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REVIEW

Swine-origin H1N1 influenza A virus and dental practice: a critical review

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Abstract Since the spring of 2009, there have been a considerable number of infected as well as fatal cases by virologically confirmed swine-origin H1N1 influenza A virus (S-OIV). The virus continues to spread globally. The World Health Organization (WHO) has now raised the level of S-OIV influenza pandemic alert to phase 6 ('the pandemic phase') because of the human-to-human transmission of the virus and the community-level outbreaks worldwide. The WHO also issues its concerns about the global surveillance, the diagnostic capacity for the infection and the pandemic preparedness plan in every country. However, no critical review on S-OIV influenza and dental practice published in the literature exists hitherto. Based on information up to November 2009, the aim of this article was to summarise significant data on this novel virus and a clinical practice guideline for dental professionals.

Keywords H1N1 influenza · Influenza A · Swine flu · Dental practice · Practice guideline

Introduction

On 27 April 2009, the World Health Organization (WHO) reported patients infected by swine-origin H1N1 influenza A virus (S-OIV) in several countries: seven fatal cases in Mexico; 40, six and one virologically confirmed cases in the USA, Canada and Spain, respectively. This new pathogen has spread faster than any previous viruses, resulting in rapid spread worldwide [1, 2]. Until now, although seemingly substantially underreported, over 503,536 confirmed patients and at least 6,260 deaths have been documented (the latest data on 8 November 2009) [3].

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On 11 June 2009, the WHO declared the first pandemic of the 21st century caused by the S-OIV and raised the level of 'pandemic' alert from phase 5 to level 6 ('the pandemic phase'): sustained human-to-human transmission and community-level outbreaks in at least one other country in two or more different WHO regions. The WHO also voices great concern about the global surveillance, the diagnostic capacity for the infection and the pandemic preparedness plan in every country [1, 2, 4].

The paucity of growing information from various experts such as the large number of bulletins, publications, e-mails and websites, is observed. However, there is no critical review on S-OIV influenza and dental practice in the literature thus far. Only a few editorial comments were published in general dental journals [5, 6]. The aim of this article was to review significant data on this novel pathogen and to summarise a clinical practice guideline for dental practitioners.

Search strategy and selection criteria

We searched PubMed/Medline, Embase and Google Scholar using the search terms 'swine influenza' or 'H1N1 influenza'. Papers or articles published up to November 2009, containing relevant information were analysed; some pertinent articles were selected and included in this review. No language restriction was applied.

Review of literature

Virology of novel H1N1 influenza virus

Influenza A viruses (Family *Orthomyxoviridae*, Genus *Influenzavirus A*) are single-stranded, negative-sense RNA viruses, comprising eight genome segments that are enveloped by a lipid bilayer containing haemagglutinin (HA) and neuraminidase (NA) glycoproteins. Both surface proteins are the key antigen targeted by human humoural immunity and are used to subtype the virus: 16 H (H1-H16) and 9 N (N1-N9) subtypes. Thus, theoretically there are 16×9 serologic subtypes. All subtypes are found in aquatic wildfowl; only some in other animals: H1 and H3 in pigs, H3 and H7 in horses, and recently equine H3 subtype in dogs in North America. Six serotypes infect humans: H1, H2, H3, H5, H7 and H9 [7–10].

In 1918, there was the highly contagious influenza outbreak caused by H1N1 influenza virus, and it spread to nearly every world region, commonly known as 'Spanish flu'. This virus remains endemic in pigs to date. Infected and asymptomatic carrier pigs can transmit three swine influenza A viruses: H1N1, H3N2 and H1N2, to other hosts. Their tracheal epithelial cell surface also contains α2,3-galactose- and α2,6-galactose-linked sialic acid receptors for avian (any H, N) and human (H1N1 and H3N2) influenza viruses, respectively. As an intermediate host, porcine natural susceptibility contributes to a host-species jump of viruses and allows a random evolution of new genetic lineages: 'avian-like' and 'human-like' swine lineages in the same cell of the same host. The 'avian/human reassortant' viruses seemed to be involved in the 1957 to 1963 (A/H2N2; 'Asian flu') and 1968 to 1970 (A/H3N2; 'Hong Kong flu') pandemics [1, 2, 4, 7, 9–11].

At times, zoonotic transmission of 'classical' swine H1N1 virus occurs, leading to flu-like illness with a mortality rate of 17%. Human-to-human transmission is rare. However, the vaccine campaign in the USA was terminated because the vaccine caused Guillain-Barré syndrome (risk, 1/100,000) and subsequent deaths [7, 10, 11].

It remains unknown how and where the new virus emerged exactly. The first two infected cases in the USA had no history of swine contact [12]. An evolutionary analysis shows that multiple reassortment of the viral lineages may have occurred between 9.2 and 17.2 years before the current outbreak [2]. Genetically, S-OIV differs greatly from the predecessor swine and human influenza isolates [1]. It is a 'quadruple' reassortant (derived from four lineages). Of the eight genome segments, its NA (N1) and M segments are derived from Eurasian avian-like swine H1N1 lineages. The other 6 RNA segments are from the North American 'triple-reassortant' lineages: HA (H1), NP and NS from 'classical' porcine H1N1 lineage; PB2 and PA from avian lineage; PB1 from seasonal human H3N2 lineage. Movement of live pigs between Eurasia and North America may be the main cause of the multiple reassortment events and subsequent genetic 'mixing-vessel' [1, 2, 4, 8–10, 12]. Roles of each genome segments in viral pathogenicity were fully detailed by other authors [4, 9, 10]. More data need to be collected on multigenic interplay between viral and host factors.

Influenza A's pandemic potential results from the absence of life-long immunity in humans [8]. In case of S-OIV, it may be due to its 'antigenic drift': considerable changes in both HA and NA surface antigens, 27.2% and 18.2% of the amino acid sequence, from prior H1N1 isolates in 2008. The antigenic drift enables the virus to escape the pre-existing antibodies and the 'herd immunity' [11]. Gallaher [11] suggested that penetration of the novel virus into humans seems unsuccessful because its estimated prevalence is far lower than that of an 'ordinary' strain of influenza. Either incrementally adaptive mutations in HA and NA proteins of circulating viruses ('antigenic drift') or further genetic reassortment in animal reservoirs may render the virus better adaptable to human replication and

spread [11]. However, in some countries such as Chile the S-IOV has indeed been replacing the seasonal influenza viruses. It was found to be the dominant strain in March and June 2009 (autumn and winter of the southern hemisphere) [13]. Further investigations on transmissibility and virulence of the S-OIV during the winter, the typical transmission season for influenza, are desirable [7].

Age-stratified epidemiology data suggest that most of the confirmed S-OIV-infected cases in Mexico and the USA are ≤60 years of age. It is probable that intense immune selection pressure from the 'herd immunity' against the viruses occurs in 'some' persons aged > 60 years. This finding suggests that H1N1 viruses circulating in humans before 1950 have the closer homology to classical swine H1N1 viruses and S-OIV than seasonal H1N1 viruses. A possible explanation of this might be that immune response is greatly stimulated after the first exposure to antigens during childhood (the 'original antigenic sin' concept), whereas antigenic cross-reactivity between S-OIV and seasonal H1N1 influenza viruses is uncommon [4, 7, 12, 14].

Clinical aspects of novel H1N1 influenza

The incubation period ranges from 2 to 7 days. The median age of 642 patients in the USA was reportedly 20 years (range, 3 months to 81 years) [10, 12]. Diagnosis of S-OIV influenza is challenging. Similarly to seasonal influenza (with the exception of vomiting and diarrhoea), there is no specific symptom. Common symptoms include fever, cough and sore throat. Headache, fatigue, rhinorrhoea, chill, myalgia, nausea, abdominal pain, diarrhoea, vomiting, shortness of breath and joint pain may be found. Most symptoms are self-limiting [1, 15]. During the initial phase of the pandemic in Mexico and the USA, young age was found to be a risk factor of morbidity and mortality [14–16].

Some evidence suggests that in most cases, the illness is mild, self-resolving and short lived. The virus itself is less virulent than contemporary seasonal influenza viruses. However, a substantial group of patients are at high risk of developing significant complications. This 'mild' pandemic has led to over 503,536 confirmed cases and at least 6,260 deaths in more than 206 countries and overseas territories/communities (data up to 8 November 2009) [3]. Case-fatality rates, albeit probably underestimated, in Mexico are approximately 0.4%, ranging from 0.3% to 1.5%, and seem to be low outside that country (<0.2%). Many deaths result from severe pneumonia with multifocal infiltrates, and rapid progression to severe sepsis with multi-organ system failure with findings such as acute respiratory distress syndrome, fever, leukocytosis or leukopenia, liver impairment, renal failure, rhabdomyolysis, and hypotension [4, 7, 15–17]. Direct injury of respiratory epithelium with a secondary cytokine storm is a possible mechanism of tissue damage. However, severe illness and death occurs even in previously healthy persons that are usually young to middle-aged. Possible causes of death are delayed hospitalisation and delayed initiation of antiviral therapy [16]. Further work is required to investigate the pathogenicity of this virus and the mechanisms by which it causes complications.

Antigen detection testing, either rapid/point-of-care or immunofluorescence, can differentiate between influenza A and B, but not between seasonal (H3 or H1) and the novel H1N1 influenza. The definite diagnosis of S-IOV is based on viral nucleic acid detection in specimens from a nose or throat swab or a combination of both [15]. The WHO recommends using three laboratory confirmation methods: (1) specific reverse-transcriptase-polymerase-chain-reaction testing to distinguish S-OIV from seasonal influenza viruses; (2) the isolation and identification of S-OIV; or (3) the detection of a 4-fold rise of neutralisation or haemagglutination inhibition test for antibodies to S-OIV [7].

In areas without established transmission, the Australian Society for Infectious Diseases and the Swine Influenza Task Force of the Thoracic Society of Australia and New Zealand suggest that anyone with acute febrile respiratory illness: a fever, ≥38 C or a good history, with cough and/or sore throat, be tested for the S-OIV. In endemic regions, testing is advisable only for severely unwell patients or those at risk of complications, or in individuals working with vulnerable populations. Early treatment is recommended whenever feasible [15].

Preventive and therapeutic measures

Two antiviral drugs for influenza A are available on the market: M2 proton channel blockers and neuraminidase inhibitors. M2 proton channel inhibitors effectively block the M2 ion channel. Hence, they inhibit the influx of protons from the acidified endosome into the infected virion during virus entry; this endosomal acidification facilitates the disassembly of the viral structure, allows the RNA to enter the host nucleus, and subsequently initiates a round of viral replication. These agents have no activity against influenza B, almost all A/H3N2 viruses and many human isolates of avian A/H5N1 viruses. Neuraminidase inhibitors interfere with the enzymatic activity of influenza A and B neuraminidase, which is one of three transmembrane proteins coded by the influenza genome. This enzymatic activity is necessary for the release and dispersal of progeny viral particles from the infected cells. Neuraminidase inhibitors are active against influenza A and B viruses, including the avian H5N1 strain [9, 10].

Serine-to-asparagine mutation at amino acid position 31 on the M2 gene of S-OIV demonstrates its resistance to ion channel blockers: amantadine and rimantadine. Instead, this virus responds to the neuraminidase inhibitors: oseltamivir and zanamivir. Although both drugs are well tolerated, oseltamivir is the drug of choice because of its convenient administration route, which is oral [1, 9, 10, 12, 15].

Many factors affect treatment decision: the disease prevalence in the region, a history of contact, characteristics of the illness, presence of established complications, co-morbidities and risk factors, onset of illness, availability of antiviral agents, and the healthcare policies. In seasonal influenza patients, early antiviral therapy (within 36–48 h of symptom onset) mitigates the length of symptoms, antibiotic use, morbidity, and recovery time [10, 15]. Oseltamivir treatment correlates with survival of hospitalised pneumonia patients caused by human influenza A/H3N2, A/H1N1 or B viruses [18].

The updated WHO guidelines suggest antiviral therapy be started within 72 h from the onset of the symptoms in patients with (1) shortness of breath, hypoxia, and fast or laboured breathing in children, which would suggest oxygen impairment or cardiopulmonary insufficiency; (2) altered mental status, unconsciousness, drowsiness, and seizures, which suggest central nervous system complications; (3) evidence of sustained virus replication or invasive secondary bacterial infection; or (4) severe dehydration, expressed as decreased activity, dizziness, decreased urine output, and lethargy [19].

However, mass use of antiviral drugs could potentially lead to selection pressure for antiviral drug resistance. Seasonal H1N1 influenza viruses resistant to oseltamivir have strikingly increased over the past few years. Notably, antiviral-resistant strains may spread rapidly, affecting the pandemic outcomes [9, 20]. As of 22 October 2009, the WHO announced 32 confirmed cases with oseltamivir-resistant S-OIV variants, regardless of immunocompromised status and history of oseltamivir use. Zanamivir is recommended in patients infected with oseltamivir-resistant influenza viruses [21]. Primary influenza pneumonitis is best treated with oseltamivir. Secondary bacterial pneumonia requires appropriate antibiotics; common causative agents include group A streptococcus, *Staphylococcus aureus* and *Streptococcus pneumoniae* [10, 11, 15]. Research on other antiviral drugs such as peramivir, CS-8958, T-705, and monoclonal antibodies to HA proteins, is under way [9]. On 24 October 2009, the US President Barack Obama has declared H1N1 influenza to be a national emergency. Meanwhile, the US Food and Drug Administration (FDA) has authorised emergency use of peramivir, the only intravenous neuraminidase inhibitor, in hospitalised patients with antiviral-resistant S-OIV strains, even though this drug has not been approved for seasonal influenza [22]. Cheng et al. [15] extensively described the treatments on this influenza.

Droplet (up to 1–2 m) and contact spread (patient-to-patient and via fomites) are the principal modes of S-OIV transmission. Small droplet and airborne transmission may occur in a low-humidity environment. Diarrhoea in some cases suggests faecal viral shedding and possibly faecal-oral transmission. Despite lack of strong evidence, all bodily fluids should be considered infective until further data are proven otherwise [10, 12, 15]. Wearing surgical face masks plus frequent hand washing helps prevent the disease transmission amongst household contact when implemented early after symptom onset [23].

Seasonal influenza vaccine protects against seasonal influenza A/H1N1 and A/H3N2 viruses and influenza B viruses, but not S-OIV. 'Antigenic drift' makes seasonal vaccination repeated every 1–3 years [9, 24]. Because seasonal influenza hampers diagnosis of the S-OIV infection, the benefit of differentiating the diseases prioritises the use of this vaccine in high-risk groups: children aged ≤5 years, persons aged ≥60 years, children and adolescents aged ≤18 years who take long-term aspirin and who are at risks for Reye's syndrome after influenza, patients with underlying disease: asthma, cardiorespiratory diseases, diabetes mellitus, renal failure, or morbid obesity, immunocompromised hosts, pregnant women, nursing home residents and healthcare staff [4, 15, 25]. A recent in vitro study suggested the possible existence of pre-existing immunity against this novel virus in general population [26].

The first batches of vaccine against S-OIV have been launched since autumn 2009. In October 2009, four pandemic vaccines were available within Europe, three of which were authorised for use in any European Union countries and the other for use in Hungary. The vaccine strain is mainly based on the initial isolate of influenza A/California/7/2009 (H1N1)v or a reassortment based on the same isolated strain and a more fast-growing influenza A (H1N1) strain (PR8) that is called influenza A/California/7/2009 (H1N1)v-like [25].

Occupational exposure is at a higher risk of the infection; thereby, surveillance programmes should include swine workers and healthcare providers [2, 10]. Apart from patients in at-risk groups, the WHO suggests that healthcare personnel be immunised as a first priority because of greater hazard exposure [25, 27]. However, dividing people into priority groups seems unethical because it breaches the United Nations' Declaration of Human Rights: 'All human beings are born free and equal in dignity and rights '. Due to limitations in vaccine supply worldwide, vaccine distribution requires more considerations [28].

Although a recent survey of US citizens indicates the higher demand for novel H1N1 vaccine exceeding that for

seasonal vaccine, over half of them may not be willing to be immunised. This requires a very aggressive and culturally appropriate public information campaign and strong recommendations from healthcare providers [29]. Many issues on pandemic vaccines remains unclear, including appropriate doses, optimal antigen content in vaccine, duration of immune response, a risk of Guillain-Barré syndrome, and long-term safety data [4, 25].

Guideline for dental practitioners

In May 2009, the Harvard School of Dental Medicine, USA, was closed due to S-OIV infection in dental students [30, 31]. It is unknown how much dental clinical settings are and will be affected by this influenza. Strict adherence to infection control guidelines is therefore essential. However, the guidelines are changeable, depending upon update information. One should follow the websites of health authorities.

In this review, we pursue the recommendations by the California Dental Association (CDA) [32] and the Interim Centers for Disease Control and Prevention (CDC) Guidance for Clinicians and Healthcare Professionals [33]. These guidelines suggest early detection of known or suspected cases with S-OIV infection: fever and influenza-like illness. The ill person should be placed in a private room with the door kept closed. A disposable surgical mask, towel paper and no-touch receptacles must be offered [10, 15, 32–34]. Masking the coughing patient, when tolerated, stops the detection of the virus 20 cm away [35]. Elective dental treatment must be postponed and the patients should be advised to seek appropriate medical care [10, 15, 32–34]. Viral transmission occurs until 7 days after symptoms resolve [10]. If urgent dental care is needed, an airborne infection isolation room with negative-pressure air handling with 6 to 12 air changes per hour is necessary. High-risk aerosol-generating dental procedures require a 'fit-tested' disposable respirator (N95, P2 mask or equivalent), eye protection (goggles or face shield), impervious gown and gloves. This personal protection equipment (PPE) is pivotal to prevent direct skin, conjunctival and inhaling exposure. During PPE removal, self-inoculation should be avoided [10, 15, 32–34].

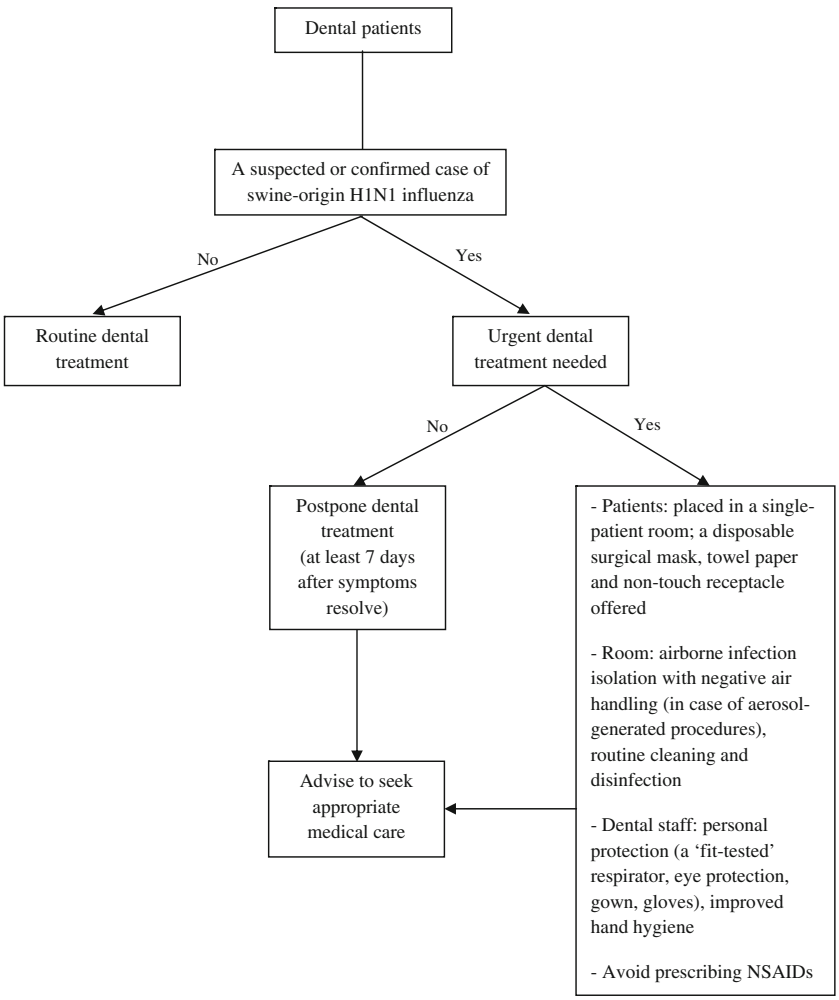

Fig. 1 Dental management of suspected or confirmed cases of swine-origin H1N1 influenza based on the recommendations of the California Dental Association and the US Centers for Disease Control and Prevention

Maintaining an arm's length from other persons whenever feasible is helpful because the virus can survive on inanimate surfaces and is transmitted through direct human contact [10, 11, 32, 33]. Hand washing with non-antimicrobial soap and water, alcohol-based hand rub, or antiseptic handwash after contacting with respiratory secretions and contaminated objects/materials is recommended, along with routine cleansing and disinfection. In areas with established transmission, dental staff should have access to chemoprophylaxis and early treatment if symptoms develop [15, 32, 33].

Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided because they may enhance viral virulence, aggravate symptoms, and subsequent multi-organ failure. However, this requires further confirmation [17, 36]. Antipyretics may risk the patients on decreased immune response and prolonged illness [37].

Good knowledge and attitude does not guarantee strict adherence to infection control practices [38]. The CDC calls for attention of healthcare providers, institutions and organisations to barriers to adherence to its infection control guidelines: (1) a belief that these practices are unnecessary, inconvenient, or disruptive; (2) lack of availability of PPE; (3) inadequate training in infection control; (4) failure to establish effective, systematic approaches to safety of healthcare staff; and (5) failure to recognise patients and activities that warrant specific infection-control practices [34]. We summarises an algorithm for managing dental patients in the era of S-OIV influenza in Fig. 1.

Conclusion

S-OIV is the newly emerging RNA virus, even though it remains unknown where and how it evolved. Genetic mutations, which may results in 'antigenic shift' (major genetic rearrangements between strains, associated with pandemics) and antigenic drifts (more minor genetic variations associated with epidemics), helps the virus escape the human natural immunity. Clinically, the manifestations are not different from those of contemporary human seasonal influenza, requiring particular tests for the definite diagnosis. Neuraminidase inhibitors are effective in most cases. Strict adherence to infection control guidelines is critical to control the disease. Unless it is urgent, dental treatment in 'suspected' or 'confirmed' patients should be deferred to *'at least'* 7 days after symptoms resolve. Close vigilance and early viral therapy for the presumed infection in dental staff are pivotal, especially in areas affected by this novel virus.

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References

1. Naffakh N, van der Werf S (2009) April 2009: an outbreak of swine-origin influenza A (H1N1) virus with evidence for human-to-human transmission. Microbes Infect 11:725–728. doi:10.1016/j.micinf.2009.05.002
2. Smith GJ, Vijaykrishna D, Bahl J, Lycett SJ, Worobey M, Pybus OG et al (2009) Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. Nature 459:1122–1125. doi:10.1038/nature08182
3. The World Health Organization (WHO) (2009) Pandemic (H1N1) — update 74 (revised 13 November 2009). Available at: http://www.who.int/csr/don/2009_11_13/en/index.html. Accessed 20 November 2009
4. Chang LY, Shih SR, Shao PL, Huang DT, Huang LM (2009) Novel Swine-origin Influenza Virus A (H1N1): the first pandemic of the 21st century. J Formos Med Assoc 108:526–532
5. Glick M (2009) Do dentists have a role in fighting the latest H1N1 pandemic? J Am Dent Assoc 140:1072–1074
6. [No authors listed] (2009) Swine flu advice for dentists issued. Br Dent J 206: 511. doi:10.1038/sj.bdj.2009.443
7. Malik Peiris JS, Poon LL, Guan Y (2009) Emergence of a novel swine-origin influenza A virus (S-OIV) H1N1 virus in humans. J Clin Virol 45:169–173. doi:10.1016/j.jcv.2009.06.006
8. Gatherer D (2009) The 2009 H1N1 influenza outbreak in its historical context. J Clin Virol 45:174–178. doi:10.1016/j.jcv.2009.06.004
9. Neumann G, Noda T, Kawaoka Y (2009) Emergence and pandemic potential of swine-origin H1N1 influenza virus. Nature 459:931–939. doi:10.1038/nature08157
10. Michaelis M, Doerr HW, Cinatl J Jr (2009) Novel swine-origin influenza A virus in humans: another pandemic knocking at the door. Med Microbiol Immunol 198:175–183. doi:10.1007/s00430-009-0118-5
11. Gallaher WR (2009) Towards a sane and rational approach to management of Influenza H1N1 2009. Virol J 6:51. doi:10.1186/1743-422X-6-51
12. Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S et al (2009) Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 360:2605–261
13. The World Health Organization (2009) New influenza A (H1N1) virus: Global epidemiological situation, June 2009. Wkly Epidemiol Rec 84: 249-257. Available at http://www.who.int/wer/2009/wer8425.pdf. Accessed 20 November 2009
14. Chowell G, Bertozzi SM, Colchero MA, Lopez-Gatell H, Alpuche-Aranda C, Hernandez M et al (2009) Severe respiratory disease concurrent with the circulation of H1N1 influenza. N Engl J Med 361:674–679
15. Cheng AC, Dwyer DE, Kotsimbos AT, Starr M, Korman TM, Buttery JP et al (2009) Summary of the Australasian Society for Infectious Diseases and the Thoracic Society of Australia and

New Zealand guidelines: Treatment and prevention of H1N1 influenza 09 (human swine influenza) with antiviral agents. Med J Aust 191:142–145
16. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, Hernandez M, Quiñones-Falconi F, Bautista E et al (2009) Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. N Engl J Med 361:680–689
17. Hama R (2009) A/H1N1 flu. NSAIDs and flu. BMJ 338:b2345. doi:10.1136/bmj.b2345
18. Hanshaoworakul W, Simmerman JM, Narueponjirakul U, Sanasuttipun W, Shinde V, Kaewchana S et al (2009) Severe human influenza infections in Thailand: Oseltamivir treatment and risk factors for fatal outcome. PLoS One 4:e6051. doi:10.1371/journal.pone.0006051
19. Lowes R. New Guidelines on H1N1 Influenza Urge Quicker Use of Antivirals. Medscape Medical News. Available at http://www.medscape.com/viewarticle/712255?sssdmh=dm1.555636&src=nldne&uac=138772SY. Accessed 20 November 2009
20. Dharan NJ, Gubareva LV, Meyer JJ, Okomo-Adhiambo M, McClinton RC, Marshall SA et al (2009) Infections with oseltamivir-resistant influenza A(H1N1) virus in the United States. JAMA 301:1034–1041. doi:10.1001/jama.2009.294
21. The World Health Organization (2009) Oseltamivir-resistant pandemic (H1N1) 2009 influenza virus, October 2009. Wkly Epidemiol Rec 84: 453-459. Available at http://www.who.int/wer/2009/wer8444.pdf. Accessed 20 November 2009.
22. Flapan D. Obama Announces H1N1 National Emergency. Medscape Medical News. Available at http://www.medscape.com/viewarticle/711258?sssdmh=dm1.547694&src=nldne&uac=138772SY. Accessed 20 November 2009.
23. Cowling BJ, Chan KH, Fang VJ, Cheng CK, Fung RO, Wai W et al (2009) Facemasks and hand hygiene to prevent influenza transmission in households: a randomized trial. Ann Intern Med 151:437–446
24. Centers for Disease Control and Prevention (CDC) (2009) Serum cross-reactive antibody response to a novel influenza A (H1N1) virus after vaccination with seasonal influenza vaccine. MMWR Morb Mortal Wkly Rep 58:521–524
25. Johansen K, Nicoll A, Ciancio BC, Kramarz P (2009) Pandemic influenza A(H1N1) 2009 vaccines in the European Union. Euro Surveill 14: 19361. Available at: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19361. Accessed 20 November 2009.
26. Greenbaum JA, Kotturi MF, Kim Y, Oseroff C, Vaughan K, Salimi N et al (2009) Pre-existing immunity against swine-origin H1N1 influenza viruses in the general human population. Proc Natl Acad Sci U S A 106:20365–20370. Available at http://www.pnas.org/content/106/48/20365.long.doi:10.1073/pnas.0911580106
27. Zarocostas J (2009) Healthcare workers should get top priority for vaccination against A/H1N1 flu, WHO says BMJ 339:b2877. doi:10.1136/bmj.b2877
28. Peterson M (2009) Do WHO Guidelines on Pandemic Influenza Follow Biomedical Ethics? Science. Available at: http://www.sciencemag.org/cgi/eletters/324/5928/702#12326. Accessed 20 November 2009
29. Maurer J, Harris KM, Parker A, Lurie N (2009) Does receipt of seasonal influenza vaccine predict intention to receive novel H1N1 vaccine: Evidence from a nationally representative survey of U.S. adults. Vaccine 27:5732–5734. doi:10.1016/j.vaccine.2009.07.080
30. Morton CC (2009) Quick Emergency Response Casts Light on Science Of Detection, Prevention and Control. News from Harvard Medical, Dental and Public Health Schools. Available at: http://focus.hms.harvard.edu/2009/051509/flu_central.shtml. Accessed 20 November 2009
31. Flier JS, Donoff B, Rosenthal D (2009) H1N1 Update – Classes to Resume for Medical and HST Students. Message to Longwood Campus, Harvard Medical School. Available at: http://web.med.harvard.edu/sites/RELEASES/html/050409_community_letter.html. Accessed 20 November 2009
32. The California Dental Association (CDA) (2009) H1N1 Flu – Swine Flu Information for California Dental Practices. Available at: http://www.cda.org/popup/h1n1_flu_-_swine_flu_information_for_california_dental_practices. Accessed 20 November 2009
33. Centers for Disease Control and Prevention (CDC) (2009) the Interim CDC Guidance for Clinicians and Healthcare Professionals. Available at: http://www.cdc.gov/h1n1flu/. Accessed 20 November 2009
34. Centers for Disease Control and Prevention (CDC) (2009) Novel influenza A (H1N1) virus infections among healthcare personnel - United States, April-May 2009. MMWR Morb Mortal Wkly Rep 58:641–645
35. Johnson DF, Druce JD, Birch C, Grayson ML (2009) A quantitative assessment of the efficacy of surgical and N95 masks to filter influenza virus in patients with acute influenza infection. Clin Infect Dis 49:275–277. doi:10.1086/600041
36. Herxheimer A, Clarke M, Edwards R, Jefferson T, Loke Y (2009) A/H1N1 flu. Time for case-control studies of NSAIDs and oseltamivir. BMJ 339:b3048. doi:10.1136/bmj.b3048
37. Johnson G (2009) A/H1N1 flu. HPA advice on antipyretics contradicts NICE guideline. BMJ 339:b3050. doi:10.1136/bmj.b3050
38. Apisarnthanarak A, Phattanakeitchai P, Warren DK, Fraser VJ (2008) Impact of knowledge and positive attitudes about avian influenza (H5N1 virus infection) on infection control and influenza vaccination practices of Thai healthcare workers. Infect Control Hosp Epidemiol 29:472–474. doi:10.1086/587495