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HIGH INFECTIVITY AND PATHOGENICITY OF INFLUENZA A PESTILENCE VIA AEROSOL AND DROPLET TRANSMISSION

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ABSTRACT

Influenza virus could also be transmitted through the respiratory route by inhalation of an aerosol of non-sedimenting droplets, or by deposition of sedimenting droplets within the upper tract. Whichever of those is that the predominant route for infection with the influenza virus has been subjecting to continuing debate, leading to detailed studies of aerosol versus droplet exposure. A decisive knowledge gap preventing a satisfying conclusion is an absence of a well-defined human dose-response model for the influenza virus.

This study uses a hierarchical approach generalizing over twelve human challenge studies collected in a very literature search. the excellence is formed between aerosol and intranasal inoculation. The results indicate high infectivity via either route, but intranasal inoculation ends up in about 20 times lower infectivity than when the virus is delivered in an inhalable aerosol.

A scenario study characterizing exposure to airborne virus near a coughing infected person during a room with little ventilation demonstrates that with these dose-response models the chances of infection by either aerosol or sedimenting droplets are approximately equal. Droplet transmission ends up in a rather higher illness risk thanks to the upper doses involved.

Establishing a dose-response model for influenza provides a firm basis for studies of interventions reducing exposure to different classes of infectious particles. More studies are needed to clarify the role of various modes of transmission in other settings.

KEYWORDS: Influenza A virus; Dose response; Droplet exposure; e Aerosol exposure Infection risk;

INTRODUCTION

Transmission of influenza is believed to occur through contact with small infectious particles. Infectious virus present in or on the mucosae of the upper tract is expelled through coughing or sneezing, or perhaps through normal exhalation, producing small droplets that will contain various amounts of virus (Fabian et al., 2008, Blachere et al., 2009). Droplets that are sufficiently little may evaporate rapidly, leaving a microscopic particle that may remain suspended within the air for an indefinite time (Riley, 1974). While a part of the produced infectious particles is also sufficiently small for a non-sedimenting aerosol, the rest of the expelled droplets is greater and tends to be aloof from the air by sedimentation (Duguid, 1946). Viruses present on surfaces (skin or inanimate) could also be transferred to the mucosa by hand and still cause infection (Ryan et al., 2001). Viruses may thus infect by different routes. The relative importance of those routes for transmission has been debated intensively but it remains unclear if any route is dominant (Tellier, 2006, Weber and Stilianakis, 2008).

The different modes of transmission of respiratory infections could also be studied by quantitative modeling of production of droplets containing virus and their transport to mucosal surfaces during a susceptible host (Xie et al., 2007, Atkinson and Wein, 2008, Nicas and Jones, 2009). Although such studies describe exposure to respiratory virus with considerable sophistication, one essential stage within the infection chain, the dose-response relation for infection, has remained relatively obscure. Infectivity estimates are supported small data sets containing few observations and biological variation (heterogeneity) in infectivity is ignored.

The present paper attempts to fill this gap by employing a hierarchical approach to dose-response modeling, supported data from several human challenge studies reported in scientific journals. this permits us to supply a quantitative description of the infectivity of the influenza a plague in humans, either by aerosol inoculation or by intranasal droplet inoculation, including its heterogeneity among hosts and virus isolates. Supported these dose-response models, improved estimates of the danger of infection (and of acute respiratory symptoms) are often calculated for aerosol and droplet transmission. For a given exposure scenario the relative strengths of either transmission mode can then be estimated.

The improved dose-response information contributes to quantitative estimates of the infectious droplet transmission process by including variation in host susceptibility likewise as variation in infectivity among different virus isolates.

DOSE-RESPONSE ASSESSMENT

A literature study of human challenge experiments with influenza virus has produced two sets of studies, with virus delivered either via aerosol inhalation or via intranasal droplet inoculation. Aerosol inoculation may allow the virus to succeed in a smaller bronchial where receptor densities are high (Hatch, 1961) and infection is also more likely. Alternatively, deposition of alittle droplet of virus suspension onto the nasal mucosa may function a model for transmission via droplets of sedimenting sizes (Brankston et al., 2007)

To analyze these dose-response data, a hierarchical model is employed, extending the hit theory model for microbial infection (Haas, 1983, Teunis and Havelaar, 2000) to a multilevel framework (Teunis et al., 2008b).

DOSE-RESPONSE MODEL

When exposed to a sample taken from a well-mixed microbial suspension the probability of exposure to 1 or more infectious virus particles is

$$\mathrm{Prob}_{\exp}(cV) = 1 - \mathrm{e}^{-cV}$$

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assuming volume V was inoculated from a suspension of Poisson distributed particles with concentration c.

In case each particle is equally infectious, the dose-response relation for infection is (Riley and O'Grady, 1961)

$$\mathrm{Prob}_{\mathrm{inf}}(cV|p_m) = 1 - \mathrm{e}^{-p_m cV}$$

where any infectious virus survives the host barriers to infection with probability pm (Teunis and Havelaar, 2000). Biological variation in host susceptibility and virus infectivity could also be expressed as (random) variation in pm. The resulting (marginal) dose-response model

$$\mathrm{Prob}_{\mathrm{inf}}(cV|\alpha,\beta) = 1 -_1 F_1(\alpha, \alpha+\beta; -cV)$$

where 1F1 could be a (Kummer) confluent hypergeometric function and α and β the parameters of a beta distribution describing the variation in pm, is that the beta-Poisson model for microbial infection (Haas, 1983, Teunis and Havelaar, 2000).

A person infected with the influenza virus may develop symptoms of acute respiratory disease with probability again betting on the inoculated dose. A conditional dose-response model for illness in infected subjects is defined as

$$\mathrm{Prob}_{\mathrm{ill|inf}}(cV|\eta, r) = 1 - (1+\eta cV)^{-r}$$

of infection (parameters η and r describe a (gamma) distribution for the dose-dependent duration of infection). Details is found in Teunis et al. (1999).

As subject status is binary (infected or not, symptomatic or not) the model could also be analyzed with a binomial likelihood function (Teunis and Havelaar, 2000) which will be extended to a two-level framework (Teunis et al., 2002, Teunis et al., 2008b). Additional information on statistical analysis is provided in an internet appendix (supporting information).

DOSE-RESPONSE DATA

Three studies administered the virus through inhalation of an identical aerosol of influenza a pandemic isolated from patients (5 different isolates, shown in Table 1). Twelve papers reported on influenza a deadly disease challenge through intranasal droplet inoculation, three of which looked as if it would re-report results from an earlier study, leaving nine studies with 14 different isolates (Table 2). Note that the oldest study (Henle et al., 1946) only documented illness responses: numbers of infected subjects (excreting virus) weren't reported. Because illness is conditional on infection these data still provide information about the infectivity of the virus.

Table 1. Wild-type influenza virus challenge studies with aerosol inoculation.

Reference	Virus type	Dose ($TCID_{50}$)	Exposed	Infected	Ill
Henle et al. (1946)	A (F-12)	0.6×10^{10}[a]	4	–[b]	4
		0.6×10^{10}[a]	4	–[b]	4
		0.6×10^{9}[a]	4	–[b]	1
		0.6×10^{8}[a]	4	–[b]	1
	A (F-99)	$0.6\times10^{8.5}$[a]	6	–[b]	5
		$0.6\times10^{8.5}$[a]	4	–[b]	4
		$0.6\times10^{7.5}$[a]	6	–[b]	2
	A (PR-8)	$0.6\times10^{8.2}$[a]	33	–[b]	27
Jao et al. (1965)	A2 (Elisberg)	30	30	–[c]	12
Alford et al. (1966)	A2/Bethesda/10/63	126	3	0	0[d]
		78	3	0	0[d]
		59	3	1	0
		1	1	1	1
		2	4	1	0
		5	9	4	3

a.Not tissue culture but ID50 in chick embryos.

b.Not studied.

c.Virus excretion and sero conversion were studied but not reported.

d.These subjects were presumably immune, as that they had high antibody levels to the virus.

Table 2. Wild-type influenza virus challenge studies with nasal inoculation.

Reference	Virus type	Dose ($TCID_{50}$)	Exposed	Infected
Henle et al. (1946)	A (F-12)	10^{10a}	4	–[b]
	A (F-99)	$10^{8.5a}$	6	–[b]
Murphy et al. (1973)	A/Bethesda/88 (H3N2)	$10^{4.5}$	7	7
Murphy et al. (1980)	A/Hong Kong/77 (H1N1)	$10^{4.2}$	6	6
	A/Udorn/72 (H3N2)	$10^{4.0}$	6	5
	A/Alaska/77 (H3N2)	$10^{4.2}$	8	8
Clements et al. (1983)	A/Alaska/6/77 (H3N2)	$10^{4.2}$	8	8
Clements et al. (1984b)	A/Washington/897/80 (H3N2)	$10^{6.0}$	24	23
Clements et al. (1984a)	A/Washington/897/80 (H3N2)[d]	$10^{6.0}$	24	23
Murphy et al. (1984)	A/California/10/78 (H1N1)			
Murphy et al. (1985)	A/Washington/897/80 (H3N2)[d]			
Clements et al. (1986)	A/Washington/897/80 (H3N2)[d]			
Snyder et al. (1986)	A/California/10/78 (H1N1)			
	A/Korea/1/82 (H3N2)			
Sears et al. (1988)	A/Texas/1/85 (H1N1)			
	A/Bethesda/1/85 (H3N2)			
Youngner et al. (1994)	A/Kawasaki/9/86 (H1N1)			

a.Not tissue culture but ID50 in chick embryos.

b.Not studied.

c.Of these subjects, 6 had severe symptoms with fever, 1 had mild symptoms without a fever.

d.Same as Clements et al. (1984b).

particle. In most studies, the virus dose was expressed in TCID50 units. this can be the median 50% tissue culture infectious dose (TCID50). Assuming perfect susceptibility 1 TCID50 would correspond to log2 ≈ 0.69 infectious virus particles because the dose-response for a wonderfully susceptible host system is Pinf(D) = 1 − e− D, hence 1 − e− TCID50 = 0.5. this is often quite near 1 and so we feel safe in assuming that 1 TCID50 approximately equals 1 infectious virus particle (Blachere et al., 2009). In one in every of the studies the dose was expressed as 50% infectious dose in chick embryo culture (Henle et al., 1946). Chick embryos also are a sensitive medium (Hirst, 1942) and it doesn't seem very likely that the chick embryo assay is a smaller amount susceptible than the tissue culture assay by over an order of magnitude (Donald and Isaacs, 1954). Therefore, within the following analysis, it's assumed that 1 EID50 = 1 TCID50 = 1 virus

Exposure

Droplets are generated during breathing, coughing, or sneezing as expelled air strikes surfaces covered with mucus within the upper tract. Various accounts are published of the diameters of the fluid particles produced during either of those activities, with comparable outcomes (Duguid, 1946, Loudon and Roberts, 1967, Xie et al., 2009). A review of airborne infectious particle emission (Nicas et al., 2005) describes three different studies reporting particle size distributions. To not unduly complicate the subsequent account of airborne exposure the sizes recorded in one study (Loudon and Roberts, 1967) are used, because that study provides a close account of the particle size distribution, combining small non-sedimenting particles and huge size particles that sediment rapidly. The reported particle diameters range from 1 μm to quite 1.5 mm, and also the frequencies counted within the air expelled with 90 coughs are given.

There appears to be a bimodal distribution of small and huge particles (Fig. 1) and a binary mixture of lognormal distributions provides a decent fit of those observed particle

sizes. Small particles have a mean size of three.0 μm (99% range 1.27–6.25 μm). the common diameter of huge particles is 111.4 μm (99% range 8.7–616.6 μm). a touch but half the particles are within the small size class (48.3%). Note that, assuming spherical particles, this implies that the full volume within the small particle class is about 2.4 × 10− 6 of the whole volume of all expelled particles.

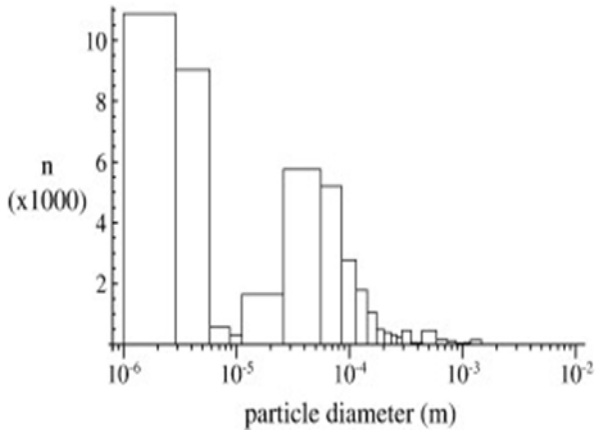

Fig. 1. Counts of particles of varied diameters within the air expelled by (90) coughs (Loudon and Roberts, 1967).

Sedimentation of fluid particles

A very basic description of sedimentation of fluid particles will be given by considering only gravitational and frictional forces

$$\begin{cases} mx''(t) = -bx'(t) \\ my''(t) = -by'(t) - mg \end{cases} \quad \begin{cases} x(0) = 0, x'(0) = a \\ y(0) = h, y'(0) = 0 \end{cases} \tag{5}$$

where x and y are horizontal and vertical distances, m is the mass of the fluid particle, g is the gravitational constant and b is a frictional coefficient. Initial height above the floor is h (m) and particles are expelled with initial horizontal velocity a (m/s). For spherical particles

$$m = \tfrac{4}{3}\pi r^3 \rho(\text{kg}), \quad b = 6\pi\eta r(\text{kg s}^{-1}) \tag{6}$$

where $\eta = 1.82 \times 10^{-5}$ (kg m^{-1} s^{-1}) and $g = 9.81$ (m s^{-2}). Eq. (5) can be solved to yield

$$x(t) = \tfrac{am}{b}\left(1 - e^{-\frac{b}{m}t}\right); \quad y(t) = h - \tfrac{mg}{b}t + \tfrac{m^2 g}{b^2}\left(1 - e^{-\frac{b}{m}t}\right) \tag{7}$$

so that the time a particle is suspended can be estimated (Fig. 2a). For a given initial velocity the horizontal distance travelled appears to only depend on particle diameter in a fairly narrow range, from 40 μm to 1 mm (Fig. 2b).

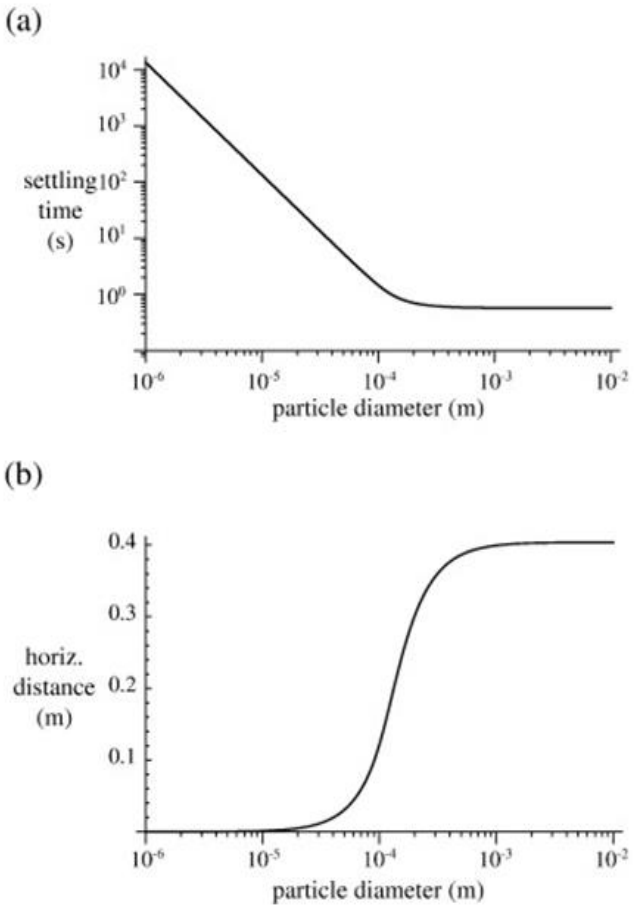

Fig. 2. (a) Average settling time (in s) for a particle produced at body height (1.6 m) to achieve the ground, as a function of particle diameter. (b) The horizontal distance (in m) traveled when a particle is expelled with velocity 1 m/s and falls 0.8 m (half body height).

A sedimenting particle is assumed to be expelled in a very random direction within a cone-shaped region (Tang et al., 2009) of angle α steradians (1 steradian corresponds to an apex angle of ≈ 65.5° in a very cross-section of the cone). The expanse of the bottom of the cone (as a spherical cap) is

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$$S_c = \alpha d^2 \quad (8)$$

when d is the horizontal distance travelled by the particle. See Fig. 3. The volume of the cone is approximately

$$V_c = \frac{\pi d^3}{3}\left(1 - \frac{\alpha}{2\pi}\right) + \frac{\alpha^2 d^3}{4\pi}\left(1 - \frac{\alpha}{6\pi}\right) \quad (9)$$

(Nicas and Sun, 2006, Atkinson and Wein, 2008).

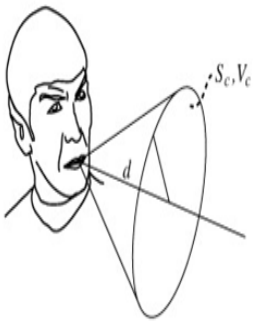

Fig. 3. The conical region where sedimenting droplets (> 10 μm) may occur after expulsion through coughing or sneezing. The horizontal distance d (and the circular area Sc and also the corresponding volume Vc) depends on the initial velocity and also the particle size.

INHALATION OF AEROSOL

If an individual resides in an exceedingly room with little ventilation where another infected person produces virus suspended in aerosol, the probability of inhaling a suspended particle (e.g. a droplet nucleus) is

$$P_{\text{inhal}}\left(\tau, Q_r, V_0\right) = 1 - \mathrm{e}^{-\frac{Q_r \tau}{V_0}}$$

assuming perfect mixing, where V0 is that the room volume (m3), Qr is that the respiration rate (m3 s− 1) and τ is that the continuance, i.e. the common time the particle remains in suspension (as in Fig. 2a). it'll be assumed that the respiration rate is 50 l/min and also the room volume is 3 × 4 × 4 = 48 m3. When the receiving subject remains within the room for an outlined period T, say 1 h, the probability of inhalation is decided by Min (τ, T) rather than τ.

DROPLET INOCULATION

In the same situation as above: a closed room with an individual coughing, and another one who could also be close enough to be exposed, the probability of contact with sedimenting infectious droplets is also considered. Above (sedimentation of fluid particles) the degree of space was calculated where an expelled droplet is also found (Eq. (9), see Fig. 3)

Assuming that contact with such a droplet may occur in a very rectangular volume where the receiving person are often (in an area of 4 × 4 m2 a volume of roughly 2 × 16 = 32 m3) the probability of contact is proportional to Vc/32. alittle fraction of the exposed body surfaces is mucosa (Nicas and Sun (2006) assume 15 cm2 = 15 × 10− 4 m2) and also the probability of a droplet hitting exposed mucosa is proportional to fifteen × 10− 4/Sc. The probability of contact through a sedimenting infectious droplet then is

$$P_{\text{droplet}} = \frac{15\times10^{-4}}{32}\frac{V_c}{S_c} = Kd \quad (11)$$

with d again the horizontal distance travelled by the droplet, and

$$K = \frac{15\times10^{-4}}{16\times9.6}\left(\frac{\pi}{3}\left(1 - \frac{\alpha}{2\pi}\right) + \frac{\alpha^2}{4\pi}\left(1 - \frac{\alpha}{6\pi}\right)\right)\frac{1}{\alpha} \quad (12)$$

where the solid angle α describes the dispersion in direction of sedimenting droplets.

SIMULATION OF EXPOSURE

The following scenario was assumed: an infectious person produces droplets containing the virus by coughing, with size distribution as in Fig. 1. The median horizontal velocity was assumed to be 2 m/s, its maximum (95 percentile) 12.5 m/s, and a gamma distribution was accustomed simulate its variation (parameters r = 0.65, λ = 5.48). supported a hierarchical model analysis of nasal excretion data (Baccam et al., 2006) the concentration of virus was assumed to be

lognormal with mean 108 and 95% range 105–1012 (m− 3). At the time of coughing another person enters the area and remains there for 1 h, while there's neither little ventilation nor strong air movements.

The probabilities of exposure and infection (and acute symptoms of respiratory illness) were estimated for one infectious particle (either sedimenting or non-sedimenting), and for a coughing attack consisting of a Poisson distributed number of coughs (15 coughs average) and negative binomially distributed numbers of particles per cough, average 466 (Loudon and Roberts, 1967), and dispersion parameter ρ = 10 (Teunis et al., 2008b). The resulting distribution of numbers of particles is shown in Fig. 10a.

Virus inactivation thanks to aerosol formation and drying wasn't accounted for because it's likely that the periods required are longer than the 1 h scenario assumed here. a discount in infectivity of but 1 log unit has been reported after 6 h suspension in air temperature (Harper, 1961), at high humidity survival could also be lower (Hemmes et al., 1960)

RESULTS

Dose-response assessment

The dose-response relations for infection, illness among infected, and illness are shown in Fig. 4, Fig. 5, Fig. 6. These graphs show 'best fit' dose-response relations for all individual isolates, still because the (posterior) density of the anticipated probabilities (of infection, illness has given infection, or illness unconditionally). The latter densities will be thought of as estimates of infection or illness risk, generalized from the whole set of included dose-response relations. The outer margins correspond to a 99% predictive interval. See online supporting information for more explanation and extra results. Also shown are the observed fractions, as far as these are often calculated.

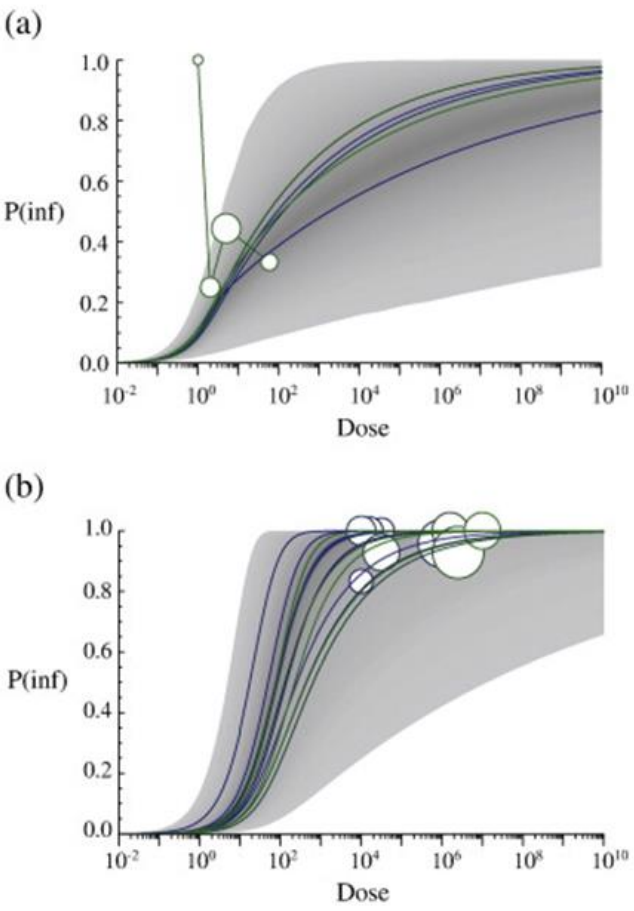

Fig. 4. Dose-response for infection by wild type influenza a scourge, via aerosol or intranasal droplet inoculation. 'Best fit' dose-response relations and density graph of predicted infection risk as a function of dose (margins span 99% interval). Also shown may be a bubble chart of observed fractions (symbol size proportional to numbers exposed).

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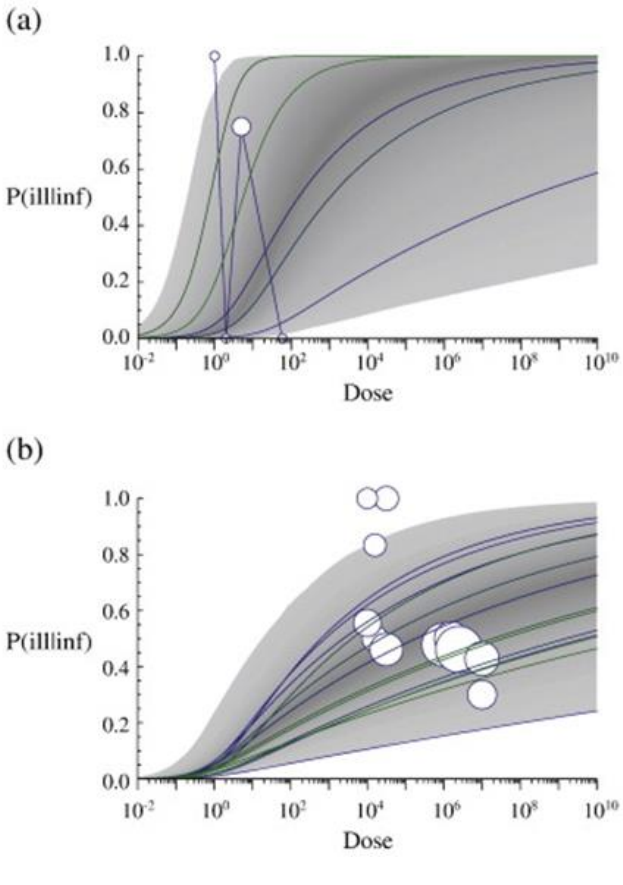

Fig. 5. Dose-response for illness given infection by wild type influenza a virulent disease, via aerosol or intranasal droplet inoculation. ‘Best fit’ dose-response relations and density graph of predicted conditional illness risk as a function of dose. Also shown may be a bubble chart of observed fractions (symbol size proportional to numbers infected).

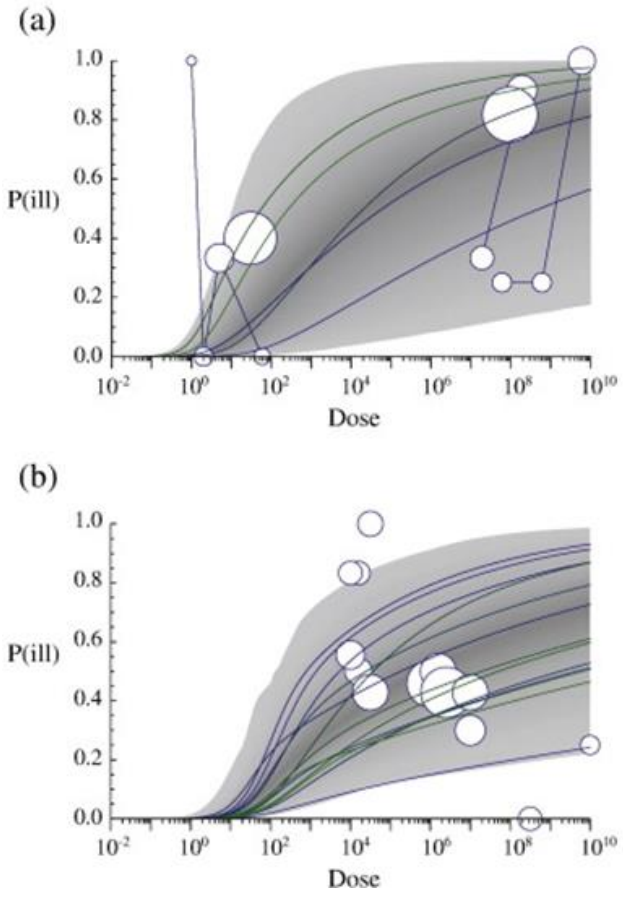

Fig. 6. Dose-response for illness by wild type influenza a deadly disease, via aerosol or intranasal droplet inoculation. ‘Best fit’ dose-response relations and density graph of predicted illness risk as a function of dose. Also shown may be a bubble chart of observed fractions (symbol size proportional to numbers exposed).

The dose-response relation for infection is totally determined by the infectivity of one infectious unit (pm within the model described above). Its distribution also can be determined, as shown in Fig. 7, for aerosol and intranasal droplet inoculation.

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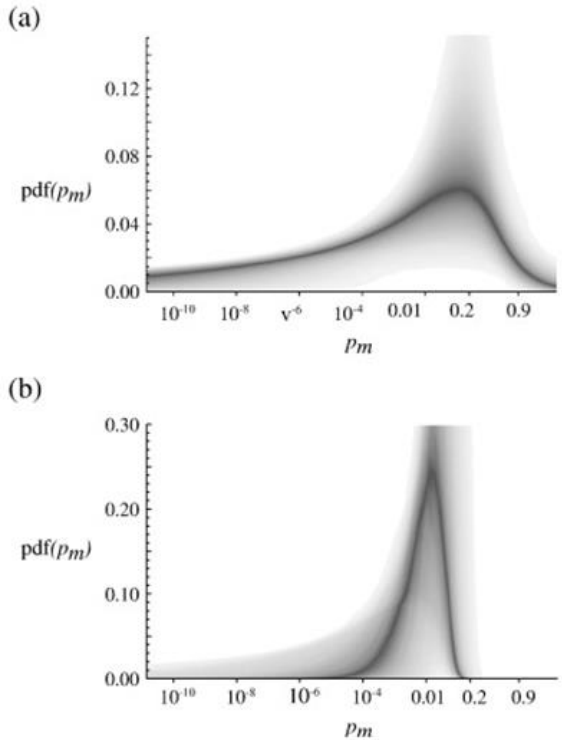

Fig. 7. Distribution of single virus unit infectivity for wild type influenza a deadly disease, via aerosol inoculation and via intranasal droplet inoculation. Density chart determined from (posterior) predictive distribution of the infectivity parameters.

Aerosol inoculation of influenza an epidemic (Fig. 4a) leads to high infectivity, mainly due to the responses to low doses (Jao et al., 1965, Alford et al., 1966).

Aerosol inoculation is about 20 times as efficient as intranasal droplets in causing infection, but with greater variability (Fig. 7).

SIMULATED RISK

Using the scenario outlined above a town simulation of the risks of exposure (i.e. inhalation or mucosal contact with a minimum of one infectious virus particle) and infection are often simulated. The conditional dose-response relations for acute illness among infected subjects could also be accustomed also estimate illness risks.

The probability of contact with an expelled fluid particle as a function of its diameter is shown in Fig. 8a, for sedimenting and non-sedimenting particles. Also shown are the chances of exposure to virus, infection, and acute respiratory symptoms (Figs. 8b–d).

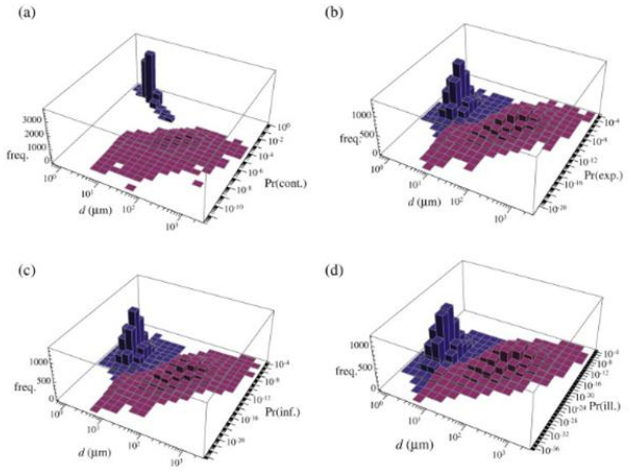

Fig. 8. Probabilities of contact with a fluid particle (a), exposure to the infectious virus (b), infection (c), and symptoms of acute respiratory disease (d), as a function of the diameter of the expelled particle. Histograms for the 2 different transmission routes, aerosol inhalation, and droplet inoculation, are shown in blue and red, respectively.

Fig. 9 shows risks related to the presence of one infectious particle, either non-sedimenting (aerosol) or sedimenting (droplet), with diameter drawn indiscriminately from the distribution defined by Loudon and Roberts (1967). The probability of exposure thanks to either transmission route is approximately equal, as is that the infection risk. The probability of acute respiratory symptoms is higher with droplets because the dose involved is probably going to be higher. Note that the distribution of risk is extremely skewed, with mean risks near the 95 percentile or maybe above that level.

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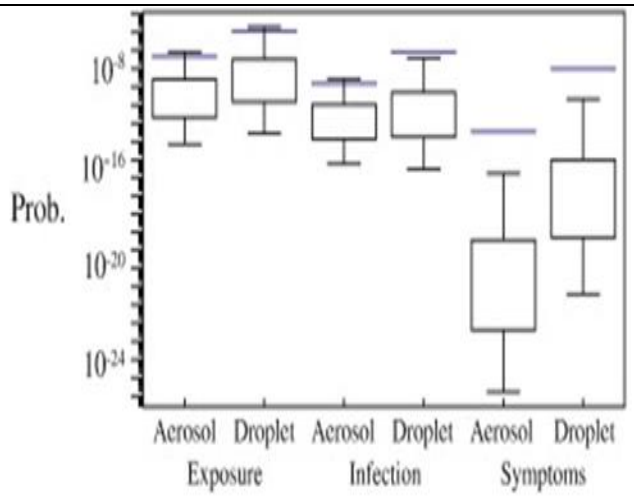

Fig. 9. Box plots of simulated risk of exposure to the infectious virus, infection, and acute disease, when within the given scenario one infectious particle is produced, either non-sedimenting (aerosol) or sedimenting (droplet). Boxes indicate quartiles, whiskers 95% ranges, and also the horizontal lines indicate mean risks.

The simulated risks related to the assembly of a greater number of infectious particles are shown in Fig. 10, for the numbers of particles resembling a coughing attack.

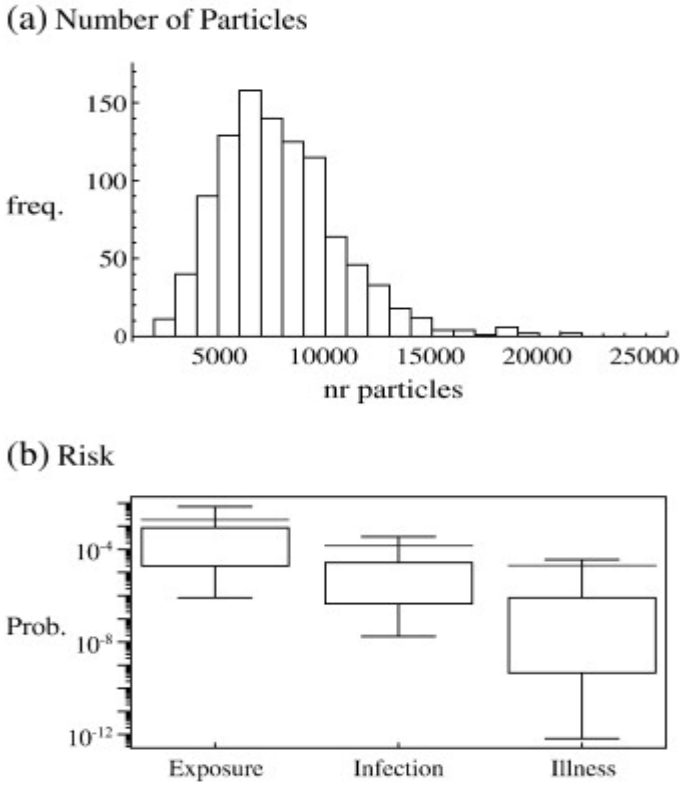

Fig. 10. Numbers of particles expelled in an exceedingly coughing attack (a) and box plots of simulated risk of exposure to the infectious virus, infection, and acute disease (b). Boxes indicate quartiles, whiskers 95% ranges, and therefore the horizontal lines indicate mean risks.

DISCUSSION

Previous studies on exposure issues in transmission of influenza have considered epidemic dynamics (Atkinson and Wein, 2008, Chen et al., 2009, Li et al., 2009) or not, dealing only with transmission mechanisms (Nicas and Sun, 2006, Nicas and Jones, 2009). All of those studies have ignored heterogeneity, both in virus infectivity (and pathogenicity) and in susceptibility of the human hosts. the utilization of a hierarchical framework has not only allowed us to use a two-parameter model that features a (beta) distribution characterizing heterogeneity at the extent of the one challenge study but also to characterize the variation among studies, representing different viruses isolates.

It should be noted that volunteers in human challenge studies usually are young adults in good general health, selected to not develop severe illness. Although often the immune status of the volunteers isn't known, especially within the older studies, the high observed infection and illness rates suggest low levels of immunity to infection or illness. In immune subjects, the probability of illness (and possibly infection) is not up to in those with no immunity, given equal exposure. Therefore, when repeated exposure to similar virus strains is probably going, the health risks could also be below estimated here.

The dose-response relation for illness among infected subjects implies that low dose exposure may result in infection, thanks to the high infectivity of the virus, but of these infected only alittle proportion may become ill. Exposure to high doses of virus leads to most of the infected subjects also becoming ill. A shedding event releasing high

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numbers of viruses within the environment may therefore result in clusters of cases that may be detected in disease surveillance. Where low numbers of viruses are present transmission could also be mostly asymptomatic, and therefore the odd person developing symptoms cannot easily be linked to other cases infected by the identical source. When exposure to the airborne virus is reduced, for example by population-wide use of face masks, the relative decrease in numbers of illnesses is anticipated to be greater than the relative decrease in transmission, by numbers infected.

The quantitative characterization of influenza virus infectivity (and pathogenicity) provides a stronger basis for prospective studies of the consequences of interventions, specifically those interventions that reduce exposure, for example, the effect of mask use on the spread of pandemic influenza (Brienen et al., 2010).

In calculating the virus content of differently sized particles the virus concentration was assumed constant in order that, given the virus concentration, the quantity of viruses during a particle of any size depends only on its volume. Sequestration of the virus into fluid particles may however not be independent of particle size, and if this were the case the relative contributions of variously sized particles to exposure, infections, and symptoms as shown in Fig. 7 may change.

It is worth noting here that virus in suspension may often be aggregated, causing the virus to be present in clumps of variable numbers of single viruses or virions, rather than a totally dispersed suspension of virions (Wei et al., 2007). If the inoculum should contain aggregates the effect on the dose-response relation would be a rise in apparent heterogeneity (compared to a monodisperse suspension of the identical virus): any suspended particle then may incorporates 1 or more virions, each of variable infectivity (Teunis et al., 2008a).

In freshly shredded influenza virus most particles is also infectious: particle counts and TCID50 don't differ greatly (Wei et al., 2007). Even the EID50, the five hundred infectious dose in chick embryo culture has been estimated to correspond to but 10 particles, also supporting the belief that TCID50 and EID50 are approximately equal. However, when the virus has been exposed to environmental conditions the fraction of infectious particles may decrease rapidly (Horsfall, 1954, Horsfall, 1955, Choppin and Tamm, 1960). Such loss of infectivity might not be important within the scenario considered here, but must be taken into consideration when considering exposure to the virus in natural conditions.
The estimated probabilities of exposure and infection are within the identical order of magnitude, indicating that one cannot readily discard either route as unimportant for transmission. The advantage of sedimenting droplets carrying the next virus load is compensated by their smaller chance of contact combined with the lower infectivity of upper tract inoculation. Similarly, the more efficient inoculation of small aerosol particles is compensated by their smaller virus content. for instance, outdoor aerosol transmission isn't likely thanks to dilution and dispersion by ambient wind speeds and turbulence, whereas in closed environments, particularly with low ventilation, aerosol transmission is more likely.

Despite equal infection risks, the corresponding risks of acute respiratory disease are somewhat higher for droplets, thanks to the upper dose that's involved larger particles.

Influenza virus may additionally be transmitted through hand contact with contaminated surfaces. Surface-to-hand-to-mucosa contacts weren't considered during this study because the aim was to check aerosol and droplet transmission within the absence of human behavioral factors, as these are poorly understood and also the proximity of infectious and susceptible subjects can't be easily quantified.

To improve the estimates of transmission of respiratory

virus, further studies of exposure are needed to see how efficiently airborne virus could also be transferred within the presence of ventilation, the relation between human contact behavior and droplet infection, and most significantly, the role of contaminated surfaces within the transmission of influenza.

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