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The Effects of Excluding Infected Foodworkers on Norovirus Burden in the U.S.

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Abstract

The Effects of Excluding Infected Foodworkers on Norovirus Burden in the U.S.
By Wen Yang

Noroviruses are the most commonly reported cause of acute gastroenteritis in the United States. Analyses of norovirus outbreak data indicate infected foodworkers to cause the majority of foodborne norovirus outbreaks. A deterministic, population-based compartmental model was used to assess variable compliance with the current FDA Food Code recommendations for all workers infected with norovirus to stay home from work while they are experiencing symptoms as well as ≥ 48 hours after their symptoms subside. We modeled the number and proportion of norovirus cases averted, in comparison to a baseline scenario assuming exclusion of 66.7% of symptomatic foodworkers and 0% of asymptomatic foodworkers nationally. Our findings underscored the increased benefit of excluding asymptomatic foodworkers in addition to symptomatic foodworkers. Assuming the referent is true, a maximum of 14.7 million cases have already been avoided annually. By excluding 100% of symptomatic foodworkers, 8.3 million norovirus cases can be averted annually. By also excluding 100% of asymptomatic foodworkers for 2 days, 9.5 million norovirus cases can be avoided annually. When varying the proportion of symptomatic foodworker exclusion (Φ_1) for any given proportion of asymptomatic foodworker exclusion for 2 days (Φ_2 and Φ_3, where $\Phi_2=\Phi_3$), 18–64 year-olds experienced the largest change in number of cases averted per year (absolute range of 13.0 million cases) while 0–4 year-olds experienced the smallest change (absolute range of 3.2 million cases). When varying Φ_2 and Φ_3 for 2 days for any given Φ_1, 18–64 year-olds experienced the largest change in number of cases averted (reaching 700,124 at 66.67% symptomatic foodworker exclusion) while 0–4 year-olds or 65+ year-olds experienced the smallest change (reaching 168,422 cases at 66.67% symptomatic foodworker exclusion), depending on Φ_1. In comparison, 65+ year-olds experienced the greatest change in proportion of baseline cases averted while 0-4 year-olds experienced the smallest change, no matter if we varied Φ_1 or varied Φ_2 and Φ_3, holding the other constant. Our findings support the current FDA Food Code recommendation as well as future modeling of interventions that target foodworkers and address reasons for which foodworkers decide to work while ill.

The Effects of Excluding Infected Foodworkers on Norovirus Burden in the U.S.

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Chapter I

Background

Norovirus casts a heavy disease burden on the U.S. population and its means of infecting a human host are complicated. In a given year, norovirus infections account for an estimated 19-21 million illnesses in the United States (*1*). Norovirus infection in humans is a public health consequence of strain diversity, host susceptibility, human behavior and the environment. In order to mitigate its future burden, it is imperative to understand norovirus features on the individual- and population-levels.

Phylogenetic analyses reveal a great deal of diversity among noroviruses, which represent a single genus in the *Caliciviridae* family (*2*). Currently, there are 6 established norovirus genogroups, with genogroup VII awaiting consensus approval from the international norovirus working group (*3*). Each genogroup has subsequent genotypes that are further classified into strains (*3, 4*). The majority of human norovirus outbreaks are caused by the genogroup 2 type 4 (GII.4) viruses, which yield a new strain every 2 to 4 years (*5*). The emergence of new strains supports the notion of genetic drift driven by population immunity and is often, but not always, associated with increases in number of outbreaks (*6-10*).

Certain characteristics of norovirus infection of humans facilitate the spread of norovirus. First, lack of lasting immunity underpins the possibility of repeated infections throughout an individual's life (*4*). The duration of immunity to norovirus is estimated to fall between 4.1 and 8.7 years according to mathematical models (*11*). In addition, two human challenge studies estimate immunity to last at least 6 months, according to Johnson et al. (*12*) and 2 months to 2 years according to Parrino et al. (*13*). The human

ID_{50} for norovirus may be as few as 18.2 genomic equivalent copies, according to human challenge studies using two norovirus strains (*14-16*). Furthermore, there is a long duration of norovirus shedding observed in human challenge studies, which peaks at a median of 4 days and lasts up to 8 weeks after virus inoculation (*17*).

The epidemiologic features of norovirus are unique in terms of the specific populations it infects and its seasonality, transmission routes, and environmental stability. Norovirus is capable of infecting people of all ages but incidence rates of severe disease are highest for adults ≥65 years-old in terms of deaths and children <5 years-old in terms of outpatient visits, emergency department visits, and hospitalizations (*1*). Norovirus cases occur year round, with 63%-73% of estimated monthly incidence falling between October and March in the U.S. (*1*). The rapid spread of norovirus occurs by direct and indirect transmission routes including person-to-person by fecal-oral transmission; ingestion of aerosolized vomitus; and contact with contaminated fomites, food, or water, as reviewed in (*2*). Also, noroviruses can remain infectious at temperatures ranging from 0-60°C and can resist many disinfectants (*4, 18*). These epidemiologic features of norovirus demand innovative prevention strategies.

Preventing the transmission routes from particular cases of norovirus can prevent downstream norovirus infections in a population. One approach to reducing norovirus burden in a population is through vaccinating specific groups of people. Norovirus vaccines are still under development and have been hampered by gaps in our understanding of norovirus immunity, as previously described (*11*). Until recently, in a study conducted by Jones et al. in which they developed an *in vitro* infection model for human noroviruses (*19*), there have been technical challenges of growing norovirus in cell culture (*20*). In light of these challenges, alternative approaches to curtail future norovirus burden in the U.S. should be explored.

Norovirus burden in the United States

National surveillance for individual cases of norovirus does not exist, but various methods have been developed and utilized to bypass this challenge. Findings from these various methods were consolidated in a review conducted by Hall et al. in 2013 to estimate incidence rates of norovirus in the U.S. from 1993 to 2011 (*1*). The methods fell into three general categories: laboratory-confirmed population-based surveillance, indirect modeling and attributable proportion extrapolation. For each method, there were differences across studies in the data sources, age groups, norovirus-associated outcomes and/or data periods. Across all three methods, there are also differences in the limitations inherent to each method. Hall et al. compared the results for each method and triangulated the results to estimate 19-21 million illnesses, 1.7-1.9 million outpatient visits, 400,000 emergency department visits, 56,000-71,000 hospitalizations and 570-800 deaths per year due to norovirus in the U.S. (*1*).

Norovirus outbreaks in the United States

National surveillance of norovirus disease in the U.S. is limited to norovirus disease outbreaks through two complementary systems, the National Outbreak Reporting System (NORS) and CaliciNet. Established by the Centers for Disease Control and Prevention (CDC) in 2009, NORS is an expansion of the electronic Foodborne Outbreak Reporting System (eFORS), which operated from 1998-2008 (*21*). eFORS was specifically designed for foodborne disease outbreaks, while NORS also reports on enteric outbreaks transmitted through water, food, person-to-person, or direct animal contact (*22*). Also established in 2009, CaliciNet is a laboratory-based surveillance network of state, local, and regulatory public health laboratories that perform sequencing of noroviruses identified in outbreaks (*23*). Data from CaliciNet are used to track the emergence of new norovirus strains and to potentially link geographically distinct outbreaks associated with a common exposure.

NORS tracks U.S. foodborne disease outbreaks using data collected from state, local and territorial health departments, a process that is systematic but has its limitations. A foodborne disease outbreak is comprised of ≥2 similar illnesses epidemiologically linked to a common exposure (e.g. a setting or a food). Confirmed norovirus outbreaks are those for which 2 ill individuals are positive for norovirus, as determined by reverse transcription PCR, enzyme immunoassay, or electron microscopy (*24*). In the absence of diagnostic testing, suspected norovirus outbreaks are those for which reasonable clinical or epidemiologic evidence exists. One approach to defining a suspected norovirus outbreak is using the Kaplan criteria. Developed in 1982, the Kaplan criteria defines suspected norovirus outbreaks based on the following four specifications: vomiting in >50% of affected individuals, mean (or median) incubation period of 24-48 hours, mean (or median) duration of illness of 12-60 hours and no bacterial pathogen in stool culture (*25*).

NORS has its limitations. To start, NORS has incomplete demographic data, such as age group and sex. This problem has been addressed by extrapolating the relative proportions of those demographic factors to the total number of reported outbreak-associated illnesses (*22*). Also, there is the issue of state-to-state variation in reporting rates, which may introduce bias to some reported outbreak characteristics. From 2009-2012, for instance, there was a 100-fold difference in reporting rates between the states with highest and lowest reporting rates out of 43 states (*22*).

To date, attributes of foodborne norovirus outbreaks have been described for confirmed and suspected norovirus outbreaks that were reported in NORS between 2009 and 2012 by Hall et al. to identify the factors contributing to contamination and methods of food preparation (*22*). The foods implicated in outbreaks were classified based on a categorization scheme of 17 mutually exclusive commodity groups according to practical considerations (*26*). Food vehicles contaminated with one or more ingredients from a single commodity were classified as that commodity. Food vehicles contaminated with ingredients from more than one commodity were classified as complex. Outbreak reports were further categorized by contributing factors (e.g. food handler contact, cross contamination during preparation, contaminated raw product and insufficient cooking and/or heating), point of contamination (e.g. production or processing vs. preparation or service), setting of food preparation (e.g. commercial, institutional, private and other), and whether a food handler was implicated as the source of contamination.

The findings from the study conducted by Hall et al. provide preliminary insight into which aspects of foodborne norovirus disease outbreaks deserve attention. Among outbreaks with a single implicated commodity (32%), leafy greens comprised 30%, fruits/nuts 21% and mollusks 19% of those reports (*22*). Additionally, the majority of outbreaks implicated food contaminated during preparation or service (92%), food prepared in a restaurant setting (64%) and food workers implicated as the source (70%)

(*22*). A notable exception to these trends is all mollusk-associated outbreaks were caused by contamination during production or processing (*21*).

EHS-Net Studies

Based on foodborne norovirus disease outbreak data, the CDC stresses three specific recommendations from the Food and Drug Administration (FDA) Food Code in order to reduce contamination of ready-to-eat foods by foodworkers, namely (i) supervision by a certified kitchen manager (CKM), (ii) proper handwashing by all employees and (iii) exclusion of all ill food workers from work for ≥48 hours after symptoms subside (*22, 27*). The Food Code makes a number of recommendations for guarding against foodborne illness in food establishments, with its most recent version released in 2013 (*27*). These three recommendations are supported by three individual studies conducted by the Environmental Health Specialists Network (EHS-Net) of the CDC on restaurants in the U.S. Restaurants were defined as establishments that prepared and served food or beverages to customers, and excluded establishments such as food carts, mobile food units, temporary food stands, supermarkets, restaurants in supermarkets and caterers.

In a systematic environmental evaluation conducted from June 2002 through June 2003, EHS-Net sought to identify differences in restaurants that have and have not had foodborne disease outbreaks (*28*). Specifically, 22 restaurants in which an outbreak occurred were compared to 347 restaurants in which an outbreak had not occurred in this time period. The major difference in outbreak versus non-outbreak restaurants was the presence of a CKM. Specifically, 71% of non-outbreak restaurants had a CKM while this was the case for only 32% of outbreak restaurants. A univariate analysis found the odds of being an outbreak restaurant was 0.2 (95% CI, 0.1-0.5) when comparing restaurants with and without CKMs. Furthermore, CKMs were found to be associated with fewer outbreaks of norovirus specifically. A multivariate analysis could not be performed due to a small sample of outbreak restaurants, which was a result of the limited availability of EHS-Net specialists.

The second study conducted by Green et al. observed foodworkers who worked in restaurants that were randomly selected from catchment areas of six EHS-Net states. Green et al. recorded workers engaging in approximately 8.6 work activities per hour that required hand washing, but attempted to wash their hands for 32% of such work activities and appropriately washing their hands for only 27% of work activities (*29*). Attempted and appropriate hand washing were significantly lower among foodworkers when gloves were worn (18% and 16%) compared to when gloves were not worn (37% and 30%) (*29*).

The third study conducted by Carpenter et al. sought to understand the experiences and characteristics of foodworkers who work while ill. Foodworkers were interviewed from a random selection of restaurants located in each of the nine EHS-Net states. Approximately 50 restaurants were visited per state. Carpenter et al. found 60% (292/491) of foodworkers reported working a shift while ill in the previous year (*30*). What is more, nearly 20% of workers said they worked at least one shift while experiencing symptoms of diarrhea or vomiting (*30*). Of the 97 who experienced these symptoms, 39.2% reported working on one shift whereas the remaining 60.8% reported working two or more shifts during the previous year (*30*). A multivariate analysis was conducted to investigate the association between working one or more shifts while ill with symptoms of diarrhea or vomiting and workers' characteristics and beliefs. Those who rated fear of losing their job or leaving coworkers short-staffed, compared to those who rated those factors to have little to no influence, had a significantly higher odds of actually working one or more shifts while ill (*30*).

Mathematical modeling

The assessment of reducing norovirus burden in the U.S. through better adherence to Food Code recommendations by ill foodworkers is conditional on investigating the impact these changes have on the overall burden of norovirus. In order to do this, we employed compartmental models, which are useful for predicting population-level effects of interventions that are difficult to implement or measure by tracking disease states within a population (*31*). Deterministic models produce the average value of the outcome variable and population-based models capture the typical experience of multiple groups of individuals, both without sacrificing computational efficiency (*31*). Incorporating age and time, specifically, allows one to quantify how the effects of an intervention progress over time and differently for various age-groups (*31*). Past applications of deterministic, population-based compartmental models to study norovirus transmission include a study conducted by Simmons et al. to estimate the duration of immunity to noroviruses (*11*).

Model inputs for studying norovirus infections within a population can be estimated from literature, if observable, or can be estimated in the modeling process, if not observable. The current state of empirical data for foodworkers' hand hygiene practices is not suitable for compartmental models (*29*), this aspect will be absent from our modeling here. On the other hand, the percentage of symptomatic foodworkers who properly exclude themselves from work has been quantified (*30*), deeming the factor of infected foodworker exclusion appropriate for incorporation into a deterministic, population-based mathematical model. Accordingly, this study aims to (i) build a deterministic, compartmental model that will serve as the framework for investigating the effects of infected foodworker exclusion on the number of norovirus cases in the U.S., (ii) estimate how the annual norovirus burden changes as a result of excluding varying proportions of infected foodworkers and (iii) estimate how the annual norovirus burden changes as a result of excluding asymptomatic foodworker for various durations of time.

Significance

NoroCORE, a collaborative project that started in 2011, has the long-term goal of translating relevant research into actions that reduce the burden of norovirus and other foodborne viruses in the U.S. This study will in part actualize one of the NoroCORE objectives within epidemiology and risk analysis, specifically the development of an epidemiologic model for assessment of food safety interventions. What is more, the burden estimates generated from scenarios in this study will serve as a good comparison to burden estimates generated from scenarios of vaccinating specific age groups (i.e. infants or elderly) in the U.S., which is also currently being explored by the CDC. While the parameters being altered in the study are behavioral by nature, the change in behavior might be rooted in policy change, educational campaigns, or other interventions. The findings of this study will be the first attempt to quantify the impacts of reducing norovirus burden through changes in the behavior of infected foodworkers.

Chapter II

Introduction

Noroviruses are the most commonly reported cause of acute gastroenteritis in the United States (*32*). In a given year in the U.S., norovirus infection causes an estimated 19-21 million illnesses, 1.7-1.9 million outpatient visits, 400,000 emergency department visits, 56,000-71,000 hospitalizations, and 570-800 deaths (*1*). People of all ages may be infected by norovirus. However, incidence rates of deaths are highest for adults ≥65 years-old whereas incidence rates of outpatient visits, emergency department visits, and hospitalizations are highest among children <5 years-old (*1*).

The efficient transmission of norovirus is in part due to the multiple transmission pathways by which the pathogen reaches a human host. Norovirus infections involve can occur by direct person-to-person contact or by indirect transmission routes, through contact with contaminated fomites, food or water (reviewed in (*2*)). Both direct and indirect transmission routes may involve fecal-oral transmission and/or ingestion of aerosolized vomitus (reviewed in (*2*)). Preventing the transmission routes from particular cases of norovirus can prevent downstream norovirus infections in a population. In order to most efficiently curtail the number of norovirus cases in the future, it is critical to understand which transmission routes have most commonly led to norovirus cases in the past.

The most obvious challenge in defining norovirus cases by transmission route is the absence of a national surveillance system that specifically tracks individual cases of norovirus. The only national surveillance of norovirus disease in the U.S. tracks norovirus disease outbreaks. Established in 2009, the National Outbreak Reporting

System (NORS) stores reports of enteric disease outbreaks transmitted through water, food, person-to-person, or direct animal contact (*22*). From 2009 to 2012, 4,318 norovirus disease outbreaks were reported, with 23% of those outbreaks attributed to foodborne transmission as the primary mode of transmission (*22*). The majority of foodborne norovirus disease outbreak reports indicated food contaminated during preparation or service (92%), food prepared in a restaurant setting (64%) and foodworkers as the source of contamination (70%) (*22*). Even so, these outbreak statistics may underestimate the true frequency of attributes, resulting from a lack of incentive among foodworkers to report disease and asymptomatic infections (*33*).

Studies on the characteristics of the restaurant industry and foodworkers' behavior provide insight into the potential points for intervention that deserve attention when developing public health strategies to reduce future norovirus burden. To start, it has been shown that the presence of a certified kitchen manager (CKM) is associated with fewer norovirus-associated outbreaks in restaurants and with the absence of bare-hand contact with ready-to eat foods when outbreaks do take place (*28*). Secondly, foodworkers have been observed to attempt to wash their hands before 32% of work activities that require hand washing, and appropriately wash their hands before only 27% of such work activities (*29*). In addition, nearly 20% of foodworkers report having worked at least one shift in the past year while experiencing diarrhea or vomiting (*30*). Fear of losing their job or leaving coworkers short-staffed significantly influences foodworkers' decision to work while ill (*30*).

Based on these restaurant studies and outbreak surveillance data, the Centers for Disease Control and Prevention (CDC) stress three specific recommendations from the

Food and Drug Administration (FDA) Food Code to reduce norovirus contamination of ready-to-eat foods by foodworkers, namely (i) supervision by a certified kitchen manager (CKM), (ii) proper handwashing by all employees and (iii) exclusion of all ill food workers from work for ≥48 hours after symptoms subside (*22, 27*). While it is important to address the barriers to foodworkers' compliance with these Food Code recommendations, it is unknown what quantity of norovirus cases would actually be averted through changes in foodworker behavior.

In order to quantify potential changes in the annual burden of norovirus in the U.S. resulting from changes in infected foodworker behavior, we employed compartmental models. Compartmental models are useful for predicting population-level effects of interventions that are difficult to implement or measure by tracking the state of infection and immunity within a population (*31*). By incorporating time and age, these models are capable of predicting how the effects of an intervention progress over time and differently for various age-groups (*31*). Since the current state of data for foodworkers' hand hygiene practices is not suitable for compartmental models (*29*), this aspect will be absent from our modeling here. On the other hand, the percentage of symptomatic foodworkers who properly exclude themselves from work has been quantified (*30*), deeming the factor of infected foodworker exclusion appropriate for incorporation into a deterministic, population-based mathematical model. What is more, ill foodworkers represent the greatest source of foodborne norovirus outbreaks (*22*), as previously discussed. This study aims to (i) build a deterministic, compartmental model that will serve as the framework for investigating the effects of infected foodworker exclusion on the number of norovirus cases in the U.S., (ii) estimate how the annual norovirus burden changes as a result of excluding varying proportions of infected foodworkers and (iii) estimate how the annual norovirus burden changes as a result of excluding asymptomatic foodworker for various durations of time.

Methods

Model Design: states of infection and immunity

To measure the states of norovirus infection and immunity in the population, two deterministic, population-based compartmental models were used (Figure 1). The models, in their simplest form, tracked five states of norovirus infection and immunity, or compartments, namely susceptible to infection or disease (S), exposed (E), symptomatically infected (I), asymptomatically infected (A) and recovered (R). Individuals transition between compartments at fixed rates (Table 1). Those susceptible to infection or disease are infected at the force of infection (i.e. $\lambda_{tot,i}(t)$ or $\lambda_{3,j}(t)$) (see Appendix) and move into the exposed compartment. Individuals then move to the symptomatically infected, asymptomatically infected and recovered compartments at a rate equal to the inverse of the duration spent in the previous disease compartment (i.e. $1/\mu_s$, $1/\mu_a$ and $1/\rho$, Table 1). Recovered individuals are either subject to re-infection but not disease (i.e. asymptomatic infection) at the force of infection or lose natural immunity by waning and return to the susceptible state (i.e. $1/\theta$, Table 1).

Model Design: age- and employment-structure

The models further distinguish the population by age (i.e. 0-4 year-olds, 5-17 year-olds, 18-64 year-olds and 65+ year-olds) and by foodworker employment (i.e.

consumers or foodworkers). For every age group, occupants are lost due to death or by ageing into the next age group (except 65+ year-olds). Furthermore, a proportion (τ) of 5-17 year-olds age into the 18-64 year-old age group as foodworkers and remain foodworkers until they retire, are lost to death, or age into the 65+ age group. The proportion τ is equal to the number of people who are retiring or dying out of the foodworker population divided by the number of people ageing out of the 5-17 year-old age group. Although the minimum working age in the U.S. is 14 years-old (*34*) and about half of 65 year-olds are still working (*35*), the foodworker population was restricted to the 18-64 year-old age group for computational efficiency. The foodworker population was maintained at 8.2 million, which is the number of Americans estimated to work in food preparation and serving related occupations, according to the Bureau of Labor Statistics 2013 Occupational Employment Statistics (*36*).

We assumed the consumer population experiences a force of infection from consumer-consumer contact and from consumer-foodworker contact (i.e. $\lambda_{tot,i}(t)$, Appendix), while the foodworker population experiences a force of infection that is equivalent to only consumer-consumer contact (i.e. $\lambda_{3,j}(t)$, Appendix). Both forces of infection assume asymptomatic individuals are 5% as infectious as symptomatic individuals (*37*). Contact rates amongst consumers were a further adaptation from the European POLYMOD Study (*38*) used in Simmons et al. (*11*) (Table 2). The contact rates of consumers with foodworkers were derived from the 2011-2012 National Health and Nutrition Examination Survey (NHANES) (*39, 40*) by taking the weighted average of away-from-home meals by age within each age group.

Model Design: exclusion of infected foodworkers

In order to fulfill the study objective of predicting the burden of norovirus disease averted when excluding infected foodworkers, additional compartments were created in order to model the exclusion of various proportions of infected foodworkers from work (i.e. I'_E and A'_E) and/or for various periods of time when asymptomatic (i.e. A'_1 and A'_2). By excluding foodworkers from work, we limit the force of infection experienced by consumers from foodworkers by reducing the number of occupants in the E', I', and A' compartments. Φ_1 is the proportion of symptomatic foodworkers who are excluded from work, Φ_2 is the proportion of foodworkers who continue to be excluded from work when asymptomatic, and Φ_3 is the proportion of foodworkers who are excluded from work after working while symptomatic. A $\Phi_3 > 0$ might reflect the situation in which the foodworker fails to exclude him or herself from work while symptomatic but is subsequently excluded after a symptomatic episode at the workplace (e.g. public vomiting event) and remains excluded from work afterwards. Model equations can be found in the Appendix. The model was constructed, fitted, and simulated using Berkeley Madonna (University of California at Berkeley, California).

Model Fitting

The referent scenario was defined as excluding from work $66.\bar{6}\%$ symptomatic foodworkers and zero asymptomatic foodworkers. This was based on the 20% of foodworkers that reported working at least one shift in the past year while ill with diarrhea or vomiting reported by Carpenter et al. (*30*) and the 0.6 episodes of acute diarrheal illness per person per year in the U.S. reported by Jones et al. (*41*). We defined the quotient of 0.2/0.6 to be the proportion of working ill foodworkers (i.e., not excluded), thus the inverse was used as the baseline proportion of ill foodworkers that were excluded (Φ_1). Although exclusion of asymptomatic foodworkers is also recommended for two days after symptoms resolve (*22, 27*), data on compliance with this recommendation was unavailable and thus was kept at zero in the referent scenario.

By minimizing the difference between simulated and desired outputs, two parameters were fit, namely the probability of infection given exposure through direct person-to-person contact (κ) and the probability of disease given exposure when in contact with infectious foodworker (p). The κ and *p* parameters were adjusted such that (A) the referent scenario would yield a national burden of 20 million norovirus cases, based on the findings from Hall et al. (*1*), and (B) the national burden would be reduced by 15.7% when direct foodborne transmission is removed from the population (i.e. $\lambda_{i,fw}(t) = 0$). We assumed the attributes of the norovirus outbreaks reported from 2009 to 2012, as described in Hall et al. (*22*), are representative of all norovirus cases that occur in the U.S. The 15.7% was derived from the product of (i) the proportion of all norovirus outbreaks reported in NORS between 2009 and 2012 that were foodborne (i.e. 1008 norovirus outbreaks reported with foodborne as the primary mode of transmission divided by 4318 total norovirus outbreaks reported from 2009 to 2012), (ii) the proportion of foodborne norovirus outbreaks in which food was not prepared in a private setting (i.e. the difference of 904 foodborne norovirus outbreaks for which a setting of food preparation was reported minus 37 outbreaks where food was prepared in private residence divided by 904), and (iii) the proportion of foodborne norovirus outbreaks in which an infected foodworker was implicated as the source (i.e. 364 foodborne norovirus outbreaks reporting infected foodworker as implicated source of contamination divided by 520 foodborne norovirus outbreaks for which factors contributing to food contamination were reported)(*22*). When testing criterion (B), direct foodborne transmission was removed by holding consumer-consumer force of infection for each age group (i.e. $\lambda_{3,j}(t)$) constant and by setting the consumer-foodworker force of infection (i.e. $\lambda_{3,fw}(t)$) to zero.

Model Simulations

In order to model the overall incidence of norovirus in the U.S. as a result of excluding infected foodworkers from work, we predicted the number of norovirus cases averted relative to the referent scenario by ranging the proportion of excluded symptomatic foodworkers (i.e. Φ_1 range = [0,1]) as well as asymptomatic foodworkers, irrespective of previous symptomatic exclusion (i.e. Φ_2 range = Φ_3 range = [0,1]). The proportions of asymptomatic exclusion were set equal (i.e. $\Phi_2 = \Phi_3$) for all scenarios for which this specification was permitted by the model construct. For instance, if 0% of symptomatic foodworkers are excluded from work (i.e. $\Phi_1 = 0$), then there are zero foodworkers to continue excluding as asymptomatic foodworkers (i.e. $\Phi_2 = 0$), per model construct. On the other hand, if 100% of symptomatic foodworkers are excluded from work (i.e. $\Phi_1 = 1$), then there are zero working symptomatic foodworkers to exclude when asymptomatic (i.e. $\Phi_3 = 0$), per model construct. Here, it was assumed that excluded asymptomatic foodworkers were excluded for 2 days (i.e. $\rho_1 = 2$), per FDA Food Code recommendations. The proportion of excluded symptomatic foodworkers (i.e. Φ_1 = [0,1]) and the proportion of excluded asymptomatic foodworkers (i.e. $\Phi_2 = \Phi_3 =$

[0,1]) were discretized at 0.1, yielding 121 pairs of parameter values for model simulations.

We also investigated the number of norovirus cases averted for excluding 50% asymptomatic foodworkers for a positive, whole number of days, regardless of previous symptomatic exclusion (i.e. $\Phi_2 = \Phi_3 = 0.5$). For any given number of days of asymptomatic exclusion, we still assumed 66.$\bar{6}$% of symptomatic foodworkers did not work (i.e. $\Phi_1 = 0.6\bar{6}$). For 10 days exclusion of 50% asymptomatic foodworkers, the A'_2 compartment was removed and the live, excluded asymptomatic foodworkers who did not age into the 65+ age group moved directly to the recovered state.

Results

Model fitting

Table 1 reports the fitted values for the fully parameterized model, namely the probability of infection due to direct person-to-person transmission, κ, of 0.7137 and the probability of disease given exposure when in contact with infectious foodworkers, p, of 0.52284. The fully parameterized model under the referent scenario appropriately predicted an annual national burden of 20 million norovirus cases and a 15.7% reduction in norovirus burden when direct foodborne transmission was removed from the population.

Model simulations: Proportion of foodworkers excluded

Figure 2 shows that the number of cases averted per year for each age group was more sensitive to changes in the proportion of symptomatic foodworkers excluded than to changes in the proportion of asymptomatic foodworkers excluded. When varying the proportion of symptomatic foodworker exclusion for any given proportion of asymptomatic foodworkers excluded (i.e. $\Phi_2 = \Phi_3 =$ constant), 18–64 year-olds experienced the largest and 0–4 year-olds the smallest change in number of cases averted per year. Under the referent assumption of 0% asymptomatic foodworker exclusion, the number of cases averted per year for 18–64 year-olds ranged from -8.4 million cases (i.e., 8.4 million additional norovirus cases than in the referent scenario) at 0% symptomatic foodworker exclusion to 4.6 million cases averted at 100% symptomatic foodworker exclusion (absolute range of 13.0 million cases). In contrast, under the referent assumption of 0% asymptomatic foodworker exclusion, the number of cases per year for 0-4 year-olds ranged from 1.8 million additional cases at 0% symptomatic foodworker exclusion to 1.4 million cases averted at 100% symptomatic foodworker exclusion (absolute range of 3.2 million cases).

When varying the proportion of asymptomatic foodworker exclusion for any given proportion of symptomatic foodworkers excluded (i.e. $\Phi_1 =$ constant), 18–64 year-olds, again, experienced the largest change in number of cases averted per year. The change in the number of cases averted per year was smallest for 0-4 year-olds when excluding ≤50% of symptomatic foodworkers and for 65+ year olds when excluding ≥60% of symptomatic foodworkers. Under the referent assumption of $66.\bar{6}\%$ symptomatic foodworker exclusion, the number of cases averted per year for 18–64 year-olds reached 700,124 cases at 100% asymptomatic foodworker exclusion. In contrast, under the referent assumption of $66.\bar{6}\%$ symptomatic foodworker exclusion, the number of cases averted per year for 65+ year-olds reached 168,422 cases at 100% asymptomatic foodworker exclusion.

Figure 3 shows that the proportion of cases averted per year for each age group was also more sensitive to changes in the proportion of symptomatic foodworkers excluded than to the proportion of asymptomatic foodworkers excluded. When varying the proportion of symptomatic foodworker exclusion for any given proportion of asymptomatic foodworkers excluded (i.e. $\Phi_2 = \Phi_3 =$ constant), 65+ year-olds experienced the largest and 0–4 year-olds the smallest change in proportion of referent cases averted per year. Under the referent assumption of 0% asymptomatic foodworker exclusion, the proportion of referent cases averted per year for 65+ year-olds ranged from -1.11 baseline cases (i.e., 111% more norovirus cases) at 0% symptomatic foodworker exclusion to 0.51 baseline cases (i.e., 51% fewer norovirus cases) at 100% symptomatic foodworker exclusion. In contrast, under the referent assumption of 0% asymptomatic foodworker exclusion, the proportion of referent cases averted per year for 0-4 year-olds only ranged from -0.35 baseline cases at 0% symptomatic foodworker exclusion to 0.28 baseline cases at 100% symptomatic foodworker exclusion.

When varying the proportion of asymptomatic foodworker exclusion for any given proportion of symptomatic foodworkers excluded (i.e. $\Phi_1 =$ constant), 65+ year-olds experienced the largest and 0–4 year-olds the smallest change in proportion of referent cases averted per year. Under the referent assumption of $66.\overline{6}\%$ symptomatic foodworker exclusion, the proportion of referent cases averted per year for 65+ year-olds reached 0.08 baseline cases at 100% asymptomatic foodworker exclusion. In contrast, under the referent assumption of $66.\overline{6}\%$ symptomatic foodworker exclusion, the proportion of referent cases averted per year for 0-4 year-olds reached 0.04 baseline cases at 100% asymptomatic foodworker exclusion.

Model simulations: Duration of foodworker exclusion

Figure 4 shows the number of cases averted per year when 50% asymptomatic foodworkers were excluded for varying number of asymptomatic days. The reported number of cases averted per year is still with respect to the number of norovirus cases under referent conditions. The number of cases averted per year ranged from 0.3 million cases at 1 day of asymptomatic exclusion to 3.1 million cases at 10 days of asymptomatic exclusion (absolute range of 2.8 million cases). For any given number of days of asymptomatic exclusion, 18-64 year olds experienced the greatest number of cases averted annually, ranging 0.17 million cases at 1 day exclusion to 1.75 million cases at 10 days exclusion (absolute range of 1.58 million cases). The number of cases averted annually for 0–4 year-olds, 5–17 year-olds, and 65+ year-olds did not differ by more than 0.066 million on any given day. Among these three age groups, the number of cases averted ranged 0.042 million on day 1 by 65+ year-olds and 0.48 million on day 10 by 0-4 year-olds.

Comparison of scenarios

Table 3 contains the full range of number of norovirus cases averted per year from baseline, under the assumption the referent is true. By excluding $66.\bar{6}$% symptomatic foodworkers and assuming 0% asymptomatic exclusion, our model estimates a maximum average of 14.7 million norovirus cases have already been avoided. If all infected foodworkers are excluded only while symptomatic, 8.3 million norovirus cases are averted annually. However, if all infected foodworkers are excluded while symptomatic and continue to be excluded for 2 days post-symptomatic (i.e., 100% compliance with current recommendations), 9.5 million norovirus cases are avoided annually.

Discussion

The results of this study highlight the relative impacts of symptomatic and post-symptomatic exclusion of ill food workers on the incidence of norovirus in the U.S. A key strength of our model was its predictive capabilities of estimating the impact of infected foodworker exclusion for a range of scenarios. These scenarios would otherwise be impractical and/or costly to test on a nationally representative sample. By incorporating multiple transmission pathways of norovirus at the population-level, we were able to evaluate both the direct and indirect effects of food worker exclusion interventions. Furthermore, our model was constructed in such a way that allows for (i) comparison of results with other population-level interventions such as vaccines and (ii) modeling other interventions targeting foodworkers in the future, which are discussed later in this section.

The reason the model predicted a greater effect of symptomatic exclusion than asymptomatic exclusion on norovirus burden is because our model had a built-in peak for infectiousness. We assumed the infectiousness of foodworkers during their incubation and asymptomatic periods was 5% that of their symptomatic period. As mentioned before, comparing symptomatic individuals to asymptomatic individuals, the greater shedding (*17*) and transmission potential (*37*) is supported in other studies. The specific assignment of 5% was adopted from the model input parameters used by Simmons et al. to estimate the duration of immunity to noroviruses. The biological basis for this differential infectiousness is rooted in the transmission potential of the symptoms themselves, namely acute onset diarrhea and vomiting. One example of how symptomatic individuals can facilitate the efficient transmission of norovirus would be the likely transmission of norovirus concluded from a 2008 plane flight from Boston, Massachusetts to Los Angeles, California, where six passengers reported to have experienced vomiting or diarrhea during the flight (*42*). All ill passengers were part of the same tour company, and during the days following the flight, seven non-tour group passengers met the case definition for norovirus disease (*42*). Another example of the likely contribution of norovirus transmission from symptomatic individuals was in January 2009 on a cruise ship, where person-to-person transmission was suspected to lead to an outbreak(*43*). A cohort study found that case passengers, compared to non-case passengers, were significantly more likely to have an ill cabin mate and to have witnessed the single public vomiting event while boarding (*43*).

The age-group specific characteristics of model estimates can be explained by decisions in the model construct, which are rooted in empirical data. For instance, the age groups defined in the model were not comprised of an equal number of occupants at equilibrium. The 18-64 year-old age group experienced the greatest number of cases averted compared to other age groups because it possessed the greatest number of occupants compared to other age groups. In comparison, 65+ year-olds experienced the greatest proportion of baseline cases averted, because the number of away-from-home meals eaten per day, as estimated from NHANES, relative to the number of direct person-to-person contacts per day, as adapted from the POLYMOD study, was greatest among 65+ year-olds compared to other age groups.

Our model found that eliminating norovirus transmission from infected foodworkers, which is responsible for approximately 16% of norovirus outbreaks nationally, could avert almost half of the norovirus burden of the referent scenario. This finding speaks to the indirect benefits of targeted interventions, which has been predicted in a comparative analysis of rotavirus transmission dynamics after introducing a rotavirus vaccine in England and Wales (*44*). Specifically, five different models were validated against reported rotavirus gastroenteritis (RVGE) data based on AIC values and exhibited good fits. One year following the introduction of the vaccine, the incidence of severe RVGE was reduced 1.8-2.9 times more than what was expected from direct effects (28%-50% reduction) (*44*). Five years following the vaccine introduction, the incidence of severe RVGE was reduced by 1.1-1.7 times more than what was expected from direct effects (54%-90% reduction) (*44*). Our results suggest that similar indirect benefits might be realized through exclusion of infected food workers, as these individuals can amplify community transmission through widespread exposure to contaminated food. Such foodborne illnesses in turn seed numerous subsequent chains of transmission.

A detailed and complex approach comes with its unique set of limitations. The linear behavior of the number of cases averted per year from excluding asymptomatic foodworkers for an increasing number of asymptomatic days (Figure 4) is a consequence of assuming post-symptomatic infectiousness remains constant at 5% the infectiousness of symptomatic foodworkers for the entire duration of the asymptomatic state. While this discontinuous change in infectiousness to a smaller, constant value reflects evidence that asymptomatic shedders contribute less to transmission (*37*), it does not reflect the gradual reduction in norovirus shedding observed in human challenge studies (*17*) nor does it reflect the potential changes in human behavior over the course of the symptomatic and post-symptomatic periods. Additionally, the probability of infection due to direct person-to-person contact (κ) and the probability of disease given exposure when in contact with an infectious foodworker (p) were not informed by empirical data, thus requiring use of our model to estimate these two input parameters. Thirdly, each parameter input would realistically have a probability distribution, but we simplified this aspect of reality for computational efficiency. Ideally, probability distributions for each parameter estimate would reflect norovirus strain diversity and differences in the history of infection and immunity for individuals nationally.

Our findings support the current FDA Food Code recommendation of excluding all infected foodworkers while they are symptomatic as well as ≥48 hours after symptoms subside. While the parameters being altered in the study are behavioral by nature, the change in behavior might be realized through policy change, educational campaigns, incentives (e.g., sick pay), or other interventions that address the reasons for which foodworkers decide to work while ill (*30*). Studies that model the social network of excluded infected foodworkers, non-excluded infected foodworkers, and consumers are needed in the future in order to compare the potential economic value and public health benefits of specific interventions targeting foodworkers.

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Tables

Table 1. Model parameters

Parameter	Variable	Value	Source
Demographics			
Number of foodworkers in population	fw_population	8,209,000	Bureau of Labor Statistics, 2013 report
Number of individuals in population			
0-4 year olds	$population_1$	21,636,837	CDC Wonder Dataset: 2011 Census Projections
5-17 year olds	$population_2$	53,122,768	CDC Wonder Dataset: 2011 Census Projections
18-64 year olds	$population_3$	195,720,222	CDC Wonder Dataset: 2011 Census Projections
65+ year olds	$population_4$	41,121,053	CDC Wonder Dataset: 2011 Census Projections
Disease natural history			
Duration of incubation period, hr	μ_s	32.8	T. Devasia et al 2014
Duration of symptoms, d	μ_a	2	T. Devasia et al 2015
Duration of asymptomatic infectiousness, d	ρ	10	Atmar et. al 2008
Duration of asymptomatic infectiousness of foodworkers excluded from work, d	ρ_1	2 if referent, otherwise 0	Modeled
Duration of asymptomatic infectiousness of foodworkers after returning to work, d	ρ_2	$10-\rho_1$	Atmar et. al 2008
Duration of immunity, d	θ	1875	Simmons et al 2013
Transmission			
Relative infectiousness during incubation and asymptomatic period	Pre, Post	0.05	Sukhrie et al. 2011
Probability of disease given exposure when in contact with infectious consumer			
0-4 year-olds	q_1	0.2083897	Estimated
5-64 year-olds	q_2	0.03173352	Estimated
65+ year-olds	q_3	0.01960296	Estimated
Contact rate with foodworkers, away from home meals per day			
0-4 year-olds	avg_fw_1	0.269762846	Estimated from NHANES 2011-2012
5-17 year-olds	avg_fw_2	1.083640553	Estimated from NHANES 2011-2012
18-64 year-olds	avg_fw_3	0.567061083	Estimated from NHANES 2011-2012

Exclusion of foodworkers from work (referent)			
proportion of foodworkers not working while he/she is symptomatic	Φ_1	2/3	Carpenter et al 2013, Jones et al 2007
proportion of excluded symptomatic foodworkers who continue to not work while he/she is asymptomatic	Φ_2	0	Baseline assumption
proportion of working symptomatic foodworkers who do not work while he/she is asymtpomatic	Φ_3	0	Baseline assumption
Fitted parameters			
Probability of infection due to direct person-to-person transmission	κ	0.7137	Fitted
Probability of disease given exposure when in contact with infectious foodworker	p	0.52284	Fitted

Table 2. Number of contacts per day between individuals of two age groups (c_{ij}*avg_cons_i)

Ages (years)	0 to 4	5 to 17	18 to 64	65+
0 to 4	2.23939	1.46061	4.1053	0.313636
5 to 17	0.531421	9.83074	4.85666	0.300991
18 to 64	0.645888	2.10011	10.5063	0.691179
65+	0.375	0.989128	5.25272	1.91667

Source: Mossong et. al 2008 and further adapted from Simmons

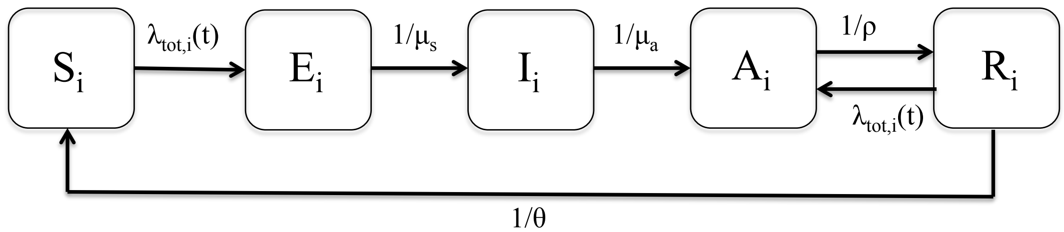
Table 3. Number of annual norovirus cases and annual cases averted in the U.S. compared against referent scenario

Scenario description	Proportion of symptomatic foodworkers excluded (Φ1)	Proportion of asymptomatic foodworkers excluded (Φ2 and Φ3)	Number of norovirus cases (million/year)	Number of norovirus cases averted (million/year)
No exclusion of infected foodworkers	0	0	34.7	-14.7
Baseline	2/3	0	20.0	referent
All infected foodworkers excluded only while symptomatic	1	0	11.7	8.3
All infected foodworkers excluded while symptomatic and 2 days asymptomatic	1	1*	10.5	9.5

* Φ3=0, per model structure

Figures

(a)



(b)

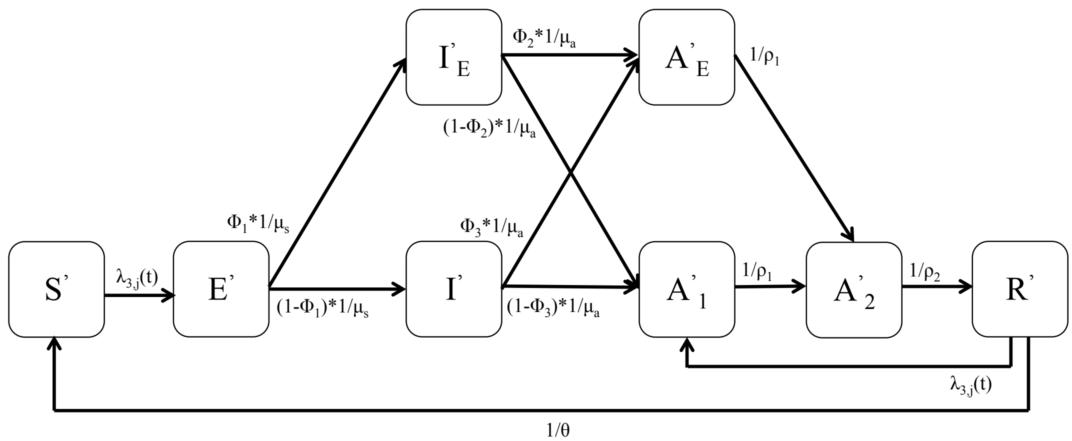


Figure 1: Schematic diagram of states of infection and immunity among (a) consumer and (b) foodworker populations. (a) The consumer population is born into the susceptible compartment and becomes exposed at the total force of infection ($\lambda_{tot,i}(t)$). The total force of infection is comprised of a force from other consumers and a force from foodworkers. For a given consumer in age group i, the force of infection he or she experiences from foodworkers is greater than that from consumers. Once exposed, the population becomes symptomatic at a rate inverse to the incubation period ($1/\mu_s$). The infected population becomes asymptomatic at a rate inverse to the duration of symptomatic infection ($1/\mu_a$) before recovering at a rate inverse to the duration of asymptomatic infection ($1/\rho$). The recovered population can either become asymptomatically infected at the total force of

infection or become susceptible by waning of natural immunity (1/θ). For a given state of infection, a proportion of young adults (i=2) become foodworkers at adult age (i=3) and return to the consumer population at elderly age (i=4), all the while remaining in the same state. (b) The foodworker population progresses through states of infection and immunity in the same fashion as the consumer population, except the force of infection experienced by susceptible foodworkers is just that among the consumer population. Foodworkers may experience exclusion from work when symptomatic (I'_{E3}) and/or when asymptomatic (A'_{E3}). Excluded asymptomatic foodworkers may return to work before he or she stops shedding virus. The duration of asymptomatic infection remains the same (10 days) regardless of the duration of exclusion.

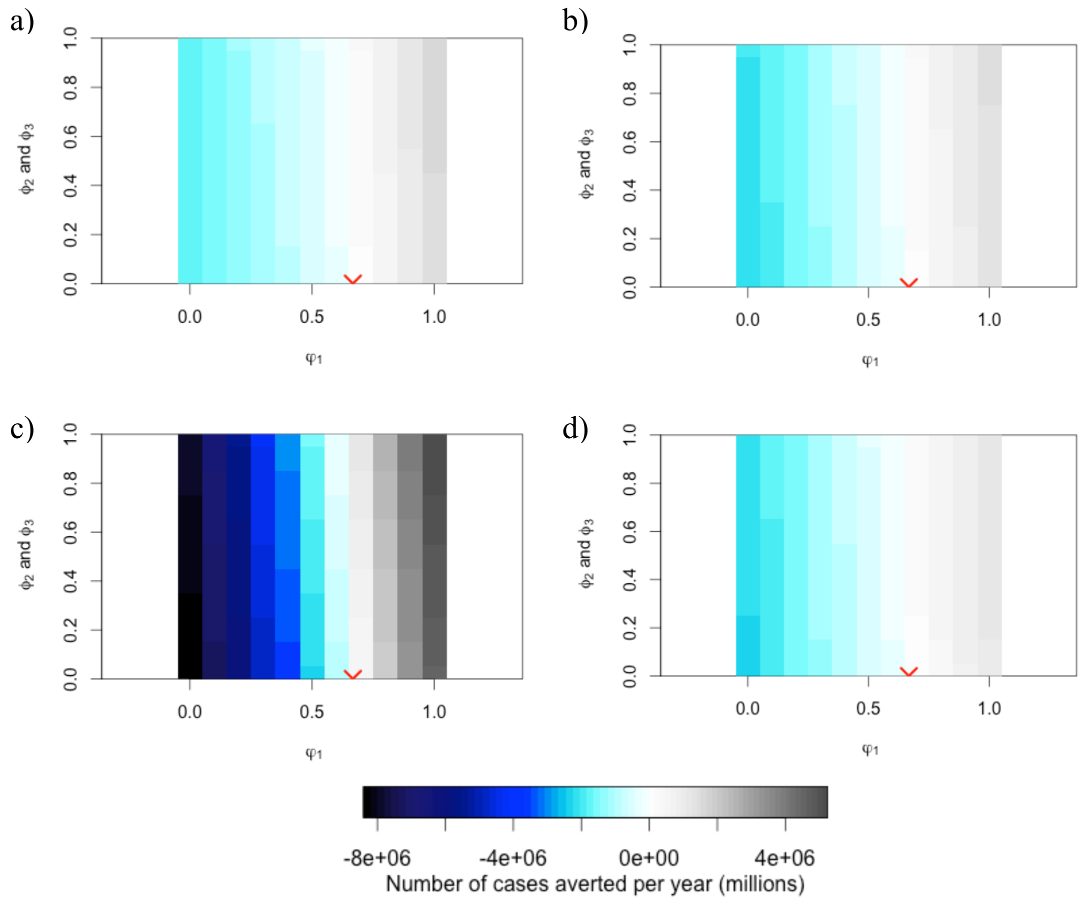


Figure 2: Number of norovirus cases averted annually for a) 0-4 year-olds, b) 5-17 year-olds, c) 18-64 year-olds, d) >65 year-olds. The red arrow points to the baseline scenario. These outputs result from proportions (ranging 0 to 1) of the foodworker population excluded from work for entirety of symptomatic period and for two days out of ten possible days while asymptomatic. In the majority of scenarios, the proportions of asymptomatic exclusion are the same in value regardless of symptomatic exclusion (i.e. $\Phi_2 = \Phi_3$). When 0% of symptomatic foodworkers are excluded from work (i.e. $\Phi_1 = 0$), it is impossible to model continued exclusion of asymptomatic foodworkers (i.e. $\Phi_2 = 0$), per model construct. When 100% of symptomatic foodworkers are excluded from work (i.e. $\Phi_1 = 1$), it is impossible to model exclusion of asymptomatic foodworkers who worked while symptomatic (i.e. $\Phi_3 = 0$), per model construct.

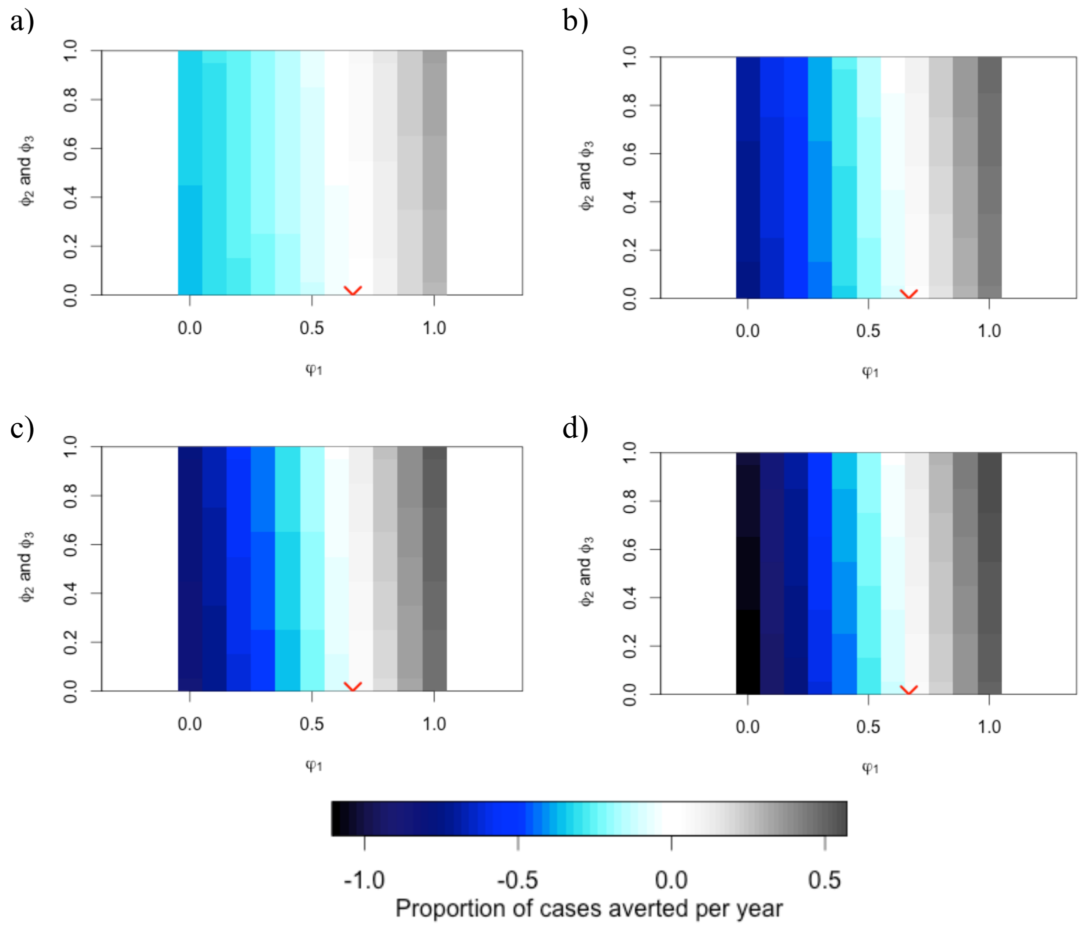


Figure 3: Proportion of norovirus cases averted annually for a) 0-4 year-olds, b) 5-17 year-olds, c) 18-64 year-olds, d) >65 year-olds. The red arrow points to the baseline scenario. These outputs result from proportions (ranging 0 to 1) of the foodworker population excluded from work for entirety of symptomatic period and for two days out of ten possible days while asymptomatic. In the majority of scenarios, the proportions of asymptomatic exclusion are the same in value regardless of symptomatic exclusion (i.e. $\Phi_2 = \Phi_3$). When 0% of symptomatic foodworkers are excluded from work (i.e. $\Phi_1 = 0$), it is impossible to model continued exclusion of asymptomatic foodworkers (i.e. $\Phi_2 = 0$), per model construct. When 100% of symptomatic foodworkers are excluded from work (i.e. $\Phi_1 = 1$), it is impossible to model exclusion of asymptomatic foodworkers who worked while symptomatic (i.e. $\Phi_3 = 0$), per model construct.

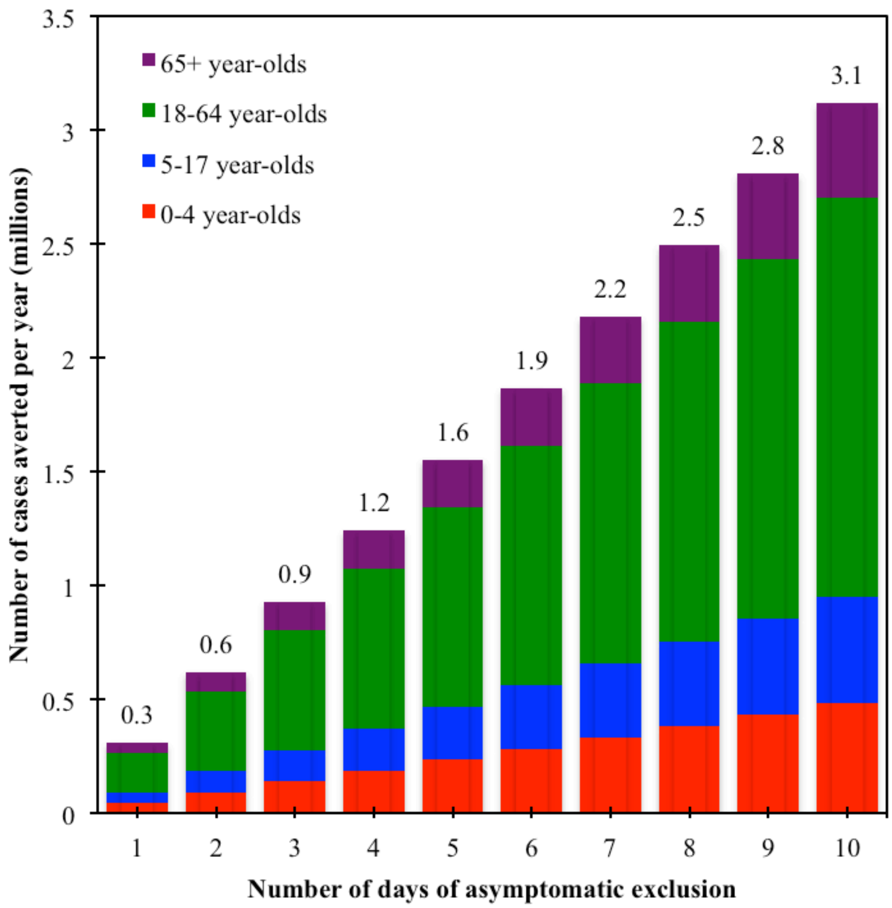


Figure 4: Number of norovirus cases averted annually from baseline for a given number of days of excluding 50% asymptomatic foodworkers (i.e. $\Phi_2 = \Phi_3 = 0.5$). Here, it is still assumed that $66.\bar{6}$% symptomatic foodworkers are excluded (i.e. $\Phi_1 = 0.6\bar{6}$). Population totals are denoted for each day excluded and the counts are further broken down into age groups 0-4 years-old, 5-17 years-old, 18-64 years-old, and >65 years-old.

Chapter III

- The results of this study highlight the indirect benefits of targeting food workers, specifically, in norovirus interventions
- The findings of this study underscore the importance of excluding both symptomatic and asymptomatic foodworkers from work, as recommended in the FDA Food Code
- The model developed in this study provides a tool for evaluation of future interventions targeting food workers, such as policies regarding paid sick-leave or vaccination

Appendix

Equations

$$\frac{\partial S_i}{\partial t} = B + \frac{1}{\theta}R_i - \left(a_i + \lambda_{tot,i}(t) + D_i\right)S_i + (1-\tau)S_{i-1}a_{i-1} + \delta S' a_{i-1}$$

$$\frac{\partial E_i}{\partial t} = \lambda_{tot,i}(t)S_i - \left(a_i + \frac{1}{\mu_s} + D_i\right)E_i + (1-\tau)E_{i-1}a_{i-1} + \delta E' a_{i-1}$$

$$\frac{\partial I_i}{\partial t} = \frac{1}{\mu_s}E_i - \left(a_i + \frac{1}{\mu_a} + D_i\right)I_i + (1-\tau)I_{i-1}a_{i-1} + \delta I' a_{i-1}$$

$$\frac{\partial A_i}{\partial t} = \frac{1}{\mu_a}I_i + \lambda_{tot,i}(t)R_i - \left(a_i + \frac{1}{\rho} + D_i\right)A_i + (1-\tau)A_{i-1}a_{i-1} + \delta A' a_{i-1}$$

$$\frac{\partial R_i}{\partial t} = \frac{1}{\rho}A_i - \left(a_i + \frac{1}{\theta} + \lambda_{tot,i}(t) + D_i\right)R_i + (1-\tau)R_{i-1}a_{i-1} + \delta R' a_{i-1}$$

$$\frac{\partial S'}{\partial t} = \frac{1}{\theta}R' - \left(a_3 + \lambda_{3,i}(t) + D_3\right)S' + \tau S_2 a_2$$

$$\frac{\partial E'}{\partial t} = \lambda_{3,i}(t)S' - \left(a_3 + \frac{\phi_1}{\mu_s} + \frac{1-\phi_1}{\mu_s} + D_3\right)E' + \tau E_2 a_2$$

$$\frac{\partial I'_s}{\partial t} = \frac{\phi_1}{\mu_s}E' - \left(a_3 + \frac{\phi_2}{\mu_a} + \frac{1-\phi_2}{\mu_a} + D_3\right)I'_s$$

$$\frac{\partial I'}{\partial t} = \frac{1-\phi_1}{\mu_s}E' - \left(a_3 + \frac{\phi_3}{\mu_a} + \frac{1-\phi_3}{\mu_a} + D_3\right)I' + \tau I_2 a_2$$

$$\frac{\partial A'_s}{\partial t} = \frac{\phi_2}{\mu_a}I'_s + \frac{\phi_3}{\mu_a}I' - \left(a_3 + \frac{1}{\rho} + D_3\right)A'_s$$

$$\frac{\partial A'_1}{\partial t} = \frac{1-\phi_2}{\mu_a}I'_s + \frac{1-\phi_3}{\mu_a}I' + \lambda_{3,i}(t)R' - \left(a_3 + \frac{1}{\rho_1} + D_3\right)A'_1 + \tau A_2 a_2$$

$$\frac{\partial A'_2}{\partial t} = \frac{1}{\rho_1}(A'_1 + A'_s) - \left(a_3 + \frac{1}{\rho_2} + D_3\right)A'_2$$

$$\frac{\partial R'}{\partial t} = \frac{1}{\rho_2}A'_2 - \left(a_3 + \frac{1}{\theta} + \lambda_{3,i}(t) + D_3\right)R' + \tau R_2 a_2$$

where B = $\begin{cases} deaths & \mathrm{i} = 1 \\ 0 & \mathrm{else} \end{cases}$

$$i = j = \begin{bmatrix} 1 & young\ child \\ 2 & old\ child \\ 3 & adult \\ 4 & elderly \end{bmatrix}$$

τ = $\begin{cases} 1 & i = 1 \\ 0 & i = 2,4 \\ (\mathrm{retire\_all} + \mathrm{dead\_fw})/(\mathrm{population}_2 * \mathrm{age\_rate}_2) & i = 3 \end{cases}$

δ = $\begin{cases} 1 & \mathrm{i} = 4 \\ 0 & \mathrm{else} \end{cases}$

$$\rho = \rho_1 + \rho_2 = 10$$

$$S_0 = a_0 = a_1 = E_0 = I_0 = A_0 = R_0 = 0$$

Force of Infection:

$$\lambda_{tot,i}(t) = \lambda_{i,j} + \lambda_{i,fw}$$

$$\lambda_{i,j}(t) = \kappa * avg\_cons_i * q_i * seas \sum_{j}^{4} \frac{c_{ij} * (Pre * E_j + I_j + Post * A_j)}{population_j}$$

$$\lambda_{i,fw}(t) = \frac{avg\_fw_i * p_i * seas * (Pre * E' + I' + Post * A')}{fw\_population}$$

where $seas = 1 + \beta_1 \cos(2\pi years + \omega)$