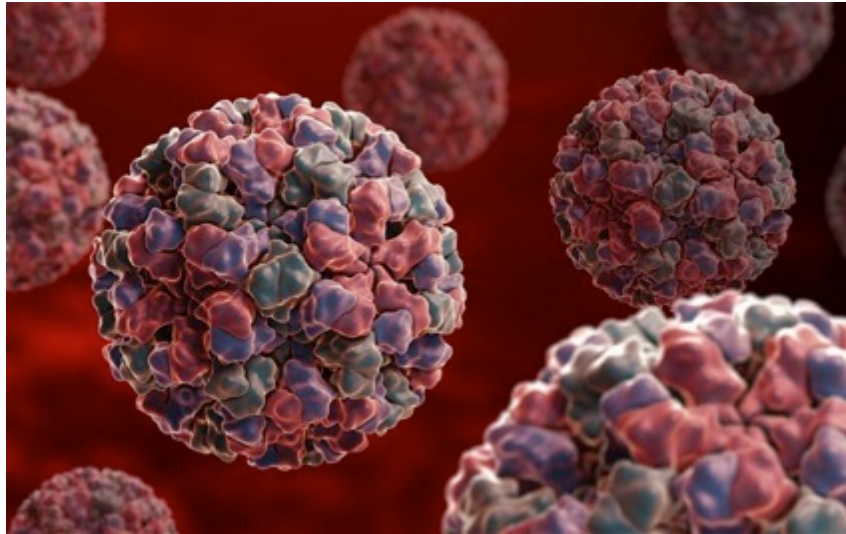


A model for estimating norovirus variability and depuration times



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Industrial Supervisor – Dr Nick Taylor (Cefas)

Motivation

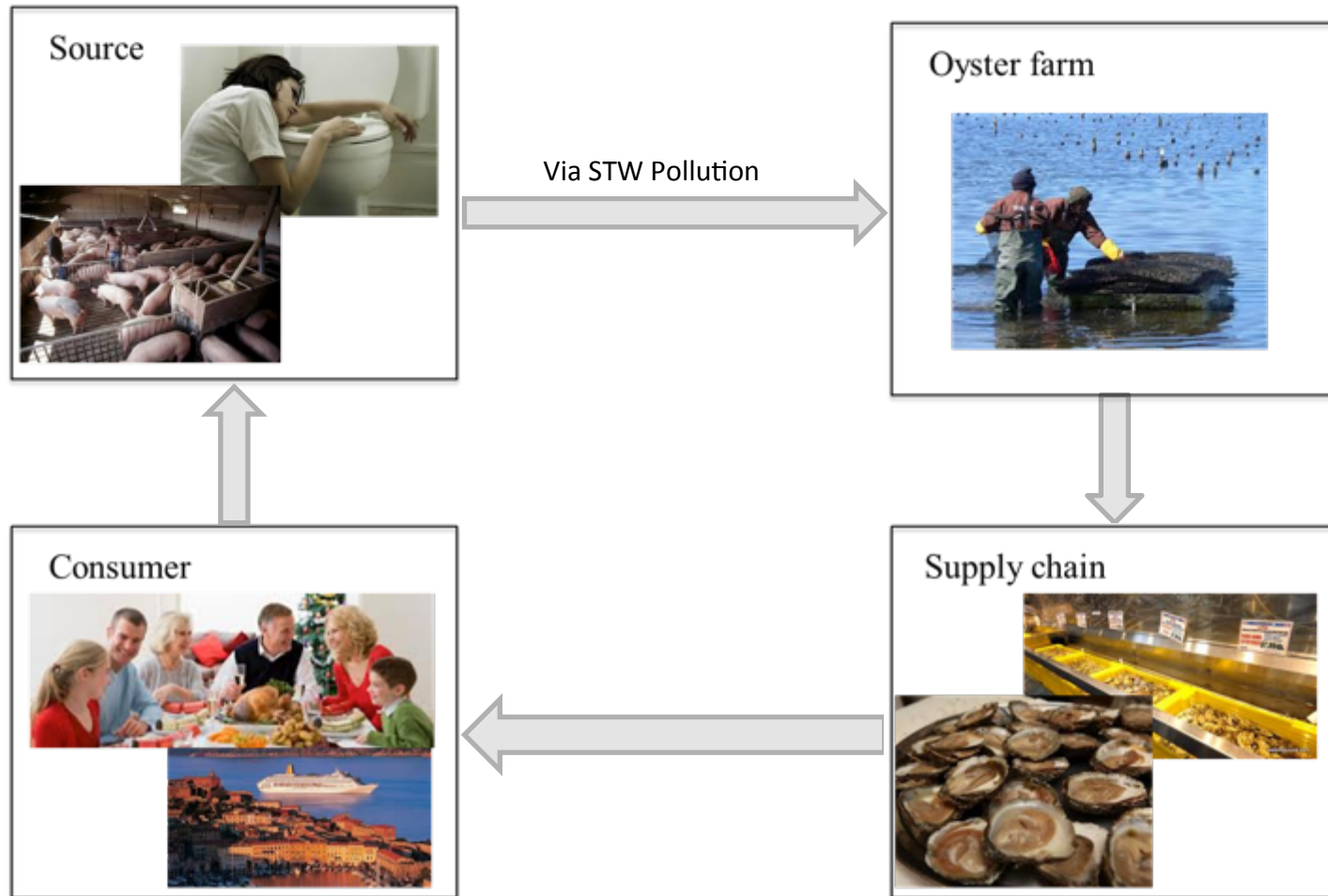
- Assist shellfish industry with norovirus (NoV) reduction
- Constructing a mathematical framework that describes *depuration*
- Provide estimates for optimal depuration times

Reduce NoV in Oysters:



Reduce NoV Outbreaks

Pathogen Dynamics



Depuration Stage

- Oysters are flushed with clean water
- Reduces bacterial (*E. coli*) & particulate contaminants
- Has less impact on viral counts in oysters
- Costs incurred to depurate
- Can reduce oyster quality



Depuration Model Construction

Consider 2 separate aspects of NoV in oysters and combine into 1 model:

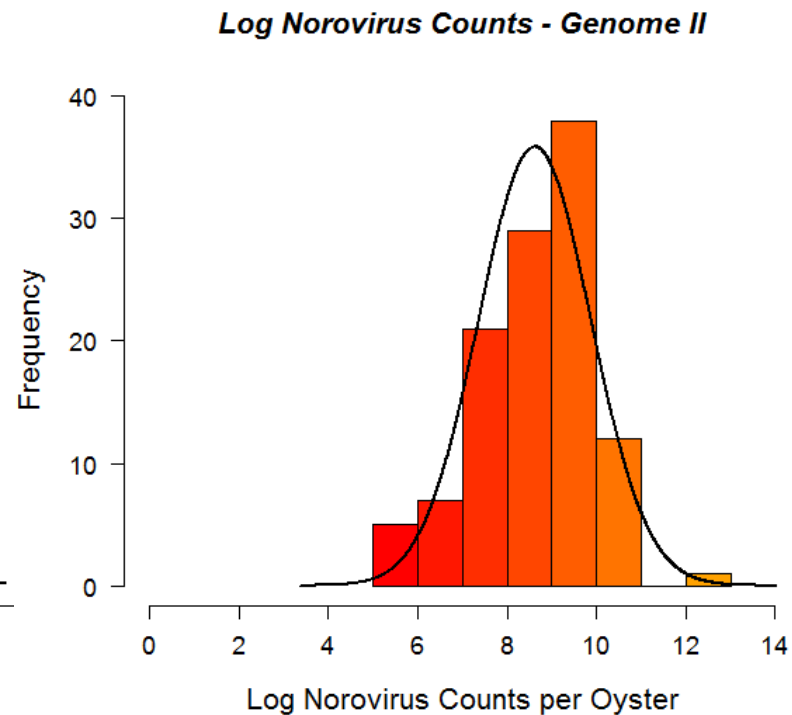
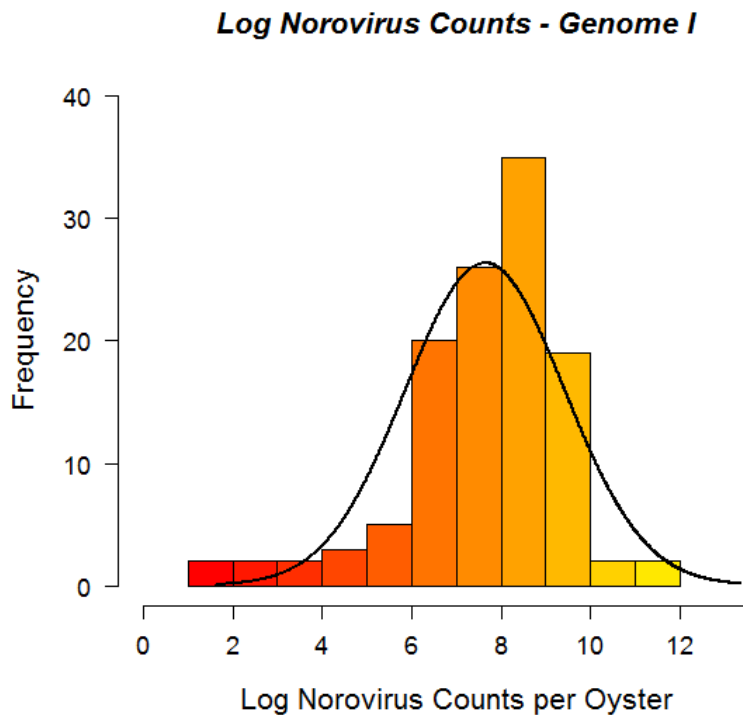
Population's NoV distribution pre-depuration

Depuration effect on population's NoV distribution

Pre-Depuration Model

Use existing pre-Depuration data (courtesy - james.lowther@cefas.co.uk)

- Both genotypes well-described by log-normality



Pre-Depuration Model

- Lognormal probability density function is:

$$P(x \leq 0) = \frac{1}{\sqrt{2\pi} \sigma \leq 0} \frac{1}{x \leq 0} \exp\left(-\frac{(\ln(x \leq 0) - \mu \leq 0))^2}{2\sigma \leq 0^2}\right)$$

- Assume a constant NoV decay rate due to depuration per oyster:

$$x \leq t = x \leq 0 e^{-\lambda t}$$

(depuration decay rate - λ ; NoV load per oyster during depuration - $x \leq t$)

In-Depuration Model

- Vary parameter of $P(x|t)$ with decay rate function to produce In-Depuration Model:

$$P(x|t) = \frac{1}{\sqrt{2\pi}\sigma} x|t \exp\left(-(\ln(x|t) + \lambda t - \mu) / \sigma\right)^2$$

$x|t$ – NoV load per oyster at time t

$P(x|t)$ – likelihood of an oyster having a specific NoV load

σ – standard deviation of log- $x|t$ data

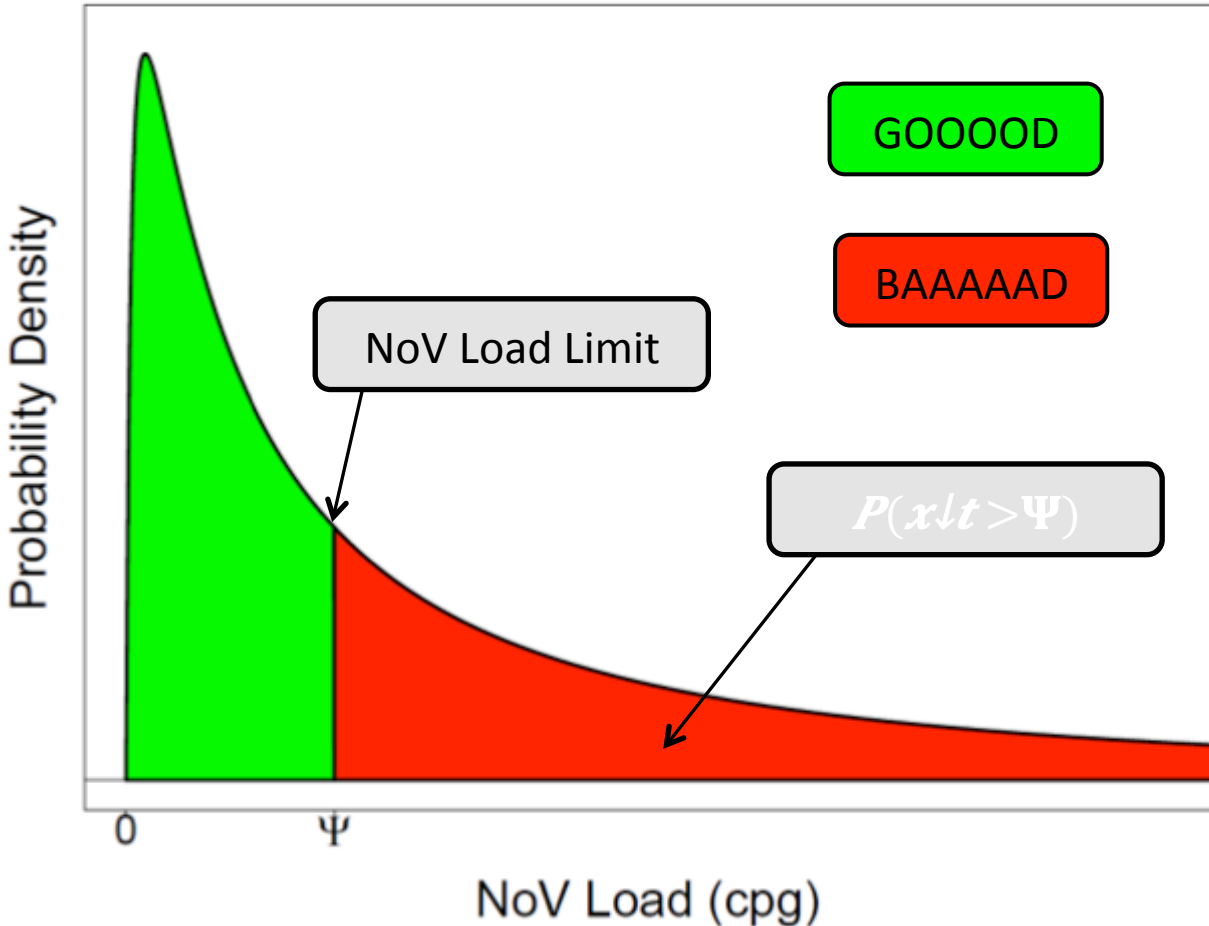
μ – mean of log- $x|t$ data

λ – Decay rate of NoV load per oyster due to depuration

t – Time into depuration process

NoV Load Threshold Limit

- Do
- In
- (Ψ)



y)

mit

Minimum Depuration Time

Assign a second threshold (ϕ) as likelihood that a random oyster has NoV load below NoV load limit Ψ :

$$P(x \leq t > \Psi) = \int_{\Psi}^{\infty} \frac{1}{\sqrt{2\pi\sigma^2}} x \exp(-(\ln(x) + \lambda t - \mu)^2 / 2\sigma^2) dx = 1 - \phi$$

Now solve for time t :

$$t = T(\mu, \sigma) = \lambda^{-1} (\sqrt{2} \sigma \operatorname{erf}^{-1}(2\phi - 1) - \ln(\Psi) + \mu)$$

$T(\mu, \sigma)$ - Minimum depuration time required to reduce NoV loads in oyster population to within acceptable levels

Practicalities of the Model

- Are current test protocols compatible with In-Depuration model?
- How do we estimate NoV variability ($\sigma \downarrow 0$)?
- In-Depuration model provides solutions to both questions...

Compatibility & Practicality

- Current NoV test provides :
 - 10-oyster homogenates pre-Depuration
 - average of 10 oysters from 1 site (\bar{x})
- For log-normal distribution, arithmetic average (\bar{x}) is related to μ by:

$$\mu = \ln(\bar{x}) - \sigma^2 / 2$$

Variability Estimation - 1

Minimum Depuration Time equation can be rewritten as

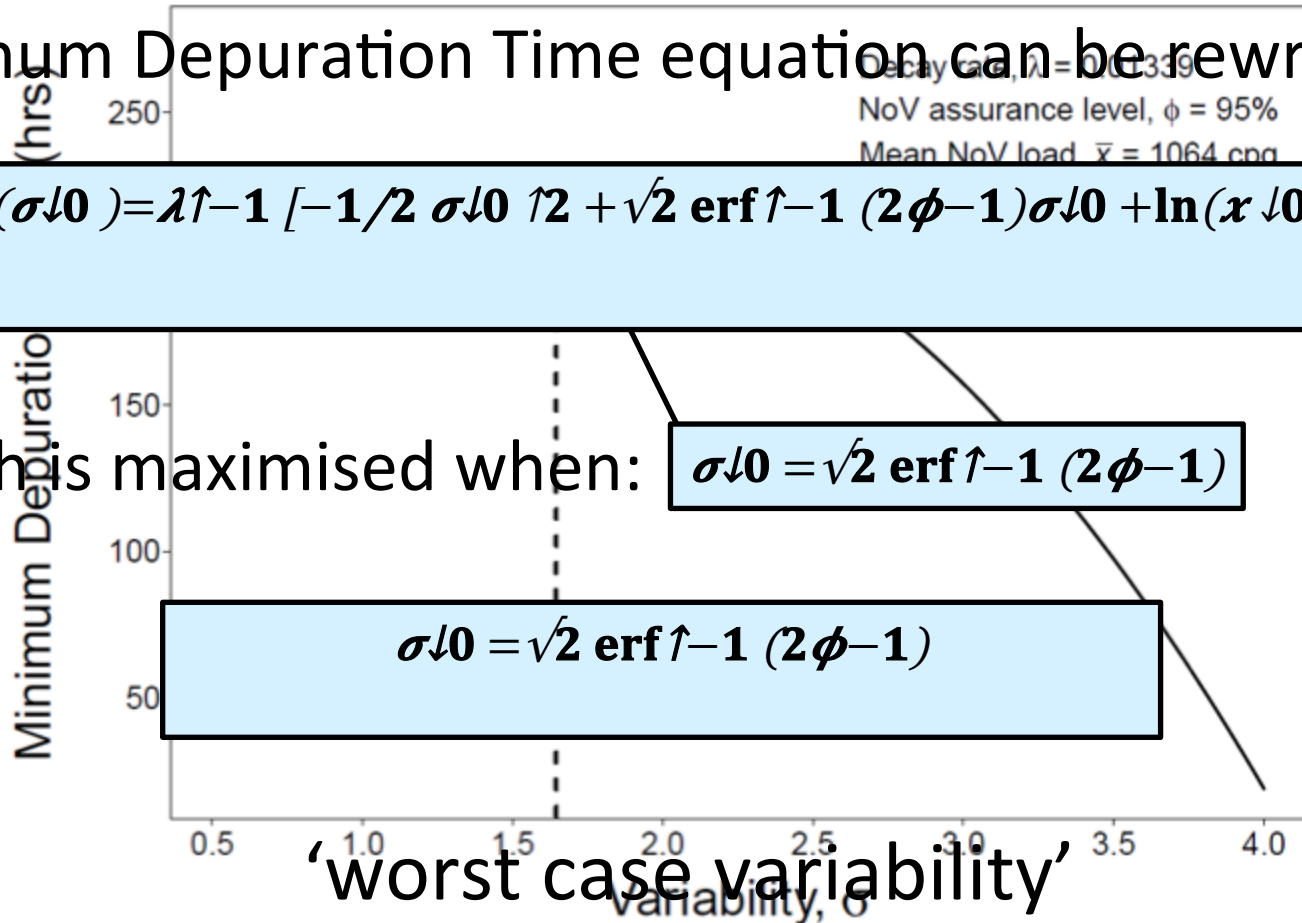
$$T(\sigma) = \lambda^{-1} \left[-\frac{1}{2} \sigma^2 + \sqrt{2} \operatorname{erf}^{-1}(2\phi - 1) \sigma + \ln(x / \Psi) \right]$$

which is maximised when:

$$\sigma = \sqrt{2} \operatorname{erf}^{-1}(2\phi - 1)$$

$$\sigma = \sqrt{2} \operatorname{erf}^{-1}(2\phi - 1)$$

‘worst case variability’



Variability Estimation – 2

Substituting worst case variability into $T(\sigma \downarrow 0)$:

$$T_{\downarrow WCV} = \lambda^{-1} [(\text{erf}^{-1}(\sqrt{2\phi - 1}))^2 + \ln(x \downarrow 0 / \Psi)]$$

$T_{\downarrow WCV}$ - Minimum depuration time using estimated worst case variability

Parameters of Model

Minimum depuration time can be calculated independent of NoV variability and uses only 4 parameters:

$x \downarrow 0$ – measured by current testing

λ – current study by FSA/SSA Ltd

Ψ – Will be legislated for by EU

ϕ – NoV assurance level (may be legislated for)

Minimum Depuration Times using literature-derived parameters

	$\phi=75\%$	$\phi=80\%$	$\phi=85\%$	$\phi=90\%$	$\phi=95\%$	$\phi=99\%$
$\lambda=0.0134$	142	151	165	186	226	327
$\lambda+10\%$	129	138	150	169	205	297
$\lambda+25\%$	113	121	132	149	181	262
$\lambda+50\%$	95	101	110	124	151	218
$\lambda+100\%$	71	76	82	93	113	163

(Time in hours)

Parameters derived from:

λ, Ψ – Dore, Keaveney, Flannery, Rajko-Nenow (2010) *Management of health risks associated with oysters harvested from a norovirus contaminated area, Ireland, February-March 2010*. Euro surveillance 15: pii/19567.

χ - Lowther, Gustar, Powell, Hartnell, Lees (2012) *Two-year systematic study to assess norovirus contamination in oysters from commercial harvesting areas in the United Kingdom*. Applied & environmental microbiology 78:5812-5817.

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Applicability To Other Pathogens

- FRNA+ Bacteriophage (potential NoV indicator – closer correlation than *E.coli*)
- Hepatitis A (Similar transmission pathways to NoV)
- Hepatitis E (est. 20 million humans infected per year)

Thank you for listening...

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