Development of an Aerosol Concentration Model to Vary Exposure Duration with Infectious Agents

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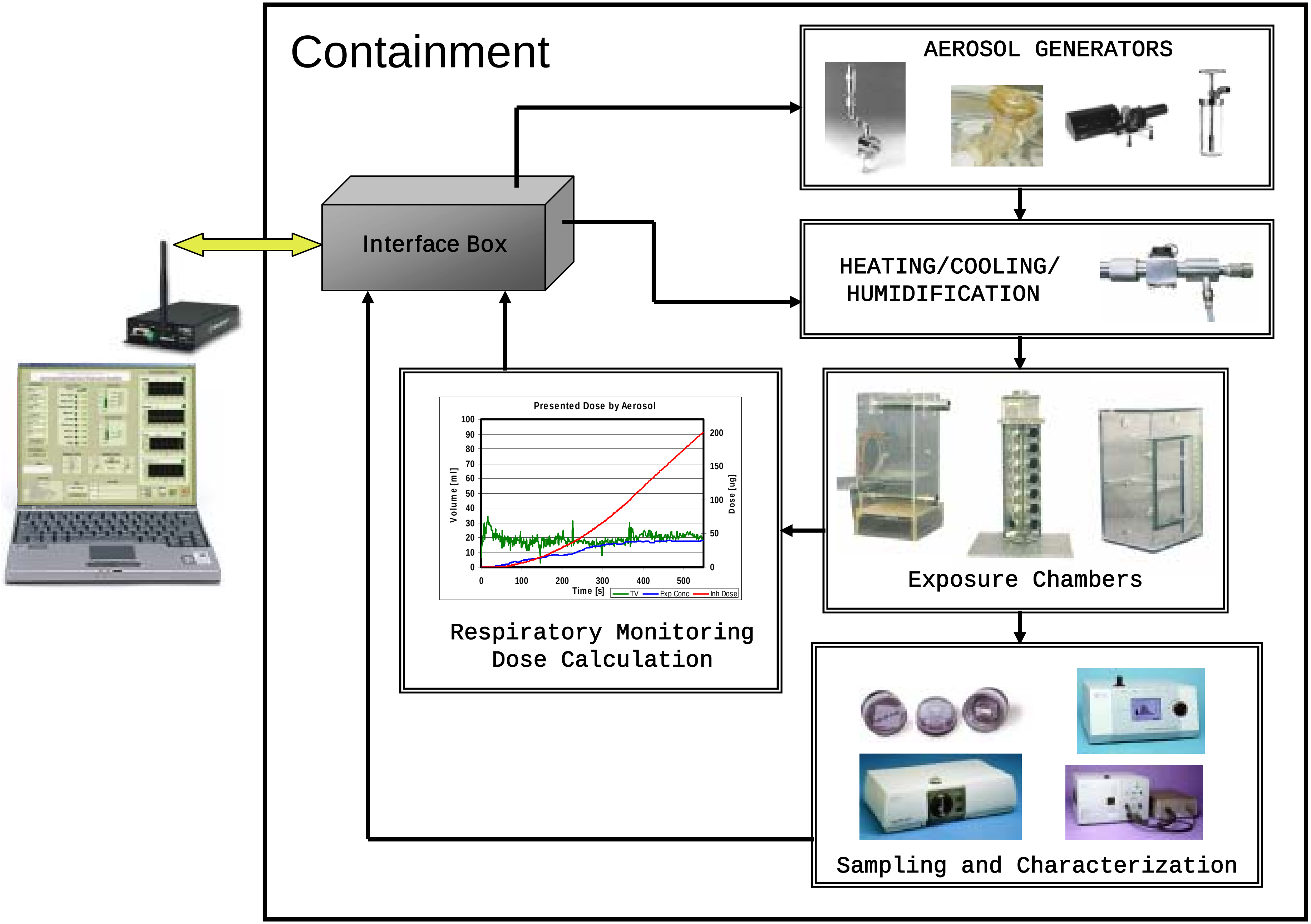
Aerobiology Mission

- Develop appropriate animal models
  - Define pathogenesis/mechanism of toxicity/toxicology
  - Develop surrogate markers of efficacy
- Develop new bioaerosol technologies
  - Precision and accuracy of dose control
  - Aerosol size
  - Environmental conditions

Aerosol Challenge

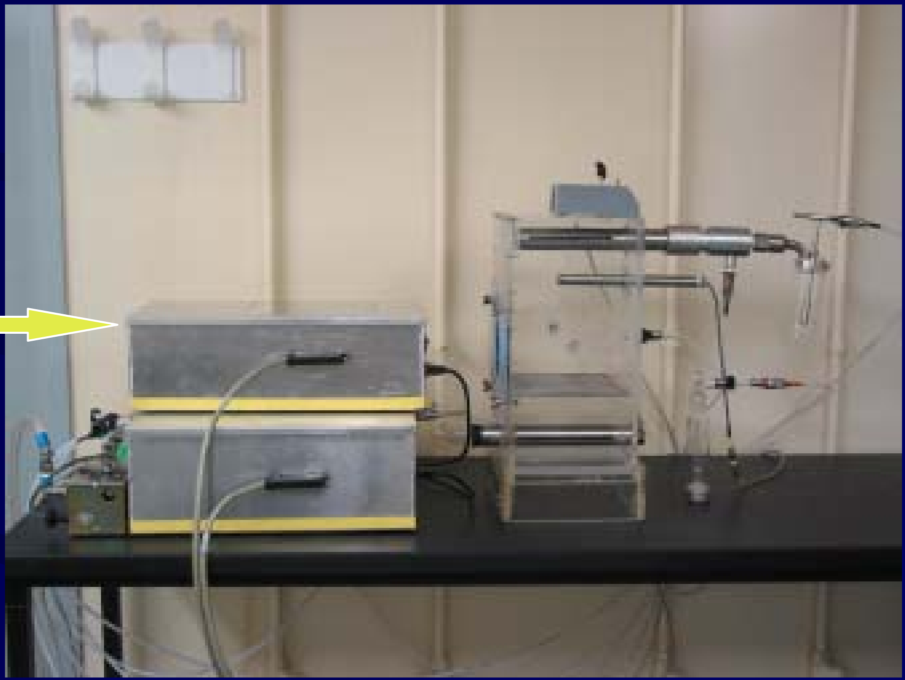
- Deliver challenge agent by aerosol
- Under desired conditions
  - Temperature
  - Humidity
  - Particle size
- At the required dose



Integrated Aerosol Control and Management Platform

System Hardware

Workstation



Containment

Challenge Dose

Respiratory Function

Aerosol Concentration

Exposure Duration

Challenge Dose

$$D\left(t_{\exp}\right) = \int_0^{t_{\exp}} R(t)C(t)\,dt$$

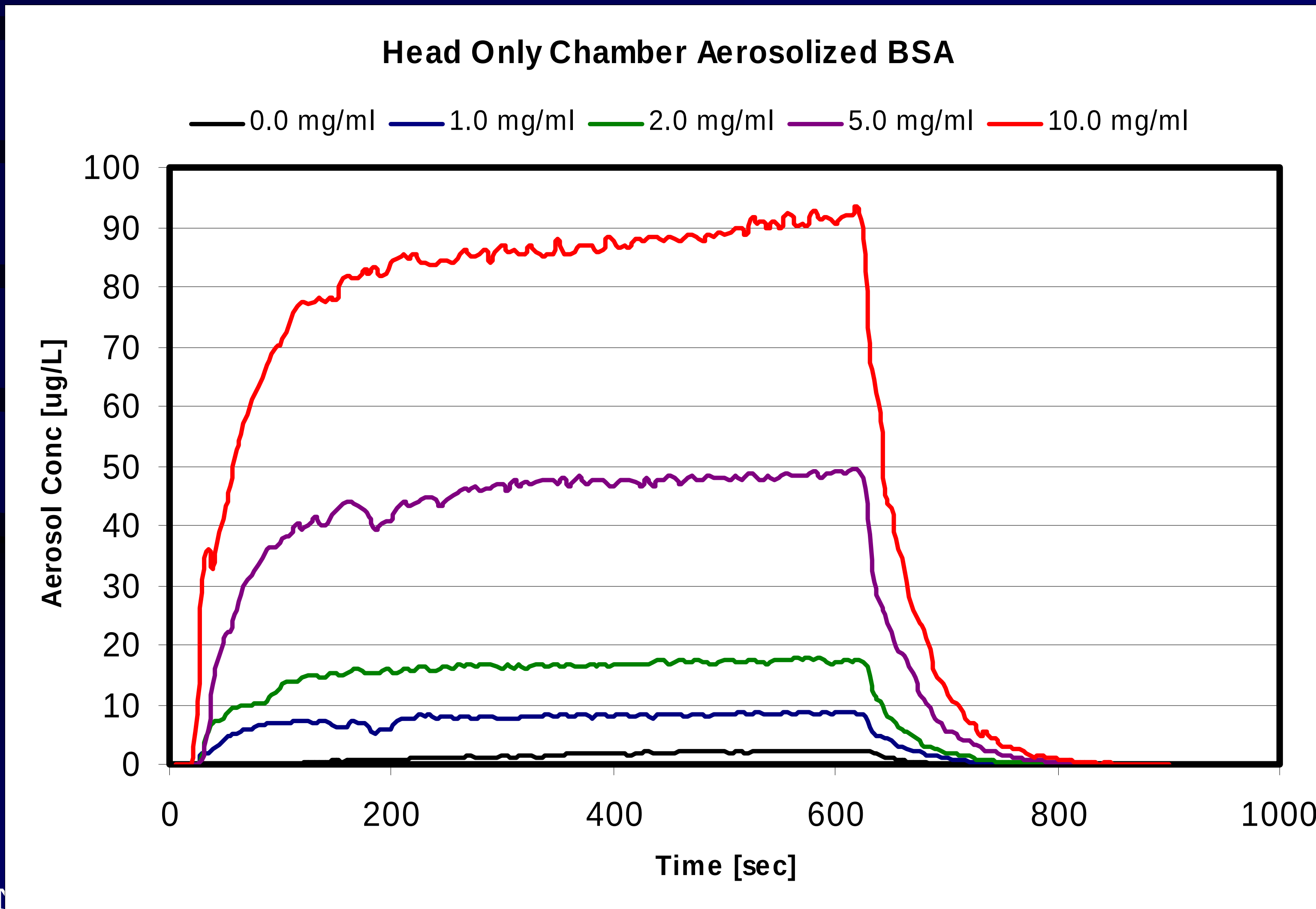
Toxin Dose Control

- Calculate dose integral in real-time

$$D\left(t_{\exp}\right) = \int_0^{t_{\exp}} R(t)C(t)dt$$

- Exposure duration dictated by measurements
- Automatic compensation for variations in R(t) and C(t)
- Real-time dose calculation controls t_{exp}

Chamber Concentration

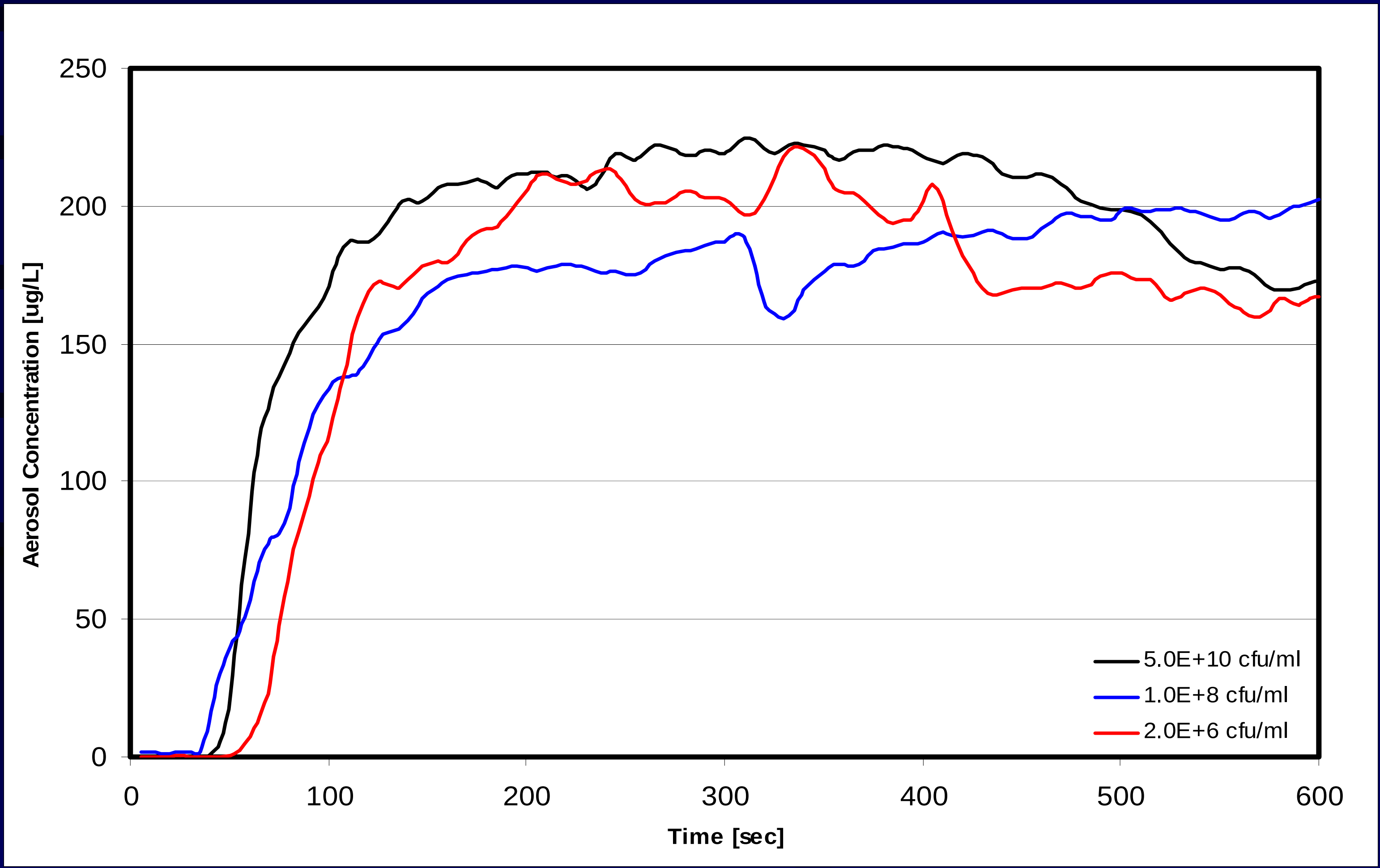


Other Biologics

- Viral and bacterial agents aerosolized in a carrier medium
- Media contain proteins
- Can media and biologic aerosol concentrations be deconvolved?

$$D\left(t_{\exp}\right) = \int_0^{t_{\exp}} R(t)C(t)dt$$

Yersinia pestis in HIB



Solution: Model Concentration

- Provide C(t) mathematically
- Aerosol system then automatically compensates for R(t) variations
- Dose control through adjustment of t_{exp}

$$D\left(t_{\exp}\right) = \int_0^{t_{\exp}} R(t)C(t)dt$$

Concentration Model

- Aerosol generation phase

$$C(t) = A\left(1 - e^{-kt}\right)$$

  - *A* – scaling factor related to aerosol generation efficiency
  - *k* – time constant related to system volume and flow rates

Concentration Model

- Aerosol generation phase

$$C(t) = A\left(1 - e^{-kt}\right)$$

  - *A* – scaling factor related to aerosol generation efficiency
  - *k* – time constant related to system volume and flow rates
- Chamber air wash phase

$$C(t) = C(t_{\exp})e^{-k(t-t_{\exp})}$$

  - t_{exp} – exposure time

Aerosol Model Form

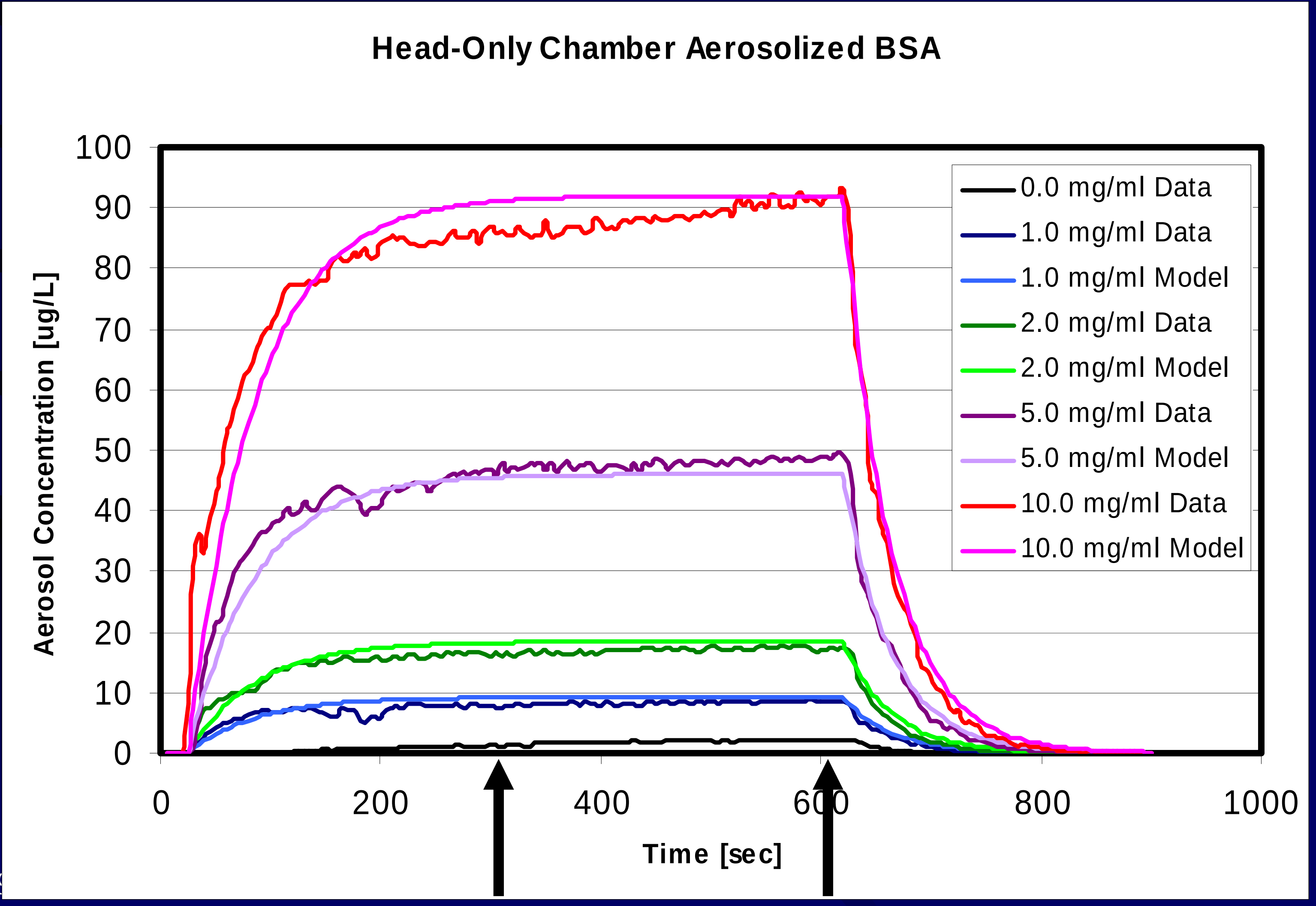
- 16.3 L head-only chamber volume
- 16.0 lpm system flow rate
- Aerosol generation:

$$C(t) = A\left(1 - e^{\frac{-16.0\,lpm \times t}{16.3\,L}}\right)$$

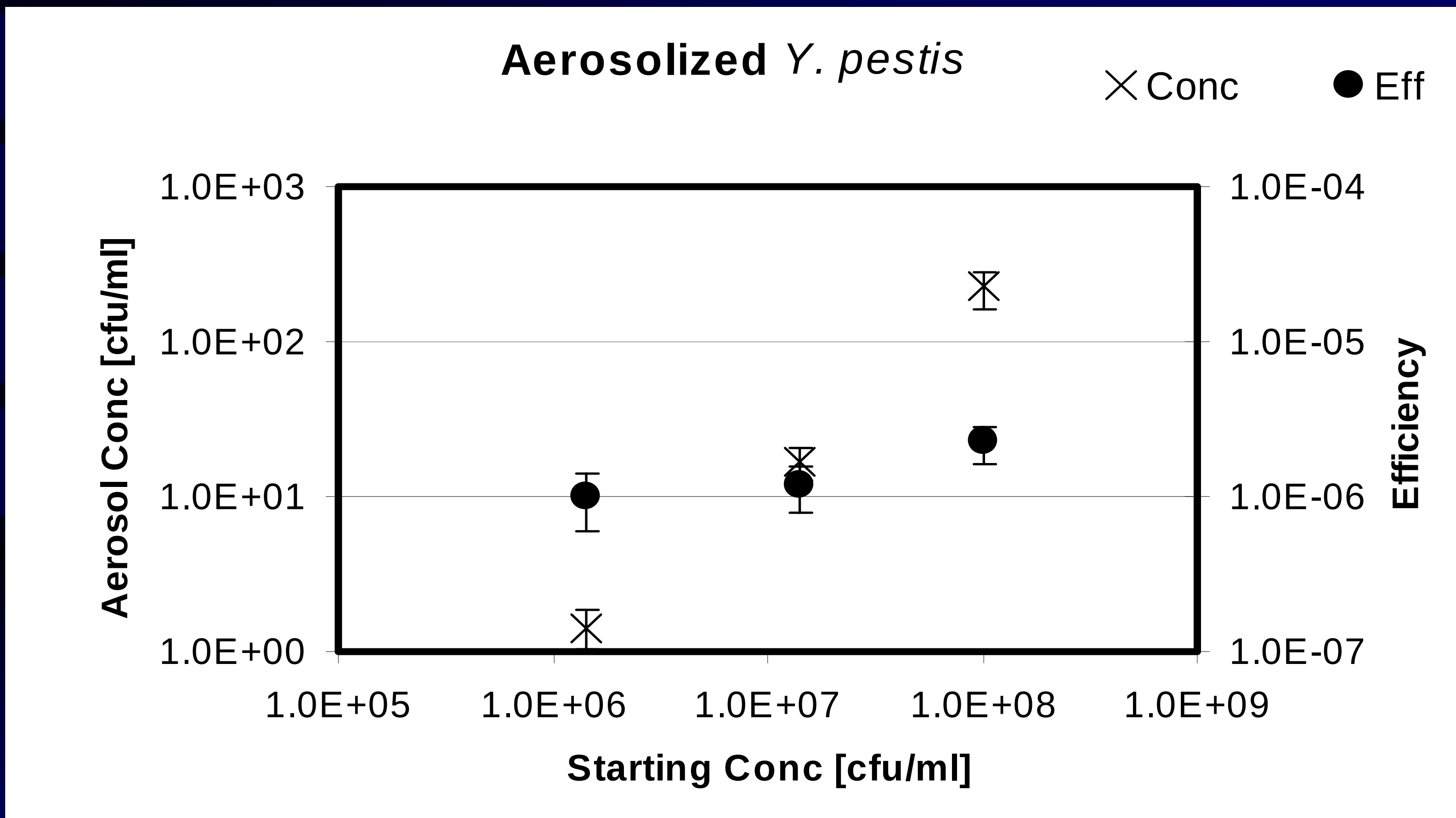
- Chamber air wash:

$$C(t) = C(t_{\exp})e^{-\frac{16.0\,lpm}{16.3\,L}(t - t_{\exp})}$$

Concentration Model



Efficiency Measurement



Efficiency = 1.2e-6

Chamber Wash Dose

- Integrated concentration over 5 minutes
- Multiplied by R(t)

$$D(t)_{wash} = \int_{t_{\exp}}^{t_{\exp}+5} C(t_{\exp})R(t)e^{-\frac{16.0lpm}{16.3L}(t-t_{\exp})}dt$$

Chamber Wash Dose

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- Multiplied by R(t)

$$D(t)_{wash} = \int_{t_{\exp}}^{t_{\exp}+5} C(t_{\exp})R(t)e^{-\frac{16.0lpm}{16.3L}(t-t_{\exp})}dt$$

- Take *R(t)* as a constant, *R*

$$D(t)_{wash} = \frac{16.3L}{16.0lpm}RC(t_{\exp})$$

Completed Model

$$D_{tot} = R * Eff * SC * \left\{ \left(\int_0^t 1 - e^{-\frac{16.0lpm}{16.3L}t} dt \right) + \frac{16.3L}{16.0lpm} \left(1 - e^{-\frac{16.0lpm}{16.3L}t} \right) \right\}$$

Completed Model

$$D_{tot} = R * \underbrace{Eff * SC}_{\text{Steady State Concentration}} * \left\{ \left(\int_0^t 1 - e^{-\frac{16.0lpm}{16.3L}t} dt \right) + \frac{16.3L}{16.0lpm} \left(1 - e^{-\frac{16.0lpm}{16.3L}t} \right) \right\}$$

Steady State Concentration

Completed Model

$$D_{tot} = R * Eff * SC * \left\{ \left(\int_0^t 1 - e^{-\frac{16.0lpm}{16.3L}t} dt \right) + \frac{16.3L}{16.0lpm} \left(1 - e^{-\frac{16.0lpm}{16.3L}t} \right) \right\}$$

Delivered Dose

Completed Model

$$D_{tot} = R * Eff * SC * \left\{ \left(\int_0^t 1 - e^{-\frac{16.0lpm}{16.3L}t} dt \right) + \frac{16.3L}{16.0lpm} \underbrace{\left(1 - e^{-\frac{16.0lpm}{16.3L}t} \right)}_{\text{Current Concentration}} \right\}$$

Completed Model

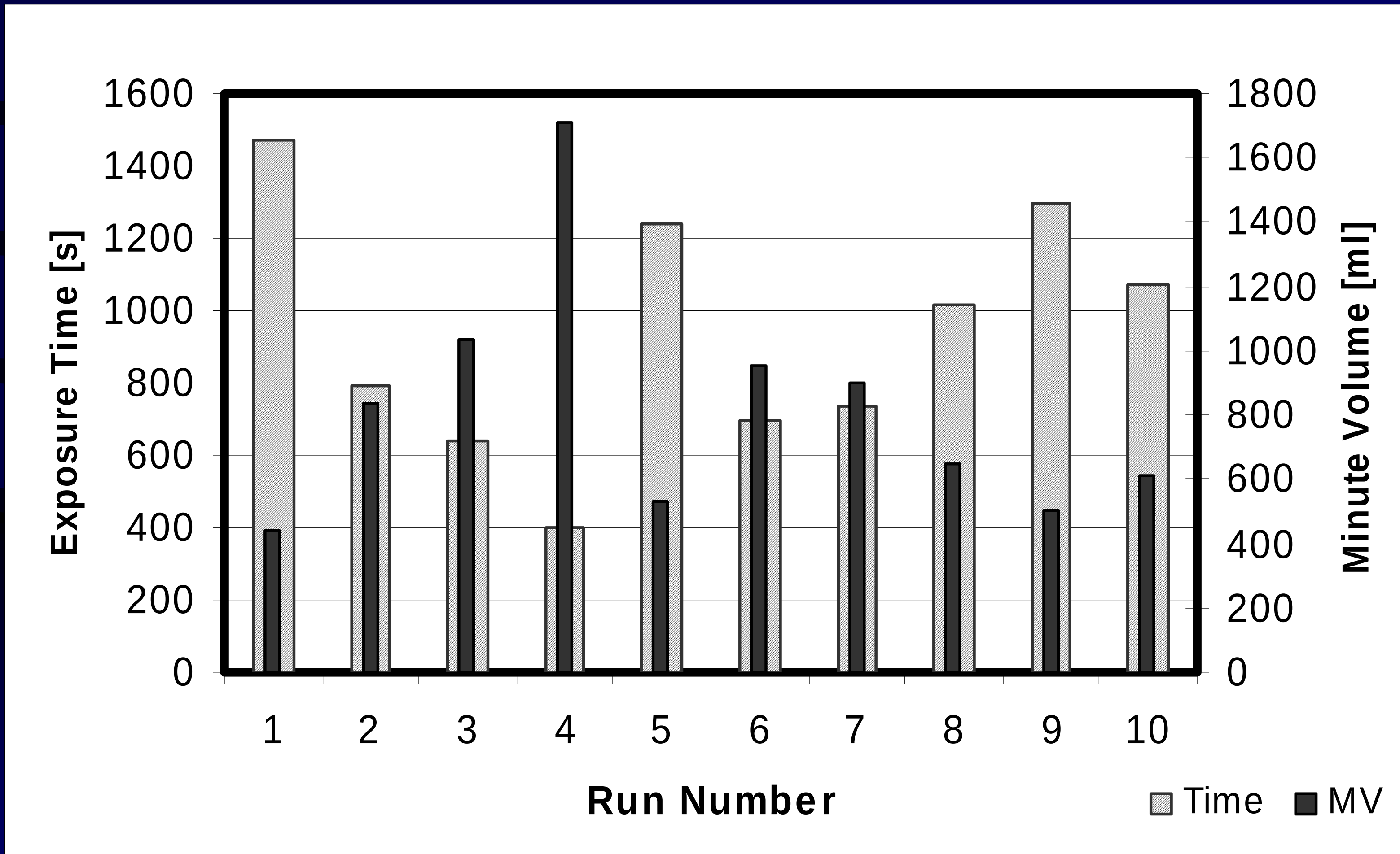
$$D_{tot} = R * Eff * SC * \left\{ \left(\int_0^t 1 - e^{-\frac{16.0lpm}{16.3L}t} dt \right) + \frac{16.3L}{16.0lpm} \left(1 - e^{-\frac{16.0lpm}{16.3L}t} \right) \right\}$$

Dose *to be delivered* during air chamber wash

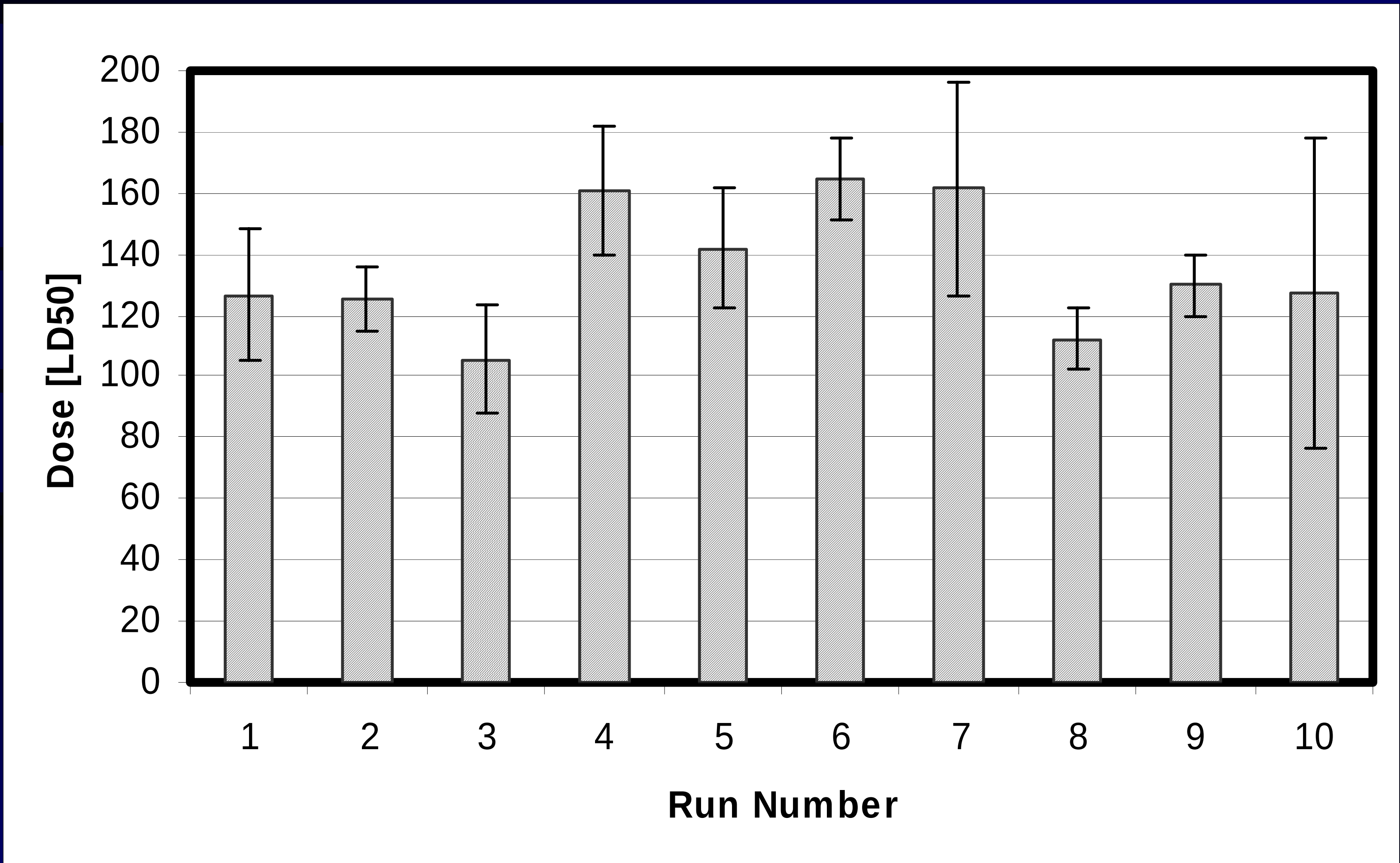
Y. pestis Aerosol Challenge

- 10 NHP
- Target dose of 75 LD_{50} (25,700 cfu)
- Minute volumes – determined by plethysmography before exposure
- Starting concentration: 2e+6 cfu/ml
- Aerosol efficiency: 1.2e-6

Y. pestis Challenge



Y. pestis Challenge



Y. pestis Challenge Results

- Using concentration model:
  - Dose range: 106 - 165 LD_{50}
  - 140 ± 20 LD_{50}
  - Coef of Var: 0.14
- t_{exp} range: 397 – 1475 sec
- Aerosol generation efficiency – 2.2e-6
  - Accounts for deviation of mean dose

Comparison to Standard Exposure

- Statistics are governed by MV measurements:
  - MV range: 442 – 1790 ml
  - MV average: 800 ± 400 ml
  - Coef of Var: 0.5
- Dose estimation based on matching means:
  - Dose range: 74 - 287 LD_{50}
  - Dose average: 140 ± 70 LD_{50}
  - Coef of Var: 0.5

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Three-fold reduction in C of V

Conclusions

- Improved precision of delivery of dose by aerosol to subjects with widely varying respiratory minute volumes
- Accuracy still dictated by efficiency estimates
- Three-fold reduction in coefficient of variation of dose delivery in aerosol challenge
- Isolation of biological response to aerosol challenge dose rather than to artifacts of exposure methodology

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Research was conducted in compliance with the Animal Welfare Act and other Federal statutes and regulations relating to animals and experiments involving animals and adheres to principles stated in the *Guide for the Care and Use of Laboratory Animals*, National Research Council, 1996. The facility where this research was conducted is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International.