



# H1N1 vaccines in a large observational cohort of patients with inflammatory bowel disease treated with immunomodulators and biological therapy

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## See Commentary, p 433

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## ABSTRACT

**Background** Safety data are lacking on influenza vaccination in general and on A (H1N1)v vaccination in particular in patients with inflammatory bowel disease (IBD) receiving immunomodulators and/or biological therapy.

**Aims and methods** The authors conducted a multicentre observational cohort study to evaluate symptoms associated with influenza H1N1 adjuvanted (Pandemrix, Focetria, FluvalP) and non-adjuvanted (Celvapan) vaccines and to assess the risk of flare of IBD after vaccination. Patients with stable IBD treated with immunomodulators and/or biological therapy were recruited from November 2009 until March 2010 in 12 European countries. Harvey—Bradshaw Index and Partial Mayo Score were used to assess disease activity before and 4 weeks after vaccination in Crohn's disease (CD) and ulcerative colitis (UC). Vaccination-related events up to 7 days after vaccination were recorded.

**Results** Of 575 patients enrolled (407 CD, 159 UC and nine indeterminate colitis; 53.9% female; mean age 40.3 years, SD 13.9), local and systemic symptoms were reported by 34.6% and 15.5% of patients, respectively. The most common local and systemic reactions were pain in 32.8% and fatigue in 6.1% of subjects. Local symptoms were more common with adjuvanted (39.3%) than non-adjuvanted (3.9%) vaccines ( $p < 0.0001$ ), whereas rates of systemic symptoms were similar with both types (15.0% vs 18.4%,  $p = 0.44$ ). Among the adjuvanted group, Pandemrix more often induced local reactions than FluvalP and Focetria (51.2% vs 27.6% and 15.4%,  $p < 0.0001$ ). Solicited adverse events were not associated with any patient characteristics, specific immunomodulatory treatment, or biological therapy. Four weeks after vaccination, absence of flare was observed in 377 patients with CD (96.7%) and 151 with UC (95.6%).

**Conclusion** Influenza A (H1N1)v vaccines are well tolerated in patients with IBD. Non-adjuvanted vaccines are associated with fewer local reactions. The risk of IBD flare is probably not increased after H1N1 vaccination.

## INTRODUCTION

In April 2009, the Center for Disease Control and Prevention identified two cases of human infection with influenza A (H1N1)v characterised by a unique combination of gene segments that had

## Significance of this study

### What is already known about this subject?

- ▶ Patients with inflammatory bowel disease (IBD) treated with immunomodulators and biological therapy are a fragile population.
- ▶ Protection against influenza disease is achieved by vaccination in immunocompetent individuals. For immunocompromised patients (the study sample described here), data for clinical protection from infection are lacking. Antibody seroconversion response is variable, with some studies suggesting good immunogenicity and others showing poor response.

### What are the new findings?

- ▶ The types of adverse events after influenza A H1N1 vaccination in patients with IBD are similar to those reported in the immunocompetent population.
- ▶ Solicited adverse events after influenza A H1N1 vaccination are not related to type of IBD or type of immunomodulators and biological therapy.
- ▶ Adjuvanted vaccines induce more local symptoms than non-adjuvanted vaccine in patients with IBD receiving immunomodulatory and biological therapy.
- ▶ In a very large majority of patients, adjuvanted and non-adjuvanted influenza vaccines do not affect IBD activity.

### How might it impact on clinical practice in the foreseeable future?

- ▶ This study brings new evidence on the good safety profiles of adjuvanted and non-adjuvanted influenza vaccines in the immunocompromised IBD population and indicates that such vaccines are unlikely to induce flare up in patients with IBD. It is therefore a very important message in case of future pandemics.

not been identified in human influenza A virus.<sup>1</sup> Additional cases were rapidly reported, leading WHO to declare a pandemic phase level 6, indicating widespread human infection. This caused

anxiety, especially among physicians and patients who were potentially immunocompromised. Prevention of influenza is usually achieved by vaccination, and new vaccines directed towards the influenza A (H1N1)v infection were manufactured. Two large studies have produced reassuring data on the efficacy and safety of these novel vaccines, whether in an MF59-adjuvant form or not, in young and middle-aged adults.<sup>2,3</sup> These data are difficult to extrapolate to other categories of people, particularly adults who have underlying immune suppression, which is the group for whom the influenza A (H1N1)v vaccine is particularly recommended. Patients with inflammatory bowel disease (IBD) belong to a younger population, are affected with a chronic immune-mediated inflammatory disorder, and are immunocompromised to some extent when immunomodulators such as corticosteroids, methotrexate, thiopurines and anti-tumour necrosis factor agents are used. Because of this immunosuppression, national and international recommendations and expert advice have emphasised the need to vaccinate patients with IBD and immunocompromised conditions against influenza infection.<sup>4</sup> However, data on the global safety and efficacy of adjuvanted and non-adjuvanted vaccines are lacking in patients with IBD.

We conducted a European multicentre prospective study to (i) evaluate unsolicited and solicited local and systemic symptoms associated with influenza H1N1 vaccination in patients with IBD receiving immunomodulatory and/or biological therapy, (ii) compare rates and types of unsolicited and solicited local and systemic symptoms in adjuvanted and non-adjuvanted H1N1vaccines, (iii) assess the risk of flare of IBD following H1N1 vaccination, and (iv) search for factors associated with increased adverse events or disease flare.

## METHODS

### Study design

We conducted a multicentre, prospective cohort study from November 2009 through March 2010 in 12 European countries. Patients with IBD were recruited consecutively during outpatient visits in 24 academic and non-academic IBD centres. They were eligible if they had a stable inflammatory disease at the time of the visit (left to the physician discretion), they were treated with one or more immunomodulator and/or biological therapy, and a single- or two-dose vaccination for H1N1 virus was planned according to national recommendations. A stable disease was defined as one without signs of activity (biological, endoscopic or clinical) and not requiring any treatment modification for the IBD. The only exclusion criteria were an active inflammatory disease (left to the physician discretion). The type of vaccine was decided by the national health authorities. The vaccine was administered by intramuscular injection according to the manufacturer's recommendations either by the general practitioner or in a government vaccination centre. Patients who had received the H1N1 vaccine before the outpatient visit were not included. Validated clinical activity indexes—Harvey–Bradshaw Index (HBI)<sup>5</sup> and Partial Mayo Score (PMS)<sup>6</sup>—were used for Crohn's disease (CD) and ulcerative colitis (UC), respectively, to assess disease activity (boxes 1 and 2). Data from each patient were collected using a standardised questionnaire. During the outpatient visit and before vaccination, all patients were scored. Four weeks after the last dose of H1N1vaccine, patients were contacted by phone to assess the IBD clinical activity index and the presence of unsolicited and solicited local (pain, redness, warmth, swelling) and systemic (shivering, fever >38°C, unusual fatigue, malaise, headache, muscle pain, arthralgia, use of pain killers) symptoms occurring within 7 days

### Box 1 Harvey–Bradshaw Index, a simple index of Crohn's disease activity

- A. General well-being:
  - 0 = very well
  - 1 = slightly below par
  - 2 = poor
  - 3 = very poor
  - 4 = terrible
- B. Abdominal pain:
  - 0 = none
  - 1 = mild
  - 2 = moderate
  - 3 = severe
- C. Number of liquid stools per day:
- D. Abdominal mass:
  - 0 = none
  - 1 = dubious
  - 2 = definite
  - 3 = definite and tender
- E. Complications: (score 1 per item)
  - Arthralgia
  - Uveitis
  - Erythema nodosum
  - Aphthous ulcers
  - Pyoderma gangrenosum
  - Anal fissure
  - New fistula, abscess

of vaccination. Symptoms were considered to be present or absent. As in clinical trials,<sup>2</sup> unsolicited and solicited events were considered vaccine-related if occurring within 7 days of

### Box 2 Partial Mayo Score, a scoring system for assessment of ulcerative colitis activity

- Stool frequency\*
  - 0 = normal number of stools for this patient
  - 1 = 1–2 stools more than normal
  - 2 = 3–4 stools more than normal
  - 3 = 5 or more stools than normal
- Rectal bleeding†
  - 0 = no blood seen
  - 1 = streaks of blood with stool less than half the time
  - 2 = obvious blood with stool most of the time
  - 3 = blood alone passed
- Physician's global assessment‡
  - 0 = normal
  - 1 = mild disease
  - 2 = moderate disease
  - 3 = severe disease

\*Each patient served as his or her own control to establish the degree of abnormality of the stool frequency.

†The daily bleeding score represented the most severe bleeding of the day.

‡The physician's global assessment acknowledged the three other criteria, the patient's daily record of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

vaccination. Adverse reactions were defined as any reaction that persisted beyond 7 days after vaccination. Serious adverse reactions were defined as any reaction that necessitated hospitalisation. Approval for the study protocol was obtained from the central and local ethics committees, and the study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each subject. The study was scientifically supported by the European Crohn's and Colitis Organisation (ECCO).

### Vaccines

Four vaccines directed against the 2009 H1N1 virus were used in the study. All vaccines were non-live and licensed in the European Union at the time of the pandemic. Three vaccines were adjuvanted (Pandemrix, Focetria and FluvalP) and one was non-adjuvanted (Celvapan). According to manufacturers' and national recommendations, either a single injection or two injections were administered to the patients. The composition of the vaccines differed as follows:

**Pandemrix:** one dose (0.5 ml) contains split influenza virus, inactivated, containing 3.75 µg antigen equivalent to A/California/7/2009 (H1N1)v-like strain (X-179A); AS03 adjuvant composed of squalene (10.69 mg), DL- $\alpha$ -tocopherol (11.86 mg) and polysorbate 80 (4.86 mg); 5 µg thiomersal (excipient).

**Focetria:** one dose (0.5 ml) contains 7.5 µg influenza virus surface antigens of strain A/California/7/2009 (H1N1)v-like strain (X-181); adjuvant MF59C.1 containing squalene 9.75 mg, polysorbate 80 1.175 mg and sorbitan trioleate 1.175 mg.

**FluvalP:** one dose (0.5 ml) contains 6 µg whole virion, reassortant A/California/7/2009 (H1N1)v-like strain and adjuvant aluminium phosphate gel.

**Celvapan:** one dose (0.5 ml) contains whole virion influenza vaccine, inactivated, containing 7.5 µg antigen of pandemic strain A/California/07/2009 (H1N1)v.

### Patient characteristics, side effects and disease activity

Clinical data included age, sex, pregnancy, disease duration, IBD phenotype according to the Montreal classification,<sup>7</sup> type and dosage of the immunomodulator and biological therapy, unsolicited and solicited local and systemic symptoms. A solicited adverse record is derived from organised data collection systems, whereas an unsolicited adverse event is any adverse event spontaneously reported or reported after questioning. Combined therapy was defined as the concomitant use of two or more drugs (immunomodulators and/or biological therapy). All self-reported reactions were recorded independently of their severity. Number of bowel movements a day and onset of diarrhoea or bloody diarrhoea within 7 days of vaccination were recorded. Disease activity at baseline (before vaccination) and 4 weeks after vaccination was assessed by the HBI and PMS in CD and UC patients, respectively. Absence of flare was defined as either decreased, unchanged or increased (by a maximum of 2 points) clinical activity index score. For both UC and CD patients, an increase of 3 points or more observed 4 weeks after vaccination was considered to be a clinical flare according to the literature.<sup>8–11</sup> Additional vaccinations with seasonal influenza vaccine and pneumococcal polysaccharide vaccine were recorded. Dates of all vaccinations and events were noted.

### Statistical analysis

Patients with incomplete data were not included in the analysis. All statistical analysis was performed using SAS software V.9.1. Continuous data are expressed as mean (SD) or median (IQR) when appropriate. Qualitative data are expressed as frequency

and percentage.  $p < 0.05$  was considered significant. To study the relation between qualitative variables,  $\chi^2$  test or Fisher exact test was performed. The difference in a continuous variable according to a binary variable was studied using the Student *t* test. Variables with  $p < 0.2$  were introduced into a stepwise multivariate logistic regression (significance level for entering effects, 0.2; significance level for removing effects, 0.05). The stability of the model was assessed by a bootstrap method.<sup>12</sup> The bootstrap resampling method was based on 500 replicates of the initial dataset. Logistic multivariate regression with stepwise selection at the 0.2 level was performed on each of these replicates. The inclusion of the variable in the final model was confirmed if this candidate variable was selected in at least 80% of these 500 analyses.

### RESULTS

Demographic, clinical characteristics and immunomodulatory treatments of patients are given in table 1. Of 733 patients who were eligible and signed an informed consent, 124 decided not to receive the vaccine. A total of 609 subjects who were administered the H1N1 vaccines were enrolled in the study, but complete data were available for 575 subjects. An adjuvanted vaccine was given to 499 patients, and a non-adjuvanted vaccine to 76. A second-dose H1N1 vaccine was given to 212 patients (66.0% and 34.0% in the adjuvanted and non-adjuvanted group, respectively) separated by a median of 23 days. The mean age of the subjects was 40.3 years (SD 13.9); 53.9% were women, and six were pregnant. Of the 575 subjects, 407 had CD, 159 had UC, and nine had indeterminate colitis. Median disease duration was 9 years for CD (IQR 4.2–15), 7 years for UC (IQR 4–13), and 3.5 year for indeterminate colitis (IQR 3–5). All patients were treated with one or more immunomodulators or biological therapy. Of the 575 patients, 41.7% were given monotherapy and 58.3% received combined therapy. Seasonal influenza vaccine was given additionally to 328 patients (57.0%), 68.8% of them ( $n=196$ ) before the H1N1 vaccine (median 28 days; IQR 15–42.5) and 23.1% ( $n=66$ ) on the same day; 8.1% received seasonal vaccination after the H1N1 vaccine (median 25 days; IQR 11–31). Pneumococcal vaccine was administered in 12.2% ( $n=70$ ) of all patients. The baseline characteristics were similar among patients with adjuvanted and non-adjuvanted vaccines except for the use of infliximab, the number of H1N1 injections, the presence of perianal disease, and the use of pneumococcal vaccine (table 1).

### Safety analysis

#### Solicited local and systemic reactions

Data from all 575 patients were included in safety analyses. Solicited local and systemic reactions during the first 7 days after the first dose of H1N1 vaccine are shown in table 2. Local and systemic solicited reactions appeared mostly on the day after vaccination, and disappeared within 48–72 h. No unsolicited events, adverse reactions or serious adverse reactions were reported.

The most common local reaction after any type of vaccine was pain at the injection site, reported by 189 (32.8%) subjects. Swelling, redness and warmth was present in 35 (6.1%), 30 (5.2%) and 10 (1.7%) patients, respectively. With the same subtype of vaccine, patients with CD and UC had similar rates of local symptoms. No severe local reactions were reported. Pain was more common after injection of the adjuvanted vaccine than with non-adjuvanted vaccine (37.3% vs 3.9%,  $p < 0.0001$ ). Among the adjuvanted group, Pandemrix induced local reactions more often than FluvalP and than Focetria (51.2% vs 27.6% and

**Table 1** Demographic, clinical characteristics and immunomodulatory treatments of 575 patients according to H1N1 vaccine group

	All patients (N=575)	Adjuvanted vaccines (N=499)	Non-adjuvanted vaccine (N=76)	p Value†
<b>Demographic characteristics</b>				
Sex				<b>0.331</b>
Male, n (%)	263 (46.1)	224 (45.3)	39 (51.3)	
Age (years), mean (SD)	<b>40.3 (14.0)</b>	40.4 (14.1)	40.1 (13.1)	<b>0.892</b>
Pregnancy, n (%)	<b>6 (1.0)</b>	6 (1.2)	0 (0)	<b>1</b>
<b>Clinical characteristics</b>				
IBD phenotype*				
CD, n (%)	<b>407 (70.8)</b>	348 (69.7)	59 (77.6)	
UC, n (%)	<b>159 (27.6)</b>	142 (28.5)	17 (22.4)	<b>0.242</b>
IC, n (%)	<b>9 (1.6)</b>	9 (1.8)	0 (0)	
Disease duration (years), median (IQR)	<b>8 (4;15)</b>	8 (4;15)	9.5 (4;16)	<b>0.576</b>
Age of diagnosis				
A1	<b>53 (13.2)</b>	46 (13.3)	7 (12.0)	
A2	<b>277 (69.1)</b>	241 (69.4)	36 (66.7)	<b>0.858</b>
A3	<b>71 (17.7)</b>	60 (17.3)	11 (20.3)	
Disease location				
L1	<b>118 (30.0)</b>	101 (29.4)	17 (33.3)	
L2	<b>99 (25.2)</b>	84 (24.5)	15 (29.4)	<b>0.404</b>
L3	<b>176 (44.8)</b>	158 (46.1)	18 (35.3)	
L4	<b>22 (5.5)</b>	16 (4.7)	6 (11.1)	<b>0.099</b>
Disease behaviour				
B1	<b>180 (48.0)</b>	152 (47.5)	28 (50.9)	
B2	<b>107 (28.5)</b>	91 (28.4)	16 (29.1)	<b>0.798</b>
B3	<b>88 (23.5)</b>	77 (24.1)	11 (20.0)	
p+	<b>102 (25.6)</b>	95 (27.5)	7 (13.0)	<b>0.022</b>
Extent of UC				
E1	<b>15 (10.1)</b>	13 (9.7)	2 (13.3)	
E2	<b>53 (35.6)</b>	48 (35.8)	5 (33.3)	<b>0.903</b>
E3	<b>81 (54.3)</b>	73 (54.5)	8 (53.4)	
<b>Immunomodulatory treatments</b>				
Corticosteroids, n (%)	<b>65 (11.3)</b>	52 (10.4)	13 (17.1)	<b>0.086</b>
Azathioprine/6MP, n (%)	<b>319 (55.5)</b>	274 (54.9)	45 (59.2)	<b>0.482</b>
Methotrexate, n (%)	<b>39 (6.8)</b>	36 (7.2)	3 (3.9)	<b>0.289</b>
Anti-TNF therapies, n (%)	<b>280 (48.7)</b>	251 (50.3)	29 (38.2)	<b>0.048</b>
Infliximab, n (%)	<b>171 (29.7)</b>	157 (31.5)	14 (18.4)	<b>0.02</b>
Adalimumab, n (%)	<b>98 (17)</b>	84 (16.8)	14 (18.4)	<b>0.732</b>
Certolizumab, n (%)	<b>11 (1.9)</b>	9 (1.8)	2 (2.6)	<b>0.646</b>
Calcineurin inhibitors, n (%)	<b>3 (0.5)</b>	3 (0.6)	0 (0)	<b>1</b>
Others, n (%)	<b>13 (2.3)</b>	8 (1.6)	5 (6.6)	<b>0.019</b>
Monotherapy, n (%)	<b>240 (41.7)</b>	205 (41.1)	35 (46.1)	<b>0.413</b>
<b>Receipt of additional vaccines</b>				
H1N1 booster (2nd injection), n (%)	<b>212 (36.9)</b>	140 (28.1)	72 (94.7)	<b>0.001</b>
Seasonal influenza vaccine, n (%)	<b>328 (57)</b>	291 (58.3)	37 (48.7)	<b>0.114</b>
Pneumococcal vaccine, n (%)	<b>70 (12.2)</b>	68 (13.6)	2 (2.6)	<b>0.006</b>

Adjuvanted vaccines are Pandemrix, Focetria and FluvaxP. Non-adjuvanted vaccine is Celvapan.

\*According to Montreal classification.

†Depicts difference between adjuvanted vaccines and non-adjuvanted vaccine.

CD, Crohn's disease; IBD, inflammatory bowel disease; IC, indeterminate colitis; TNF, tumour necrosis factor; UC, ulcerative colitis; 6-MP, 6 mercaptopurine.

15.4%,  $p < 0.0001$ ). Patients with local reactions were younger than patients without (mean age 38.7 (SD 13.6) vs 41.2 (SD 14.1),  $p = 0.039$ ). Local symptoms were observed in 36.7% of patients aged below 50 years old and in 28.2% of patients above 50 years ( $p = 0.06$ ). Administration of seasonal influenza vaccine did not influence the rate of local symptoms due to H1N1 vaccine (data not shown). Patients who received seasonal vaccine and H1N1 vaccine on the same day tended to experience more local symptoms than patients who received separated

**Table 2** Solicited local and systemic adverse effects within 7 days of receipt of first dose of adjuvanted or non-adjuvanted vaccines

Effect	Adjuvanted vaccine			Non-adjuvanted vaccine
	Pandemrix (AS03) (N=295)	Focetria (MF59) (N=175)	FluvalP (aluminium phosphate) (N=29)	Celvapan (N=76)
<b>Local reaction</b>				
Any reaction, n (%)	160 (54.2)	28 (16.0)	8 (27.6)	3 (3.9)
Pain, n (%)	151 (51.2)	27 (15.4)	8 (27.6)	3 (3.9)
Redness, n (%)	26 (8.8)	4 (2.3)	0 (0)	0 (0)
Warmth, n (%)	10 (3.4)	0 (0)	0 (0)	0 (0)
Swelling, n (%)	33 (11.2)	2 (1.1)	0 (0)	0 (0)
<b>Systemic reaction</b>				
Any reaction, n (%)	64 (21.7)	11 (6.3)	0 (0)	14 (18.4)
Shivering, n (%)	3 (1.0)	1 (0.6)	0 (0)	0 (0)
Fever $\geq 38^\circ\text{C}$ , n (%)	16 (5.4)	2 (1.1)	0 (0)	4 (5.3)
Unusual fatigue, n (%)	24 (8.1)	4 (2.3)	0 (0)	7 (9.2)
Malaise, n (%)	19 (6.4)	1 (0.6)	0 (0)	5 (6.6)
Headache, n (%)	17 (5.8)	3 (1.7)	0 (0)	1 (1.3)
Muscle pain, n (%)	15 (5.1)	3 (1.7)	0 (0)	0 (0)
Arthralgia, n (%)	5 (1.7)	1 (0.6)	0 (0)	1 (1.3)
Use of pain killers, n (%)	16 (5.4)	0 (0)	0 (0)	1 (1.3)
<b>Increased bowel movements per day, diarrhoea and/or bloody diarrhoea</b>				
Any IBD, n (%)	10 (3.4)	5 (2.9)	0 (0)	7 (9.2)
Crohn's disease, n	8	3	0	5
Ulcerative colitis, n	2	2	0	2
Indeterminate colitis, n	0	0	0	0

IBD, inflammatory bowel disease.

injections (45.5% vs 37.0%,  $p = 0.22$ ). In multivariate analysis, after bootstrap resampling, the type of vaccine was the only factor related to the rate of local solicited reactions.

The most common systemic reaction was fatigue, reported by 35 (6.1%) patients. No significant differences in the rate of systemic reaction were found between adjuvanted and non-adjuvanted vaccines, although they were more common in the Pandemrix group (21.7% vs 18.4%). A total of 17 (3.0%) subjects reported use of pain killers. Twenty-two subjects (3.8%) reported body temperature  $> 38^\circ\text{C}$ . No severe adverse side effects were noted. With the same subtype of vaccine, patients with CD and UC had similar rates of systemic symptoms except fatigue, which was more common in CD patients vaccinated with Pandemrix (10.2% vs 1.6%,  $p = 0.031$ ). Administration of seasonal influenza vaccine at any time did not influence the rate of systemic symptoms due to H1N1 vaccine (data not shown). No association was found between rate of systemic symptoms and age ( $p = 0.477$ ).

Rates of any local or systemic solicited adverse events were not associated with any specific immunomodulatory treatment or biological therapy (data not shown). Moreover, there was no difference in the rates of local (37.2% vs 33.6%,  $p = 0.38$ ) or systemic (18.3% vs 14.4%,  $p = 0.67$ ) reactions in patients receiving monotherapy or combined therapy.

#### Effect of vaccination on IBD activity

Only 3.9% of patients (16 CD and six UC) had an increase in daily bowel movements and increased diarrhoea or bloody stools during the first week after H1N1 vaccination. The reaction lasted for a median of 5 days and resolved spontaneously, except in one patient, who needed to increase corticosteroid dosage, and another, who was started on budesonide in addition to methotrexate. This phenomenon was observed with all types of

vaccine except FluvallP, and was more common with Celvapan than with adjuvanted vaccines (9.2% vs 3.0%,  $p=0.018$ ). Of the 15 patients who received the adjuvanted vaccines, nine had symptoms after the first dose and six after the second dose, whereas all seven patients vaccinated with Celvapan, the non-adjuvanted vaccine, had symptoms after the first dose. Interestingly, six of these patients received a second dose of Celvapan and tolerated the second injection well. Immunomodulatory treatments or biological therapy did not influence the occurrence of such adverse reaction. CD and UC patients were similarly affected (3.9% vs 3.8%,  $p=0.93$ ). Of note, occurrence of these symptoms was independent of the age of patients.

Data on follow-up disease activity were available for 554 patients and are given in table 3. Patients were scored at baseline and 4 weeks (median 31 days; IQR 28–37) after the last administration of H1N1 vaccine. The median disease activity score at baseline was 1 (IQR 0–3) and 1 (IQR 0–2) for CD and UC, respectively. Thirty-four CD patients (8.7%) had a HBI score above 5 points, and 22 UC patients (13.9%) had a PMS above 3 points. Four weeks after the last vaccination, absence of flare was observed in 377 patients with CD (96.7%) and 151 with UC (95.6%). Thirteen CD patients (3.3%) had a median rise of 5 (IQR 4–7) points, and seven UC (4.4%) patients had a median rise of 3 (IQR 3–5) points. Evolution of disease activity in patients with slightly higher scores at baseline was similar to those with the lowest score (data not shown). Increase in disease activity was not related to type of vaccine ( $p=0.33$ ) or type of IBD ( $p=0.20$ ).

Of the 22 patients who experienced increased daily bowel movements, diarrhoea or bloody diarrhoea during the first week after vaccination, three of the 19 for whom data were available (15.8%) had an increase of 3 or more points in their disease activity score 4 weeks after vaccination. UC patients were more likely than CD patients to keep an increased disease activity (one CD and two UC).

**DISCUSSION**

During last winter, the availability of vaccines against influenza H1N1v infection across Europe was variable. Most European countries used the adjuvanted forms of the vaccine, with composition and type of adjuvants varying from one vaccine to another. The use of adjuvanted and non-adjuvanted influenza vaccines in general had never been investigated in a large cohort of patients with IBD. The number of subjects included in the study allowed us to estimate the frequency of local and systemic reactions with good precision. The safety and tolerability profiles of adjuvanted and non-adjuvanted influenza vaccines were favourable in this large cohort of patients. In our study, more than half of patients with IBD additionally received the seasonal influenza vaccine according to the European recom-

mendations at the time of the pandemic. However, we observed a very low rate of pneumococcal vaccination despite recommendations and the well-known pneumococcal pneumonia complications that occur after influenza infection. Our study may underestimate the true percentage of pneumococcal vaccination, as some patients may have received this vaccine a few years before the study.

The side effect profile of H1N1 vaccines in immunocompromised patients with IBD, particularly the type of solicited adverse events, is consistent with previous reports in the immunocompetent population.<sup>2</sup> The most common local symptom observed with all types of vaccine was pain at the injection site, as observed with other studies in immunocompetent subjects.<sup>2 3 13</sup> Other local symptoms were otherwise rare. Systemic symptoms such as unusual fatigue, myalgia, headache and malaise were found similarly to previous reports in the immunocompetent population, although large variations exist and correlate mostly with the type of vaccine. This indicates that the reactions seen in patients with IBD are similar to those expected in the general population and are not influenced by either the inflammatory intestinal disease itself or any immunomodulatory treatment or biological therapy. However, direct comparison of the tolerance between immunocompetent and immunocompromised patients is not easy. We did not observe any association between any immunomodulatory treatment or biological therapy and the rate of local or systemic symptoms. As expected, administration of adjuvanted vaccines was associated with an increased incidence of solicited local reactions, which were all transient, as classically reported by previous studies.<sup>14–17</sup> In multivariate analysis, only the type of vaccine correlated with rate of local symptoms. Surprisingly, we observed important variations in terms of solicited local reactions within the adjuvanted group. Pandemrix, Focetria and FluvallP differ in composition in terms of viral strain doses and the type of adjuvant used. This may account for these differences. We found, like others,<sup>13</sup> that administration of seasonal influenza on the same day as the H1N1 vaccine led to more local symptoms. Systemic reactions were observed similarly in patients receiving adjuvanted or non-adjuvanted vaccines, although headache, arthralgia, muscle pain and use of pain killers were more common with Pandemrix than with non-adjuvanted vaccine. In trials comparing systemic symptoms in non-adjuvanted and MF59-adjuvanted vaccines, no significant difference in frequency or severity was observed.<sup>2</sup> In our study, systemic reactions were observed in 89 of 575 patients (15.5%). Observed rates of systemic symptoms were similar with adjuvanted and non-adjuvanted vaccines (15.0% vs 18.4%). The 95% CI for the difference was –12% to 6%, and therefore our trial may not have enough power to highlight differences between the adjuvanted and non-adjuvanted group. Gastrointestinal symptoms occurring within 7 days of vaccination were much more common with Celvapan than with adjuvanted vaccines. The European Medicines Agency indicated recently that gastrointestinal symptoms such as nausea, diarrhoea and abdominal pain were common ( $\geq 1/100$  to  $< 1/10$ ) with Celvapan and uncommon ( $\geq 1/1000$  to  $< 1/100$ ) with Pandemrix or Focetria in non-IBD immunocompetent patients.<sup>18</sup> These symptoms, also observed in our cohort, may therefore not be related to IBD but to the vaccine itself.

Regular concerns, particularly in patients with immune-mediated inflammatory disease (IMID), arise around adjuvanted vaccines despite numerous data showing a good safety profile.<sup>19</sup> Part of clinicians' concerns about the safety of vaccination in IMID originated from a number of case reports suggesting an effect of vaccination on IMID onset or course.<sup>20</sup> These publications led to a belief among some clinicians that vaccination

**Table 3** Evolution of clinical inflammatory bowel disease (IBD) score 4 weeks after vaccination

IBD clinical score activity	CD (N=390)	UC (N=158)	IC (N=6)
HBI at baseline, median (IQR)	1 (0;3)	–	–
PMS at baseline, median (IQR)	–	1 (0;2)	1 (0;2)
Absence of flare, n (%)	377 (96.7)	151 (95.6)	5 (83.3)
Rise of 3 points, n (%)	1 (0.2)	4 (2.5)	0 (0)
Rise of 4 points, n (%)	3 (0.8)	1 (0.6)	1 (16.7)
Rise of $\geq 4$ points, n (%)	9 (2.3)	2 (1.3)	0 (0)

CD, Crohn's disease; HBI, Harvey–Bradshaw Index; IC, indeterminate colitis; PMS, Partial Mayo Score; UC, ulcerative colitis.

might trigger a flare of the underlying IMID. Live vaccines are generally contraindicated in immunocompromised patients, so reports dealing with their effect on disease activity are rare. In a relatively small retrospective study, measles–mumps–rubella booster vaccination in children with juvenile idiopathic arthritis appeared safe, as vaccination did not induce infection, nor did it significantly increase disease activity or medication use.<sup>21 22</sup> For non-live vaccines, substantial literature data support the conclusion that immunisation of IMID patients does not increase clinical or laboratory parameters of disease activity.<sup>23</sup> Most of this evidence comes from medium-sized controlled trials in which disease activity was mostly assessed from general clinical symptoms and pain scores. Some studies also used standardised clinical disease activity scores such as the Systemic Lupus Erythematosus Disease Activity Index<sup>24</sup> and the Disease Activity Score in rheumatoid arthritis.<sup>25</sup> We provide new information on the effect of adjuvanted and non-adjuvanted influenza vaccines on the IBD activity. Two studies have shown the effect of influenza vaccination in 51 and 146 paediatric and young adult patients with IBD. They did not show modification of disease activity after administration of trivalent influenza non-adjuvanted vaccine.<sup>26 27</sup> Although imperfect, clinical scores such as HBI and PMS are useful tools in clinical trials. In our cohort, before vaccination, all patients had a stable inflammatory disease. This was left to the physician discretion, but was also well reflected by the low HBI and PMS values obtained at baseline. In CD, a decrease of 3 points in the HBI score is recognised as response to therapy.<sup>8</sup> In previous studies, it has been shown that the PMS performed as well as the full Mayo Score in identifying clinical response.<sup>9</sup> However, criteria for defining a response in UC is less clear, as authors identify a change of 2, 2.5 or 3 points in the PMS as a significant response.<sup>9 11</sup> Hence, in our study, an increase of 3 points for either HBI or PMS was considered a significant flare. With these criteria, only a minority of patients had an increased score 4 weeks after vaccination. In these patients, the flare up was not related to either type of IBD or type of vaccine administered. If an increase of 2 points in the PMS is considered as clinically significant, the percentage of UC patients with a stable disease 4 weeks after H1N1 vaccination falls slightly from 95.6% to 93.7%. Therefore, no matter the criteria used to define clinical flare in UC, in the vast majority of patients with UC, disease activity appears to remain stable after vaccination. Taken together, our results indicate that the risk/benefit ratio of influenza vaccination in patients with IBD treated with immunomodulators and biological therapy is probably highly in favour of a vaccination strategy.

There are some limitations of this study. The main one concerns the assessment of HBI and PMS by phone 4 weeks after the vaccine. Physical confirmation was not possible, but we believe that the effect of this limitation is low. Indeed, when a large modification of the physical examination occurs, it is often accompanied by new symptoms, and we assume that significant modification had therefore been reported. However, use of phone records may lead to underestimation or overestimation of these clinical scores. The second limitation concerns the confounding bias (unrelated to vaccine administration) regarding an increased score 4 weeks after receipt of the vaccine. We cannot rule out the possibility of drugs, non-steroidal anti-inflammatory drugs, viral or bacterial digestive infection, or stress being responsible for increasing the score 4 weeks after vaccination.

In conclusion, our results support the good safety profile of adjuvanted and non-adjuvanted influenza vaccine in patients with IBD and bring new evidence that use of adjuvanted vaccine

has few or no effects on IBD activity. Nevertheless, definitive conclusions can only be derived from well-conducted, randomised, placebo controlled trials or large registries. However, this study provides evidence that adjuvanted and non-adjuvanted influenza vaccines are unlikely to induce re-activation in patients with IBD and will help us to manage large distributions of adjuvanted or non-adjuvanted vaccines in the case of further pandemics.

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In addition to the authors, the following investigators participated in the study: Rita Monterubbianesi (S Camillo-Forlanini Hospital, Rome, Italy), Benedikt Blaha (Wilhelminenspital, Vienna, Austria), Monica Cesarini (University of Rome Sapienza, Policlinico Umberto, Rome, Italy), Thomas Haas (Paracelsus Medical University, Salzburg, Austria) and Reingard Platzer (Landesklinikum, Wiener Neustadt, Austria). Alfredo Papa (Università Cattolica del Sacro Cuore Rome, Italy), Gianluca Andrisani (Università Cattolica del Sacro Cuore Rome, Italy), Naila Arebi (St Marks Hospital London UK), Javier P Gisbert (La Princesa and CIBERehd Madrid, Spain).

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