Date: Thu, 1 Nov 2001 09:50:47 -0500 (EST)
From: Matthew S. Meselson <msm@wih.harvard.edu>
Subject: dose response, etc

Le Duc

Dear Jim,

Not knowing if any of what follows would be new or of any use to CDC people, here are some comments on three topics.

1) Anthrax Dose Response: The often cited value of 8,000 spores for the LD50 for inhalation anthrax comes from experiments done on cynomolgus monkeys at Fort Detrick in the 1950s under contract with the Parsons company. Joe Jemski, who led the work, can provide many details but the written records so far as I know cannot be located. Other experiments with cynomolgus and rhesus monkeys and fairly well characterized aerosol particle size distributions have given published LD50 values ranging from 2,000 to 50,000 spores inhaled. The cause of the rather wide spread is uncertain. Variables include anthrax strain and culture medium, method of spore preparation and storage, aerosol suspension liquid and aerosol particle size distribution, nasal or mouth breathing, the species, age and condition of the monkeys, etc.

Of course, knowing the LD50 does not tell you, for example, the LD10 or the LD1. We have no good experimental knowledge of the dose that would infect, say, 1% of exposed monkeys under some specified experimental conditions. And that's monkeys, not people.

It is an unfounded assumption that there is a threshold dose, below which no infection can result. For both experimental and theoretical reasons the assumption of a threshold is untenable. It should be presumed that even one spore can initiate infection, albeit with very low probability. Understanding this is essential for the design of sound policy and procedures.

If spores act independently in causing infection the attack rate would be 1-ext[-0.69(dose/LD50)].

If we take LD50 as 8,000, the attack rate from the above expression for one spore inhaled per person would be 0.000086 or roughly 0.01 percent.

On the basis of independent action one would expect longer incubation periods to be associated with lower doses.

2) Alteration of LD50:
Whatever the LD50 for a particular anthrax aerosol and a particular human population, there is old literature from the US and the UK stating that the LD50 can be reduced by a factor of 10 or more by adding detergent (SDS, I believe), chromate, and certain other substances to the spore preparation. This could be relevant both to the epidemiology of what we are seeing and to analytic procedures for forensic investigation.

3) Silica: Cabosil, a product of Cabot Corporation described on the web may be used as an anti-coagulant and consists of very highly porous flame-produced silica particles with sub-micron dimensions. Spores mixed with such material may be aerosolizable from the initial powder preparation with very little energy input. Surrounded with such silica particles, spores may have approximately the same aerosolization

particles, spores may have approximately the same aerosolization propensity as would the pure silica preparation itself. Once suspended in air and subsequently deposited on surfaces, I would think that re-aerosolization in respirable particle size would be unlikely but experiments with non-pathogenic anthrax spores and cabosil-like materials could tell us. Cabosil and perhaps similar products, sometimes used, for example, to thicken ketchup and other foods are commercially available.

All good wishes,

Matt.

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