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

Jean-François Rahier, Pavol Papay, Julia Salleron, Shaji Sebastian, Manuela Marzo, Laurent Peyrin-Biroulet, Valle Garcia-Sanchez, Walter Fries, Dirk P van Asseldonk, Klaudia Farkas, Nanne K de Boer, Taina Sipponen, Pierre Ellul, Edouard Louis, Simon T C Peake, Uri Kopylov, Jochen Maul, Badira Makhoul, Gionata Fiorino, Yazdan Yazdanpanah, Maria Chaparro, for the European Crohn’s and Colitis Organisation (ECCO)

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, FluvaxP) 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 FluvaxP 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 not been identified in human influenza A virus. Additional cases were rapidly reported, leading WHO to declare a pandemic phase level 6, indicating widespread human infection. This caused...
arthralgia, use of pain killers) symptoms occurring within 7 days
of vaccination. Symptoms were considered to be present or
absent. As in clinical trials, unsolicited and solicited events
were considered vaccine-related if occurring within 7 days of

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

<table>
<thead>
<tr>
<th>A. General well-being:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = very well</td>
</tr>
<tr>
<td>1 = slightly below par</td>
</tr>
<tr>
<td>2 = poor</td>
</tr>
<tr>
<td>3 = very poor</td>
</tr>
<tr>
<td>4 = terrible</td>
</tr>
<tr>
<td>B. Abdominal pain:</td>
</tr>
<tr>
<td>0 = none</td>
</tr>
<tr>
<td>1 = mild</td>
</tr>
<tr>
<td>2 = moderate</td>
</tr>
<tr>
<td>3 = severe</td>
</tr>
<tr>
<td>C. Number of liquid stools per day:</td>
</tr>
<tr>
<td>D. Abdominal mass:</td>
</tr>
<tr>
<td>E. Complications: (score 1 per item)</td>
</tr>
<tr>
<td>Arthralgia</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Stool frequency*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = normal number of stools for this patient</td>
</tr>
<tr>
<td>1 = 1–2 stools more than normal</td>
</tr>
<tr>
<td>2 = 3–4 stools more than normal</td>
</tr>
<tr>
<td>3 = 5 or more stools than normal</td>
</tr>
<tr>
<td>Rectal bleeding†</td>
</tr>
<tr>
<td>0 = no blood seen</td>
</tr>
<tr>
<td>1 = streaks of blood with stool less than half the time</td>
</tr>
<tr>
<td>2 = obvious blood with stool most of the time</td>
</tr>
<tr>
<td>3 = blood alone passed</td>
</tr>
<tr>
<td>Physician’s global assessment‡</td>
</tr>
<tr>
<td>0 = normal</td>
</tr>
<tr>
<td>1 = mild disease</td>
</tr>
<tr>
<td>2 = moderate disease</td>
</tr>
<tr>
<td>3 = severe disease</td>
</tr>
</tbody>
</table>

*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.

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) virus were manufactured.
Two large studies have produced reassuring data on the efficacy
and safety of these novel vaccines, whether in an MF59-adju-
vant form or not, in young and middle-aged adults. These data
are difficult to extrapolate to other categories of people, partic-
ularly adults who have underlying immune suppression, which
is the group for whom the influenza A (H1N1) 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 immu-
nosuppression, national and international recommendations and
expert advice have emphasised the need to vaccinate patients
with IBD and immunocompromised conditions against influ-
enza infection. 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
H1N1 vaccines, (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 outpa-
tient 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 modi-
fication 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) and Partial Mayo Score (PMS)—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 H1N1 vaccine,
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

Gut 2011;60:456–462. doi:10.1136/gut.2010.233981
457
Gut: first published as 10.1136/gut.2010.233981 on 26 January 2011. Downloaded from http://gut.bmj.com/
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 FluvaxP) 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 5.75 μg antigen equivalent to A/California/7/2009 (H1N1)v-like strain (X-179A); AS03 adjuvant composed of squalene (10.69 mg), Δ,Δ- tocopherol (11.56 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.
- FluvaxP: one dose (0.5 ml) contains 6 μg whole virion, reassembled 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, 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. 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 V9.1. 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, χ² 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. 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 753 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 54.0% in the adjuvanted and non-adjuvanted group, respectively) separated by a median of 25 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 4–15), 7 years for UC (IQR 4–15), and 3.5 years 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 the first dose of H1N1 vaccine are shown in table 2. Local and systemic solicited reactions appeared mostly on the day after 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).
Table 1  Demographic, clinical characteristics and immunomodulatory treatments of 575 patients according to H1N1 vaccine group

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>All patients (N = 575)</th>
<th>Adjuvanted vaccine (N = 499)</th>
<th>Non-adjuvanted vaccine (N = 76)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.331</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>263 (46.1)</td>
<td>224 (45.3)</td>
<td>39 (51.3)</td>
<td></td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>40.3 (14.0)</td>
<td>40.4 (14.1)</td>
<td>40.1 (13.1)</td>
<td>0.892</td>
</tr>
<tr>
<td>Pregnancy, n (%)</td>
<td>6 (1.0)</td>
<td>6 (1.2)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
</tbody>
</table>

Clinical characteristics

<table>
<thead>
<tr>
<th>IBD genotype*</th>
<th>CD, n (%)</th>
<th>UC, n (%)</th>
<th>IC, n (%)</th>
<th>Disease duration (years), median (IQR)</th>
<th>Age of diagnosis</th>
<th>Disease location</th>
<th>Disease behaviour</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>407 (70.8)</td>
<td>348 (69.7)</td>
<td>9 (1.6)</td>
<td>8 (4.15)</td>
<td>53 (13.2)</td>
<td>118 (30.0)</td>
<td>180 (48.0)</td>
</tr>
<tr>
<td></td>
<td>342 (65.7)</td>
<td>183 (36.7)</td>
<td>9 (1.8)</td>
<td>8 (4.15)</td>
<td>53 (13.2)</td>
<td>118 (30.0)</td>
<td>180 (48.0)</td>
</tr>
<tr>
<td></td>
<td>251 (46.1)</td>
<td>130 (25.5)</td>
<td>9 (1.8)</td>
<td>8 (4.15)</td>
<td>53 (13.2)</td>
<td>118 (30.0)</td>
<td>180 (48.0)</td>
</tr>
<tr>
<td></td>
<td>407 (70.8)</td>
<td>348 (69.7)</td>
<td>9 (1.6)</td>
<td>8 (4.15)</td>
<td>53 (13.2)</td>
<td>118 (30.0)</td>
<td>180 (48.0)</td>
</tr>
<tr>
<td></td>
<td>342 (65.7)</td>
<td>183 (36.7)</td>
<td>9 (1.8)</td>
<td>8 (4.15)</td>
<td>53 (13.2)</td>
<td>118 (30.0)</td>
<td>180 (48.0)</td>
</tr>
<tr>
<td></td>
<td>251 (46.1)</td>
<td>130 (25.5)</td>
<td>9 (1.8)</td>
<td>8 (4.15)</td>
<td>53 (13.2)</td>
<td>118 (30.0)</td>
<td>180 (48.0)</td>
</tr>
<tr>
<td></td>
<td>407 (70.8)</td>
<td>348 (69.7)</td>
<td>9 (1.6)</td>
<td>8 (4.15)</td>
<td>53 (13.2)</td>
<td>118 (30.0)</td>
<td>180 (48.0)</td>
</tr>
<tr>
<td></td>
<td>342 (65.7)</td>
<td>183 (36.7)</td>
<td>9 (1.8)</td>
<td>8 (4.15)</td>
<td>53 (13.2)</td>
<td>118 (30.0)</td>
<td>180 (48.0)</td>
</tr>
<tr>
<td></td>
<td>251 (46.1)</td>
<td>130 (25.5)</td>
<td>9 (1.8)</td>
<td>8 (4.15)</td>
<td>53 (13.2)</td>
<td>118 (30.0)</td>
<td>180 (48.0)</td>
</tr>
<tr>
<td></td>
<td>407 (70.8)</td>
<td>348 (69.7)</td>
<td>9 (1.6)</td>
<td>8 (4.15)</td>
<td>53 (13.2)</td>
<td>118 (30.0)</td>
<td>180 (48.0)</td>
</tr>
<tr>
<td></td>
<td>342 (65.7)</td>
<td>183 (36.7)</td>
<td>9 (1.8)</td>
<td>8 (4.15)</td>
<td>53 (13.2)</td>
<td>118 (30.0)</td>
<td>180 (48.0)</td>
</tr>
<tr>
<td></td>
<td>251 (46.1)</td>
<td>130 (25.5)</td>
<td>9 (1.8)</td>
<td>8 (4.15)</td>
<td>53 (13.2)</td>
<td>118 (30.0)</td>
<td>180 (48.0)</td>
</tr>
</tbody>
</table>

Immunomodulatory treatments

| Corticosteroids, n (%) | 65 (11.3) | 52 (10.4) | 13 (17.1) | 0.086 |
| Azathioprine/6MP, n (%) | 319 (55.5) | 274 (54.9) | 45 (59.2) | 0.482 |
| Methotrexate, n (%) | 39 (6.8) | 36 (7.2) | 3 (3.9) | 0.289 |
| Anti-TNF therapies, n (%) | 280 (48.7) | 251 (50.3) | 29 (38.2) | 0.048 |
| Infliximab, n (%) | 171 (29.7) | 157 (31.5) | 14 (18.4) | 0.02 |
| Adalimumab, n (%) | 98 (17) | 84 (16.8) | 14 (18.4) | 0.732 |
| Certolizumab, n (%) | 11 (1.9) | 9 (1.8) | 2 (2.6) | 0.646 |
| Calcineurin inhibitors, n (%) | 3 (0.5) | 3 (0.6) | 0 (0) | 1 |
| Others, n (%) | 13 (2.3) | 8 (1.6) | 5 (6.6) | 0.019 |
| Monotherapy, n (%) | 240 (41.7) | 205 (41.1) | 35 (45.6) | 0.413 |

Receipt of additional vaccines

| H1N1 booster (2nd injection), n (%) | 212 (36.9) | 140 (28.1) | 72 (94.7) | 0.001 |
| Seasonal influenza vaccine, n (%) | 328 (57) | 291 (58.3) | 37 (48.7) | 0.114 |
| Pneumococcal vaccine, n (%) | 70 (12.2) | 68 (13.6) | 2 (2.6) | 0.006 |

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

*According to Montreal classification.}

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

<table>
<thead>
<tr>
<th>Effect</th>
<th>Adjuvanted vaccine (N = 295)</th>
<th>Non-adjuvanted vaccine (N = 76)</th>
<th>p Value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local reaction</td>
<td>Any reaction, n (%) 160 (54.2) 28 (16.0) 8 (27.6) 3 (3.9)</td>
<td>Pain, n (%) 151 (51.2) 27 (15.4) 8 (27.6) 3 (3.9)</td>
<td>0.031</td>
</tr>
<tr>
<td>Systemic reaction</td>
<td>Any reaction, n (%) 64 (21.7) 11 (6.3) 0 (0) 14 (18.4)</td>
<td>Shivering, n (%) 3 (1.0) 1 (0.6) 0 (0) 0 (0)</td>
<td>0.099</td>
</tr>
</tbody>
</table>

Effect of vaccination on IBD activity

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.

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 (5.0%) subjects reported use of pain killers. Twenty-two subjects (3.8%) reported body temperature >38°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).

15.4%, p < 0.0001). Patients with local reactions were younger than patients without (mean age 38.7 (SD 15.6) 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 old (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 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.
vaccine except Fluvil®, 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 (5.9% vs 3.8%, p=0.95). 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 H1N1v 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 (15.9%) 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=0.55) or type of IBD (p=0.20).

Of the 22 patients who experienced increased daily bowel movements, diarrhea or bloody diarrhea 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 recommendations 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 H1N1v vaccines in immunocompromised patients with IBD, particularly the type of solicited adverse events, is consistent with previous reports in the immunocompetent population. 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. 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. 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 Fluvil® 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, that administration of seasonal influenza on the same day as the H1N1v 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. 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, diarrhea and abdominal pain were common (≥1/100 to <1/10) with Celvapan and uncommon (≥1/1000 to <1/100) with Pandemrix or Focetria in non-IBD immunocompetent patients. 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. 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. 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

<table>
<thead>
<tr>
<th>IBD clinical score activity</th>
<th>CD (N=390)</th>
<th>UC (N=158)</th>
<th>IC (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBI at baseline, median (IQR)</td>
<td>1 (0.3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PMS at baseline, median (IQR)</td>
<td>-</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Absence of flare, n (%)</td>
<td>377 (96.7)</td>
<td>151 (95.6)</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>Rise of 3 points, n (%)</td>
<td>1 (0.2)</td>
<td>4 (2.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rise of 4 points, n (%)</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Rise of ≥ 4 points, n (%)</td>
<td>9 (2.3)</td>
<td>2 (1.3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

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.21 22 For non-liver vaccines, substantial literature data support the conclusion that immunisation of IMID patients does not increase clinical or laboratory parameters of disease activity.23 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 Index24 and the Disease Activity Score in rheumatoid arthritis.25 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.26 27 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 recognized as response to therapy.9 However, for criteria 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.9 11 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 IBD in the case of further pandemics.

Author affiliations
1 Gastroenterology Unit, Cliniques Universitaires UCL Mont-Godinne, Yvoir, Belgium
2 Gastroenterology Unit, Medical University Vienna, Vienna, Austria
3 Biostatistics Unit, Université Lille Nord de France, CHUR Lille, France
4 Gastroenterology Unit, Hull Royal Infirmary, Hull, UK
5 Gastroenterology Unit, Università Cattolica del Sacro Cuore, Rome, Italy
6 Gastroenterology Unit, Università Henri Poincaré 1, CHU de Nancy, France
7 Gastroenterology Unit, H Reina Sofia, Cordoba, Spain
8 Gastroenterology Unit, University of Messina, Messina, Italy
9 Gastroenterology Unit, VU University Medical Center, Amsterdam, The Netherlands
10 Gastroenterology Unit, University of Szeged, Szeged, Hungary
11 Gastroenterology Unit, Kennemer Gasthuis, Haarlem, Netherlands
12 Gastroenterology Unit, Helsinki University Central Hospital, Helsinki, Finland
13 Gastroenterology Unit, Mater Dei Hospital, Msida, Malta
14 Gastroenterology Unit, Liège University and CHU Liège, Belgium
15 Gastroenterology Unit, St Marks Hospital, London, UK
16 Gastroenterology Unit, Chaim Sheba Tel Hashomer Medical Center, Ramat Gan, Israel
17 Gastroenterology Unit, Charité - Universitätsmedizin Berlin, Germany
18 Gastroenterology Unit, Rambam Human Health Care Campus, Haifa, Israel
19 Gastroenterology Unit, IBD Unit, RCCS Humanitas, Rozzano, Milan, Italy
20 Service Universitaire des Maladies Infectieuses et du Voyager, CHU Tourcoing and ATIP-Avenir INSERM U995, Tourcoing, France
21 Gastroenterology Unit, La Princesa and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain

Acknowledgements We acknowledge scientific unit support from the Cliniques Universitaires UCL Mont-Godinne, particularly Mme Michèle Duclos, for database management. We are grateful to Jean-Frédéric Colombel, Simon Travis, Walter Reinisch and Séverine Vermeire for support and guidance throughout the project.

Competing interests J-FR received lecture fees from speaking at continuing medical education events from Abbott Laboratories and Schering-Plough and paid advisory board for Glaxo SmithKline. PP received consulting fees and speaker fees from Abbott Laboratories. LB-P has received consulting fees from Abbott Laboratories and UCB Pharma. VG received lecture fees from speaking at continuing medical education events from Abbott Laboratories and MSD. WF received a research grant from Schering-Plough. TS received lecture fees from speaking at continuing education events from Abbott, MSD and Tillotts Pharma. EL received research grants from MSD, AstraZeneca and Abbott, speaker fees from Abbott, AstraZeneca, Ferring, Falk, MSD/Schering Plough, Menarini, Movets and Nycomed and he served as a consultant or advisor for Abbott, AstraZeneca, MSD/Schering Plough, Millenium, Ferring, Shire. JM has served as a consultant for Schering Plough and has received speaker fees from Abbott. YY has received travel grants, honoria for presentation at workshops and consultancy honoria from Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, Glaxo-SmithKline, Merck, Pfizer, Roche and Tibotec. BB received speaker fees from Abbott. TH received honoria from Abbott and MSD. RP received honoria from Abbott and MSD.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the UCL Mont Godinne University Hospital, Yvoir, Belgium.

Contributors J-FR and PP were involved in the study concept and design and writing the manuscript. JS performed all statistical analyses. LB-P and EL were involved in writing the manuscript. J-FR, PP, SS, MM, LB-P, VG, WS, DPvanA, NF, NLKheb, TS, PE, EL, SP, UK, JM, BM, GF and MC were all involved in acquisition of data. J-FR had full access to all of the data and takes full responsibility for the veracity of the data and analysis.

In addition to the authors, the following investigators participated in the study: Rita Monterubbiano (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 Pfister (Landeskinikum, Wiener Neustadt, Austria). Alfredo Papa (Università Cattolica del Sacro Cuore, Rome, Italy), Gianluca Andrisani (Università Cattolica del Sacro Cuore Rome, Italy), Niala Arbei (St Marks Hospital London UK), Javier P Gisbert (La Princesa and CIBERehd, Madrid, Spain).

Provenance and peer review Not commissioned; externally peer reviewed.
Inflammatory bowel disease

REFERENCES


Have confidence in your decision making.

The best clinical decision support tool is now available as an app for your iPhone. Visit bestpractice.bmj.com/app

BestPractice
FROM THE BMJ EVIDENCE CENTRE

462