cases. **Objectives:** To analyze the profile of patients with Severe Acute Respiratory Infection, aiming to allow the development of screening procedures in cases of suspected Influenza A H1N1/2009 virus cases and tailor the use of antiviral agents. **Methods:** Descriptive study carried out through the analysis of government notification files that were filled out at Hospital Santa Cruz, Brazil, in 2012. **Results:** Of the 64 cases of Severe Acute Respiratory Infection, 41 (64.1%) were males. The most affected age group was children younger than four years (56.0%). Having a comorbidity was the most prevalent factor (34.4%). The most common symptoms were cough, fever and dyspnea. The four confirmed cases of Influenza A H1N1/2009 virus were established in patients older than 50 years. Oseltamivir was prescribed to 84.4% of cases of Severe Acute Respiratory Infection and 100% of patients with Influenza A H1N1/2009 virus. **Conclusion:** It was observed that in the majority of cases there was no confirmation of the pandemic strain, which led to an overvaluation of the diagnosis and antiviral indications. Therefore, the results demonstrate the lack of a rapid test to optimize therapy.

Keywords: *Severe Acute Respiratory Infection; Influenza A Virus; Oseltamivir.*

INTRODUCTION

One of the etiological agents of Severe Acute Respiratory Infection (SARI) is the Influenza A virus (IA/2009).[1,2] SARI is a disease that can affect individuals of any age or gender, with different degrees of severity from the asymptomatic form, with an incubation period between 1 and 4 days.[1,3,4] The clinical diagnosis of IA/2009 in children younger than 4 years is difficult, as the clinical manifestations are common to other viral respiratory diseases such as those caused by respiratory syncytial virus.[5,6]

In wintertime, there is an increased incidence of respiratory diseases, mainly due to transmission that occurs through patients' airway secretions.[3,6] During the pandemic, more than 214 countries reported confirmed cases of influenza IA/2009 and, in Brazil, the official report of sustained virus circulation occurred on July 19, 2009,[7] with the peak occurring between the 31st and 32nd Epidemiological Week (EW). It was observed that the highest concentration of cases occurred in the southern states of Brazil: Paraná, Santa Catarina and Rio Grande do Sul (RS), with 18,349 confirmed cases,[8] while in RS there were 3,585.[9] In 2011, 112 IA/2009 cases were confirmed in the southern region, whereas in RS there were 103 cases in that period.[4] In 2012 1,882 IA/2009 cases were confirmed,[10] with 522 in RS.[9]

Groups that were eligible for vaccination against influenza in Brazil, including the pandemic strain, comprise the population aged > 60 years, children aged 6 months to younger than 2 years, pregnant women, the Brazilian native population, inmate populations and patients with comorbidities, according to medical indication.[11,12] The indication of vaccine protection is required, as the decrease in viral transmission is the best form of control. Segregation per priority groups is a choice made by the government and the Brazilian public health strategy decision.

School-age children have an important role in the dissemination of pandemics.[6] In a Chilean study, the age groups with the highest risk of hospitalization for IA/2009 were children younger than five years and the elderly.[13] Therefore, the expansion of immunization coverage for all age groups could reduce the negative impact of the disease in the general population routine, such as a decrease in work performance, impaired school performance and unnecessary costs on the diagnosis, treatment or hospitalization of individuals with IA/2009.

Antiviral treatment becomes important in the clinical management of SARI and takes into account information on the influenza type specificity as well as prevalence of resistance to antiviral drugs. Treatment in Brazil should be prescribed based on clinical suspicion of influenza-like illness (ILI) and SARI, regardless of risk factors or laboratory confirmation.[3,14,15] Oseltamivir should be considered the first therapeutic choice, while zanamivir should be reserved for special cases.[3,16]

The aims of this study were to evaluate and analyze the profile of patients with SARI, allowing the development of screening procedures in suspected cases of IA/2009 and tailoring the use of antiviral drugs.

MATERIALS AND METHODS

Deliniation and tool of study

The present is a descriptive study of quantitative, exploratory and retrospective approach, carried out through the analysis of compulsory notification forms from the Notifiable Diseases Information System (SINAN) of SARS cases.

Period of study

The period of study from the 13th to the 33rd (30/03-13/8) Epidemiological Week in 2012.

Place of estudy

The notification forms were filled out in Hospital Santa Cruz (HSC), and contained information on patients treated on-site and made available by the Hospital Epidemiology Center. HSC is located in the city of Santa Cruz do Sul (latitude - 29.71° and longitude - 52.42°)[17] in the countryside of the state of Rio Grande do Sul, Brazil, 150 km from the state capital, which has 182 beds.

Criterium of study

SARS was considered when the patient presented with fever, cough and dyspnea.[18] SARS specifically caused by IA/2009 was considered when the patient had laboratory confirmation by standardized molecular test (PCR - Polymerase Chain Reaction).[13,19,20] The cost analysis of vaccination and antiviral treatment was made by analyzing the data of the National Health Surveillance Agency of Brazil, and the values were converted to U.S. dollars (currency exchange in Brazil: R$ 2.13 = U.S.$ 1.00).

RESULTS

A total of 64 patients with SARI were reported between the 13th and 33rd EW (30/03-13/08), in Santa Cruz do Sul (Figure 1), in 2012, and of these, 64.1% cases were males. The peak occurred in the 30th EW, with 8 cases (Figure 2). Of all patients with SARI, 63 (98.4%) were hospitalized. The highest incidences of the disease occurred in children younger than 4 years (Figure 3), considering that 58% were males.

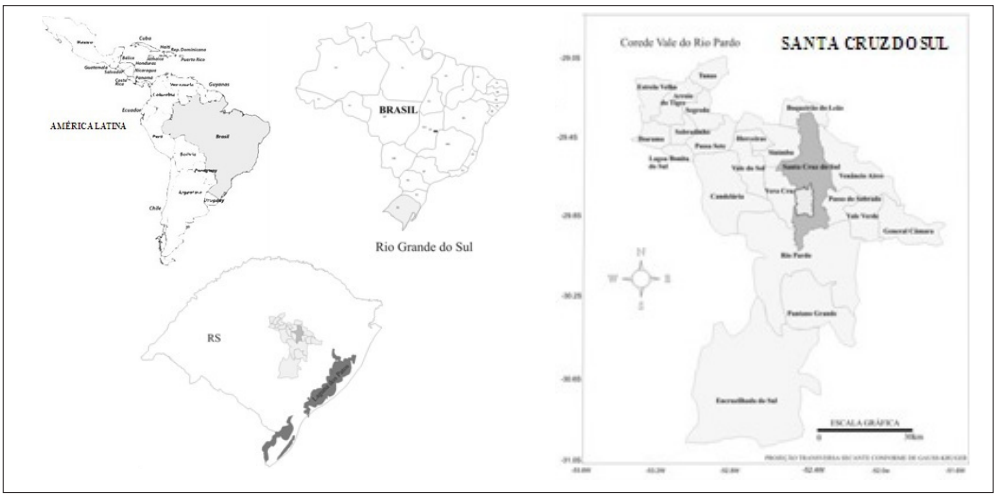

Figure 1 - Location of the municipality of Santa Cruz do Sul, RS, Brazil, 2012.

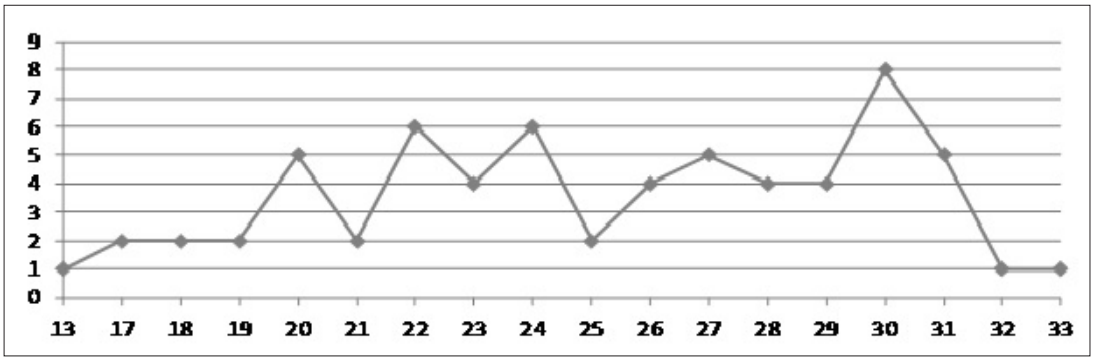

Figure 2 - Number of confirmed cases of SARI, according to the epidemiological week, Santa Cruz do Sul, RS, Brazil, 2012.

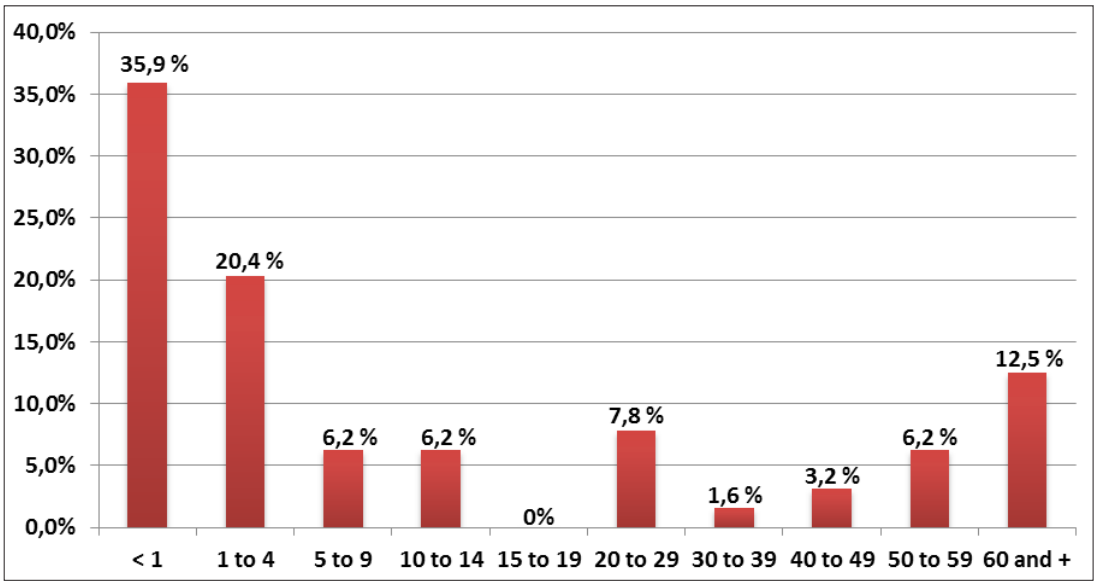

Figure 3 - Percentage of patients with SARI per age group, Santa Cruz do Sul, RS, Brazil, 2012.

The SINAN record files show four diagnostic tests that help in the screening for other viruses: PCR, sample culture, hemagglutination inhibition assay and chest X-ray. Laboratory data of sample cultures and hemagglutination inhibition assays were not requested for any patient. Chest X-ray was requested for 96.9% of patients with SARI, showing a result of interstitial infiltrate in 48.4%, consolidation in 24.2% and normal in 14.5%. Chest X-ray was requested for 2 (75%) of the confirmed cases of IA/2009, with the result showing consolidation in 66.7%, and interstitial infiltrate in 33.3%. PCR samples for IA/2009 identification were collected in 100% of cases.

The IA/2009 was confirmed in 4 cases by PCR, all in the age range of 50-59 years (75%) and 40-49 years (25%). These cases were observed in EW 20, 21, 24 and 26. Other 4 cases of SARI were caused by respiratory syncytial virus (RSV), all in children younger than four years, with no gender predominance. There was no etiology confirmation for the remaining 56 cases of SARI. Only one case of SARI did not require hospitalization.

The presence of comorbidities was observed in 22 (34.4%) of the SARI cases (Table 1). Among these cases, chronic lung disease was the predominant comorbidity (40.9%). Of the patients with chronic lung disease, 55.6% had chronic bronchitis. In 2 patients (9.1%) with IA/2009 and aged < 50 years, the comorbidities smoking (50%) and chronic lung disease (50%) predominated. The mean number of comorbidities was 1.77 / patient.

Tabela 1 – Comorbidities of patients with SARI*, Santa Cruz do Sul, RS, Brazil, 2012.

Comorbidities	N (%)
Chronic heart disease	*4 (10.3)*
Chronic lung disease	*9 (23.1)*
Chronic kidney disease	*1 (2.6)*
Immunodeficient	*5 (12.8)*
Smoker	*5 (12.8)*
Chronic metabolic disease	*1 (2.6)*
Obesity	*4 (10.3)*
Alcoholism	*3 (7.6)*
Others	*7 (17.9)*
TOTAL	***39 (100)***

**SARI= Severe Acute Respiratory Infection.*

The mortality of SARI was 6.3%, of which one case had Chronic Obstructive Pulmonary Disease (COPD), one had immunodeficiency with Guillain-Barré syndrome, and two that did not have comorbidities. One of the patients who died and had no comorbidities had IA/2009 confirmation. The most common SARI symptoms were fever, cough and rhinorrhea (Table 2). The need for hospitalization in the Intensive Care Unit (ICU)

occurred in 5 patients (7.8%) with SARI; however, none of these had IA/2009 confirmation.

Tabela 2 – Symptoms of SARI* cases, Santa Cruz do Sul, RS, Brazil, 2012.

Symptoms	SARI cases N (%)
Fever	*52 (81.3)*
Coughing	*55 (85.9)*
Chills	*8 (12.5)*
Dyspnea	*44 (68.8)*
Sore throat	*14 (21.9)*
Arthralgia	*1 (1.6)*
Myalgia	*15 (23.4)*
Rhinorrhea	*52 (81.3)*
Others	***20 (31.3)***

**SARI= Severe Acute Respiratory Infection.*

Prescription of oseltamivir occurred in 84.4% of cases of SARI and 100% of confirmed IA/2009 cases. Half of those affected by IA/2009 received treatment with antivirals on the day of admission and the others, on the day after. Data on the vaccination of patients with SARI filled out in SINAN record files were categorized as yes (18.8%), no (73.4%) and unknown (7.8%). All confirmed cases of IA/2009 had not received vaccination. Due to the high rate of antiviral treatment prescription, the cost of the treatment of the 54 patients who received oseltamivir was U.S.$ 6,577.20. The cost of vaccine was U.S.$ 3.62, totaling $195.46 for the same number of patients.

DISCUSSION

Patients diagnosed with SARI were predominantly children younger than four years, although the priority group for vaccination is age < 2 years in Brazil.[11] The observed frequency of comorbidities emphasizes the special attention to empirical therapy according to the order of SARI management protocols, despite the need for a broad differential diagnosis.

It was observed that the most prevalent signs and symptoms are similar, but due to the small number of cases it was not possible to infer other conclusions. Although patients with confirmed IA/2009 infection received treatment according to the Brazilian Ministry of Health protocol,[4] taking into account of the benefits of early therapy in reducing symptom duration and mainly reducing the occurrence of complications,[18] a large proportion of SARI cases received oseltamivir empirically, including SRV, as the test result was received after the end of the treatment. However, to improve the screening process and rationalize antiviral drug use, it is important to have a thorough medical assessment of cases of ILI and SARI,[16]

Although there is no vaccine coverage for the entire Brazilian population, the main preventive public health intervention for IA/2009 is vaccination, as it generates impacts on the reduction in hospital admission, drug costs to treat secondary infections and preventable death.[12] Thus, these results and the better cost-benefit of vaccination to the detriment of empiric treatment with oseltamivir in SARI cases, support the expansion of immunization coverage.

Even though the limited number of cases was restricted to only one center, it was observed that the use of oseltamivir was high and one must be watchful, especially when concerning children.

The pandemic of 2009 and the introduction of IA/2009 induced an undiscriminating approach. Even though the use of oseltamivir is justified to save lives in the absence of a rapid and universally available sensitive confirmatory method, a new approach for the clinical management, as well as the establishment of more appropriate criteria for therapeutic and diagnostic screening for cases of influenza are necessary and pressing. The feasibility of rapid tests with high sensitivity and specificity will represent progress, if applicable in real time.[21]

DISCLOSURE

As this is an epidemiological study of diseases with compulsory notification, the data are of public domain and, therefore, the signing of the Free and Informed Consent form and Research Ethics Committee approval are not required.

REFERENCES

1. *Moretti ML, Sinkov V, Cardoso LG, Bachur LF, Hofling CC, Angerami R et al. Lessons from the epidemiological surveillance program, during the influenza A (H1N1) virus epidemic, in a reference university hospital of Southeastern Brazil. Rev Soc Bras Med Trop 2011; 44(4): 405-11.*
2. *Baehr MF, Morín GR, Solar JAH, Olivi HR y Torres JPT. Caracterización clínica de adultos menores y mayores de 50 años hospitalizados por influenza A H1N1 2009 en un centro hospitalario privado en Santiago, Chile. Rev Chilena Infectol 2010; 27: 139-43.*
3. *Ministério da Saúde. Secretaria de Vigilância em Saúde. Emergência de Saúde Pública de Importância Internacional ESPII. Protocolo de manejo clínico de Síndrome Respiratória Aguda Grave – SRAG 2010. http://www.saude.rn.gov.br/contentproducao//aplicacao/sesap/saude_destaque/enviados/protocolo_manejo_srag_03_03_10.pdf. Acesso em 10 dezembro 2013.*
4. *Ministério da Saúde. Secretaria de Vigilância. Departamento de Vigilância em Epidemiológica. Guia de Vigilância Epidemiológica. Ministério da Saúde, 2009. http://portal.saude.gov.br/portal/arquivos/pdf/gve_7ed_web_atual.pdf. Acesso em 21 novembro 2013.*
5. *Jofré ML, Perret PC, Dabanch PJ, Abarca V, Olivares CR, Luschisinger FV et al. Influenza: reemergencia de uma antigua enfermedad y el potencial riesgo de uma nueva pandemia. Rev Chilena Infectol 2005; 22 (1): 75-88.*
6. *Scottá MC. Fatores associados à gravidade da infecção por Influenza a pandêmico (H1N1) 2009 em pacientes pediátrixos hospitalizados. Dissertação de Mestrado. Universidade do Rio Grande do Sul. Faculdade de Medicina. Porto Alegre, 2012. http://www.bibliotecadigital.ufrgs.br/da.php?nrb=000873105&loc=2013&l=bbb4ef2125cba87b. Acesso em 10 de dezembro 2013.*
7. *Ministério da Saúde. Secretaria de Vigilância em Saúde. Epidemiologia e Serviços de Saúde. Revista do Sistema Único de Saúde, 2009; http://portal.saude.gov.br/portal/arquivos/pdf/revista_vol18_n31.pdf. Acesso em 10 dezembro 2013.*
8. *Carneiro, M, Bercini MA, da Silva BL, Schaffer TG, Machado AJ, Krummenauer CE et al. The Influenza A/H1N1 Pandemic In Southern Brazil. Infect Control Hosp Epidemiol, 2011; 32: 1-1.*
9. *Governo do Estado do Rio Grande do Sul. Centro Estadual de Vigilância. Divisão de Vigilância Epidemiológica. Influenza no Rio Grande do Sul em 2012. http://www.saude.rs.gov.br/upload/1366813096_Boletim%20final%20Influenza%20no%20RS%202012.pdf. Acesso em 10 dezembro 2013.*
10. *Ministério da Saúde. Secretaria de Vigilância em Saúde. Boletim Informativo. Secretaria de Vigilância em Saúde Influenza (gripe), 2012. http://portalsaude.saude.gov.br/portalsaude/arquivos/boletim_informativo_de_influenza_21set2012_final.pdf. Acesso em 12 dezembro 2013.*
11. *Ministério da Saúde. Secretaria de Vigilância em Saúde. Campanha*

Nacional de Vacinação Contra a Influenza 2012. Informe Técnico, 2012. http://portal.saude.gov.br/portal/arquivos/pdf/informe_tecnico_campanha_influenza_2012.pdf. Acesso em 10 dezembro 2013.

12. *Brasília. Campanha Nacional de Vacinação contra a Influenza 2012. Informe técnico, 2012. http://portal.saude.gov.br/portal/arquivos/pdf/informe_tecnico_campanha_influenza_2012.pdf. Acesso em 10 dezembro 2013.*
13. *Perret PC. Influenza pandémica a un año de la primera ola: ¿Qué podemos decir ahora? Rev Chilena Infectol, 2010; 27: 144-47.*
14. *Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Protocolo de Tratamento de Síndrome Gripal (SG) e Síndrome Respiratória Aguda Grave (SRAG). 2011. http://www.saude.caop.mp.pr.gov.br/arquivos/File/gripe_a/protocolo_sindrome_gripal_srag_2011.pdf. Acesso em 10 dezembro 2013.*
15. *Carneiro M, Trench FJP, Waib LF, Pedro FL, Motta, F. Influenza H1N1 2009: revisão da primeira pandemia do século XXI. Ver AMRIGS, 2010; 54: 206-13.*
16. *Roche. Tamiflu® (fosfato de oseltamivir). Notificação de Alteração de Texto de Bula – Adequação RDC 47/09-CDS 6.0M. http://www4.anvisa.gov.br/base/visadoc/BM/BM[32345-1-0].PDF. Acesso em 10 de abril 2013.*
17. *Baden LR, Drazen MD, Kritek AP, Curfman DG, Morrissey S and Campion WD. H1N1 Influenza A Disease — Information for Health Professionals. N Engl J Med Overseas Ed, 2009; 25: 2666-67.*
18. *Ribeiro AS, Sgreccia BG, Novaes CSL, Silva CC and Kavaguti SC. Síndrome respiratória aguda grave causada por influenza A (subtipo H1N1). J Bras Pneumol, 2010; 36: 386-89.*
19. *IBGE Cidades. Santa Cruz do Sul, Rio Grande do Sul, Brasil. Dados Básicos, 2012. http://www.ibge.gov.br/cidadesat/painel/painel.php?codmun=431680. Acesso em 10 dezembro 2013.*
20. *Ministério da Saúde. Secretaria de Vigilância em Saúde. Informe Técnico de Influenza. Vigilância de Síndrome Respiratória Aguda Grave (SRAG), de Síndrome Gripal (SG) e de internações por CID J09 a J18. Brasília, 2012. http://portal.saude.gov.br/portal/arquivos/pdf/info_tecn_influenza_31_01_2012_28novo_29.pdf.Acesso em 11 dezembro 2013.*
21. *Al Johani SM and Akhter J. Comparison of the Cepheid Xpert FluA/H1N1 screening test with real time polymerase chain reaction (PCR) in detection of 2009 H1N1 Influenza A Pandemic. Afr J Microbiol, 2012; 6.*