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### ► To cite this version:

Jean-Francois Rahier, Yazdan Yazdanpanah, Nathalie Viget, Simon P L Travis, Jean-Frédéric Colombel. Systematic review: influenza A (H1N1) virus in patients with inflammatory bowel disease. *Alimentary Pharmacology and Therapeutics*, 2009, 31 (1), pp.5. 10.1111/j.1365-2036.2009.04161.x . hal-00524478

**HAL Id: hal-00524478**

**<https://hal.science/hal-00524478>**

Submitted on 8 Oct 2010

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**Systematic review: influenza A (H1N1) virus in patients  
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Journal:	<i>Alimentary Pharmacology &amp; Therapeutics</i>
Manuscript ID:	APT-0689-2009.R1
Manuscript Type:	Review Article
Date Submitted by the Author:	01-Oct-2009
Complete List of Authors:	Rahier, Jean-Francois; UCL Mont Godinne, Service d'Hépatogastroentérologie Yazdanpanah, Yazdan; Centre Hospitalier Tourcoing, Service Universitaire des Maladies Infectieuses et du Voyageur Viget, Nathalie; Centre Hospitalier Tourcoing, Service Universitaire des Maladies Infectieuses et du Voyageur Travis, Simon; John Radcliffe Hospital, Gastroenterology Colombel, Jean-Frédéric; Centre Hospitalier Universitaire de Lille, Service d'Hépatogastroentérologie
Keywords:	Inflammatory bowel disease < Disease-based, Y keyword = no topic, Z keyword = no topic, Crohn's disease < Disease-based

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4 **Systematic review: influenza A (H1N1) virus in patients with inflammatory bowel disease**  
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## Abstract

**Background:** Infection with influenza A (H1N1)<sub>v</sub> (swine flu) has caused widespread anxiety, among patients who are potentially immunocompromised, such as those being treated for inflammatory bowel disease.

**Aims:** Provide guidance for physicians and their patients on the risk, prevention and management of influenza A (H1N1)<sub>v</sub> infection.

**Methods:** Medline was searched using the following key words: 'swine flu', 'immunosuppression', 'inflammatory bowel disease', 'recommendations', 'immunization', 'vaccination'. The European Centre for Disease Prevention and Control (ECDC), the Centers for Disease Prevention and Control (CDC) and the World Health Organization (WHO) were consulted for recent papers and recommendations regarding immunocompromised patients and influenza A (H1N1)<sub>v</sub> infection.

**Results:** Pandemic influenza A (H1N1) virus predominantly affects young patients. Those who are immunocompromised due to underlying disease or treatment are considered at higher risk of complications from influenza A (H1N1). They should be offered prevention (vaccination, post-exposure prophylaxis), or treatment with antiviral drugs if affected. Pneumococcal infection is a complication of influenza infection, so pneumococcal vaccination appears advisable. Seasonal influenza vaccination is also recommended. Withdrawal of immunosuppressive treatment appears advisable during severe active infection if possible.

**Conclusions:** Pragmatic advice is the best that can be offered in current circumstances, owing to the paucity of evidence. Investigation of the impact of influenza A (H1N1)<sub>v</sub> infection in young people with chronic conditions is needed.

## Introduction

On April 2009, the Centers for Disease Control and Prevention (CDC) identified two cases of human infection with influenza A (H1N1)<sub>v</sub> characterized by a unique combination of gene segments that had not been identified among human influenza A virus [1]. Additional cases were rapidly reported leading the WHO to declare a pandemic phase level 6, indicating widespread human infection. This has caused widespread anxiety, especially among patients who are potentially immunocompromised and symptoms of serious systemic infection may be wrongly attributed to influenza A (H1N1)<sub>v</sub>.

Most cases of influenza A (H1N1)<sub>v</sub> currently seem to have uncomplicated influenza-like illnesses; the most common symptoms are cough and fever. Calculating the case fatality ratio related to influenza A (H1N1)<sub>v</sub> is highly dependent on estimates of the total number of people with the disease, which are not easy to obtain. Nevertheless, based on surveillance data and mathematical modeling, the influenza A (H1N1)<sub>v</sub> case fatality ratio seems to be higher than that of seasonal influenza, although it remains of the same order of magnitude [2, 3]. The severity and deaths associated with seasonal influenza infection result in a large part from secondary complications such as secondary bacterial pneumonia (*Streptococcus pneumoniae* or *Staphylococcus aureus*), primary viral pneumonia, and exacerbation of underlying chronic conditions [4, 5]. Initial observation suggests that children and young adults may be more susceptible to influenza A (H1N1)<sub>v</sub> than are older persons [6]. It is still unclear whether the low incidence in people over 60 years of age is due to a partial immunity from former infections with H1N1 influenza viruses. Although the median age among the persons who died with influenza A (H1N1)<sub>v</sub> is lower than those who die from seasonal influenza, when infection does occur, the percentage of deaths in the elderly seems to be higher than in other age groups [2, 3]. Pregnant women and patients with underlying conditions such as respiratory disease, cardiac disease, diabetes, obesity, or immune suppression are commonly reported in hospitalized cases and are considered at higher risk of complications [2, 6, 7]. Patients with inflammatory bowel disease (IBD) are in large part of younger age and may be immunocompromised due to their treatment. Immunomodulators commonly used in inflammatory bowel disease are corticosteroids, azathioprine, methotrexate, calcineurin inhibitors,

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5 anti-tumor necrosis factor agents or other biologics, all compromising to some extent the patient's  
6 immune response. For this reason, they might be considered as susceptible to and at high-risk from  
7 complications of novel influenza (H1N1) virus infection. In this article, we provide guidance for  
8 physicians on the risk, prevention and management of influenza A (H1N1)v infection in patients with  
9 inflammatory bowel disease. This reflects expert opinions and may complement national guidelines  
10 when available. Medline was searched using the following key words, individually and in  
11 combination: 'swine flu', 'immunosuppression', inflammatory bowel disease', 'recommendations',  
12 'immunization', 'vaccination'. The European Centre for Disease Prevention and Control (ECDC), the  
13 Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) were  
14 consulted for recent papers and recommendations regarding immunocompromised patients and  
15 influenza A (H1N1) virus infection. No definitive national guidelines are available at the time of  
16 writing.

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31 In this particular setting, strategies for care providers to prevent disease occurrence and its  
32 complications in IBD patients rely on general precautions to limit inter-human transmission of the  
33 virus, and the use of a vaccination against influenza A (H1N1)v, the use of pneumococcal  
34 polysaccharide vaccine. Post-exposure antiviral chemoprophylaxis is best implemented in specific  
35 situations and treatment of the influenza A (H1N1)v infection best adapted for patient with  
36 inflammatory bowel disease (Table 1).

#### 37 38 39 40 41 42 43 44 45 46 47 48 **Strategies to prevent influenza A (H1N1)v infection in patients with IBD:**

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51 Personal protective measures for reducing the risk of acquiring or transmitting human influenza do not  
52 differ for IBD patient than for the large public. Measures for self protection are mainly (i) avoid close  
53 contact with sick people, (ii) wash hands frequently and (iii) avoid touching his own eyes, nose or  
54 mouth [8]. Additional details data are available on the European Center for Disease Control website  
55 [http://ecdc.europa.eu/en/healthtopics/Pages/Influenza\\_A\(H1N1\)\\_Outbreak.aspx](http://ecdc.europa.eu/en/healthtopics/Pages/Influenza_A(H1N1)_Outbreak.aspx)  
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4 Prevention of influenza is usually achieved by vaccination. New vaccines directed toward the  
5 influenza A (H1N1)<sub>v</sub> infection are currently being manufactured. Two recent studies have shown  
6 reassuring data regarding the efficacy and safety of these novel vaccine, whether in an MF59-adjuvant  
7 form or not, in young and middle-aged adults [9, 10]. These data are difficult to extrapolate to adults  
8 who have underlying immune suppression, which is the group for whom the influenza A (H1N1)<sub>v</sub>  
9 vaccine is particularly recommended.  
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18 However, data on influenza A (H1N1)<sub>v</sub> vaccination may be extrapolated from the seasonal influenza  
19 vaccine. The efficacy of influenza vaccination depends on the ability of a person's immune system to  
20 respond adequately to vaccine antigen. Immune dysfunction that can potentially compromises vaccine  
21 response and effectiveness. Two studies have, however, shown that immunocompromised patients  
22 with IBD generally have an adequate response rate to influenza vaccination [11, 12]. An adequate  
23 response is observed in patients with rheumatic diseases, except for those on biological therapies,  
24 which may diminish the response to influenza vaccination [13]. Interestingly, vaccination on the day  
25 of anti-TNF administration might facilitate seroconversion [14]. Although influenza vaccination (non-  
26 live vaccine) appears to be safe in the immunocompromised, the lack of safety data on vaccines  
27 against the novel influenza A (H1N1) virus in patients on immunomodulators means that the safety  
28 and efficacy of these vaccines should be continuously monitored.  
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43 Patients with IBD on immunomodulators or biological therapy are best advised to receive the  
44 appropriate vaccine as soon as it is available, following national guidelines on vaccination against  
45 influenza A (H1N1)<sub>v</sub> [15]. Recommendations regarding influenza A (H1N1)<sub>v</sub> vaccination may differ  
46 by country, according to the amount of vaccine available, the type of vaccine used, the particular  
47 epidemiology and practical considerations. The European Medicines Agency (EMA) has very  
48 recently recommended the authorisation of two vaccines (Focetria®, Pandemrix®) for influenza  
49 pandemic (H1N1) 2009. Additional information can be found on the following website:  
50 <http://www.emea.europa.eu/influenza.home.htm> . The US Advisory Committee on Immunization  
51 Practices recently recommended the administration of influenza A (H1N1) 2009 monovalent vaccine  
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4 in patients with immunosuppression caused by medication [16]. Those patients not on  
5 immunomodulators or biological therapy are not believed to be immunocompromised and should be  
6 considered in line with the general population.  
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11 Pandemic influenza A(H1N1)v virus is likely to become the predominant circulating influenza virus as  
12 it has been demonstrated in New Zealand and Australia [7, 17]. As a result, patients with IBD on  
13 immunomodulators or biological therapy are best advised to receive the appropriate vaccine against  
14 influenza A (H1N1)v as soon as it is available. Seasonal influenza vaccine does not protect against  
15 influenza A (H1N1)v infection [17]. However, seasonal influenza vaccination should take place as  
16 usual in immunocompromised patients with IBD [18] because of the potential of co-circulation of  
17 other influenza strains along with A(H1N1)v [17]. Pneumococcal vaccination could reduce the  
18 complication rate from influenza A (H1N1)v infection in high risk groups. Vaccination  
19 recommendations for all patients with IBD include pneumococcal polysaccharide vaccine, with repeat  
20 vaccination at 5 years [19]. Pneumococcal vaccination should be implemented regardless of H1N1  
21 vaccine availability.  
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#### 40 **Post-exposure antiviral chemoprophylaxis**

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42 The currently circulating influenza A (H1N1)v is sensitive to neuraminidase inhibitors: oseltamivir  
43 (Tamiflu®) and zanamivir (Relenza®). Patients with IBD on immunomodulators or biological therapy  
44 who are close contacts of persons with confirmed or probable cases of novel influenza A (H1N1) virus  
45 infection should receive post-exposure antiviral chemoprophylaxis with either oseltamivir (75 mg  
46 daily) or zanamivir (2 inhalations of 5 mg daily). Antiviral chemoprophylaxis should be initiated  
47 within 48 hours after the last known exposure to the novel (H1N1) influenza and continued for 10  
48 days after the last known exposure to novel (H1N1) influenza [20, 21]. The use of neuraminidase  
49 inhibitors during pregnancy must depend on advice from a specialist in infectious diseases. Pre-  
50 exposure antiviral therapy should not be considered in patients with IBD. In practice it may prove  
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4 impractical to deliver appropriately timed post-exposure prophylaxis to the majority of our patients  
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6 with IBD.  
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10 **Strategies for treating suspected or confirmed influenza A (H1N1) $\nu$  infection in patients with**  
11 **IBD**  
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14 In the event of infection, the first measures are to protect family members and other close contact by  
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16 (i) maintaining good respiratory hygiene, (ii) washing hands frequently and (iii) staying at home [8].  
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18 IBD patients who are receiving immunomodulators or biological agents and who meet current case-  
19 definition for confirmed or probable cases novel influenza A (H1N1) virus infection should be treated  
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21 with antiviral drugs: oseltamivir (75mg twice daily), or zanamivir (two inhalations of 5mg twice  
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23 daily) [20], since they are at high risk of complications from influenza. The drugs should be given  
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25 within 48 hours and the earlier the better. However, some data from studies on seasonal influenza  
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27 indicate benefit for hospitalized patients even if treatment is started more than 48 hours after onset.  
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29 Neuraminidase inhibitors have been shown to reduce complications associated with influenza,  
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31 including the need for antibiotics [21, 22]. Although evidence is lacking, it seems sensible temporarily  
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33 to withdraw immunomodulator therapy at least during the symptomatic phase of infection and  
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35 probably until 24 hours after symptoms and signs of fever have resolved. Since patients not on  
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37 immunomodulators are not considered high risk, there is no need for antiviral treatment for  
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39 uncomplicated influenza A (H1N1) $\nu$  infection. On the other hand, a severe or progressive clinical  
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41 presentation should promptly be treated with antiviral therapy, with advice from an infectious  
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43 diseases' specialist, regardless of their IBD or immunocompromising condition [23]. For patients on  
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45 multiple immunomodulators who are considered to be severely immunosuppressed, higher doses of  
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47 oseltamivir may be considered, because of the risk that resistant strains may emerge. Likewise, longer  
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49 treatment duration may be considered, because of longer viral shedding in severely immunosuppressed  
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51 patients [24]. There is no known interaction between neuraminidase inhibitors and drugs used in IBD,  
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53 although methotrexate plasma levels may increase with concomitant use of oseltamivir, since both  
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55 drugs use similar metabolic excretion pathways. In vitro studies, however, suggest a minimal effect  
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5 and no clinical consequence for those on low doses of methotrexate, such as those used in IBD [25]. It  
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7 is particularly important that clinicians do not overlook conventional infection or inflammatory  
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9 conditions that may mimic the symptoms of pandemic flu, because such an oversight may have severe  
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11 consequences.

## 12 13 14 15 16 17 **Conclusion**

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19 As Gastroenterologists, we believe that it is our responsibility to motivate our patients to receive  
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21 immunisation and make sure that those measures are part of our management plan: otherwise our  
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23 patients will be left unprotected. We believe that the opportunity should be taken to vaccinate against  
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25 pneumococcal infection and that seasonal influenza vaccination should be performed as normal for  
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27 those on immunomodulators [18]. In the event of suspected infection with influenza A (H1N1)<sub>v</sub> in an  
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29 immunocompromised person, or clinically serious infection in anyone with inflammatory bowel  
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31 disease, then prompt antiviral treatment is appropriate. The situation is rapidly evolving and  
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33 recommendations may change, but this appears the most practical advice at present.  
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## 41 **Bullet points**

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44 • Patients with IBD and treated with immunomodulators are at high-risk from complications of novel  
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46 influenza (H1N1) virus infection.
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49 • General precautions to limit inter-human transmission of the virus should apply to all IBD patients  
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51 regardless of their immune status.
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54 • Patients with IBD and treated with immunomodulators should receive vaccinations against seasonal  
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56 influenza, H1N1 virus and pneumococcal polysaccharide vaccine. Vaccination in immunocompetent  
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58 patients with IBD should follow general recommendations.  
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- Post-exposure chemoprophylaxis usefully mitigates infection when used at an early stage in immunosuppressed patients.
- Severe or progressive clinical infection with influenza A (H1N1)<sub>v</sub> should be treated with antiviral therapy, with advice from an infectious diseases' specialist, regardless of their IBD or immune status.

For Peer Review

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Table 1

Clinical circumstances	Standard IBD	IBD on immunomodulators <sup>1</sup>
Vaccination against H1N1	in line with general recommendations	Yes
Vaccination against seasonal influenza virus	in line with general recommendations	Yes
Vaccination with Pneumococcal polysaccharide vaccine	Yes <sup>2</sup>	Yes
Asymptomatic patient with IBD, exposed to or in close contact with H1N1 influenza virus	Measures for self-protection	Measures for self-protection Neuraminidase inhibitors (eg oseltamivir 75mg daily) for 10 days
Patient with IBD and symptoms of mild <sup>3</sup> flu	Measures to protect family and close contacts No treatment	Measures to protect family and close contacts Neuraminidase inhibitor (eg oseltamivir 75mg twice daily) for 5 days <sup>4</sup>
Patient with IBD and symptoms of severe flu	Measures to protect family and close contacts Neuraminidase inhibitors (eg oseltamivir 75mg twice daily) for 5 days <sup>4</sup> Take specialist advice	Measures to protect family and close contacts Neuraminidase inhibitors (eg oseltamivir 75mg twice daily) for 5 days <sup>4</sup> Temporarily withdraw IM Take specialist advice

<sup>1</sup> Immunomodulators used in inflammatory bowel disease are corticosteroids, azathioprine, methotrexate, calcineurin inhibitors, anti-tumor necrosis factor agents, or other biologics. For corticosteroids, doses of prednisone  $\geq 20$  mg/d for more than 2 weeks are considered as an immunomodulator.

<sup>2</sup> According to Rahier JF, Ben-Horin S, Chowers Y, et al.; on behalf of the European Crohn's and Colitis Organisation (ECCO). European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *JCC* 2009;3:47-91.

<sup>3</sup> Defined as uncomplicated febrile illness, with systemic symptoms, but no respiratory distress or prostration

<sup>4</sup> In patients on multiple immunomodulators who are considered to be severely immunosuppressed, higher doses of oseltamivir may be considered, because of the risk that resistant strains may emerge. Likewise, longer treatment duration may be considered because of longer viral shedding in severely immunosuppressed patients [24].