prior diagnosis of fibromyalgia, age over 18 and ability to give informed consent. Exclusion criteria were a known allergy to egg products or influenza vaccine, a febrile disease in progress and pregnancy.
Each patient reported his/her complete history including the use of medications, and underwent physical examination and dolorimetry before undergoing vaccination. The fulfillment of the American College of Rheumatology (ACR) 1990 FMS classification criteria was duly documented (6). Patients filled in the widespread pain index (WPI) checklist and the symptoms severity scale (SSS), derived from the 2010-2011 ACR preliminary diagnostic criteria for FMS (7, 8) and the Hebrew version of the fibromyalgia impact questionnaire (FIQ) (9). Healthy controls (38) were recruited from the hospital staff. The study was approved by the institutional ethics committee and all patients gave a written informed consent.
Participants were vaccinated with the inactivated split virion influenza vaccine, recommended by the WHO and serum samples were collected for antibody titration. Six weeks after vaccination, patients were evaluated again and serum was collected for the second time. Patients were also asked whether they developed any direct vaccine-related side effects and how were their general health conditions following vaccination.

Immunogenicity of the vaccine
The pre- and post-immunization hemagglutination (HI) antibodies were tested at the Central Virology Laboratory of the Israeli Ministry of Health using the HI test according to the standard WHO procedure (10). Sera were tested by HI test against the three antigens included in the vaccine: A/California (H1N1), A/Perth (H3N2) and B/Brisbane. Sera were separated, code labeled, and stored at -20°C until the test was conducted. They were treated with receptor-destroying enzyme cholera filtrate to remove non-specific inhibitors, and with Turkey red blood cells to remove non-specific agglutinins. The treated sera were tested by an HI test against the three antigens included in the vaccine: A/California (H1N1), A/Perth (H3N2) and B/Brisbane. The effective dilution (test dose) of each antigen contained 4 HA units in 25 μL of antigen. Test doses were diluted in phosphate-buffered saline and added to serial dilutions of anti-serum. The HA inhibition titer was determined as the highest dilution of serum that inhibited completely the hemagglutination of red blood cells. Humoral response was defined as either a fourfold or greater increase in titer, or a rise from a non-protective baseline level of <1/40 to 1/40 after vaccination. The titer of an antiserum that did not show any inhibition was recorded as 1/10. Geometric mean titers of antibodies were calculated to assess the entire group immunity.

Statistical methods
Non-parametric tests were used in the analysis, since most parameters were not normally distributed. In addition, parametric tests were performed for the log transformation of the parameters. The statistical analysis was performed using the SPSS system for Windows, release 17.0.

RESULTS

No severe vaccination-related events were documented among patients or controls enrolled in this study.

Characteristics of patients and controls
Nineteen FMS patients and 38 healthy controls were recruited. Sixteen out of nineteen patients (84.2%) were female and their mean age was 46.6 years.

Effect of vaccination against influenza on disease activity
Vaccination against influenza was not associated with a significant worsening of any clinical index of disease activity (Table I). As shown in the table, no significant change was observed between WPI, SSS and FIQ values before and after vaccination, indicating no resulting clinical change. There was no local reaction to vaccination in any group. No severe vaccination reactions were observed.

Table I - Clinical features of fibromyalgia before and after influenza vaccination.

	Pre vaccination	Post vaccination	p
WPI (DS)	13,3 (4,7)	11 (5,4)	0,19
SSS (DS)	9,1 (1,6)	9,0 (2,7)	0,88
FIQ (DS)	67,3 (14,2)	65,9 (22,0)	0,82

The above values are means standard deviation (SD). WPI, widespread pain index; SSS, symptom severity score; FIQ, fibromyalgia impact questionnaire.

Immunogenicity of the vaccine

Six weeks after vaccination, FMS patients displayed a significant increase in the geometric mean titers of the HI antibody against H1N1 and B/Bri viruses: from 29.9 to 387.9 (p=0.0011), from 82.9 to 460.9 (p=0.0007) respectively. The increase for Perth virus was borderline from 28.8 to 96.0 (p=0.08). The rates of sero-protection (defined as antibody levels above 1/40) increased from 22.9% for H1N1 to 89.5% post vaccination (Figure 1).

DISCUSSION

This study has demonstrated that influenza vaccinations are both safe and effective in patients suffering from fibromyalgia. This conclusion is of significant practical importance for health care providers who need to inform their FMS patients about risks and benefits of vaccination.

As noted above, the potential link between FMS and prior exposure to vaccines is an issue which has raised significant interest and debate in the literature. Not only was this discussion focused on fibromyalgia *per se*, but also on the broader field of central-sensitization-related conditions as well as other multi-system and enigmatic conditions. For instance, the Gulf war syndrome, an entity with considerable clinical overlap with FMS, was considered to be potentially linked with exposure to multiple vaccinations (11, 12). More recently, a theory has been proposed regarding the possibility that vaccination-related adjuvants may induce a multi-system disorder named autoimmune syndrome induced by adjuvants (ASIA), characterized by symptoms such

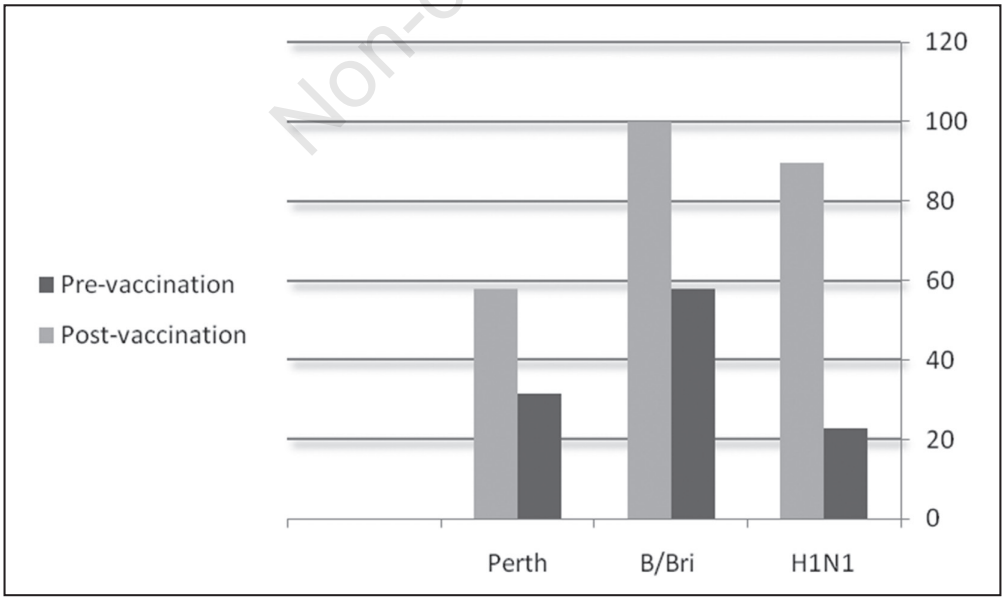

Figure 1 - Change in geometric mean titers (µg/mL) of hemagglutination antibody against influenza antigens before and 6 weeks after vaccination.

as fatigue, cognitive impairment and arthragia (13, 14). Both the ASIA syndrome and FMS have recently been reported to be associated with hepatitis B vaccination (15). Moreover, the Gulf war syndrome was also suggested to be a particular type of this syndrome (16). The chronic fatigue syndrome (CFS), another condition with considerable overlap with FMS, was also linked with vaccination in the past (17).
The postural orthostatic tachycardia syndrome, another clinical entity which overlaps CFS, has also recently been noted in association with vaccination (18).
However, as previously mentioned, infections *per se* are considered one of the potential etiological triggers for the development of FMS (19-22). Hence, avoiding vaccination is not without consequences for FMS patients, who may then be at an increased risk of contracting various infections, both viral and non-viral. The actual impact of such infections on the course of FMS patients (or individuals who may be prone to develop FMS) is hard to estimate. However, from a practical point of view, physicians treating FMS patients are frequently confronted with the question of administering the vaccine or not. Also, many patients may choose to avoid vaccination given the actual implications are still unclear. A recent study conducted on the population of Madrid (Spain) demonstrated extremely low rates of vaccination against influenza (14.2%) among FMS patients (23).
However, since influenza continues to be a major public health issue in many countries, these results underlie the importance of ascertaining the safety of vaccination in specific patient populations.
Another aspect addressed by our study is the immunological efficacy of vaccination in FMS patients. While FMS is not regarded as an autoimmune disorder and is not regularly treated with medications capable of suppressing the activity of the immune system, various subtle aspects that are typical of immune dysfunctions have frequently been documented among this patient population (24-26). Therefore, the demonstration given by this study that FMS patients can be immunized successfully against influenza is another significant outcome.
However, it is worth pointing out that this study has some limitations. The small number of participants is an obvious limitation, although, due to its exploratory nature, we consider it to be still noteworthy. Future studies should ideally investigate the relationship between vaccination of healthy pain-free individuals, and the prospective development of FMS symptoms, which has not yet been reported in the literature.

CONCLUSIONS

Influenza vaccination was safe and effective in FMS patients. No clinical change was reported following vaccination and serological evidence of successful vaccination was similar to that observed among healthy controls.
In view of these results, FMS patients should be encouraged to undergo influenza vaccination according to the standard WHO recommendations.

Key points: Despite debate in the literature regarding the role of vaccinations in many connective tissue disorders, vaccinating FMS patients against influenza is both safe and effective.

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