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LETTER TO THE EDITORS

Relapse risk in patients with multiple sclerosis after H1N1 vaccination, with or without seasonal influenza vaccination

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Dear Sirs,

The safety of vaccination in multiple sclerosis (MS) raises concern, particularly the relapse risk post-vaccination. With the recent H1N1 pandemic, people with chronic diseases, including neurological conditions such as MS, were prioritised for vaccination. Two questions therefore arise in this context: whether vaccination increases the relapse rate, and whether the relapse is more severe post-vaccination. Seasonal influenza immunisation does not increase the risk of MS exacerbation; a systematic review found no increased risk of early (3–4 weeks post-vaccination) or late (4–6 months) exacerbations [1]. Likewise, influenza vaccination resulted in no relative increase in disease-activity to controls based on new Gd-enhancing lesions on MRI [2, 3]. The evidence is less clear-cut regarding the pandemic influenza H1N1 vaccine and relapse risk. Reports from the 1970s suggested an increased risk of Guillan-Barre and MS-like syndromes following this vaccine [4], although formal controlled trials did not. Two placebo controlled studies involving 88 and 127 MS patients, reported similar frequency of MS relapses in the H1N1 and placebo-vaccinated groups [5, 6] (12 vs. 14% and 3 vs. 6.5%, respectively).

In our acute weekly relapse clinic, we recorded data from 30 consecutive patients between 11/2009 and 01/2010. During this period in the UK, all MS patients were actively offered H1N1 vaccination [7]. Relapse onset date, and H1N1/seasonal influenza vaccination status (with administration date where appropriate) were recorded. The expanded disability status scale (EDSS), multiple sclerosis impact scale (MSIS-29 v 2.0), and use of corticosteroid treatment were also documented. Eighteen (60%) of patients received either/both vaccination prior to relapse onset, leaving 40% not vaccinated (Table 1). Neither the relapse severity (EDSS/MSIS-29 v 2.0) nor the numbers receiving corticosteroid treatment were significantly different (Table 1).

The association between relapse rate and vaccination in a relapse clinic can be evaluated using a case-crossover design; as in a previous report of different vaccinations in MS relapse clinics [8]. This method compares vaccine exposure in a specified risk period immediately preceding the relapse to that in several prior control periods of equal duration, thus quantifying the relative relapse risk in the specified post-vaccination period.

Using a similar analysis in our 30 patients, 15 received H1N1 vaccination (Fig. 1a, flow chart); of whom 10

Table 1 Clinical details

	Influenza+	Influenza−
H1N1+		
N	8 (27%)	7 (23%)
EDSS	4.25 (2–7)	6 (2–6.5)
MSIS-29	66 (15.5); 95% CI 53–79	86 (15.7); 95% CI 71–100
IVMP	62.5%; 95% CI 31–86%	71%; 95% CI 36–92%
H1N1−		
N	3 (10%)	12 (40%)
EDSS	7 (2–7)	6 (1–6)
MSIS-29	60 (21.2); 95% CI 7.3–112	71 (25); 95% CI 55–89
IVMP	67%; 95% CI 21–93%	67%; 95% CI 39–86%

N number of patients [number (% of total patients)]; *EDSS* expanded disability status scale [median (range)]; *MSIS-29v 2.0* multiple sclerosis impact scale [mean (standard deviation), maximum score 116]; *IVMP* intravenous methylprednisolone treatment (% of group treated)

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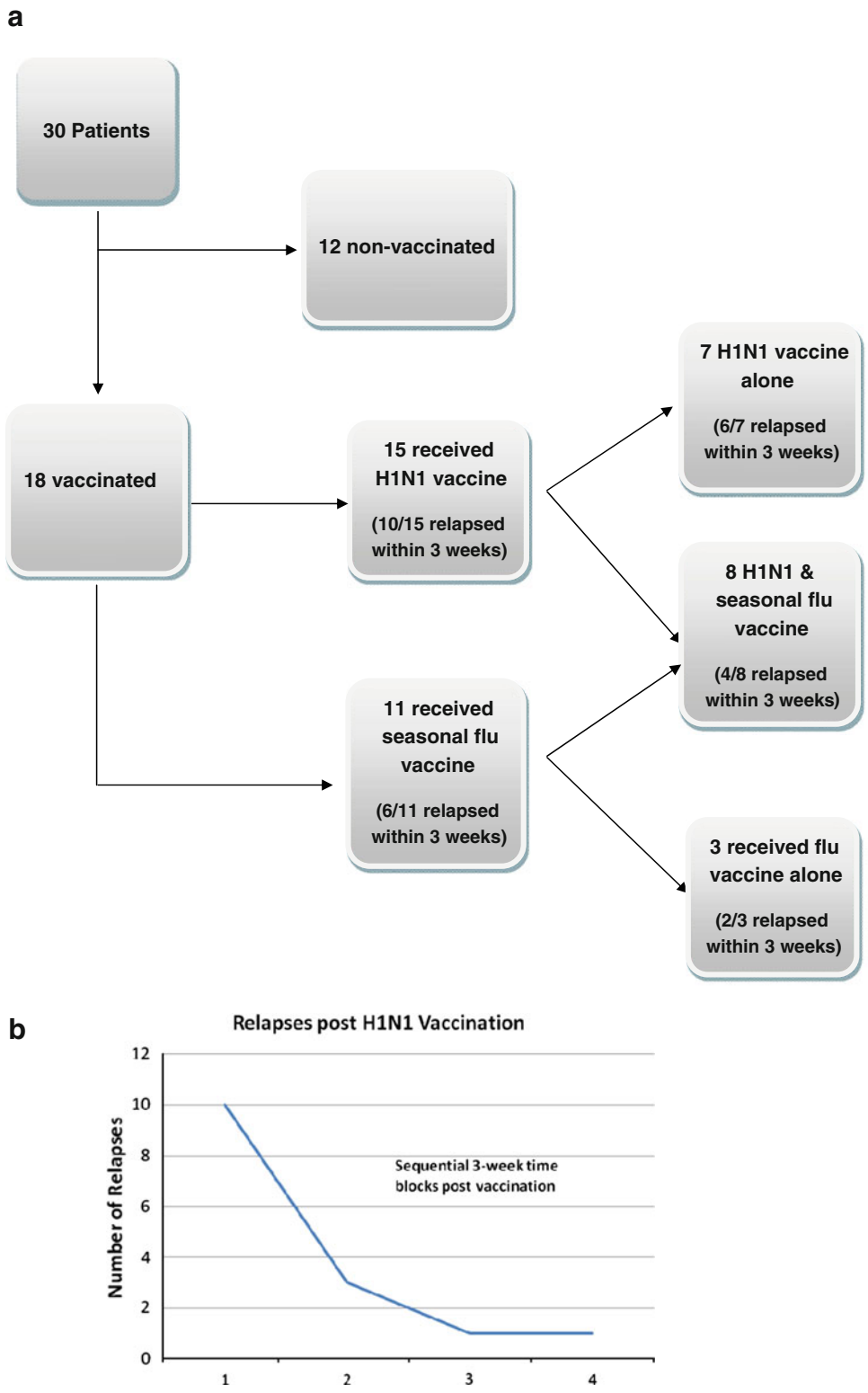

Fig. 1 **a** Flow chart of vaccination and **b** MS relapses over time, following H1N1 vaccination

patients were vaccinated within 3 weeks of MS relapse (early relapses). The five remaining patients were vaccinated within three sequential 3-week control periods immediately preceeding this reference 3-week period. Thus, 33.3% (10/30 patients) relapsed within 3 weeks of H1N1 vaccination, whereas in the preceding control

periods, 10% of those vaccinated relapsed in the first period, 3.33% in the second and 3.33% in the third (Fig. 1b), averaging a 5.53% relapse rate in the total control period (relative risk 33.3%/5.53% = 6.0; 95% CI 1.4–26.2). These data support a higher relapse risk in the early weeks following H1N1 vaccination, although the patient numbers are small and the follow-up period relatively short. Eight of the 15 H1N1-vaccinated patients also received seasonal influenza vaccination, in most cases at the same time, thus limiting the ability to identify a separate relapse risk from influenza vaccination. Six of the seven patients who received H1N1 vaccination alone relapsed in the reference period (flow chart).

Confavreux reported [8] over 600 MS patients receiving several different vaccines, 17% of whom received influenza vaccination, and found no increased relapse risk post influenza vaccination. H1N1 vaccination was not included, and there are no recent data concerning H1N1 vaccination and MS relapse risk.

These data support a greater relapse rate following H1N1 vaccination, as observed in this small cohort. A larger study could determine whether a true relationship exists; which should be balanced against the increased relapse rate and other neurological complications from H1N1 virus infection (which can occur with a frequency of $\sim$1% [9]).

Conflict of interest None.

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