Federal Expert Select Agent Panel (FESAP) Deliberations
FESAP and Biennial Review

- Established in 2010 and tasked with policy issues relevant to the security of biological select agents and toxins
- Per recommendations from HHS and USDA, tasked in 2016 with considering removal of *Coxiella burnetti*, *Rickettsia prowazekii*, *Brucella abortus*, *Brucella suis*, and *Brucella melitensis*
- Important basis for *Brucella* being put on Select Agent list was due to efforts by DOD to develop *B. suis* bioweapon in 1950s
Issues of Concern Relayed to FESAP Committee

By Suelee Robbe-Austerman, myself and others

- Loss of active brucellosis research programs in livestock or wildlife reservoirs
  - Approximately 11 locations doing work in decade prior to Select Agent Act initiation (1996)
  - Currently essentially only NADC; Colorado State has a limited capability to conduct ABL3 experiments

- Reduction in brucellosis research in other areas (laboratory and laboratory animal model research)
Regulatory requirements are resulting in some diagnostic laboratories not isolating *Brucella*
- Results in reduction of isolates sent to NVSL for genotyping and reduced epidemiologic knowledge
- Impairs regulatory responses in the field
*Brucella* underrepresented in submitted grant applications (expressed by personnel from NIH)
Cost of compliance with Select Agent rules is very high (and continues to increase)

Costs for failing to meet all regulations/requirements also very high

States with economic costs associated with brucellosis unable to conduct research projects with *Brucella* that might help mitigate disease issues

Estimated in 2001 that greater than $2 billion dollars had been invested in eradication program (Protect public investment in eradication)
- Ability to share strains/collaborate restricted
  - recent failure by ARMY to properly inactivate SA agent led to most overnight shippers not accepting Select Agent packages (est $2000-$3000 cost per shipment now)
FESAP Issues of Concern for Removal of *Brucella* spp

1. Argument that *Brucella* has a very low infectious dose
   - some agencies argued 10-100 CFU infectious dose
   - DHS indicated they had relevent data that could not be shared with anyone without an appropriate security clearance
   - Teske et al 2011 suggests approx. 1880 CFU infection dose for aerosol delivery of *B. melitensis* to rhesus monkeys
   - Teske paper indicated an infectious dose of 1885 CFU for aerosol delivery of *B. melitensis* Rev 1 to humans
- some studies extrapolate infectious dose in mice (415 CFU for *B. abortus* and 7988 CFU for *B. melitensis*) by culturing lungs but do not include trachea, upper respiratory tract, and oral cavity
- Data from NADC required total aerosol dosages of \( \geq 10^7 \text{ CFU} \) for *B. abortus* and \( \geq 10^6 \) for *B. melitensis* and above to get consistent infection in mice in a closed chamber
- aerosol dosages of $<10^3$ did not result in culture recovery from rhesus monkeys at 9 weeks (In this study the vaccinates in low *Brucella* dosages had hepatitis lesions but so did controls (no infection))
FESAP Issues of Concern for Removal of *Brucella* spp

2. Greater severity of disease with pulmonary exposure
   - human patients with pulmonary brucellosis in a country endemic with *B. melitensis* responded to treatment in a similar manner to non-pulmonary
   - Estimated that 0.6 to 16% of human cases have pulmonary infection
3. Concern of human mortality issue if used in bioterrorism attack
   - meta-analysis (Dean et al 2012) of 2385 published papers on human brucellosis did not include mortality in its analysis of clinical manifestations
   - review of 20 recent case reports (pediatric, neurobrucellosis, liver-involvement, and endocarditis) encompassing 5940 patients, many in developing countries, did not report any mortalities
- mortality in humans generally associated with endocarditis; recent literature suggests that availability of surgical valve replacement has dramatically reduced this cause of mortality
- However, a reported 12.8% spontaneous abortions and 8.1% fetal death in 101 cases of brucellosis in pregnant women in Peru (Vilchez et al 2015)
4. High incidence of laboratory exposures
   - 80% of laboratory exposures caused by *B. melitensis* and 92% related to manipulation outside of a biosafety cabinet with 3-38.6% of exposed personnel resulted in infection (Traxler et al 2013)
   - More recent publications have indicated attack rates of 9% (damaged biosafety cabinet) and 4.8% (inadequate lab facilities in developing country)
   - A number of studies have reported no seroconversions when appropriate prophylactic treatment administered after exposure
FESAP Issues of Concern for Removal of *Brucella* spp

- We argued current biosafety practices dramatically improved over historical data being used.
- Publication of laboratory exposures difficult if no seroconversions occur after exposure/accident.
FESAP Issues of Concern for Removal of *Brucella* spp

5. More laboratory exposures for *Brucella* than *Francisella* (a bacteria with low infectious dose)
   - Culture of *Brucella* common for diagnostics whereas not common for Francisella
   - Regulatory program for *Brucella* not *Francisella* leading to hundreds of thousands of samples processed related to *Brucella*
   - *Francisella* was most common lab infection in bioweapon program; Even after development of human vaccine averaged 1 case per year
6. Concern that *Brucella* cultures would be obtained from laboratories

- DHS personnel stated their experts believe that individuals with bioterrorism intent would obtain cultures from laboratories not other sources
- Epidemiologic data suggests approx. 1 in 4 bison and elk in GYA culture positive for *B. abortus* (thousands of animals)
- Recent data from feral swine in Texas indicates 1 in 8-9 animals culture positive for *B. suis*
- High prevalence of *Brucella* infection in many countries including Central and South America, Middle East and other parts of the world where oversight is limited (easier source of isolates)
- DHS analogy was if you wanted a race horse, you would go to a race track. We argued that you still need a laboratory to grow the isolate so you would have the capability to do original isolations (with less risk of exposure)
7. High medical costs associated with bioterorism event with *Brucella*

- previous paper model estimated medical costs for *Brucella* equivalent to anthrax bioweapon attack (Kaufman et al 1997)
- Data from Israel suggests that annual health care costs for patients with brucellosis only moderately higher ($1327 versus $380 for uninfected; Vered et al 2015)
Other Things to Consider

- Listing of an agent as a Select Agent is not a biosafety classification, it is related to possible use as bioweapon.
- *Brucella* should be considered a poor bioweapon: long incubation, mild clinical symptoms, not transmissible between humans, limited environmental persistence, infectious dose.
- DHS adamant during discussions that *B. suis* had to stay on Select Agent list; argument for *B. melitensis* based on high virulence and foreign animal disease.
Final report recommended delisting of *B. abortus* and *Rickettsia prowazekii*

Since that report, I have heard through several sources that DHS is against removal and that the recommendation is unlikely to be acted on this year - thought that recommendation would be left to next administration to act on

Also this year, I am aware that the Department of Defense appears to believe a threat exists for use of *B. suis*