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 $\geq 10^7$ 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

FESAP Issues of Concern for Removal of *Brucella* spp

- 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)

FESAP Issues of Concern for Removal of *Brucella* spp

- 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

FESAP Issues of Concern for Removal of Brucella spp.

- 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)

FESAP Issues of Concern for Removal of Brucella spp

- 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

FESAP Final Recommenations

- 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*