Clinical Study Report

A PHASE IIA STUDY TO ASSESS THE SAFETY AND EFFICACY OF A NEW INFLUENZA CANDIDATE VACCINE MVA-NP+M1 IN HEALTHY ADULTS

FLU 002

OXREC Number: 09/H0604/51
Eudract number: 2009-010334-21
CTA number: 21584/0247/001-0001

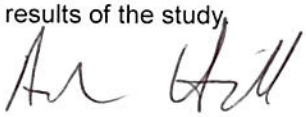
Chief Investigator:	Adrian Hill
Signature / Date:	
Report Date:	26 October 2011
Report Author:	Patrick Lillie
Sponsor:	The University of Oxford
Collaborators	Retroscreen Virology
	University of Southampton
	Quintiles Guy's Drug Research Unit

CONFIDENTIAL

Contents

1. Signature pages for clinical study report

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Signed:  Date: 25/10/20011

Print name: Prof Adrian Hill

P.I or Head of Department

Signed:  Date: 25/10/20011

Print name: Dr Alison Lawrie

Project Manager

2. TITLE PAGE

Study title:	A phase IIa study to assess the safety and efficacy of a new influenza candidate vaccine MVA NP+M1 in healthy adults
Trial code number:	FLU 002
Study description:	An open label, non randomised study of the novel influenza vaccine MVA-NP+M1 in healthy volunteers and its efficacy in a human influenza challenge
Test Vaccine:	MVA-NP+M1
Indication studied:	Safety, immunogenicity and efficacy
Location:	Oxford
Study centre(s):	Centre for Clinical Vaccinology and Tropical Medicine Old Road, Headington Oxford, OX3 7LJ John Warin Ward, Churchill Hospital, Oxford Welcome Trust Clinical Research Facility, University of Southampton, C Level, West Wing, Mailpoint 218 Southampton University Hospitals NHS Trust Southampton, SO16 6YD Guys Drug Research Unit (GDRU), Quintiles Ltd 6 Newcomen Street,London SE1 1YR
Clinical Phase:	IIa
Study dates planned:	Planned to commence May 2009.
Study dates actual:	09 June 2009 – 18 March 2010
Enrolment:	Completed – further recruitment stopped due to end of funding
Sponsor:	University of Oxford
Publication:	In preparation
GCP Statement:	This study was performed in compliance with ICH Good Clinical Practise (GCP) including the archiving of essential documents
Date of report:	26/10/2011
Author of Report:	Patrick Lillie

3. Protocol Synopsis

Objectives	Primary Objective : To assess the safety of a new influenza vaccine, MVANP+M1, when administered as a single dose to healthy volunteers. Secondary Objective: To assess the cellular immune response generated by a new influenza vaccine MVA NP+M1 when administered as a single dose to healthy adults Tertiary Objective: To assess efficacy of the vaccine by measuring viral shedding from nasal washings post Influenza challenge in adults vaccinated and non-vaccinated with MVA NP+M1
Methodology	This was an observational study. Following a preliminary safety study where 2 volunteers were vaccinated with MVA-NP+M1 and challenged with live influenza A virus (A/Wisconsin/67/2005 H3N2), a further 11 vaccinated and 11 control volunteers were also challenged.
Number of patients	Planned: 78 Analysed: 26 (11 control volunteers, 11 vaccinated volunteers challenged as part of efficacy analysis, 2 vaccinated volunteers in pilot challenge and 2 vaccinated volunteers who were not challenged)
Diagnosis and main criteria for inclusion (age, sex, type, HIV status)	Healthy adult aged 18 to 50 years Haemagglutination inhibition titre of ≤1:10 to the influenza A virus used in the challenge stage of the study Able and willing (in the Investigators' opinions) to comply with all study requirements Willing to allow the investigators to discuss the volunteer's medical history with their General Practitioner Agreement to practice barrier contraception from the start of the study until three months after the final vaccination For females, a negative pregnancy test on the days of vaccination and agreement to practice effective contraception for the entire duration of the study Agreement to refrain from blood donation during the course of the study Written informed consent
Duration of treatment	Single vaccination, with challenge taking place up to 90 days after vaccination. Follow up to 210 days post vaccination
Number of treatment groups	1 vaccine group and 1 control group
Criteria for evaluation	Primary: Occurrence and severity of adverse events post vaccination Secondary: Induction of antigen specific T cell responses Tertiary: Standardised symptom scores and viral shedding in nasal lavage fluid
Data management	An electronic database and statistical package is used for storage and analysis of the immunology results
Preventative or Therapeutic?	Preventative
Blinded or Non-Blinded?	Non-Blinded
Controlled or Non-Controlled?	Controlled
Randomised or Non-Randomised?	Non Randomised

4. ETHICS AND REGULATORY APPROVAL

4.1 INDEPENDENT ETHICS COMMITTEE APPROVAL

The study protocol and all its amendments, and the patient information sheet(s) were reviewed and approved by the appropriate independent ethics committee (Oxfordshire Research Ethics Committee A). The initial approval was received on May 19th 2009, and all subsequent amendments were approved by this committee.

4.2 ETHICAL CONDUCT OF THE STUDY

The study was performed in accordance with the declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, October 2000). The trial was conducted in agreement with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practise (GCP)

4.3 VOLUNTEER INFORMATION AND CONSENT

All volunteers provided written informed consent to participate in the study prior to being screened.

The volunteer information sheet detailed the procedures involved in the study (aims, methodology. potential risks, anticipated benefits) and the investigator explained these to each volunteer. The volunteer signed the consent form to indicate that the information had been explained and understood. The volunteer was then allowed time to consider the information presented before signing and dating the informed consent form to indicate that they fully understood the information, and willingly volunteered to participate in the study. The volunteer was given a copy of the informed consent form for their information. The original copy of the informed consent was kept in a confidential file in the Investigators centre records.

4.4 REGULATORY APPROVAL

The study was performed in compliance with the requirements of the regulatory authority, the Medicines and Healthcare products Regulatory Agency (MHRA);

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The study was submitted to the MHRA in February 2009, and gained approval from the MHRA on the 17th of April 2009. All subsequent protocol amendments were approved or notified to the MHRA as appropriate.

5. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Table II shows the principal study personnel involved in the study.

Table II: Principal study personnel

Title	Name and affiliation
Chief Investigator	Adrian Hill
Other investigator	Saul Faust Anthony Gilbert Darren Wilbraham
Lead Clinicians	Patrick Lillie Tom Havelock
Project Managers	Katherine Gantlett Alison Lawrie
Monitor	Clair Dobson
Laboratory investigators	Sarah Gilbert Tamara Berthoud Teresa Lambe

6. DESCRIPTION OF INVESTIGATIONAL PRODUCTS

The vaccine is a recombinant MVA virus expressing influenza A nucleoprotein (NP) fused to matrix protein (M1) via a flexible linker (GGGPGGG) to form a single open reading frame (NP+M1). There is very little polymorphism of these internal virus proteins between influenza A isolates. NP is 92% identical between H3N2 and H1N1 strains, and 91% identical between H3N2 and H5N1 strains. M1 is 95% identical between H3N2 and H1N1 strains, and 93% identical between H3N2 and H5N1 strains. This low level of variation appears to allow strong T cell cross-reactivity. H3N2-derived antigen sequences (from A/Panama/2007/99) have been included as this is the subtype to which most people will have memory T cell responses.

MVA-NP+M1 is manufactured under Good Manufacturing Practice conditions by Impfstoffwerk Dessau-Tornau (IDT), Germany. The vaccine is supplied as liquid in glass vials for intramuscular administration and is stored, between -65^0C and -90^0C, in a locked temperature monitored freezer, at the University of Oxford, Churchill Hospital. All movements of the study vaccine between IDT and the University of Oxford, between Oxford and Southampton, and between the locked freezer and clinic room were documented. Continuous temperature monitoring devices were used during the transport of the vaccine between IDT, Oxford and Southampton. The temperature of the shipment was documented in the MVA NP+M1 core file.

The dose (1.5×10^8 pfu) for Flu002 is based on data derived from the adverse event and immunogenicity profile of MVA-NP+M1 in the Flu001 trial. Whilst a dose of 2.5×10^8 pfu has given the highest T cell responses (compared with a dose of 5×10^7 pfu) it is also associated with a higher number of more severe adverse events. Therefore an intermediate dose of 1.5×10^8 pfu has been chosen as it is likely to give better immunogenicity than 5×10^7 pfu but with less adverse events than 2.5×10^8 pfu. The vaccine was given by the IM route as this has been shown in Flu001 to be associated with less marked local adverse events.

The virus used in the challenge was A/H3N2: A/Wisconsin/67/2005. The virus was administered intranasally as 1 mL of ~$10^{5.25}$ TCID50/mL.

7. STUDY POPULATION

The CONSORT diagram below shows the study population and screening results.

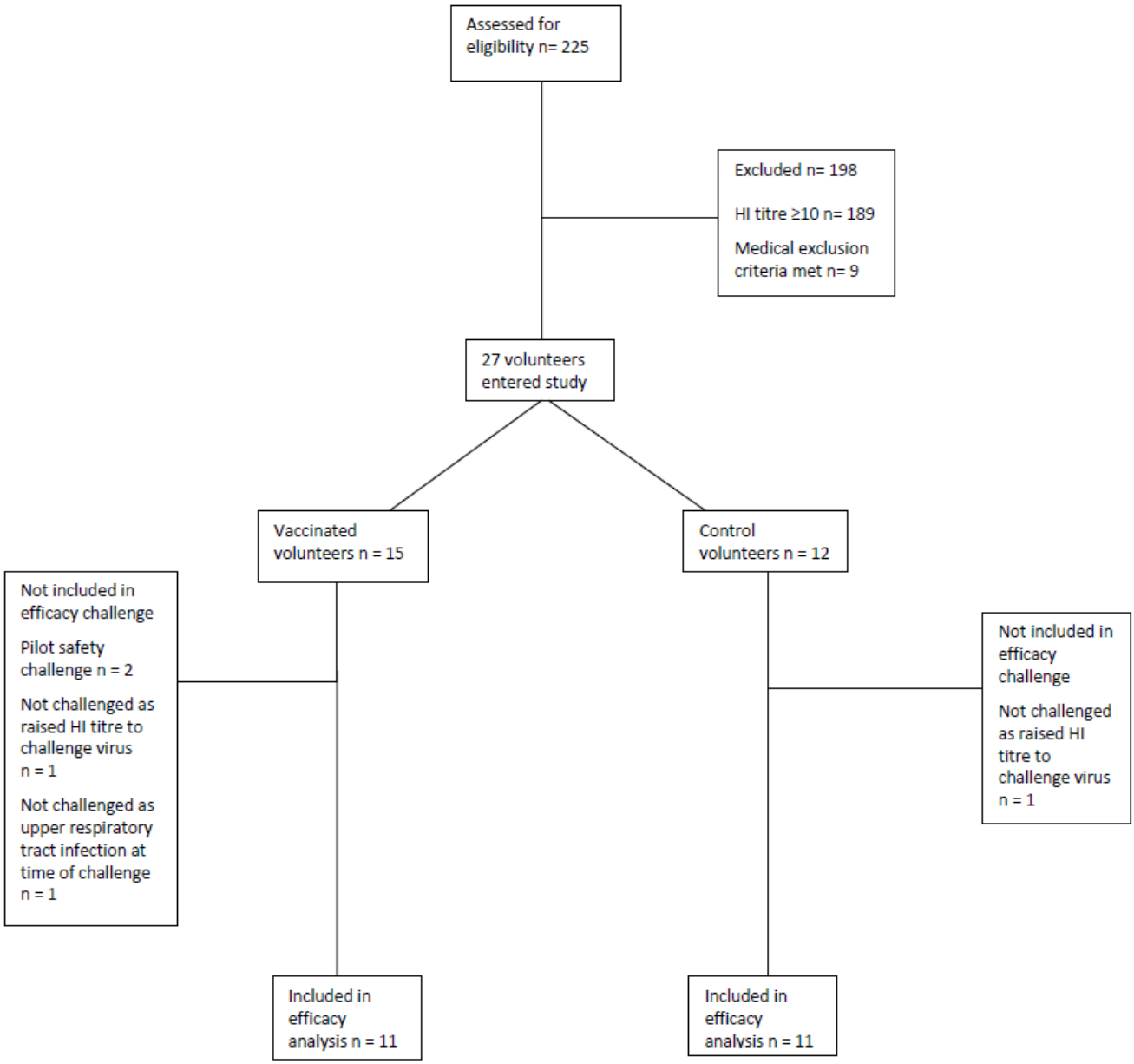


Figure 1: CONSORT diagram of study progress

8. PROTOCOL DEVIATIONS

Protocol deviations

Deviation	*Site: Oxford*	*Site: London*	*Site: Southampton*
Entry criteria	0	0	1
Withdrawal criteria	1	0	0
Incorrect dosing regimen	0	0	0
Concomitant treatment/medication	0	0	0
Other	8	4	1

Table 1: Protocol deviations

9. RESULTS

9.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The demographic details of the volunteer groups are shown in table 2.

Volunteer group	Mean age (range)	Gender
Vaccinated, challenged in main efficacy study (n=11)	28.7 (21 – 45)	F – 6 M – 5
Control, challenged in main efficacy study (n=11)	30 (18 – 43)	F – 6 M – 5
Vaccinated, challenged in pilot safety study (n=2)	42.5 (42 – 43)	F – 0 M – 2
Vaccinated, excluded prior to challenge (n=2)	23.5 (21 – 26)	F – 2 M – 0

Table 2: Demographic details of volunteers.

9.2 IMMUNOLOGY

9.2.1 Ex-vivo Interferon gamma ELISpot results prior to challenge

The primary immunological end point of the study was the interferon gamma ELISpot readout. These were performed using peptides pools consisting of 20 amino acids, overlapping by 10, of the entire matrix 1 and nucleoprotein proteins. The timeline of the study below (figure 2) shows when samples were obtained. Figure 3 shows the ELISpot results for both the vaccinated and control volunteers up to the day prior to challenge. The groups were comparable in their ELISpot responses at screening (p=0.123), but at day 29 the vaccinated group had significantly higher ELISpot responses (vaccinated median response 627, control 215 p=0.0029).

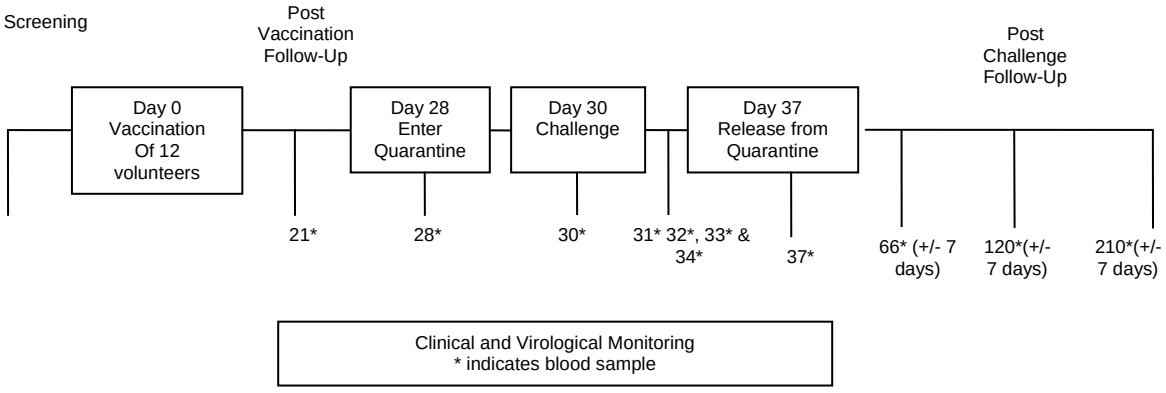


Figure 2: Timeline of study

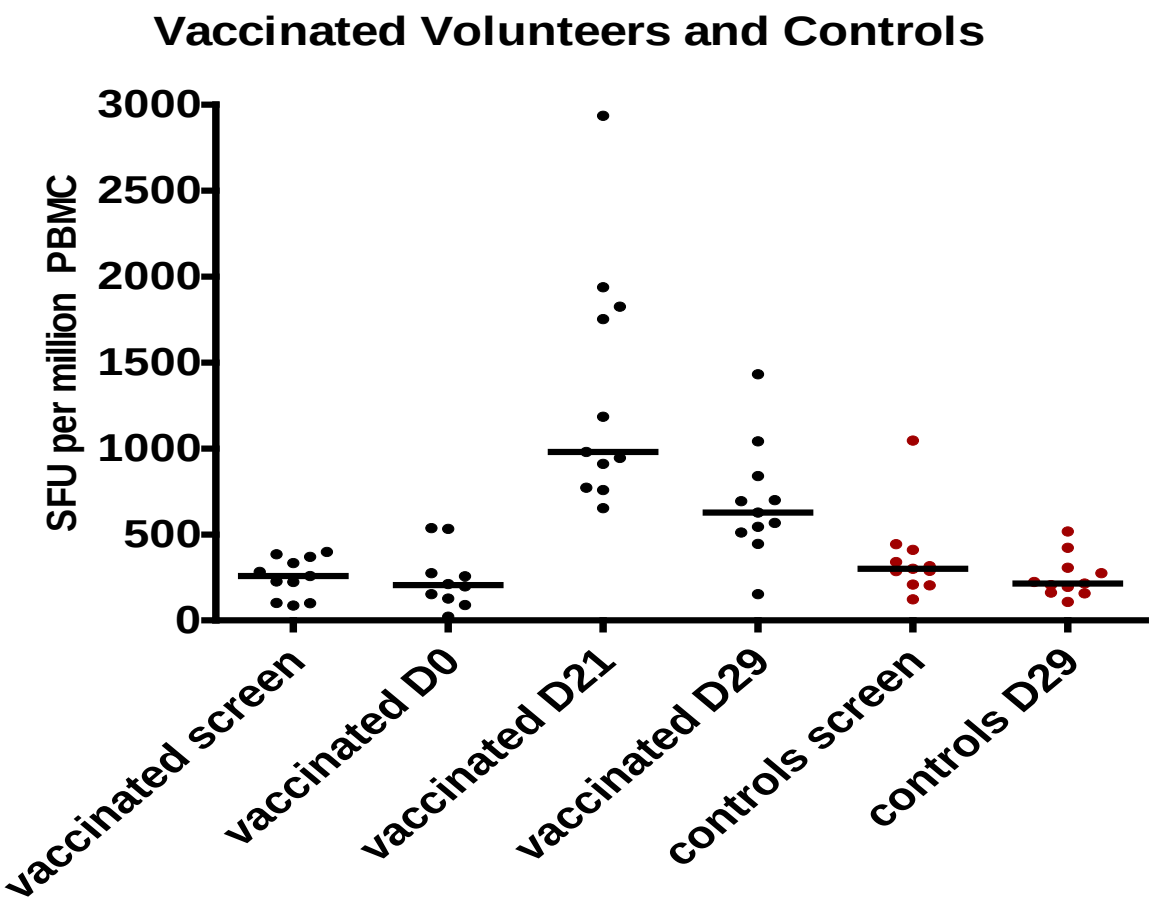
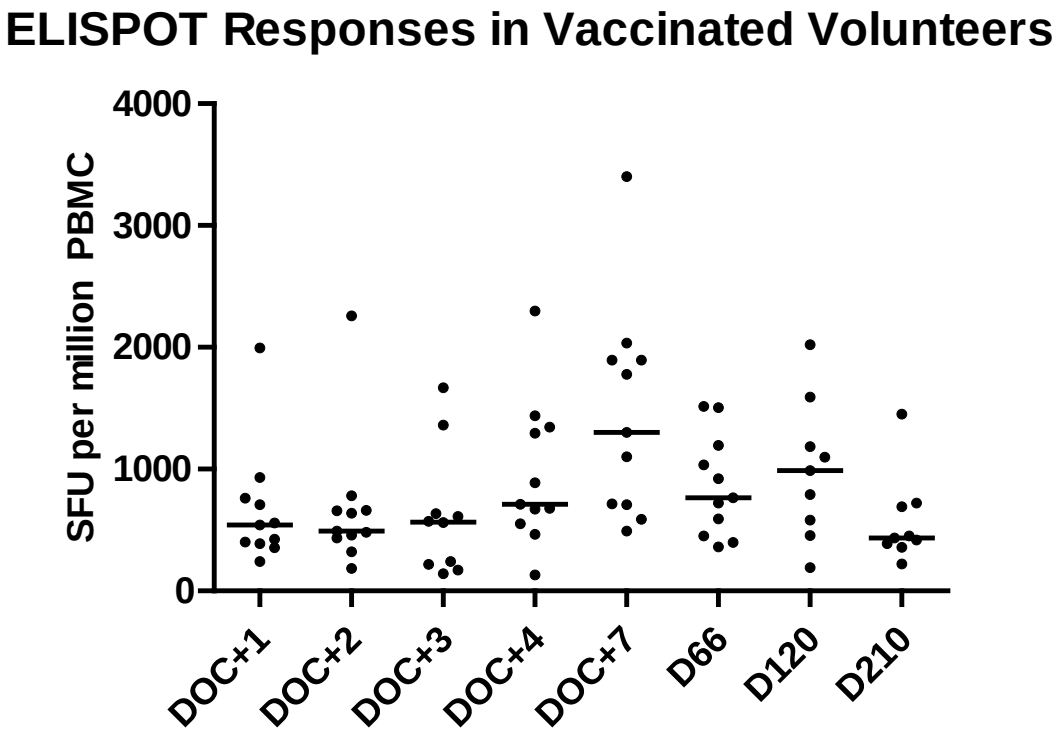


Figure 3: ELISpot responses prior to influenza challenge

9.2.1 Ex-vivo Interferon gamma ELISpot results post challenge

The ELISpot responses of both the vaccinated and control volunteers are shown in figure 4. At day of challenge (DOC) +1 (p=0.0058), and DOC + 2 (p=0.0039) the vaccinated volunteers had significantly higher ELISpot responses. By DOC +7 this difference was not present, and the groups remained comparable in their ELISpot responses out to day 210.



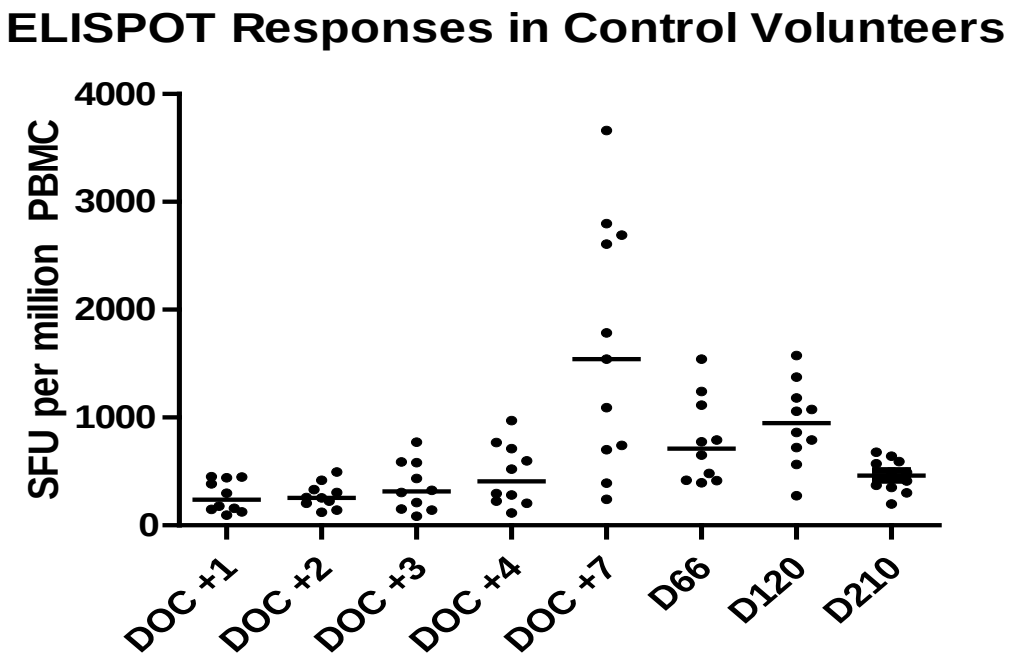


Figure 4: ELISpot response post influenza challenge

9.3 EFFICACY

9.3.1 Clinical outcomes

During the challenge phase of the study, volunteers were quarantined in an isolation unit. For the efficacy analysis, a standardised data collection sheet was used to record symptoms attributable to influenza infection. The data was collected, twice daily, from 12 hours post challenge until the end of quarantine, 7 days post challenge. In addition volunteers underwent a structured physical examination once daily by a study physician. Severity of symptoms was grade on a 0 – 3 scale, with 0 being absence of the symptom, 1 just noticeable, 2 clearly bothersome but not interrupting daily activities and 3 quite bothersome and interrupting daily activities. Volunteers also had standardised tissues counted to ascertain the degree of mucus produced post influenza challenge. Analysis of the symptom data is shown in figures 5 and 6. Volunteers were classified into no influenza disease, mild disease or moderate depending on their total summed score (no disease 0-10% of maximum score, mild 11-75%, moderate >75%). Although there was a trend towards the vaccine group having improved outcomes, none of these reached statistical significance. Table 3 summarises the main outcome measures in the study.

	Total summed score	Lab confirmed influenza disease	Moderate Severity	Amount of virus shed
Vaccinated	112	2	1	2.75×10^4
Control	168	5	4	3.30×10^5
Difference	56	3	3	3.02×10^5
Difference as % of control	33	60	75	92

Table 3: Summary of efficacy results

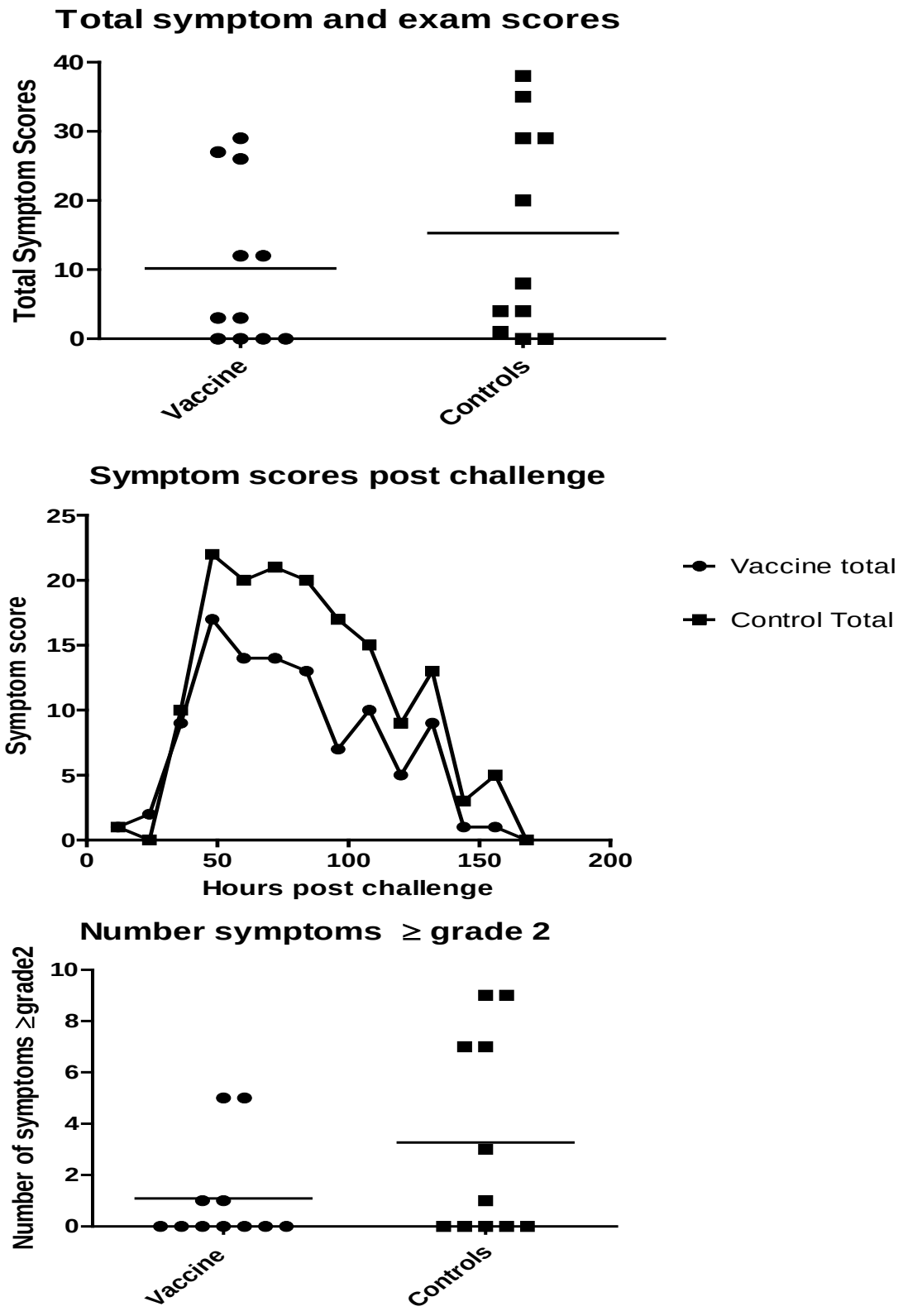


Figure 5: Clinical efficacy results

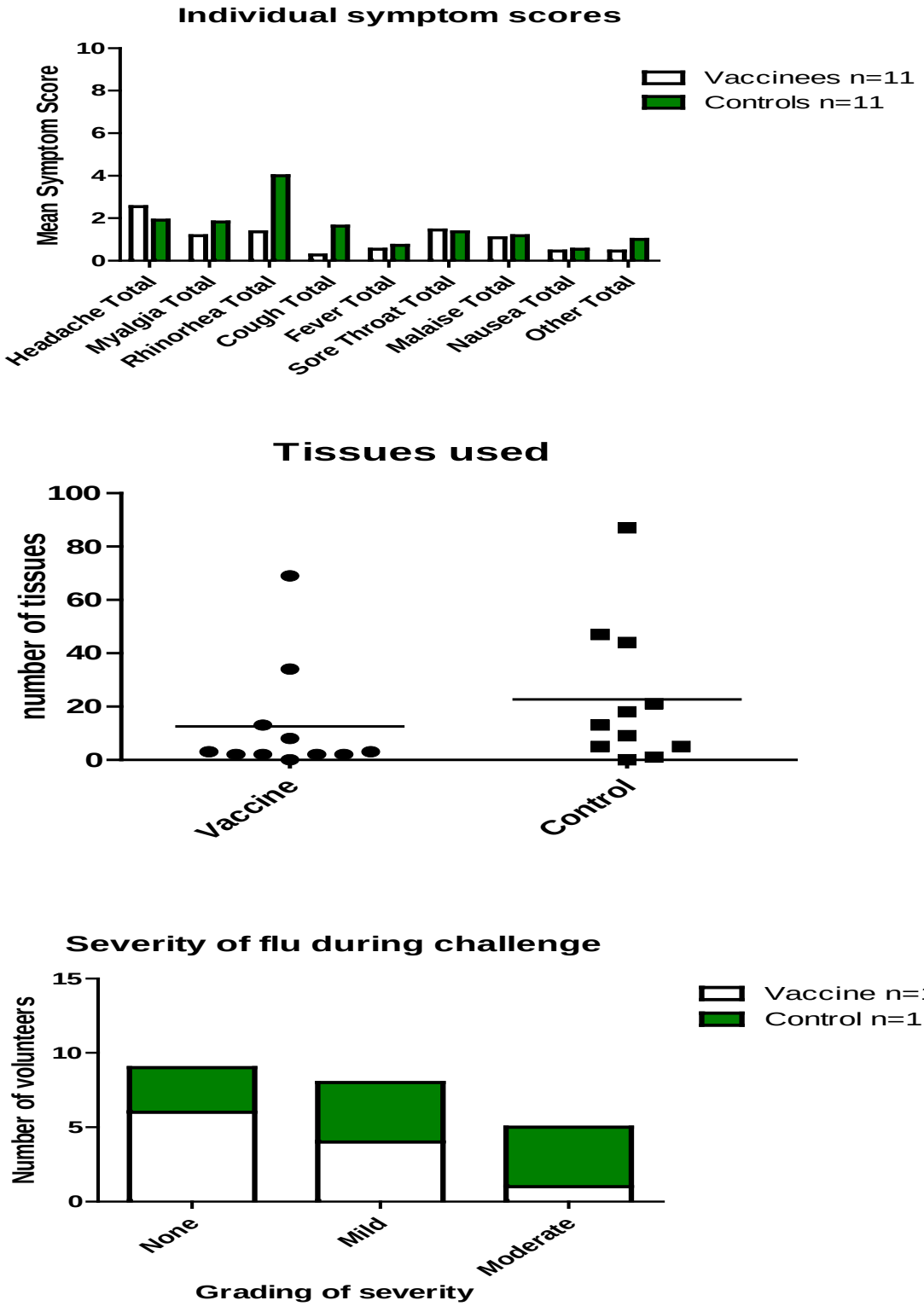


Figure 6: Severity results of influenza challenge

9.3.2 Viral Shedding

As well as the severity assessment described previously, nasal lavage samples were obtained daily from volunteers, from DOC +1 until release from quarantine on DOC +7. Figure 7 shows the viral shedding results, as well as the number of volunteers with laboratory confirmed influenza illness (illness severity of mild or greater, together with confirmed viral shedding)

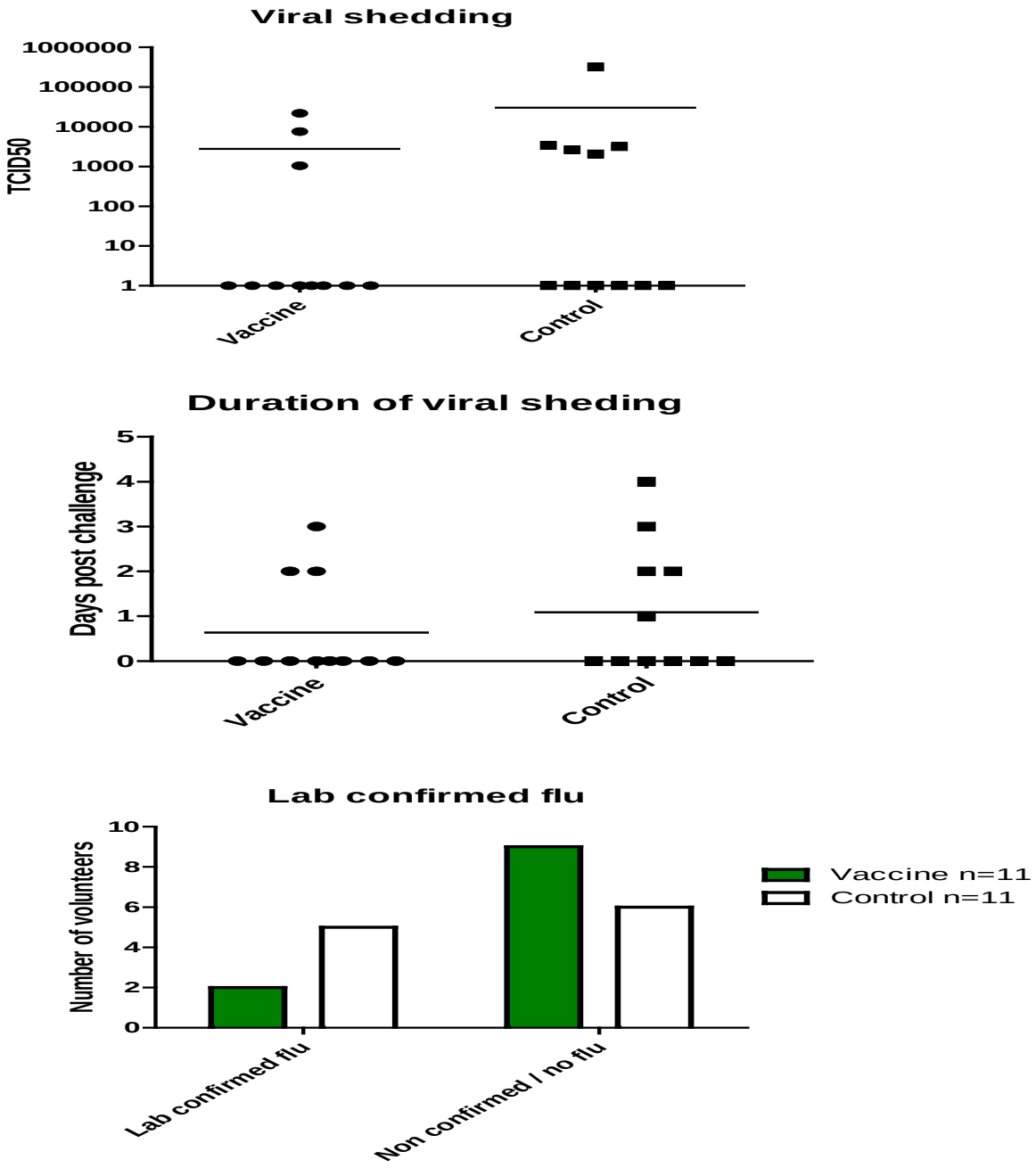


Figure 7: Viral shedding during influenza challenge

9.3.3 Correlation of efficacy and immunology results

A correlate of protection against influenza disease in the absence of antibody (as in this case) would be extremely useful, as it would allow assessment of a surrogate of efficacy without the need for challenge studies. While no correlate was identified directly in this study, a significant relationship was noted between the time of peak ELISpot response and severity. This is postulated to be due to increased lymphocyte proliferative capacity and speed of response to viral infection. Figure 8 demonstrates the relationship.

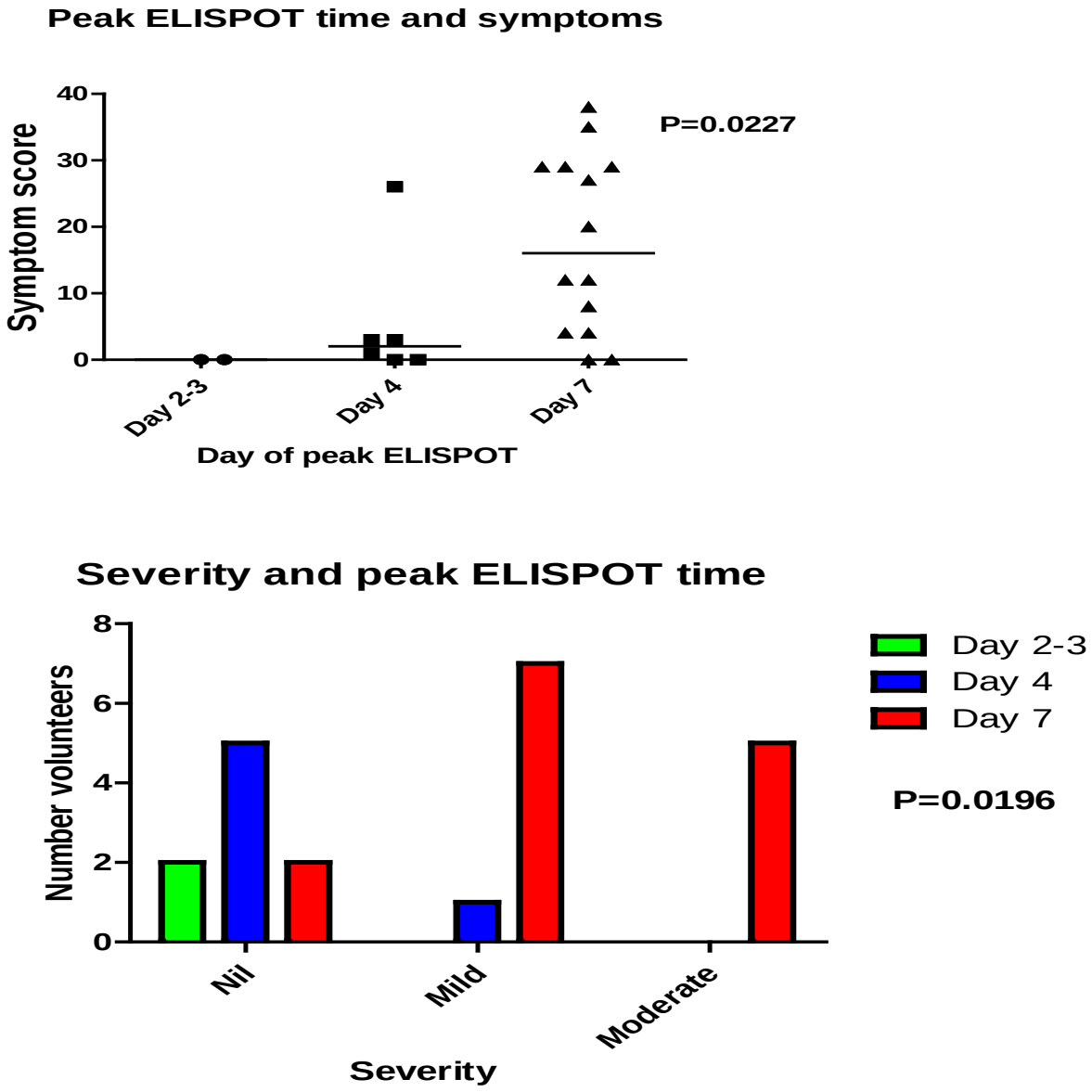


Figure 8: Correlation of time to peak ELISpot and severity

10. SAFETY EVALUATION

10.1 SAFETY RESULTS – Pilot challenge

As this study was the first to study the effect of a potent T cell stimulation vaccine on the course of influenza infection, a pilot challenge study was conducted to assess the safety of the challenge virus in 2 vaccinated volunteers, primarily to assess for severe immune-pathology in the lung. The 2 vaccinated volunteers were challenged 24 days prior to the main challenge. Both volunteers experienced symptoms consistent with influenza infection, of the upper respiratory tract only, with no evidence of severe disease or lower respiratory tract involvement and no laboratory or clinical evidence of organ dysfunction. The results of the pilot challenge were reported to an internal safety committee who reviewed the data and approved the continuation of the study to the main challenge phase. Both volunteers were well on discharge from quarantine and had no further symptoms on follow up throughout the study.

10.2 ADVERSE EVENTS (AEs)

10.2.1 Post vaccination AEs

Adverse events post vaccination were collected until entry into the quarantine unit for the challenge phase of the study. Figures 9 and 10 show the vaccination related AEs and their severity. Local adverse events had a median duration of 2 days (range 1 – 7), while systemic AEs had a median duration of 1 day (range 1 – 6).

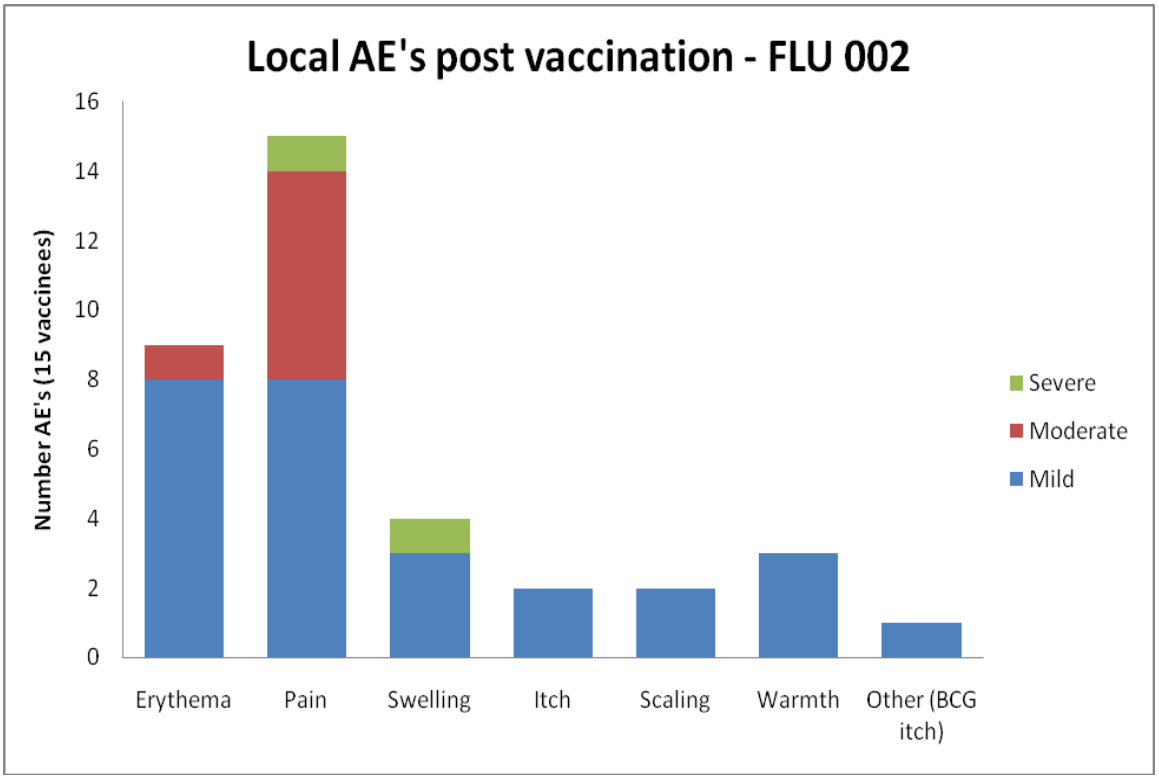


Figure 9: Local adverse events post vaccination

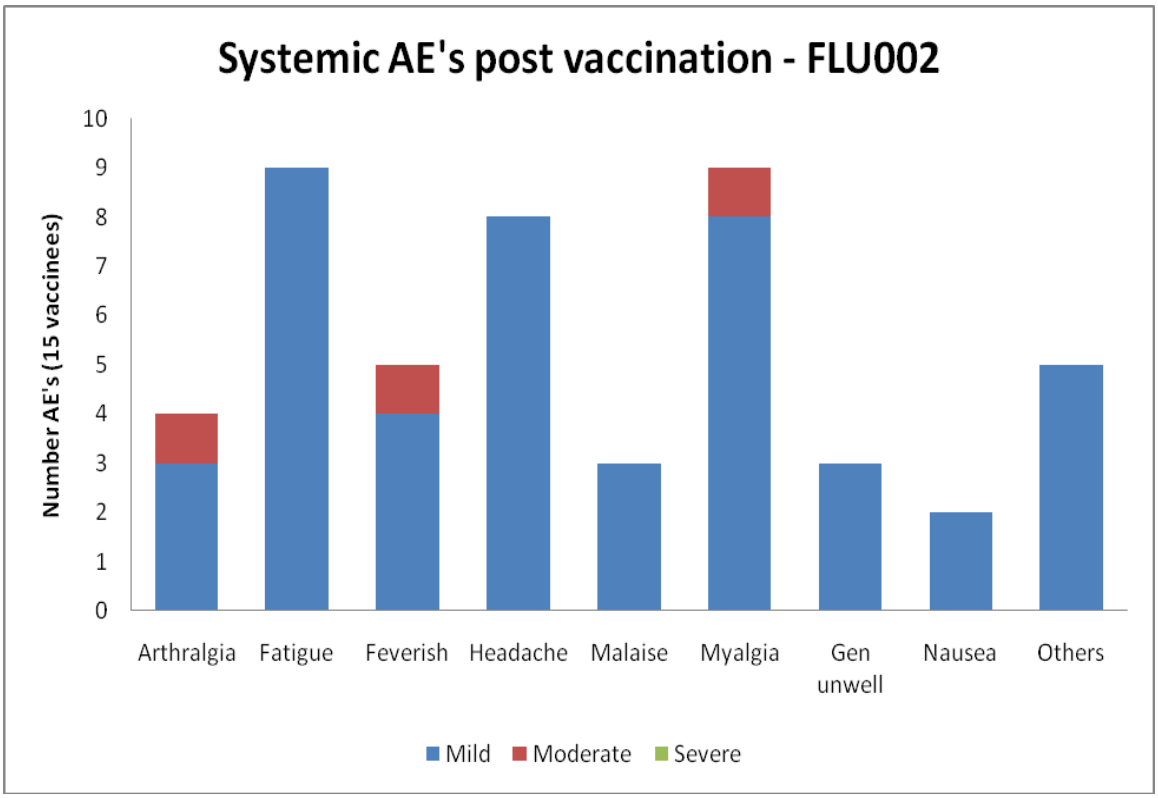


Figure 10: Systemic adverse events post vaccination

10.2.2 AEs post influenza challenge

Post influenza challenge both control and vaccinated volunteers were followed up for adverse events. At the completion of the quarantine phase, there were 12 AEs ongoing, of which 11 were mild in severity, with 1 mild AE (eczema requiring topical steroids). None of these AEs were thought to have a causal relationship with the vaccine. All had resolved by the time of the first post challenge follow up. A further 26 adverse events occurred between the release from quarantine and the end of the study. Of these 17 were mild in nature, of which 7 were ongoing at the end of the study (eczema, intermittent herpes infection, and symptoms of upper respiratory tract infections), and were being followed up by the volunteer's general practitioner. 8 moderate severity AEs were documented (nausea, diarrhoea, light headedness and disorientation in 1 volunteer eczema in 1 and cough, myalgia and rhinorrhea in another). All of these resolved by the second post challenge visit. 1 severe AE was recorded, in a volunteer who experienced a psychotic reaction after taking illicit ketamine. This volunteer was treated as an outpatient and their psychosis resolved, after receiving treatment.

10.3 SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS

There were no Serious Adverse Events during the study.

10.4 CLINICAL LABORATORY EVALUATION

No clinically significant abnormal blood test results were obtained post vaccination. In the pilot challenge one volunteer had a transient rise in their alanine transaminase on DOC +3, which had markedly reduced by the end of the quarantine phase, and had returned to normal at the first follow up visit. No other clinically significant laboratory tests were found throughout the study

10.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

No vaccinated volunteer experienced any significant physical abnormality post vaccination. During the challenge phase of the study, all volunteers underwent a daily physical examination, as well as spirometry and electrocardiography, both prior to influenza challenge and twice whilst in the quarantine unit. Other than clinical examination findings that were compatible with influenza infection (all of which resolved prior to the completion of the quarantine study) no significant findings were noted, and all spirometry and electrocardiogram results were within normal limits.

10.6 SAFETY CONCLUSIONS

All volunteers completed the study with no withdrawals due to AEs. Vaccine related adverse events were mild in the majority of cases and short lived in duration. Both vaccinated and control volunteers tolerated the influenza challenge and symptoms of influenza were again mild in the majority and all had resolved by the end of the quarantine phase. The ongoing AEs at the end of the study were all mild in severity and were under follow up as needed.

11. DISCUSSION AND OVERALL CONCLUSIONS

The FLU 002 study was the first time a potent T cell inducing vaccine has been used in an influenza challenge in an attempt to demonstrate safety and efficacy. Current influenza vaccines induce antibodies against haemagglutinin, which due to the propensity of influenza virus to mutate need to be re-formulated annually. Also the potential of new strains to emerge, as evidenced by pandemic H1N1 influenza, means that the assessment of novel influenza vaccines, capable of inducing heterosubtypic immunity is of public health importance.

The primary objective of the study was to demonstrate safety of MVA-NP+M1. Vaccine related adverse events were mild in the majority of volunteers and all had resolved by 7 days post vaccination. This is comparable to other MVA vectored vaccines and complements the data from the FLU 001 trial (which is currently ongoing). The study also set out to assess the safety of the vaccine in volunteers who subsequently undergo challenge with live influenza A virus. Theoretical concerns over this include the development of immunopathology in the lungs due to cytokine production and lymphocyte induced tissue damage. In both the pilot challenge of 2 vaccinated volunteers and the subsequent efficacy challenge of 11 vaccinated volunteers, no signs of severe end organ damage or lower respiratory tract disease were found and all volunteers completed the study without withdrawing due to AEs. Although further challenge studies will be needed, these early data are useful to inform this, and the lack of immunopathology so far is reassuring.

The secondary objective was to assess the immunogenicity of a single dose of MVA-NP+M1. There was a significant increase in the primary immunology end point of the ELISpot response by day 21, which was maintained above that seen in the control volunteers, until the 3rd of the challenge element of the study. The vaccine boosted pre existing responses around 4-5 fold prior to influenza challenge. Although no correlate of protection prior to challenge was found, the timing of the peak ELISpot responses post challenge did predict clinical response. This may be due to proliferative capability of antigen specific lymphocytes and further laboratory evaluation is ongoing to assess this.

The tertiary objective was to evaluate the clinical efficacy of the vaccine in preventing influenza illness and viral shedding. There was a trend towards vaccine efficacy across all measures, however none reached statistical significance. The magnitude of the effect (60% reduction in laboratory confirmed disease, 75% in moderate / severe disease) is comparable to that of seasonal influenza vaccine and further challenge studies may allow for refining the estimate of efficacy.

The FLU 002 study has demonstrated that a T-cell stimulating MVA vectored vaccine has safety profile that is comparable to other MVA vaccines, and that challenge studies are feasible. The efficacy results are encouraging and further evaluation of T cell stimulating vaccines against influenza can be carried out to further assess the safety and efficacy of this concept.