Mathematical Biosciences and Engineering

MBE, 20(9): 17499–17519.
DOI: 10.3934/mbe.2023777
Received: 06 April 2023
Revised: 19 July 2023
Accepted: 30 July 2023
Published: 13 September 2023

http://www.aimspress.com/journal/MBE

Research article

Extension of probability models of the risk of infections by human enteric viruses

Costantino Masciopinto*

Consiglio Nazionale delle Ricerche, Istituto di Ricerca Sulle Acque, Bari viale F. De Blasio 5, 70132 Italia

* **Correspondence:** Email: costantino.masciopinto@ba.irsa.cnr.it; Tel: +39-080-531-3395; Fax: +39-080-531-3365.

Abstract: This study presents a novel approach for obtaining reliable models and coefficients to estimate the probability of infection caused by common human enteric viruses. The aim is to provide guidance for public health policies in disease prevention and control, by reducing uncertainty and management costs in health risk assessments. Conventional dose-response (DR) models, based on the theory elaborated by Furumoto and Mickey [1], exhibit limitations stemming from the heterogeneity of individual host susceptibilities to infection resulting from ingesting aggregate viruses. Moreover, the scarcity of well-designed viral challenge experiments contributes to significant uncertainty in these DR models. To address these issues, we conducted a review of infection models used in health risk analysis, focusing on *Norovirus* (NoV) GI.1, pooled *Enterovirus group* (EV*)*, *Poliovirus 1/SM*, and *Echo-12 virus* via contaminated water or food. Using a mechanistic approach, we reevaluated the known DR models and coefficients for the probability of individual host infection in the mentioned viruses based on dose-infection challenge experiments. Specifically, we sought to establish a relationship between the minimum infectious dose (ID) and the ID having a 50% probability of initiating host infection in the same challenge experiment. Furthermore, we developed a new formula to estimate the degree of aggregation of GI.1 NoV at the mean infectious dose. The proposed models, based on "exact" beta-Poisson DR models, effectively predicted infection probabilities from ingestion of both disaggregated and aggregate NoV GI.1. Through a numerical evaluation, we compared the results with the maximum likelihood estimation (MLE) probability obtained from a controlled challenge trial with the NoV GI.1 virus described in the literature, demonstrating the accuracy of our approach. By addressing the indetermination of the unmeasured degree of NoV aggregation in each single infectious dose, our models reduce

overestimations and uncertainties in microbial risk assessments. This improvement enhances the management of health risks associated with enteric virus infections.

Keywords: infections risk assessment; dose-infection response models; *norovirus Hu/GI.1*, *Enterovirus group*, *Poliovirus 1/SM*, and *Echo-12 virus* infection model coefficients

1. Introduction

Enteric viruses are harmful pathogens that have been linked to several waterborne disease outbreaks in humans. These viruses can be found in water and food that have been contaminated with fecal waste, either directly or indirectly. They can survive and remain attached to soil sediments, with high rates of resuspension and redistribution in flowing groundwater, particularly during flood runoff events. This poses a significant risk to human health, as it can lead to severe contamination of potable wells because changes in the ionic strength of flowing water may originate high detachment rates of virions from surface collectors (i.e., soil particles) [2]. Given these risks, accurate assessments of groundwater quality are crucial, especially in the aftermath of floods [3–5]. In both the USA (e.g., Big Horn Lodge, WY; Atlantic City, WY; Coeur d'Alene, ID; Island Park, ID) [6] and Italy (Salento peninsula) [7], there have been several outbreaks caused by contaminated drinking water from fractured bedrock (e.g., limestone) aquifers, such as limestone aquifers. These aquifers have been shown to be particularly susceptible to microbial contamination by norovirus (NoV), hepatitis-A virus (HAV), rotavirus (RoV), EV, and adenovirus (AdV) [8–10].

Quantifying the microbial health risk assessment (RA) during outbreaks, particularly hepatitis A and gastrointestinal infections observed in regions such as Salento Peninsula, Italy [7], caused by ingesting contaminated food and water, is crucial for guiding public health policies for disease prevention and control. RA results are vital for community water management systems (i.e., policymakers) to evaluate water supply quality and set appropriate performance targets for wastewater treatment plants. In risk assessment, dose-response (DR) models are employed to quantify infections through various pathways of pathogenic agents delivered to the host (target). Probabilistic models and coefficient updates can reduce uncertainty and management costs in health risk assessments. DR models are based on pathogen challenges, involving experiments on volunteers, animals, or cells infected with a pathogen under controlled conditions. These experiments are necessary to study infectivity and immunogenicity in human hosts via mechanistic equations, similar to clinical trials of new vaccines. The infection risk is calculated from challenge experiments involving volunteers, determining the percentage of exposed nonimmune individuals who tested positive. DR model extrapolates the infection probability curve for increasing doses to better approach the experimental results. The physical meaning of "infectious dose" and coefficients [11] in the most commonly applied exponential and beta-Poisson approximate models are often poorly explained in many studies on RA. The term "infectious" is a requirement from the single-hit theory of the probability of infection, which posits that every single pathogen Poisson distributed in the dose must have the potential to infect the host, thereby making it "infectious." Moreover, certain studies on RA, such as those constructed by Ayuso-Gabella et al. [12] and Pecson et al. [13], utilize established literature coefficients [11] obtained from specific challenge experiments without

providing clear explanations for potential discrepancies between the volume of the applied inoculum in the dose of the studied experiment and that found in the literature. These discrepancies often arise because using an exponential or approximate beta-Poisson DR model scaling from 1 to 100 ml of inoculum volume of the dose leads to a significant horizontal shift in the curve of the predicted infection risk [14]. As suggested by Schmidt [15], when applying DR models in RA, particularly exponential and approximate beta-Poisson models, it is crucial to carefully investigate exposure assessment, specifically the estimation of the mean infectious dose. This refers to the product of the infectious pathogen concentration and the volume (or weight) of the contaminated inoculum supplied to the host. Therefore, a strong link exists between exposure assessment and the subsequent computation of the DR model. Reliable RA requires in-depth studies in different scientific fields, such as biomolecular microbiology for pathogenic agent identification and assays, medicine for understanding the pathogenesis of illness, and the health impact of infections, including host immunity and cell infection mechanistic processes. Most of this knowledge goes beyond the scope of environmental science and mathematics. The complexity involved may explain the frequent uncertainty in the results of RA [16,17]. Another concern is the identification of aggregation or non-aggregation of infectious pathogen particles in the dose delivered to the host. Gerba and Betancourt [18] explained the importance of viral aggregation for viral survival in wastewater. They demonstrated that most enteric viruses in polluted water samples appeared in aggregated forms, which increased their survival or resistance to environmental conditions and wastewater disinfection treatments. Therefore, studying how the aggregation of NoV can affect human health during environmental host exposure could lead to a more reliable estimate of the probability of infection. The uncertainty of exposure assessment, resulting from challenges in accurately predicting the number of infectious particles in the mean dose, coupled with the limited availability of specifically designed human challenge experiments in the literature, can lead to less reliable results of applied RA methods [14]. Teunis et al. [19] utilized various data sources, including outbreak data, to estimate the mean infection risk for a host exposed to a single dose of 1-NoV, resulting in values of 0.28 for *NoV GI.1* and 0.076 for less infective *NoV GII* in nonimmune (Se+) subjects. Their research indicated that *GII NoV* is associated with more severe infections, despite GI NoV being preferred in human challenge experiments due to its higher infectivity.

In this study, we sought to establish a relationship between the minimum infectious dose (ID) and the ID having a 50% probability of initiating host infection in the same challenge experiment for estimating the coefficients of individual infection risks via conventional mechanistic DR models, specifically for host inoculation with *NoV GI.1,* or pooled *Enterovirus group, Poliovirus 1/SM*, or *Echo-12 virus*. To validate the proposed coefficients, we compared the solutions of our DR model with the results of human challenge trials conducted by Teunis et al. [20], Atmar [21], Lion [22], and Mateo [23].

2. Materials and methods

In this review of dose-infection challenge experiments, we conducted a thorough reassessment of existing DR models and coefficients for the probability of individual host infection caused by Norovirus (NoV) GI.1. Our analysis focused on establishing a suitable relationship between the mean infectious dose (MID) and the corresponding infectious dose (ID) with a 50% probability of

initiating a host infection, known as ID_{50}.

Since 1967, numerous studies have been carried out to develop DR models for RA. The primary method of estimating the probability of infections has been based on the single-hit probability model (SHPM) initially proposed by Furumoto and Mickey [1]. Recently, Nilsen and Wyller [24] integrated SHPM into a stochastic framework. Subsequent methodological improvements [11,24] have recommended the utilization of functions complementary to the beta-Poisson probability distribution of SHPM for individual infections, such as the negative binomial (NB) or the gamma threshold probability distribution, among others [26]. These DR models consider variations in host-to-host susceptibility by combining single- or multi-hit Poisson probability and the conditional probability distribution of the minimum count of ingested infectious agent required to infect a host. However, the definition of the MID implies the presence of a threshold dose, which has not yet been comprehensively investigated in viral challenge experiments [17] involving NoV GI.1 inoculation [23]. For instance, Caul's experiment [27] yielded data indicating a MID for widespread aerosols containing infectious particles in the range of 10 to 100.

Furthermore, certain critical aspects of the SHPM theory, as discussed by van Abel et al. [28], Messner [29], and Schmidt [15], have not been thoroughly examined in specific DR experiments. These aspects include the effects of individual host susceptibilities to infections caused by the same transmitted pathogen. Moreover, van Abel et al. [28] observed that in some experiments, secretor Se– individuals were infected by NoV genotype GII.4; that is, they became susceptible to infection. Similarly, in a study conducted by Mateo et al. [23], one immune host exhibited severe gastroenteritis, similar to a Se-positive challenge host. Despite these findings, the literature lacks well-designed viral challenge experiments for accurately estimating the coefficients of DR models, even when considering methods that encompass all possible infectious pathogens.

To address these gaps, Rahman et al. [30] developed a mechanistic method for DR models to investigate foodborne host infection by *Listeria monocytogenes*. Their model describes the process of the host cell's resistance against infectious pathogens and considers the possibility that plasma in host cells could facilitate the release of antibodies to eliminate pathogens. Integrating such mechanistic alternative models into the single-hit theory can significantly improve health risk estimations, as they are based on the operating environmental conditions and clinical data of a single host during viral challenge infection experiments.

2.1. Conventional methods for infection probability estimation

In various RA methods, the α and β coefficients of the beta-Poisson DR model [16] are derived from past pathogen challenge experiments. These experiments were conducted by different researchers for various pathogens, such as HAV (Hepatitis A Virus) infection by Ward [31], RoV (Rotavirus) by Ward [32], Echovirus-11/12 by Shift [33], and Coxsackievirus (CV) and AdV (Adenovirus) by Couch et al. [34] (refer to Table 1). Recent experiments focusing on DR curves for NoV were conducted by Atmar et al. [20], Frenck et al. [35], and Seitz et al. [36]. Additionally, Teunis et al. [37] proposed a redefinition of the coefficients of a DR model for AdV (AdV4, AdV7, and AdV16) by grouping data from various types of dose-infection challenge experiments found in the literature and the results of infection tests on kidney pig cells.

In contrast, Strachan et al. [38] combined infection data collected from numerous global outbreaks, using data from both animal and human cells, to define a DR probability model of

infection for *E. coli O157*. They applied binomial and beta-binomial distributions in MLE to determine the α and β coefficients. Strachan et al. also proposed using DR challenge tests with surrogates of infectious pathogens, such as *E. coli O157* and *Sighella* [38]. However, it is important to note that the availability of data from pathogen challenge experiments suitable for implementing comprehensive new DR models remains limited (refer to Table 1). Furthermore, using surrogate pathogens or animal cells in challenge experiments has resulted in probability-of-infection curves that significantly differ from those obtained using known DR model coefficients.

Table 1. Coefficients of dose-response probability of infection models scaled to 1 g (or 1 ml) of the inoculum (i.e., contaminated food or water) volume size.

Dose-response model		**α and β (or β_1** for the exponential model**)**	
HAV	Exponential	1.8229	Haas and Eisenberg [39]
AdV	Exponential	2.397	Crabtree et al. [40]
NoV	Exponential	2.375	Sokolova et al. [41]
RoV	Approximate beta-Poisson	0.253 and 0.422	Teunis and Havelaar [14]
EV			
Group	Approximate beta-Poisson	0.167 and 0.191	de Man et al. [42]
Echovirus-12	Approximate beta-Poisson	0.401 and 227.2	Teunis et al. [43]
	Exponential	78.3	McBride et al. [44]; Haas et al. [45]
	Approximate beta-Poisson		
CV	Exponential	129	Mena et al. [46]

The approximate beta-Poisson model, as described in the literature, is expressed as follows.

$$P = 1 - \left(1 + \frac{ID}{\beta}\right)^{-\alpha}. \quad (1)$$

However, this formulation leads to an overestimation of the *NoV GI.1* probability of infection at low infectious doses (*ID*) compared to the "exact" beta-Poisson infections model solution [15,20,28]:

$$P = 1 - {}_1\mathrm{F}_1(\alpha; \alpha + \beta; -ID) \quad . \quad (2)$$

The model coefficients α (= 0.04) and β (= 0.055) [20] were obtained from *NoV GI.1 (8fIIa + 8fIIb)* challenge experiments for disaggregated virions in the doses. However, Teunis et al. [43] suggested that the DR model (1) can provide an acceptable probability of infection approaching an exact solution (2) when reliable model coefficients are applied, although some uncertainty may be expected in the result at low infectious doses [28] of pathogens in volunteers (i.e., hosts).

2.2. New relationships in beta-Poisson DR models

The main theoretical implication of our proposed mechanistic method, as presented in this study, is to revolve around establishing relationships between ID/β and ID/ID_{50} to enhances microbial risk

assessments methods. The ID_{50} in the approximate beta-Poisson models. can be calculated as [39, p. 163]

$$ID_{50} = \beta \left(2^{1/\alpha} - 1\right) . \quad (3)$$

as derived from specific pathogen challenge experiments. Of note, in RA, the correct application of α and β model coefficients provided in existing DR models is achieved when *ID*, ID_{50}, and β are defined for the same challenge experiment. This ensure that the mean pathogen dose supplied to the host and the model coefficients applied in the DR model refer to the same infection event [11]. In the present work, we demonstrate that using relationships between *ID*, the coefficient β, and minimum infectious dose rather than ID_{50} can lead to more reliable estimates for the probability of infection in RA, particularly for the transmission of enteric viruses to hosts. To establish this relationship, we collected ID_{50} and MID data (Table 2) from various challenge experiments involving infections caused by host inoculation with different enteric viruses [47,48].

Table 2. MID and ID_{50} values collected from challenge infection experiments on enteric viruses.

MID	ID_{50}	Pathogen	Source
1	1.26	HAV	Ward et al. [31]
1	6.17	RoV	Graham et al. [49]; Teunis and Havelaar [14]
0.83	1.66	AdV	Couch et al. [34]
		EV	
1	2	Poliovirus 1/SM	Schiff et al. [33]
17	78.3	Echo-12	Schiff et al. [33, 51]
30	69.1	Coxsackie (CV) B4-A21	Health Canada [50]; Mena et al. [46]

Table 2 presents the collected *MID* and ID_{50} values from challenge infection experiments involving enteric viruses. The best fit (R^2 = 0.91) of the *MID* vs. ID_{50} values provided the relationship shown in Figure 1 on a semi-log plane in combination with the uncertainty intervals. Microsoft Excel was utilized to derive the following regression equations:

$$MID = c_1 \cdot log\ (ID_{50}) - c_2, \quad (3a)$$

or

$$log\ (ID_{50}) = \frac{1}{c_1}(MID + c_2), \quad (3b)$$

where c_1 = 2 and c_2 = 6 are the best-fit coefficients.

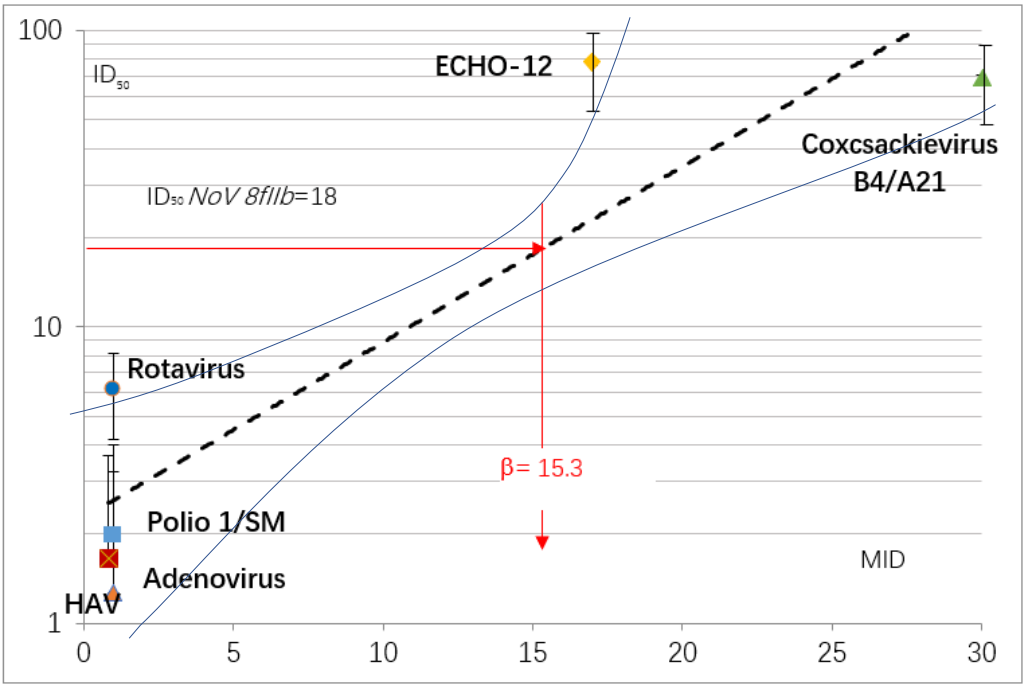


Figure 1. Best-fit relationship between MID-ID_{50} values from the collected challenge-controlled experiments and uncertainty intervals of estimations.

Our proposed mechanistic method favors simple physically-based relationships between MID and ID_{50}, rather than complex equations obtained through advanced best-fit methods and the Akaike Information Criterion (second order) [52]. To further enhance these relationships, additional ID_{50}/*MID* data from enteric virus challenge trials could be included, potentially leading to the definition of novel coefficients for beta-Poisson infection probability models derived from well-designed challenge studies.

In this study, we propose new models and coefficients to reduce overestimation and uncertainties in microbial risk assessments. By imposing an ID_{50} of 18, as estimated by Teunis et al. [20] from a NoV GI.1 challenge experiment on volunteers inoculated with the strain *NoV GI.1 8fIIb*, we calculated the *MID* of 15.3 ± 3 for *NoV GI.1* using Eq (3b) (refer to Figure 1). We defined β_{new} as equal to *MID* of 15.3 (i.e., >> 1) in 100 ml (or 1.5, scaled to 1 ml of inoculated volume). Subsequently, we calculated the corresponding model coefficient α_{new} as 0.89 (i.e., << 15.3) by inverting the known relationship (3) as follows:

$$\alpha_{new} = \frac{1}{log_2\left(\frac{ID_{50}}{\beta_{new}}+1\right)} \tag{4}$$

3. Results

3.1. Disaggregated NoV GI.1 inoculation DR models

The proposed model's coefficients were validated through comparison, as depicted in Figure 2. We considered a DR model (1) with an exact beta-Poisson solution (2) to determine the probability

of infection based on α (0.04) and β (0.055) coefficients proposed by Teunis et al. to predict the probability of infections caused by disaggregate *NoV GI.1 (8fIIa + 8fIIb)*. The exact beta-Poisson solution was obtained using Microsoft Excel, employing the Kummer confluent hypergeometric function [53], resulting in the following expression:

$$ {}_1F_1 = \sum_{n=0}^{\infty} \frac{(\alpha)_n(-ID)^n}{(\alpha+\beta)_n n!}, \tag{5} $$

where $\alpha_n = \alpha\,(\alpha+1)\cdot(\alpha+2)\cdot\ldots\cdot(\alpha+n-1)$, and similarly, $(\alpha+\beta)_n = (\alpha+\beta)\cdot(\alpha+\beta+1)\cdot\ldots\cdot(\alpha+\beta+n-1)$. The value of n represents the number of terms considered in the series, which is set to 15 in the calculations. The integral form of the beta-Poisson model probability of infection is given by [11]

$$ P = 1 - \int_0^1 \left(\frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\cdot\Gamma(\beta)} \cdot r^{\alpha-1} \cdot (1-r)^{\beta-1}\right) \cdot e^{-r\cdot ID} dr, \tag{6} $$

where "*r*" is the single-hit value of the beta-probability of infection (i.e., host susceptibility) and Γ() represents the gamma function.

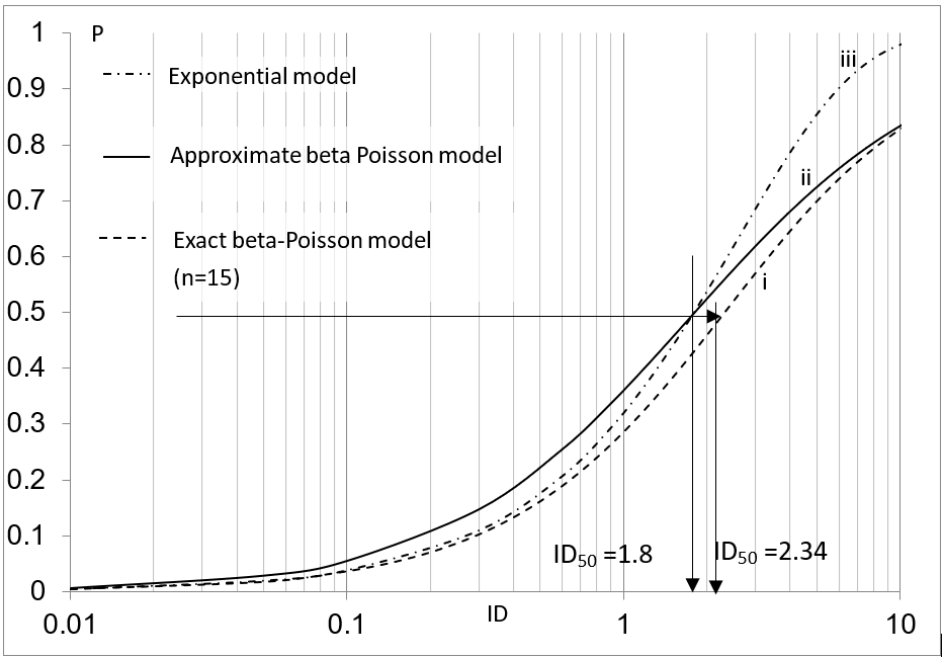


Figure 2. Probability of infection for the ingestion of *NoV GI.1 8fIIb* for ID <10 (disaggregated in 1 ml of inoculum volume): i) the exact ($1-{}_1F_1$ (α,α + β,−*ID*)) solution provided by Teunis et al. using coefficients from cumulative infections in a given challenge for strains *(8fIIa + 8fIIb)*, ii) the approximated beta-Poisson model using new coefficients (α = 0.89 and β = 1.53), and iii) the exponential model using the proposed coefficient (β_1 = 2.597), which approaches the exact beta-Poisson solution given by Eq (2).

Additionally, Figure 2 presents the infection probability obtained by the exponential model using the following expression:

$$ P = 1 - e^{-\frac{ID}{\beta_1}}, \tag{7} $$

where β_1 is the proposed coefficient with a value of 2.597. $\beta 1 = 2.597$ improves the approximate beta-Poisson solution (Eq 1), closely aligning with the exact beta-Poisson infection probabilities in the considered challenge experiment at low doses. This enhances prediction accuracy and model reliability.

Figure 3 demonstrates that the exact beta-Poisson (2) obtained using the values (0.89; 1.53) for the proposed coefficients also fits well with the infection probabilities obtained via maximum likelihood estimation (MLE) (Table 3) for *NoV GI.1 8fIIb* in the challenge experiment conducted by Teunis et al.

Table 3. Infections/doses from the MLE of *NoV GI.1 8fIIb* challenge trial [20].

ID	*0.01*	*0.1*	*0.3*	*0.5*	*0.8*	*1*	*3*	*10*	*18*	*100*	*1000*
P	0.01	0.03	0.1	0.15	0.2	0.28	0.44	0.48	0.5	0.54	0.56

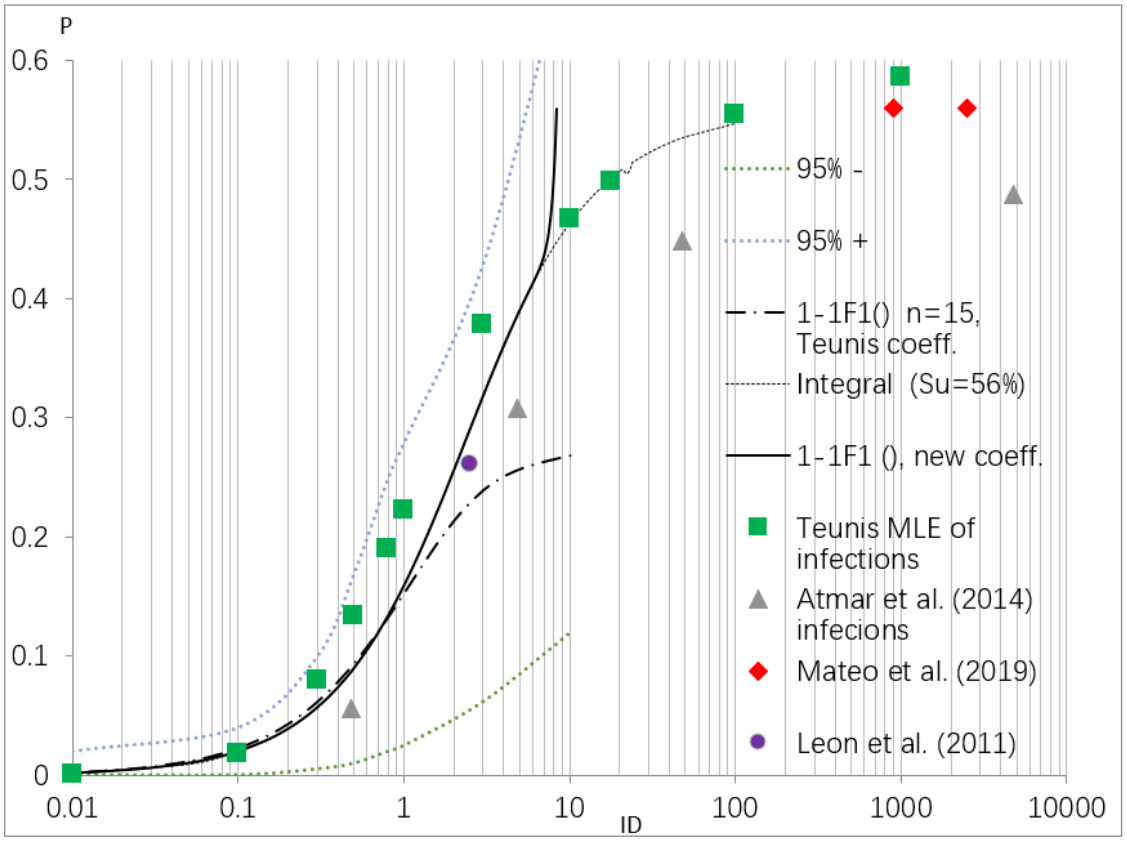


Figure 3. Exact solutions of single-hit individual infection probabilities from GI.1 *NoV 8fIIb* challenge experiments, considering the 56% host nonimmune fraction, using the values provided in the literature with $\alpha = 0.04$ and $\beta = 0.055$ [20] (dashed dot line), and new coefficients $\alpha = 0.89$ and $\beta = 1.53$ and, using Eqs (2) (solid line) and (6) (dashed line), respectively; and MLE results from Teunis et al. [20] (green-square dots) with ±95% interval (green-dot lines) and infection data from Atmar et al. [21] (grey-triangle dots), Leon [22] (violet-circle dots), and Mateo [23] (red-rhomb dots).

The model probabilities (see Figure 3) are compared with MLE results from Teunis et al. [20] challenge experiment and infection data from Atmar et al. [21], Leon [22], and Mateo [23], all adjusted for the 56% nonimmune host fraction.

The risk infection curves shown in Figure 3 confirm the appropriateness of the proposed mechanistic coefficients in fitting the exact beta-Poisson probabilities of infection (6) and approaching the MLE curve from the challenge test conducted by Teunis et al. [20], as well as the infection data from the NoV GI.1 challenge trials conducted by Atmar et al. [21], Lion [22], and Mateo [23] considering the 56% nonimmune host fraction.

The exact beta-Poisson solutions given by Eqs (2) and (6) were calculated using Microsoft Excel and MATHCAD (https://www.mathcad.com), respectively. The DR models in Figure 3 provide a mean infection risk of 0.285 (= 0.16/0.56) for Se+ host secretors exposed to only 1-NoV GI.1, which is very close to the infection risk of 0.28 recently estimated by Teunis et al. [19].

3.1.1. "Aggregate" NoV GI.1 inoculation DR models

In this section, we present three theoretical formulations of the DR model of infection from the literature, predicting the infection risk due to norovirus aggregation in doses supplied to volunteers.

The underlying experimental work by Teunis et al. aimed to explain how the aggregation [17,45] of noroviruses might affect the individual probability of infection. The infection probability for nonimmune hosts exposed to aggregated NoV virions can be expressed as [28]

$$P_i = [1 - \theta \cdot {}_2F_1(\beta, \mathbf{b}; \alpha + \beta; \boldsymbol{a})] \tag{8}$$

This probability depends, via the Gauss hypergeometric function ${}_2F_1()$, on the degree of virion aggregation (or percentage) "$\boldsymbol{a}$" in each aggregate present in the inoculated dose given to volunteers. Various challenge experiments in the literature have suggested a "log-series" probability distribution of "$\boldsymbol{a}$" among aggregations (Poisson distributed) of inocula with a corresponding mean size (i.e., number of NoV virions) μ in the mean percentages of "$\boldsymbol{a}$." Note that ϑ and **b** in Eq (8) represent transformation variables of the mean aggregate infectious dose (id).

In this study, we have revised the "beta-binomial" probability of the infection model and applied the Euler transformation [53] to Eq (8) to obtain the following:

$$P_i = (1 - \varphi)\left\{1 - \left[\vartheta \frac{\Gamma(\mathrm{c})}{\Gamma(\mathrm{b})\Gamma(\mathrm{c-b})} \int_0^1 r^{(b-1)} \cdot (1-r)^{(c-b-1)}\left(1 - r \cdot a^{-\beta}\right) dr\right]\right\}, \tag{9}$$

where

$$\vartheta = e^{-\frac{\overline{id}}{a\,\mu}}, \qquad \mu = \frac{-a}{(1-a)\cdot log(1-a)}, \tag{9a}$$

$$\mathrm{b} = \frac{\overline{id}\cdot(1-a)}{a}, \qquad c = \alpha + \beta, \tag{9b}$$

In Eq (9), the term (1 - φ) denotes the fraction of individuals who are fully susceptible (i.e., r = 1) to NoV infection caused by the aggregate dose *id*, whereas $\overline{id} = -\log[P(id)/(1 - P(id)]$ is the log transformation variable of the mean aggregate infectious dose of NoV, where P is the beta-Poisson probability given by Eq (6) for nonimmune hosts.

It is important to note that Eq (9) represents the "single hit" beta-Poisson probability of infection only for the extreme cases of $\boldsymbol{a} = 1$, or $\boldsymbol{a} = 0$. Thus, the probability of infection caused by aggregated NoV GI.1 combines the beta (continuous) probability distribution of the host-to-host susceptibility, to the negative binomial probability of infection from "clumped" virions within each dose [11].

Teunis et al. [20] estimated the model coefficients ($\alpha = 5.35 \cdot 10^{-3}$ and $\beta = 2.51 \cdot 10^{-3}$) using the MLE approach based on experimental infection probabilities from aggregated NoV 8fIIa human challenge trial. In this study, we propose different coefficients ($\alpha = 0.89$ and $\beta = 1.53$) for NoV GI.1. Additionally, Messner et al. [29] reconsidered the Eq (8) above from the Teunis model and proposed the fractional Poisson (FP) probability distribution, which can be expressed as

$$P_i = P_{(1\ -\ \varphi)} \cdot \left(1 - e^{-\frac{id}{\mu}}\right) \tag{10}$$

where P represents the corresponding beta-Poisson single-hit probability of infection at the same infectious dose. This equation is based on the *Bernoulli* probability distribution, where r can take values 1 or 0, and it provides an alternative simplified solution to the exact beta-binomial probability form given in Eqs (8) and (9) by quantifying a constant immunity host fraction.

Following Schmidt [15], the integral formulation of the single hit of "adapted" beta-Poisson (ABP) conditional probability of infections from aggregated *NoV* can be obtained by reconsidering the same challenge dataset used by Messner et al. [29]. This single-hit DR model assumes that all ingested aggregate virions are completely disengaged in the host. Therefore, the ABP model accounts for the beta distribution of the host-to-host susceptibility caused by "clumped" ingested virions. The aggregates of *NoV* are modeled with a Poisson distribution into every single dose supplied to the host, and since virions in every aggregate follow a log-distributed pattern [20], the resulting virion distribution in the administered mean dose $\overline{\imath d}$ follows a negative binomial probability distribution. The ABP probability of infection model, considering a constant host immunity fraction φ, can then be expressed as [15].

$$P_i = (1 - \varphi)\left\{1 - \int_0^1 \left(\frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\cdot\Gamma(\beta)} \cdot r^{\alpha-1} \cdot (1-r)^{\beta-1}\right) \cdot \left[1 - (1-r)^{\overline{\imath d}}\right]\right\} dr. \tag{11}$$

In this study, we purpose $\overline{\imath d}$ estimations via the extended negative binomial (ENB) (Pòlya) probability distribution (www.vosesoftware.com/riskwiki) of the aggregate virus count in the infectious dose, as given in the following equation.

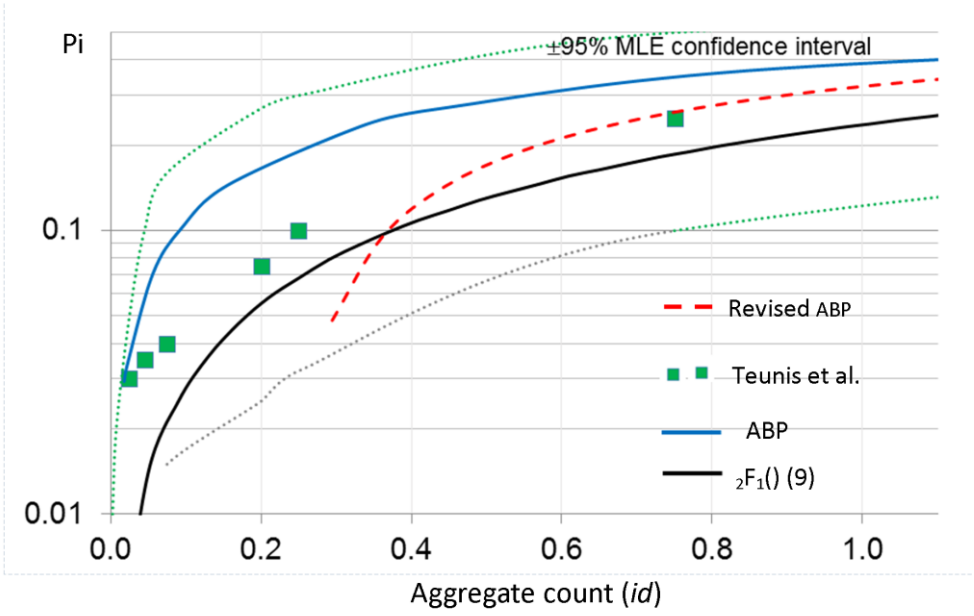
$$\overline{\imath d} = \frac{1}{\left[\frac{\Gamma(\mathbf{a}+z)}{\Gamma(\mathbf{a})\cdot\Gamma(z_i)} \cdot P_i(id)^{\mathbf{a}} \cdot (1 - P_i(id))^{z}\right]}. \tag{11a}$$

In the above Eq (11a), the mean of the ENB distribution is defined as

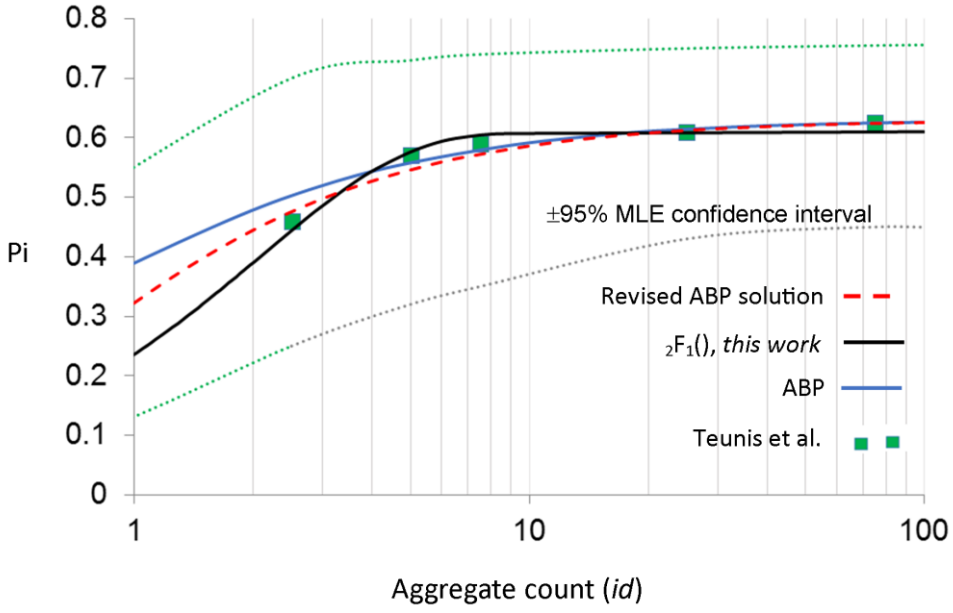
$$z = -\frac{\lambda}{[\mu \cdot log(1-\mathbf{a})]} \tag{11b}$$

where λ (the ENB parameter) is the count of the mean ingested aggregates in the dose, μ is the mean size of the aggregates as in Eq (9a), and z_i is the initial value of $\overline{\imath d}$ in the ENB distribution.

3.1.2. Validation of proposed aggregated *Nov GI.1 DR* models



(**a**)



(**b**)

Figure 4. DR model of infection probabilities caused by aggregated *NoV GI.1 8fIIa* assuming α = 0.89 and β = 1.53 and a host immune fraction φ of 37%, using Eq (9) (solid line), (11) (dashed and dot line) and (14) dashed line); a) *id* < 1; and b) *id* > 1, with 95% confidence intervals (dotted lines).

Figure 4 illustrates the results of a numerical validation of the proposed infection probability models (9) (solid line) and (11) for aggregated NoV infections. The validation was conducted using the MLE of infection counts provided by Teunis et al. [20] from a challenge experiment involving aggregate *NoV GI.1 8fIIa* infections. To ensure accurate representation, we set the product $\mu \times \mathbf{a}$ equal to 400 virions (i.e., μ = 400 virions and, $\boldsymbol{a} \cong 1$) based on Teunis et al. findings. This approach allowed us to depict the proposed probabilities using Eqs (9) and (11) in Figure 4(a),(b), respectively, for dose sizes of aggregated *NoV GI.1 8fIIa id* < 1 and *id* > 1. In specific terms, for Eq (9), we fixed $\boldsymbol{a}$ = 0.07 (i.e., 7%) and mean μ = 1 for one aggregate dose *id* of 5,714 virions to obtain $\mu \times \mathbf{a}$ = 400 virions, as seen in Teunis et al. *NoV 8fIIa* challenge experiment. Using the gamma-binomial distribution, we derived the probability (9), which accurately fitted the MLE of infections from the aggregated *NoV 8fIIa* challenge trial by setting **a** = 0.07, immunity host fraction φ = 37%, α = 0.89, and β = 1.53. The predicted mean infectious dose from Eq (9a) was 1.037, corresponding to an *id* of 5,927 virions and $\mu \times \mathbf{a}$ equal to 415 virions, showing a minimal computational discrepancy of 4% for 400 virions compared to Teunis et al.'s challenge study.

In this study, we applied the DR model (11) by setting the degree of aggregation $\boldsymbol{a}$ to 0.2, i.e., one aggregate *id* = 1980.2 virions and the mean aggregation size μ = 1.122 (from Eq (9a)). Furthermore, based on the information provided, z_i = 13.5, and subsequently $\mu \times \boldsymbol{a}$ = 449 virions (showing an 11% discrepancy concerning the input data). Finally, we set the mean count of ingested aggregate doses, λ, to 4.

The infection probability (9) aligned well with the infection data from the experiment conducted by Teunis et al. However, the ABP model (11) well approached the probability of infection caused by *NoV GI.1 8fIIa*, as calculated by Teunis et al. using MLE, for id > 2. Additionally, it is worth noting that λ (= 4) and $\boldsymbol{a}$ (= 0.2) were not independent parameters in the latter model. To establish the relationship (12) between these parameters, we initiated with the log transformation of the mean aggregate dose in the Teunis et al. dataset (refer to Eqs (9a) and (9b)). By using the single-hit beta-Poisson probability of infection *P* as given by Eq (6) and considering a dose ratio of $\lambda/(0.9 \cdot \mathrm{id}_{50})$ = 1.9, we approximated a 45% infection probability of nonimmune hosts when id_{50} was at 2.34 (refer to Figure 2).

$$\boldsymbol{a} = -log\left[\frac{P\left(\frac{\lambda}{0.9 \cdot id_{50}}\right)}{1-P\left(\frac{\lambda}{0.9 \cdot id_{50}}\right)}\right] \tag{12}$$

The relationship presented in (12) establishes a link between the degree of virion aggregation in doses, $\boldsymbol{a}$, and the mean count of the aggregates in the doses, λ. This relationship is particularly valuable in practical applications of Eqs (9) and (11) when the percentage of NoV aggregation was not measured at every dose during the challenge trial. By using Eq (12), the uncertainty in MRA can be reduced, addressing the indeterminacy in measurements of $\boldsymbol{a}$.

In Figure 4, we observe that at low doses (*id* < 0.8), the DR model (9) provides a better fit to Teunis et al. MLE of infection data compared to the ABP model (11). The ABP model considers overdispersion due to the conditional probability, specifically the negative binomial distribution [25], assuming that aggregated virions disengaged in the host. These overestimations of the probability can be partially mitigated (for *id* > 0.3) by combining the DR model (11) with the probability distribution that accounts for the probability that clumped virions may not completely disengage after the host's challenge. This combination allows us to derive the following expression:

$$P_{i_{rev}} = P_i \times P(id)^{-a} \qquad for \;\; id > 0.3 \tag{13}$$

where $\boldsymbol{a}$ = 0.2, P_i is the probability given by (11), and P is the single-hit beta-Poisson probability derived from Eq (6).

Finally, the probabilities of infection from *NoV 8fIIa*, represented by the DR models shown in Figure 4, fall within 95% confidence of the uncertainty interval of the MLE infection probabilities obtained from the challenge trial conducted by Teunis et al.

3.2. Models of risk infection from disaggregated EV

Contaminated water or food may contain multiple enteroviruses, including *Poliovirus 1/SM*, *Echo-12*, and *CV*, simultaneously. In such cases, the probability of infection by pooled EV due to the ingestion of contaminated drinking water, for instance, can be defined as follows:

$$P_i = 1 - \prod_i^{nv}\left(1 - P_{i,v}\right) \tag{14}$$

where *Pi,v* represents the probability of infection by the specific enterovirus, and *nv* is the total number of EVs detected in the water. Accurate measurement of the specific volume of the inoculum for the infectious dose [15] of each EV is essential during exposure assessment.

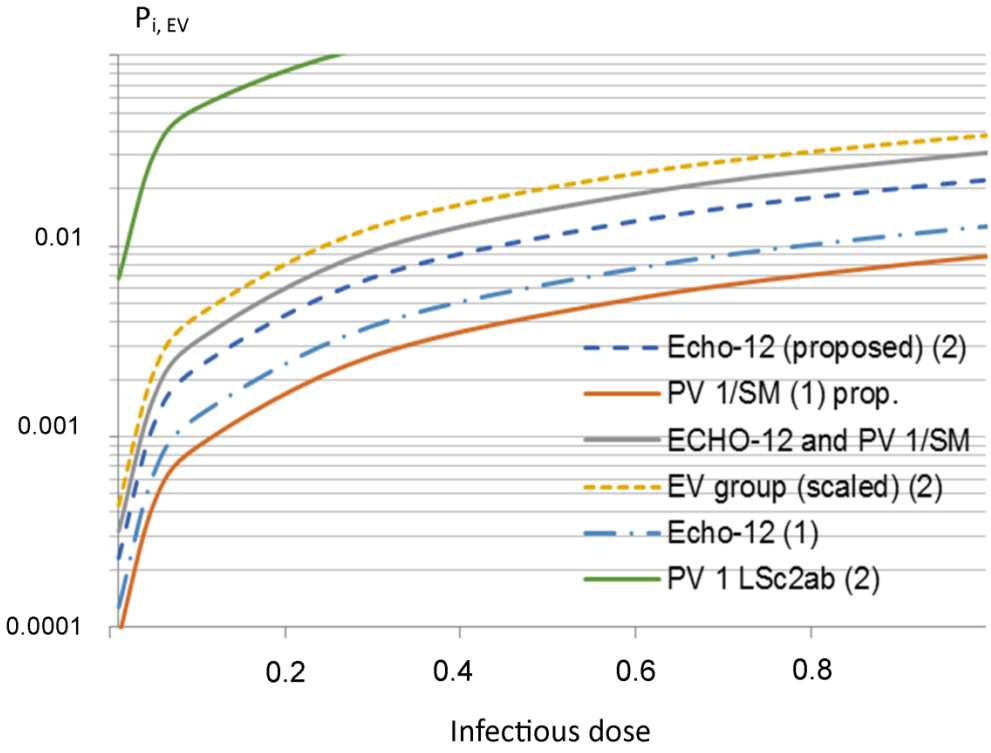


Figure 5. Exponential and approximate beta-Poisson models of infections (inocula of 1 ml) from the *EV group*, *Echo-12*, *Poliovirus 1 LSc2ab*, and *Poliovirus 1/SM* using revised model coefficients provided in the literature (refer to Table 1) and the approximate beta-Poisson (2) or exponential (1) model.

Alternatively, some studies have used the approximate beta-Poisson model with optimized coefficients, α= 0.167 and β = 0.191 (Table 1) for the pooled EV group infectious doses [42]. This DR-pooled probability of infection, which defines coefficients similar to those by Teunis et al. [43] for *Poliovirus 1 LSc2ab* (α = 0.114 and β = 0.159) in the literature, may lead to significant overestimations of the probability of EV infection at low doses (Figure 5).

Therefore, in cases where challenge trial studies are not available for MRA, we propose β_{new} = 3.82, which is obtained by downscaling the literature coefficient 0.191 defined by de Man et al. [42] for the probability of infection from *EV*, i.e., $\beta_{new} = 0.191 \times 20$. This shift in the *EV group* probability curve to the left results in a higher infection probability than the sum of the probabilities given by each single virus (refer to Figure 5).

Moreover, the exponential DR model with the coefficient defined by McBride et al. [44] and Haas et al. [45] (refer to Table 1) was used to determine the *Echo-12* infection probability trend in Figure 5, whereas for the exponential probability of infection from *PV 1/SM*, we propose a coefficient of 112.73, i.e.,

$$\beta_1 = \frac{(ID_{50}+MID)}{ID_{50}} \cdot 40, \tag{15}$$

where ID_{50} is 2 (refer to Table 2) and MID is 1.1 [34], whereas 40 is the value of the proposed downscaling coefficient.

Finally, we suggest setting the value of β_{new} to 17 for calculating the probability of infection by the *Echo-12* virus using the approximate beta-Poisson model. To arrive at this value, we matched the model coefficient with the MID value presented in Table 2. Additionally, we obtained the α_{new} value from Eq (4) by setting ID_{50} to 78.3, as determined by McBride et al. [44] and Haas [45].

4. **Discussion**

We presented suitable probability models to estimate the risk of infection from disaggregated or aggregate *NoV GI.1* in doses. We showed that our proposed approach compared favorably with the MLE obtained from results of the challenge trial conducted by Teunis et al. [20], which involved volunteers as nonimmune hosts. The model coefficients, α = 0.89 and β = 1.53, were determined using a novel $ID_{50} = f(\text{MID})$ relationship derived from the best fit of MID and ID_{50} values collected from several challenge experiments involving enteric viruses. Our results showed that the proposed relationship is effective in estimating the exact beta-Poisson probability of NoV virion infection. Importantly, the coefficients of the norovirus model were derived from ID_{50} values estimated by Teunis et al. [20] in their challenge experiments involving disaggregated *NoV GI.1 8fIIb*. Applying the new model coefficients yielded an ID_{50} of 23, deviating from the ID_{50} of 18 suggested by Teunis et al. This result was consistent with the findings of van Abel et al. [28], and it approached the ID_{50} of 26 suggested by Teunis et al. [20] for their aggregated challenge experiment with *NoV GI.1*, using inocula of strain *NoV GI.1 8fIIa* supplied to volunteers.

Nevertheless, experimental determination of MID values of human viruses is challenging due to the specific operative conditions of each challenge infection experiment, leading to significant uncertainty in the estimations. However, successful comparison of the predicted infection curves using the proposed coefficients for norovirus indicates the reliability of the MID/ID50 relationship.

However, it is essential to acknowledge the limitations in applying DR models in this study due to data scarcity and the need for further research from challenge infection experiments. Further research should not only focus on virus exposure but also combine experiment data to validate the accuracy of the proposed formulas.

For infectious dose sizes < 1 virion, the proposed revised exact beta-Poisson probabilities provided the same values as those determined by Teunis et al. [20] for disaggregated *NoV (8fIIa + 8fIIb)* infections, using coefficients $\alpha = 0.04$ and $\beta = 0.055$. However, with the latter coefficients, deviations in the solution were evident for doses >1 due to the numerical degeneration of the series values given by Eq (5), and the integral (6) did not converge. Similarly, Eq (5) degenerated when using $\alpha = 0.631$ and $\beta = 6.5 \cdot 10^5$ provided by Teunis et al. for infection probability, owing to host exposure to disaggregated *NoV GI.1 8fIIb* in doses. On the other hand, Eq (6) performed well when utilizing the proposed values, $\alpha = 0.89$ and $\beta = 1.53$. Practical examples illustrating the usefulness of the proposed dose-infection models can be found in QMRAs applied at the large-scale population level [3]. These results impact groundwater management and policy-making decisions [54] concerning drinking water supplies and crop irrigations using reclaimed water.

5. Conclusions

In this study, we presented probability models for estimating health risks of infection from disaggregated or aggregated *NoV GI.1* virions at varying doses. These models serve as valuable tools for quantifying microbial health risk assessments during outbreaks, guiding public health policies for disease prevention and control. By providing reliable models and coefficients, the uncertainty and cost of management actions in health risk assessments can be reduced. Our updated infection models were positively compared with the results of the MLE method adopted by Teunis et al. [20] in a challenge trial performed on volunteers with a nonimmune host fraction. Furthermore, we proposed a relationship (12) between the degree of virion aggregation in every single dose "$\boldsymbol{a}$" and the mean count of the aggregates in infectious doses. This relationship simplifies the practical application of DR models (9) and (11) in risk assessments by reducing the uncertainty stemming form the indetermination in the measurement of $\boldsymbol{a}$.

Enteric viruses are harmful pathogens associated with numerous outbreaks of waterborne disease in humans. They can typically be isolated from water or food directly or indirectly contaminated by fecal waste, and their ability to survive in flowing groundwater poses significant health risks, especially after flood-runoff groundwater infiltration. Therefore, after floods, it is crucial to conduct accurate assessments of the health risk associate with the quality of water supplied by public water systems. In this study, we proposed a new mechanistic approach to reliably estimate the coefficients of DR models for predicting the risk of infection with human enteric viruses.

Determination of MID from human viruses experimentally is highly uncertain, as each MID estimation depends on the specific operating conditions of a particular challenge infection experiment. Although well-designed human virus challenge experiments would enhance research on health risk assessment, they are often not available for practical risk assessments. These limitations contribute to uncertainty in the risk assessment results for models derived from the single-hit probability theory. Thus, complementary investigations are needed to support those based on the immunity theory of individual secretors (Se) currently applied. Further research is necessary to

understand the heterogeneous behavior of individual host-to-host susceptibility to the same dose of supplied pathogens and to elucidate the specific virus-cell mechanisms responsible for infectivity and pathogenesis. For instance, Rahman et al. developed a mechanistic DR model to investigate foodborne host infections caused by *Listeria monocytogenes*, offering an alternative approach to the single-hit theory that may reduce uncertainties in estimating infection risk by incorporating both the operating environmental conditions and clinical data of every host during a given challenge trial.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Acknowledgments

The author would like to acknowledge the support provided by National Research Fund FOE 2020 for the CNR project “Capitale naturale e risorse per il futuro dell’ Italia” (B55F21001990001).

Conflict of interest

The author declares that there is no conflict of interest.

References

1. W. A. Furumoto, R. Mickey, A mathematical model for the infectivity-dilution curve of tobacco mosaic virus: Theoretical considerations, *Virology*, **32** (1967), 216–223. https://doi.org/10.1016/0042-6822(67)90271-1
2. C. Masciopinto, F. Visino, Strong release of viruses in fracture flow in response to a perturbation in ionic strength: Filtration/retention tests and modeling, *Water Res.*, **126** (2017), 240–251. https://doi.org/10.1016/j.watres.2017.09.035
3. C. Masciopinto, O. De Giglio, M. Scrascia, F. Fortunato, G. La Rosa, E. Suffredini, et al., Human health risk assessment for the occurrence of enteric viruses in drinking water supplied from wells: Role of flood runoff injections, *Sci. Total Environ.*, **666** (2019), 559. https://doi.org/10.1016/j.scitotenv.2019.02.107
4. J. B. Rose, P. R. Epstein, E. K. Lipp, B. H. Sherman, S. M. Bernard, J. A. Patz, Climate variability and change in the United States: Potential impacts on water and foodborne diseases caused by microbiologic agents, *Environ. Health Perspect.*, **109** (2001), 211–220. https://doi.org/10.1289/ehp.01109s2211
5. C. K. Uejio, S. H. Yale, K. Malecki, M. A. Borchardt, H. A. Anderson, J. A. Patz, Drinking water systems, hydrology, and childhood gastrointestinal illness in central and northern Wisconsin, *Am. J. Public Health*, **104** (2014), 639–646. https://doi.org/10.2105/AJPH.2013.301659

6. *US Environmental Protection Agency*, Environmental Protection Agency: Federal Register / Vol. 71, No. 216 / Wednesday, November 8, 2006/ Rules and Regulations, in Part II, 40 CFR Parts 9, 141, and 142 (EPA–HQ–OW–2002–0061; FRL–8231–9).
7. C. Masciopinto, R. La Mantia, A. Carducci, B. Casini, A. Calvario, E. Jatta, Unsafe tap water in households supplied from groundwater in the Salento region of southern Italy, *J. Water Health*, **5** (2007), 129–148. https://doi.org/10.2166/wh.2006.054
8. A. D. Anderson, A. G. Heryford, J. P. Sarisky, C. Higgins, S. S. Monroe, R. S. Beard, et al., A waterborne outbreak of Norwalk-like virus among snowmobilers-Wyoming, 2001, *J. Infect. Dis.*, **187** (2003), 303–306. https://doi.org/10.1086/346239
9. S. U. Parshionikar, S. Willian-True, G. S. Fout, D. E. Robbins, S. A. Seys, J. D. Cassady, et al., Waterborne outbreak of gastroenteritis associated with a norovirus, *Appl. Environ. Microbiol.*, **69** (2003), 5263–5268. https://doi.org/10.1128/AEM.69.9.5263-5268.2003
10. C. Masciopinto, T. La Mantia, V. Tandoi, C. Levantesi, M. Divizia, D. Donia, et al., Analytical solution for the modeling of the natural time-dependent reduction of waterborne viruses injected into fractured aquifers, *Env. Sci. Tech*., **45** (2011), 636–642. https://doi.org/10.1021/es102412z
11. C. N. Haas, J. B. Rose, C. P. Gerba, *Quantitative microbial risk assessment*, John Wiley & Sons, Inc., Hoboken, New Jersey, 2014.
12. N. Ayuso-Gabella, D. Page, C. Masciopinto, A. Aharoni, M. Salgot, T. Wintgens, Quantifying the effect of Managed Aquifer Recharge on the microbiological human health risks of irrigating crops with recycled water, *Agric. Water Manage.*, **9** (2011), 93–102. https://doi.org/10.1016/j.agwat.2011.07.014
13. B. M. Pecson, S. C. Triolo, S. Olivieri, E. C. Chen, A. N. Pisarenko, C. C. Yang, et al., Reliability of pathogen control in direct potable reuse: Performance evaluation and RA of a full-scale 1 MGD advanced treatment train, *Water Res.*, **122** (2017), 258–268. https://doi.org/10.1016/j.watres.2017.06.014
14. P. F. M. Teunis, A. H. Havelaar, The beta-poisson dose-response model is not a single-hit model. risk analysis, *Risk Anal.*,**20** (2000), 513–520. https://doi.org/10.1111/0272-4332.204048
15. P. J. Schmidt, Norovirus dose response: Are currently available data informative enough to determine how susceptible humans are to infection from a single virus?, *Risk Anal.*, **35** (2015), 1364–1383. https://doi.org/10.1111/risa.12323
16. M. H. Weir, Dose-Response modeling and use: Challenges and uncertainties in environmental exposure, in *Manual of Environmental Microbiology*, ASM Press, 2016.
17. R. Lambkin-Williams, J. P. De Vincenzo, A COVID-19 human viral challenge model. Learning from experience, *Influenza Other Respi. Viruses*, **14** (2020), 747–756. https://doi.org/10.1111/irv.12797
18. C. P. Gerba, W. Q. Betancourt, Viral aggregation: Impact on virus behavior in the environment. Environ, *Sci. Technol.*, **1** (2017), 7318−7325. https://doi.org/10.1021/acs.est.6b058351
19. P. F. M. Teunis, F. S. Le Guyader, P. Liu, J. Ollivier, C. L. Moe, Noroviruses are highly infectious but there is strong variation in host susceptibility and virus pathogenicity, *Epidemics*, **32** (2020), 100401. https://doi.org/10.1016/j.epidem.2020.100401
20. P. F. M. Teunis, C. L. Moe, P. Liu, S. E. Miller, L. Lindesmith, R. S. Baric, et al., Norwalk virus: How infectious is it?, *J. Med. Virol*., **80** (2008), 1468–1476. https://doi.org/10.1002/jmv.21237

21. R. L. Atmar, A. R. Opekun, M. A. Gilger, M. K. Estes, S. E. Crawford, F. H. Neill, et al., Determination of the 50% human infectious dose for Norwalk virus, *J. Infect. Dis.*, **209** (2014), 1016–1022. https://doi.org/10.1093/infdis/jit620
22. J. S. Lion, D. H. Kingsley, J. S. Montes, G. P. Richards, G. M. Lyon, G. M. Abdulhafid, et al., Randomized, double-blinded clinical trial for human norovirus inactivation in oysters by high hydrostatic pressure processing, *Appl Environ Microbiol.*, **77** (2011), 5476–5482. https://doi.org/10.1128/AEM.02801-10
23. R. Mateo, L. C. Lindesmith, S. J. Garg, K. Gottlieb, K. Lin, S. Said, et al., Production and clinical evaluation of Norwalk GI.1 virus Lot 001-09NV in Norovirus vaccine development, **221** (2020), 919. https://doi.org/10.1093/infdis/jiz540
24. V. Nilsen, J. Wyller, RA for drinking water: 1. Revisiting the mathematical structure of single-hit dose-response models, *Risk Anal.*, **36** (2016), 145–162. https://doi.org/10.1111/risa.12389
25. C. N. Haas, Conditional dose-response relationships for microorganisms: Development and application, *Risk Anal.*, **22** (2002), 453–463. https://doi.org/10.1111/0272-4332.00035
26. F. Miura, D. Klinkenberg, J. Wallinga, Dose-response modelling of endemic coronavirus and SARS-CoV-2: human challenge trials reveal the individual variation in susceptibility, medRxiv, (2022). doi: https://doi.org/10.1101/2022.04.07.22273549.
27. E. O. Caul, Small round structured viruses: airborne transmission and hospital control, *Lancet*, **343** (1994), 1240–1242. https://doi.org/10.1016/s0140-6736(94)92146-6
28. N. Van Abel, M. E. Schoen, J. C. Kissel, J. S. Meschke, Comparison of risk predicted by MultIPle Norovirus dose-response models and implications for quantitative microbial risk assessment, *Risk Anal.*, **37** (2017). https://doi.org/10.1111/risa.12616
29. M. J. Messner, P. Berger, S. P. Nappier, Fractional poisson—A simple dose-response model for human Norovirus, *Risk Anal.*, 34 (2014), 1820–1829. https://doi.org/10.1111/risa.12207
30. A. Rahman, D. Munther, A. Fazil, B. Smith, J. Wu, Advancing risk assessment: mechanistic dose-response modelling of Listeria monocytogenes infection in human populations, *R. Soc. Open Sci.*, **5** (2018). http://dx.doi.org/10.1098/rsos.180343
31. R. Ward, S. Krugman, J. Giles, M. Jacobs, O. Bodansky, Infectious hepatitis—Studies of its natural history and prevention, *New Eng. J. Med.*, **258** (1958), 402–416.
32. R. L. Ward, D. I. Bernstein, E. C. Young, J. R. Sherwood, D. R. Knowlton, G. M. Schiff, Human rotavirus studies in volunteers: Determination of infectious dose and serological response to infection, *J. Infect. Dis.*, **154** (1986), 871–880. https://doi.org/10.1093/infdis/154.5.871
33. G. M. Schiff, G. M. Stefanovic, B. Young, J. K. Pennekamp, *Determination of minimal infectious dose of an Enterovirus in drinking water*, Health Effects Research Laboratory, 1993.
34. R. B. Couch, V. Knight, R. G. Douglas, S. H. Jr., Black, B. H. Hamory, The minimal infectious dose of adenovirus type 4: The case for natural transmission by viral aerosol, *Trans. Am. Clin. Climatol. Assoc.*, **80** (1969), 205–211.
35. R. Frenck, D. I. Bernstein, M. Xia, P. Huang, W. Zhong, S. Parker, et al., Predicting susceptibility to norovirus GII.4 by use of a challenge model involving humans, J. Infect. Dis., **206** (2012), 1386–1393. https://doi.org/10.1093/infdis/jis514
36. S. R. Seitz, J. S. Leon, K. J. Schwab, G. M. Lyon, M. Dowd, M. McDaniels, et al., Norovirus infectivity in humans and persistence in water, Appl. Environ. Microbiol., (2011), 6884–6888. https://doi.org/10.1128/AEM.05806-11

37. P. Teunis, J. Schijven, S. Rutjes., A generalized dose-response relationship for adenovirus infection and illness by exposure pathway, *Epidemiol. Infect.*, **144** (2016), 3461–3473. https://doi.org/10.1017/S0950268816001862
38. N. J. C. Strachan, T. M. P. Doyle, F. Kasuga, O. Rotariu, I. D. Ogden, Dose-response modelling of Escherichia coli O157 incorporating data from foodborne and environmental outbreaks, *Int. J. Food Microbiol.*, **103** (2005), 35–47. https://doi.org/10.1016/j.ijfoodmicro.2004.11.023
39. C. N. Haas, J. N. S. Eisenberg, Risk assessment, in *Water Quality: Guidelines, Standards & Health*, IWA Publishing, London, UK, (2001), 161–374.
40. K. D. Crabtree, C. P. Gerba, J. B. Rose, J. B. Rose, Waterborne adenovirus: a risk assessment, *Water Sci. Technol.*, **35** (1997), 1–6. https://doi.org/10.1016/S0273-1223(97)00225-4
41. E. Sokolova, S. R. Petterson, O. Dienus, F. Nyström̈d, P. E. Lindgren, T. J. R. Pettersson, Microbial risk assessment of drinking water based on hydrodynamic modelling of pathogen concentrations in source water, *Sci. Total Environ.*, **526** (2015), 177–186. https://doi.org/10.1016/j.scitotenv.2015.04.040
42. H. de Man, H. H. J. L. van den Berg, E. J. T. M. Leenen, , J. F. Schijven, F. M. Schets, J. C. van der Vliet, F. van Knapen, A.M. de Roda Husman, Quantitative assessment of infection risk from exposure to waterborne pathogens in urban floodwater, *Water Res.*, **48** (2014), 90–99. http://dx.doi.org/10.1016/j.watres.2013.09.022
43. P. F. M. Teunis, van der Heijden, van der Giessen, A. H. Havelaar, *The dose-response relation in human volunteers for gastro-intestinal pathogens*, National Insitute of Public Health Inspectorate, Ministry of Public Health, The Netherland, 1996.
44. G. B. McBride, Norovirus dose-response in sewage-related RA: The importance of virus aggregation., in *7th International Congress on Environmental Modelling and Software*, San Diego, California, USA, 2014.
45. C. N. Haas, J. B. Rose, C. P. Gerba, *Quantitative Microbial Risk Assessment*, Wiley, NY, 1999.
46. K. D. Mena, C. P. Gerba, C. N. Haas, J. B. Rose, Risk assessment of waterborne Coxsackievirus, *Am. J. Water Works Assoc.*, **95** (2003), 122–131. https://doi.org/10.1002/j.1551-8833.2003.tb10413.x
47. S. Yezli, J. A. Otter, Minimum infective dose of the major human respiratory and enteric viruses transmitted through food and the environment, *Food Environ. Virol.*, **3** (2011.), 1–30. https://doi.org/10.1007/s12560-011-9056-7
48. *Health Canada, Public Health Agency of Canada*, Pathogen Safety Data Sheets: Infectious Substances – Norovirus, 2019. Available from: https://www.canada.ca/en/public-health/services/laboratory-biosafety-biosecurity/pathogen-safety-data-sheets-risk-assessment/norovirus-pathogen-safety-data-sheet.html.
49. D. Y. Graham, G. R. Dufour, M. K. Estes, The minimal infective dose of rotavirus, *Arch. Virol.*, **92** (1987), 261–271. https://doi.org/10.1007/BF01317483
50. Health Canada, Public Health Agency of Canada. Pathogen Safety Data Sheets: Infectious Substances, Coxsackievirus, 2018. Available from: https://www.canada.ca/en/public-health/services/laboratory-biosafety-biosecurity/pathogen-safety-data-sheets-risk-assessment.html.

51. G. M. Schiff, G. M. Stefanovic, E. C. Young, D. S. Sander, J. K. Pennekamp, R. L. Ward, Studies of echovirus-12 in volunteers: Determination of minimal infectious dose and the effect of previous infection on infectious dose, *J. Infect. Dis.*, **150** (1984), 858–866. https://doi.org/10.1093/infdis/150.6.858
52. K. P. Burnham, D. R. Anderson, *Model selection and multimodel inference: A practical information-theoretic approach*, Springer-Verlag, 2002.
53. M. Abramowitz, I. Stegun, *Handbook of mathematical functions, with formulas, graphs, and mathematical tables*, Dover Publications, Inc., New York, US, 1972.
54. C. Masciopinto, M. Vurro, N. Lorusso, D. Santoro, C. N. Haas, Application of QMRA to MAR operations for safe agricultural water reuses in coastal areas, *Water Res.*, **8** (2020), 100062; https://doi.org/10.1016/j.wroa.2020.100062

AIMS Press