

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Clark TW, Pareek M, Hoschler K, et al. Trial of 2009 influenza A (H1N1) monovalent MF59-adjuvanted vaccine. *N Engl J Med* 2009;361:2425-35. DOI: 10.1056/NEJMoa0907650.

(PDF updated December 16, 2009.)

## **Supplementary Appendix**

### **INCLUSION CRITERIA**

1. Mentally competent adults, who have signed an informed consent form after having received a detailed explanation of the study protocol.
2. Male or female subjects  $\geq 18$ -50 years who are either healthy or have a stable medical condition.
3. Able to understand and comply with all study procedures and to complete study diaries
4. Individuals who can be contacted throughout the study and are available for all study visits
5. Females should either be using secure contraceptive precautions including a) the oral contraceptive pill, b) condom/barrier contraception c) partner has had a vasectomy, d) be surgically sterilised, or e) post-menopausal (defined as at least two years since the last menstrual period)

### **EXCLUSION CRITERIA**

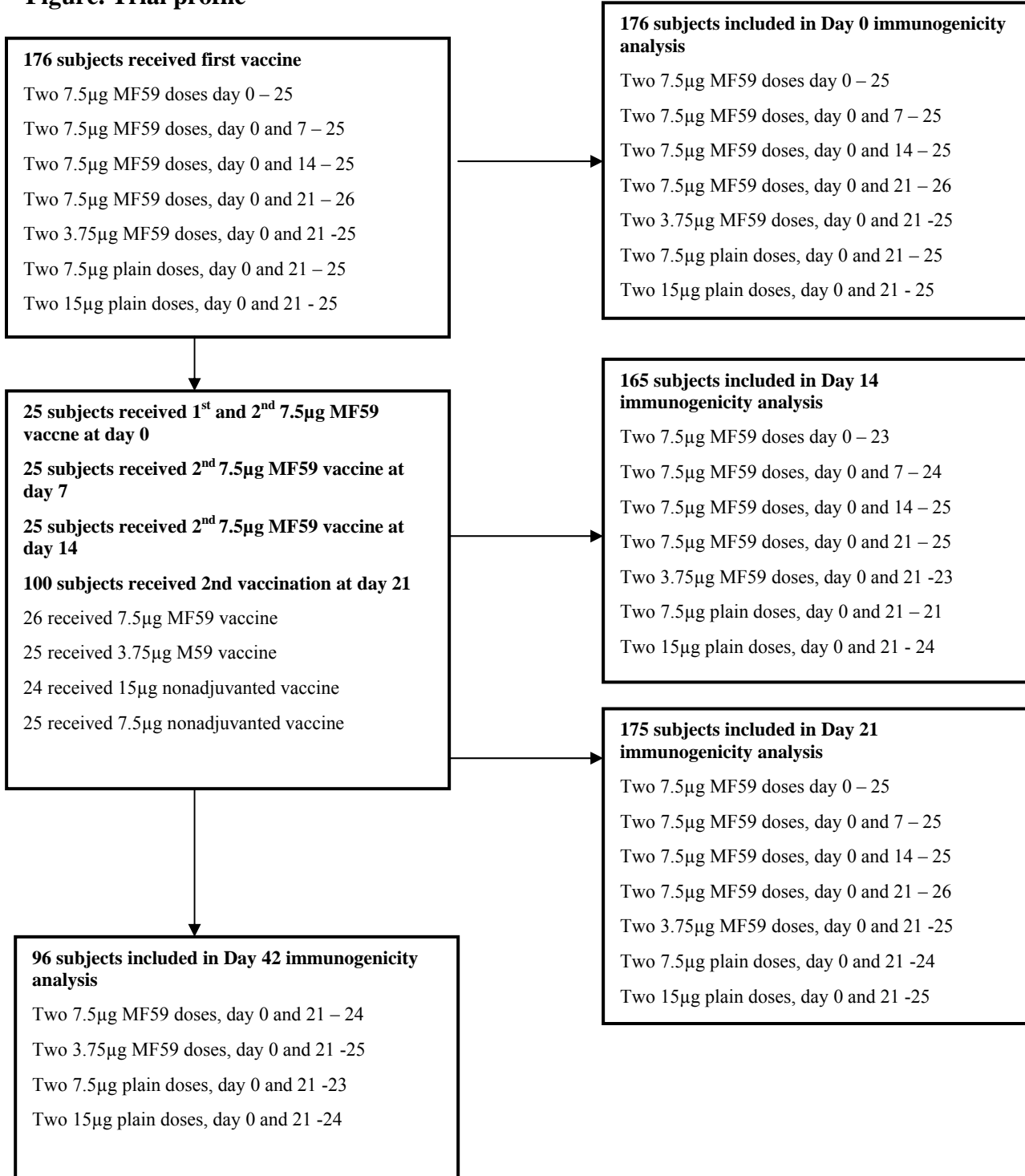
1. Any clinically significant concurrent illness or unstable medical condition including: malignant tumours, autoimmune illnesses (including rheumatoid arthritis), acute or progressive renal or hepatic pathology, chronic obstructive pulmonary disease requiring oxygen therapy, and any active neurological disorder.
2. Individuals with a history of anaphylaxis or serious reactions to vaccines; hypersensitivity to influenzal viral protein, neomycin or polymixin, or products containing mercury.
3. Persons with known immunosuppressive disease or who use systemic immunosuppressive drugs (including chloroquine, gold or penicillamine to suppress a chronic disease process), or have received in the last 6 months radiotherapy or chemotherapy.
4. Subjects who are at high risk of developing illnesses of the immune system.
5. Individuals who are taking immunostimulant therapy or interferon
6. Individuals who have received blood products or immunoglobulins parenterally during the preceding three months.
7. Women should not be pregnant or lactating.

8. Women who refuse to use a reliable contraceptive method throughout the study
9. Known or suspected drug abuse.
10. Individuals who have received another vaccine or investigational medicinal product in the preceding 2 weeks.
11. Unable to lead an independent life either physically or mentally
12. Regularly drink more than 40 units of alcohol weekly
13. Individuals who have had acute respiratory pathology or infections requiring systemic antibiotic or antiviral therapy during the preceding 7 days (chronic antibiotic therapy for prevention of urinary tract infections is acceptable).
14. Individuals who had a temperature  $>38^{\circ}\text{C}$  in the preceding 3 days.
15. Individuals who, in the opinion of the investigator, have conditions that might complicate interpretation of the study results.
16. Individuals who have had confirmed pandemic influenza H1 infection

## **Laboratory assays**

Antibody responses were detected by neutralization and hemagglutination-inhibition with turkey erythrocytes using standard methods at the Centre for Infections, Health Protection Agency, UK with cell-culture virus, X-179A, and egg-grown NIBRG-121, the reverse-genetic virus containing hemagglutinin and neuraminidase from A/California/7/2009 (H1N1v) supplied by the National Institute for Biological Standards and Controls (NIBSC), UK. Negative control was pooled human sera, positive sera control was ferret antisera raised to A/California/7/2007 (NIBSC). Sera were tested using two-fold serial dilution. For hemagglutination-inhibition, RDE-treated sera were tested at an initial dilution of 1:8 and those that were negative were assigned a titer of 1:4. Sera were titrated to determine absolute endpoint titers: for sera that showed titers  $\geq 1024$ , a further dilution series was performed ending at a dilution of 1:32768. For neutralization, heat treated sera were tested at an initial dilution of 1:10, and those that were negative were assigned a titer of 1:5. The final dilution was 1:320 and those greater were assigned a value of 1:640. The neutralization assay was performed by infection of a MDCK cell suspension and final infectivity was detected by the use of monoclonal antibody directed against influenza nucleoprotein in an EIA detection format. Sera were tested in duplicate and the geometric mean value used for analysis.

**Figure. Trial profile**



**Table.** Proportion (percentage and 95% confidence intervals) of subjects with solicited local and systemic adverse reactions during the seven days after **first** dose of vaccine. Subjects used a subjective scale to grade adverse events. Symptoms were considered mild if they did not interfere with daily activities and moderate if caused some impairment and severe if affected daily activities and required medical attention

	MF59-adjuvanted vaccine				Nonadjuvanted Vaccine		
	3.75µg Day 0 and 21 25	7.5 µg Day 0 and 21 26	7.5 µg Day 0 and 14 25	7.5 µg Day 0 and 7 25	7.5 µg Both doses on Day 0 25	7.5 µg Day 0 and 21 25	15 µg Day 0 and 21 25
<b>Pain</b>							
None	44 (24.4-65.1)	27 (11.6-47.8)	24 (9.4-45.1)	44 (24.4-65.1)	16 (4.5-36.1)	64 (42.5-82.0)	58 (36.6-77.9)
Mild	40 (21.1-61.3)	58 (36.9-76.6)	48 (27.8-68.7)	48 (27.8-68.7)	76 (54.9-90.6)	36 (17.9-57.5)	38 (18.8-59.4)
Moderate	16 (4.5-36.1)	15 (4.4-34.9)	28 (12.1-49.4)	8 (0.9-26.0)	8 (0.9-26.0)	0 (0-13.7)	4 (0.1-21.1)
Severe	0 (0-13.7)	0 (0-13.2)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	0 (0-14.2)
<b>Redness</b>							
0mm	100 (86.3-100)	96 (80.4-99.9)	84 (63.9-95.5)	88 (68.8-97.5)	88 (68.8-97.5)	80 (59.3-93.2)	92 (73.0-98.9)
1-4mm	0 (0-13.7)	0 (0-13.2)	16 (4.5-36.1)	12 (2.5-31.2)	12 (2.5-31.2)	16 (4.5-36.1)	4 (0.1-21.1)
≥5mm	0 (0-13.7)	4 (0.1-19.6)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	4 (0.1-20.4)	4 (0.1-21.1)
<b>Swelling</b>							
0mm	96 (79.6-99.9)	96 (80.4-99.9)	92 (73.9-99.0)	96 (79.6-99.9)	84 (63.9-95.5)	96 (79.6-99.9)	96 (78.9-99.9)
1-4mm	4 (0.1-20.4)	4 (0.1-19.6)	4 (0.1-20.4)	0 (0-13.7)	12 (2.5-31.2)	4 (0.1-20.4)	4 (0.1-21.1)
≥5mm	0 (0-13.7)	0 (0-13.2)	4 (0.1-20.4)	4 (0.1-20.4)	4 (0.1-20.4)	0 (0-13.7)	0 (0-14.2)
<b>Bruising</b>							
0mm	100 (86.3-100)	96 (80.4-99.9)	96 (79.6-99.9)	96 (79.6-99.9)	92 (73.9-99.0)	100 (86.3-100)	96 (78.9-99.9)
1-4mm	0 (0-13.7)	4 (0.1-19.6)	0 (0-13.7)	4 (0.1-20.4)	4 (0.1-20.4)	0 (0-13.7)	4 (0.1-21.1)
≥5mm	0 (0-13.7)	0 (0-13.2)	4 (0.1-20.4)	4 (0.1-20.4)	4 (0.1-20.4)	0 (0-13.7)	0 (0-14.2)
<b>Muscle aches</b>							
None	80 (59.3-93.2)	69 (48.2-85.7)	72 (50.6-87.9)	64 (42.5-82.0)	36 (17.9-57.5)	80 (59.3-93.2)	62 (40.6-81.2)
Mild	12 (2.5-31.2)	27 (11.6-47.8)	12 (2.5-31.2)	32 (14.9-53.5)	52 (31.3-72.2)≠	20 (6.8-40.7)	38 (18.8-59.4)
Moderate	8 (0.9-26.0)	4 (0.1-19.6)	16 (4.5-36.1)	4 (0.1-20.4)	12 (2.5-31.2)	0 (0-13.7)	0 (0-14.2)

Severe	0 (0-13.7)	0 (0-13.2)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	0 (0-14.2)
Chills							
None	96 (79.6-99.9)	96 (80.4-99.9)	100 (86.2-100)	100 (86.2-100)	84 (63.9-95.5)	96 (79.6-99.9)	96 (78.9-99.9)
Mild	0 (0-13.7)	0 (0-13.2)	0 (0-13.7)	0 (0-13.7)	8 (0.9-26.0)	0 (0-13.7)	0 (0-14.2)
Moderate	4 (0.1-20.4)	4 (0.1-19.6)	0 (0-13.7)	0 (0-13.7)	8 (0.9-26.0)	4 (0.1-20.4)	4 (0.1-21.1)
Severe	0 (0-13.7)	0 (0-13.2)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	0 (0-14.2)
Malaise							
None	92 (73.9-99.0)	85 (65.1-95.6)	100 (86.2-100)	100 (86.2-100)	76 (54.5-90.6)	96 (79.6-99.9)	96 (78.9-99.9)
Mild	4 (0.1-20.4)	11 (2.4-30.2)	0 (0-13.7)	0 (0-13.7)	24 (9.4-45.1)	4 (0.1-20.4)	0 (0-14.2)
Moderate	4 (0.1-20.4)	4 (0.1-19.6)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	4 (0.1-21.1)
Severe	0 (0-13.7)	0 (0-13.2)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	0 (0-14.2)
Headache							
None	84 (63.9-95.5)	69 (48.2-85.7)	76 (54.5-90.6)	84 (63.9-95.5)	60 (38.7-78.9)	76 (54.5-90.6)	71 (48.9-87.4)
Mild	16 (4.5-36.1)	27 (11.6-47.8)	20 (6.8-40.7)	12 (2.5-31.2)	36 (17.9-57.5)	20 (6.8-40.7)	25 (9.8-46.7)
Moderate	0 (0-13.7)	4 (0.1-19.6)	4 (0.1-20.4)	4 (0.1-20.4)	4 (0.1-20.4)	4 (0.1-20.4)	4 (0.1-21.1)
Severe	0 (0-13.7)	0 (0-13.2)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	0 (0-14.2)
Nausea							
None	96 (79.6-99.9)	81 (60.6-93.4)	92 (73.9-99.0)	92 (73.9-99.0)	88 (68.8-97.5)	92 (73.9-99.0)	88 (67.6-97.3)
Mild	4 (0.1-20.4)	11 (2.4-30.2)	8 (0.9-26.0)	4 (0.1-20.4)	12 (2.5-31.2)	4 (0.1-20.4)	8 (1.0-26.9)
Moderate	0 (0-13.7)	8 (0.9-25.1)	0 (0-13.7)	4 (0.1-20.4)	0 (0-13.7)	4 (0.1-20.4)	4 (0.1-21.1)
Severe	0 (0-13.7)	0 (0-13.2)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	0 (0-14.2)
Fever >38	0 (0-13.7)	0 (0-13.2)	0 (0-13.7)	0 (0-13.7)	4 (0.1-20.4)	0 (0-13.7)	0 (0-14.2)
Analgesic use	20 (6.8-40.7)	4 (0.1-19.6)	8 (0.9-26.0)	0 (0-13.7)	20 (6.8-40.7)	8 (0.9-26.0)	4 (0.1-21.1)

≠Muscle aches were reported more frequently in the group receiving both doses of M59-adjuvanted vaccine on day 0 than in other groups (p=0.02 by Fisher's exact test)

**Table.** Proportion (percentage and 95% confidence intervals) of subjects with solicited local and systemic adverse reactions during the seven days after **second** dose of vaccine. Subjects used a subjective scale to grade adverse events. Symptoms were considered mild if they did not interfere with daily activities and moderate if caused some impairment and severe if affected daily activities and required medical attention

	MF59-adjuvanted vaccine				7.5 µg Both doses on Day 0	Nonadjuvanted Vaccine	
	3.75µg Day 0 and 21	7.5 µg Day 0 and 21	7.5 µg Day 0 and 14	7.5 µg Day 0 and 7		7.5 µg Day 0 and 21	15 µg Day 0 and 21
	25	26	25	25	25	25	25
<b>Pain</b>							
None	60 (38.7-78.9)	24 (9.4-45.1)	32 (14.9-53.5)	68 (46.5-85.1)	NA	72 (50.6-87.9)	71 (48.9-87.4)
Mild	24 (9.4-45.1)	64 (42.5-82.0))	52 (31.3-72.2)	32 (14.9-53.5)	NA	28 (12.1-49.4)	25 (9.7-46.7)
Moderate	16 (4.5-36.1)	12 (2.5-31.2)	16 (4.5-36.1)	0 (0-13.7)	NA	0 (0-13.7)	4 (0.1-21.1)
Severe	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	NA	0 (0-13.7)	0 (0-14.2)
<b>Redness</b>							
0mm	96 (79.6-99.9)	96 (79.6-99.9)	96 (79.6-99.9)	92 (73.9-99.0)	NA	96 (79.6-99.9)	84 (62.6-95.3)
1-4mm	0 (0-13.7)	0 (0-13.7)	4 (0.1-20.4)	8 (0.9-26.0)	NA	4 (0.1-20.4)	8 (1.0-26.9)
≥5mm	4 (0.1-20.4)	4 (0.1-20.4)	0 (0-13.7)	0 (0-13.7)	NA	0 (0-13.7)	8 (1.0-26.9)
<b>Swelling</b>							
0mm	92 (73.9-99.0)	96 (79.6-99.9)	88 (68.8-97.5)	100 (86.2-100)	NA	96 (79.6-99.9)	92 (73.0-98.9)
1-4mm	4 (0.1-20.4)	4 (0.1-20.4)	12 (2.5-31.2)	0 (0-13.7)	NA	4 (0.1-20.4)	4 (0.1-21.1)
≥5mm	4 (0.1-20.4)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	NA	0 (0-13.7)	4 (0.1-21.1)
<b>Bruising</b>							
0mm	96 (79.6-99.9)	92 (73.9-99.0)	92 (73.9-99.0)	96 (79.6-99.9)	NA	96 (79.6-99.9)	96 (78.9-99.9)
1-4mm	0 (0-13.7)	4 (0.1-20.4)	4 (0.1-20.4)	0 (0-13.7)	NA	4 (0.1-20.4)	4 (0.1-21.1)
≥5mm	4 (0.1-20.4)	4 (0.1-20.4)	4 (0.1-20.4)	4 (0.1-20.4)	NA	0 (0-13.7)	0 (0-14.2)
<b>Muscle aches</b>							
None	76 (54.9-90.6)	72 (50.6-87.9)	68 (46.5-85.1)	88 (68.8-97.5)	NA	88 (68.8-97.5)	83 (62.6-95.3)
Mild	8 (0.9-26.0)	20 (6.8-40.7)	16 (4.5-36.1)	12 (2.5-31.2)	NA	12 (2.5-31.2)	13 (2.7-32.4)

Moderate	16 (4.5-36.1)	8 (0.9-26.0)	16 (4.5-36.1)	0 (0-13.7)	NA	0 (0-13.7)	4 (0.1-21.1)
Severe	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	NA	0 (0-13.7)	0 (0-14.2)
Chills							
None	92 (73.9-99.0)	92 (73.9-99.0)	88 (68.8-97.5)	100 (86.2-100)	NA	96 (79.6-99.9)	96 (78.9-99.9)
Mild	8 (0.9-26.0)	8 (0.9-26.0)	4 (0.1-20.4)	0 (0-13.7)	NA	0 (0-13.7)	4 (0.1-21.1)
Moderate	0 (0-13.7)	0 (0-13.7)	8 (0.9-26.0)	0 (0-13.7)	NA	4 (0.1-20.4)	0 (0-14.2)
Severe	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	NA	0 (0-13.7)	0 (0-14.2)
Malaise							
None	88 (68.8-97.5)	80 (59.3-93.2)	88 (86.2-100)	96 (79.6-99.9)	NA	100 (86.2-100)	96 (78.9-99.9)
Mild	8 (0.9-26.0)	20 (6.8-40.7)	8 (0.9-26.0)	4 (0.1-20.4)	NA	0 (0-13.7)	4 (0.1-21.1)
Moderate	4 (0.1-20.4)	0 (0-13.7)	4 (0.1-20.4)	0 (0-13.7)	NA	0 (0-13.7)	0 (0-14.2)
Severe	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	NA	0 (0-13.7)	0 (0-14.2)
Headache							
None	80 (59.3-93.2)	80 (59.3-93.2)	72 (50.6-87.9)	88 (86.2-100)	NA	72 (50.6-87.9)	84 (62.6-95.3)
Mild	12 (2.5-31.2)	20 (6.8-40.7)	12 (2.5-31.2)	8 (0.9-26.0)	NA	24 (9.4-45.1)	8 (1.0-26.9)
Moderate	8 (0.9-26.0)	0 (0-13.7)	16 (4.5-36.1)	4 (0.1-20.4)	NA	4 (0.1-20.4)	8 (1.0-26.9)
Severe	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	NA	0 (0-13.7)	0 (0-14.2)
Nausea							
None	100 (86.2-100)	88 (86.2-100)	92 (73.9-99.0)	100 (86.2-100)	NA	92 (73.9-99.0)	92 (73.0-98.9)
Mild	0 (0-13.7)	12 (2.5-31.2)	4 (0.1-20.4)	0 (0-13.7)	NA	4 (0.1-20.4)	8 (1.0-26.9)
Moderate	0 (0-13.7)	0 (0-13.7)	4 (0.1-20.4)	0 (0-13.7)	NA	4 (0.1-20.4)	0 (0-14.2)
Severe	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	0 (0-13.7)	NA	0 (0-13.7)	0 (0-14.2)
Fever >38	0 (0-13.7)	0 (0-13.7)	4 (0.1-20.4)	0 (0-13.7)	NA	4 (0.1-20.4)	0 (0-13.7)
Analgesic use	8 (0.9-26.0)	4 (0.1-20.4)	8 (0.9-26.0)	0 (0-13.7)	NA	8 (0.9-26.0)	8 (1.0-26.9)

**Unsolicited adverse reactions following MF59-adjuvanted vaccine**

Three subjects reported self-limiting diarrhea that resolved within 48 hours; one of whom took loperamide as over-the-counter treatment. Three subjects reported coryza that resolved within 72 hours. One subject reported toothache that resolved after 5 days. One subject reported a transient itchy rash over the right forearm that resolved within 48 hours.

**Table.** Unsolicited adverse reactions following 7.5µg MF59-adjuvanted vaccine (n=8)

Reaction	1 <sup>st</sup> dose vaccine	2 <sup>nd</sup> dose vaccine	Duration (days)	Medication taken	Outcome
Diarrhoea	Yes	No	2	None	Resolved
Diarrhoea	Yes	No	2	None	Resolved
Diarrhoea	No	Yes	2	Loperamide	Resolved
Coryza	Yes	No	2	Paracetamol	Resolved
Coryza	Yes	No	3	None	Resolved
Coryza	No	Yes	1	None	Resolved
Itchy rash over right forearm	Yes (administered in left arm)	No	2	None	Resolved
Toothache	Yes	No	5	Paracetamol Ibuprofen	Resolved

### Unsolicited adverse reactions following nonadjuvanted vaccine

One subject developed diarrhea that resolved within 48 hours. One subject developed generalized pruritis in the absence of a rash, that resolved with antihistamines after 48 hours. Two subjects developed coryzal symptoms that resolved within 72 hours. One subject complained of muscular shoulder pain that did not require any analgesia and resolved after 48 hours. One subject complained of back pain that was longstanding and resolved with diazepam and diclofenac.

**Table.** Unsolicited adverse reactions following nonadjuvanted vaccine (n=7)

Reaction	1 <sup>st</sup> dose vaccine	2 <sup>nd</sup> dose vaccine	Duration (days)	Medication taken	Outcome
Diarrhoea	Yes	No	2	None	Resolved
Pruritis	Yes	No	2	Chlorpheniramine	Resolved
Coryza	Yes	No	3	None	Resolved
Coryza	No	Yes	1	None	Resolved
Muscular Shoulder pain	Yes	No	2	None	Resolved
Sore throat	Yes	No	1	None	Resolved
Backpain	Yes	No	1	Diazepam Diclofenac	Resolved

### **Severe adverse reaction**

One subject (female, Asian, 39 years) who received two doses of 3.75ug MF59-adjuvanted vaccines on day 0 and 21 reported severe left sided chest pain 10 days after the first dose. She was admitted to an acute medical ward and had a chest radiograph and electrocardiograph that were interpreted as normal. Blood tests including complete blood count, urea and electrolytes, liver function tests, C-reactive protein and troponin I were all within normal limits. A diagnosis of musculoskeletal chest pain was made and she was treated with paracetamol and diclofenac. The pain improved and she was discharged from hospital after 48 hours. The chest pain was felt to be unlikely to be related to vaccination.

### **Vaccine-related adverse reaction**

A probable vaccine-related adverse reaction was reported. One subject (female, Asian, 34 years) who received two 7.5µg MF59-adjuvanted vaccines on day 0 (July 24 2009) reported a purpuric rash over her lower limbs, commencing on day 17 post-vaccination (August 10 2009) and spontaneously resolving within 72 hours. Further questioning revealed that she had consulted her family practitioner in May 2009 for recurrent, self limiting intermittent rash over lower limbs in the 12 months prior to the study. Investigations in May 2009 included a complete blood count, urea and electrolytes, liver function tests, and C-reactive protein, all of which were within normal values. An autoimmune profile demonstrated positive antinuclear antibodies (1:1600) with positive extractable nuclear antigen antibodies (anti-Ro and anti-La). Antibodies to double stranded DNA and rheumatoid factor were negative. She was not taking any medication for any reason, and did not disclose any of these medical details at enrolment. Investigations initiated by the study investigators following her rash included complete blood count, urea and electrolytes, liver function tests, bone profile, immunoglobulins and C-reactive protein all of which were reported within normal values. Antibodies to HIV, hepatitis B and C were negative. An autoimmune profile was unchanged from May 2009 and cryoglobulins were negative. She was referred to rheumatology with a provisional diagnosis of an underlying connective tissue disease. No treatment was given.

**Table.** Hemagglutination-inhibition responses against reverse-genetic NIBRG-121 virus in subjects receiving one or two doses of 7.5µg of MF59-adjuvanted vaccine

Geometric mean titers and geometric mean ratios at each day/day 0 with 95% CI are shown. The percent (and 95% CI) of subjects achieving seroconversion and seroprotection at each post vaccination visit is based on the total number of subjects tested. Seroprotection: defined as titer  $\geq 1:40$ ; Seroconversion defined as pre-vaccination titer of  $< 1:10$  and post vaccination titer of  $\geq 1:40$  or pre-vaccination titer  $> 1:10$  and  $\geq 4$ -fold increase in titer; **Figures in bold fulfill European Committee for Human Medicinal Products (CHMP) criteria.** \*denotes fulfils US Food and Drug Administration Center for Biologics Evaluation and Research (CBER) criteria

	Regulatory immunogenicity criteria		Number of 7.5µg of MF59-adjuvanted vaccine doses			
	CHMP	CBER	One dose, 7.5µg MF59 Day 0	Two doses 7.5µg MF59 and days of administration		
			Day 0	Day 0	Days 0 and 7	Days 0 and 14
Number of subjects			25	25	25	25
<b>Antibody responses with 95 percent CI at Day 0</b>						
Geometric mean titer	-	-	6.4 (4.0-10.2)	6.1 (3.8-9.8)	4.8 (3.7-6.2)	7.5 (4.5-12.6)
Seroprotection $\geq 40$	-	-	12 (2.5-31.2)	12 (2.5-31.2)	4 (0.1-20.4)	12 (2.5-31.2)
<b>Antibody responses with 95 percent CI at Day 14</b>						
Geometric mean titer			149.3 (66.9-333.0)	291.8 (159.5-533.9)	421.5 (268.1-662.8)	135.0 (48.4-376.8)
Geometric mean ratio (day 14 GMT/day 0 GMT)	>2.5	-	<b>23.3 (9.8-55.6)</b>	<b>47.9 (23.3-98.3)</b>	<b>87.9 (53.7-143.4)</b>	<b>17.9 (6.0-53.4)</b>
Seroconversion	>40%	LL of 95% CI >40%	<b>75 (53.2-90.2)*</b>	<b>87 (66.4-97.2)*</b>	<b>96 (78.9-99.9)*</b>	<b>64 (42.5-82.0)*</b>
Seroprotection (titer $\geq 40$ )	>70%	LL of 95% CI >70%	<b>83 (62.6-95.3)</b>	<b>91 (71.9-98.9)*</b>	<b>100 (85.7-100)*</b>	<b>72 (50.6-87.9)</b>
<b>Antibody responses with 95 percent CI at Day 21</b>						
Geometric mean titer			142.7 (65.7-309.9)	241.7 (142.1-411.1)	280.3 (156.7-501.1)	278.9 (135.9-572.2)
Geometric mean ratio (day 21 GMT/day 0 GMT)	>2.5	-	<b>22.3 (9.4-52.6)</b>	<b>39.7 (20.2-77.8)</b>	<b>58.4 (31.9-106.9)</b>	<b>37.1 (16.0-85.8)</b>
Seroconversion	>40%	LL of 95% CI >40%	<b>72 (50.6-87.9)*</b>	<b>84 (63.9-95.5)*</b>	<b>92 (73.9-99.0)*</b>	<b>84 (63.9-95.4)*</b>
Seroprotection (titer $\geq 40$ )	>70%	LL of 95% CI >70%	<b>80 (59.3-93.2)</b>	<b>88 (68.8-97.5)</b>	<b>96 (79.6-99.9)*</b>	<b>88 (68.8-97.5)</b>