CASE STUDY B

NOROVIRUSES OUTBREAK AT NORTHERN ARIZONA UNIVERSITY

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1. INTRODUCTION

1.1 Background.

An outbreak of norovirus that affected 115 individuals occurred in a major university between July 18 and July 31, 2005. Sixty-one patients (51%) were participants or staff of the wrestling camp that began on July 17, 2006. The outbreak peaked on July 20th with 50 cases. Gender and symptom information of 103 cases were available, 24 (23%) were women and 79 (77%) were men; symptoms included nausea, vomiting and diarrhea in 20 (19.4%), 83(80.6%) and 91 (88.3%) cases, respectively. 13.6% of patients experienced nausea, vomiting and diarrhea. Attack rate at the wrestling camp, where most cases originated was 30.3%. No fatalities occurred during this outbreak (Norovirus Outbreak Report, 2005).

Between July 30 and August 1, 2005, surfaces in residence halls and the wrestling facility, such as bathroom sink handles, toilet seats and toilet handles were disinfected with a bleach solution containing 5000 ppm free chlorine. Environmental testing by nested RT-PCR found that 45% of samples of surfaces previously disinfected were positive for norovirus. After the second round of disinfection, the percentage of surfaces testing positive was reduced to less than 25%. Since RT-PCR results do not provide information on survival or infectivity of norovirus on surfaces, these results cannot be used to determine whether or not these surfaces are safe for public access.

1.2 Pathogen of concern.

Noroviruses (NV) are formerly classified as Norwalk-like viruses. It was first identified in a gastroenteritis outbreak in Norwalk, OH in 1968. Norovirus consists of small, circular and single-stranded RNA. They belong to the family of *Caliciviridae* and are approximately 23-35 nm in diameter (Embrey et al. 2002). Noroviruses have low infectious dose ($<10^2$ viral particles) and can cause prolonged asymptomatic shedding in infected individuals for up to two weeks. Symptoms associated with a norovirus infection include nausea, vomiting, diarrhea, low grade fever and headache. In rare cases, norovirus illness can lead to severe dehydration. The incubation period of the illness is usually 24-48 hours, but can be as short as 12 hours. In most people, a norovirus infection is self-limiting, with symptoms lasting for about 1 or 2 days. Studies show that as many as 30% of infections may be asymptomatic. Recovery is usually complete with no long-term sequelae.

The virus is spread from one infected person to another by direct contact, aerosols, fomites, food or water (CDC, Chin, 2000). The virus can also be aerosolized during vomiting and when diarrhea stools are flushed in a toilet. Projectile vomiting is a characteristic feature of the disease and this could give rise to droplets (Caul, E.O., 1994). Noroviruses are extremely stable in the environment. They are stable in less than 10 parts per million (ppm) chlorine and can withstand freezing and heating to 60 °C (Nwachcuku and Gerba 2004). Substantial strain diversity leads to short-lived host immunity to infection and permits re-infection. This makes the development of a vaccine that offers lifelong protection impossible (Glass et al. 2001). Norovirus outbreaks are difficult to control because the virus spreads rapidly in closed environments often resulting in secondary attack rates of >50% (Caul 1994).

The estimated total number of cases of norovirus infection per year is 23 million in the United States alone (Mead 1999). Norovirus outbreaks constituted for 9% of waterborne-disease outbreaks of gastroenteritis associated with recreational water during 1993-2002 and 16.7% waterborne-disease outbreaks of gastroenteritis associated with recreational water during 2001-2002. Noroviruses have been implicated in 96% of the outbreaks of acute nonbacterial gastroenteritis in the US documented by the Centers for Disease Control and Prevention (CDC) between 1996 and 1997 (Fankhauser et al., 1998). Between 1995 and 2002, approximately 80% of gastrointestinal outbreaks reported in the Netherlands were related to NV (Koopmans et al. 2002).

1.3 Objectives.

The goals of this microbial risk assessment are:

1. To assess the potential human risk associated with exposure to noroviruses through fomite and airborne transmission via aerosolization..
2. To determine critical points for control.
3. To set up preventive measures for future outbreak associated with pathogens with similar pathogenicity and exposure pathways.

This risk assessment will mainly focus on two exposure pathways:

1. Fomite transmission
2. Airborne transmission

2. ASSUMPTIONS

1. Inactivation/die off of viruses on fomites: 100% of viral particles depositing on fomites are infectious at the time of deposit. Doultree et al. (1999) reported that T_{99} for feline calicivirus, a norovirus surrogate, is 10 days at 20 °C.
2. Frequency of fecal excretion for asymptomatic cases is one-fourth the frequency of the symptomatic cases.
3. Frequency of vomit excretion is three per day.
4. The aerosolization data for bacteriophage MS2 was used for the estimation of the aerosolization of the viral particles from feces during toilet flushing
5. The percentage of aerosolized viral particles from vomitus is equal to the percentage of aerosolized viral particles from feces.
6. The surface area of fomites is calculated from general data.
7. In cases where data for human noroviruses are not available, data for other viruses with similar characteristics are used. Dose-response data for rotavirus will be used to estimate risk associated with norovirus infection because these two viruses are presumed to have infectious dose between 10-100 virus particles (LeBaron et al. 1990). .
8. The effectiveness of hypochlorite/detergent-based cleaning procedure recommended for eliminating fecal contamination from surfaces and prevention of transfer to clean surfaces and hands was based on data obtained from experiments conducted on diluted fecal suspension (1 to 10 and 1 to 80).
9. Transfer percentage from finger to lip was based on bacteria data (Gibson, L.L., et al., 2002).
10. We assume two independent mixing venues where transmission can occur: the first is the bathroom where fecal contamination dominates; the second is the general mixing venue where contamination of fomites occurs after vomiting, leading to aerosoliztion and immediate deposition onto fomites.
11. We assume the contamination concentration in both mixing venues to be homogenous within venue.
12. We assume an infinite, homogenous population size for ease of modeling at this initial stage of analysis.
13. We assume the following natural history of infection in which S stands for susceptible, E stands for incubating, I stands for infectious and asymptomatic, D stands for infectious and clinically ill, and R stands for recovered.

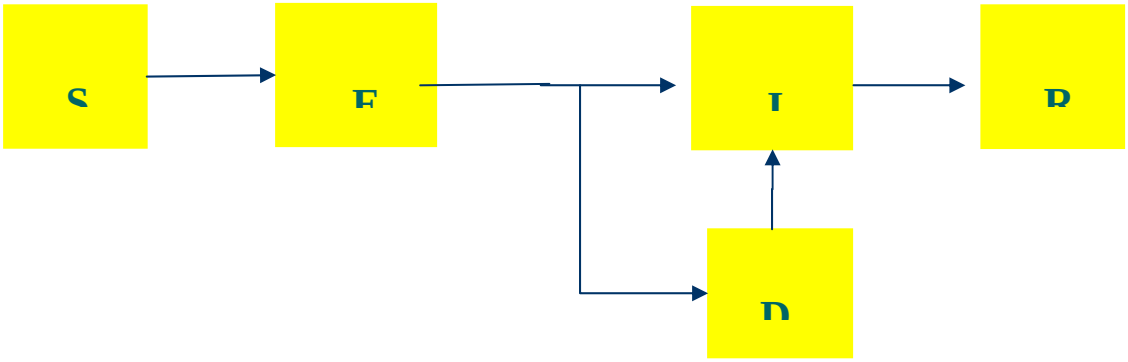

Figure 1: Model of the Norovirus natural history of infection.

3. UNCERTAINTIES AND LIMITATIONS

1. We do not know the number of people who were initially exposed to the virus during the initial vomiting event.
2. The model does not consider transmission to people outside the dormitory.
3. The correlations between viral RNA detection and numbers of viral particles and their infectivity are not clear. For example, recovery of the detection method, and fraction of the detected pathogens that is infectious were not determined.

4. METHODS

4.1 Exposure Pathways

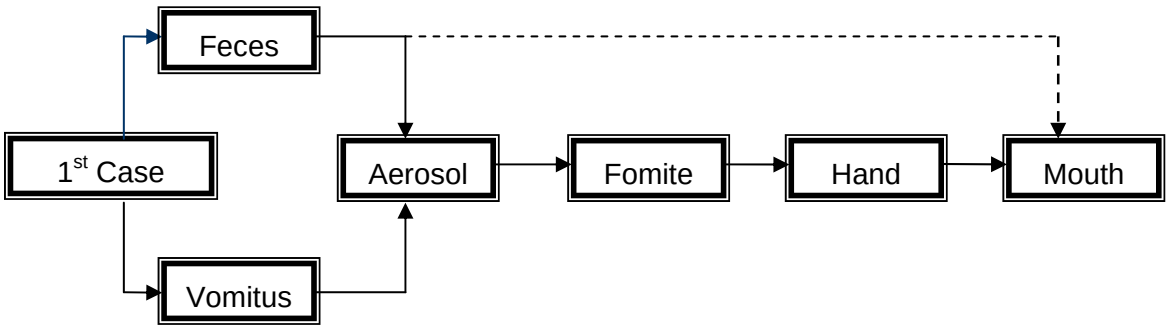

Figure 2: Pathways of Norovirus transmission from case 1 to case 2

4.2 Data

A. Index Case via Feces

a. Frequency of excretion (# of excretion/day):
    i. symptomatic: 4 (Dr. Gerba, personal communication)
    ii. Asymptomatic: 1 (Assumption)
b. Mass of excretion (g/excretion): 120 (Dr. Gerba, personal communication)
c. Excretion rate (particles/g): 3×10^8 (Chan, Martin, C. W., et al., 2006)

Result: Number of viral particles originated from feces per day = 1.4×10^{11}

B. Index Case via Vomitus

a. Frequency of excretion (# of excretion/day): 3 (Assumption)
b. Excretion rate (viral particles per excretion): 3×10^7 (Caul, 1994)

Result: Number of viral particles from vomitus per day = 9×10^7

C. Feces-Aerosolization from toilet flushing

a. Percentage of aerosolized particles after flushing: 6.3×10^{-7} % (Barker and Jones, 2005)

Result: Number of viral particles originated from toilet flushing per day = 9.1×10^4

D. Vomitus-Aerosolization

a. Percentage of aerosolized microbes: 6.3×10^{-7} (Assumed to be equal to the aerosolization data for feces, refer to ***C***)

Result: Number of viral particles aerosolized when vomiting per day =19

E. Aerosol- Fomites

a. Percentage of deposited microbes: 100% (Barker and Jones, 2005)

Result: Number of aerosolized viral particles deposited on formite per day= 9×10^4

F. Fomites-Hand

a. Frequency to bathroom per day: 6 (Dr. Gerba, personal communication)
b. Number of surface contact per visit: 5 (Dr. Gerba, personal communication)
c. Contact area per event (m^2/event): 6.4×10^{-2} (Dr. Gerba, personal communication)
d. Surface area of fomites: 2480 m^2 (Source: Calculations; surface area of fomites)
e. Transfer percentage from fomite to Hand: 10% (Dr. Gerba, personal communication)

Result: Number of viral particles transferred to hand per day: 65

G. Hand to lip

a. Transfer percentage from fingertip to lip: 24.6% (Gibson, L.L., et al., 2002)

Result: Number of viral particles transferred to lip per day: 15.25

Final result: dose: 15.25 viral particles per day per person per patient

Asymptomatic Proportion
30% of shedders will not show symptoms (Norovirus Outbreak 2005)

Length of Incubation Period
12-48 hours (Norovirus Outbreak 2005)

Shedding Period
a. Symptomatic Shedding: 1-2.5 days (Norovirus Outbreak 2005)
b. Asympotmatic Shedding: up to 14 days (Norovirus Outbreak 2005)

4.3 Dose-response model

Because no model is available for the dose-response relationship of noroviruses, the probability of infection was estimated using dose-response model for rotavirus to get conservative estimates. The relationship is expressed by the following Poisson-binomial model (Haas, 1993).

$$P(D) = 1 - \left(1 + \frac{D}{N_{50}}\left(2^{1/\alpha} - 1\right)\right)^{-\alpha}$$

where $N_{50} = 5.60$ and $\alpha = 0.265$

The probability of transmission given exposure to one particle (β) is 0.02193. The probability of infection for any sufficiently low dose is equal to the product of β and the daily dose.

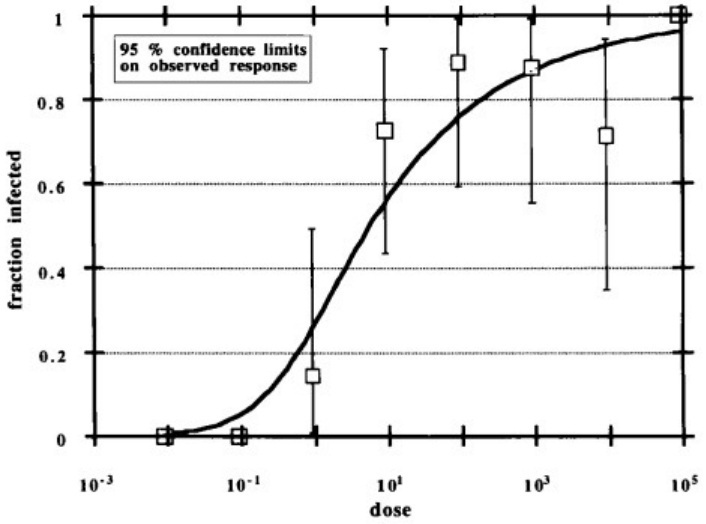

Figure 2. Comparison of beta-poisson model to rotavirus infectivity data

4.4 Transmission Model

A. Introduction

We constructed an ordinary differential equation based model of Norovirus transmission to model the specific NAU outbreak. We used an environmental contamination model in which the dose of virus a person received determined the likelihood of transmission to them. Using available outbreak data, data from the literature, expert opinions, and our best guesses, we estimated values for all relevant transmission parameters. The differential equations are available upon request, but are not presented here for the sake of brevity.

B. Model fit

Using our initial parameter estimates, the outbreak did not take off given one infectious person immigrating to the dorm. This indicates that either our parameter estimates are flawed, or the model implementation is not of a realistic enough form to directly use

realistic parameter values within it. Both situations are possible and are probably occurring at the same time. Figure 3 shows the dynamics of the transmission model without any model fitting. Note that the black line represents the proportion susceptible, and that its value is listed on the left y-axis, while all other states are associated with the right y-axis values.

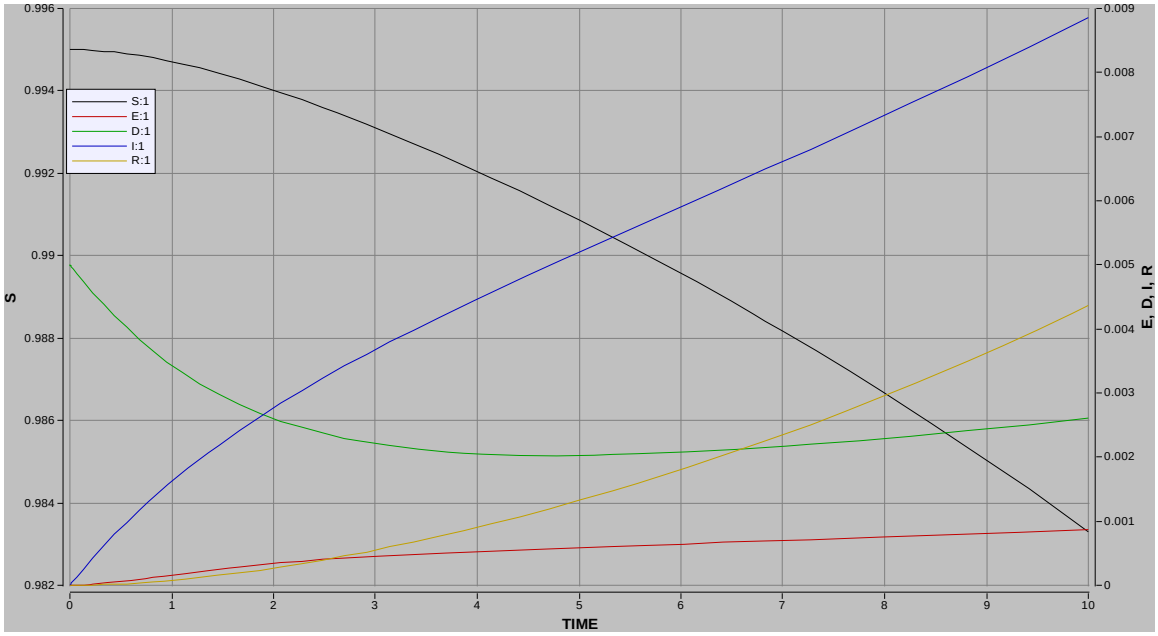

Figure 3. Model dynamics with no fitting

To better fit our model to the data, we conducted a series of analyses which are not listed here. One of the more parsimonious ways to fit the model was to assume that the transmission probability from fomite to hand was 50% (rather than 10%), and also that the transmission probability from hand to mouth was 50% (rather than 10%). Using these parameters, figure 4 was constructed. Note that all the values of all the states are now on the same scale, associated with the right y-axis.

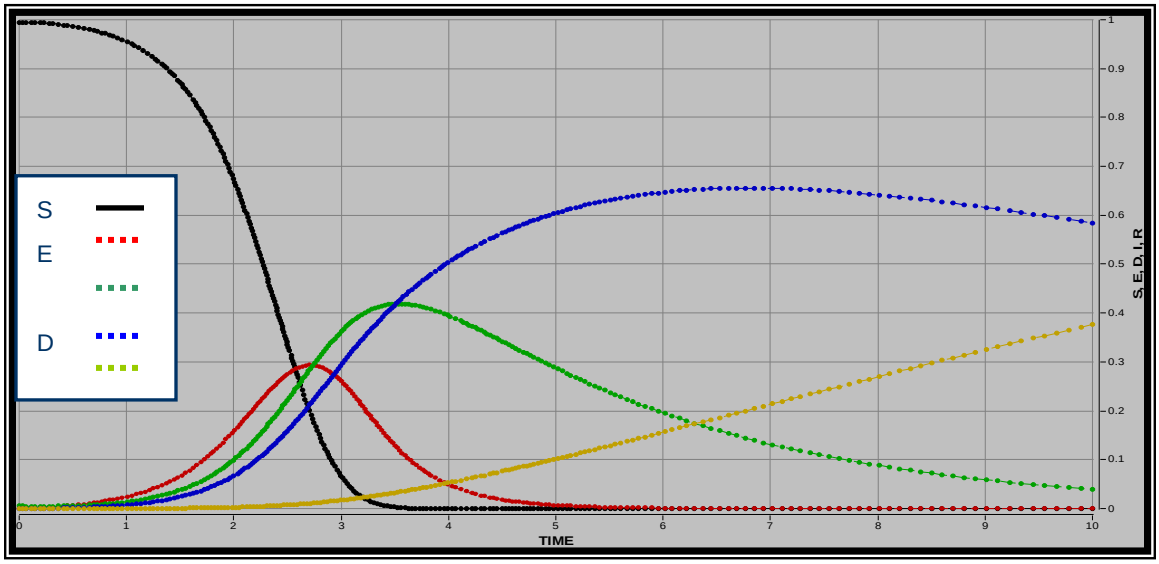

Figure 4. Model dynamics with fitting

C**.** Uses of this model

1. This model was used to estimate the concentration of contamination after the outbreak had occurred in the bathroom venue, as well as the general mixing venue. These values were then used to calculate the required reduction to achieve safe contamination levels.
2. This model was used to estimate the amount of time required for the virus to decay on its own until safe values were achieved assuming no other intervention. The period was found to be roughly three months.

5. RESULTS AND CONCLUSIONS

5.1 Cleaning strategy to prevent outbreak or to clean-up dorms

5.1.1 Preventing first spread of outbreak

Scenario

A healthy person A shares a bathroom with a symptomatic patient B. B sheds loose stools four times a day and vomits three times a day. How can A be protected from infection?

Assumptions

Acceptable risk of infection was set at 10^{-4}[infection/bathroom visit].

Results

Acceptable conc. on fomites:	2.9×10^{-4} [particles/m^2]
Required $\log_{10}$ reduction:	7.7 [Log_{10}]

Discussion

Technically, it is impossible to clean up bathroom using bleach every time someone sheds loose stool (or every day). Instead, we recommend closing lids of toilet when you flush under all conditions.

5.1.2 Cleaning Gabaldon dorm after the outbreak

Scenario

A norovirus outbreak has occurred. To re-open the Garaldon dorm, how do we make sure that the building is free of infectious norovirus before re-opening?

Assumptions

Noroviruses concentrations of bathroom and general fomites at day 10 (the last day of outbreak) were used as the initial concentration. Acceptable risk of infection was assumed at 10^{-4}[infection/bathroom visit].

Results

Required $\log_{10}$ reduction

Bathroom fomites:	6.4 [Log_{10}]	6.5 [Log_{10}]
General fomites:	2.1 [Log_{10}]	2.1 [Log_{10}]

Discussion

The Ct value of chlorine inactivation for aggregated feline calicivirus in water was reported as 29.6 [mg/L.min] (Thurston-Enriquez, et al., 2003). Though this value is not for survival on fomites, the cleaning strategy taken after the outbreak seems to be sufficient considering much higher Ct should be achieved by using 5,000 [mg/L] of free chlorine. In addition, roughly same percentage of positive environmental results were obtained from toilet handle/toilet seat and lavatory handles post-first and post-second cleanings, showing signs of re-contamination instead of insufficient cleaning. The cleaning sufficiency was not as good as estimated. The cleaning may not be done as recorded or detected noroviruses by RT-PCR may not be viable.

6. PREVENTION STRATEGIES

In accordance with our findings above, we recommend the following prevention strategies:

1. If vomiting occurs in a public place, like a café, the place needs to be vacated and disinfected immediately by trained personnel with detergent and water and treated with hypochlorite 5000 ppm for 1 min.
2. Bathrooms and living areas occupied by infected persons should be cleaned frequently with detergent and water and treated with hypochlorite 5000 ppm for 1 min for up to 30 days after infection.
3. Bathrooms in the dormitory require appropriate cleaning materials and separate materials used for each specific surface.
4. Organize a public meeting for residents in the dorm to make sure everyone is aware of the outbreaks and follow the guidelines provided (e.g. hand washing for one min; close the toilet lid when flushing and spray the room with disinfectant spray after using the restroom).
5. Post, fact sheets and hand-washing signs regarding the outbreak in the bathroom.

7. MONITORING APPROACHES

Below are the recommended monitoring approaches:

1. Workers in cafeteria and residential halls should be trained in cleaning up potentially infectious waste.
2. Install toilet lid on every toilet in the dorm.

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Appendix

Aerosolization from feces:
Source: Barker and Jones, 2005

MS2 Bacteriophage (PFU m^{-3})	
Time	**Untreated bowl water**
Before flush	Not detected
After flush	
1 min	2420 (691)
30 min	178 (91)
60 min	27 (25)

() Values given in parenthesis are standard error of the mean for three replicates

Surface area of fomites

Source: Assumptions
Room dimensions: 7.6m x 6.2m
Café dimensions: 14m x 7m