Appendices

A Selection of challenge studies

Table A1 lists all challenge studies on norovirus that were found. For some of these studies (**????**), there remains uncertainty whether the used inoculum was identical to the 8fIIa inoculum that was titrated by RT–PCR in **?**. Studies with unknown virus concentration cannot be used. For the remaining older studies, (**??????????**) it was established that this was the same inoculum as titrated in **?**. However, at the time that the 8fIIa inoculum was titrated by qPCR, the virus suspension appeared to show considerable aggregation, complicating its use in dose response assessment. The analysis in **?** assumed that aggregates were stable when diluted, so that dosing the inoculum involved diluting intact aggregates. Since it can only be assumed that the virus attained its current state at some time in the past, it remains unknown whether the inoculum was in the same aggregation state during any of the older challenge studies with 8fIIa . As **?** was the largest to date, involving 75 volunteers, it was decided to select only that most recent study and ignore the older studies. As a check, a model was run with all GI.1 studies, including older studies (**??????????**), and compared with a model using only the newer studies (**???**). The resulting dose response relations were not different (not shown here).

Two studies, one published previously (**?**), used Snow Mountain virus (GII.2). The concentration of SMV in the inoculum (3.17×10^6 GC/ml) was determined when the same inoculum was used in a more recent challenge study, when qPCR had become available.

The study of **?** reports responses to Montgomery virus, of which no sample was available for analysis. Therefore this challenge experiment was not included.

Five different challenge experiments used Hawaii virus (GII.1), four of which have been published (**????**). These studies all used the same virus suspension for inoculation, with concentration 1.24×10^6 GC/ml.

The two studies on GII.4 (**??**) reported the inoculum titer in PCR detectable units (PDU), determined by endpoint titration using conventional (presence–absence) RT–PCR. As no qPCR data are available, we assumed PDU units equivalent to GC (genome copy) units.

Information about the concentration of virus suspensions used for the human challenge studies in Tables A3, A4, A5, A6, A7, and A8 is summarized in Table A2.

Table A1: Reported norovirus human challenge studies. Studies used in this analysis are in boldface. Titration (Titr) of inocula in Table A2. The question mark for studies using the Norwalk (GI.1) 8fIIa inoculum indicates uncertainty about the aggregation state of the inoculum while it was aging. Numbers of different doses applied (Doses), numbers of volunteers challenged (Exp), infected (Inf), and ill (Ill). Newer studies report secretor status, a few studies selected only Se^+ volunteers.

		Inoculum			Volunteers			Secretor
Reference	type	Name	Titr	Doses	Exp	Inf	Ill	status
?	GI.1	NA	NA	1	9	NA	7	NA
?	GI.1	8fIIa	(a)?	1	19	NA	7	NA
?	GI.1	8fIIa(?)	?	1	7	NA	4	NA
?	GI.1	8fIIa	(a)?	1	52	NA	30	NA
?	GI.1	8fIIa(?)	?	1	16	NA	11	NA
?	GI.1	8fIIa	(a)?	1	15	NA	12	NA
?	GI.1	8fIIa	(a)?	1	15	NA	9	NA
?	GI.1	8fIIa	(a)?	1	12	NA	6	NA
?	GI.1	8fIIa(?)		1	7	NA	4	NA
?	GI.1	8fIIa	(a)?	1	59	40	32	NA
?	GI.1	8fIIa	(a)?	1	16	14	11	NA
?	GI.1	8fIIa	(a)?	1	42	29	25	NA
?	GI.1	8fIIa	(a)?	1	50	41	28	NA
?	GI.1	8fIIa	(a)	8	75	22	15	+/-
?	GI.1	8fIIb	(b)	3	33	18	8(9)	+/-
?	GI.1	42399	(c)	4	49	21	14	+/-
?	GI.1	8fIIb	(b)	1	20	10	6	+
?	GI.1	8fIIb	(b)	1	15	7		+
?	GII.2	SMV	(d)	5	12	9	9	NA
This paper	GII.2	SMV	(d)	3	15	9	7	+/-
?		Montgomery	NA	1	18	NA	5	NA
?	GII.1	Hawaii	(e)	1	23	NA	11	NA
?	GII.1	Hawaii	(e)	1	7	NA	4	NA
?	GII.1	Hawaii	(e)	1	3	NA	1	NA
?	GII.1	Hawaii	(e)	1	10	5	8	NA
This paper	GII.1	Hawaii	(e)	1	2	2	1	+/-
?	GII.4	Farm.Hills	(f)	1	40	17	12	+/-
?	GII.4	Farm.Hills	(g)	1	48	30	16	+

Table A2: Titers of inocula used in the analysis. The titer reported in **?** was 1.2×10^5 PDU/ml (RT-PCR units/ml), and 1 RT-PCR PDU was reported to be equivalent to 400 GC as determined by qPCR, thus the titer is 4.8×10^7 genome copies (GC)/ml.

	Name	titer	units	Reference
a	8fIIa	3.24×10^9	GC/ml	**?**
b	8fIIb	6.92×10^8	GC/ml	**?**
c	42399	4.8×10^7	GC/ml	**?**
d	SMV*	3.17×10^6	GC/ml	this paper
e	Hawaii	1.24×10^6	GC/ml	this paper
f	Farmington Hills	5×10^4	PDU/ml	**?**
g	Farmington Hills	4.4×10^4	PDU/ml	**?**

* A note on the titration of SMV inoculum: a partial SMV plasmid DNA (2179 nt) was used to construct SMV RNA transcripts. Suspensions of SMV transcripts of known numbers of genome equivalent copies were serially diluted and used to quantify the genomic copies of SMV inoculum used in this study. SMV inoculum was diluted 10–fold and 100–fold with DEPC–treated water in triplicate tubes, and then SMV RNA was released using the heat–release RNA extraction method (**?**). Subsequently, a norovirus GII broadly–reactive TaqMan quantitative RT–PCR was performed to quantitate SMV genome copies using the method described by **?**. See **?** for a detailed description. The concentration and numbers of genomic copies of the RNA transcripts were determined as previously described (**?**).

B Challenge data used for analysis

Table A3: Norwalk virus data: 8fIIa inoculum. Dose as inoculated volume (μl) and genome copies (GC). Volunteers by secretor status (Se^-, Se^+, or unknown): exposed (Exp.), infected (Inf.) and symptomatic (Sympt.).

Dose		Se^-			Se^+			Se unknown		
μl	GC	Exp.	Inf.	Sympt.	Exp.	Inf.	Sympt.	Exp.	Inf.	Sympt.
GI.1 (8fIIa) (**?**)										
1.0×10^{-6}	3.24×10^1	2	0	0	8	0	0			
1.0×10^{-5}	3.24×10^2	2	0	0	9	0	0			
1.0×10^{-4}	3.24×10^3	6	0	0	9	3	1			
1.0×10^{-3}	3.24×10^4	1	0	0	3	2	1			
1.0×10^{-1}	3.24×10^6	2	0	0	8	7	6			
1.0×10^{0}	3.24×10^7	3	0	0	7	3	1			
1.0×10^{1}	3.24×10^8	2	0	0	3	2	2			
1.0×10^{2}	3.24×10^9	4	0	0	6	5	4			
Total		22	0	0	53	22	15			

Table A4: Norwalk virus data: 8fIIb inoculum. Dose as inoculated volume (μl) and genome copies (GC). Volunteers by secretor status (Se^-, Se^+, or unknown): exposed (Exp.), infected (Inf.) and symptomatic (Sympt.).

Dose		Se^-			Se^+			Se unknown		
μl	GC	Exp.	Inf.	Sympt.	Exp.	Inf.	Sympt.	Exp.	Inf.	Sympt.
GI.1 (8fIIb) (**?**)										
1.0×10^0	6.92×10^5	2	0	0	8	3	2			
1.0×10^1	6.92×10^6	4	0	0	18	14	7			
3.0×10^1	2.08×10^7	0	0	0	1	1	NA			
Total		6	0	0	27	18	9(10)			
GI.1 (8fIIb) (**?**)										
1.0×10^3	6.92×10^8				20	10	6			
GI.1 (8fIIb) (**?**)										
3.3×10^2	2.31×10^8				15	7	NA			

Table A5: Norwalk virus data: 42399 inoculum. Dose as inoculated RT–PCR units and genome copies (GC). Volunteers by secretor status (Se^-, Se^+, or unknown): exposed (Exp.), infected (Inf.) and symptomatic (Sympt.).

Dose		Se^-			Se^+			Se unknown		
RT–PCR	GC	Exp.	Inf.	Sympt.	Exp.	Inf.	Sympt.	Exp.	Inf.	Sympt.
GI.1 (42399) (**?**)										
4.8×10^{-1}	1.92×10^2	3	0	0	13	1	1			
4.8×10^0	1.92×10^3	1	0	0	13	7	5			
4.8×10^1	1.92×10^4	2	0	0	8	7	4			
4.8×10^3	1.92×10^6	2	0	0	7	6	4			
Total		8	0	0	41	21	14			

Table A6: SMV inoculum. Dose as inoculated volume (μl) and genome copies (GC). Volunteers by secretor status (Se^-, Se^+, or unknown): exposed (Exp.), infected (Inf.) and symptomatic (Sympt.).

Dose		Se^-			Se^+			Se unknown		
μl	GC	Exp.	Inf.	Sympt.	Exp.	Inf.	Sympt.	Exp.	Inf.	Sympt.
GII.2 (**?**)										
1.0×10^0	3.17×10^3							2	0	0
1.0×10^1	3.17×10^4							2	2	2
1.0×10^2	3.17×10^5							2	2	2
5.0×10^2	1.58×10^6							4	3	3
1.0×10^3	3.17×10^6							2	2	2
Total								12	9	9
GII.2										
1.0×10^{-2}	3.17×10^1	1	0	0	4	0	0			
1.0×10^0	3.17×10^3	1	0	0	4	4	3			
1.0×10^2	3.17×10^5	1	1	1	4	4	3			
Total		3	1	1	12	8	6			

Table A7: Hawaii virus inoculum. Dose as inoculated volume (μl) and genome copies (GC). Volunteers by secretor status (Se^-, Se^+, or unknown): exposed (Exp.), infected (Inf.) and symptomatic (Sympt.).

Dose		Se^-			Se^+			Se unknown		
μl	GC	Exp.	Inf.	Sympt.	Exp.	Inf.	Sympt.	Exp.	Inf.	Sympt.
GII.1 (**?**)										
4.0×10^3	4.96×10^6							23	NA	11
GII.1 (**?**)										
4.0×10^3	4.96×10^6							7	NA	4
GII.1 (**?**)										
3.0×10^3	3.72×10^6							3	NA	1
GII.1 (**?**)										
1.0×10^3	1.24×10^6							10	5	8
GII.1										
5.0×10^3	6.20×10^6	1	1	0	1	1	1			

Table A8: GII.4 inoculum. Dose as inoculated volume (μl) and genome copies (GC). Volunteers by secretor status (Se^-, Se^+, or unknown): exposed (Exp.), infected (Inf.) and symptomatic (Sympt.).

Dose		Se^-			Se^+			Se unknown		
μl	GC	Exp.	Inf.	Sympt.	Exp.	Inf.	Sympt.	Exp.	Inf.	Sympt.
GII.4 (**?**)										
1.0×10^0	5.00×10^4	17	2	1	23	16	13			
GII.4 (**?**)										
1.0×10^0	4.40×10^3	0	0	0	48	30	18			

C Outbreak data used for analysis

Table A9: Oyster outbreak data. Numbers of oysters consumed (range is given when individual intake was not known), and numbers exposed and ill. No fecal samples were collected, infection status was unknown. In the first outbreak (also published in **?**) secretor status was known. The concentrations of GI and/or GII virus are listed in Table A10, a – e for the first set of outbreaks (**?**); f – j for the second set (not published previously). Dose as number of oysters (# oysters) and genome copies (GC). Subjects by secretor status (Se^-, Se^+, or unknown): exposed (Exp.), infected (Inf.) and symptomatic (Sympt.).

Dose		Se^-			Se^+			Se unknown		
# Oysters	GC	Exp.	Inf.	Sympt.	Exp.	Inf.	Sympt.	Exp.	Inf.	Sympt.
GII.4 **?**										
NA	a	0	NA	0	1	NA	1	0	NA	0
2	a	0	NA	0	3	NA	3	0	NA	0
3	a	3	NA	0	17	NA	12	1	NA	1
4	a	2	NA	0	2	NA	2	0	NA	0
6	a	1	NA	1	4	NA	3	0	NA	0
GII.4, GII.8, GII.9, GI.4 **?**										
1 – 6	b							36	NA	21
GI.1 **?**										
7	c							1	NA	1
9	c							2	NA	2
18	c							1	NA	1
GI **?**										
4 – 6	d							2	NA	2
GI, GII **?**										
4 – 6	e							27	NA	11
GI, GII (Le Guyader)										
4 – 6	f							6	NA	6
GI (Le Guyader)										
4 – 6	g							9	NA	9
GI, GII (Le Guyader)										
4 – 6	h							79	NA	22
GI (Le Guyader)										
4 – 6	i							8	NA	5
GI, GII (Le Guyader)										
4 – 6	j							4	NA	4

Table A10: Concentration of GI or GII NoV in oysters, collected from outbreaks associated with the consumption of oysters. Titrated by quantitative RT–PCR (qPCR) (**?**) and/or by digital PCR (dPCR) (**?**). Both outcomes are in the same units and can be used jointly. $<$ indicates detection but not quantifiable. Multiple data are separated by commas. All reported data were used to estimate parameters of a distribution characterising variation in concentration, as in (**?**), see section E.

		Genome copies/oyster			
		GI		GII	
	Outbreak	qPCR	dPCR	qPCR	dPCR
a	GII.4	NA		18, 955, 38, 0	
b	GII.4, GII.8, GII.9, GI.4	125		25,25	
c	GI.1	85, 237		NA	
d	GI	275, 6783		NA	
e	GI, GII	2300		1100	
f	GI, GII	1090	295	1210	132
g	GI	446	NA	$<$	NA
h	GI, GII	119, 819	71, 30, 132	376, 1250	30
i	GI	NA	68	NA	NA
j	GI, GII	$<$	22	$<$	22

D Dose response models

Anyone exposed to norovirus can become infected, implying that intestinal tissues are colonized and that a seroresponse is mounted (**?**). They may also develop symptoms of acute enteric illness, but that is not always the case: a fraction of infected subjects may remain asymptomatic, clearing infection without ever becoming ill. Therefore, there are two dose response relations to be considered: a dose dependent probability of infection, and a conditional probability of acute illness, given that a subject was infected. Anyone failing to become infected and thus not colonized nor seroconverted, is assumed to not proceed to develop acute gastroenteritis.

Briefly, the models used are

Infection The Beta Poisson model for microbial infection

$$P_{\text{inf}}(cV) = 1 - {}_1F_1(\alpha, \alpha+\beta, -cV) \tag{A.1}$$

where ${}_1F_1$ refers to the (Kummer) confluent hypergeometric function (**?**). The parameters (α, β) can be transformed as below

$$\begin{aligned} u_1 &= \tfrac{\alpha}{\alpha+\beta}; \quad & w_1 &= \log\left(\tfrac{u_1}{1-u_1}\right) \\ v_1 &= \alpha+\beta; \quad & z_1 &= \log(v_1) \end{aligned} \tag{A.2}$$

so that w_1 is a measure of infectivity (location) and z_1 a measure of variation in infectivity (spread). This transformation greatly improves parameter estimation (**???**).

Illness The hazard model of illness dose response

$$P_{\text{ill}|\text{inf}}(cV) = 1 - \left(1 + \frac{cV}{\eta}\right)^{-r} \tag{A.3}$$

implies that while infected, the risk that a person develops acute gastroenteric symptoms may also depend on dose: the higher the inoculated dose, the higher the risk that an infected person also has symptoms. This means that at low doses the risk of acute illness is proportional to the dose squared.

As argued in **?** a motivation for this model may be found in noting that only during infection there is a nonzero hazard of developing acute symptoms, so that longer duration of infection causes an increased risk of acute illness. Parameter transformation identical to the infection parameters

$$\begin{aligned} u_2 &= \tfrac{r}{r+\eta}; \quad & w_2 &= \log\left(\tfrac{u_2}{1-u_2}\right) \\ v_2 &= r+\eta; \quad & z_2 &= \log(v_2) \end{aligned} \tag{A.4}$$

again translates the parameters r and η into a location parameters w_2 and a spread parameter z_2.

E Implementation notes

The hypergeometric functions are lacking in JAGS. Instead, the beta–binomial model for infection conditional on the ingested number of viruses (**?**) can be used

$$P_{\text{inf}}(n) = 1 - \frac{\Gamma(\alpha+\beta)\Gamma(\beta+n)}{\Gamma(\beta)\Gamma(\alpha+\beta+n)} \tag{A.5}$$

where n is a Poisson variate, thus providing a good approximation to eqn. (A.1), as shown in (**?**).

Adaptations for non–Poisson inocula are needed: in **?** the inoculum was likely aggregated. Furthermore, in the foodborne outbreaks exposure was not well controlled as in challenge studies, with variation in concentration among oysters (**?**).

Virus aggregation was modeled by assuming the inoculum was from a Poisson distributed suspension of aggregates with sizes distributed as a logarithmic series (**?**). The numbers of viruses in a volume V then are negative binominally distributed with parameters

$$\text{scale: } \pi = 1 - a; \quad \text{shape: } \rho = \frac{CV}{-\log(1-a)} \tag{A.6}$$

where C is the concentration of virus aggregates and a the parameter of the logarithmic series distribution. Aggregates consisted of virus in a sticky matrix that were considered unlikely to dissociate upon dilution, as used for dosing the inocula. Therefore a was assumed to be a constant.

Overdispersion of the virus concentration in oyster tissue in the shellfish outbreaks was modeled by assuming the variation in concentration gamma distributed (**?**). The numbers of viruses in a portion V then are negative binomially distributed with parameters

$$\text{scale: } \pi = \frac{1}{1+\lambda V}; \quad \text{shape: } \rho = \rho \tag{A.7}$$

where λ and ρ are the scale and shape parameters of the gamma distributed virus concentration, respectively.

As in **?** the transformed dose response parameters were estimated by host factors (secretor status ss: Se^+ or Se^-) and pathogen factors (genogroup gg: GI or GII).

Note that in shellfish outbreaks it is not uncommon to find mixed infections. Like in **?**, mixed GI/GII infections were treated as two independent concurrent infections, where the probability of illness, the observable outcome, was calculated as

$$\begin{aligned} P_{\text{ill,GI}} &= P_{\text{inf,GI}} P_{\text{ill|inf,GI}} \\ P_{\text{ill,GII}} &= P_{\text{inf,GII}} P_{\text{ill|inf,GII}} \\ P_{\text{ill}} &= 1 - (1 - P_{\text{ill,GI}})(1 - P_{\text{ill,GII}}) \end{aligned} \tag{A.8}$$

When secretor status was unknown, it was treated as missing with an (informed prior) beta$(79, 19)$ distribution, as used previously (**?**).

Location parameters w and spread (or variation in infectivity or pathogenicity) parameters z were treated differently.

Location of infectivity (w_1) and pathogenicity (w_2) were given normal priors. For secretor status (ss) and genogroup (gg)

$$\begin{aligned} w_1(\text{ss},\text{gg}) &\sim N(\mu_{1,\text{ss},\text{gg}}, \tau_{w,1}) \\ w_2(\text{ss},\text{gg}) &\sim N(\mu_{2,\text{ss},\text{gg}}, \tau_{w,2}) \end{aligned} \tag{A.9}$$

and fixed precision $\tau_{w,1}$ and $\tau_{w,2}$, respectively ($\tau \equiv 1/\sigma^2$). The parameters for variation (spread) in infectivity and pathogenicity were given normal priors

$$\begin{aligned} z_1 &\sim N(\mu_{z,1}, \tau_{z,1}) \\ z_2 &\sim N(\mu_{z,2}, \tau_{z,2}) \end{aligned} \tag{A.10}$$

not differentiating between genogroup and secretor status effects.

Initial runs with broad priors ($\tau_{w,1}, \tau_{w,2} = 0.01$) indicated highly dispersed posteriors for the illness parameter w_2 among host categories, while the infectivity parameter w_1 appeared similar for all three host categories. To account for possibly elevated pathogenicity in outbreaks the (conditional) illness dose response parameters for outbreaks were then estimated as an additional category

$$\begin{aligned} w_3(\text{ss},\text{gg}) &\sim N(\mu_{3,\text{ss},\text{gg}}, \tau_{w,3}) \\ z_3 &\sim N(\mu_{z,3}, \tau_{z,3}) \end{aligned} \tag{A.11}$$

while assuming that their infectivity parameters were similar to those of the challenge studies, i.e. the infectivity parameters (w_1, z_1) were assumed to all have the same prior distribution (**?**).

Both strain variation and host variation in infectivity were given hyperpriors $\mu_{1,\ldots} \sim N(0, 0.01)$, and strain and host variation in pathogenicity were also assumed $\mu_{2,\ldots} \sim N(0, 0.01)$. The remaining precision of w_1 and w_2 within host and strain, $\tau_{w,\ldots} = 1$. Priors for z_1 and z_2 were $N(0, 1)$.

The model was specified and run in JAGS (v4.3.0) (**?**) from R (v3.5.2) (**?**) using rjags (v4-8) (**?**). Source code can be found in Appendix I. Four parallel chains were run; after a burn–in of 10^3 iterations, the model was run for 10^4 iterations, thinning down to a posterior sample of size $4 \times 1000 = 4000$. Convergence was checked by inspection of posteriors.

F Additional tables

Table A11: Infectious dose required for 1% infection or illness (secretor–positives and negatives), and for 50% infection or illness (secretor–positives). Outcomes are given as mean predicted value, median (0.5 quantile: $Q_{0.500}$), and 95% range ($Q_{0.025}$ – $Q_{0.975}$).

				mean	$Q_{0.500}$	$Q_{0.025}$	$Q_{0.975}$
$InfD_{01}$	Se^-	GI		1.1×10^9	1.5×10^3	2.4×10^{-1}	9.3×10^9
$InfD_{01}$	Se^-	GII		1.5×10^7	5.5×10^0	6.1×10^{-2}	2.5×10^4
$InfD_{01}$	Se^+	GI		6.3×10^{-2}	2.8×10^{-2}	1.1×10^{-2}	2.9×10^{-1}
$InfD_{01}$	Se^+	GII		1.3×10^0	2.6×10^{-1}	1.8×10^{-2}	7.2×10^0
$InfD_{50}$	Se^+	GI		1.8×10^8	2.9×10^0	8.3×10^{-1}	6.0×10^4
$InfD_{50}$	Se^+	GII		2.6×10^8	9.5×10^1	1.4×10^0	1.6×10^8
$IllD_{01}$	Se^-	GI	Ch	1.2×10^9	5.2×10^3	1.2×10^0	1.1×10^{10}
$IllD_{01}$	Se^-	GII	Ch	4.8×10^8	3.7×10^2	9.7×10^{-1}	2.2×10^9
$IllD_{01}$	Se^+	GI	Ch	7.3×10^3	3.6×10^{-1}	4.6×10^{-2}	1.6×10^1
$IllD_{01}$	Se^+	GII	Ch	9.8×10^3	2.2×10^0	1.3×10^{-1}	1.6×10^2
$IllD_{50}$	Se^+	GI	Ch	1.1×10^9	4.8×10^2	1.8×10^0	1.5×10^{10}
$IllD_{50}$	Se^+	GII	Ch	8.1×10^8	3.5×10^3	5.9×10^0	7.5×10^9
$IllD_{01}$	Se^-	GI	Ob	1.4×10^9	2.2×10^3	2.5×10^0	1.5×10^{10}
$IllD_{01}$	Se^-	GII	Ob	1.6×10^8	2.0×10^1	2.4×10^{-1}	2.3×10^7
$IllD_{01}$	Se^+	GI	Ob	2.1×10^{-1}	1.1×10^{-1}	1.9×10^{-2}	1.1×10^0
$IllD_{01}$	Se^+	GII	Ob	4.8×10^0	8.8×10^{-1}	6.2×10^{-2}	2.5×10^1
$IllD_{50}$	Se^+	GI	Ob	2.4×10^8	4.7×10^0	9.6×10^{-1}	9.8×10^5
$IllD_{50}$	Se^+	GII	Ob	4.2×10^8	2.6×10^2	2.9×10^0	1.2×10^9

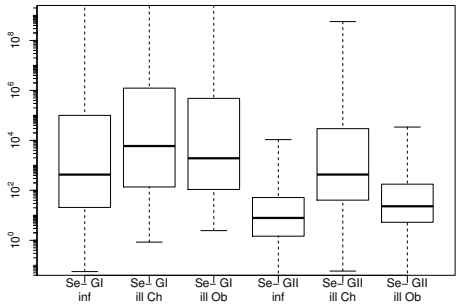
Table A12: Probability of infection or illness when exposed to a dose of 1 infectious virus (GC). Outcomes are given as mean predicted value, median (0.5 quantile: $Q_{0.500}$), and 95% range ($Q_{0.025}$ – $Q_{0.975}$).

				mean	$Q_{0.500}$	$Q_{0.025}$	$Q_{0.975}$
$P_{\text{inf}}(1)$	Se^-	GI		7.0×10^{-4}	7.9×10^{-6}	4.8×10^{-9}	4.4×10^{-3}
$P_{\text{inf}}(1)$	Se^-	GII		1.5×10^{-2}	2.6×10^{-3}	3.3×10^{-5}	1.2×10^{-1}
$P_{\text{inf}}(1)$	Se^+	GI		2.8×10^{-1}	2.7×10^{-1}	3.1×10^{-2}	5.6×10^{-1}
$P_{\text{inf}}(1)$	Se^+	GII		7.6×10^{-2}	3.5×10^{-2}	1.6×10^{-3}	3.9×10^{-1}
$P_{\text{ill}}(1)$	Se^-	GI	Ch	8.6×10^{-5}	1.5×10^{-7}	2.0×10^{-11}	3.4×10^{-4}
$P_{\text{ill}}(1)$	Se^-	GII	Ch	1.2×10^{-3}	6.4×10^{-5}	3.2×10^{-7}	7.8×10^{-3}
$P_{\text{ill}}(1)$	Se^+	GI	Ch	6.4×10^{-2}	3.3×10^{-2}	1.3×10^{-3}	3.0×10^{-1}
$P_{\text{ill}}(1)$	Se^+	GII	Ch	1.5×10^{-2}	3.8×10^{-3}	4.3×10^{-5}	1.1×10^{-1}
$P_{\text{ill}}(1)$	Se^-	GI	Ob	6.3×10^{-5}	2.7×10^{-7}	2.4×10^{-11}	6.1×10^{-4}
$P_{\text{ill}}(1)$	Se^-	GII	Ob	5.1×10^{-3}	4.7×10^{-4}	2.2×10^{-6}	5.0×10^{-2}
$P_{\text{ill}}(1)$	Se^+	GI	Ob	2.0×10^{-1}	1.7×10^{-1}	8.7×10^{-3}	5.1×10^{-1}
$P_{\text{ill}}(1)$	Se^+	GII	Ob	3.5×10^{-2}	1.2×10^{-2}	8.9×10^{-5}	2.2×10^{-1}

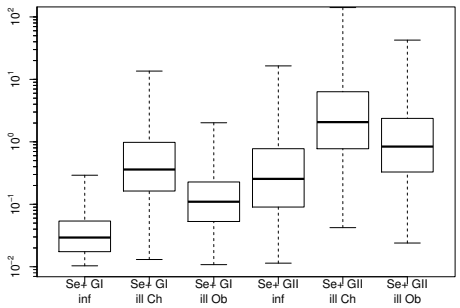
Table A13: Parameter estimates for the dose response models (see Appendix D). Outcomes are given as mean predicted value, median (0.5 quantile: $Q_{0.500}$), and 95% range ($Q_{0.025}$ – $Q_{0.975}$).

				mean	$Q_{0.500}$	$Q_{0.025}$	$Q_{0.975}$
α	Se^-	GI		6.05×10^{-2}	9.20×10^{-6}	1.18×10^{-9}	1.36×10^{-1}
β	Se^-	GI		2.70×10^{1}	3.61×10^{-1}	8.03×10^{-4}	2.22×10^{2}
α	Se^-	GII		1.15×10^{-1}	1.86×10^{-2}	2.54×10^{-4}	5.71×10^{-1}
β	Se^-	GII		1.28×10^{2}	7.75×10^{0}	1.16×10^{-2}	8.93×10^{2}
α	Se^+	GI		9.48×10^{-1}	3.93×10^{-1}	1.44×10^{-2}	4.00×10^{0}
β	Se^+	GI		3.96×10^{0}	7.67×10^{-1}	1.14×10^{-2}	1.62×10^{1}
α	Se^+	GII		7.61×10^{-1}	2.30×10^{-1}	1.23×10^{-2}	5.01×10^{0}
β	Se^+	GII		4.14×10^{1}	5.04×10^{0}	1.05×10^{-1}	3.72×10^{2}
r	Se^-	GI	Ch	4.45×10^{-1}	2.30×10^{-2}	1.04×10^{-5}	3.42×10^{0}
η	Se^-	GI	Ch	5.22×10^{0}	8.32×10^{-2}	1.02×10^{-4}	3.89×10^{1}
r	Se^-	GII	Ch	6.87×10^{-2}	1.58×10^{-2}	3.01×10^{-4}	3.27×10^{-1}
η	Se^-	GII	Ch	1.76×10^{0}	5.68×10^{-2}	5.12×10^{-5}	1.43×10^{1}
r	Se^+	GI	Ch	1.79×10^{-1}	5.14×10^{-2}	3.01×10^{-3}	1.08×10^{0}
η	Se^+	GI	Ch	4.52×10^{-1}	2.54×10^{-2}	3.18×10^{-5}	3.77×10^{0}
r	Se^+	GII	Ch	3.54×10^{-1}	1.19×10^{-1}	6.55×10^{-3}	2.08×10^{0}
η	Se^+	GII	Ch	1.06×10^{1}	2.94×10^{-1}	2.33×10^{-4}	9.99×10^{1}
r	Se^-	GI	Ob	2.22×10^{1}	2.63×10^{-2}	1.86×10^{-5}	7.50×10^{1}
η	Se^-	GI	Ob	3.03×10^{1}	7.88×10^{-2}	5.60×10^{-5}	4.32×10^{1}
r	Se^-	GII	Ob	3.45×10^{1}	4.91×10^{-1}	3.16×10^{-3}	2.35×10^{2}
η	Se^-	GII	Ob	2.63×10^{1}	6.08×10^{-1}	5.77×10^{-4}	2.09×10^{2}
r	Se^+	GI	Ob	5.26×10^{1}	3.19×10^{0}	1.01×10^{-1}	3.91×10^{2}
η	Se^+	GI	Ob	2.81×10^{1}	8.01×10^{-1}	2.29×10^{-3}	1.13×10^{2}
r	Se^+	GII	Ob	5.18×10^{1}	1.50×10^{0}	3.17×10^{-2}	3.73×10^{2}
η	Se^+	GII	Ob	1.13×10^{2}	1.11×10^{0}	1.08×10^{-3}	9.21×10^{2}

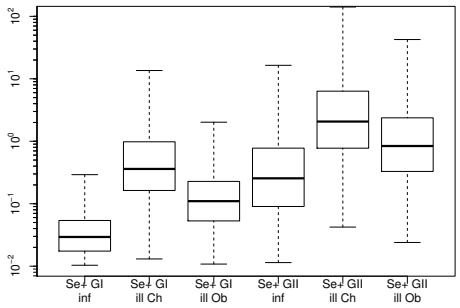
G Additional figures



(a) Se^{-}: ID_1



(b) Se^{+}: ID_1



(c) Se^{+}: ID_1: no aggregates

Figure A1: Dose to achieve 1% infection or illness in secretor–negative subjects (a), same in secretor–positive subjects (b). Dose for 1% illness separately for challenge studies (Ch) and outbreaks (Ob). (c) Estimated ID_1 for infection and illness in secretor–positive subjects, when data from the first experiment (Table A3) are removed. Compare with Figure A1b.

H Use in risk modelling

Posterior estimates of dose response parameters, as represented in the contour graphs in Figure 6, are characterized as a sample from a bivariate normal distribution

$$\begin{array}{l}(w_1(\text{ss}), z_1(\text{gg})) \sim N(\boldsymbol{\mu}_1(\text{ss}, \text{gg}), \boldsymbol{\Sigma}_1(\text{ss}, \text{gg})) \\ (w_2(\text{ss}), z_2(\text{gg})) \sim N(\boldsymbol{\mu}_2(\text{ss}, \text{gg}), \boldsymbol{\Sigma}_2(\text{ss}, \text{gg}))\end{array} \tag{A.12}$$

for infection and illness, respectively. Estimates for the mean vector

$$\boldsymbol{\mu} = \begin{pmatrix} \text{mean}(w) \\ \text{mean}(z) \end{pmatrix}$$

and the covariance matrix

$$\boldsymbol{\Sigma} = \begin{pmatrix} \text{var}(w) & \text{cov}(w, z) \\ \text{cov}(w, z) & \text{var}(z) \end{pmatrix}$$

can be found in Table A14. Using those estimates, it is trivial to generate (w, z) pairs for any combination of secretor status and genogroup as a bivariate normal random sample.

Then, for infection parameters

$$\begin{array}{ll} u_1 = \frac{\mathrm{e}^{w_1}}{1+\mathrm{e}^{w_1}}; & v_1 = \mathrm{e}^{z_1} \\ \alpha = v_1 u_1; & \beta = v_1(1-u_1) \end{array} \tag{A.13}$$

and for illness parameters

$$\begin{array}{ll} u_2 = \frac{\mathrm{e}^{w_2}}{1+\mathrm{e}^{w_2}}; & v_2 = \mathrm{e}^{z_2} \\ r = v_2 u_2; & \eta = v_2(1-u_2) \end{array} \tag{A.14}$$

so that a sample of (α, β) and (r, η) pairs is obtained for any secretor status or genogroup combination.

Table A14: Parameter estimates: multivariate normal parameters, provided for risk modellers who want to create posterior predictive parameters samples, see **?** for more information. Outcomes are given as mean predicted value, median (0.5 quantile: $Q_{0.500}$), and 95% range ($Q_{0.025} - Q_{0.975}$).

		mean(w)	mean(z)	var(w)	cov(w, z)	var(z)
Infection						
Se^-	GI	-1.06×10^{1}	-9.76×10^{-1}	9.30×10^{0}	4.28×10^{-1}	1.07×10^{1}
Se^-	GII	-5.79×10^{0}	1.80×10^{0}	5.04×10^{0}	-4.64×10^{0}	7.95×10^{0}
Se^+	GI	-6.08×10^{-1}	1.94×10^{-1}	1.79×10^{0}	-1.03×10^{0}	2.54×10^{0}
Se^+	GII	-3.16×10^{0}	1.82×10^{0}	2.88×10^{0}	-2.01×10^{0}	3.64×10^{0}
Illness, Challenge						
Se^-	GI	-1.66×10^{0}	-1.73×10^{0}	1.03×10^{1}	-1.38×10^{0}	8.08×10^{0}
Se^-	GII	-1.27×10^{0}	-2.15×10^{0}	9.16×10^{0}	-4.33×10^{0}	5.11×10^{0}
Se^+	GI	9.26×10^{-1}	-2.07×10^{0}	7.26×10^{0}	-2.14×10^{0}	3.06×10^{0}
Se^+	GII	-6.60×10^{-1}	-4.36×10^{-1}	8.34×10^{0}	-4.30×10^{0}	4.69×10^{0}
Illness, Outbreaks						
Se^-	GI	-9.19×10^{-1}	-1.63×10^{0}	1.09×10^{1}	-4.63×10^{-1}	1.08×10^{1}
Se^-	GII	1.27×10^{-2}	7.20×10^{-1}	7.13×10^{0}	-1.27×10^{0}	8.09×10^{0}
Se^+	GI	1.74×10^{0}	1.82×10^{0}	5.55×10^{0}	-7.08×10^{-1}	4.64×10^{0}
Se^+	GII	4.14×10^{-1}	1.73×10^{0}	7.76×10^{0}	-1.67×10^{0}	6.19×10^{0}

I Source code

R code to collect literature data and prepare R objects for transfer to JAGS.

```
## Human volunteer data

# The first two sets are empty data, for prediction purposes
challenge.1 <- list(genotype="G1",
                    se=c(0,1),
                    qty=c(1,1),
                    qty.rn=c(NA,NA),
                    conc.g1=c(1e3,rep(NA,4)),
                    conc.g2=rep(NA,5),
                    expos=c(1,1),
                    infec=c(NA,NA),
                    sympt=c(NA,NA));
challenge.2 <- list(genotype="G2",
                    se=c(0,1),
                    qty=c(1,1),
                    qty.rn=c(NA,NA),
                    conc.g1=rep(NA,5),
                    conc.g2=c(1e3,rep(NA,4)),
                    expos=c(1,1),
                    infec=c(NA,NA),
                    sympt=c(NA,NA));

# Teunis et al. (2008) Norwalk virus: How infectious is it?
# Journal of Medical Virology 80(8):1468-1476
challenge.3 <- list(genotype="G1.1-8FIIa",
                    se=c(rep(0,2),rep(1,8),rep(0,2),rep(1,9),
                         rep(0,6),rep(1,9),rep(0,1),rep(1,3),
                         rep(0,2),rep(1,8),rep(0,3),rep(1,7),
                         rep(0,2),rep(1,3),rep(0,4),rep(1,6)),
                    qty=c(rep(1e-6,10),rep(1e-5,11),
                          rep(1e-4,15),rep(1e-3,4),
                          rep(1e-1,10),rep(1e0,10),
                          rep(1e1,5),rep(1e2,10)), # aggregated
                    qty.rn=c(NA,NA),
                    conc.g1=c(3.24e7,rep(NA,4)),
                    conc.g2=rep(NA,5),
                    expos=rep(1,75),
                    infec=c(rep(0,2),rep(0,8),rep(0,2),rep(0,9),
                            rep(0,6),rep(0,6),rep(1,3),rep(0,1),
                            rep(0,1),rep(1,2),rep(0,2),rep(0,1),
                            rep(1,7),rep(0,3),rep(0,4),rep(1,3),
                            rep(0,2),rep(0,1),rep(1,2),rep(0,4),
                            rep(0,1),rep(1,5)),
                    sympt=c(rep(0,2),rep(0,8),rep(0,2),rep(0,9),
                            rep(0,6),rep(0,8),rep(1,1),rep(0,1),
                            rep(0,2),rep(1,1),rep(0,2),rep(0,2),
                            rep(1,6),rep(0,3),rep(0,6),rep(1,1),
                            rep(0,2),rep(0,1),rep(1,2),rep(0,4),
                            rep(0,2),rep(1,4)));
challenge.4 <- list(genotype="G1.1-8FIIb",
                    se=c(rep(0,2),rep(1,8),rep(0,4),rep(1,18),
                         rep(1,1)),
                    qty=c(rep(1e0,10),rep(1e1,22),
                          rep(3e1,1)), # disaggregated
                    qty.rn=c(NA,NA),
                    conc.g1=c(6.92e5,rep(NA,4)),
                    conc.g2=rep(NA,5),
                    expos=rep(1,33),
                    infec=c(rep(0,2),rep(0,5),rep(1,3),rep(0,4),
                            rep(0,4),rep(1,14),rep(1,1)),
                    sympt=c(rep(0,2),rep(0,6),rep(1,2),rep(0,4),
                            rep(0,11),rep(1,7),rep(NA,1)));
# Dolin et al. 1982: Detection by immune electron microscopy of the
# Snow Mountain agent of acute viral gastroenteritis.
# Journal of Infectious Diseases 146(2):184-189.
challenge.5 <- list(genotype="G2.2: SMV",
                    se=c(rep(1,2),rep(1,2),rep(1,2),rep(0,1),
                         rep(1,3),rep(1,2)),
                    # se=c(rep(NA,2),rep(NA,2),rep(NA,2),rep(NA,1),
                    #      rep(NA,3),rep(NA,2)),
                    qty=c(rep(1,2),rep(10,2),rep(100,2),rep(500,4),
                          rep(1000,2)),
                    qty.rn=c(NA,NA),
                    conc.g1=rep(NA,5),
                    conc.g2=c(3.17e3,rep(NA,4)),
                    expos=c(rep(1,2),rep(1,2),rep(1,2),rep(1,4),
                            rep(1,2)),
                    infec=c(rep(0,2),rep(1,2),rep(1,2),rep(0,1),
                            rep(1,3),rep(1,2)),
```

```
                    sympt=c(rep(0,2),rep(1,2),rep(1,2),rep(0,1),
                            rep(1,3),rep(1,2)));
# Chapel Hill SMV challenge study
challenge.6 <- list(genotype="G2.2: SMV",
                    se=c(rep(0,1),rep(1,4),rep(0,1),rep(1,4),
                         rep(0,1),rep(1,4)),
                    qty=c(rep(1e-2,1),rep(1e-2,4),rep(1,1),rep(1,4),
                          rep(1e2,1),rep(1e2,4)),
                    qty.rn=c(NA,NA),
                    conc.g1=rep(NA,5),
                    conc.g2=c(3.17e3,rep(NA,4)),
                    expos=c(rep(1,1),rep(1,4),rep(1,1),rep(1,4),
                            rep(1,1),rep(1,4)),
                    infec=c(rep(0,1),rep(0,4),rep(0,1),rep(1,4),
                            rep(1,1),rep(1,4)),
                    sympt=c(rep(0,1),rep(0,4),rep(0,1),rep(0,1),
                            rep(1,3),rep(1,1),rep(0,1),rep(1,3)));
# Atmar et al (2014) Determination of the 50% human infectious dose
# for Norwalk virus.
# Journal of Infectious Diseases 209(7):1016-1022
challenge.7 <- list(genotype="G1.1",
                    se=c(rep(0,2),rep(1,7),rep(0,2),rep(1,8),
                         rep(0,1),rep(1,13),rep(0,3),rep(1,13)),
                    qty=c(rep(4800,9),rep(48,10),rep(4.8,14),
                          rep(0.48,16)),
                    qty.rn=c(NA,NA),
                    conc.g1=c(400,rep(NA,4)),
                    conc.g2=rep(NA,5),
                    expos=rep(1,49),
                    infec=c(rep(0,2),rep(0,1),rep(1,6),
                            rep(0,2),rep(0,1),rep(1,7),
                            rep(0,1),rep(0,6),rep(1,7),
                            rep(0,3),rep(0,12),rep(1,1)),
                    sympt=c(rep(0,2),rep(0,3),rep(1,4),
                            rep(0,2),rep(0,4),rep(1,4),
                            rep(0,1),rep(0,8),rep(1,5),
                            rep(0,3),rep(0,12),rep(1,1)));
# Frenck et al (2012) Predicting susceptibility to norovirus GII.4
# by use of a challenge model involving humans
# Journal of Infectious Diseases 206(9):1386-1393
challenge.8 <- list(genotype="G2.4",
                    se=c(rep(0,17),rep(1,23)),
                    qty=rep(1,40),
                    qty.rn=c(NA,NA),
                    conc.g1=rep(NA,5),
                    conc.g2=c(5.0e4,rep(NA,4)),
                    expos=rep(1,40),
                    infec=c(rep(0,16),rep(1,1),
                            rep(0,7),rep(1,16)),
                    sympt=c(rep(0,16),rep(0,1),
                            rep(0,10),rep(1,13)));
# Bernstein et al (2015) Norovirus Vaccine Against Experimental Human
# GII.4 Virus Illness: A Challenge Study in Healthy Adults.
# Journal of Infectious Diseases 211:870-878
challenge.9 <- list(genotype="G2.4",
                    se=rep(1,48),
                    qty=rep(1,48),
                    qty.rn=c(NA,NA),
                    conc.g1=rep(NA,5),
                    conc.g2=c(4.4e3,rep(NA,4)),
                    expos=rep(1,48),
                    infec=c(rep(1,30),rep(0,18)),
                    sympt=c(rep(1,18),rep(0,30)));

# Seitz et al. (2011)
challenge.10 <- list(genotype="G1.1-8FIIb",
                    se=rep(1,20),
                    qty=rep(1e3,20),
                    qty.rn=c(NA,NA),
                    conc.g1=c(6.92e5,rep(NA,4)),
                    conc.g2=rep(NA,5),
                    expos=rep(1,20),
                    infec=c(rep(0,10),rep(1,10)),
                    sympt=c(rep(0,10),rep(0,4),rep(1,6)));

# Leon et al. (2011)
challenge.11 <- list(genotype="G2.1-8FIIb",
                    se=rep(1,15),
                    qty=rep(3.33e2,15),
                    qty.rn=c(NA,NA),
                    conc.g1=c(6.92e5,rep(NA,4)),
                    conc.g2=rep(NA,5),
                    expos=rep(1,15),
                    infec=c(rep(0,8),rep(1,7)),
```

```
                    sympt=c(rep(0,8),rep(NA,7)));

# Wyatt et al (1974) Comparison of three agents of acute infectious
# nonbacterial gastroenteritis by cross-schallenge in volunteers.
# Journal of Infectious Diseases 129(6):709-714
challenge.12 <- list(genotype="G2.1",
                    se=rep(NA,23),
                    qty=rep(4e3,23),
                    qty.rn=c(NA,NA),
                    conc.g1=rep(NA,5),
                    conc.g2=c(1.24e6,rep(NA,4)),
                    expos=rep(1,23),
                    infec=rep(NA,23),
                    sympt=c(rep(1,11),rep(0,12)));

# Levy et al (1976) Jejunal adenylate cyclase activity in human
# subjects during viral gastroenteritis.
# Gastroenterology 70:321-325
challenge.13 <- list(genotype="G2.1",
                    se=rep(NA,7),
                    qty=rep(4e3,7),
                    qty.rn=c(NA,NA),
                    conc.g1=rep(NA,5),
                    conc.g2=c(1.24e6,rep(NA,4)),
                    expos=rep(1,7),
                    infec=rep(NA,7),
                    sympt=c(rep(1,4),rep(0,3)));

# Meeroff et al (1980) Abnormal gastric motor function in viral
# gastroenteritis.
# Annals of Internal Medicine 92(3):370-373
challenge.14 <- list(genotype="G2.1",
                    se=rep(NA,3),
                    qty=rep(3e3,3),
                    qty.rn=c(NA,NA),
                    conc.g1=rep(NA,5),
                    conc.g2=c(1.24e6,rep(NA,4)),
                    expos=rep(1,3),
                    infec=rep(NA,3),
                    sympt=c(rep(1,1),rep(0,2)));

# Treanor et al (1988) Development of en enzyme immunoassay for the
# Hawaii agent of virual gastroenteritis.
# Journal of Virological Methods 22(2-3):207-214
challenge.15 <- list(genotype="G2.1",
                    se=rep(NA,10),
                    qty=rep(1e3,10),
                    qty.rn=c(NA,NA),
                    conc.g1=rep(NA,5),
                    conc.g2=c(1.24e6,rep(NA,4)),
                    expos=rep(1,10),
                    infec=rep(NA,10),
                    sympt=c(rep(1,8),rep(0,2)));

# Chapel Hill Hawaii virus challenge study
challenge.16 <- list(genotype="G2.1",
                    se=c(rep(0,1),rep(1,1)),
                    qty=c(rep(5e3,1),rep(5e3,1)),
                    qty.rn=c(NA,NA),
                    conc.g1=rep(NA,5),
                    conc.g2=c(1.24e6,rep(NA,4)),
                    expos=c(rep(1,1),rep(1,1)),
                    infec=c(rep(1,1),rep(1,1)),
                    sympt=c(rep(0,1),rep(1,1)));

## Outbreak data

# The first two sets are empty, for prediction purposes
outbreak.1 <- list(genotype="G1",
                   se=c(0,1),
                   qty=c(4,4),
                   qty.rn=c(4,6),
                   conc.g1=c(1e3,rep(NA,4)),
                   conc.g2=rep(NA,5),
                   expos=c(1,1),
                   infec=c(NA,NA),
                   sympt=c(NA,NA));
outbreak.2 <- list(genotype="G2",
                   se=c(0,1),
                   qty=c(4,4),
                   qty.rn=c(4,6),
                   conc.g1=rep(NA,5),
                   conc.g2=c(1e3,rep(NA,4)),
                   expos=c(1,1),
```

```
                  infec=c(NA,NA),
                  sympt=c(NA,NA));

# Thebault et al. (2013) Infectivity of GI and GII noroviruses
# established from oyster related outbreaks.
# Epidemics 5(2):98-110
outbreak.3 <- list(genotype="G2.4",
                  se=c(rep(0,6),rep(1,27),NA),
                  qty=c(3,4,3,4,6,3,4,3,3,4,3,2,3,3,6,3,3,3,6,3,
                        3,3,2,3,3,3,3,6,6,3,2,NA,3,3),
                  qty.rn=c(2,6),
                  conc.g1=rep(NA,5),            # G1
                  conc.g2=c(18,955,37.75,0,NA), # G2
                  expos=rep(1,34),
                  infec=rep(NA,34),
                  sympt=c(0,0,0,0,1,0,1,1,1,1,0,1,0,0,0,1,1,1,1,1,
                          1,0,1,1,1,1,1,1,1,1,1,1,0,1));
outbreak.4 <- list(genotype="G2.4, G2.8, G2.4, G2.9, G1.4",
                  se=rep(NA,36),
                  qty=rep(NA,36),
                  qty.rn=c(1,6),
                  conc.g1=c(125,NA,NA,NA,NA),   # G1
                  conc.g2=c( 25,25,NA,NA,NA),   # G2
                  expos=rep(1,36),
                  infec=rep(NA,36),
                  sympt=c(rep(1,21),rep(0,15)));
outbreak.5 <- list(genotype="G1.1",
                  se=rep(NA,4),
                  qty=c(7,9,9,18),
                  qty.rn=c(7,18),
                  conc.g1=c(85,237,NA,NA,NA),   # G1
                  conc.g2=rep(NA,5),            # G2
                  expos=rep(1,4),
                  infec=rep(NA,4),
                  sympt=rep(1,4));
outbreak.6 <- list(genotype="G1",
                  se=rep(NA,2),
                  qty=rep(NA,2),
                  qty.rn=c(4,6),
                  conc.g1=c(275,6783,NA,NA,NA), # G1
                  conc.g2=rep(NA,5),            # G2
                  expos=rep(1,2),
                  infec=rep(NA,2),
                  sympt=rep(1,2));
outbreak.7 <- list(genotype="G1, G2",
                  se=rep(NA,27),
                  qty=rep(NA,27),
                  qty.rn=c(4,6),
                  conc.g1=c(2300,NA,NA,NA,NA),  # G1
                  conc.g2=c(1100,NA,NA,NA,NA),  # G2
                  expos=rep(1,27),
                  infec=rep(NA,27),
                  sympt=c(rep(1,11),rep(0,16)));

# Le Guyader (2018)
outbreak.8 <- list(genotype="G1, G2",
                  se=rep(NA,6),
                  qty=rep(NA,6),
                  qty.rn=c(4,6),
                  conc.g1=c(1090,295,NA,NA,NA),  # G1
                  conc.g2=c(1210,132,NA,NA,NA),  # G2
                  expos=rep(1,6),
                  infec=rep(NA,6),
                  sympt=rep(1,6));
outbreak.9 <- list(genotype="G1",
                  se=rep(NA,9),
                  qty=rep(NA,9),
                  qty.rn=c(4,6),
                  conc.g1=c(446,NA,NA,NA,NA),   # G1
                  conc.g2=c(NA,NA,NA,NA,NA),    # G2 ??????? (non detect)
                  expos=rep(1,9),
                  infec=rep(NA,9),
                  sympt=rep(1,9));
outbreak.10 <- list(genotype="G1, G2",
                  se=rep(NA,79),
                  qty=rep(NA,79),
                  qty.rn=c(4,6),
                  conc.g1=c(119,819,71,30,132),    # G1
                  conc.g2=c(376,1250,30,NA,NA),    # G2
                  expos=rep(1,79),
                  infec=rep(NA,79),
                  sympt=c(rep(1,22),rep(0,57)));
outbreak.11 <- list(genotype="G1",
                  se=rep(NA,8),
```

```
                  qty=rep(NA,8),
                  qty.rn=c(4,6),
                  conc.g1=c(68,NA,NA,NA,NA),    # G1
                  conc.g2=rep(NA,5),            # G2
                  expos=rep(1,8),
                  infec=rep(NA,8),
                  sympt=c(rep(1,5),rep(0,3)));
outbreak.12 <- list(genotype="G1, G2",
                  se=rep(NA,4),
                  qty=rep(NA,4),
                  qty.rn=c(4,6),
                  conc.g1=c(22,rep(NA,4)),      # G1
                  conc.g2=c(22,rep(NA,4)),      # G2
                  expos=rep(1,4),
                  infec=rep(NA,4),
                  sympt=rep(1,4));

hstnam  <- c("challenge","outbreak");
stnum   <- c( 1, 2, 3, 4, 5, 6, 7, 8, 9,10,11,12,13,14,15,16,
              1, 2, 3, 4, 5, 6, 7, 8, 9,10,11,12);
expnum  <- c( 1, 2, 3, 4, 5, 6, 7, 8, 9,10,11,12,13,14,15,16,
            17,18,19,20,21,22,23,24,25,26,27,28);
strains <- c(15,16, 1, 1, 2, 2, 1, 3, 3, 1, 1, 4, 4, 4, 4, 4,
             17,18,5, 6, 7, 8, 9,10,11,12,13,14);
hosts   <- c( 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,
              2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2);
n.dose  <- c( 2, 2,75,33,12,15,49,40,48,20,15,23, 7, 3,10, 2,
              2, 2,34,36, 4, 2,27, 6, 9,79, 8, 4);
n.challenge <- 2 + 14;
typ <- c(); se <- c(); intk <- c(); intk.rn <- c();
conc <- array(NA,dim=c(max(expnum),2,5));
expos <- c(); infec <- c(); sympt <- c(); exn <- c();
stnam <- c(); obn <- c();
for(k in 1:length(n.dose)){
  typ <- c(typ,rep(strains[k],n.dose[k]));
  stn <- eval(parse(text=paste(hstnam[hosts[k]],".",stnum[k],sep="")))$genotype;
  exn <- c(exn,rep(expnum[k],n.dose[k]));
  qty <- eval(parse(text=paste(hstnam[hosts[k]],".",stnum[k],sep="")))$qty;
  qrn <- eval(parse(text=paste(hstnam[hosts[k]],".",stnum[k],sep="")))$qty.rn;
  cg1 <- eval(parse(text=paste(hstnam[hosts[k]],".",stnum[k],sep="")))$conc.g1;
  cg2 <- eval(parse(text=paste(hstnam[hosts[k]],".",stnum[k],sep="")))$conc.g2;
  exs <- eval(parse(text=paste(hstnam[hosts[k]],".",stnum[k],sep="")))$expos;
  ses <- eval(parse(text=paste(hstnam[hosts[k]],".",stnum[k],sep="")))$se;
  inf <- eval(parse(text=paste(hstnam[hosts[k]],".",stnum[k],sep="")))$infec;
  smp <- eval(parse(text=paste(hstnam[hosts[k]],".",stnum[k],sep="")))$sympt;
  stnam <- c(stnam,stn);
  intk <- c(intk,qty[1:n.dose[k]]);
  intk.rn <- rbind(intk.rn,as.vector(qrn));
  conc[k,1,] <- as.vector(cg1);
  conc[k,2,] <- as.vector(cg2);
  se <- c(se,ses[1:n.dose[k]]);
  expos <- c(expos,exs[1:n.dose[k]]);
  infec <- c(infec,inf[1:n.dose[k]]);
  sympt <- c(sympt,smp[1:n.dose[k]]);
}
aggr <- rep(0,length(exn));
aggr[exn==3] <- 1;
n.ch <- length(which(exn<=n.challenge));
n.ob <- max(exn)-n.challenge;
last <- length(exn);

n.conc <- array(NA,dim=c(max(exn),2));
for(k.exp in 1:max(exn)){
  for(k.gg in 1:2){
    n.conc[k.exp,k.gg] <- length(which(!is.na(conc[k.exp,k.gg,])));
  }
}

do.ch <- which(exn<=n.challenge & exn>2);
do.ob <- which(exn > n.challenge+2);
gg <- array(1,dim=c(last,2));
for(k in 1:last){
  if(n.conc[exn[k],1]==0) gg[k,1] <- 0;
  if(n.conc[exn[k],2]==0) gg[k,2] <- 0;
}
gx <- gg[,1]*1+gg[,2]*2;
n.se <- 2; # Se+, Se-
n.gg <- 2; # GG1, GG2
n.ep <- 3; # infected, symptoms challenge, symptoms outbreak
sep <- exn; sep[sep<=n.challenge] <- 2; sep[sep>n.challenge] <- 3;

se.init <- rep(NA,last);
for(k in 1:last){
  if(is.na(se[k]) & !is.na(infec[k])) se.init[k] <- infec[k];
```

```
  if(is.na(se[k]) & is.na(infec[k])) se.init[k] <- sympt[k];
}

# [host,endpoint,(mu,tau)]
# [1,1,1],[2,1,1],[1,2,1],[2,2,1],[1,1,2],[2,1,2],[1,2,2],[2,2,2]
prior.w <- array(c(rep(-1,12),rep(0.1,12)),dim=c(n.se,n.gg,3,2));
prior.w[2,,1,2] <- 0.1;
prior.w[1,,1,1] <- -10;
prior.z <- array(c(rep(-1,12),rep(0.1,12)),dim=c(n.se,n.gg,3,2));
tau.w <- rbind(c(1,1,1),c(1,1,1))*1;
tau.z <- rbind(c(1,1,1),c(1,1,1))*1;

prior.rho.a <- c(6,1e3);
prior.rho.c <- c(4,10);
prior.lambda.c <- c(4,1e3);
prior.se <- c(79,19);

conc[n.challenge+3,2,4] <- NA;

drdata <- list("prior.w"=prior.w,"tau.w"=tau.w,
               "prior.z"=prior.z,"tau.z"=tau.z,
               "prior.rho.a"=prior.rho.a,
               "prior.rho.c"=prior.rho.c,
               "prior.lambda.c"=prior.lambda.c,
               "prior.se"=prior.se,
               "do.ch"=do.ch,"do.ob"=do.ob,
               "n.gg"=n.gg,"gg"=gg,"gx"=gx,"n.tp"=max(typ),"typ"=typ,
               "n.exp"=max(exn),"exn"=exn,"ch.exp"=n.challenge,
               "n.conc"=n.conc,"conc"=conc,"intk.rn"=intk.rn,
               "n.se"=n.se,"se"=se,"aggr"=aggr,"sep"=sep,
               "intk"=intk,"expos"=expos,"infec"=infec,
               "sympt"=sympt);

drinit <- list("se"=se.init);
```

JAGS code defining the multilevel dose response model.

```
model{
  # parent nodes: hyperparameters
  for(k.se in 1:n.se){
    for(k.gg in 1:n.gg){
      for(k.ep in 1:3){
        mu.w[k.se,k.gg,k.ep] ~ dnorm(prior.w[k.se,k.gg,k.ep,1],
                                     prior.w[k.se,k.gg,k.ep,2]);
        mu.z[k.se,k.gg,k.ep] ~ dnorm(prior.z[k.se,k.gg,k.ep,1],
                                     prior.z[k.se,k.gg,k.ep,2]);
      }
    }
  }
  for(k.tp in 1:n.tp){
    for(k.se in 1:n.se){
      for(k.gg in 1:n.gg){
        for(k.ep in 1:3){
          w[k.tp,k.se,k.gg,k.ep] ~ dnorm(mu.w[k.se,k.gg,k.ep],tau.w[k.se,k.ep]);
          z[k.tp,k.se,k.gg,k.ep] ~ dnorm(mu.z[k.se,k.gg,k.ep],tau.z[k.se,k.ep]);
          u[k.tp,k.se,k.gg,k.ep] <- exp(w[k.tp,k.se,k.gg,k.ep])/
                                    (1+exp(w[k.tp,k.se,k.gg,k.ep]));
          v[k.tp,k.se,k.gg,k.ep] <- exp(z[k.tp,k.se,k.gg,k.ep]);
          a[k.tp,k.se,k.gg,k.ep] <- u[k.tp,k.se,k.gg,k.ep]*
                                    v[k.tp,k.se,k.gg,k.ep];
          b[k.tp,k.se,k.gg,k.ep] <- (1-u[k.tp,k.se,k.gg,k.ep])*
                                    v[k.tp,k.se,k.gg,k.ep];
}
      }
    }
  }
  rho.a ~ dgamma(prior.rho.a[1],prior.rho.a[2]);
  for(k in do.ch) { # all challenge studies
    pse[k] ~ dbeta(prior.se[1],prior.se[2]);
    se[k] ~ dbern(pse[k]);
    # infection
    lambda.agg[k,gx[k]] ~ dgamma(rho.a,rho.a/intk[k]);
    lambda.dis[k,gx[k]] ~ dgamma(1000,1000/intk[k]);
    dose[k,gx[k]] <- ifelse(aggr[k]==1,lambda.agg[k,gx[k]],
                                       lambda.dis[k,gx[k]])*
                     conc[exn[k],gx[k],1];
    num[k,gx[k]] ~ dpois(dose[k,gx[k]]);
    gamma[k,gx[k]] <-
      loggam(a[typ[k],1+se[k],gx[k],1]+b[typ[k],1+se[k],gx[k],1]) -
      loggam(a[typ[k],1+se[k],gx[k],1]+b[typ[k],1+se[k],gx[k],1]+num[k,gx[k]]) +
      loggam(b[typ[k],1+se[k],gx[k],1]+num[k,gx[k]]) -
      loggam(b[typ[k],1+se[k],gx[k],1]);
    prinf[k,gx[k]] <- ifelse(se[k]==0 && gx[k]==1,0,(1-exp(gamma[k,gx[k]])));
    infec[k] ~ dbin(prinf[k,gx[k]],expos[k]);
    # symptoms
    prill[k,gx[k]] <- (1-pow(1+(dose[k,gx[k]]/b[typ[k],1+se[k],gx[k],sep[k]]),
                             -a[typ[k],1+se[k],gx[k],sep[k]]));
    sympt[k] ~ dbin(prill[k,gx[k]],infec[k]);
  }
  for(k.exp in (ch.exp+1):n.exp){ # estimate concentrations in oysters
    for(k.gg in 1:n.gg){
      rho.c[k.exp,k.gg] ~ dgamma(prior.rho.c[1],prior.rho.c[2]);
      lambda.c[k.exp,k.gg] ~ dgamma(prior.lambda.c[1],prior.lambda.c[2]);
      for(k.cnc in 1:n.conc[k.exp,k.gg]){
        conc[k.exp,k.gg,k.cnc] ~
  dgamma(rho.c[k.exp,k.gg],lambda.c[k.exp,k.gg]);
      }
    }
  }
  for(k in do.ob) {
    intk[k] ~ dpois(sqrt(intk.rn[exn[k],1]*intk.rn[exn[k],2]))
              T(intk.rn[exn[k],1],intk.rn[exn[k],2]);
    pse[k] ~ dbeta(prior.se[1],prior.se[2]);
    se[k] ~ dbern(pse[k]);
    for(k.gg in 1:n.gg){
      lambda[k,k.gg] ~ dgamma(rho.c[exn[k],k.gg],lambda.c[exn[k],k.gg]);
      dose[k,k.gg] <- intk[k]*lambda[k,k.gg];
      num[k,k.gg] ~ dpois(dose[k,k.gg]);
      nvr[k,k.gg] <- ifelse(gg[k,k.gg]==0,0,num[k,k.gg]);
      # infection
      gamma[k,k.gg] <-
        loggam(a[typ[k],1+se[k],k.gg,1]+b[typ[k],1+se[k],k.gg,1]) -
        loggam(a[typ[k],1+se[k],k.gg,1]+b[typ[k],1+se[k],k.gg,1]+nvr[k,k.gg]) +
        loggam(b[typ[k],1+se[k],k.gg,1]+nvr[k,k.gg]) -
        loggam(b[typ[k],1+se[k],k.gg,1]);
      prinf[k,k.gg] <- (1-exp(gamma[k,k.gg]));
      # symptoms
      prill[k,k.gg] <- (1-pow(1+(dose[k,k.gg]/b[typ[k],1+se[k],k.gg,sep[k]]),
                              -a[typ[k],1+se[k],k.gg,sep[k]]));
```