

Use of a Probabilistic Infectious Dose Model for Estimating Airborne Pathogen Infection Risk: Application to Respiratory Protection

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ABSTRACT

A generic, quantitative risk framework is described to assist in selecting respiratory protection against airborne pathogens. A probabilistic infectious dose model is used, in which it is assumed that a single organism can infect the host with a specified probability; in contrast, a deterministic model assumes there is some threshold number of organisms which, if received, infects the host with certainty. The framework accounts for variability in exposure intensity, in respirator efficacy, and in susceptibility to infection among individuals. The dose received without regard to respiratory protection is modeled as a Poisson random variable, the respirator penetration value is modeled as a standard beta random variable, and variability in host susceptibility is captured by modeling the probability of infection per organism as a standard beta random variable. Although the exact equations for computing infection risk when respiratory protection is worn require numerical integration, simple approximation formulae are presented which are health-conservative in slightly overestimating infection risk. An application to selecting respirators to be worn by unvaccinated healthcare workers against variola major virus (the etiologic agent of smallpox) is presented.

Keywords: airborne pathogens, microbial risk assessment, bioterrorism, respirators and infectious aerosols

INTRODUCTION

Infection control practitioners argue that the selecting respiratory protection against airborne pathogens is not comparable to selecting respirators against chemical agents, because (i) there are no occupational exposure limits (OELs) for airborne pathogens, (ii) individuals vary in susceptibility to infection by a given pathogen, and (iii) it is not yet feasible to measure pathogen exposure intensity (Pfeiffer, 2004; Pollack, 2004). On a conceptual level, however, the selection process is analogous to that used for airborne chemicals. First, an OEL is a surrogate for acceptable risk, and it is possible (albeit complicated) to specify an acceptable risk of infection. Second, for a given chemical, individuals vary in their susceptibility to the chemical's toxic effects; however, the OEL for a chemical usually includes a "safety factor" to protect more sensitive individuals, and in that manner the OEL accounts for interindividual variability in susceptibility. Third, the general industry respirator standard of the Occupational Safety and Health Administration (OSHA) permits estimating airborne chemical exposure via mathematical modeling in lieu of making direct measurements (OSHA, 1998); similar exposure modeling can be applied to airborne pathogens (Nicas, et al., 2005).

This paper presents a generic, quantitative risk framework to assist in selecting respiratory protection to meet an identified acceptable infection risk value. The framework accounts for variability in exposure intensity, in respirator efficacy from wearing to wearing, and in susceptibility to infection among individuals. On the other hand, respirator recommendations for specific pathogens are not offered, because specifying an acceptable risk value involves complex decision-making beyond the scope of this analysis, and because in the author's view, that decision-making is best undertaken by OSHA and other public health agencies.

INFECTIOUS DOSE MODELS

The infectious inhalation dose model used in this analysis is probabilistic or "non-threshold". The simplest probabilistic model assumes that a single organism can infect the host with a probability denoted P_S , where the subscript S signifies "successful infection". The fact that a single organism can infect means there is no threshold number of organisms (other than one) required for infection; another description is that only "one hit" is required. Where D is the number of organisms deposited in the appropriate region(s) of the respiratory tract, the risk of infection is $1 - (1 - P_S)^D$. The logic of the algebra is as follows. The probability that a single deposited organism will not infect the host is $1 - P_S$. The probability that D organisms will not infect the host is the product of the independent probabilities that each organism will not infect the host, or $(1 - P_S)^D$. The risk of infection is the complement of the probability of not being infected, thus: Risk = $1 - (1 - P_S)^D$. If the value of P_S is the same across individuals, the infectious dose 50% value, denoted ID_{50} , can be somewhat loosely described as that deposited dose which produces a 50% likelihood of infection in any host. A probabilistic model can account for variability in susceptibility to infection by treating the P_S value as variable across individuals, as will be explained.

In contrast, a deterministic or "threshold" model assumes that if the host receives some threshold number (or greater) of organisms, infection is certain to occur, whereas if the host receives fewer than the threshold number of organisms, infection is certain not to occur. Variability in susceptibility to infection is reflected by interindividual variability in the threshold dose value, and the ID_{50} is that deposited dose which will infect 50% of the population with certainty.

In general, the available published data on infection by airborne pathogens are too sparse to permit distinguishing between the probabilistic and deterministic frameworks. For example, in a previous analysis of experimental data for inhalation anthrax, it was found that a deterministic model provided a better fit to guinea pig mortality data than did several probabilistic models, but that a probabilistic model provided a slightly better fit to monkey mortality data than did a deterministic model (Nicas and Hubbard, 2002). The "one hit" probabilistic framework is used here because it is consistent with observed dose-infection response data for a variety of organisms (Haas, et al., 1999), it has traditionally been used for modeling infection by waterborne pathogens (Teunis, et al., 1996), and it tends to be more health conservative and less computationally intensive than the deterministic framework.

LACK OF VARIABILITY IN HOST SUSCEPTIBILITY

No Respirator Use

Lack of variability in host susceptibility signifies that the pathogen has the same P_S value in all individuals. For a fixed integer dose received D, the conditional risk of infection R_D is:

Eq. 1
$$R_D = 1 - (1 - P_S)^D$$

In practice, the dose received can be treated as a random variable. It is assumed that D is a Poisson random variable with mean μ_D , which is denoted $D \sim \text{Poisson}(\mu_D)$. The unconditional or mean risk of infection R is found by summing R_D across all possible dose values $D = k$ weighted by the corresponding probabilities that $D = k$:

$$\text{Eq. 2} \quad R = 1 - \sum_{k=0}^{\infty} (1 - P_S)^k \frac{\mu_D^k \exp(-\mu_D)}{k!} = 1 - \exp(-[\mu_D \times P_S])$$

Respirator Use

The algebraic effect of wearing respiratory protection is to reduce the dose received. Let P denote the respirator penetration value. If D is the dose received without respiratory protection, the expected dose received with respiratory protection is $D \times P$. It has been traditional to model respirator penetration values using a lognormal distribution. The mean penetration value, μ_P , is related to the GM and GSD parameters by: $\mu_P = \text{GM} \times \exp(0.5 \times \ln^2 \text{GSD})$. The mode of the penetration values, m , is related to the GM and GSD parameters by: $m = \text{GM} \div \exp(\ln^2 \text{GSD})$.

However, in a previous analysis it was argued that a respirator wearer's penetration values can be modeled using a standard beta distribution (Nicas, 1994). The probability density function (pdf) for a standard beta distribution of penetration values is:

$$\text{Eq. 3} \quad f_P(p) = \frac{\Gamma(\alpha + \beta)}{\Gamma(\alpha)\Gamma(\beta)} p^{\alpha-1} (1-p)^{\beta-1}$$

where $\alpha > 0$ and $\beta > 0$, and where $\Gamma(a)$ is the gamma function for argument a . The mean penetration value is related to the α and β parameters by: $\mu_P = \alpha \div (\alpha + \beta)$. It happens that a standard beta distribution, which describes values on the interval $[0,1]$, is a more natural descriptor for respirator penetration values than is a lognormal distribution, because the former distribution is truncated at one (the maximum penetration value) whereas the latter distribution extends to infinity.

If a lognormal distribution has a mean less than 0.1 and a GSD < 3.5 , the probability density curves for the standard beta and lognormal distributions are similar. The standard beta distribution parameters α and β are defined in terms of μ_P and m as follows:

$$\text{Eq. 4} \quad \alpha = \frac{\mu_P}{\mu_P - m}$$

$$\text{Eq. 5} \quad \beta = \frac{1 - \mu_P}{\mu_P - m}$$

Therefore, if one specifies the GM and GSD of a lognormal distribution, and thereby specifies μ_P and m , one can use Equations 4 and 5 to specify, respectively, the parameters α and β of a corresponding beta distribution. Figure 1 shows a hypothetical lognormal density curve (the solid line) for air-purifying elastomeric halfmask respirator penetration values with GM = .0315 and GSD = 2 such that $\mu_P = .04$ and $m = .0195$. Figure 1 also shows a hypothetical standard beta density curve (the dashed line) for air-purifying elastomeric halfmask respirator penetration values with $\alpha = 1.95$ and $\beta = 46.7$, such that $\mu_P = .04$ and $m = .0195$ as for the lognormal curve. For the lognormal density curve, 4.8% of all values exceed $P = 0.1$, while for the standard beta density curve, 3.8% of all values exceed $P = 0.1$. Note that both density curves are consistent with an assigned protection factor (APF) of 10 for an air-purifying elastomeric halfmask respirator as recommended by the National Institute for Occupational Safety and Health (NIOSH), because less than 5% of workplace protection factor values are below 10, which also signifies that less than 5% of penetration values exceed 0.1 (NIOSH, 2004).

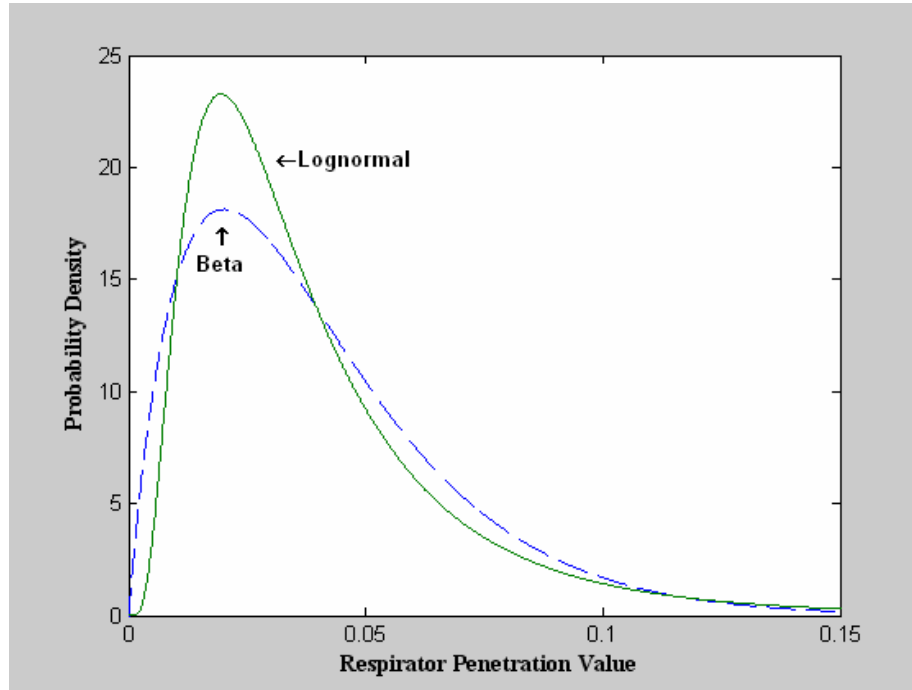


Figure 1. Air-purifying halfmask respirator penetration values alternatively modeled by a lognormal density function with GM = .0315 and GSD = 2, and by a standard beta density function with $\alpha = 1.95$ and $\beta = 46.7$. For both density functions, $\mu_p = .04$ and $m = .0195$.

It is hereafter assumed that respirator penetration values are adequately described by a standard beta distribution, or $P \sim \text{Beta}(\alpha, \beta)$. If $D \sim \text{Poisson}(\mu_D)$ for all individuals, and if the pathogen has the same P_S value across hosts, the unconditional infection risk is:

$$\text{Eq. 6} \quad R = 1 - \sum_{k=0}^{\infty} \left[\int_{p=0}^1 \left(\frac{1}{W} \sum_{j=0}^k (1 - P_S)^j \frac{(k \times p)^j \exp(-k \times p)}{j!} \right) f_p(p) dp \right] \frac{\mu_D^k \exp(-\mu_D)}{k!}$$

where $W = \sum_{j=0}^k \frac{(k \times p)^j \exp(-k \times p)}{j!}$, and where $f_p(p)$ is the pdf for respirator penetration defined by

Equation 3. The structure of Equation 6 is as follows. For a given integer dose that would have been received without respiratory protection (indexed by k), and for a given value of respirator penetration ($P = p$), the adjusted expected dose is $k \times p$. Because the actual dose received must be an integer, the dose received with respiratory protection (indexed by j) is treated as a truncated Poisson random variable with mean $k \times p$, and the expected value of $(1 - P_S)^j$ is computed using the truncated Poisson probabilities that the adjusted dose equals j given that the adjusted expected dose is $k \times p$. In this context, truncation signifies that the integer value j cannot exceed k , the inhaled integer dose without respiratory protection, whereas in theory Poisson-distributed values go to infinity. Multiplication by the factor $1/W$ within the brackets ensures that the truncated Poisson probabilities sum to one. For a given value k , computation of the expected value of $(1 - P_S)^j$ is performed for each value $P = p$, and is weighted by the corresponding probability that $P = p$, as indicated by the integration operation. The bracketed term is the expected value of not being infected conditioned on the value k . The bracketed term is then weighted by the probability that the integer dose that would have been received without respiratory protection equals k .

There is no analytical solution for Equation 6, but the expression can be numerically integrated. In this regard, numerical integration using the bounded standard beta distribution for P is computationally advantageous compared to numerical integration using the unbounded lognormal distribution. To solve Equation 6, the author used MATLAB™ software (version 6p5) which has an internal function that generates values of the standard beta pdf given values for the α and β parameters, and an internal function that generates Poisson probabilities given values for the μ_D parameter. The Appendix provides a MATLAB™ code written by the author that solves Equation 6. Figure 2 shows the effect of respiratory protection in reducing the unconditional risk of infection for $0 \leq \mu_D \leq 30$ for a hypothetical scenario in which $P_S = 0.2$ and an air-purifying halfmask respirator is worn such that $P \sim \text{Beta}(\alpha = 1.95, \beta = 46.7)$. This P distribution has $\mu_D = .04$, and is the same beta distribution depicted in Figure 1. The curve labeled “No Respirator” was computed by Equation 2, and the solid-line curve labeled “Respirator (Exact)” was computed by Equation 6.

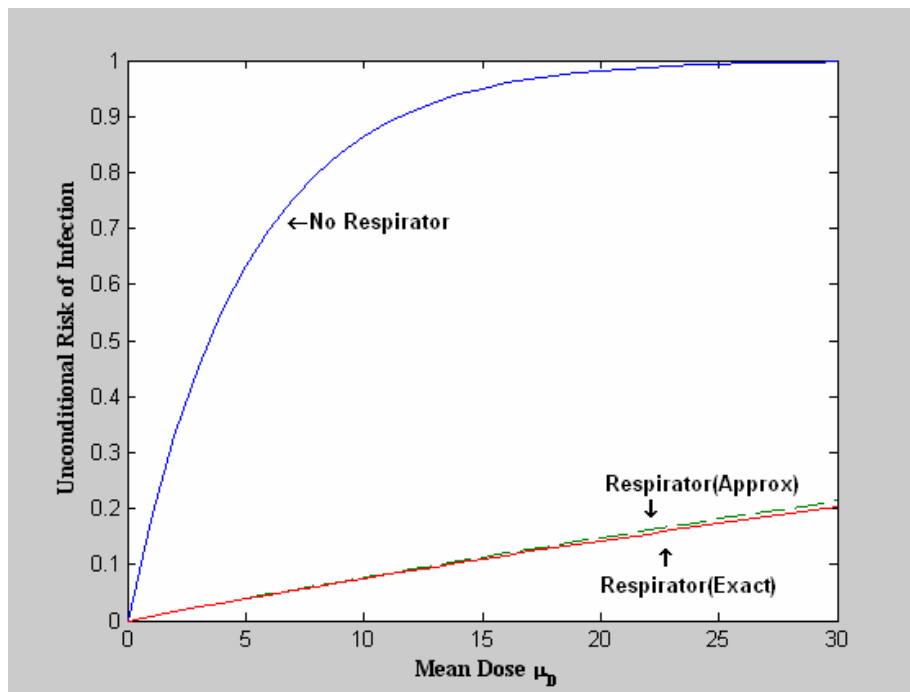


Figure 2. The unconditional risk of infection given expected inhaled doses without respiratory protection ranging $\mu_D = 0$ to $\mu_D = 30$, and given $P_S = 0.2$. The curve labeled “No Respirator” shows infection risk without the use of respiratory protection. The curve labeled “Respirator (Exact)” shows the reduced risk, as computed by Equation 6, due to using an air-purifying halfmask respirator with penetration values described by a standard beta distribution with $\alpha = 1.95$ and $\beta = 46.7$. The curve labeled “Respirator (Approx)” shows the reduced risk, as computed by Equation 7, due to using the same air-purifying halfmask respirator.

Although Equation 6 is the exact expression for computing R while accounting for variability in D and P , it is admittedly complex and its solution requires running a computer code. It happens that the following simpler approximation usually suffices:

Eq. 7
$$R \cong 1 - \exp(-[\mu_D \times \mu_P \times P_S])$$

In Figure 2, the dashed-line curve labeled “Respirator (Approx)” was computed by Equation 7. The Equation 7 approximation overestimates the unconditional risk of infection by less than 6% (relative to Equation 6) across the μ_D values shown.

Figure 2 shows that for a fixed P_S value, infection risk increases as the expected dose increases, which is intuitively reasonable. It is also true that for a fixed μ_D value, infection risk increases as P_S increases. Although R can be graphed as a function of P_S , it is perhaps more informative to graph R as a function of the pathogen's ID_{50} value, because microbial risk assessors usually speak in terms of the ID_{50} rather than the probability of infection per organism. To numerically specify the ID_{50} , it is not strictly proper to use Equation 1 and set ID_{50} equal to that D value for which $R_D = 0.5$. The reason is that the dose received must be an integer quantity, yet setting $R_D = 0.5$ in Equation 1 will produce a non-integer D value, in general. An alternative approach is to use Equation 2 involving the mean (expected) dose, which need not be an integer, and define the ID_{50} as the mean dose that yields $R = 0.5$. Therefore:

$$\text{Eq. 8} \quad ID_{50} = - \frac{\ln(0.5)}{P_S}$$

Figure 3 shows the effect of respiratory protection in reducing the unconditional risk of infection given $D \sim \text{Poisson}(\mu_D = 10)$, across a range of pathogen ID_{50} values (from 0.70 to 20), where it is assumed that an air-purifying elastomeric halfmask respirator is worn such that $P \sim \text{Beta}(\alpha = 1.95, \beta = 46.7)$. This P distribution has $\mu_P = .04$, and is the same beta distribution depicted in Figure 1. In Figure 3, the curve labeled “No Respirator” was computed by Equation 2, and the curve labeled “Respirator” was computed by Equation 6.

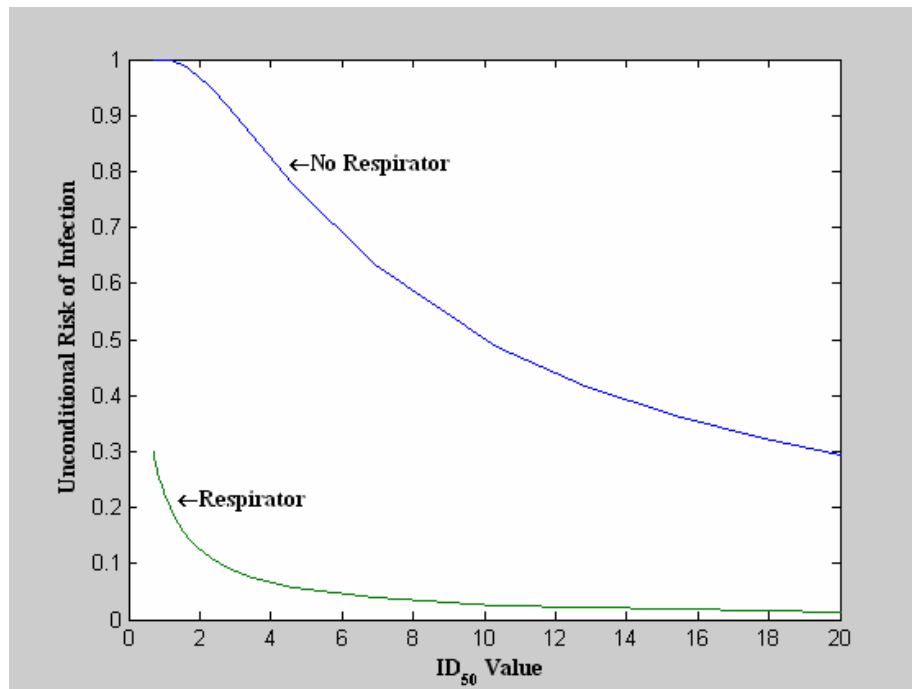


Figure 3. The unconditional risk of infection given an expected inhaled dose without the use of respiratory protection of $\mu_D = 10$, across a range of ID_{50} values from 0.70 to 20 (corresponding to P_S values ranging from, respectively, 0.99 to .035). The curve labeled “No Respirator” shows infection risk without the use of respiratory protection. The curve labeled “Respirator” shows the reduced risk, as computed by Equation 6, due to using an air-purifying halfmask respirator with penetration values described by a standard beta distribution with $\alpha = 1.95$ and $\beta = 46.7$.

Note that in Figure 3, $R > .05$ when $ID_{50} < 5$ (corresponding to $P_S > 0.13$) despite respirator use. This circumstance signifies that given an expected dose of 10 organisms without the use of respiratory protection, and given an acceptable air-purifying elastomeric halfmask respirator penetration distribution (less than 5% of penetration values exceed 0.1), infection risk exceeds 5% if the pathogen has high infectivity such that $ID_{50} < 5$. Infection risk can be decreased by using a respirator which affords a lower mean penetration value, or by reducing exposure intensity without regard to respiratory protection.

VARIABILITY IN HOST SUSCEPTIBILITY

No Respirator Use

A traditional way to account for host variability in susceptibility to infection is to model P_S as a standard beta random variable (Haas, et al., 1999; Teunis, et al., 1996). To avoid confusion with the respirator penetration distribution, the beta parameters for the P_S distribution are denoted δ and ε , such that the mean P_S value is $\mu_{P_S} = \delta/(\delta+\varepsilon)$, and the pdf is:

$$\text{Eq. 9} \quad g_{P_S}(p_s) = \frac{\Gamma(\delta + \varepsilon)}{\Gamma(\delta)\Gamma(\varepsilon)} p_s^{\delta-1} (1-p_s)^{\varepsilon-1}$$

For a fixed integer dose D , for $P_S \sim \text{Beta}(\delta, \varepsilon)$, and for no respirator use, the conditional cohort risk of infection, denoted $R_{\text{Coh},D}$, is:

$$\text{Eq. 10} \quad R_{\text{Coh},D} = 1 - \int_0^1 (1-p_s)^D \frac{\Gamma(\delta + \varepsilon)}{\Gamma(\delta)\Gamma(\varepsilon)} p_s^{\delta-1} (1-p_s)^{\varepsilon-1} dp_s = 1 - \frac{\Gamma(D + \varepsilon)\Gamma(\delta + \varepsilon)}{\Gamma(D + \delta + \varepsilon)\Gamma(\varepsilon)}$$

If $D \sim \text{Poisson}(\mu_D)$ for all cohort members, and if respiratory protection is not used, the cohort mean risk of infection R_{Coh} (the infection risk for a randomly selected cohort member) is:

$$\text{Eq. 11} \quad R_{\text{Coh}} = 1 - \sum_{k=0}^{\infty} \frac{\Gamma(k + \varepsilon)\Gamma(\delta + \varepsilon)}{\Gamma(k + \delta + \varepsilon)\Gamma(\varepsilon)} \times \frac{\mu_D^k \exp(-\mu_D)}{k!}$$

For a given mean dose, R_{Coh} increases as μ_{P_S} increases, but for a given μ_{P_S} value, R_{Coh} decreases as the variability across hosts in P_S increases. Table I compares the cohort mean infection risk at two μ_D values (1 and 10) across a range of μ_{P_S} values (.01 to 0.99) given no variability (%CV = 0) versus maximum variability in the P_S distribution. Maximum variability pertains when a fraction of the population (equal to the μ_{P_S} value) has $P_S = 1$, and the complementary fraction has $P_S = 0$. For a binary {0,1} distribution of P_S , the “probabilistic” model becomes a deterministic model, and the maximum variance and the maximum %CV are:

$$\text{Eq. 12} \quad \max(\text{Variance}) = (0 - \mu_{P_S})^2 \times (1 - \mu_{P_S}) + (1 - \mu_{P_S})^2 \times \mu_{P_S} = \mu_{P_S} \times (1 - \mu_{P_S})$$

$$\text{Eq. 13} \quad \max(\%CV) = \frac{\sqrt{\max(\text{Variance})}}{\mu_{P_S}} \times 100\%$$

As seen by inspecting the first two columns of Table I, $\max(\%CV)$ is higher at the lower μ_{P_S} values. For nearly every μ_{P_S} value at either mean dose, R_{Coh} is lower at $\max(\%CV)$ than at $\%CV = 0$; the relative difference is greater at the lower μ_{P_S} values. Note that at $\mu_D = 10$ and $\max(\%CV)$, R_{Coh} equals the μ_{P_S} value as expected; in contrast, for $\%CV = 0$, the R_{Coh} tends toward one. The latter result pertains when $\mu_{P_S} > 0$ and $\%CV = 0$, because everyone is susceptible to infection, and given a sufficiently high mean dose, everyone becomes infected.

Table I. The Cohort Mean Risk of Infection at a Mean Dose of 1 versus 10, Given Minimum Variability ($\%CV = 0$) versus Maximum Variability in the Beta Distribution of P_S Values for μ_{P_S} Values from .01 to 0.99

μ_{P_S}	Maximum $\%CV$	$\mu_D = 1$		$\mu_D = 10$	
		$\%CV = 0$	$\max(\%CV)$	$\%CV = 0$	$\max(\%CV)$
0.01	995	0.01	0.0063	0.095	0.01
0.05	436	0.049	0.032	0.39	0.05
0.1	300	0.095	0.063	0.63	0.1
0.2	200	0.18	0.13	0.86	0.2
0.3	153	0.26	0.19	0.95	0.3
0.4	122	0.33	0.25	0.98	0.4
0.5	100	0.39	0.32	0.99	0.5
0.6	82	0.45	0.38	1	0.6
0.7	65	0.5	0.44	1	0.7
0.8	50	0.55	0.51	1	0.8
0.9	33	0.59	0.57	1	0.9
0.95	23	0.61	0.6	1	0.95
0.99	10	0.63	0.63	1	0.99

Table I indicates that for low μ_{P_S} values, assuming a constant P_S value across hosts can lead to substantially overestimating infection risk if the P_S distribution is highly variable. Although the author is not aware of a typical $\%CV$ value that can be applied to the P_S distribution of an airborne pathogen, available published data for *Bacillus anthracis* spores (inhalation anthrax), variola major virus (smallpox), *Francisella tularensis* bacilli (tularemia), and *Coxiella burnetii* bacteria (Q fever) indicate that close to 100% of exposed test animal and/or human hosts are infected at sufficiently high doses. With reference to Table I, close to 100% infection of exposed hosts indicates either that the $\%CV$ must be moderate, or that the μ_{P_S} value is close to one; in both circumstances, the overestimation error due to assuming a constant P_S value is relatively small. Note that for inhalation anthrax in *Macacus rhesus* monkeys due to *B. anthracis* spore exposure, the estimated parameters for the P_S distribution are $\delta = 60$ and $\varepsilon = 3.6 \times 10^6$, such that $\%CV = 13\%$ (Nicas and Hubbard, 2002); these δ and ε values correspond to $\mu_{P_S} = 1.7 \times 10^{-5}$ and $ID_{50} = 59,000$. The minor effect of $\%CV = 25\%$ will be illustrated subsequently.

Respirator Use

Assume that $D \sim \text{Poisson}(\mu_D)$ for all cohort members, that $P \sim \text{Beta}(\alpha, \beta)$ for all cohort members, and that $P_S \sim \text{Beta}(\delta, \varepsilon)$ across cohort members. The cohort mean infection risk is:

Eq. 14

$$R_{\text{Coh}} = 1 -$$

$$\sum_{k=0}^{\infty} \left[\int_{p_s=0}^1 \int_{p=0}^1 \left(\frac{1}{W} \sum_{j=0}^k (1-p_s)^j \frac{(k \times p)^j \exp(-k \times p)}{j!} \right) g_{p_s}(p_s) f_p(p) dp dp_s \right] \frac{\mu_D^k \exp(-\mu_D)}{k!}$$

where W is the same term that appears in Equation 6, $f_p(p)$ is the pdf for respirator penetration values defined by Equation 3, and $g_{p_s}(p_s)$ is the pdf for p_s values defined by Equation 9. The structure of Equation 14 is similar to that of Equation 6. The difference is that the expected value of $(1 - P_S)^j$ is computed using the beta distribution probabilities that P_S takes on different values. For a given value k , computation of the expected value of $(1 - P_S)^j$ is performed for each value $P = p$ weighted by the corresponding probability that $P = p$, and for each value $P_S = p_s$ weighted by the corresponding probability that $P_S = p_s$, as indicated by the double integration operation. The bracketed term is the expected value of not being infected conditioned on the value k , and this expected value is weighted by the probability that the integer dose that would have been received without respiratory protection equals k .

There is no analytical solution for Equation 14, so the expression was numerically integrated by a MATLAB™ code analogous to that provided in the Appendix; an additional *for* loop was coded to account for the beta distribution probabilities that P_S takes on different values. Figure 4 shows the effect of respiratory protection in reducing the cohort mean infection risk across a range of pathogen ID_{50} values (from 0.71 to 20), where it is assumed that variability in host susceptibility to infection is adequately described by $\%CV = 25\%$ for the P_S distribution. Note that for the ID_{50} values of 0.71 and 0.73, the corresponding values μ_{p_s} are, respectively, 0.97 and 0.95, and the maximum $\%CV$ values for the P_S distributions are, respectively, 17.6% and 22.9%. The $\%CV$ values for $ID_{50} = 0.71$ and $ID_{50} = 0.73$ were set close to these maxima at, respectively, 15% and 20%. For $ID_{50} \geq 0.77$, $\%CV = 25\%$ for the P_S distribution. In Figure 4, it is assumed that $D \sim \text{Poisson}(\mu_D = 10)$ for all cohort members, and that an air-purifying elastomeric halfmask respirator is worn such that $P \sim \text{Beta}(\alpha = 1.95, \beta = 46.7)$ for all cohort members. The latter P distribution has $\mu_P = .04$, and is the same beta distribution depicted in Figure 1. The solid-line curve labeled “No Respirator” was computed by Equation 11, and the solid-line curve labeled “Respirator” was computed by Equation 14. As expected, respirator use reduces the cohort mean infection risk, although $R_{\text{coh}} > .05$ when $ID_{50} < 5$ despite respirator use. To further decrease infection risk, a respirator affording a lower mean penetration value must be used, or exposure intensity without regard to respiratory protection must be reduced.

Equations 11 and 14 are exact expressions for computing R_{coh} without respirator use versus with respirator use, respectively, while accounting for variability in D and P_S (and variability in P in Equation 14). Both expressions are complex and require solution via a computer code. It happens that when a respirator is worn, the following simpler approximation usually suffices:

Eq. 15

$$R_{\text{Coh}} \cong 1 - \exp(-[\mu_D \times \mu_P \times \mu_{p_s}])$$

When a respirator is not worn, the approximate solution involves setting $\mu_P = 1$ in Equation 15. In Figure 4, the dashed-line curve labeled “No Respirator” was computed by Equation 15 with $\mu_P = 1$, and the dashed-line curve labeled “Respirator” was computed by Equation 16 with $\mu_P = .04$. The approximate solution for no respirator use overestimates infection risk by less than 3% relative to the exact solution

(Equation 11) across the μ_D values shown. The approximate solution with respirator use overestimates infection risk by 10% or less relative to the exact solution (Equation 14) across the μ_D values shown.

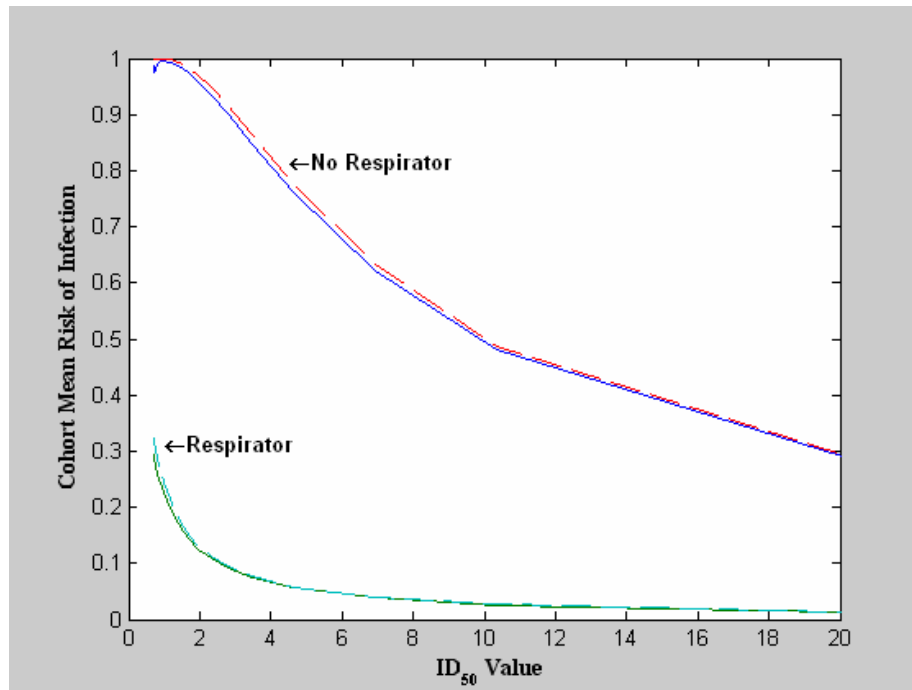


Figure 4. The cohort mean infection risk given an expected inhaled dose without the use of respiratory protection of $\mu_D = 10$, across ID_{50} values ranging from 0.71 to 20 (corresponding to μ_{P_S} values ranging from, respectively, 0.97 to .035). For $ID_{50} \geq 0.77$, the P_S values were described by a standard beta distribution with parameters δ and ε chosen to provide %CV = 25%. For ID_{50} values of 0.71 and 0.73, the P_S values were described by standard beta distributions with parameters δ and ε chosen to provide, respectively, %CV = 15% and %CV = 20%. The curve labeled “No Respirator” shows infection risk without the use of respiratory protection. The curve labeled “Respirator” shows the reduced risk due to using an air-purifying halfmask respirator with penetration values described by a standard beta distribution with $\alpha = 1.95$ and $\beta = 46.7$.

DISCUSSION

A relatively simple and health-conservative approach to estimating infection risk is to use approximation Equation 15 which relies on the mean values μ_D , μ_P and μ_{P_S} . By not accounting for variability in D, P and P_S , the approximation equation slightly overestimates the cohort mean infection risk relative to the exact solutions if the %CV for the P_S distribution is moderate. In turn, this slight overestimation error would lead to selecting a respirator with a lower μ_P value than required to meet the acceptable risk level.

To illustrate the selection process, Figure 5 shows the cohort mean infection risk at an expected dose $\mu_D = 10$, across a range of ID_{50} values up to 30, for no respirator use versus the use of three alternative types of respiratory protection – an air-purifying elastomeric halfmask respirator (halfmask), an

air-purifying fullface respirator (fullface), and a hooded powered air-purifying respirator (PAPR) – all equipped with high efficiency filters. For the halfmask it is assumed as before that $\mu_P = .04$. For the fullface, it is assumed that $P \sim \text{Beta}(\alpha = 1.95, \beta = 241.44)$ such that $\mu_P = .008$ and 4.1% of penetration values exceed 0.02. The latter statistic signifies that only 4.1% of workplace protection factors are less than 50, which is the NIOSH recommended fullface APF value (NIOSH, 2004). Thus, the assumed fullface penetration distribution satisfies the NIOSH APF criterion. For the hooded PAPR, it is assumed that $P \sim \text{Beta}(\alpha = 1.95, \beta = 4866)$ such that $\mu_P = .0004$ and 4.1% of penetration values exceed 0.001. The latter statistic signifies that only 4.1% of workplace protection factors are less than 1000. Although 1000 is 40-fold greater than the NIOSH APF value of 25 for a hooded PAPR (NIOSH, 2004), the assumed PAPR penetration distribution satisfies the OSHA APF of 1000 for certain hooded PAPR devices as used in the pharmaceutical industry (OSHA, 2002). Note that the OSHA APF for these PAPR devices was based on measurements of simulated workplace protection factors (Cohen, et al., 2001), and that OSHA has proposed an APF of 1000 for PAPRs with hoods or helmets (OSHA, 2003).

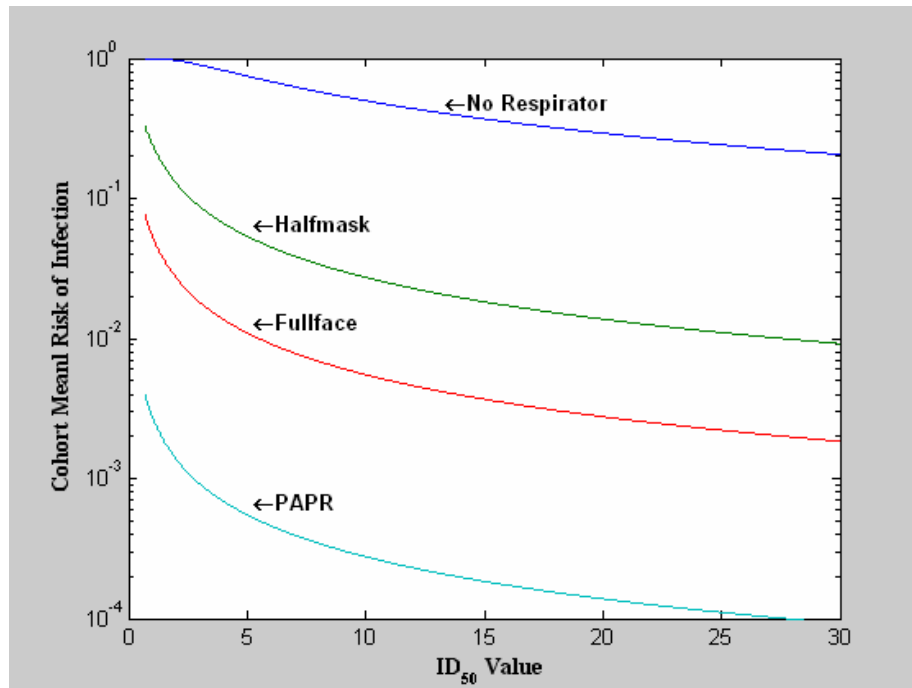


Figure 5. The cohort mean infection risk given an expected inhaled dose without the use of respiratory protection of $\mu_D = 10$, across ID_{50} values ranging from 0.7 to 30. The curve labeled “No Respirator” shows infection risk without the use of respiratory protection, as computed by Equation 15 with $\mu_P = 1$. The curve labeled “Halfmask” shows the reduced risk, as computed by Equation 15, due to using an air-purifying halfmask respirator with $\mu_P = .04$. The curve labeled “Fullface” shows the reduced risk, as computed by Equation 15, due to using an air-purifying fullface respirator with $\mu_P = .02$. The curve labeled “PAPR” shows the reduced risk, as computed by Equation 15, due to using a hooded PAPR with $\mu_P = .0004$.

Next, assume that variola major virus is the pathogen of concern for unvaccinated healthcare workers who might attend victims of a bioterrorist attack. Based on an analysis of the experimental smallpox literature, a probabilistic infectious dose model is appropriate with $\mu_{P_s} \cong 0.1$ (Nicas, et al., 2004); the corresponding ID_{50} is 6.9. Past case reports indicate that between 21% and 96% (average 58%) of unvaccinated persons exposed to smallpox cases become infected (Fenner, et al., 1988). Again, in

reference to Table I, a percent infection close to 100% indicates that the degree of variability in the variola major P_S distribution must be fairly low, because the maximum percent infected given a P_S distribution which is binary $\{0,1\}$ with $\mu_{P_S} = 0.1$ would be only 10%. The case reports are reasonably consistent with assuming a typical mean dose of $\mu_D = 10$, which in combination with $\mu_{P_S} = 0.1$, produces a cohort mean infection risk of 0.63 (63%) absent respiratory protection.

According to Figure 5 (and Equation 15), a halfmask would provide $R_{Coh} = .039$, a fullface would provide $R_{Coh} = .0080$, and a PAPR would provide $R_{Coh} = .00040$. If the acceptable risk of smallpox infection is .05, all three respirators suffice. If the acceptable infection risk is .01, the fullface and PAPR are adequate and the halfmask is inadequate. If the acceptable infection risk is .001, only the PAPR is appropriate. It is assumed that work in a health care environment is not more strenuous than work in the pharmaceutical industry, in which case the OSHA APF = 1000 for select PAPR devices as used in the pharmaceutical industry should also apply to use of the same PAPR devices by health care workers.

CONCLUSIONS

In any real-world circumstance, selecting respiratory protection against an airborne pathogen will involve expert judgment. However, an expert cannot categorize a risk (for example, low, medium, high) without some order-of-magnitude numerical criteria in mind, for example, 1×10^{-5} is "low risk" while 1×10^{-2} is "high risk". Without numbers attached to the risk categories, the ranking is unclear in the expert's own mind and unclear to others. Once order-of-magnitude ranking criteria are established, the expert still needs a way to numerically estimate risk so that it can be categorized. This paper presents such a quantitative method. Clearly, the procedure requires specifying parameter values involving pathogen infectivity, exposure intensity, and respirator efficacy, and estimates of these parameters will be uncertain. However, this same uncertain information would enter into making an expert judgment regardless of whether a numerical risk estimate was offered. The advantages of a quantitative approach are that specific information needs are identified, the risk estimation process is transparent and, although not described here, the degree of uncertainty in the risk estimate can be characterized via an uncertainty analysis. In addition, the respirator user is permitted an informed choice concerning which respirator to wear; in other words, the respirator user can decide which risk value he or she is willing to assume.

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Appendix

The Numerical Solution for Equation 6

Equation 6 of the main text (reproduced below) estimates infection risk for an individual for whom: (i) the inhaled dose without respiratory protection is a Poisson random variable with mean μ_D , (ii) the respirator penetration value is a standard beta random variable with parameters α and β , and (iii) each pathogen received has success probability P_S of initiating infection:

$$R = 1 - \sum_{k=0}^{\infty} \left[\int_{p=0}^1 \left(\frac{1}{W} \sum_{j=0}^k (1 - P_S)^j \frac{(k \times p)^j \exp(-k \times p)}{j!} \right) f_p(p) dp \right] \frac{\mu_D^k \exp(-\mu_D)}{k!}$$

where $W = \sum_{j=0}^k \frac{(k \times p)^j \exp(-k \times p)}{j!}$, and where $f_p(p)$ is the beta pdf for respirator penetration. The

following MATLAB™ code is used to solve this expression given the parameters: $\mu_D = 10$, $\alpha = 1.95$, $\beta = 46.7$, $P_S = 0.2$.

```
% MATLAB code to solve Equation 6
meandose = 10; alpha = 1.95; beta = 46.7; psuccess = 0.2;
DOSES1 = (0:1:30)';
POISSPROBS1 = poisspdf(DOSES1,meandose);
deltapen = .0001;
```

```

PENVALUES = (.0001:deltapen:1)';
BETAPROBS = deltapen*betapdf(PENVALUES,alpha,beta);
OUTPUT = zeros(31,1);
for k = 0:30
    tempdose = k;
    DOSES2 = (0:1:k)';
    TEMPINTEGRAL = zeros(10000,1) ;
    for p = 1:10000
        temppen = (p/10000) - 0.5*deltapen;
        meanDP = tempdose*temppen;
        POISSPROBS2 = poisspdf(DOSES2,meanDP);
        W = sum(POISSPROBS2(:,1));
        POISSPROBS2 = (1/W)*POISSPROBS2;
        tempsum = 0;
        for j = 0:k
            tempsum = tempsum + ((1 - psuccess)^j)*POISSPROBS2(j+1,1);
        end
        TEMPINTEGRAL(p,1) = tempsum*BETAPROBS(p,1);
    end
    sum2 = sum(TEMPINTEGRAL(:,1));
    OUTPUT(k+1,1) = sum2*POISSPROBS1(k+1,1);
end
Risk = 1 - sum(OUTPUT(:,1))

```

To begin, the parameter values are assigned. The code uses the internal function *poisspdf* to compute the probabilities that different integer doses up to 30 (without regard to respiratory protection) are received; these probabilities are stored in the matrix POISSPROBS1. Given $\mu_D = 10$, the probability is one that the dose will be between 0 and 30. Next, the code uses the internal function *betapdf*, in combination with the small increment $\text{deltapen} = .0001$, to compute the probabilities that different respirator penetration values are experienced; these probabilities are stored in the matrix BETAPROBS. In the alternative, the internal function *betacdf* could be used with further manipulation to compute the penetration value probabilities. The first *for* loop (indexed by *k*) considers each integer dose (without regard to respiratory protection) from 0 to 30. For each integer dose, the second *for* loop (indexed by *p*) considers each respirator penetration value from .00005 to 0.99995 at increments of .00005. For each integer dose and each penetration value, a new expected dose (termed *meanDP*) is computed. Given the *meanDP*, the internal function *poisspdf* is used to compute the probabilities that different integer doses up to *k* are received; these probabilities are stored in the matrix POISSPROBS2. The probabilities in POISSPROBS2 are multiplied by the factor $1/W$ to ensure that the probabilities sum to one. For each *meanDP* value, the third *for* loop (indexed by *j*) finds the expected value (termed *tempsum*) of the function $(1 - P_S)^j$ from *j* = 0 to *k*. The expected value *tempsum* is multiplied by the probability that the respirator penetration value equals the indexed value *p*, and the product is stored in the matrix TEMPINTEGRAL. The sum of the products in TEMPINTEGRAL is multiplied by the probability that the integer dose without regard to respiratory protection equals the indexed value *k*, and this product is stored in the matrix OUTPUT. The sum of the 31 products in the OUTPUT matrix is the probability that that infection does not occur. The complement is the risk of infection. For the specified parameter values, the code yields $R = .075$. Note that approximation Equation 7 yields $R = .077$.