



Probabilistic modeling for an integrated temporary acquired immunity with norovirus epidemiological data



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ARTICLE INFO

Article history:

Received 5 October 2018

Accepted 22 April 2019

Available online 27 April 2019

Handling Editor: J. Wu

Keywords:

Quantitative risk assessment

Probabilistic modeling

Immunity integrated modeling

ABSTRACT

Integration of acquired immunity into microbial risk assessment for illness incidence is of no doubt essential for the study of susceptibility to illness. In this study, a probabilistic model was set up as dose response for infection and a mathematical derivation was carried out by integrating immunity to obtain probability of illness models. Temporary acquire immunity from epidemiology studies which includes six different *Norovirus* transmission scenarios such as symptomatic individuals infectious, pre- and post-symptomatic infectiousness (low and high), innate genetic resistance, genogroup 2 type 4 and those with no immune boosting by asymptomatic infection were evaluated.

Simulated results on illness inflation factor as a function of dose and exposure indicated that high frequency exposures had immense immunity build up even at high dose levels; hence minimized the probability of illness. Using *Norovirus* transmission dynamics data, results showed, and immunity included models had a reduction of 2–6 logs of magnitude difference in disease burden for both population and individual probable illness incidence. Additionally, the magnitude order of illness for each dose response remained largely the same for all transmission scenarios; symptomatic infectiousness and no immune boosting after asymptomatic infectiousness also remained the same throughout. With integration of epidemiological data on acquired immunity into the risk assessment, more realistic results were achieved signifying an overestimation of probable risk of illness when epidemiological immunity data are not included. This finding supported the call for rigorous

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Peer review under responsibility of KeAi Communications Co., Ltd.

integration of temporary acquired immunity in dose-response in all microbial risk assessments.

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1. Introduction

The adoption of quantitative approach in modeling epidemiological risk over the years has gained interest in the field of disease modeling and epidemiology. This approach has led to the use of adopting techniques in characterizing uncertainty of input parameters with cumulative density functions, probability density functions and probability mass functions.

Mathematical epidemiology of diseases with compartmental models have covered almost all forms of diseases emphasizing the different transmission approaches with intervention inclusion models. Yet, only a few studies have been concentrating on using the same approach for the pathogen of interest causing such diseases. The transition of infection to illness for pathogens has received less attention in quantitative risk modeling (Havelaar & Swart, 2014). This is as a result of lack of integration of epidemiological studies approach in quantitative risk assessment, such as a quantitative model of a susceptible individual suffering from pathogenic attack, transiting from partial recovery to become susceptible again (Swart, Tomasi, Kretzschmar, Havelaar, & Diekmann, 2012).

In the light of the above, this study attempts to apply the integration of mathematical epidemiological method into quantitative risk assessment for modeling probability of illness by incorporating acquired immune function to predict the expected probability of illness for exposure to norovirus, a major gastrointestinal pathogenic virus.

2. Literature and review of mathematical probability of infection

Developing a mathematical dose response relationship is the same as establishing the relations between level of pathogen, exposure and the measure of likelihood occurrence of adverse effects (Haas, Rose, & Gerba, 2014, pp. 267–321). Furumoto and Mickey (1967) in estimating the consequences of exposure to different level of pathogens noted that, the process of infection is considered to be two sequential sub processes, namely;

- i. One or more organism(s) or virus particles ingested is (are) capable of causing diseases
- ii. An ingested organism/virus particle can become inactivated to multiply to cause infection/disease by host susceptible responses, and only a fraction of the ingested organisms reaches a site where infection can begin by breaking all barriers within the body immune system.

Hence, ingestion precisely j organism from exposure with a mean dose d is expressed as

$$P1(j|d) \tag{1}$$

Therefore, probability of k surviving pathogen particles to initiate an infection process is also express as

$$P2(k|j) \tag{2}$$

Assuming independency for the two processes, the probability of k organisms surviving to initiate infection by breaking all defense mechanism within the body is given by the independent event

$$P(k) = \sum_{j=1}^{\infty} P1(j|d)P2(k|j) \tag{3}$$

The least number of organisms (k_{min}) surviving to initiate an infection leads to a probability of infection

$$P_{inf}(d) = \sum_{k=k_{min}}^{\infty} \sum_{j=k}^{\infty} P1(j|d)P2(k|j) \tag{4}$$

Where (k_{min}) is not the minimal infection dose or threshold needed to be reached to cause an infection.

2.1. Derivation of exponential dose response model

Characterizing the distribution of organisms between each dose as random and assuming independency for each ingested organism has an identical survival probability¹ r and $k_{min} = 1$ (thus for a single hit assumption). Hence from Poisson distribution of organisms with the use of equation (1) leads to

$$P1(j|d) = \frac{d^j}{j!} e^{-d} \tag{5}$$

From equation (5) incorporating equation (2), survival means of organisms to cause an infection is modeled with binomial distribution leading to

$$P2(k|j) = \frac{j!}{k!(j-k)!} (1-r)^{j-k} \tag{6}$$

Hence, substituting equations (5) and (6) into equation (4) and accounting for infectivity of the virus ‘ r ’ leads to the expression below

$$\begin{aligned} P_{inf}(d) &= \sum_{k=k_{min}}^{\infty} \sum_{j=k}^{\infty} \left[\frac{d^j}{j!} e^{-d} \right] \left[\frac{j!}{k!(j-k)!} (1-r)^{j-k} \right] \\ &= \sum_{k=k_{min}}^{\infty} \frac{(dr)^k e^{-dr}}{k!} \sum_{j=k}^{\infty} \frac{[d(1-r)]^{j-k} e^{-d(1-r)}}{(j-k)!} \end{aligned} \tag{7}$$

But $\sum_{k=k_{min}}^{\infty} \frac{(dr)^k e^{-dr}}{k!} = 1$, hence

$$P_{inf}(d) = 1 - \left[\sum_{k=0}^{k_{min}-1} \frac{(dr)^k e^{-dr}}{k!} \right] \tag{8}$$

With the earlier single hit assumption (thus one organism survived is capable to cause an infection) $k_{min} = 1$ yields

$$P_{inf}(d) = 1 - e^{-rd} \tag{9}$$

2.2. Derivation of the Beta-Poisson dose response model

Replacing equation (6) with a mixture distribution with respect to the parameter r to account for variability in the infectivity interaction probability yields equation (10)

$$P2(k|j) = \int_0^1 \left[\frac{j!}{k!(j-k)!} (1-r)^{j-k} r^k \right] f(r) dr \tag{10}$$

Equation (6) through various mathematical formulation yields equation (10), therefore, a mixture distribution application on equation (9) for a variation in the dose to dose in the poison distribution yields

$$\begin{aligned} P_{inf}(d) &= \int_0^1 [1 - e^{-rd}] f(r) dr \\ &= \int_0^1 f(r) dr - \int_0^1 e^{-rd} f(r) dr \end{aligned} \tag{11}$$

¹ This is a probability that an organism survives all barriers of defense mechanism and initiate and infectious focus within cell.

$$= 1 - \int_0^1 e^{-rd} f(r) dr \quad (12)$$

Let the variation on dose to dose assume the beta distribution and for the purposes of a great deal of flexibility due to its suitable applications (Haas et al., 2014, pp. 267–321), hence incorporating into equation (12) yields

$$P_{\text{inf}}(d) = 1 - \int_0^1 \left[\frac{\Gamma(\vartheta + \beta)}{\Gamma(\vartheta)\Gamma(\beta)} r^{\vartheta-1} (1-r)^{\beta-1} \right] e^{-rd} dr \quad (13)$$

The integral can best be expressed as confluent hyper-geometric function of the first kind written as a series expansion

$${}_1F_1(\vartheta, \vartheta + \beta, -d) = 1 + \frac{\Gamma(\vartheta + \beta)}{\Gamma(\vartheta)} \sum_{j=1}^{\infty} \frac{\Gamma(\vartheta + j)}{\Gamma(\vartheta + \beta + j)} \frac{(-d)^j}{j!} \quad (14)$$

Therefore, the exact solution of the beta –Poisson model can be written as

$$P_{\text{inf}}(d) = \frac{\Gamma(\vartheta + \beta)}{\Gamma(\vartheta)} \sum_{j=1}^{\infty} \left[\frac{\Gamma(\vartheta + j)}{\Gamma(\vartheta + \beta + j)} \frac{(-1)^{j-1} (d)^j}{j!} \right] \quad (15)$$

Teunis et al. (2008) noted that, the ingestion of a virion is based on whether it is aggregated or disaggregated, as virion particles may or may not be aggregated depending on the circumstances of the environment. Hence the confluent hyper-geometric function yields:

$$P_{\text{inf}}(d) = 1 - {}_1F_1(\vartheta, \vartheta + \beta, -d) \quad (16)$$

Furumoto and Mickey (1967) derived the following expression approximation to equation (14) based on the certain valid parameter values, thus when $\beta \leq 1$ and $\vartheta < \beta$ the simple relation holds.

$$P_{\text{inf}}(d) = 1 - \left(1 + \frac{d}{\beta} \right)^{-\alpha} \quad (17)$$

Furumoto and Mickey (1967) noted, any changes in β cause the Beta Poisson dose response relation to be shifted along the dose axis without changing shape. However, the hyper-geometric relation cannot be scaled due to its non-scalability of the beta distribution for r (Teunis, 2005).

2.3. Beta Poisson to fractional Poisson model

Accounts from Teunis et al. (2008) noted, in applying equation (16) for quantification of probability of illness, human ingestion of virus particles found to share a common probability (r) independently capable of initiating infection in subjects, though it is admitted some subjects may have very small values of r near zero and vice versa. Therefore, the aggregated norovirus infection probability is a beta function parameters described as

$$P_{\text{inf}}(d, \vartheta, \beta) = 1 - {}_2F_1(\vartheta, d(1-a)/a, \vartheta + \beta; -a/(1-a)) \quad (18)$$

Where ϑ , β are shape parameters of beta distribution, a is the particle size, hence mean aggregate size $\mu(a)$ is of the form

$$\mu(a) = -a/((1-a)\ln(1-a)) \quad (19)$$

The result in probability of subjects receiving exactly zero aggregate is $(e^{-d/\mu(a)})$ and those with one or more aggregate is $1 - (e^{-d/\mu(a)})$.

3. Integration of temporary immunity in dose response model

Messner, Berger, and Nappier (2014) noted that, variation in probability of infection across a susceptible population is described with a mixture distribution by the use of beta parameters, hence describing individual probability of infection with Bernoulli distribution as a mixture model.

$$r \sim \text{Bernoulli}(p)$$

Therefore, individual probability of infection is exactly 1 with probability p and exactly 0 with probability $1 - p$, and cannot assume any value within the interval 0-1 with a parameter derivation of ψ , this incorporation led to probability of infection described by as:

$$\text{Pinf}(dose, \psi) = \psi \left(1 - e^{-d/\mu(a)} \right) \tag{20}$$

3.1. Exposure scenarios

Given that, illness is independent of its previous events, then the probability of illness can be described with a Bernoulli distribution with fixed exposure (E) for a period of time in a known population of size N (Messner et al., 2014). Therefore, the total sum of illness could be derived as a “Naïve Model” (Hass et al., 1999) described as $\text{Pill} = \text{Pill|infPinf}$, hence the derivation is given as

$$I = \sum_{k=1}^N \sum_{j=1}^E \text{Pill|inf}(d_{j,k}) \text{Pinf}(d_{j,k}) \tag{21}$$

For cases of independency of infection to exposure, $\text{Pill|inf} = \phi$, the conditional probability could be described for a single exposure as $\text{Pill} = \phi \text{Pinf}(d)$. This resulting as a constant average dose, hence total number of illness for individual exposure is

$$I = NE\phi \text{Pinf}(d) \tag{22}$$

3.1. Acquired immunity from exposure

An individual may move from a disease susceptible compartment to full protection, partial protection and to total waning off of protection to become susceptible again. The acquired immunity for frequent exposure in a Susceptible (S), Full protection (P) and Partial protection (Q) (SPQ compartmental model) has the parameters shown in Table 1.

The deterministic first order differential equation for SPQ model can be described as follows;

$$\left. \begin{aligned} f_1 &= \frac{dS}{da} = \gamma Q - \lambda S \\ f_2 &= \frac{dP}{da} = \lambda(Q + S) - \alpha P \\ f_3 &= \frac{dQ}{da} = \alpha P - (\gamma + \lambda)Q \end{aligned} \right\} \tag{23}$$

where, all parameters are positive, thus $S(0), P(0)$ and $Q(0) > 0$. The Jacobian is represented as;

Table 1
Description of Parameters used in the Model.

| Symbols | Description |
|-----------|--|
| α | Loss of full immunity |
| γ | Loss of partial immunity |
| λ | Force of infection |
| π | Proportion of the susceptible involving of illness |
| S | Susceptible population |
| P | Fully protected after infection |
| Q | Partial protection |

$$J = \frac{df}{da_j} = \begin{bmatrix} \frac{df_1}{dS} & \frac{df_1}{dP} & \frac{df_1}{dQ} \\ \frac{df_2}{dS} & \frac{df_2}{dP} & \frac{df_2}{dQ} \\ \frac{df_3}{dS} & \frac{df_3}{dP} & \frac{df_3}{dQ} \end{bmatrix} = \begin{pmatrix} -\lambda & 0 & \gamma \\ \lambda & -\alpha & \lambda \\ 0 & \alpha & -(\lambda + \gamma) \end{pmatrix} \quad (24)$$

For $\det(J - XI) = 0$, the resulting characteristic equation is

$$J - XI = \begin{pmatrix} -\lambda - X & 0 & \gamma \\ \lambda & -\alpha - X & \lambda \\ 0 & \alpha & -(\lambda + \gamma) - X \end{pmatrix} \quad (25)$$

$$X^3 + \lambda X^2 + \gamma X^2 + \alpha X^2 + \alpha \lambda X + \alpha \gamma X + \lambda X^2 + \lambda^2 X + \lambda \gamma X = 0$$

$$X^3 + \lambda X^2 + \gamma X^2 + \alpha X^2 + \lambda X^2 + \alpha \lambda X + \alpha \gamma X + \lambda^2 X + \lambda \gamma X = 0$$

$$X^3 + (2\lambda + \gamma + \alpha)X^2 + (\alpha\lambda + \alpha\gamma + \lambda^2 + \lambda\gamma)X = 0$$

$$X[X^2 + (2\lambda + \gamma + \alpha)X + (\alpha\lambda + \alpha\gamma + \lambda^2 + \lambda\gamma)] = 0 \quad (26)$$

Therefore, the eigenvalues of the characteristics equation are

$$X_1 = 0, X_2 = -(\alpha + \lambda), X_3 = -(\lambda + \gamma) \quad (27)$$

and the corresponding eigenvectors are: $(\alpha\gamma, \lambda(\lambda + \gamma), \alpha\lambda), (-\gamma, (\gamma - \alpha), \alpha), (1, 0, -1)$.

According to Swart et al. (2012) if R is assigned to be the average number of individual transition Susceptible compartment to Fully protection compartment before ultimately dying of natural cause, assuming no individual dies from illness from exposure, such a transition can be defined as $R = \lambda \int_0^\infty s(a)F(a)da$, where $s(a)$ is the probability of individual susceptibility at age 'a', and $F(a)$ is the individual probability to survive until age 'a'. Therefore, the full and partial waning of immunity is given as;

$$\frac{d}{da} \begin{pmatrix} s \\ p \\ q \end{pmatrix} = \begin{pmatrix} -\lambda & 0 & \gamma \\ \lambda & -\alpha & \lambda \\ 0 & \alpha & -(\lambda + \gamma) \end{pmatrix} \begin{pmatrix} s \\ p \\ q \end{pmatrix} \quad (28)$$

$$s(0) = 1, p(0) = 0, q(0) = 0$$

The general solution using the eigenvalues and eigenvectors of equation are

$$\begin{pmatrix} s(a) \\ p(a) \\ q(a) \end{pmatrix} = C_1 \begin{pmatrix} \alpha\gamma \\ \lambda(\gamma + \lambda) \\ \alpha\lambda \end{pmatrix} + C_2 \begin{pmatrix} -\gamma \\ (\gamma - \alpha) \\ \alpha \end{pmatrix} \exp[-a(\alpha + \lambda)] + C_3 \begin{pmatrix} 1 \\ 0 \\ -1 \end{pmatrix} \exp[-a(\gamma + \lambda)]$$

$$\begin{pmatrix} 1 \\ 0 \\ 0 \end{pmatrix} = C_1 \begin{pmatrix} \alpha\gamma \\ \lambda(\gamma + \lambda) \\ \alpha\lambda \end{pmatrix} + C_2 \begin{pmatrix} -\gamma \\ (\gamma - \alpha) \\ \alpha \end{pmatrix} + C_3 \begin{pmatrix} 1 \\ 0 \\ -1 \end{pmatrix} \quad (29)$$

$$1 = \alpha\gamma C_1 - \gamma C_2 + C_3$$

$$0 = \lambda(\gamma + \lambda)C_1 + (\gamma - \alpha)C_2$$

$$0 = \alpha\lambda C_1 + \alpha C_2 - C_3$$

$$C_1 = \frac{1}{(\alpha + \lambda)(\gamma + \lambda)}, C_2 = \frac{\lambda}{(\alpha - \gamma)(\alpha + \lambda)}, C_3 = \frac{\alpha\lambda}{(\alpha - \gamma)(\gamma + \lambda)}$$

$$\left. \begin{aligned} \begin{pmatrix} s(a) \\ p(a) \\ q(a) \end{pmatrix} &= \frac{1}{(\alpha + \lambda)(\gamma + \lambda)} \begin{pmatrix} \alpha\gamma \\ \lambda(\gamma + \lambda) \\ \alpha\lambda \end{pmatrix} \\ &+ \frac{1}{(\alpha - \gamma)(\alpha + \lambda)} \begin{pmatrix} -\gamma \\ (\gamma - \alpha) \\ \alpha \end{pmatrix} \exp[-a(\alpha + \lambda)] \\ &+ \frac{\alpha\lambda}{(\alpha - \gamma)(\gamma + \lambda)} \begin{pmatrix} 1 \\ 0 \\ -1 \end{pmatrix} \exp[-a(\gamma + \lambda)] \end{aligned} \right\} \tag{30}$$

The relevant solution for quantification of expected number of transition into the susceptible compartment after waning of immunity is given as;

$$s(a) = \frac{\alpha\lambda(\alpha + \lambda)\exp[-a(\gamma + \lambda)] + \alpha\gamma(\alpha - \gamma) - \gamma\lambda(\gamma + \lambda)\exp[-a(\alpha + \lambda)]}{(\alpha - \gamma)(\alpha + \lambda)(\gamma + \lambda)} \tag{31}$$

Let the probability to survive until age ‘a’ be described by a survival function $F(a) = \begin{cases} 1, & 0 \leq a \leq A \\ 0, & a > A \end{cases}$, where A is the life expectancy of the population under study, consequently, the total transition from S to P of an individual is

$$\left. \begin{aligned} R &= \frac{\alpha\lambda^2}{(\alpha - \gamma)(\gamma + \lambda)^2} [1 - \exp[-A(\gamma + \lambda)]] \\ &- \frac{\gamma\lambda^2}{(\alpha - \gamma)(\alpha + \lambda)^2} [1 - \exp[-A(\alpha + \lambda)]] \\ &+ \frac{\alpha\lambda\gamma A}{(\alpha + \lambda)(\gamma + \lambda)} [1 - \exp[-A(\gamma + \lambda)]] \end{aligned} \right\} \tag{32}$$

$$\lim_{A \rightarrow \infty} \frac{R}{A} = \frac{\alpha\lambda\gamma}{(\alpha + \lambda)(\gamma + \lambda)} \tag{33}$$

Hence

$$R = \lambda A \frac{\alpha\gamma}{(\alpha + \lambda)(\gamma + \lambda)} \equiv \lambda A \tau \tag{34}$$

Henceforth, defining force of infection as $\lambda = EPinf(d)$ where E is the total number of days of exposure to a pathogen, and whereas the factor τ is obtained from binomial model of exposure as described in [Messner et al. \(2014\)](#).

$$\begin{aligned} \tau &= \frac{\alpha\gamma}{(\alpha + \gamma)(\gamma + \lambda)} \\ \tau &= \frac{\alpha\gamma}{[\alpha + EPinf(d)][\gamma + EPinf(d)]} \end{aligned} \tag{35}$$

From [Messner et al. \(2014\)](#), characterizing the impact of immunity by the inflation factor scaling the **naïve model** leads to the **immunity model** given as

$$I = \tau NE\phi P_{inf}(d) \tag{36}$$

As dose $d \rightarrow \infty$ (Higher dose level), $P_{inf}(d) \approx 1$, Hence the **immunity model** in such a scenario is described as

$$I = \tau NE\phi \tag{37}$$

3.2. Hazard and survival functions for dose dependent conditional probability of illness

Modeling the hazard function of illness, let $0 \leq t < A$, where A is the entire period of infection for time t , therefore, the hazard function $H(t)$ for probability of illness given infection from equation (12) can now be written as;

$$H(t) = P(\text{ill}|\text{inf} : u) = 1 - \exp\left[-\int_0^t h(t)dt\right], \quad 0 \leq t < A \tag{38}$$

$$h(t) = -\frac{d}{dt} \ln[1 - F(t)] = -\frac{d}{dt} \ln S(t)$$

$$H(t) \stackrel{\text{def}}{=} \int_0^t h(u)du, \quad t > 0$$

$$= -\ln[1 - F(t)]$$

$$= -\ln S(t)$$

$$S(t) = \exp(-H(t))$$

$$f(t) = h(t)\exp(-H(t)) \tag{39}$$

Scaling the infection period leads to an integral of the hazard function $H(t/A)$ over the period of infection and assuming an exponential model for the survival function, if the scale factor is η , Messner et al. (2014) shown such equation as

$$P(\text{ill}|\text{inf}; A) = 1 - \exp(-\eta A) \tag{40}$$

Adoption of Gamma distribution for the unknown infection duration A to account for individual heterogeneity in resistance and persistence of host to colonization of infection leads to

$$g(A; \omega, d) = \frac{d^{-\omega}}{\Gamma(\omega)} A^{\omega-1} \exp\left(\frac{-A}{d}\right)$$

$$P(\text{ill}|\text{inf}) = \int_{r=0}^{\infty} [1 - \exp(-\eta A)] \left[\frac{d^{-\omega}}{\Gamma(\omega)} A^{\omega-1} \exp\left(\frac{-A}{d}\right) \right] dA$$

$$= \int_{r=0}^{\infty} \left[\frac{d^{-\omega}}{\Gamma(\omega)} A^{\omega-1} \exp\left(\frac{-A}{d}\right) \right] dA - \int_{r=0}^{\infty} \left[A^{\omega-1} \exp\left(\frac{-A}{d}\right) \right] \exp(-\eta A) dA$$

$$= 1 - \frac{d^{-\omega}}{\Gamma(\omega)} \int_{r=0}^{\infty} \left[A^{\omega-1} \exp\left(\frac{-A(1 + \eta)}{d}\right) \right] dA \tag{41}$$

$$P(\text{ill}|\text{inf}) = 1 - (1 + \eta d)^{-\omega}$$

Where ω and ηd are the shape and scale parameters of an underlying Gamma distribution for duration of infection describing the heterogeneity in response of subjects (Messner et al., 2014; Teunis et al. 1999, 2008).

$$P_{\text{ill}|\text{inf}} = 1 - (1 + \eta d)^{-\rho} \tag{42}$$

Therefore, the **dose model** is given as

$$I = NE\left(1 - (1 + \eta d)^{-\rho}\right)P_{\text{inf}}(d) \tag{43}$$

3.3. Combined model with immunity and dose dependence

The **dose-immunity** model combines the effects of acquired immunity and dose-dependent conditional probability of illness (equation (37) and equation (43)) (Messner et al., 2014) as

$$I = \tau NE \left(1 - (1 + \eta d)^{-\rho} \right) P_{\text{inf}}(d) \quad (44)$$

4. Data assimilation, results and discussions

4.1. Probabilistic simulation and data assimilation

Modeling the acquired temporary immune probability of illness requires multifaceted data input parameters to describe the various relations and probability distributions as shown in Table 2. Data was gathered from various literature studies reporting on cases of norovirus based on quantitative risk assessment procedure. To improve on the results from limited data described in the available literature studies, simulations were performed based on the available data using Markov Chain Monte Carlo with hypercube sampling procedure for 100,000 iterations for each simulations. Computations were performed in Matrix Laboratory (MatLab) (www.mathworks.com/) and in R (www.rproject.org/) and using the mc2d package (Pouillot et al., 2015) with output designs carried out in Palisade Decision Suite (www.palisade.com/risk/) and @Risk built-in software for Excel version 7.5.2. Input parameters for the modeling are as shown in Table 2.

4.1.1. Results on the modeling

The inclusion of temporary acquired immunity data for risk estimation gives a much lesser estimate of risk of illness compared to the naïve approach currently in use, as indicated (Fig. 1). Comparatively, using the median risk of illness estimate, the dose model has an approximately 1 log less estimate than the naïve model. The immunity model recorded 2 logs less to the naïve model and a 1 log less to the dose model.

Moreover, by incorporating the disease immunity protection for the probability of illness given infection, the dose-immunity model had 3 logs, 2 logs and 1 log of magnitude less to the naïve model, dose model and immunity model respectively.

The impact measured by the inclusion of temporary acquired immunity shows a great difference in infection to illness estimation. Assuming a fixed dose of 1 norovirus particle, a constant daily exposure per annum and assigning a uniform distribution for the loss of full and partial immunity, the result shows a decline on incidence of illness from naïve, dose-model, immunity model and dose-immunity model, the immunity waning effect the total number that result in illness within the population, the illness number level saw a sharp decline when immunity model is used instead of naïve model, and hence by incorporating the effect of the dose dependent, the dose model and the dose-immunity model resulted in a further decline in prediction of illness numbers (Fig. 2).

Table 2
Input parameter values.

| Parameter | Description | Estimate | Estimate Value(s) | Unit |
|----------------------|--|-------------------------|-------------------|---|
| P_{inf} | Probability of infection | Estimate from equations | | – |
| d | Arithmetic Mean Dose per exposure per occasion | Variable | [1,1000]~[500.5] | – |
| $\mu(a)$ | Parametric Mean dose | | 1106 | Teunis et al. (2008) |
| ψ | The infection probability for subjects with disaggregated dose | | 0.722 | Messner et al. (2014) |
| A | Life Expectancy | | 63 | |
| P_{ill} | Probability of illness | Calculated | Median [5.40E-04] | – |
| $P_{\text{ill inf}}$ | probability of illness given infection | Calculated | Median [1.08E-03] | – |
| N | Assumed Population for simulation | | 2.50E+07 | Population pyramids (2015) |
| E | Total Exposure | Uniform distribution | [208,365]~[286.5] | (Mara, Hamilton, Sleight, & Karavarsamis, 2010; Seidu et al., 2008) |
| ρ, η | Dose response parameters for illness given infection | | 0.086, 2.60E-03 | Teunis et al. (2008) |
| α | Loss of full immunity | Uniform distribution | [8,13]~[10] | Simmons, Gambhir, Leon, and Lopman (2013) |
| γ | Loss of partial immunity | Uniform distribution | [3,6]~[5] | Simmons et al. (2013) |
| λ | Force of infection | Estimated from equation | 0.238165 | – |
| τ | Inflation factor | Estimated from equation | 0.793116 | – |

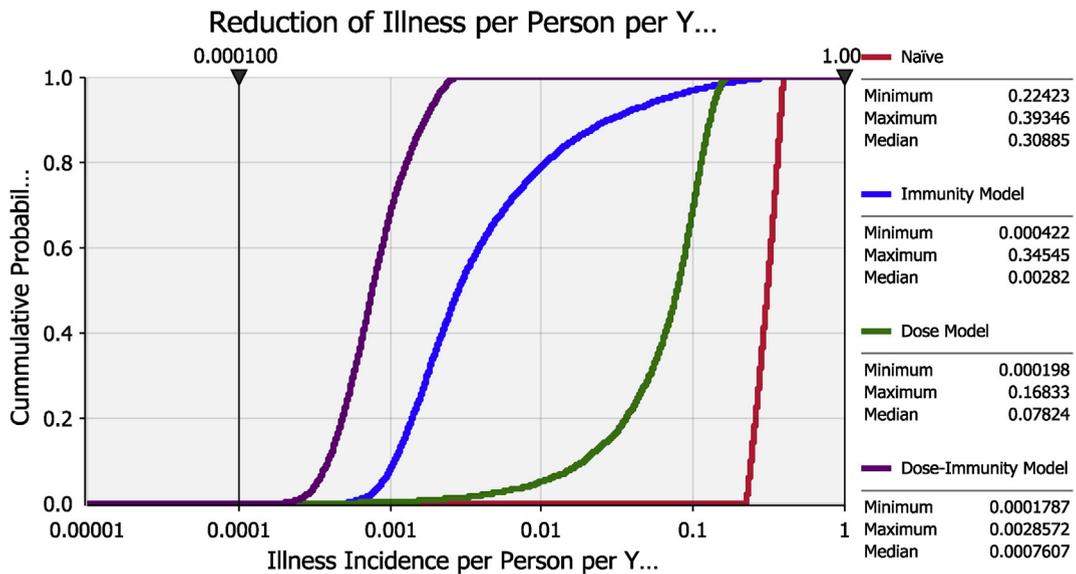


Fig. 1. Reduction of Risk of Illness per Person per year for Exposure.

4.2. Application to different illness scenarios with norovirus epidemiological data

The various transmission scenarios of *norovirus* included in this study are as described below;

• Symptomatic Individual Infectious

Only symptomatic individuals are infectious. This comprises individuals in the population under the assumption that all exposed individuals are susceptible to *norovirus* infection and none is genetically resistant. It is worth noting that the naïve model dose do not relate to symptomatic individuals infectiousness. The earlier refers to estimation of risk without inclusion of temporary acquired immunity.

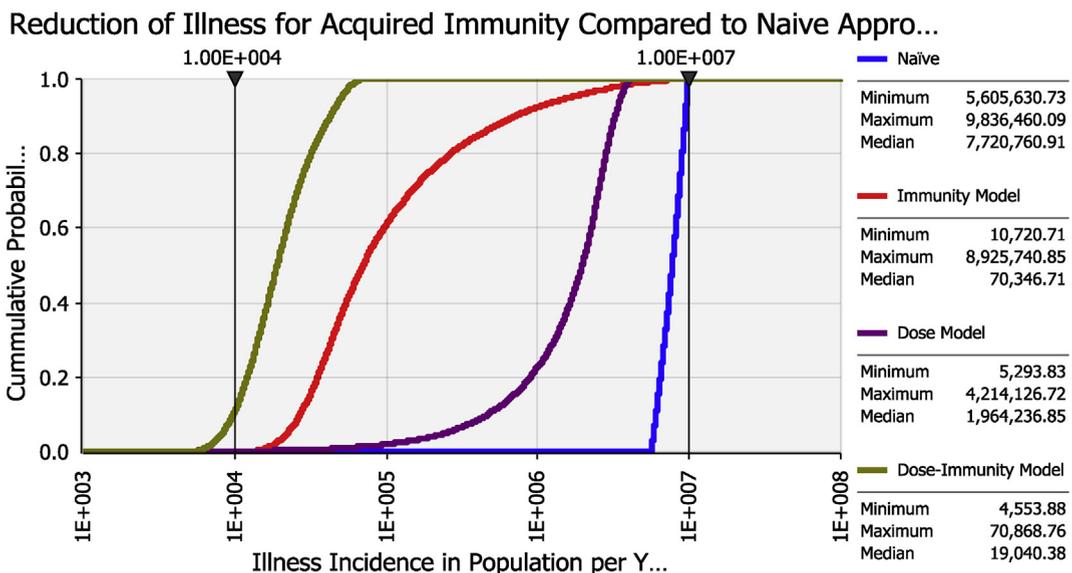


Fig. 2. Reduction of risk of illness for acquired immunity for population.

- **Pre-symptomatic and Post-symptomatic infectiousness (Low)**

Pre-symptomatic persons are individuals exposed but yet to be symptomatic of the infection (Ozawa et al., 2007; Simmons et al., 2013; Sukhrie et al., 2012; Sukhrie, Siebenga, Beersma, & Koopmans, 2010; Teunis et al., 2014).

- **Pre-symptomatic and Post-symptomatic infectiousness (High)**

In this scenario, individuals exposed and asymptomatic (Teunis et al., 2014).

- **Innate Genetic Resistance**

This is based on the assumption that part of the population is completely resistant to infection and disease, thus possessing the non-secretor phenotype and therefore playing no role in transmission process. However, such individuals do make contact with persons included in the empirical incidence estimate (Frenck et al., 2012). This is also different from immunity model or dose-immunity models; the innate genetic resistance is the inclusion of individuals whose genetic make-up excludes them from infectiousness, yet forms part of the population.

- **Scenario E: Genogroup 2 Type 4 (GII.4)**

The previous four (4) transmission scenarios assume all *norovirus* to be anti-genetically indistinguishable. In this scenario, it is assumed that only GII.4 strains are infectious. The incidence of GII.4 is estimated based on values from (Huynen et al., 2013; Nordgren, Kindberg, Lindgren, Matussek, & Svensson, 2010; Vega et al., 2011); (Frenck et al., 2012) (Simmons et al., 2013).

- **Scenario F: No Immune Boosting by Asymptomatic Infection**

Persons do not travel from recovery of illness to direct asymptomatic individuals, the only pathway out of the recovery from illness is through waning of full and partial immunity to become susceptible again.

Data input for modeling scenarios above are based on epidemiological studies shown in Table 3.

4.2.1. Results on the modeling

The Incidence of illness/infection models.

The transmission dynamics in all scenarios had probability of infection/illness incidence for dose-immunity model within $3.32 \times 10^{-8} - 7.11 \times 10^{-8}$, immunity model falls within $8.76 \times 10^{-6} - 1.12 \times 10^{-5}$, dose model falls within $1.19 \times 10^{-3} - 1.21 \times 10^{-3}$ and Naïve model falls within $1 \times 10^{-1} - 3.09 \times 10^{-1}$ (Table 4). A difference of 7 logs (median values) of magnitude was found between the dose-immunity and the naïve model for all epidemiological transmission dynamics. Five and 3 logs differences for dose-immunity as against the dose model and the immunity model, respectively. Hence, the probability of infection/illness decreases from the naïve, the dose model, the immunity model and the dose-immunity model. The individual infection/illness risk estimates for various immunity-incorporated models (dose-immunity, immunity) across the transmission scenarios gave a much lesser risk incidence as compared to the naïve and the dose-model approaches (Figs. 3–8).

Transmission dynamics.

Across the different transmission dynamics scenarios with respect to their loss of partial and full temporary immunity protection levels (Table 4), a comparison of models of the epidemiological scenarios using their median values did not show a

Table 3
Norovirus epidemiological data for modeling.

| Parameter | Scenario A | Scenario B | Scenario C | Scenario D | Scenario E | Scenario F |
|--|------------|------------|------------|------------|------------|------------|
| Loss of full immunity ($\alpha_{\text{per year}}$) | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| Loss of partial immunity ($\gamma_{\text{per year}} (\times 10^{-4})$) | 4.22–7.02 | 4.12–6.85 | 2.42–4.02 | 5.39–8.44 | 3.42–4.91 | 4.17–7.02 |
| Duration of incubation μ_s (days) | 1 | 1 | 1 | 1 | 1 | 1 |
| Duration of asymptomatic infection ρ (days) | 10 | 10 | 10 | 10 | 10 | 10 |
| Duration of symptoms μ_a (days) | 2 | 2 | 2 | 2 | 2 | 2 |
| Relative infectiousness during asymptomatic infection period | 0 | 0.05 | 0.25 | 0 | 0 | 0 |
| Relative infectiousness during incubation period | 0 | 0.05 | 0.25 | 0 | 0 | 0 |
| Strains Included | All | All | All | All | GII.4 | All |
| Boosting of immunity by asymptomatic infection | Yes | Yes | Yes | Yes | Yes | No |
| Total Exposure for Annual quantification (days) | 1–365 | 1–365 | 1–365 | 1–365 | 1–365 | 1–365 |

Parameter values (Huynen et al., 2013; Simmons et al., 2013; Sukhrie et al., 2010, 2012; Tribble et al., 2010).

Table 4
Annual Individual risk of Illness for Dose-Response Models without Temporal Acquired Immunity.

| Scenarios/Models | Naïve Model | | | Dose Model | | |
|--|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| | Median | Mean | StDev | Median | Mean | StDev |
| Symptomatic Individual Infectious | 3.09×10^{-1} | 3.09×10^{-1} | 4.89×10^{-2} | 1.21×10^{-3} | 1.50×10^{-3} | 1.22×10^{-3} |
| Pre-symptomatic and Post-symptomatic infectiousness (Low) | 3.09×10^{-1} | 3.09×10^{-1} | 4.86×10^{-2} | 1.19×10^{-3} | 1.20×10^{-3} | 1.22×10^{-3} |
| Pre-symptomatic and Post-symptomatic infectiousness (High) | 3.09×10^{-1} | 3.09×10^{-1} | 4.89×10^{-2} | 1.20×10^{-3} | 1.50×10^{-3} | 1.21×10^{-3} |
| Innate Genetic Resistance | 3.09×10^{-1} | 3.09×10^{-1} | 4.89×10^{-2} | 1.21×10^{-3} | 1.49×10^{-3} | 1.21×10^{-3} |
| Geno-group 2 Type 4 (GI.4) | 3.09×10^{-1} | 3.09×10^{-1} | 4.89×10^{-2} | 1.19×10^{-3} | 1.49×10^{-3} | 1.21×10^{-3} |
| No Immune Boosting by Asymptomatic Infection | 3.09×10^{-1} | 3.09×10^{-1} | 4.89×10^{-2} | 1.21×10^{-3} | 1.50×10^{-3} | 1.22×10^{-3} |

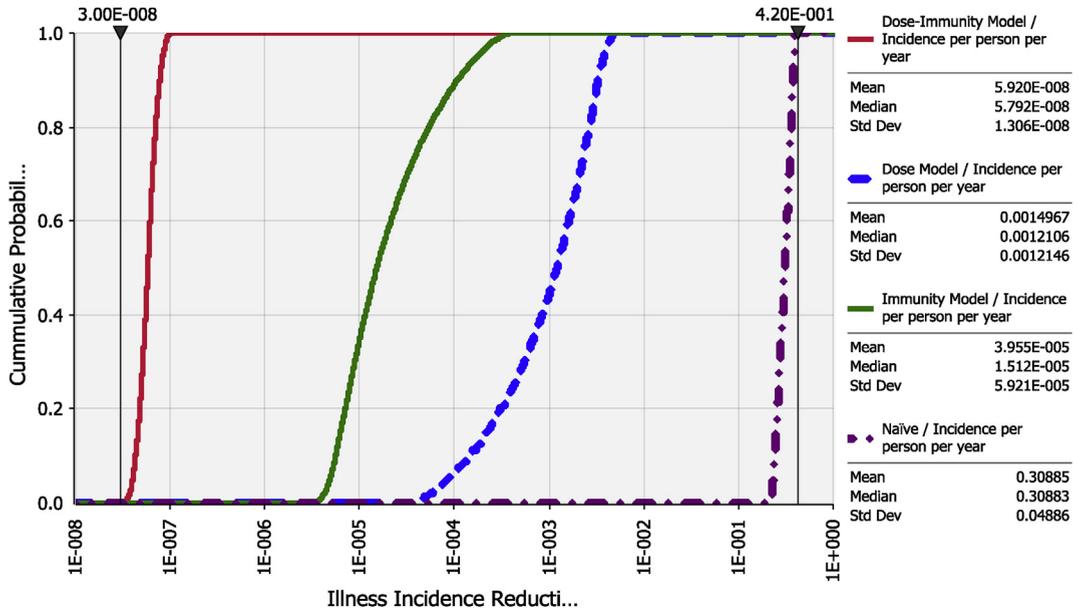


Fig. 3. Reduction of risk of illness for 'Symptomatic infectiousness' of norovirus per Person per Year.

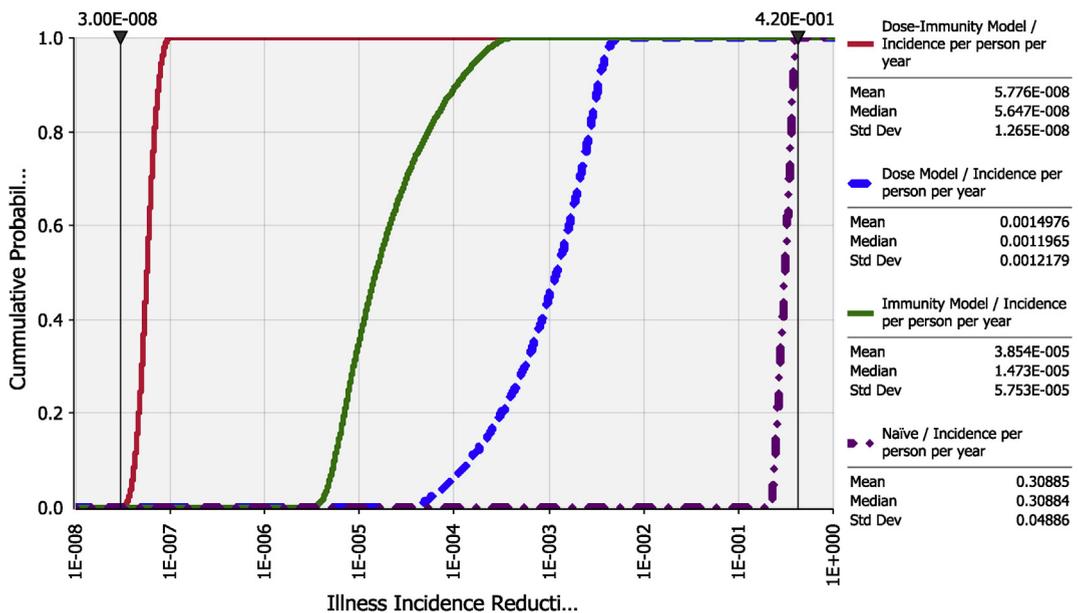


Fig. 4. Reduction of risk of illness for 'Pre-Symptomatic and Post-Symptomatic infectiousness Low' of norovirus per Person per Year.

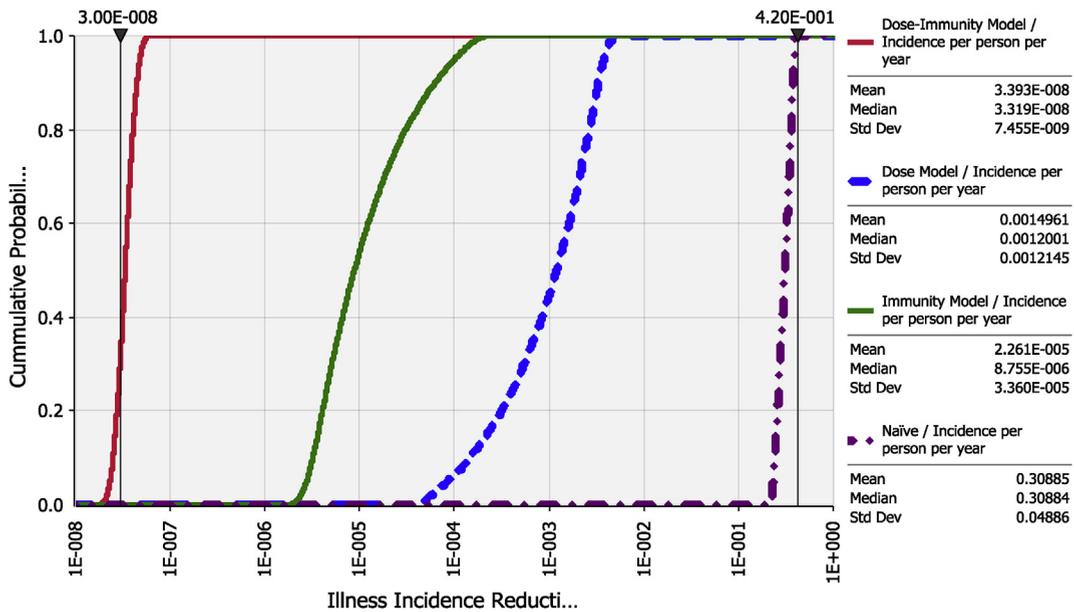


Fig. 5. Reduction of risk of illness for 'Pre-Symptomatic and Post-Symptomatic infectiousness High' of norovirus per Person per Year.

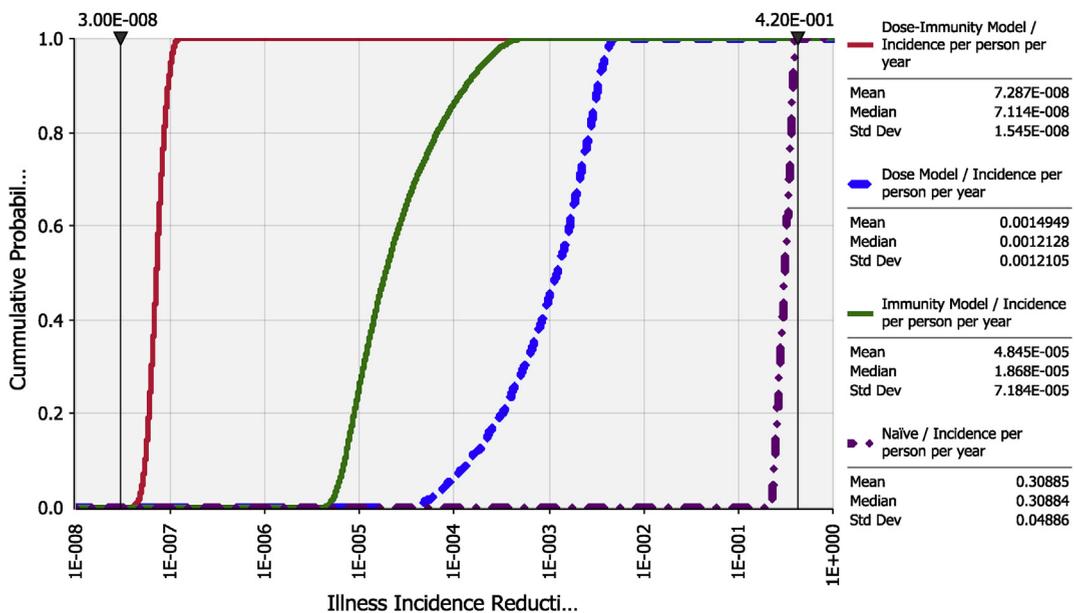


Fig. 6. Reduction of risk of illness for 'Innate Genetic Resistance' of norovirus per Person per Year.

difference in order of magnitude from transmission scenario to scenario with the exception of the immunity dose model which had 1 log less for pre-symptomatic and post-symptomatic low. Therefore, difference in the probability of infection/illness is not sensitive to the epidemiological transmission scenarios, thus, *norovirus* transmissions dynamics does not influence the probability of infection/illness predictions (Table 5).

Furthermore, the findings observed no difference for all infection response models of the transmission dynamics for symptomatic infectiousness' and the 'no immune boosting after asymptomatic infectiousness' (Tables 4 and 5). This confirms the study by Teunis et al. (2014) which indicates that shedding of virus is similar for both symptomatic and asymptomatic infectiousness. However, it is worth noting that some differences were recorded studies for shedding of virus of infected subjects (Atmar, Opekum, & Gilger, 2008). These differences are attributed to the genotype studied (Teunis et al., 2014). Nevertheless, the difference in numbers shed could not have clinical significance, hence such indifference in risk estimate of illness as seen in this study is not unusual.

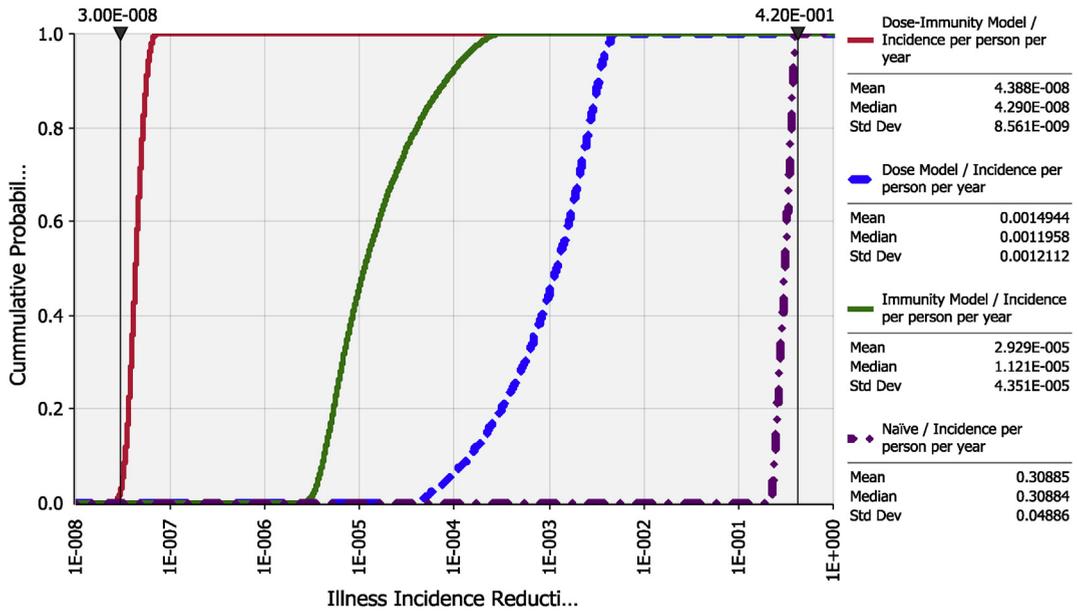


Fig. 7. Reduction of risk of illness for 'Genogroup II Type 4' of norovirus per Person per Year.

Considering the findings under models without temporarily acquired immune inclusion (Table 4), both the median values and mean values as well as their deviations were found to be the same for 'pre-symptomatic and post – symptomatic (high)' and 'symptomatic infectiousness' as well as recording similar estimates for 'innate genetic resistance and geno-group 2 Type 4' transmissions dynamics. This finding was not realized under any of the models or scenarios when acquired immunity is incorporated in the modeling process.

5. Conclusion

Applying the models to the norovirus data, resulted with the same trend of movement on the various dose-response models, and individual level of illness incidence reduction was much better measured by immunity incorporated models.

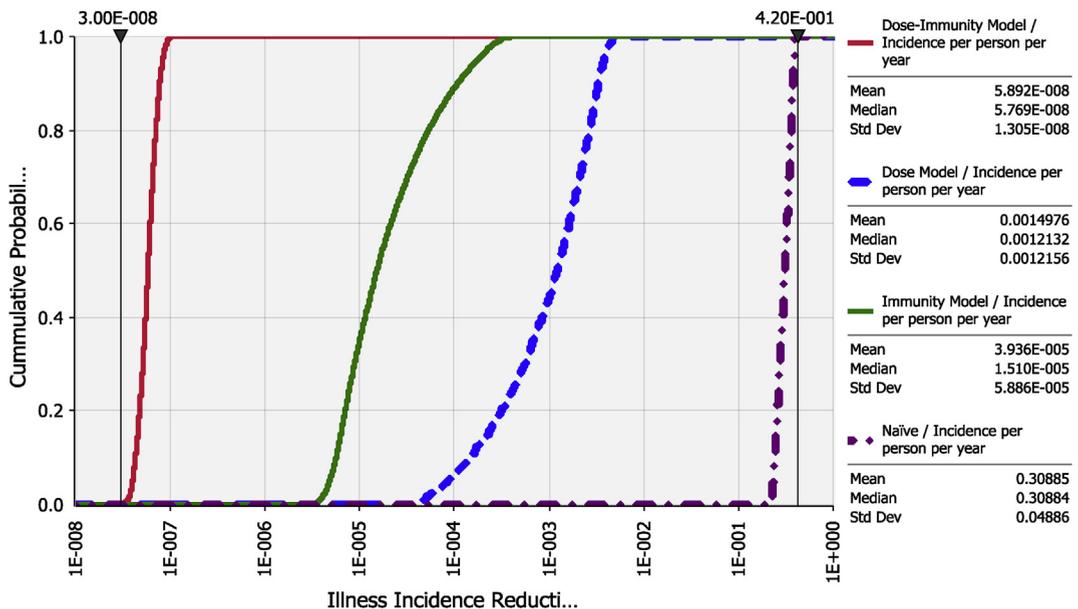


Fig. 8. Reduction of risk of illness for 'No Immune Boosting after Asymptomatic Infection' of norovirus per Person per Year.

Table 5
Annual risk of Illness for Dose-Response Models with Temporal Acquired Immunity.

| Scenarios/Models | Immunity Model | | | Dose-Immunity Model | | |
|--|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| | Median | Mean | StDev | Median | Mean | StDev |
| Symptomatic Individual Infectious | 1.51×10^{-5} | 3.96×10^{-5} | 5.92×10^{-5} | 5.77×10^{-8} | 5.92×10^{-8} | 1.31×10^{-8} |
| Pre-symptomatic and Post-symptomatic infectiousness (Low) | 1.47×10^{-5} | 3.85×10^{-5} | 5.75×10^{-5} | 5.65×10^{-8} | 5.78×10^{-8} | 1.27×10^{-8} |
| Pre-symptomatic and Post-symptomatic infectiousness (High) | 8.76×10^{-5} | 2.26×10^{-5} | 3.36×10^{-5} | 3.32×10^{-8} | 3.39×10^{-8} | 7.46×10^{-9} |
| Innate Genetic Resistance | 1.87×10^{-5} | 4.85×10^{-5} | 7.18×10^{-5} | 7.11×10^{-8} | 7.29×10^{-8} | 1.55×10^{-8} |
| Genogroup 2 Type 4 (GI.4) | 1.12×10^{-5} | 2.93×10^{-5} | 4.35×10^{-5} | 4.29×10^{-8} | 4.39×10^{-8} | 8.56×10^{-9} |
| No Immune Boosting by Asymptomatic Infection | 1.51×10^{-5} | 3.94×10^{-5} | 5.89×10^{-5} | 5.77×10^{-8} | 5.89×10^{-8} | 1.31×10^{-8} |

The immunity incorporated models tend to predict a lower illness/infection incidence, while the non-immunity incorporated models do not. Again, the immunity dependent models (immunity and dose-immunity models) meet the more stringent WHO infection/illness threshold of 1.0×10^{-6} per person per exposure in all transmission scenarios.

The resulting magnitude of decrease in probability estimation of risk of illness is having a pronounced effect on the estimation of diseases as a result of incorporation of the temporary immune dose response, irrespective of the scenario of transmission of infected individuals, hence the results agree with Swart et al., 2012 and Havelaar & Swart, 2014.

These modeling results throw more light on the overestimation of the probable infection/illness as a result of the use of naïve and dose models approach. It is important to note that the immunity model, which is a buildup of inclusion for immune system response in the first stage, is a better estimation in terms of predicting the reality of infection/illness of exposure than the naïve approach. The lower estimates for the immunity-incorporated models indicates the impacts of the temporary immune response to offer full protection and always results in lower estimates as compared to the naïve estimates (Tribble et al., 2010). It is also important to note that the dynamics of the norovirus transfer from person to person does not influence the responses of the models, hence the prediction models superimpose on the type of the transmission of the virus.

Data availability

All data used are shown on the tables.

Conflicts of interest

The authors have no conflict of interest in the paper.

Funding statement

This work was supported by DANIDA SaWaFo project with grant number 11-058DHI.

Acknowledgement

We would like to acknowledge the support of Rejoice Ametepy at SaWaFo office, KNUST, Kumasi Ghana.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.idm.2019.04.005>.

References

- Atmar, R. L., Opekum, A. R., & Gilger, M. A. (2008). Norwalk virus shedding after experimental human infection. *Emerging Infectious Diseases*, 14(10), 1553–1557.
- Frenck, R., Bernstein, D. I., Xia, M., Huang, P., Zhong, W., Parker, S., et al. (2012). Predicting susceptibility to norovirus GI.4 by use of a challenge model involving humans. *Journal of Infectious Diseases*, 206(9), 1386–1393.
- Furumoto, W. A., & Mickey, R. (1967). A mathematical model for the infectivity-dilution curve of tobacco mosaic virus: Theoretical considerations. *Virology*, 32, 216–223. [https://doi.org/10.1016/0042-6822\(67\)90271-1](https://doi.org/10.1016/0042-6822(67)90271-1).
- Haas, C. N., Rose, J. B., & Gerba, C. P. (1999). *Quantitative microbial risk assessment*. Wiley.
- Haas, C. N., Rose, J. B., & Gerba, C. P. (2014). *Conducting the dose-response assessment. Quantitative microbial risk assessment* (2nd ed.). Wiley.
- Havelaar, A. H., & Swart, A. N. (2014). Impact of acquired immunity and dose-dependent probability of illness on quantitative microbial risk assessment. *Journal of Risk Analysis*, 34, 1807–1819. <https://doi.org/10.1111/risa.12214>.
- Huynen, P., Mauroy, A., Martin, C., Bavado, B. L. G., Boreux, R., Thiry, E., et al. (2013). Molecular epidemiology of norovirus infections in symptomatic and asymptomatic children from Bobo Dioulasso, Burkina Faso. *Journal of Clinical Virology*, 58(3), 515–521.
- Mara, D., Hamilton, A., Sleight, A., & Karavarsamis, N. (2010). *Options for updating the 2006 WHO guidelines* (pp. 4–11).
- Messner, M. J., Berger, P., & Nappier, S. P. (2014). Fractional Poisson—a simple dose-response model for human norovirus. *Journal of Risk Analysis*, 34, 1820–1829. <https://doi.org/10.1111/risa.12207>.

- Nordgren, J., Kindberg, E., Lindgren, P. E., Matussek, A., & Svensson, L. (2010). Norovirus gastroenteritis outbreak with a secretor-independent susceptibility pattern, Sweden. *Emerging Infectious Diseases*, *16*(1), 81–87.
- Ozawa, K., Oka, T., Takeda, N., & Hansman, G. S. (2007). Norovirus infections in symptomatic and asymptomatic food handlers in Japan. *Journal of Clinical Microbiology*, *45*(12), 3996–4005.
- Pouillot, R., Van Doren, J. M., Woods, J., Plante, D., Smith, M., Goblick, G., et al. (2015). Meta-analysis of the reduction of norovirus and male-specific coliphage concentrations in wastewater treatment plants. *Applied and Environmental Microbiology*, *81*(14), 4669–4681.
- Seidu, R., Heistad, A., Amoah, P., Drechsel, P., Jenssen, P. D., & Stenström, T. A. (2008). Quantification of the health risk associated with wastewater reuse in Accra, Ghana: A contribution toward local guidelines. *Journal of Water and Health*, *6*, 461–471. <https://doi.org/10.2166/wh.2008.118>.
- Simmons, K., Gambhir, M., Leon, J., & Lopman, B. (2013). Duration of immunity to norovirus gastroenteritis. *Emerging Infectious Diseases*, *19*, 1260–1267. <https://doi.org/10.3201/eid1908.130472>.
- Sukhrie, F. H. a, Siebenga, J. J., Beersma, M. F. C., & Koopmans, M. (2010). Chronic shedders as reservoir for nosocomial transmission of norovirus. *Journal of Clinical Microbiology*, *48*(11), 4303–4305.
- Sukhrie, F. H., Teunis, P., Vennema, H., Copra, C., Thijs Beersma, M. F., Bogerman, J., et al. (2012). Nosocomial transmission of norovirus is mainly caused by symptomatic cases. *Clinical Infectious Diseases*, *54*(7), 931–937. <https://doi.org/10.1093/cid/cir971>.
- Swart, A. N., Tomasi, M., Kretzschmar, M., Havelaar, A. H., & Diekmann, O. (2012). The protective effects of temporary immunity under imposed infection pressure. *Epidemics*, *4*, 43–47. <https://doi.org/10.1016/j.epidem.2011.12.002>.
- Teunis, P. F. (2005). A reconsideration of the Campylobacter dose–response relation. *Epidemiology*, *133*, 583–592. <https://doi.org/10.1017/S0950268805003912>.
- Teunis, P. F., Nagelkerke, N. J., & Haas, C. N. (1999). Dose response models for infectious gastroenteritis. *Journal of Risk Analysis*, *19*, 1251–1260.
- Teunis, P. F. M., Moe, C. L., Liu, P., Miller, S. E., Lindesmith, L., Baric, R. S., et al. (2008). Norwalk Virus : How infectious is It ? *Journal of Medical Virology*, *80*(8). <https://doi.org/10.1002/jmv.1476>.
- Teunis, P. F. M., Sukhrie, H. A. F., Vennema, H., Bogerman, J., Beersma, F. C. M., & Koopmans, M. (2014). Shedding of norovirus in symptomatic and asymptomatic infections. *Epidemiology and Infection*, *143*(08), 1–8. <https://doi.org/10.1017/S095026881400274X>.
- Tribble, D. R., Baqar, S., Scott, D. A., Oplinger, M. L., Trespalacios, F., Rollins, D., et al. (2010). Assessment of the duration of protection in Campylobacter jejuni experimental infection in humans. *Infection and Immunity*, *78*, 1750–1759. <https://doi.org/10.1128/IAI.01021-09>.
- Vega, E., Barclay, L., Gregoricus, N., Williams, K., Lee, D., & Vinje, J. (2011). Novel surveillance network for norovirus gastroenteritis outbreaks, United States. *Emerging Infectious Diseases*, *17*(8), 1389–1395.