Anthrax vaccine: who needs it and when?

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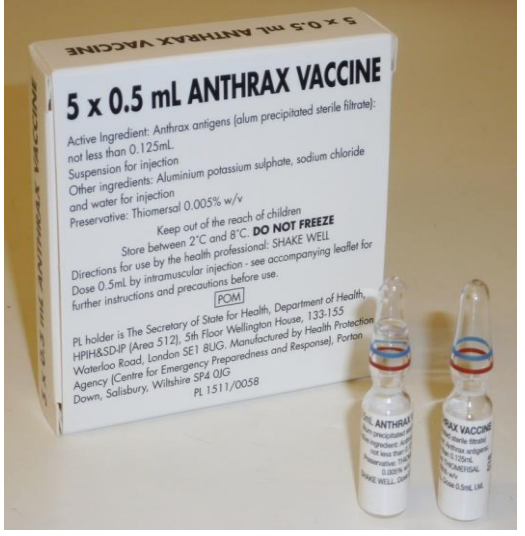
Licensed anthrax vaccines



Anthrax Vaccine Precipitated (AVP) - UK

- Alum precipitated filtrate of non-encapsulated Sterne strain
- Contains PA, some LF, trace of EF
- Adjuvant: aluminium sulphate
- 0, 3, 6 & 32 weeks; then annual boosters

Anthrax Vaccine Adsorbed (AVA, Biothrax) - USA

- Al_2O_3 adsorbed filtrate of non-encapsulated strain V770-NP1-R
- Contains PA and trace of LF
- Adjuvant: alhydrogel
- 0, 2, 4 weeks, 6, 12, 18 months; then annual boosters

Live Attenuated Anthrax Vaccine (LAAV) - FSU

- Spores of non-encapsulated STI-1 strain
- 0 & 4 weeks; then annual boosters

Non-clinical studies of anthrax vaccine efficacy

Reviewed by Saile & Quinn (2011) in *Bacillus Anthracis* and Anthrax, Bergman NH (ed)

- Best models are rabbit and non-human primates (NHPs)
- Passive transfer studies using serum from previously immunised humans or animals are supportive
- Vaccines containing PA with an aluminium based adjuvant optimal
- When 3 doses given at 7-14 day intervals these vaccines protect against supra-lethal inhaled spore challenge
- Early (1950s-1970s) studies suggest prolonged (up to 3-4 years) protection provided in NHP models

Challenge studies with rabbits vaccinated with Aluminium-adjuvanted PA (PHE Porton, 2016)

- AVP and AVA protect against inhaled spore challenges at multiple lethal doses
- GUP regimen: 3 doses at 0, 4 + 8 weeks followed by challenge (LD_{50} range: 58-190) at 14 weeks
- PEP regimen: 2 doses at 0 + 7 days with levofloxacin for 7 days after challenge (LD_{50} range: 110-300)

Studies in HLA transgenic mice (Ascough *et al* 2014)

- Immunodominant epitopes in mice recognized by T cells from humans with previous infection or AVP vaccination
- Protective immunity from lethal challenge conferred by a subunit vaccine comprising these epitopes

How long does immunity to anthrax antigens last?

Cases of second episode of anthrax after recovery from cutaneous infection?

- **Georgia -** none recorded since records began in 1940s (P Imnadze)
- **Turkey -** no confirmed cases (2 possible) since 1975 (M Doganay)
- **Russia -** 3 repeat cases in 1940s at intervals of 8, 15 & 20 years (E Shlyakov)
- **USA -** 2 repeat cases in 1920, 1 individual with 3 episodes, 1 repeat case in 1972 (P Turnbull)
- **UK -** 2 repeat cases in 1912, 1 repeat case after 25 year gap reported in 1982 (P Turnbull)

Cases of anthrax infection in vaccinated individuals?

- **Georgia -** none in laboratory staff given LAAV, or animals given live spore vaccine
- **Turkey -** no human vaccination programme, but no cases in animals given live spore vaccine
- **USA -** CDC survey of AVA use in industry (1960-70): 3 doses considered protective
- **UK -** anthrax-like illness (2012) in one previously vaccinated (5 doses AVP) individual – survived

Reported cases of infection in previously infected or vaccinated individuals are very rare

Studies of adaptive immune responses to anthrax toxin antigens

Cutaneous Anthrax Patients in Turkey & AVP recipients in UK

- Strong T cell memory was detectable several years after antibiotic-treated anthrax infection & vaccination with AVP
- Major target of T cell immunity in both infected and vaccinated individuals was LF, notably domain IV
- Responses to LF were of similar magnitude in both groups, but responses to PA were greater in infected patients
- One specific CD4 T cell epitope targeted within LF domain IV preferentially seen after infection, but not vaccination

Natural exposure to cutaneous anthrax gives long-lasting T cell immunity encompassing infection-specific epitopes.
RJ Ingram *et al. J. Immunol*. 2010; 25: 6089-6097. doi:10.4049/jimmunol.0901581

Adaptive immune responses following cutaneous anthrax infection or vaccination in Georgia

- Cutaneous anthrax produced strong IFN-γ responses to all three antigens and antibody responses to PA & LF
- AVP produced IFN-γ responses to EF and antibody responses to all three antigens
- AVA and LAAV vaccinees had antibody responses to PA only and no IFN-γ responses to any antigen
- TNA titres correlated with Anti-PA Ab titres in AVA and LAAV vaccinees and anti-LF Ab titres in AVP vaccinees

A comparison of the adaptive immune response between recovered anthrax patients and individuals receiving three different anthrax vaccines.
TR Laws *et al*, PLoS ONE 11(3): e0148713. doi:10.1371/journal.pone.0148713

Vaccines & cutaneous infection: qualitatively different, quantitatively similar immune responses

AVP Booster Study: phase 4 clinical trial

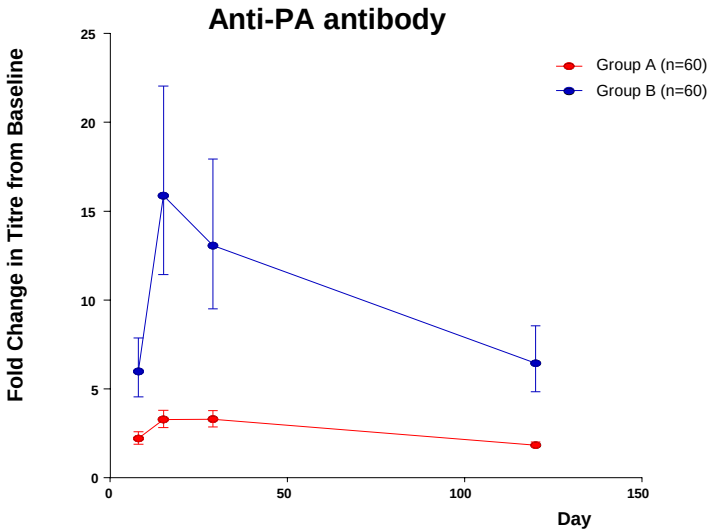
- Two groups of healthy volunteers (n=60 each)

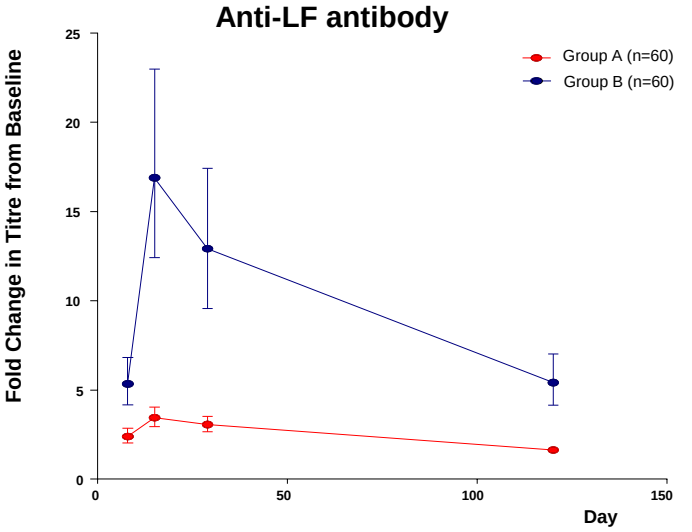
  Group A: regular annual boosters

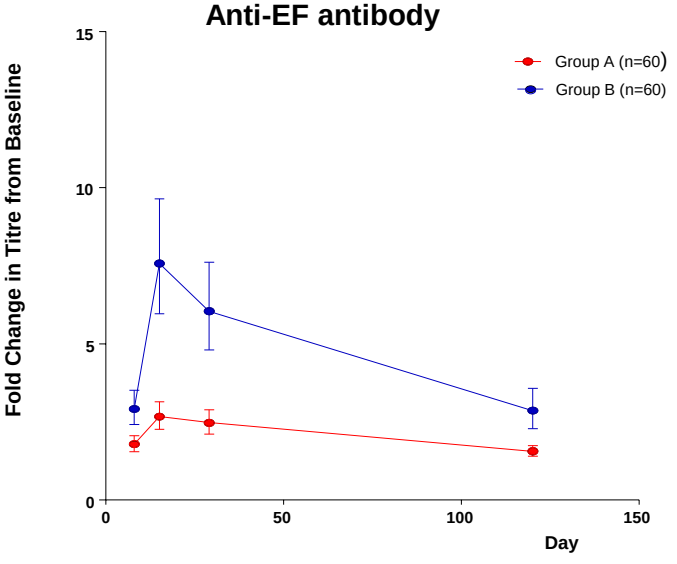
  Group B: >2 years since last dose

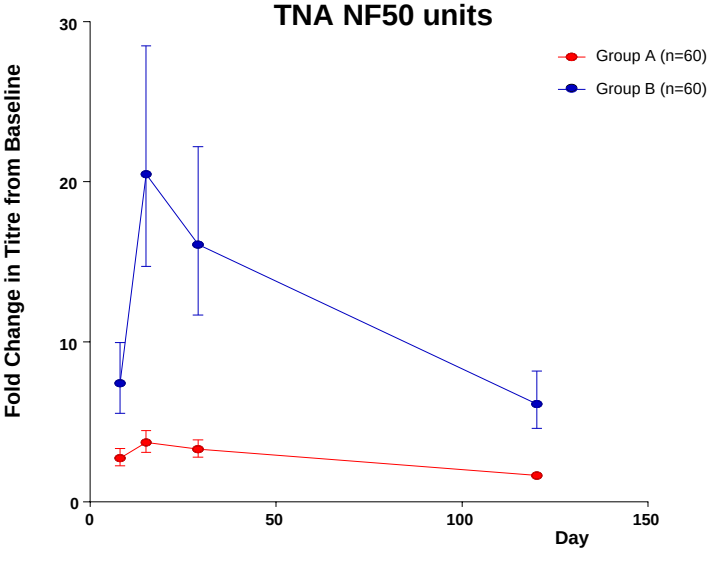
- Entry criteria
  - Male or female, 18-60 years old: *[M 66; F 54; Age 26-59]*
  - Previously received 4 dose primary schedule of AVP
  - No history of severe reaction to AVP
- Booster dose of AVP on Day 1
  - Single batch given to all subjects
- Vaccination site assessment: Days 1, 3, 8, 15, 29, 120
- Diary cards for Days 1-15
- Blood samples for serology: Days 1, 8, 15, 29, 120
  - Anti-PA, anti-LF and anti-EF IgG titres (ELISA)
  - Toxin Neutralisation Assay (TNA) titres

Fold change from baseline titres: GM Ratio +/- 95% CI

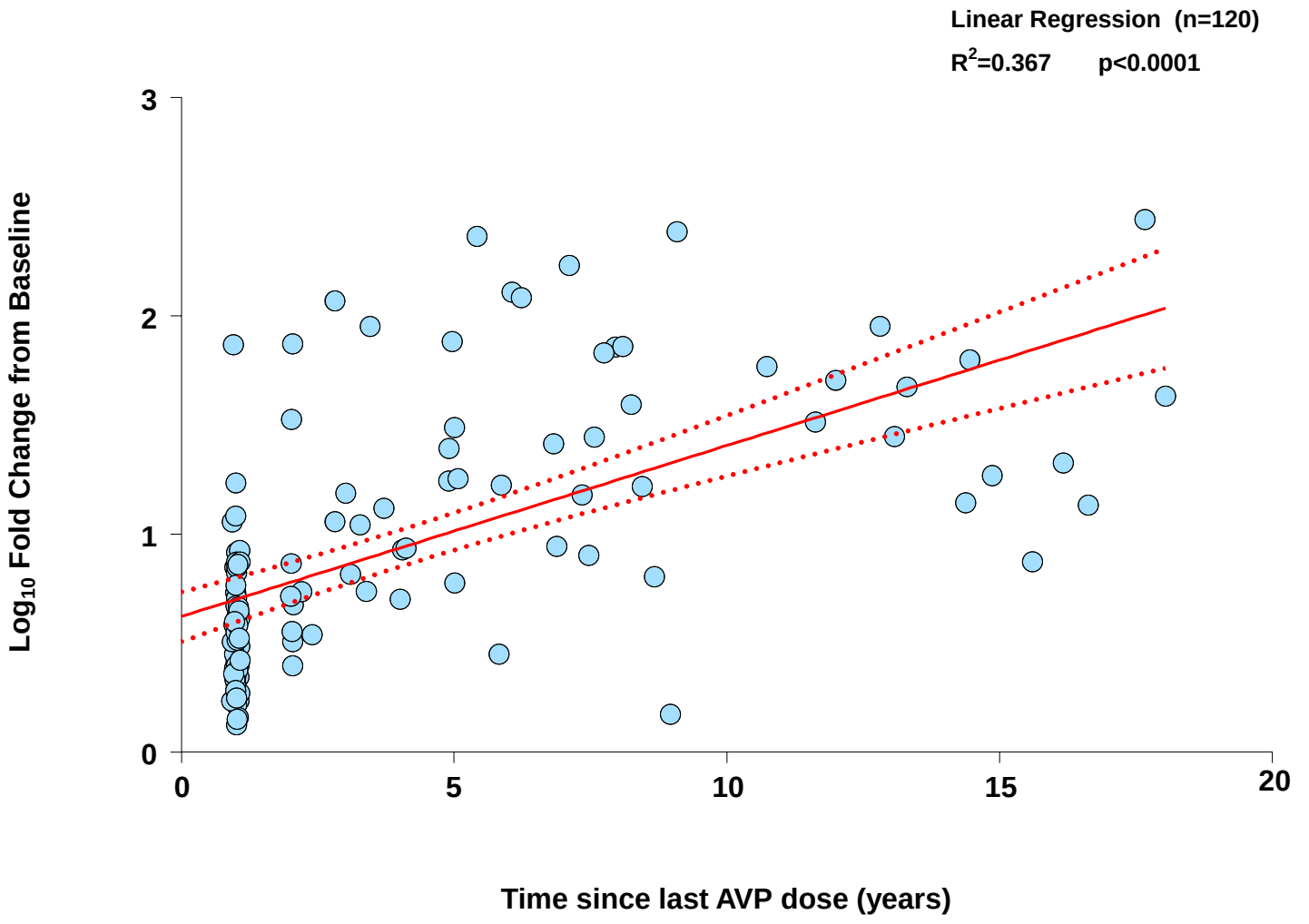




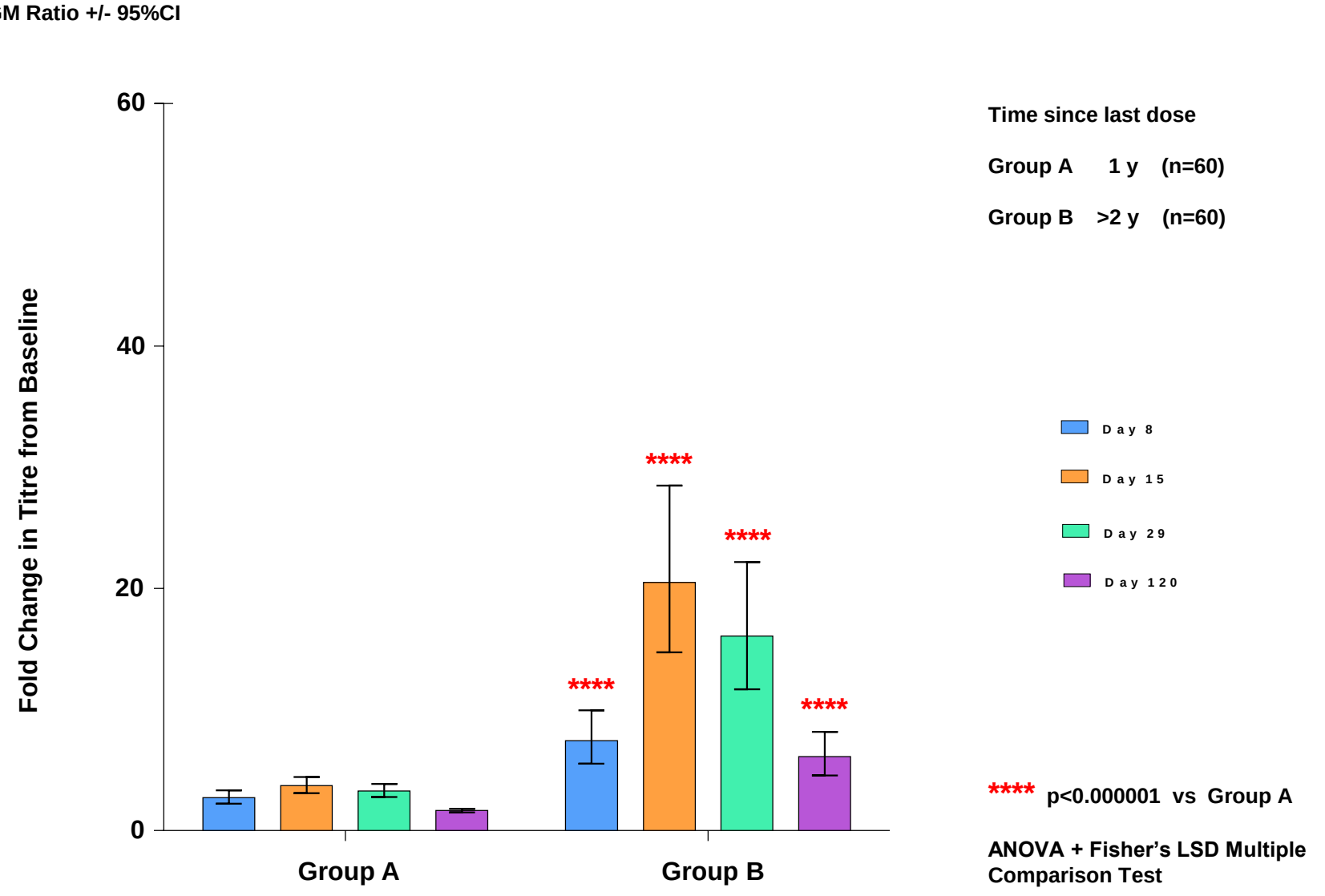




Day 15 post-booster TNA titres vs: *Time since previous dose of AVP*



TNA titres after booster at increasing intervals since previous dose



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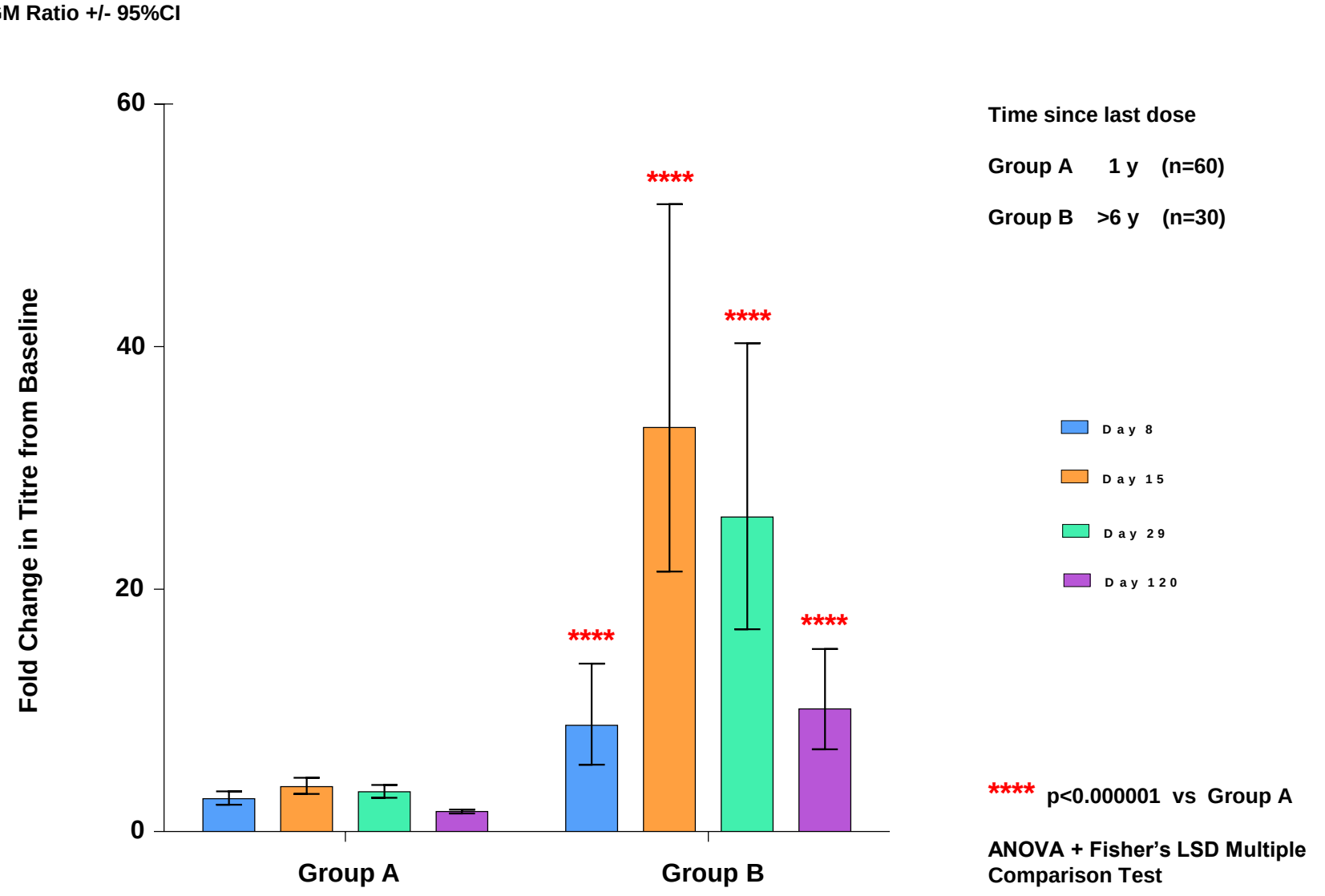

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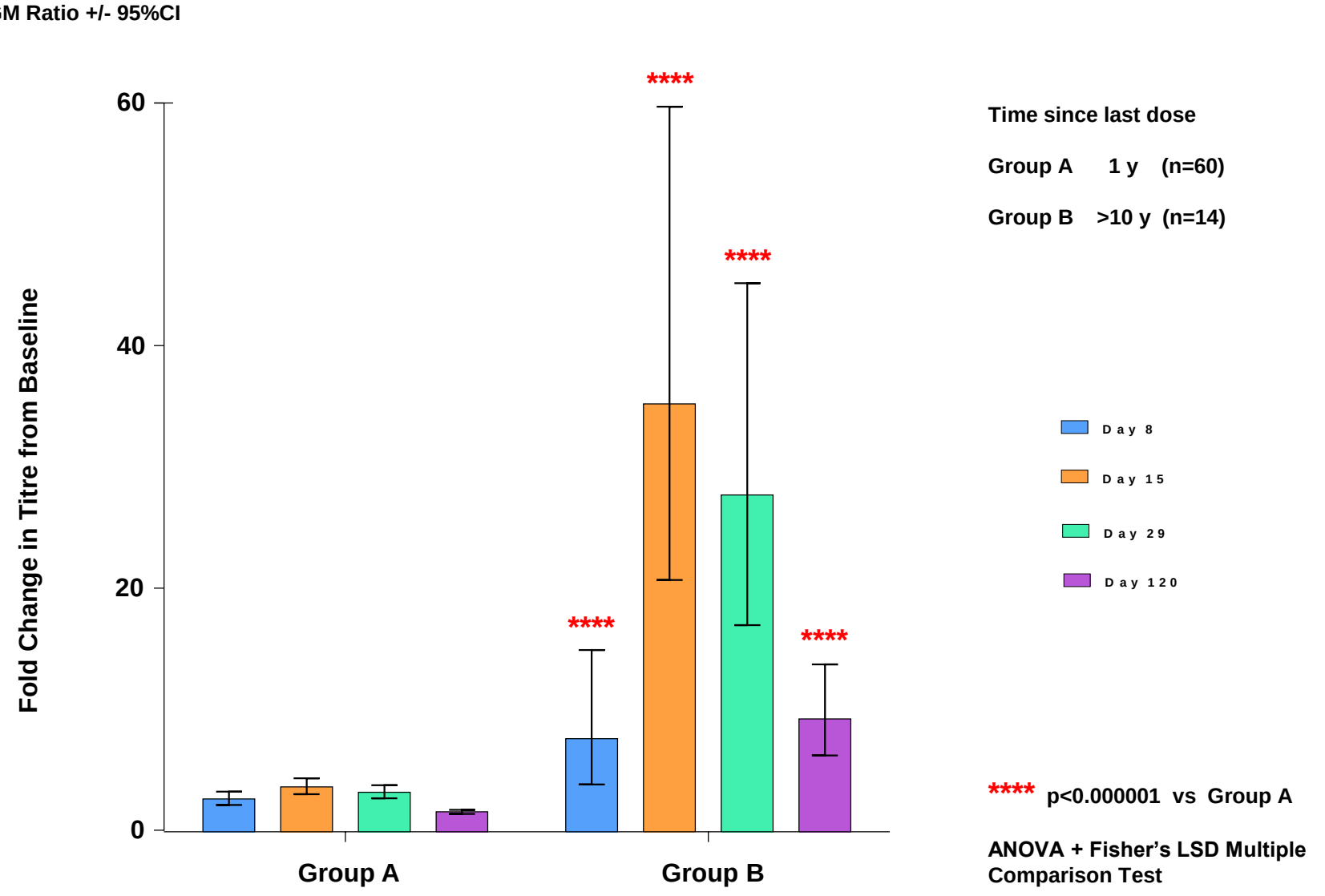
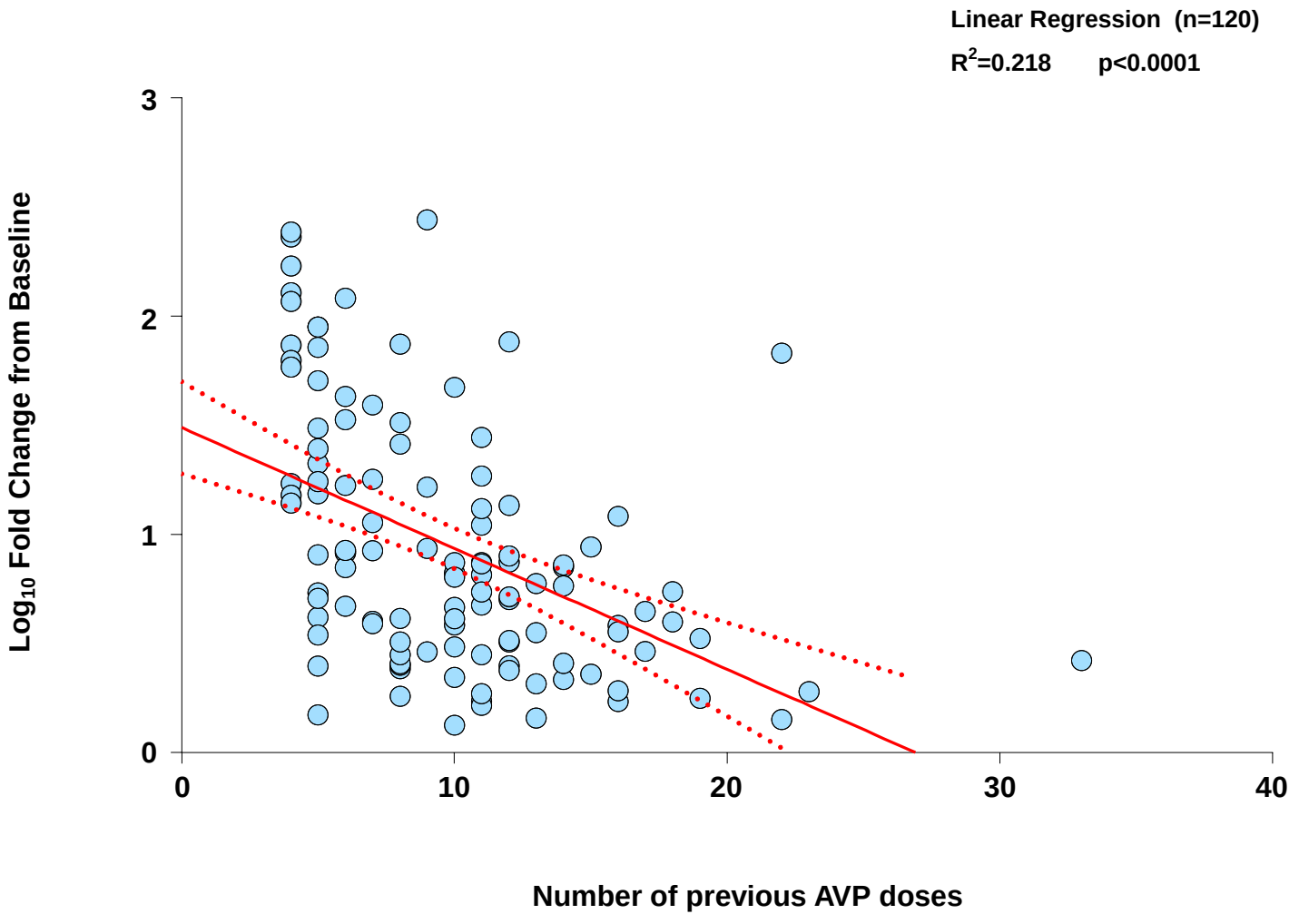
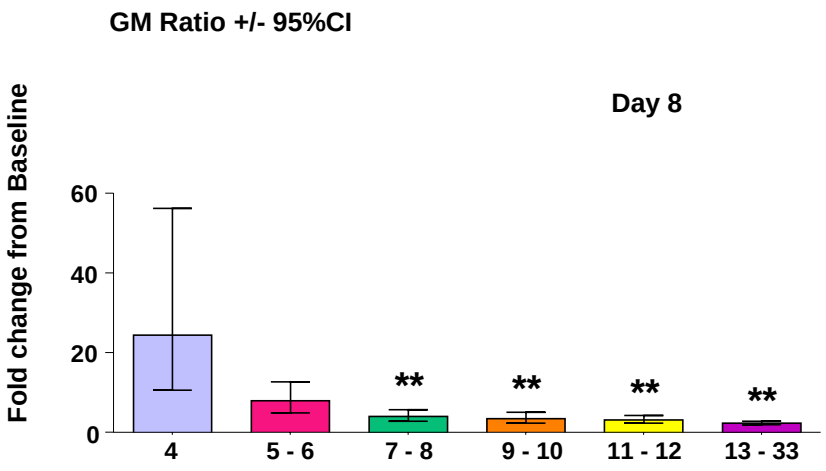
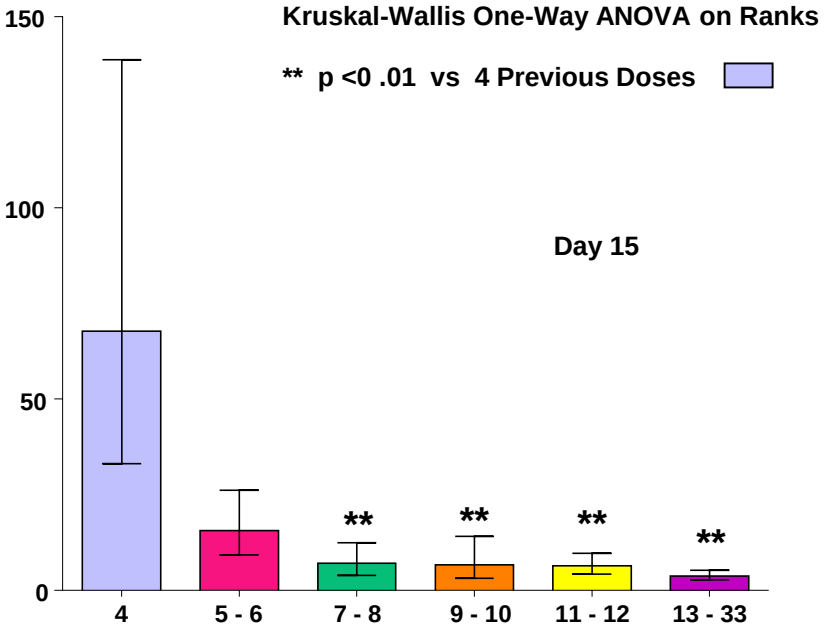


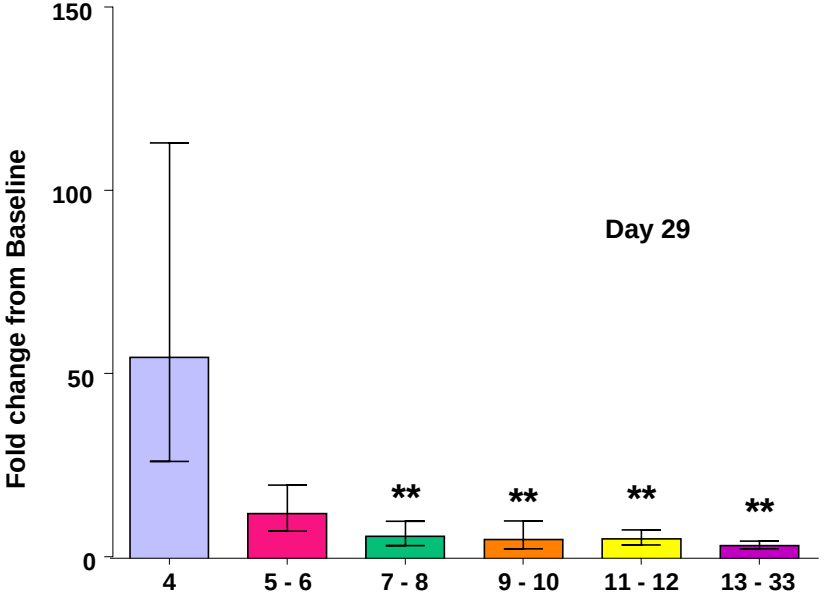
Day 15 post-booster TNA titres vs: *Number of previous AVP doses*

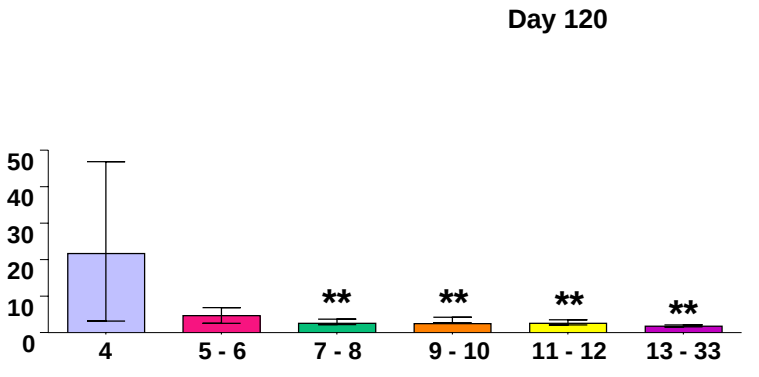


TNA titres after booster vs:
Number of previous AVP doses









Conclusions from Dstl AVP Booster Study

- **AVP induces significant immune responses against all 3 anthrax toxins**
  - High titres of IgG binding PA, LF & EF measured by ELISA
  - High titres in Toxin Neutralisation Assay (TNA) – correlate of efficacy
- **Booster doses of AVP have**
  - Low incidence of local reactions
    - Slightly more in delayed booster group, impact on daily activity minimal
  - Few systemic symptoms overall
    - More in delayed booster group, impact on daily activity generally none or mild
- **Increasing intervals since last dose associated with greater serological responses**
  - TNA responses parallel changes in anti-PA and anti-LF antibody titres
  - Maximal responses seen 10 or more years after last dose
- **Magnitude of responses decreases with increasing total number of doses**
  - Highest values observed after 4-dose primary schedule only
  - Multiple doses (7 or more) may produce tolerance to vaccine antigens

AVA clinical studies

Pittman *et al* (2014) Vaccine 32: 5131-5139. doi: 10.1016/j.vaccine.2014.03.076

- Prospective clinical study in US military personnel: anti-PA Ab and TNA titre responses
- 4th dose of AVA given on schedule at 6 months or following variable delay
- Serological responses to Dose 4 delayed by 5-7 years non-inferior to those given at 6 months

Wright *et al* (2014) Vaccine 32: 1019-1028. doi: 10.1016/j.vaccine.2013.10.039

- Large clinical trial comparing different AVA primary schedules with licensed 6 dose subcutaneous schedule
- Intra-muscular dosing regimens had non-inferior immunogenicity & fewer local reactions than subcutaneous
- 3 dose priming series (0, 1 & 6 months) with booster at 42 months non-inferior to more complex schedules

Schiffer *et al* (2015) Vaccine 33: 3709-3716. doi: 10.1016/j.vaccine.2015.05.091

- Study of cross-species bridging of immune correlates of protection identified in animal NHP models
- All models predicted high survival probabilities for reduced dosing schedules from 7 to 43 months
- Data indicated that 4-IM and 5-IM are both viable alternatives to current AVA schedule

Environments with detectable levels of anthrax spores

Belgian goat-hair processing factory (Kissling *et al* 2012; Epidemiol. Infect.140, 879-886)

- No cases of anthrax reported since 1991 despite viable anthrax spores present in raw goat hair & air dust
- Overall 8/66 (12%) employees were seropositive for anti-PA antibodies:
  - Processing raw goat hair: 30%
  - Sorting raw goat hair: 20%
  - Less exposed roles: 3%

Villagers in Kars region, northeast Turkey (Baillie, Doganay & Sahin, 2016)

- Serum from 64 (24%) of 271 volunteers positive for anti-PA or anti-LF antibodies
- Of these 64, 49 had previous cutaneous infection, but 15 had no history of disease

Railway construction workers in Kars, northeast Turkey (Baillie, Doganay & Sahin, 2016)

- Serum collected from 64 volunteers operating construction machinery on Kars to Tbilisi railway project
- Toxin specific antibodies present in 2 of 11 individuals who had worked on a BA contaminated burial site
- Out of remaining 53 workers, 4 had toxin specific antibodies

Low dose spore exposure unlikely to pose risk of infection for unvaccinated individuals

Anthrax in the UK: Evidence of Absence or Absence of Evidence?

Recorded cases of human anthrax infection in UK in last 35 years

- **Cutaneous – 18** since 1981, occupational in origin when identified, one probably while working in Africa
- **Gastro-intestinal –** none
- **Inhalation – 2** in 2006 & 2008, making drums with imported hides
- **Drug injection – 47** cases (14 deaths) in Glasgow region in 2009-10; further **7** cases in UK during 2012-13

Occupational uptake of anthrax vaccine

- Military personnel and Containment Laboratory Staff are offered vaccine (AVP)
- Vets and abattoir workers not vaccinated
- Individuals in other occupations with potential for exposure to anthrax spores are not vaccinated

Animal anthrax infection in UK

- Classified as an exotic infection
- Rare sporadic outbreaks: 3 since 1998
- Animals are not vaccinated in UK

Anthrax in the UK: circumstances with potential for infection

Spores can enter the body through:

- **Skin -** handling hides, butchering meat, or sorting hair/wool from infected animals
- **Gut -** eating infected meat
- **Lung -** inhaling spores while processing infected animal material (hair, wool, bone meal), or from deliberate release
- **Muscle -** injecting contaminated recreational drugs (*e.g*. skin-popping)
- **Blood -** injecting contaminated recreational drugs

Circumstances with potential for infection:

- **Holidays abroad -** Cutaneous infection from hides bought on holiday or injury sustained hiking in endemic area
- **Contaminated food -** Chance of anthrax in regulated food chain negligible, but imported bush meat a risk
- **Occupational -** Cutaneous infection from imported animal material very rare, no inhalation cases since 1940
- **Recreational -** Spores inhaled (drum-makers) or injected (drug-users)
- **Deliberate release -** examples: Aum Shinrikyo in Tokyo (1993); Anthrax Letters in USA (2001)

Summary

Support for vaccine efficacy

- Non-clinical efficacy studies: 3 doses of vaccine (PA + Al) give prolonged protection against inhaled challenge
- CDC survey of AVA use in industry (1960-70): 3 doses considered protective
- Reported cases of repeated cutaneous anthrax infection in one individual very rare
- Licensed vaccines and cutaneous infection: qualitatively different, quantitatively similar immune responses

Anthrax toxin antigens in vaccines produce prolonged T and B cell memory

- Primary schedule: 3 doses for AVP or AVA , 2 doses for LAAV are likely to be sufficient
- Booster doses (AVP and AVA) induce rapid serological responses – peak at ~14 days

Very low probability of occupational exposure to spores in UK

- Rare sporadic cases in livestock, 18 human cases in UK since 1981
- In recent years recreational exposure has posed greatest risk of infection
- Low dose spore exposure unlikely to pose risk of infection for unvaccinated individuals (Belgian & Kars studies)
- Regular booster dose not required - only needed if event indicating risk of significant spore exposure occurs

Discussion : Suggestions for vaccine use

General Use Prophylaxis (GUP)

- Primary schedule on starting employment
- Response to identified spore challenge: Booster dose of AVP & antibiotic for 7-10 days
- Annual booster doses not required, but boost at 10 years after last dose if still in relevant occupation
- Based on appropriate risk assessment, offer vaccine to individuals in traditional at risk occupations:
  - workers in abattoirs, animal product importation & processing facilities
  - military personnel, microbiologists in containment laboratories
- Offer vaccination to individuals involved in consequence management of deliberate spore release events

Post-Exposure Prophylaxis (PEP)

- 3 doses of AVP at 0, 14 and 28 days
- Course of appropriate antibiotic for first 14-21 days
- Regular follow-up for 6 months after 3rd dose
- Offer 4th dose of vaccine at 6 months to complete primary schedule

Thank you for your attention….