FINAL SCIENTIFIC REPORT

Modelling the Foodborne Transmission Mechanisms for Norovirus: A Study for the Food Standards Agency

FS241027

April 2014

David C Lane

This report should be viewed/printed in colour

Executive Summary

Norovirus is an enteric virus which generated an estimated three million UK cases of infectious intestinal disease in 2009. The main vector for norovirus is person-to-person contact but it can also be transmitted via a number of food-related mechanisms and is estimated to be the third most common source of foodborne disease in the UK, with more than 70,000 such cases p.a.
The purpose of this study was to develop a system dynamics simulation model to: improve understanding of the foodborne transmission mechanisms; give insight into the relative importance of foodborne transmission; indicate where FSA might target its efforts to reduce foodborne transmission. This work evolved into two parts.

Part I involved the construction of a system dynamics model. A multi-agency expert team was consulted and discussed the model at a workshop. The model drew on existing person-to-person work but replaced an exogenous 'forcing term' for foodborne transmission with a set of internalised (endogenised) mechanisms. The effects modelled were: contamination of bivalve shellfish via sewage; contamination of soft berry fruits and leafy vegetables via the use of sludge as a fertiliser, via infectious harvesters, via infectious food processers, and via infectious food preparers in home and catering settings; contamination of other foodstuffs via infectious food preparers in home and catering settings.
The conclusion was that it was indeed possible to disaggregate the foodborne routes as plausible causal mechanisms and that the modelling was useful to improve understanding of the mechanisms. The detail of the model, in the case of unknown parameter values, could be used to create an agenda for future research. In the case of parameter values that can, in principle, be influenced, the model indicated where FSA should target its efforts in support of the FSA's 'Foodborne Disease Strategy'.

Part II employed an extended person-to-person model in a very different way than previously, using both closed-form mathematical solutions and simulation runs. Calibrating the model using new data allows the prevalence of norovirus to be calculated: the number of individuals susceptible, exposed, recovered immune etc. By exploring scenarios the model then generates some striking results concerning policy options.
Foodborne infections make up only ~2½ % of the incidence rate. Yet if foodborne infections doubled, modelling shows infections rising by a full 1/3. Reducing them by half produces a 25% reduction in total incidence. Removing all foodborne cases produces a 75% reduction in norovirus, cases falling to 750,000 annually. These non-linear effects indicate that actions which have reduced foodborne infections to their current level have yielded significant benefit and that more benefit could be gained by further actions.
However, this must be seen in the context of the model's much greater sensitivity to the person-to-person behaviour effects. Increasing these effects only 10% triples the incidence

rate, whilst a decrease of only 25% causes incidence to collapse to ~10% its current value. This high sensitivity yields two conclusions. First, the observed variation in norovirus incidence over time may be explicable in terms of small changes in human behaviour. Simulation demonstrates this. Second, it is not just foodborne incidence that should be considered for any future actions. Norovirus should be considered in an holistic manner, the benefits of targeting person-to-person effects being judged on the same basis as the benefits for reducing foodborne effects. In this way the modelling acts as an organizing, or prioritising framework for discussions on interventions.

Eight specific recommendations are made:-

1) The new representations of foodborne transmission – in model diagrams and equations – should be made available, both to communicate current thinking and to offer a framework for critique.
2) Means of reducing foodborne transmission should be analysed in terms of practicality and cost using the set of intervention parameters produced in this study.
3) The set of those foodborne transmission parameters whose values are not currently known should be considered for agenda-setting for future work, contributing to discussions on research priorities.
4) The goal of fully endogenising the foodborne mechanisms in the style of Part 1 should be re-considered, bearing in mind the limited data that exists but also the 'imported strawberries problem', the fact that infections can result from foodstuffs produced outside the area of the population of interest. How such modelling might add to the policy process should also be critically re-evaluated.
5) Since norovirus prevalence depends also on person-to-person transmission, an holistic view should be adopted and interventions in person-to-person behavioural effects explored. This would involve work by appropriate agencies on what character such interventions might take, as well as analysis of their practicality and cost.
6) Uncertainties relating to causal mechanisms and parameter values in the current model should be explored using alternative model formulations and sensitivity analysis.
7) Heterogeneity of effects operating in the world should be included in the model and explored using stochastic variables.
8) Further modelling explorations, in the style of Part 2, should be conducted, to see the effects of stochastic changes to foodborne infections and the consequences of sudden outbreaks. Additionally, a simple model of a partly endogenised foodborne effect should be explored, disaggregating the current exogenous 'forcing term' into parts produced inside and outside the UK, and which represents the timescales on which different effects operate. Such a model has the potential to contribute to policy making and to the effective targeting of interventions aimed at reducing UK norovirus prevalence.

Contents

Frequently Used Abbreviations

BFLV	-	berry fruits and leafy vegetables
DCL	-	report author
FSA	-	Food Standards Agency
IID	-	infectious intestinal disease
MAD	-	mesophilic anaerobic digestion
NVGC	-	norovirus genome copies
SFD	-	stock/flow diagram

1 Introduction

This chapter sets the scene for the report. It introduces the subject of the research, norovirus, and describes the existing state of mathematical modelling of the infections that it causes in humans. It then records the aims of the FSA study and the contribution that this report makes to fulfil those aims. Finally, this chapter outlines the structure of the remainder of this report.

1.1 On Norovirus

Noroviruses are commonly known as the 'winter vomiting bug', and were previously referred to as 'Norwalk-like viruses'.[1] They are 'enteric viruses', simple sub-microscopic entities which only reproduce inside a host cell and which can inhabit the human intestinal tract [22]. In technical terms, they "are a genetically and antigenically diverse group of non-enveloped RNA viruses constituting 1 of the 4 genera of the family *Caliciviridae*" [36, p. 6]. Norovirus[2] is the most commonly identified cause of infectious intestinal disease and acute gastroenteritis in the USA and in Western Europe [12, 23, 41]. In the UK, norovirus generated around 2.8 million estimated cases in 2009. As the common name suggests, cases of norovirus exhibit a strong seasonality with much higher frequencies in the winter months [39, 47, 55] (See Fig. 1.1 overleaf).

Humans infected with norovirus may experience acute (i.e. very sudden) nausea, explosive vomiting and diarrhoea. In fact, such events may be the first indication of infection. Infected individuals may also experience high temperature, stomach cramps and headaches. Dehydration may produce complications and infection is more dangerous for the very young and the significantly elderly. Outbreaks are also observed in hospitals and residential homes where the effects of norovirus may be exacerbated by other existing conditions [30]. Greatly unpleasant as the experience is, it is usually self-limiting, with most people recovering from such symptoms after ~48 hours [26]

Norovirus transmission involves a link from one person to another. Sometimes this occurs directly, via bodily contact hand or airborne transmission. Sometimes it is indirect, via food, or water, or a 'fomite' (an object or material). Hence, although there is some conceptual overlap [6], transmission can usefully be thought of as occurring primarily via two routes; person-to-person and foodborne. With both routes it is noteworthy that norovirus requires a very low infectious dose, with perhaps only 1-100 virus particles being necessary to effect transmission [7, 27].

1. For detailed references concerning Norovirus, see [36].
2. From this point on, this term is used to refer both to the group of viruses and to the intestinal infection that they can produce in humans.

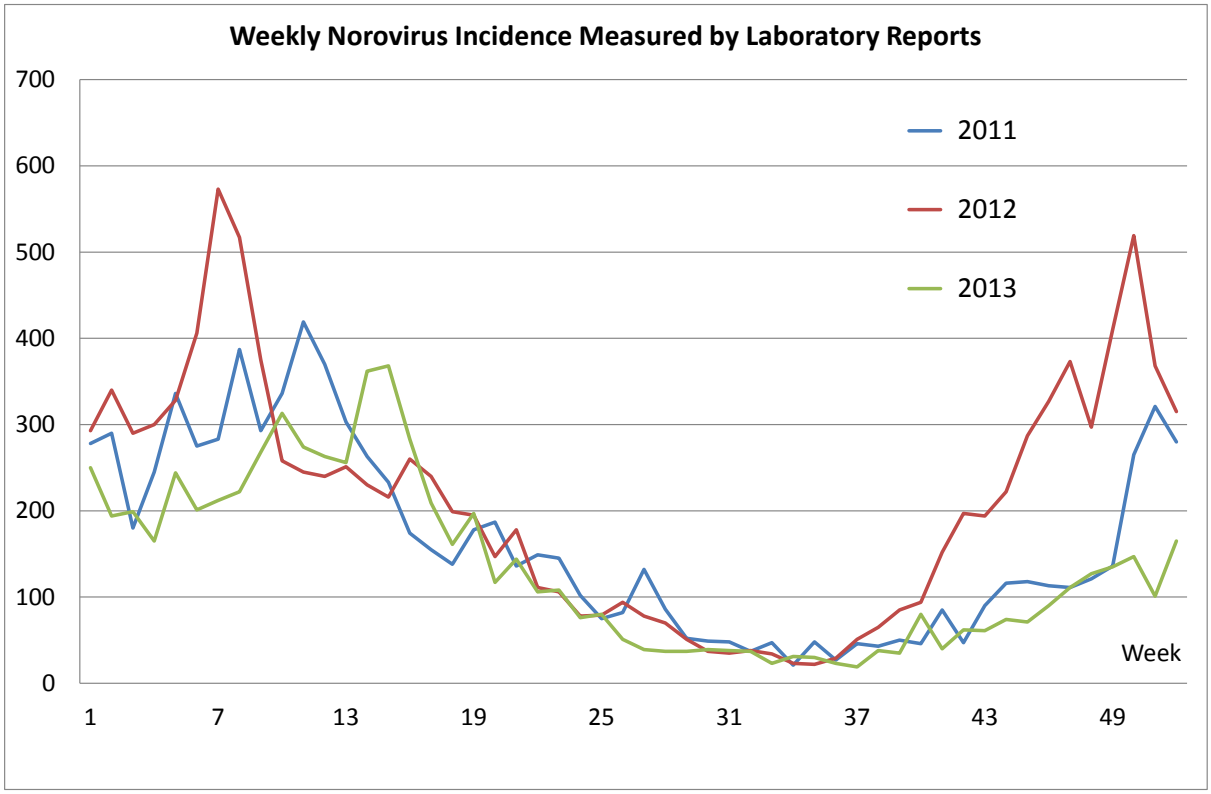


Figure 1.1: Weekly incidence of norovirus in England and Wales as measured by laboratory reports confirming presence of the virus in referred cases. Note the seasonality. Source: Public Health England via the Food Standards Agency.[3]

Person-to-person transmission can result from accidental ingestion of faecal matter. However, it can also result from airborne transmission: there is known to be an aerosol effect which may operate in a 1m radius around any faeces or vomitus produced by a sufferer [40].[4] This effect is exacerbated by the sudden onset of the symptoms of norovirus infection: vomiting and diarrhoea may occur in a public, or shared, place, thus contributing to further exposure. Additionally, the virus can easily be passed on from hand to hand or via contaminated surfaces.[5] Very high levels of hand hygiene can mitigate these effects but, as

3. Care is required when comparing this graph with data and model output on UK Norovirus incidence presented later in this report. For 2008-9, total community presence of Norovirus was estimated to be 287.6 greater than the figures shown here for laboratory reports [57]. Additionally, England and Wales constitute ~ 91% of the UK population. Therefore on this graph a weekly figure of ~200 laboratory reports corresponds to an annual incidence figure of ~3 million cases (~200x287.6x52/0.91).
4. The spread of Norovirus via vomiting is vividly illustrated in a video concerning work at the UK's Health and Safety Laboratory. See: http://www.cbsnews.com/8301-204_162-57565694/cdc-says-new-norovirus-strain-caused-140-outbreaks-since-september/
5. The ease with which can be passed on via different contamination routes has similarities with

stated previously, a distinctive feature of norovirus is that only very small dosages of contaminant are believed to be necessary for person-to-person transmission to occur. Norovirus is known to be the cause of significant outbreaks in health and social care institutions [25, 39] and on cruise-ships, a direct result of the ease of transmission exacerbated by the restricted mixing space of even a large liner [46, 62, 63].

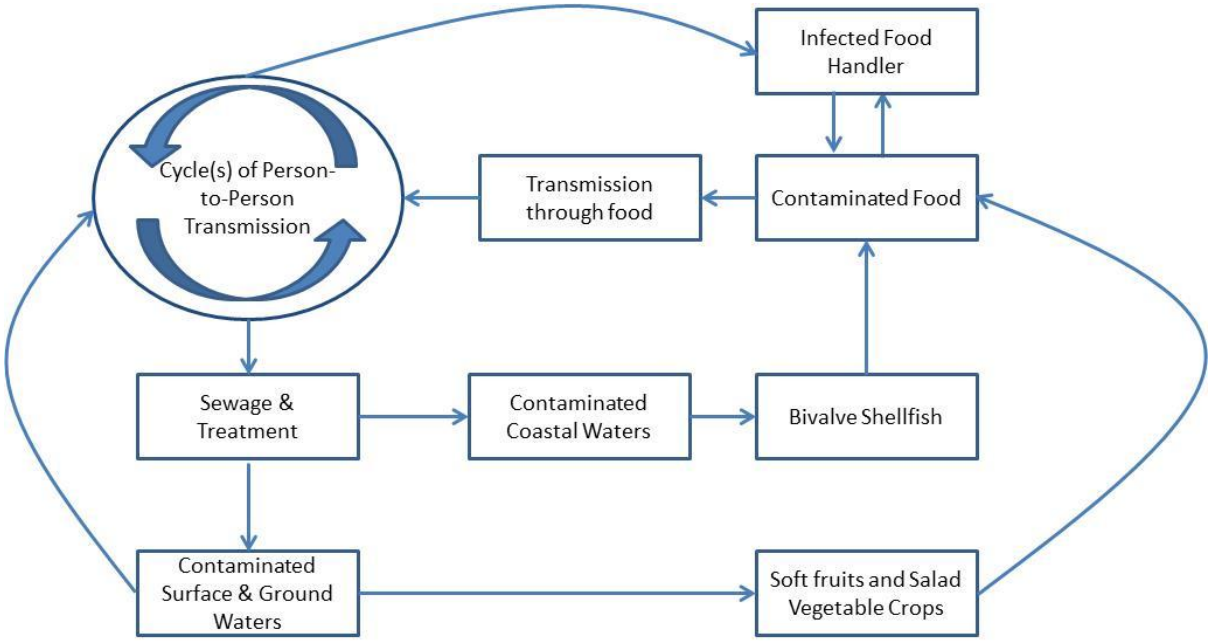


Figure 1.2: Representation of norovirus transmission routes [13] after [36].

As with many enteric viruses, norovirus can also be transmitted via a number of food-related mechanisms (See Fig. 1.2). Cooking partially or totally reduces the viability of norovirus, thus reducing the probability of infection and possibly the severity of any infection [4, 61]. However, this still leaves a number of routes by which infected humans can pass norovirus via the food chain [53]. As a result, in the USA norovirus is the main cause of foodborne disease [54], whilst FSA estimates at the commencement of this project indicated that norovirus is the second most common source of foodborne disease in the UK, with an estimated 300,000 cases p.a.[6]

healthcare associated infections such as Clostridium difficile. A description of the multi-vector, multi-platform nature of Clostridium difficile, expressed in the form of a system dynamics simulation model, may be found in [3].

6. This implies that ~10% of all cases result from foodborne transmission. However, this figure was always employed with considerable caution. Subsequent research – reported in Chapter 8 –

The food-related routes by which infected humans can pass norovirus include: bivalve shell fish (eaten raw after growth in coastal waters, these may contain genomes from the sewage of sufferers); contamination of some foods via washing with irrigation water (which may be polluted with sewage); contamination via exposure to sludge fertiliser (derived from human faeces); harvesting and processing of berry fruits and leafy vegetables (again, via infected individuals); food preparation (infected food caterers and home preparers may transfer norovirus to food if they are themselves infected)[7].

Although food is not the major route of norovirus infection, it is a significant one. This is not just due to the spikes of cases on Valentine's Day (associated with increased consumption of oysters) [8] and high profile cases of outbreaks in renown restaurants [24, 42]. The foodborne transmission routes are the clear result of activities within the human-managed food chain and are therefore an obvious point of intervention for the FSA, which is interested in reducing norovirus incidence.

1.2 Pre-existing Person-to-Person Modelling

The 'state-of-the-art' in the mathematical modelling of norovirus when this study was undertaken was contained in a report by Lawrence *et al.* [36]. This used a well-established approach to epidemiological modelling, being in essence an extension of the standard 'SEIR model' [45].

The model concentrates on the person-to-person transmission of norovirus, dividing the homogenously mixing population into those who are effectively immune to norovirus and those who are susceptible. Person-to-person contact then creates individuals who are exposed to norovirus and who subsequently go on to be infectious. These ultimately recover and, after an immune period, return to be susceptible. These mechanisms are treated in some detail.

Foodborne transmission mechanisms are present, to the extent that they are included as an exogenous factor in the model equations, the effect being calibrated in line with assumptions about norovirus. However, their treatment is considerably less developed than that of the person-to-person effects. This model was used as the starting point for the work reported here.

---

produced a figure of 2.5%, implying around 73,000 cases per year, making norovirus the UK's third most common source of foodborne disease, falling just behind the bacteria *C. perfringens* (~79,000) and with *Campylobacter* as the leading cause (~286,000) [57].

7. The complexity of such vectors is illustrated by data supplied by HPA to FSA on those Norovirus outbreaks in England and Wales identified as either foodborne or foodborne then person to person. The data for 2009-2011 includes two cases in which 'red meat' is cited as the infection source – despite these very probably having been cooked foodstuffs. Another case described directly to the author was a case of contamination from tomato soup; such a hot dish would not normally be seen as a source of Norovirus but an infectious chef had added fresh basil to the meal as a garnish.

1.3 Purpose of The FSA study

The FSA interest in norovirus stems from a wish to understand how important the foodborne effects are on the extent of transmissions and, hence, the scale of outbreaks.

This is part of a broader picture in which the aspiration to, "reduce foodborne disease using a targeted approach" is an established FSA Strategic Objective [14]. For this purpose five main pathogens are considered: *Campylobacter*, *Salmonella*, *E. coli* O157, *Listeria monocytogenes* and norovirus. With an estimated incidence rate of tens of thousands of foodborne cases per year, norovirus is one of the most common sources of foodborne disease in the UK.[8] However, the situation is made complicated by the fact that, unlike the other major pathogens, norovirus does not grow within foods or originate in them and so food is not, in itself, believed to be a major source of infection. Rather, as described in Section 1.1 above, infected humans can, via a number of mechanisms, infect a range of foods which act as vectors, producing further transmission. To understand the significance of foodborne transmission it is therefore necessary to grasp the interplay between this range of transmission routes and the more common person-to-person transmission.

Self-evidently, there is not one main food route to target and the relative importance of each cannot be said to be completely understood. This makes it difficult, with current knowledge, to craft interventions aimed at reducing the number of cases.

In the context of this general understanding, the FSA commissioned this present piece of research with the aim of supporting the development of a simulation model that would: improve understanding of the nature of the foodborne transmission mechanisms; give insight into the relative importance of foodborne transmission; begin to give an indication of where across the various transmission mechanisms FSA might target its efforts to reduce foodborne transmission. The task was therefore to conceptualise, formulate and parameterise[9] a mathematical model of which included both the person-to-person effects and the primary foodborne infection mechanisms.

It was envisaged that the model would help inform the FSA's strategy for tackling norovirus in the following ways. First, by supporting an assessment of whether reducing risks in the food chain might have a material effect on human cases. Second, by allowing the development of a better understanding of the relative contributions of the food-related routes of transmission. Third, by facilitating an assessment of where risk reduction might be most beneficial. Last, by identifying gaps where further work may be required.

A further requirement of the study was that the model should be produced using the system dynamics approach.

8. New research places Norovirus as the third on the list of foodborne disease, falling just behind the bacteria C. perfringens and with Campylobacter as the leading cause [57].
9. In fact, doubts were expressed from the very start by FSA staff as to whether it would be possible, given current knowledge, completely to parameterise such a model.

1.4 Report Layout

The research reported here takes a twin-track approach. This remainder of this report therefore proceeds as follows.

Part 1 gives an account of modelling work which endogenises the foodborne mechanisms, presenting a System Dynamics model of transmission which includes a range of foodborne effects. This is based on a version of the existing person-to-person model, re-written in System Dynamics terms and extended (Chapter 2) and includes detailed representations of the mechanisms understood to be producing various foodborne transmission routes for (Chapters 3-6). Part 1 closes with a consideration of issues related to the parameters of such a model, which might indicate a priority for future research and which might be considered as points of intervention (Chapter 7).

Part 2 describes a different approach, one which aims to calculate the scope of the foodborne effects. This work is based on a re-calibrated version of the existing person-to-person model (Chapter 8). Mathematical analysis is performed on this model to see the effects of changing the parameters controlling both the person-to-person and the foodborne effects. The analysis provides useful insight into the relative strengths of these effects and the consequences of changing them (Chapter 9). The following chapter repeats this style of analysis but via a new System Dynamics model which is able to explore uncertainty about the relative effects of the two different types of infectives (Chapter 10). The work in these three chapters directly addresses the question of how changes in both person-to-person infectivity and the foodborne effect influence overall incidence of cases

Chapter 11 provides conclusions to the research in Parts 1 & 2 whilst Chapter 12 makes recommendations for future research. Acknowledgements and References are also provided (Chapters 13 and 14 respectively).

Part 1 Endogenising the Foodborne Mechanisms

2 Person-to-Person Model Sector

The start point for modelling the foodborne transmission processes of norovirus is the sector representing person-to-person transmission. For this sector the model proposed by Lawrence *et al.* [36] was drawn on, though a number of additional features were added. This chapter provides a description of that person-to-person sector and how it was then employed within the broader 'FSA NoV Model', the model created for this research.

First, the key assumptions regarding variables and main mechanisms are described. These assumptions are then presented mathematically, as a set of ordinary differential equations (ODEs). The symbols used in System Dynamics modelling are then introduced, followed by a presentation of the person-to-person effects in the form of a simulation model using that modelling iconography. In the penultimate section a description is given of how this person-to-person sector relates to the range of foodborne mechanisms described in subsequent chapters. Finally, the process used to develop the modelling assumptions for that range of mechanisms is described.

2.1 Key Assumptions

The people sector of the 'FSA NoV Model' follows the assumptions of [36] and further details can be found there. To assist comparison, whilst the variable names and explanations given here are those developed for this specific FSA project, some of the algebraic symbols used in [36] are also referred to.

The model assumes a population in which there are births and deaths, with these two processes balancing to produce a steady headcount for the variable 'Population Size N'.[10] That population is then divided into two groups.

The first is the 'Permanently Protected'. This 'stock' of people is the part of the population that lack the receptors that enable them to respond to norovirus, and that may be thought of as immune to infection from the virus. They need to be represented in the model because they are part of the mixing population, and therefore influence the size of person-to-person contact effects. The proportion of the population falling into this category is represented in the parameter 'Proportion of Pop Non Susceptible to NV Chi'. In [36] the symbol χ is used for this parameter.

The remainder of the population can be infected by norovirus and these people are handled

10. For clarity, model variables are normally indicated in this manner from this point on in the report.

using five categories, or stocks.

The first, 'Susceptible Individuals', contains that part of the population which is not immune to the virus for any reason and which can therefore become infected if exposed to it. The other four categories are immune to infection – not because they are permanently protected but rather because they are suffering, or have recently suffered, from norovirus.

The second stock is 'Exposed Individuals'. Referred to as "Responders" in [36], these are individuals who have been exposed to norovirus but are not yet infectious. The average time in this exposed category is given by the parameter 'Latent Period'. In [36] the symbol α is used for the reciprocal this parameter.

After this period, norovirus produces effects on exposed individuals. One group, 'Infectious Symptomatics Is', develop symptoms and become infectious because they shed the virus by various means, including the production of vomit and faeces. It is therefore this group that experiences infection as an illness. This does not occur in all cases of exposure. Instead, a proportion given by the parameter 'Asymptomatic Carriage Proportion' moves into the second group. This group is 'Infectious Asymptomatic Ia'. These are norovirus-carrying individuals who show no readily detectible signs of infection and have no symptoms but may still shed the virus [2]. However, the extent to which asymptomatic viral shedders are infectious is currently not well known.

Individuals dwell in either of these two infectious stocks for a period. This is known to vary considerably [44]. Here an average duration is used and this is given by the parameter 'Infectious Period'. The symbol γ is used in [36] for the reciprocal of this parameter.

All infectious individuals move on to the fifth and last of the stocks that model the progress of those who are not protected from norovirus. The category 'Recovered Immune' contains those who have recovered from a bout of norovirus, or who are simply no longer shedding the virus. These individuals retain immunity to subsequent infection for a period. However, the acquired immunity eventually wains. This happens after an average time given by the parameter 'Period of Immunity'. In [36] the symbol δ is used for the reciprocal this parameter. Individuals therefore flow back into the stock of susceptibles.[11]

Individuals also exit each of these five stocks as a result of death: there is a 'Life Expectancy' for all categories. In contrast, births only flow into the Susceptibles stock, since all those born of those in any of these five stocks are themselves susceptible. The parameter controlling the birth rate is the same as that for the death rate, to ensure a constant population. In [36] the symbol μ is used for this parameter. It relates reciprocally to a 78

11. These mechanisms imply a straightforward route through immunity. This is reasonable for an initial model and the fact that, in actuality, there is no sudden cut-off for immunity is partly represented by the exponential aging formulation in the model, which can be interpreted as implicitly expressing the idea of a slow decline of immunity over an average time. However, those who are 'partially immune' may have their immunity increased again if they are exposed to norovirus [43] and this effect is not represented in the model.

year life expectancy.

The final process to be described is that by which individuals are exposed to norovirus. There are two mechanisms for this. The first relates to foodborne effects. In the Lawrence *et al.* model these are included as an exogenous effect, or forcing term 'Theta' (θ). The value of this parameter is the proportion of susceptibles who are exposed per time period as a result of foodborne effects. This approach is continued in the following two sub-sections but in Section 2.5 the more complex, endogenised formulations for these effects are discussed.

The second exposure mechanism, and the central concern of this model sector, treats the homogenously mixing susceptible individuals. These people mix with all population categories and therefore may encounter those infected with norovirus and be exposed to the virus. This happens for a range of reasons: viral shedding may occur for a period prior to the development of symptoms, an infected individual therefore remaining in a social setting; the onset of illness may be so rapid that infectious symptomatic individuals vomit or defecate in relatively public spaces, so exposing others; healthy individuals may be involved in caring for someone with the illness; infectious individuals may return to social settings such as work prior to complete recovery.[12] All such situations are combined into an 'Exposure Rate' in the model which uses a standard epidemiological formulation: the rate is endogenously formulated as being proportional to the number of susceptibles multiplied by the number of infectious individuals, divided by the total mixing population. The parameter 'Beta' (β in [36]) is the number of 'encounters' per day that susceptibles are engaged in and which can result in exposure if it is an infectious person who is so encountered.

In an extension of the earlier work, the model now contains a more complex handling of the effects of the two infectious groups, reflecting the evolving knowledge in this area [5] [2]. The parameter 'Weighting for Infectious Asymptomatics' is introduced to address the fact that the extent to which asymptomatic viral shedders are infectious is not well known.[13] This parameter allows their infectivity to be set at a proportion of the infectivity of symptomatic individuals - probably less than one. This parameter is employed in the new variable 'Effective Mixing Infectious Population', which therefore represents the number infectious people who can expose susceptibles to norovirus. This new feature means that the model expresses the uncertainty about the role in person-to-person transmission of infectious asymptomatic individuals and, as discussed in Section 9.5, can be used to explore the effects of that uncertainty.

12. What is – implicitly – excluded are mechanisms associated with food preparation. The person-to-person mechanism treats only direct touching, or contacts mediated by bodily products; it excludes contacts mediated in any way by food or food preparation. In the original model such mechanisms are expressed via the parameter Theta described above and these foodborne mechanisms are explicitly handled in the new structures described in Chapters 5 and 6.
13. According to Amar et al. [2] some 16% of asymptomatics are shedding norovirus, and this figure is thought to be higher for children (as high as 30% for children younger than 12 months) because children spread their excreta more widely than adults.

2.2 ODEs for the Model Sector

The assumptions described above can be presented mathematically as a set of ODEs. In much of the remainder of this report the modelling work will be presented in the form of System Dynamics diagrams, the actual simulation model having been provided to the FSA. However, there are two main reasons for first presenting the assumptions of the person-to-person sector of the 'FSA NoV Model' in ODE form. First, showing the actual differential equations at this point is useful in facilitating a shift into the symbols of System Dynamics modelling. Second, the analytical work reported in Part 2 returns to these ODEs and uses them extensively.

To simplify the style of the ODEs, Table 2.1 below lists the main variables using both the long variable names employed in 2.1 (and in the System Dynamics model presented in 2.4) alongside the short names for the equivalent (or related) variable in the ODEs.[14]

Model Variable, or Parameter	**Symbol in ODEs**
Population Size N	N
Susceptible Individuals	S
Exposed Individuals	E
Infectious Symptomatic Is	Is
Infectious Asymptomatic Ia	Ia
Recovered Immune	R
Asymptomatic Carriage Proportion	κ
Weighting for Infectious Asymptomatics	ϖ
Effective Mixing Infectious Population	I
Proportion of Pop Non Susceptible to NV Chi	χ
Latent Period	α (r)
Infectious Period	γ (r)
Period of Immunity	δ (r)
Life Expectancy	μ (r)

Table 2.1: Main model variables listed as they appear in the 'FSA NoV Model' and as they appear in the ODEs. Symbols marked (r) have a reciprocal relationship with the respective long name parameter.

14. This listing also aids comparison with the equations used in [36], since other than 'κ' and 'ϖ', the same short names are used there.

This then allows the main mechanisms of the person-to-person sector of the model to be stated mathematically:

$$\frac{dS}{dt} = -\left(\frac{\beta I}{N} + \theta\right)S + \delta R + \mu([1-\chi]N - S)$$

$$\frac{dE}{dt} = \left(\frac{\beta I}{N} + \theta\right)S - (\mu + \alpha)E$$

$$\frac{dIs}{dt} = \alpha(1-\kappa)E - (\gamma + \mu)Is$$

$$\frac{dIa}{dt} = \alpha\kappa E - (\gamma + \mu)Ia$$

$$\frac{dR}{dt} = \gamma(Ia + Is) - (\mu + \delta)R$$

$$I = Is + \varpi Ia$$

2.3 Model Representation in System Dynamics Model

A central requirement of the research was the production of a simulation model built using the system dynamics approach [13].

System dynamics modelling was created specifically for the modelling of social systems [34]. It uses ideas from servo-mechanism theory to represent the state variables in a system, their connecting flows and the causal connections between the other variables. The aim is to represent the causal mechanisms hypothesised as operating in a given system. These mechanisms invariably involve non-linear relationships, as well as feedback loops, which may be reinforcing or balancing in nature. Such representations, or models - provide a platform for the simulation of the time evolutionary behaviour of that system and to allow

experimentation with different policies and their effects on behaviour [16] [18] [15].
A distinctive feature of the System Dynamics approach is the use of a set of symbols, or icons, to represent the modelling assumptions [32] [35]. Different software packages vary to some extent but, essentially, all distinguish between three types of variables: auxiliaries, stocks and flows. These are then displayed in a 'stock/flow diagram', or SFD, as illustrated in Fig. 2.1.
Auxiliaries appear simply as a name. Single line arrows going into the variable name indicate influences from other model variables. The value of an auxiliary is instantaneously established by the values of those influencing variables, as calculated via the functional relationship that defines the auxiliary. Single line arrows emerging from auxiliaries indicate influencing relationships that they have on other model variables.

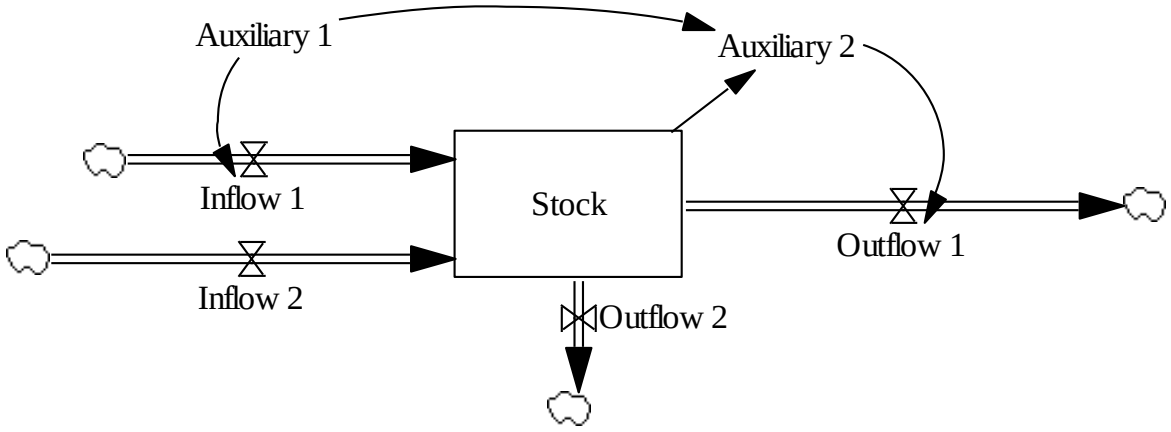


Figure 2.1: A stock/flow diagram illustrating the iconography of System Dynamics modelling.

Stocks are represented as rectangles and flows (or flow rates) as labelled double arrows with a double-triangle valve symbol. Stocks are the 'state variables' of a system. They can be thought of as bath tubs, with water flowing in from various taps and flowing out from a range of plugholes. Hence, the value of a stock is created by accumulating all of the inflows, decummulating all of the outflows and recalling how much water was in the bath at first. In other words:

Stock Value = Accumulation (All inflows – All outflows) + Initial Stock Value

Or, expressing the relationship using mathematical calculus:-

$$Stock\ (t) = \int_0^t All\ inflows - All\ outflows\ dt\ +\ Stock(0)$$

So, referring specifically to Fig. 2.1, these symbols express the mathematical relationship:-

$$Stock\ (t) = \int_0^t Inflow\ 1 + Inflow\ 2 - Outflow\ 1 - Outflow\ 2\ dt\ +\ Stock(0)$$

Modern System Dynamics modelling packages have a graphical user interface which allows the symbols shown in Fig. 2.1 to be drawn directly on a computer screen. The key point is that the act of creating such a diagram automatically generates differential equations representing these integrating processes. In other words, drawing the symbols in Fig. 2.1 automatically generates the above integral equation; the symbols drive the calculus.
Clearly such figures do not express all of the mathematical relationships in a model. For example, Fig. 2.1 also implies that:

Inflow 1 = Some Function of (Auxiliary 1)

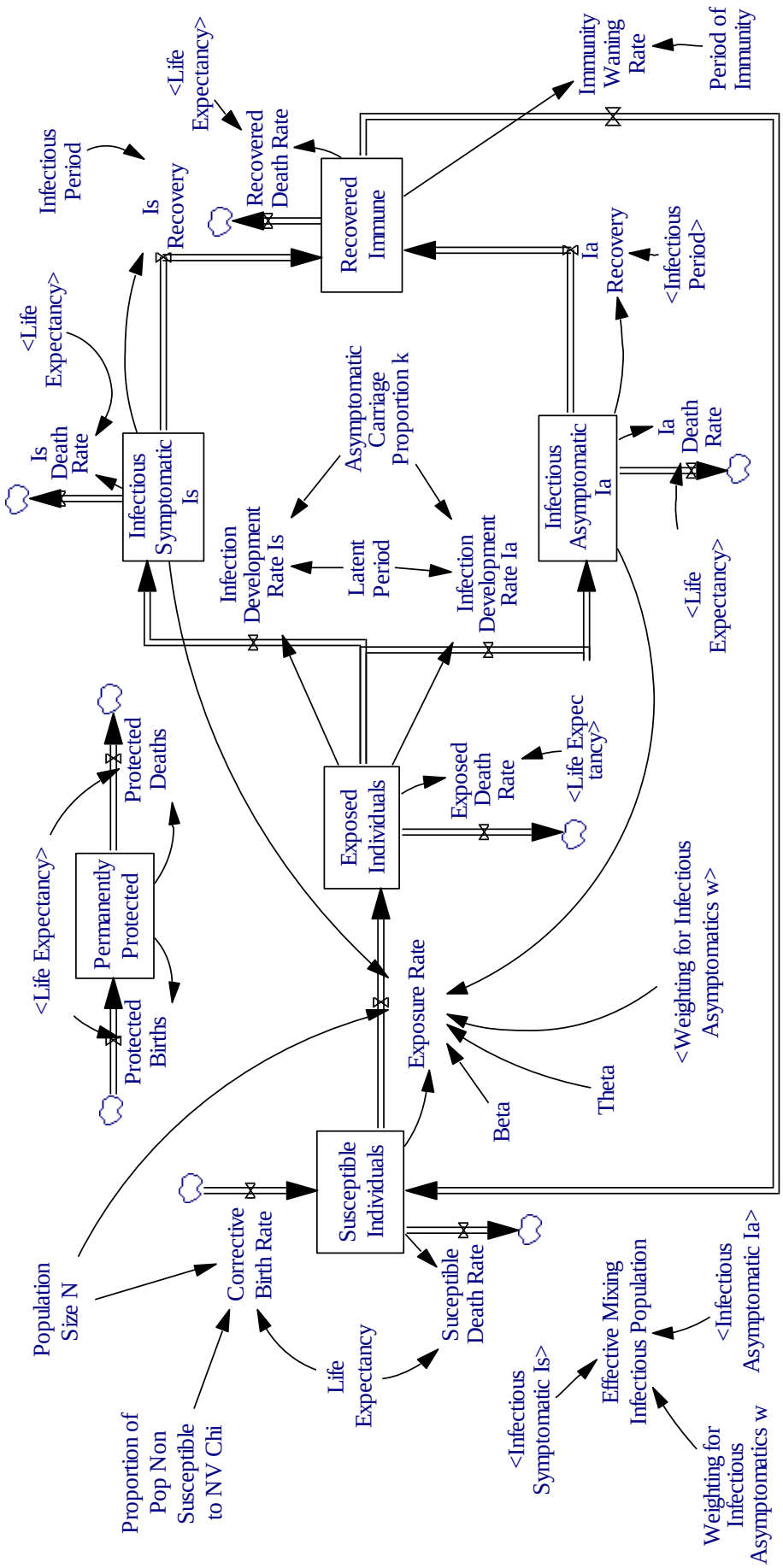
Auxiliary 2 = Some Function of (Auxiliary 1 & Stock)

The nature of these functional relationships will be established by 'double-clicking' on the symbol for a variable and writing an equation involving the influencing variable(s). However, the SFD still provides an organising framework, in that it records the influencing variables which must be included in such equations.
Diagrams such as that in Fig 2.1 themselves express the central mathematical assumptions of a System Dynamics model. The remainder of this report therefore uses these symbols as the chief means of explaining the contents of the 'FSA NoV Model'. The full model has been supplied to the FSA. Moreover, the model has itself been documented, so that each variable contains an explanation of its conceptual meaning and of the algebraic formulation by which its values are determined. Consequentially, Chapters 3 to 6 do not repeat this mathematical detail but instead provide the stock/flow diagrams of the model sector under discussion, along with comments that offer an overview of the modelling assumptions employed.

2.4 System Dynamics Model

The assumptions described in 2.1 and 2.2 were modelled using the system dynamics package Vensim [9]. The model treats the whole UK population. The results are shown below as a stock/flow diagram.

Figure 2.2 (next page): Representation of the person-to-person sector of the 'FSA NoV Model' using the iconography of system dynamics modelling using the Vensim software. In this figure the foodborne effects are still represented by a simple forcing term, Theta. For the endogenised version see Section 2.5 and Figs. 2.3 and 2.5.


Recovered Immune
Infectious Symptomatic Is
Infectious Asymptomatic Ia
Exposed Individuals
Susceptible Individuals
Permanently Protected
Immunity Waning Rate
Period of Immunity
Infectious Period
Is Recovery
Recovered Death Rate
<Life Expectancy>
Ia Recovery
<Infectious Period>
Asymptomatic Carriage Proportion k
Is Death Rate
Ia Death Rate
Infection Development Rate Is
Latent Period
Infection Development Rate Ia
Exposed Death Rate
<Life Expectancy>
Protected Deaths
Protected Births
Exposure Rate
Beta
Theta
<Weighting for Infectious Asymptomatics w>
Population Size N
Corrective Birth Rate
Suceptible Death Rate
Life Expectancy
Proportion of Pop Non Susceptible to NV Chi
<Infectious Symptomatic Is>
Effective Mixing Infectious Population
<Infectious Asymptomatic Ia>
Weighting for Infectious Asymptomatics w

2.5 Approach to Modelling the Foodborne Mechanisms

In the following chapters this person-to-person sector of the model is amended by the inclusion of modelling assumptions aiming to represent a range of foodborne transmission mechanisms. This chapter closes with a summary of the general nature of that modelling and an account of the process by which it was developed.

The central concern of System Dynamics is exploring how sets of feedback effects in the structure of social systems can endogenously produce behaviour over time [17, 50]. This fits well with the general approach taken in modelling the foodborne effects. Simply put, these are not a forcing term, an effect external, or exogenous, to human activity. Rather, they are the result of humans infected with norovirus.

The approach taken in modelling was to endogenise the foodborne transmission mechanisms. Modelling therefore involved tracing out the feedback loops which link infective humans with the range of food-related activities and which eventually cycle back to influence humans. In other words, causal chains were constructed which start with the two infectives stocks in the person-to-person sector, then pass through representations of the processes involving different food transmission routes, and finally pass back into that sector to influence the 'Exposure Rate'.

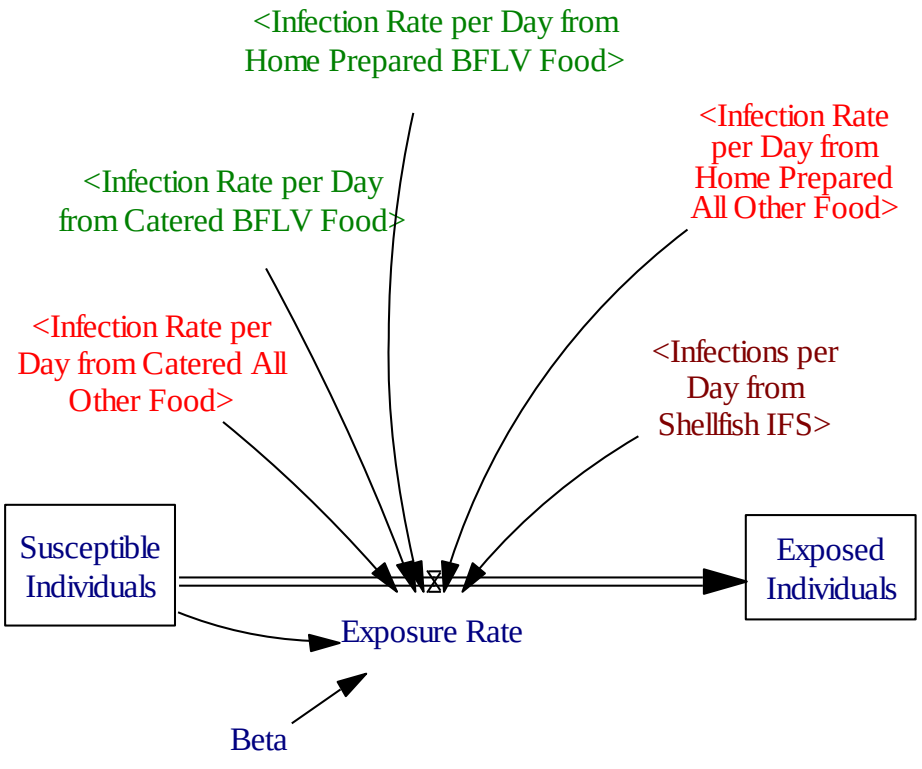


Figure 2.3: Simplified detail of the person-to-person sector of the 'FSA NoV Model' showing the influences on the 'Exposure Rate' in the final version. The exogenous forcing term, Theta has been replaced by the various endogenised foodborne effects discussed in the following chapters.

The mechanisms that were modelled concerned: contamination of bivalve shellfish via sewage; contamination of soft berry fruits and leafy vegetables via the use of sludge as a fertiliser, via infectious harvesters, via infectious food processers, and via infectious food preparers in both home and catering settings; and contamination of other foodstuffs via infectious food preparers in both home and catering settings.

The specifics of each are discussed in the following chapters but they share this general form: to remove the Theta in the previous model and replace it with an endogenous mechanism. This is not only a more accurate representation of these effects in conceptual terms. The act of modelling also allows a detailed hypothesis to be framed regarding the steps through those mechanisms. Such hypotheses are useful in clarifying what is known and what it still to be determined regarding our understanding of these effects.

2.6 Process for Modelling the Foodborne Mechanisms

Brief comment is appropriate on the process used to construct the model sectors that follow. The model was constructed by the author (DCL). The process drew on a literature review but also on detailed interviews which DCL conducted with the members of a team of experts assembled by the FSA for this express purpose. Over a period of some months DCL conducted telephone interviews with team members, consulted recommended literature and supplied team members with copies of parts of the emerging foodborne sectors.

A key meeting was then held in November 2012 in London. The aim of this meeting was to move from discussing individual foodborne sectors with individual experts in the respective areas, to a discussion in which the structure of the entire model was considered. All of the individuals who had previously been consulted agreed to attend the meeting. These were drawn from the following organisations: Animal Health & Veterinary Laboratories Agency (AHVLA); Centre for Environment, Fisheries & Aquaculture Science (CEFAS); Food & Environment Research Agency (FERA); Health Protection Agency (HPA)[15] and the FSA itself. Lastly, one team member was a member of faculty at a UK university.

The workshop was designed and facilitated by DCL, with support from FSA staff. Large coloured prints of the stock/flow diagrams for each sector of the entire model were created and displayed on the walls of the conference room. This meant that any attendee could look at any part of the model at any time. The central focus of the room was a projected image of the part of the model under discussion at any given time. (The figure below shows some of this layout.) A key feature of system dynamics is that the modelling assumptions are explicit, presented clearly and openly in the model diagrams and in the underlying equations. This ‘precision’ – meaning lack of ambiguity [16] – is important in allowing false modelling assumptions to be corrected and sound modelling assumptions to generate

15. Whilst this organisation has now become ‘Public Health England’ it was the HPA at the time of this work.

confidence in the minds of an audience.

After a reprise of the existing person-to-person model [36] and a reminder of the purpose of the FSA study, the workshop proceeded as follows. Each new sector was presented, with detailed areas of the model 'zoomed in on' via the projected image. At the request of participants, model variables were examined, their individual equations exposed for scrutiny. Cross-referencing was facilitated by the large prints. The assumptions of each sector were presented, concerns and corrections noted. As a break in the structure of the afternoon, a peripatetic approach was employed in the workshop's second half. Participants were encouraged to gather, standing, around each of the large posters and offer comment (be it affirmation or correction). The diagrams were sketched on to represent changes that needed to be included in the model.

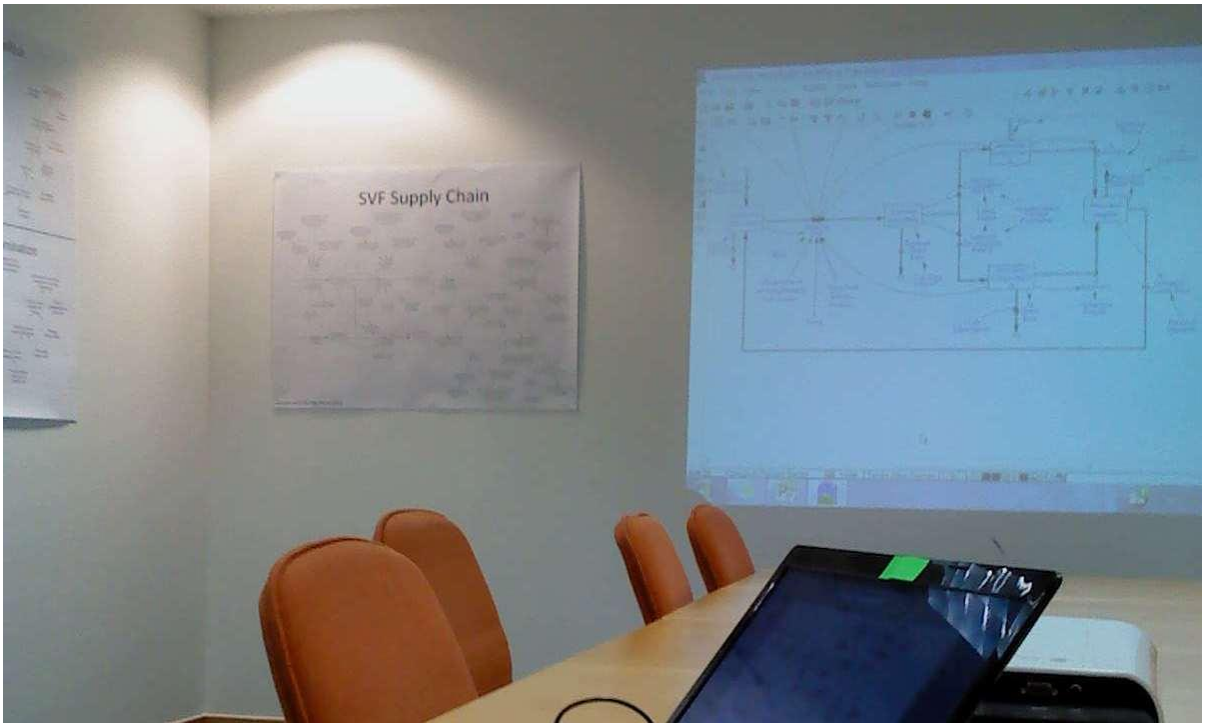
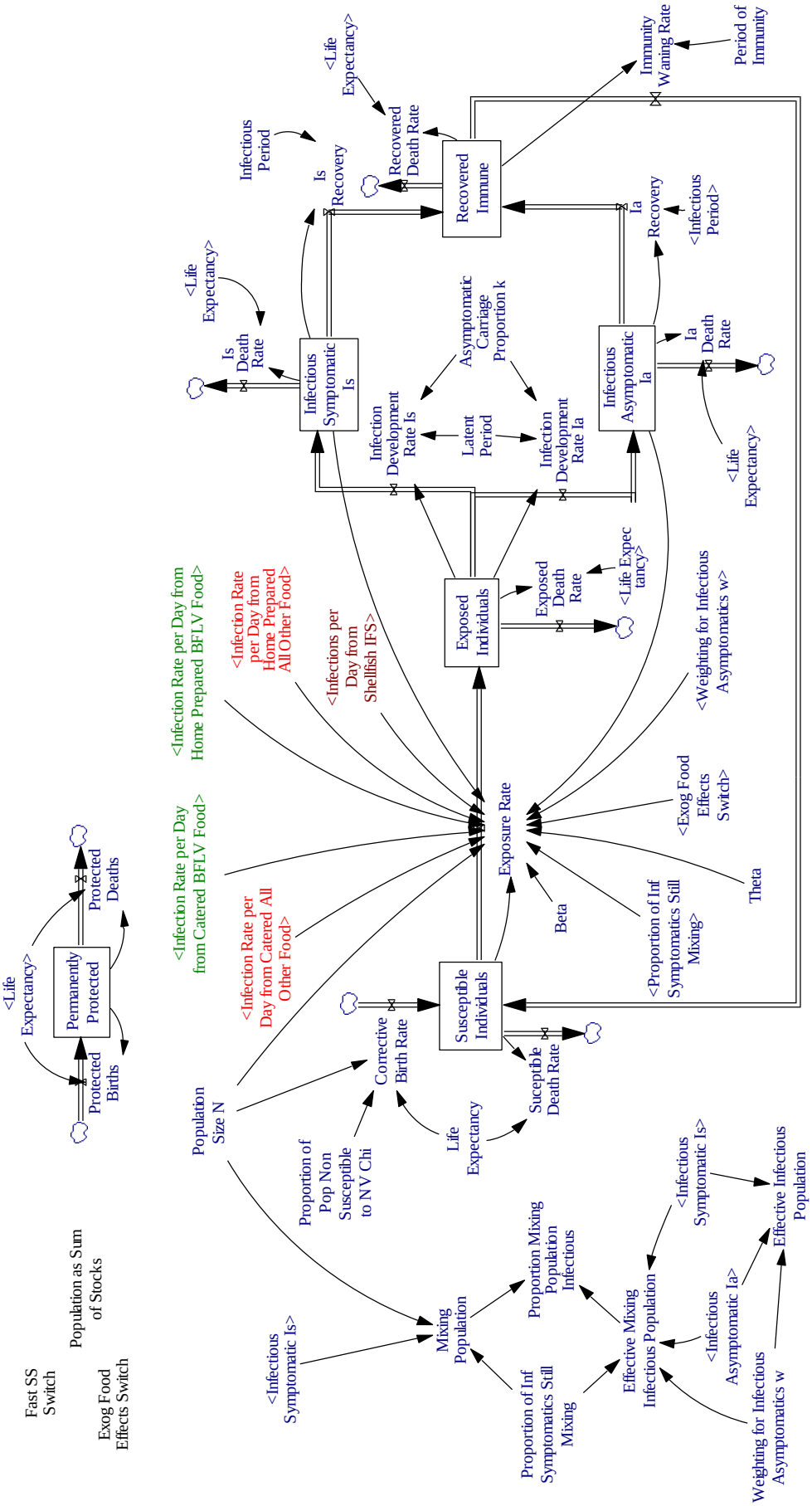


Figure 2.4: The layout of the room at the FSA offices in London at which the project workshop was held. On the right hand side is the person-to-person sector projected from the laptop computer in the foreground. To the left, large posters of some of the foodborne mechanisms can be seen.

The workshop was a success in 'validating' the majority of the modelling work and in eliciting changes necessary to satisfy the team. Further modelling by DCL followed. A version of the work was presented at the FSA's 'Foodborne Viruses Research Conference' held in London in January 2013. This event brought the model under further scrutiny (though not in the same depth as the workshop) and facilitated further literature consultation and model re-work.

The model as presented here has benefited immeasurably from the contributions of the members of the expert team. However, responsibility for any errors in the model lies solely with the author and his FSA colleagues.

Figure 2.5 (next page): Full stock/flow diagram of the person-to-person sector of the 'FSA NoV Model'. Here the foodborne effects have been endogenised, with the 'Exposure Rate' now formed from a number of model variables calculated in the new, food-related sectors of the model discussed in the following chapters.


Fast SS Switch
Exog Food Effects Switch
Population as Sum of Stocks
Permanently Protected
Protected Deaths
Protected Births
<Life Expectancy>
Susceptible Individuals
Exposed Individuals
Infectious Symptomatic Is
Infectious Asymptomatic Ia
Recovered Immune
Exposure Rate
Beta
Theta
Population Size N
Corrective Birth Rate
Susceptible Death Rate
Life Expectancy
Proportion of Pop Non Susceptible to NV Chi
Exposed Death Rate
<Life Expectancy>
Infection Development Rate Is
Infection Development Rate Ia
Latent Period
Asymptomatic Carriage Proportion k
Is Death Rate
Ia Death Rate
Is Recovery
Ia Recovery
Recovered Death Rate
Infectious Period
<Infectious Period>
Immunity Waning Rate
Period of Immunity
<Infection Rate per Day from Home Prepared BFLV Food>
<Infection Rate per Day from Home Prepared All Other Food>
<Infections per Day from Shellfish IFS>
<Infection Rate per Day from Catered BFLV Food>
<Infection Rate per Day from Catered All Other Food>
<Exog Food Effects Switch>
<Weighting for Infectious Asymptomatics w>
<Proportion of Inf Symptomatics Still Mixing>
Mixing Population
Proportion Mixing Population Infectious
Effective Mixing Infectious Population
<Infectious Symptomatic Is>
<Infectious Asymptomatic Ia>
Effective Infectious Population
Proportion of Inf Symptomatics Still Mixing
Weighting for Infectious Asymptomatics w

3 Transmission Mechanisms For Shellfish

This chapter introduces the structural assumptions used in the 'FSA NoV Model' to represent the foodborne transmission mechanisms associated with bivalve shell fish (primarily oysters but including some others).

The mechanisms can be summarised as follows: norovirus genome copies (NVGCs) are excreted from infectious humans; they pass into sewage, which undergoes various treatment stages before discharge into the ocean; in estuary farms they are slowly absorbed by bivalve shellfish; these are then harvested and consumed by humans [38]. The following sections show this sector of the model in detail.

3.1 People to Shellfish Transmission

The figure below illustrates the part of the 'FSA NoV Model' relating to transmission from people to shellfish. A complete version of the sector's SFD is reproduced at the end of the chapter and a full equation listing is available in the copy of the model supplied to the FSA.

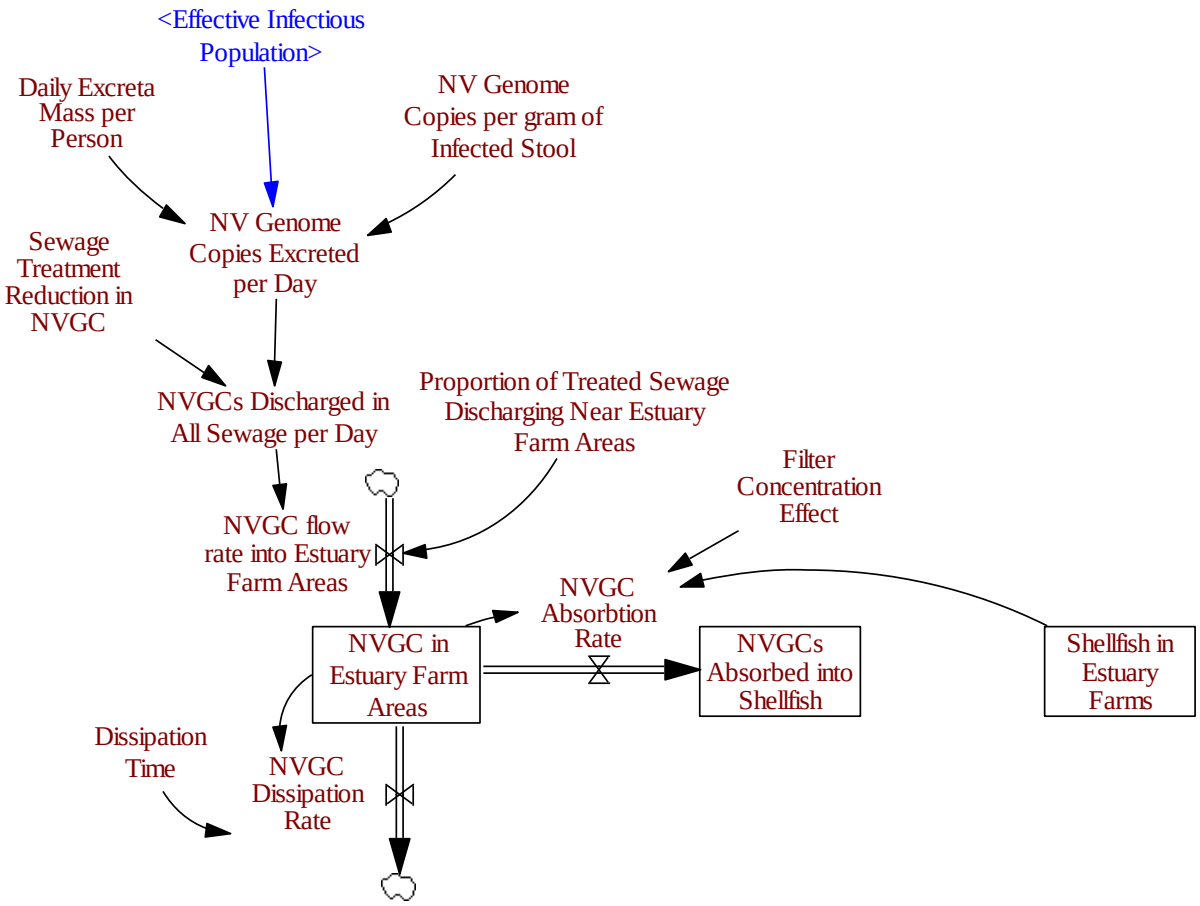


Figure 3.1: Stock/flow diagram illustrating the part of the 'Bivalve Shellfish' sector of the 'FSA NoV Model' relating to people-to-shellfish transmission. Note that a bracketed variable is one the value of which is calculated elsewhere in the model.

In summary the modelling assumptions are as follows. Individuals in the population spread norovirus in their faeces. The number of these individuals is the 'Effective Infectious Population'. In simple terms this is simply the sum of the symptomatic infectives and the asymptomatic infectives. However, the model is formulated so as to allow the role of the asymptomatics to be varied (see parameter 'Weighting for Infectious Asymptomatics' in Sections 2.1 and 2.2). That modelling assumption leads to the blue variable in Fig. 3.1, which has emerged from the person-to-person sector of the model. These individuals excrete faeces, each gram of which will contain a certain number of genome copies. Whilst a total number of genome copies are excreted per day, the various sewage treatment processes reduce the number of genome copies actually discharged into the ocean. This number is effectively reduced further because only a proportion of the treated sewage is discharged into estuaries in which the farming of bivalve shellfish occurs. However, this flow then accumulates in the waters in estuary farm areas.

That accumulation of genome copies will dissipate over a given time, both because the waters themselves change and also because the genome copies do not remain viable disease carriers indefinitely. However, shellfish being grown in such estuaries, by their very nature, filter the waters around them and so concentrate and absorb norovirus.

3.2 Shellfish to People Transmission

Figure 3.2 shows the SFD for the part of the 'FSA NoV Model' relating to shellfish to people transmission. A complete version of the SFD of this sector is reproduced at the end of this chapter whilst a full equation listing is available in the copy of the model supplied to the FSA.

The modelling assumptions may be summarised as follows. Shellfish are assumed to be farmed sustainably, that is, the harvesting rate is equal to the rate at which new shellfish start to grow. The harvesting rate depends on the rate of eating shellfish meals and the number of shellfish eaten at each meal. Given the stock of absorbed genome copies and the number of shellfish, the model calculates the average number of genome copies per harvested shellfish. As these are removed from the beds the genome copies flow out of the estuary system – being retained in the harvested shellfish. The genome copies amount in the harvested shellfish is reduced via depuration, a post-harvest purification process, lowering the number of genome copies consumed in a meal.

The consumption rate of shellfish allows the model to calculate the daily ingestion rate of norovirus genome copies. Knowing how many norovirus genome copies are, on average, necessary for transmission (suspected to be a very low number [7, 27]) then indicates how many shellfish diners would, potentially, be infected by norovirus as a result of their meal. However, this number must be corrected to account for the proportion that is in a position to be infected, for example, recovered immune individuals must be factored out.

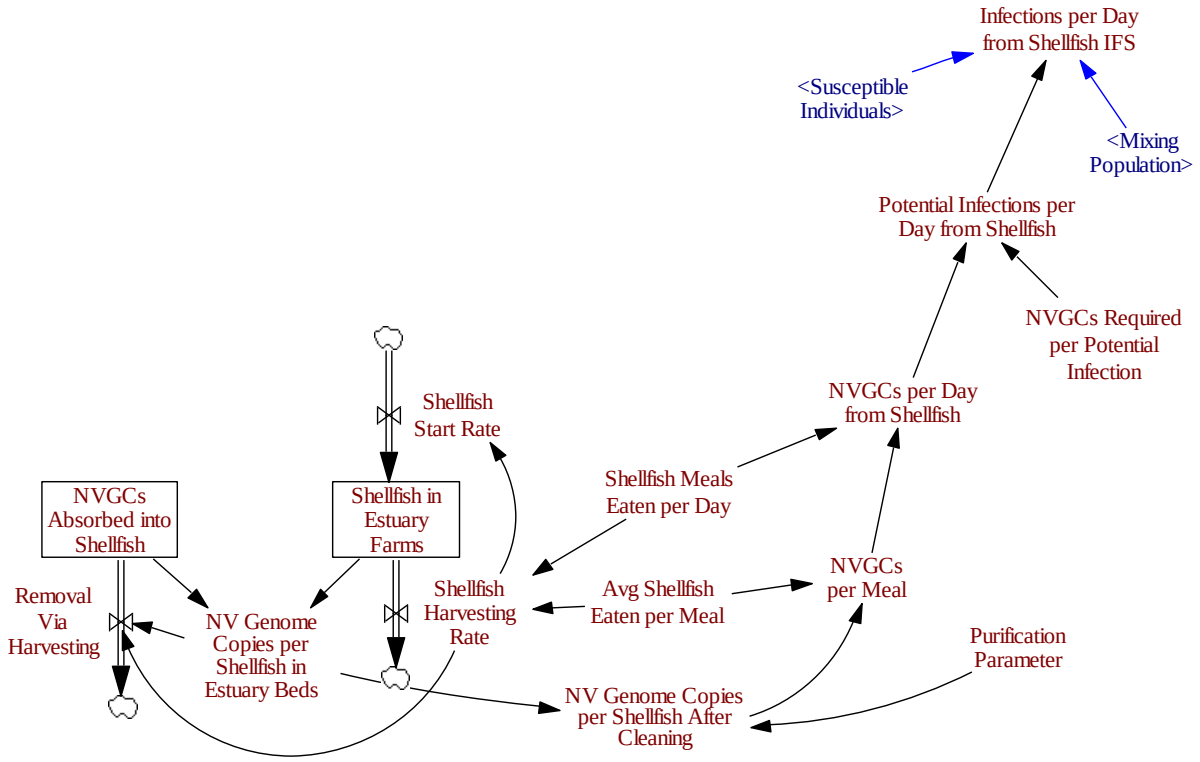
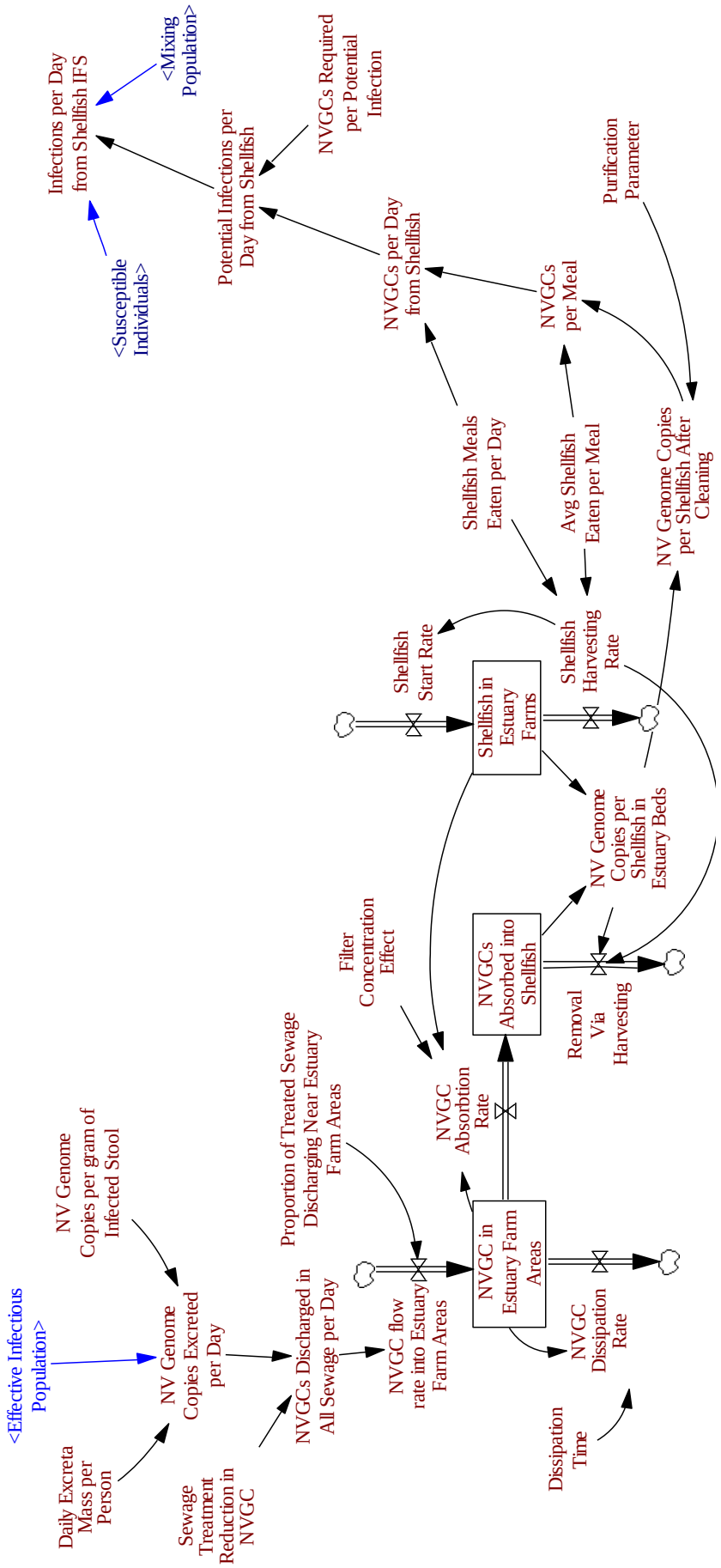


Figure 3.2: Stock/flow diagram illustrating the shellfish to people transmission elements of the 'Bivalve Shellfish' sector of the 'FSA NoV Model'.

This last model variable, 'Infections per Day from Shellfish IFS', passes back into the person-to-person model, being one element of the variable 'Exposure Rate' (see Section 2.5). In this manner the involvement of bivalve shellfish in the transmission of norovirus is represented explicitly in the model, the mechanisms for the foodborne effect having been modelled in a manner which endogenises this effect.

Figure 3.3 (Overleaf): Full stock/flow diagram of the 'Bivalve Shellfish' sector of the 'FSA NoV Model' relating to people-to-shellfish transmission.


<Mixing Population>
Infections per Day from Shellfish IFS
NVGCs Required per Potential Infection
Potential Infections per Day from Shellfish
<Susceptible Individuals>
Purification Parameter
NVGCs per Day from Shellfish
NVGCs per Meal
Shellfish Meals Eaten per Day
Avg Shellfish Eaten per Meal
NV Genome Copies per Shellfish After Cleaning
Shellfish Start Rate
Shellfish Harvesting Rate
Shellfish in Estuary Farms
NV Genome Copies per Shellfish in Estuary Beds
Filter Concentration Effect
NVGCs Absorbed into Shellfish
Removal Via Harvesting
NV Genome Copies per gram of Infected Stool
Proportion of Treated Sewage Discharging Near Estuary Farm Areas
NVGC Absorbtion Rate
<Effective Infectious Population>
NV Genome Copies Excreted per Day
NVGCs Discharged in All Sewage per Day
NVGC flow rate into Estuary Farm Areas
NVGC in Estuary Farm Areas
NVGC Dissipation Rate
Daily Excreta Mass per Person
Sewage Treatment Reduction in NVGC
Dissipation Time

4 Transmission Mechanisms For Sludge

This chapter introduces the structural assumptions used in the 'FSA NoV Model' to represent the foodborne transmission mechanisms associated with sludge, a fertiliser derived from human faeces which, despite careful usage protocols, may pass into certain foodstuffs.

Note that the only foodstuffs considered in this sector are those eaten uncooked (excluding bivalve shellfish). The term 'berry fruits and leafy vegetables' - BFLV – is used for these.

The mechanisms can be summarised as follows: genome copies pass from infectious humans into sewage, some of which is separated out as sludge; the sludge goes through treatment stages before being applied to soil; some soil adheres to BFLVs when they are harvested; hence some NVGCs are consumed by humans. The following sections show this sector of the model in detail.

4.1 People to Sludge Transmission

Figure 4.1 overleaf illustrates the part of the 'FSA NoV Model' relating to transmission from people into sludge. A complete version of the SFD of this sector is reproduced at the end of this chapter whilst a full equation listing is available in the copy of the model supplied to the FSA.

In summary the modelling assumptions of this sector are as follows. As described in the previous chapter, infectious individuals excrete a certain number of genome copies per day. This variable is calculated in the shellfish sector of the model (see Fig. 3.1). It is brought into this sector of the model too, providing an appropriate start point. The blue arrow in the figure therefore indicates that, for the purposes of the sludge sector of the model, this can be thought of as the starting link from the person-to-person sector. Knowledge of the total volume of sewage produced in the UK yields a figure for norovirus genome copies per litre of sewage. However, the production of sludge dilutes this concentration because sludge is separated from the effluent element of sewage.[16] Additionally, there are very particular requirements for the production of sludge used in agriculture. The raw sludge has applied to it a feed of bacteria which anaerobically digest solids, breaking down molecules, a method known as mesophilic anaerobic digestion, or MAD. It is this treated sludge that is used as a fertiliser.

However, that usage is subject to two further effects. First, it is not employed for a period of time - of the order of months. Second, both the genome copy decay effect resulting from that delay, and the distribution of the sludge as it is applied to top soil produce a further dilution effect. However, at the end of this complex set of mechanisms the presence of

16. The requirements for sludge preparation are summarised in the 'Safe Sludge Matrix' which can be found via www.water.org.uk or via www.adas.co.uk/matrix. See also [20].

genome copies per litre of sludge used is present in the model.

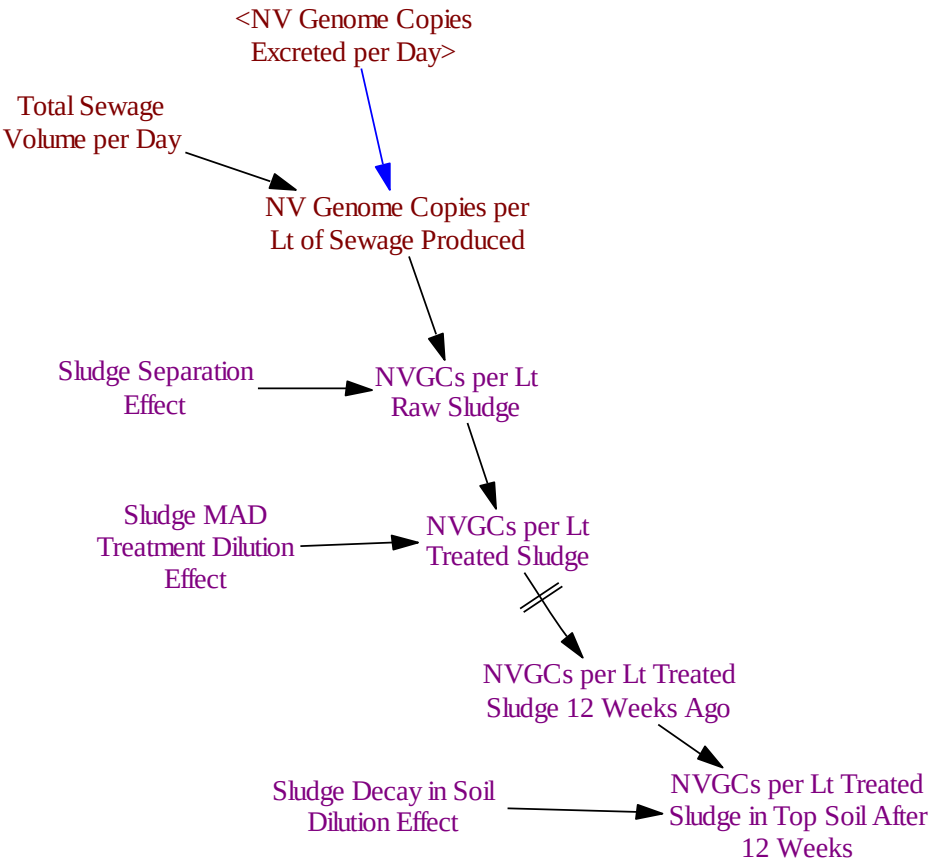


Figure 4.1: Stock/flow diagram illustrating the part of the 'Sludge Contamination' sector of the 'FSA NoV Model' relating to people-to-sludge transmission. The double lines indicate the presence of a delay mechanism, implying the presence of an additional stock in the system.

4.2 Sludge to Food Transmission

Figure 4.2 overleaf shows the SFD for the first stage of the 'FSA NoV Model' relating to the processes by which sludge can pass into certain foods. A complete version of the SFD of this sector is reproduced at the end of this chapter whilst a full equation listing is available in the copy of the model supplied to the FSA.

Knowledge of the amount of norovirus genome copies present in topsoil from which food is harvested, combined with knowledge of how many portions of BFLV are grown using a litre of sludge, allows the calculation of norovirus genome copies presence in each BFLV food

portion.[17] However, only a fraction (possibly 2%) of norovirus genome copies remain on the foodstuffs after harvesting, the remainder staying in the ground. The model contains this harvesting dilution effect. There is a further dilution effect (possibly 90% reduction) resulting from washing the BFLVs. Finally, a factor is applied that indicates how the presence of norovirus genome copies maps over to the probability that a food portion grown using sludge can be deemed 'contaminated'.

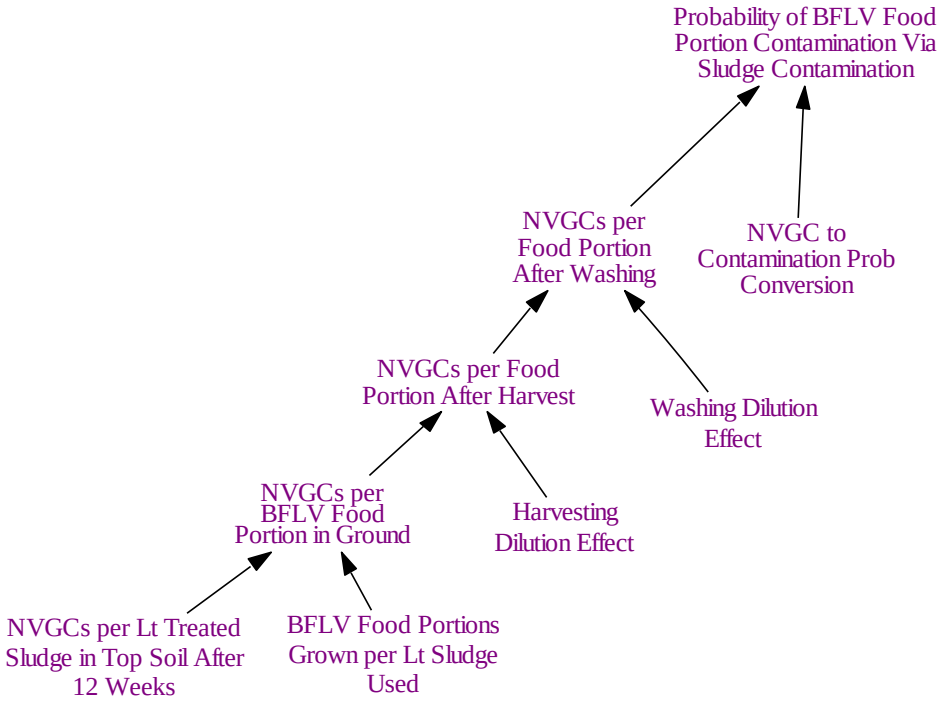


Figure 4.2: Stock/flow diagram illustrating the first stage of the transmission elements by which genome copies from sludge can contaminate certain foods in the 'Sludge Contamination' sector of the 'FSA NoV Model'.

The second stage of the processes by which sludge can pass into certain foods (and hence back into the person-to-person sector of the model) is represented in a different sector of the 'FSA NoV Model'. Part of that sector is shown in the SFD overleaf (Fig. 4.3). A complete version of the SFD of this sector is reproduced at the end of this chapter whilst a full equation listing is available in the copy of the model supplied to the FSA.

17. Although the model uses the organising concept of a food portion (the amount consumed as part of a meal) it would be a conceptually straightforward to re-cast the model to use, for example, kg of food stuffs.

The model calculates the probability that a portion of BFLV food harvested from sludge fertilised fields will be contaminated, that is, still have adhering to it some volume of the sludge fertiliser used to grow it. This variable is passed from the 'Sludge Contamination' sector. It is also necessary to scale up by the number of portions harvested daily, and to scale down because not all such portions are grown using sludge fertiliser.

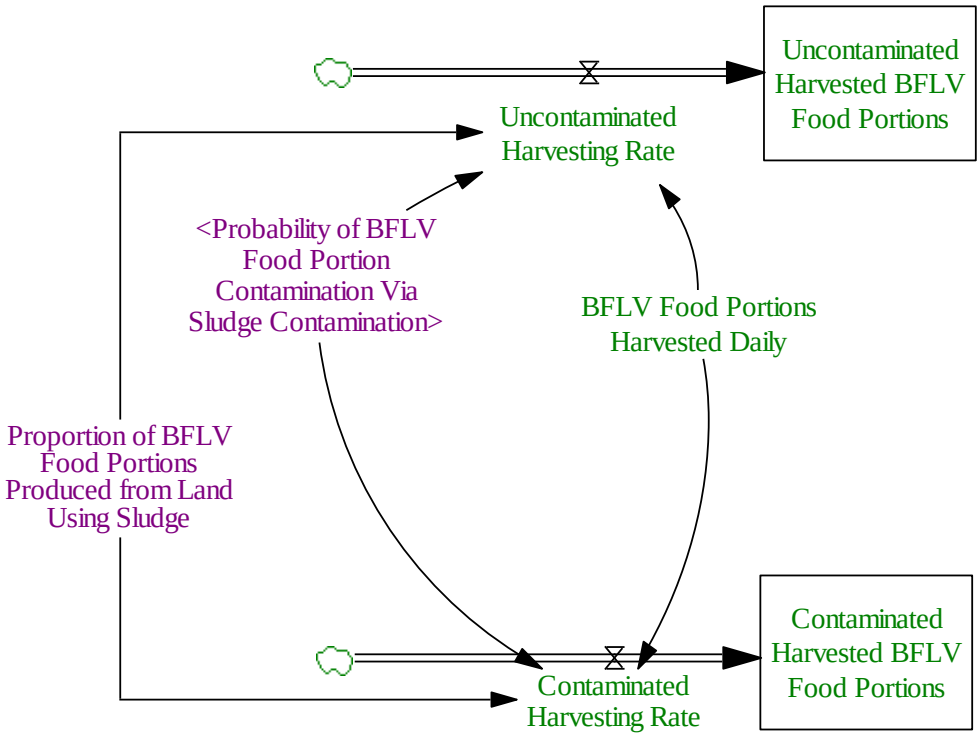
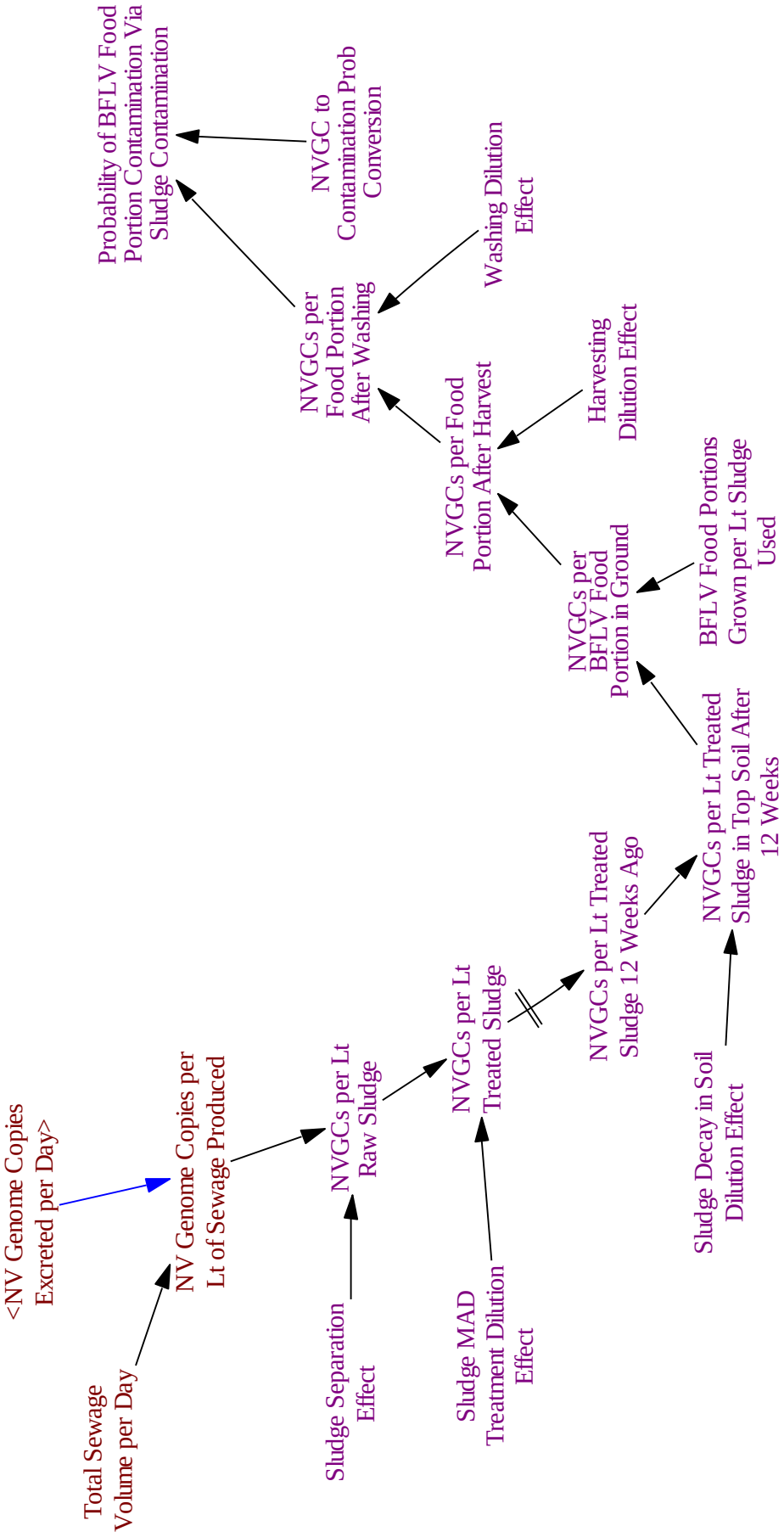


Figure 4.3: Stock/flow diagram illustrating the second stage of the transmission elements by which genome copies from sludge can contaminate certain foods. This is a detail from the 'Berry Fruit & Leafy Vegetable Supply Chain' sector of the 'FSA NoV Model'.

The result of that calculation are flows of food portions which pass into the two stocks representing the 'harvested' stage of the BFLV supply chain. These are divided into uncontaminated and contaminated. It is this second stock which feeds into the variable that passes back into the person-to-person model. The details of this complex process are discussed in the next chapter.

Figure 4.4 (overleaf): Full stock/flow diagram of the 'Sludge Contamination' sector of the 'FSA NoV Model' relating to people-to-sludge transmission.


<NV Genome Copies Excreted per Day>
NV Genome Copies per Lt of Sewage Produced
Total Sewage Volume per Day
NVGCs per Lt Raw Sludge
Sludge Separation Effect
NVGCs per Lt Treated Sludge
Sludge MAD Treatment Dilution Effect
NVGCs per Lt Treated Sludge 12 Weeks Ago
Sludge Decay in Soil Dilution Effect
NVGCs per Lt Treated Sludge in Top Soil After 12 Weeks
NVGCs per BFLV Food Portion in Ground
BFLV Food Portions Grown per Lt Sludge Used
NVGCs per Food Portion After Harvest
Harvesting Dilution Effect
NVGCs per Food Portion After Washing
Washing Dilution Effect
NVGC to Contamination Prob Conversion
Probability of BFLV Food Portion Contamination Via Sludge Contamination

5 Mechanisms in the BFLV Supply Chain

This chapter introduces the 'FSA NoV Model' assumptions for the foodborne transmission mechanisms associated with contamination of 'BFLV' foodstuffs. This refers to soft fruit (including berries), salads, and vegetables eaten raw. These foods can be contaminated by a number of processes: by sludge, by contaminated harvesters, by contaminated food processers, and by contaminated food preparers in both home and catering settings. These effects all involve links from the person-to person section of the model and they loop back to provide influences on the human 'Exposure Rate' their (see Fig. 2.3).

The 'Berry Fruit & Leafy Vegetable Supply Chain' sector of the model has a complex structure. Taken together, the following sections show this sector of the model in detail. However, it is presented in an incremental fashion.

5.1 Overview of the Contamination Stages

The core of the 'Berry Fruit & Leafy Vegetable Supply Chain' sector of the 'FSA NoV Model' is a chain of stocks which keep tracks of whether BFLV foods at different stages are contaminated or not. The figure below illustrates the SFD for this core; a complete version of the SFD of this sector is reproduced at the end of this chapter whilst a full equation listing is available in the copy of the model supplied to the FSA.

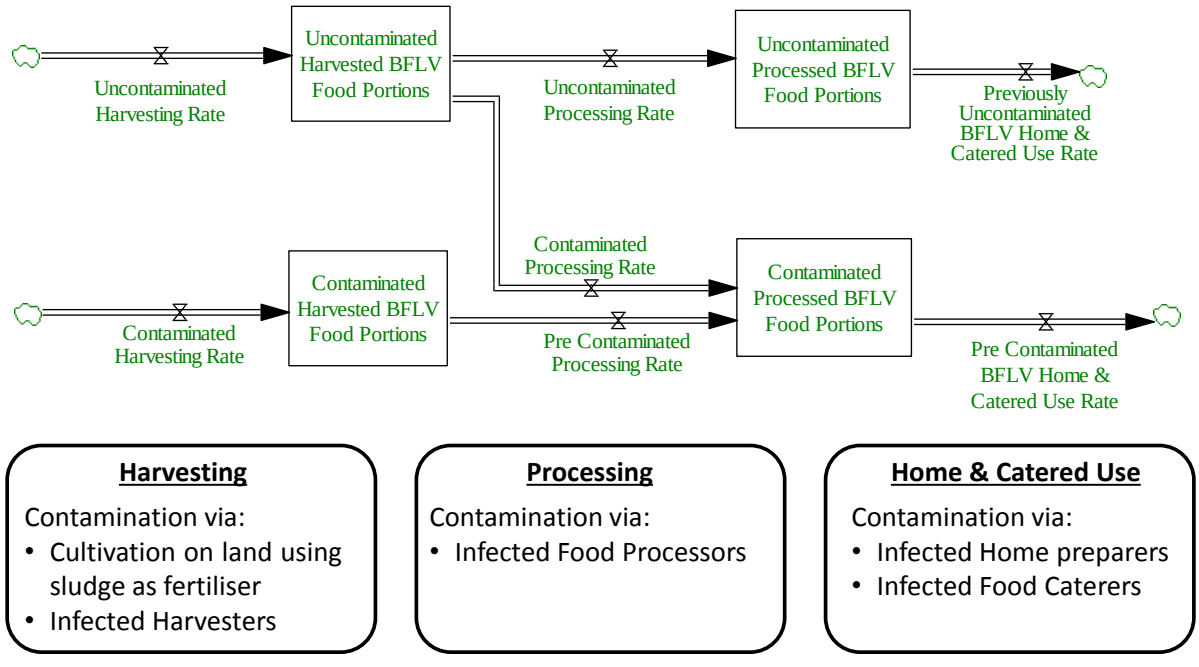


Figure 5.1: Illustration of the core of the 'Berry Fruit & Leafy Vegetable Supply Chain' sector of the 'FSA NoV Model'. This is a chain of stocks for contaminated and uncontaminated BFLV foods, annotated here with information on the production stages and the different means of contamination.

In summary, these foods are harvested (removed from the ground), then processed into forms suitable for distribution and sale, and then finally used in either home or catered environments. The top row of stocks contains uncontaminated BFLV foods whilst the bottom row contains contaminated portions. The range of mechanisms that lead to contamination at each stage is indicated in the above figure and presented in more detail in the following sections of this chapter.

5.2 Contamination in the Harvesting Stage

The figure below shows a detail of the SFD for the part of the 'Berry Fruit & Leafy Vegetable Supply Chain' sector of the 'FSA NoV Model'. This detail displays the model components relating to foodstuff contamination at the harvesting stage. A complete version of the SFD of this sector is reproduced at the end of this chapter whilst a full equation listing is available in the copy of the model supplied to the FSA.

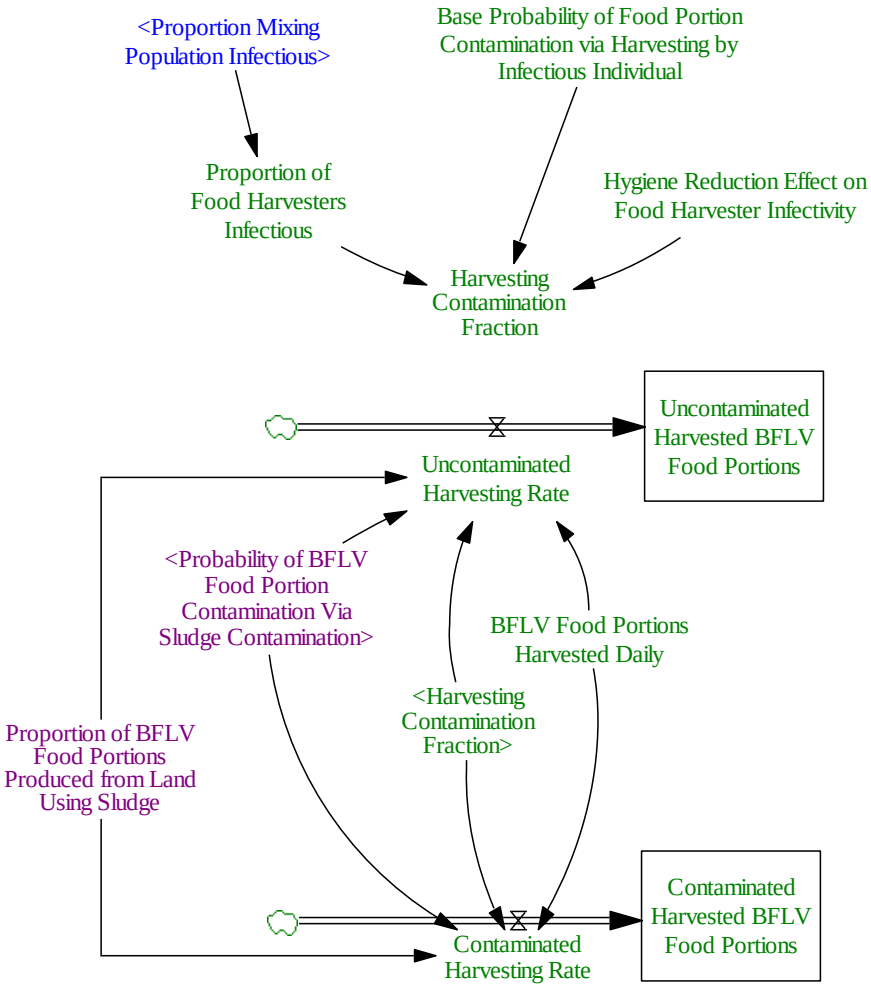


Figure 5.2: Stock/flow diagram illustrating the two contamination mechanisms associated with the harvesting in the 'Berry Fruit & Leafy Vegetable Supply Chain' sector of the 'FSA NoV Model'.

There are two mechanisms. The first concerns sludge and has been discussed in Section 4.2. The second effect concerns contamination directly from harvesters who are themselves carriers.

At any given time a certain proportion of the population is infectious and yet still mixing. This variable is the pathway from the person-to person sector of the model. This proportion may be different for harvesters, who might be more inclined to withdraw from working. There is a 'base' probability that a BFLV food portion will, in principle, be contaminated if it is harvested by an infectious individual.[18] This effect may, in practice, be reduced if harvesters give more attention to hygiene than the normal population although circumstances and attitudes may lead to the effect being increased. This generates the fraction of BFLV food portions that will be contaminated during the process of harvesting.

Those still uncontaminated flow into the upper of the two stocks. Note that for a food portion to emerge from the harvesting stage uncontaminated it must avoid both the sludge and harvesting related probabilities. The model includes this calculation.

5.3 Contamination in the Processing Stage

The next stage of the food chain represents the processing of portions of BFLV, for example, the washing and wrapping of lettuce, or the bundling of spring onions.

The figure overleaf shows a detail of the SFD for that part of the 'Berry Fruit & Leafy Vegetable Supply Chain' sector of the 'FSA NoV Model'. A complete version of the SFD of this sector is reproduced at the end of this chapter whilst a full equation listing is available in the copy of the model supplied to the FSA.

There is an average time taken to process the BFLV food portions. Food portions that have been contaminated at the harvesting stage remain contaminated, simply moving to the next stage of the chain. The new contamination process modelled is similar to those discussed in Section 5.2. A certain proportion of those involved in processing will be infectious. This proportion may be the same as that in the general population but the model allows it to be different. Food processors will take hygiene precautions which reduce the probability that NVGCs will be passed from them to the food that they handle.

18. The harvesting of BFLV items is not mechanised and the individuals involved do not normally wear gloves. To give one example, Norovirus may lodge under the fingernails of an infective individual if he/she defaecates and does not practice good hand hygiene. The Norovirus can then be passed from beneath the fingernail as he/she picks a berry off its stem. This effect can be exacerbated by poor toilet and hand-washing facilities on farms where the BFLV crops are grown.

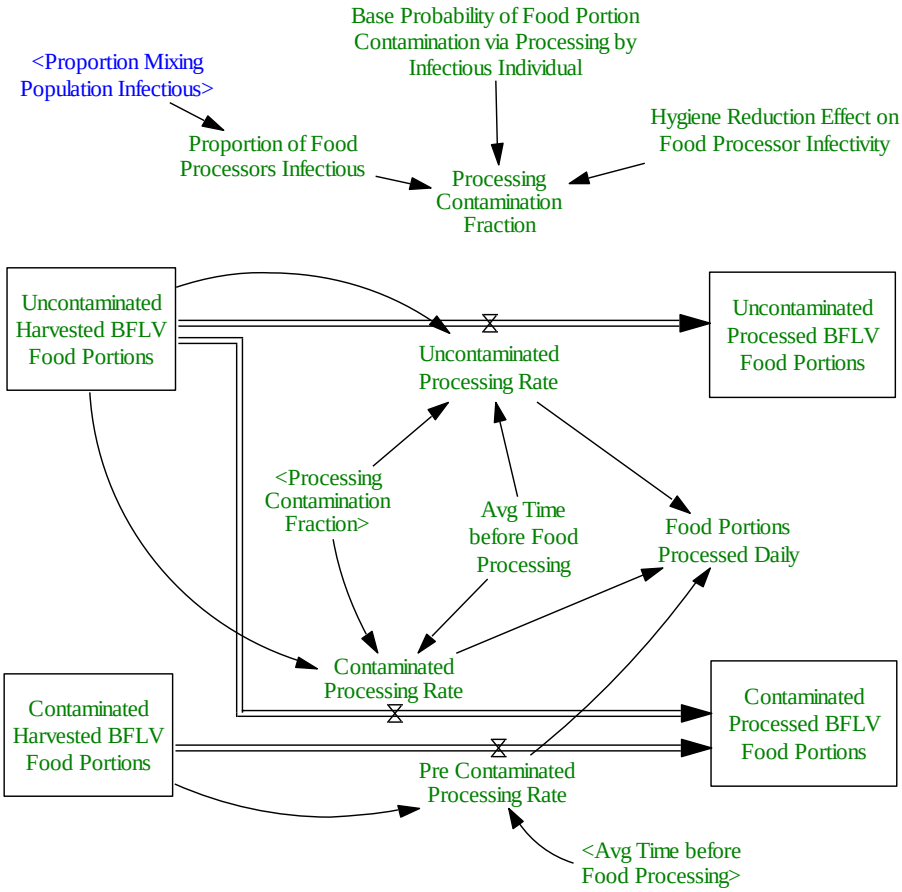


Figure 5.3: Stock/flow illustrating the operation of the contamination mechanism associated with the processing stage of the 'Berry Fruit & Leafy Vegetable Supply Chain' sector of the 'FSA NoV Model'

5.4 Contamination When Prepared for Home Use

The final stage of the food chain involves the actual preparation (and consumption) of the BFLV foodstuffs. The model divides this preparation stage into two: portions consumed at home and portions consumed in a catered environment. In this context 'home' refers to any food preparation process in which the food handling is done by someone who will themselves eat the food, or who eats other food from the same food preparation area. Such preparation is not subject to legislation and hygiene inspection; only education and advice can alter behaviour.

Figure 5.4 overleaf shows a detail of the SFD for the home preparation element of the 'Berry Fruit & Leafy Vegetable Supply Chain' sector of the 'FSA NoV Model'. A complete version of the SFD of this sector is reproduced at the end of this chapter whilst a full equation listing is available in the copy of the model supplied to the FSA.

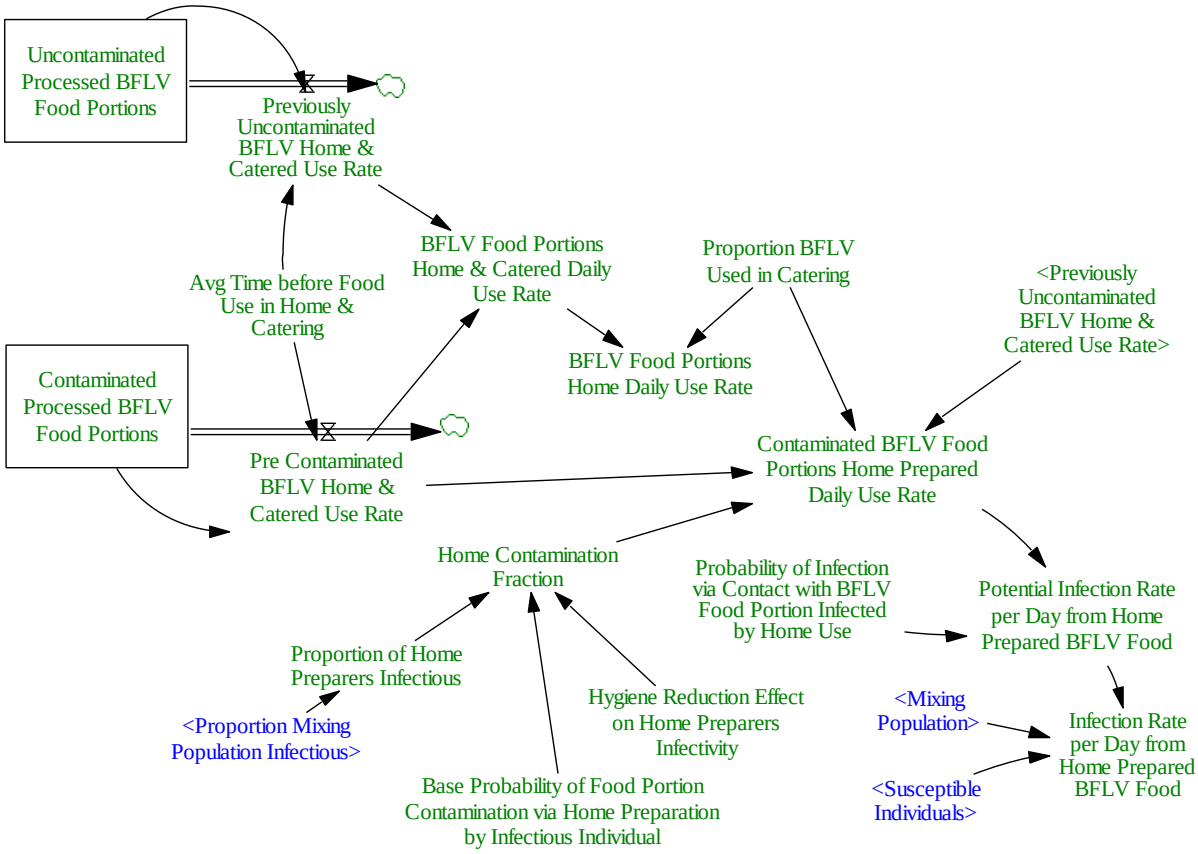


Figure 5.4: Stock/flow diagram illustrating the contamination mechanism associated with home BFLV food portion preparation in the 'Berry Fruit & Leafy Vegetable Supply Chain' sector of the 'FSA NoV Model'

Food portions emerge from the food chain either pre-contaminated (bottom flow) or not contaminated (top flow). A proportion is used in catering settings and this proportion is factored out. There is a base probability that a home BFLV food preparer who has norovirus will contaminate the food they prepare. This variable is shown in the centre at the bottom of Fig. 5.4. The calculations proceed in a manner similar to that of the previous phases. A proportion of food handlers will be infectious. This may be less than the proportion in the general population (ill individuals may avoid food preparation). They may take extra hygiene measures to reduce their infectivity. What is produced is a figure for the fraction of BFLV portions contaminated in a home setting. This figure is applied to the number of previously uncontaminated portions and to this is added the number of pre-contaminated portions. What emerges is a total number of contaminated food portions that have been prepared in the home.

It is not certain that each such portion will produce an infection. There are two reasons for this. First, the probability that a contaminated portion would produce infection may not be

one. Second, such portions must be served to a susceptible individual for an infection to occur. These calculations produce an actual number of people infected with norovirus via this mechanism, shown in the lower right hand corner of Fig. 5.4. This is one of the model variables seen to loop back into the person-to person sector of the model in Fig. 2.3.

5.5 Contamination When Prepared for Catered Use

The remaining portions of BFLV foodstuffs are prepared in catering environments. In this context 'catered' refers to any food preparation process in which the food handling is done by those other than those who consume the food. This therefore includes restaurants, fast food establishments, staff canteens, etc. Such preparation is subject to legislation and hygiene inspection to influence behaviour.

The figure below shows a detail of the SFD for this catering preparation element of the 'Berry Fruit & Leafy Vegetable Supply Chain' sector of the 'FSA NoV Model'. A complete version of the SFD of this sector is reproduced at the end of this chapter whilst a full equation listing is available in the copy of the model supplied to the FSA.

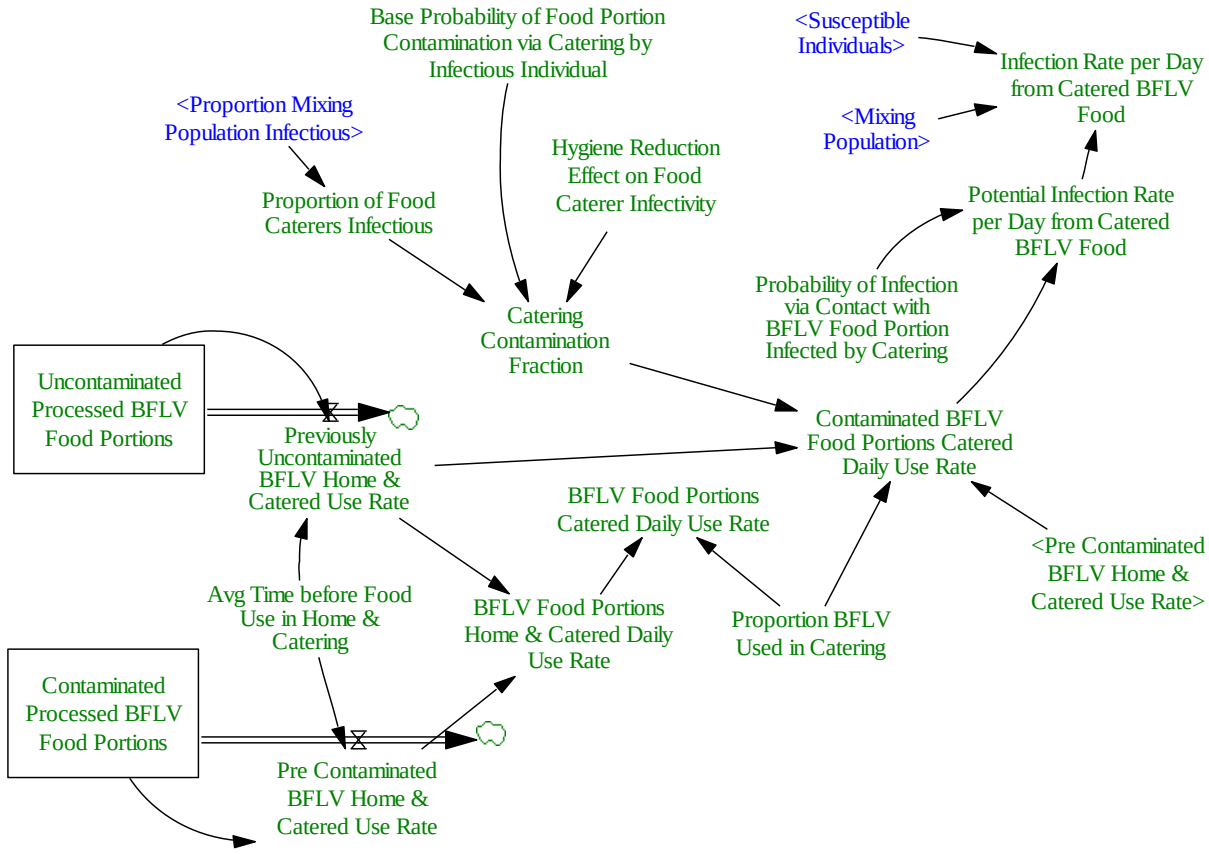
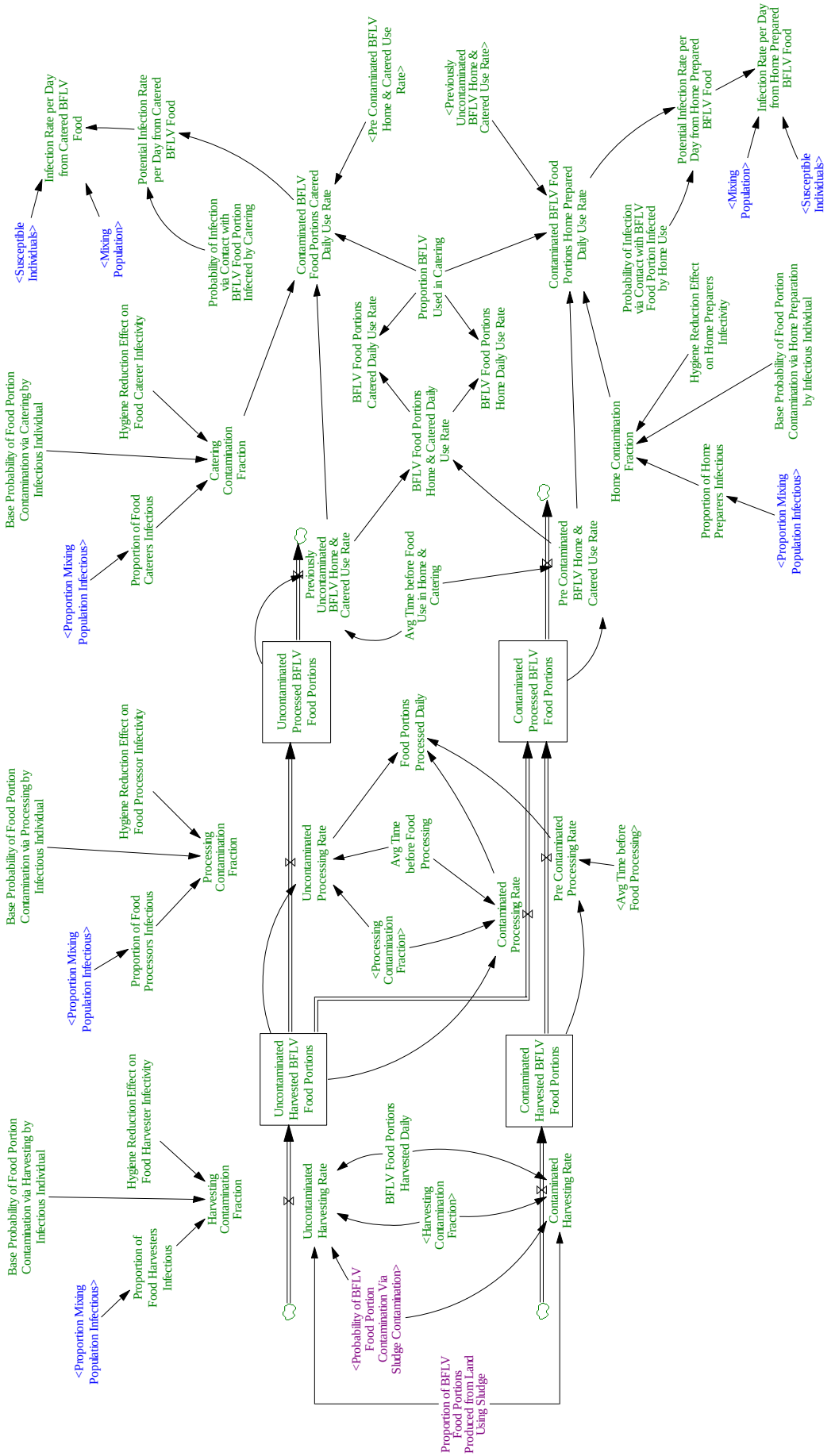


Figure 5.5: Stock/flow diagram illustrating the model's contamination mechanism associated with BFLV food portion preparation in catering environments in the 'Berry Fruit & Leafy Vegetable Supply Chain' sector of the 'FSA NoV Model'.

The model assumptions are very much in line with those for the home preparation activity. Food portions emerge from the food chain either pre-contaminated (bottom flow) or not contaminated (top flow). A proportion is used in catering settings and only this proportion is included. There is a base probability that a BFLV food preparer in a catering setting who has norovirus will contaminate the food they prepare. This variable is shown in the centre at the top of Fig. 5.5. A proportion of food handlers will be infectious. This may be less than the proportion in the general population as ill individuals are encouraged to avoid food preparation.[19] They would be expected to take careful hygiene measures to reduce their infectivity. What is produced is a figure for the fraction of BFLV portions contaminated in a catering setting. Again, this figure is applied to the number of previously uncontaminated portions and to this is added the number of pre-contaminated portions. What emerges is a total number of contaminated food portions that have been prepared in catering settings.
Not all such portions will produce an infection: the probability that a contaminated portion would produce infection may not be one; such portions might not be served to a susceptible individual. These calculations produce an actual number of people infected with norovirus via BFLV in a catering setting, shown in the upper right hand corner of Fig. 5.5. This variable loops back into the person-to person sector of the model, as shown in Fig. 2.3.

Figure 5.6 (Overleaf): Full stock/flow diagram of the 'Berry Fruit & Leafy Vegetable Supply Chain' sector of the 'FSA NoV Model'.

19. However, it is a particular feature of this industry that it tends to offer low wages and poor sickness benefits. It therefore attracts workers who may find it very difficult, for financial reasons, to lose a day's pay by declaring themselves sick.


Infection Rate per Day from Catered BFLV Food
Potential Infection Rate per Day from Catered BFLV Food
<Susceptible Individuals>
<Mixing Population>
Probability of Infection via Contact with BFLV Food Portion Infected by Catering
Contaminated BFLV Food Portions Catered Daily Use Rate
<Pre Contaminated BFLV Home & Catered Use Rate>
<Previously Uncontaminated BFLV Home & Catered Use Rate>
Contaminated BFLV Food Portions Home Prepared Daily Use Rate
Potential Infection Rate per Day from Home Prepared BFLV Food
Infection Rate per Day from Home Prepared BFLV Food
Probability of Infection via Contact with BFLV Food Portion Infected by Home Use
Base Probability of Food Portion Contamination via Catering by Infectious Individual
Hygiene Reduction Effect on Food Caterer Infectivity
Catering Contamination Fraction
Proportion of Food Caterers Infectious
<Proportion Mixing Population Infectious>
BFLV Food Portions Catered Daily Use Rate
Proportion BFLV Used in Catering
BFLV Food Portions Home Daily Use Rate
BFLV Food Portions Home & Catered Daily Use Rate
Hygiene Reduction Effect on Home Preparers Infectivity
Home Contamination Fraction
Proportion of Home Preparers Infectious
Base Probability of Food Portion Contamination via Home Preparation by Infectious Individual
Previously Uncontaminated BFLV Home & Catered Use Rate
Avg Time before Food Use in Home & Catering
Pre Contaminated BFLV Home & Catered Use Rate
Uncontaminated Processed BFLV Food Portions
Contaminated Processed BFLV Food Portions
Base Probability of Food Portion Contamination via Processing by Infectious Individual
Hygiene Reduction Effect on Food Processor Infectivity
Processing Contamination Fraction
Proportion of Food Processors Infectious
Uncontaminated Processing Rate
Food Portions Processed Daily
Avg Time before Food Processing
<Processing Contamination Fraction>
Contaminated Processing Rate
Pre Contaminated Processing Rate
<Avg Time before Food Processing>
Uncontaminated Harvested BFLV Food Portions
Contaminated Harvested BFLV Food Portions
Base Probability of Food Portion Contamination via Harvesting by Infectious Individual
Hygiene Reduction Effect on Food Harvester Infectivity
Harvesting Contamination Fraction
Proportion of Food Harvesters Infectious
Uncontaminated Harvesting Rate
BFLV Food Portions Harvested Daily
<Harvesting Contamination Fraction>
Contaminated Harvesting Rate
<Probability of BFLV Food Portion Contamination Via Sludge Contamination>
Proportion of BFLV Food Portions Produced from Land Using Sludge

6 Contamination of Other Foodstuffs

Although berry fruits and leafy vegetables are of particular interest when considering the foodborne mechanisms for transmission the virus can be acquired via other foodstuffs. This chapter introduces the 'Other Foods Contamination' sector, the part of the 'FSA NoV Model' in which those mechanisms are represented.

In summary the route is straightforward: contamination of other foodstuffs can occur via contaminated food preparers. This occurs in both home and catering settings.[20] The following sections show this sector of the model in detail.

6.1 Contamination When Prepared for Home Use

The figure below shows the SFD for the part of the 'FSA NoV Model' relating to the contamination of other types of foods during their preparation in a home setting. A complete version of the SFD of this sector is reproduced at the end of this chapter whilst a full equation listing is available in the copy of the model supplied to the FSA.

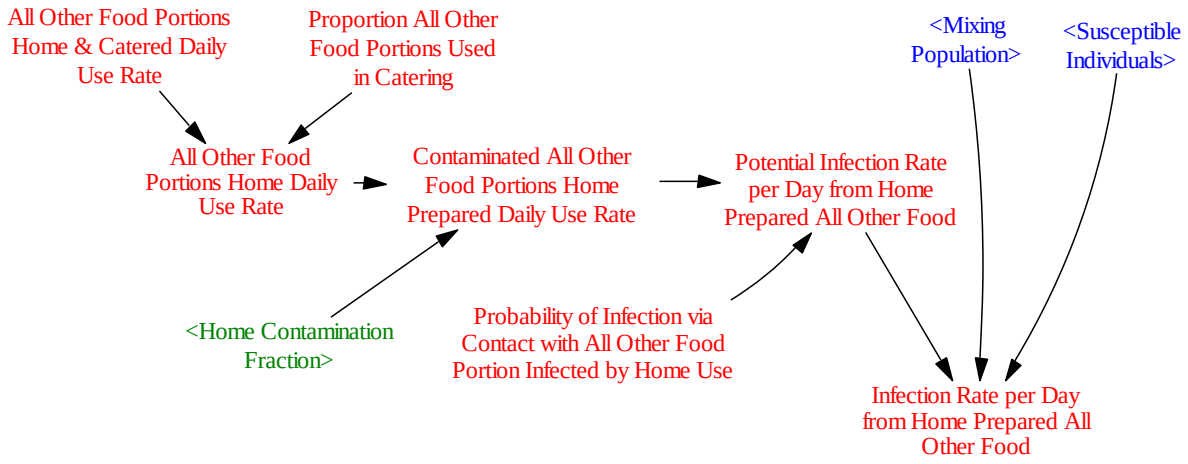


Figure 6.1: Stock/flow diagram showing the contamination mechanism associated with the home preparation of all other types of food. Taken from the 'Other Foods Contamination' sector of the 'FSA NoV Model'.

In both home and catered settings an average number of portions of all other foods are eaten per day (top left hand corner). A proportion is used in catering settings and this proportion is factored out. Of the remainder, a fraction will be contaminated as a result of

20. The definitions of 'home' and 'catered' use are the same as those used in Chapter 5.

preparation. (The construction of this variable is discussed in Section 5.4). This fraction is applied to the number of portions consumed in a home setting to produce the total number of norovirus contaminated portions of all other foods that have been prepared in the home. It is not certain that each such portion will produce an infection. The probability that a contaminated portion would produce infection may not be one, and such portions must be served to a susceptible individual for an infection to occur. These calculations produce an actual number of people infected with via this mechanism, shown in the lower right hand corner of Fig. 6.1. This is one of the model variables seen to loop back into the person-to person sector of the model in Fig. 2.3.

6.2 Contamination When Prepared for Catered Use

The remaining portions of other foodstuffs are prepared in catering environments. The figure below shows the SFD for the part of the 'FSA NoV Model' relating to the contamination of these. A complete version of the SFD of this sector is reproduced at the end of this chapter whilst a full equation listing is available in the copy of the model supplied to the FSA.

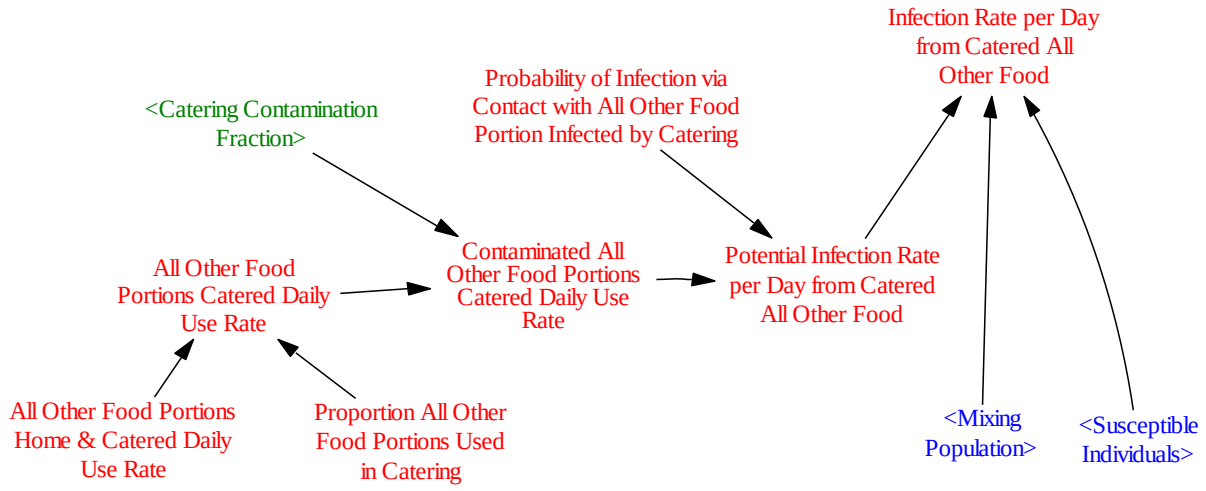


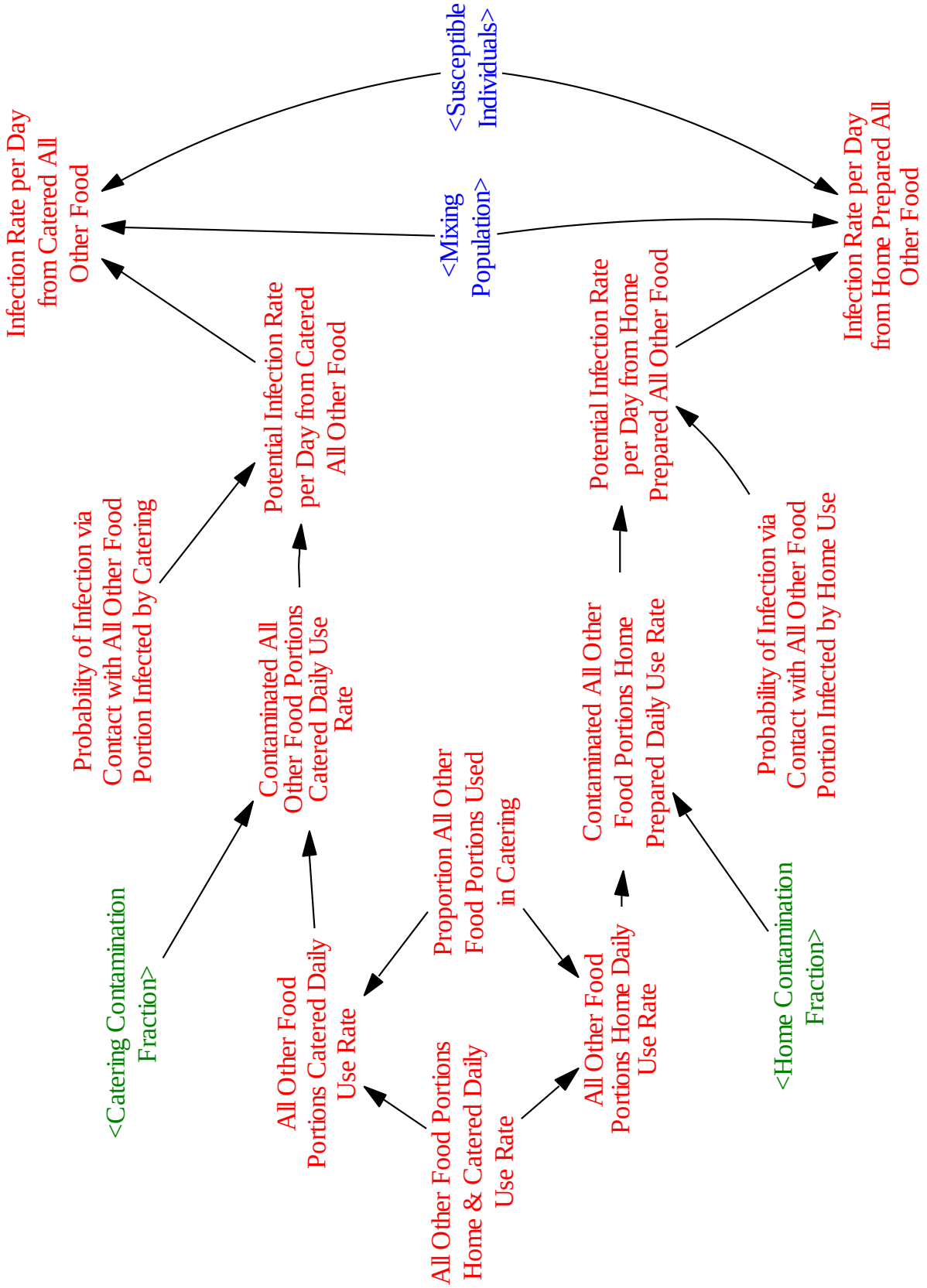
Figure 6.2: Stock/flow diagram of the contamination mechanism associated with all other types of food prepared in a catering environment, as represented in the 'Other Foods Contamination' sector of the 'FSA NoV Model'.

Again, the model assumptions are very much in line with those for the home preparation activity. In both home and catered settings an average number of portions of all other foods are eaten per day (bottom left hand corner). Only the proportion used in catering settings is considered here. A fraction of the remainder will be contaminated as a result of preparation. (The construction of this variable is discussed in Section 5.5). This fraction is

applied to the number of portions consumed in catering settings to produce the total number of norovirus contaminated portions of all other foods that have been prepared via catering.

Not all such portions will produce an infection; the probability that a contaminated portion produces an infection may not be one, and it is necessary for such a portion to be consumed by a susceptible individual for an infection to occur. These calculations produce an actual number of people infected with via this mechanism, shown in the lower right hand corner of Fig. 6.2. This is one of the model variables seen to loop back into the person-to person sector of the model in Fig. 2.3.

Figure 6.3 (Overleaf): Full stock/flow diagram of the 'Other Foods Contamination' sector of the 'FSA NoV Model'.


Infection Rate per Day from Catered All Other Food
<Susceptible Individuals>
<Mixing Population>
Infection Rate per Day from Home Prepared All Other Food
Probability of Infection via Contact with All Other Food Portion Infected by Catering
Potential Infection Rate per Day from Catered All Other Food
Potential Infection Rate per Day from Home Prepared All Other Food
Probability of Infection via Contact with All Other Food Portion Infected by Home Use
<Catering Contamination Fraction>
Contaminated All Other Food Portions Catered Daily Use Rate
Contaminated All Other Food Portions Home Prepared Daily Use Rate
<Home Contamination Fraction>
All Other Food Portions Catered Daily Use Rate
Proportion All Other Food Portions Used in Catering
All Other Food Portions Home Daily Use Rate
All Other Food Portions Home & Catered Daily Use Rate

7 Model Parameters

The information given so far about the 'FSA NoV Model' concerns its causal structure, the stock and flow relationships and the instantaneous functional relationships. However, the model also contains many parameters and these are considered in the chapter.

7.1 A Framework For Model Parameters

It had been indicated before the project began that many of the parameters that were likely to emerge in the modelling study would not be known (see footnote 9 on p. 13). This proved to be the case.[21] However, the very detail of the model allows the parameters to be understood in more depth.

For each parameter in each sector of the model we might ask two questions. First: is the value known now (in the sense that it is currently documented or can straightforwardly be calculated from data in other research) or is its value currently unknown? Second is the value of the parameter, whatever it might be, fixed (being an attribute of nature or a consequence of large scale activities well beyond the scope and/or interests of the FSA), or could it, at least in principle be altered as a result of changes in human behaviour that the FSA might work to bring about? Those two questions give rise to the framework shown below, which organises the parameters into four categories.

	Fixed Value	**Alterable Value**
Known Value	Fixed, Known	Alterable, Known
Unknown Value	Fixed, Unknown	Alterable, Unknown

Table 7.1: A 2x2 organising framework for the parameters emerging from the 'FSA NoV Model'.

21. The system dynamics approach places considerable importance on the idea that a model may contain parameters whose values are not known but which can useful be estimated judgmentally as part of the modelling process. Obtaining such estimates was one of the reasons for the November 2012 workshop. Whilst this was successful in eliciting some values, the attendees stood firm on other parameters, providing sound scientific arguments for why even the broadest estimation was not possible at the current state of knowledge. This phenomenon – unwillingness on the part of domain experts to offer even judgemental estimates of unknown parameters – is observed frequently by decisions analysts, seemingly becoming more pronounced as the knowledge of the experts on whom parameters elicitation is attempted increases.

This matrix provides an organising framework for the parameters because it assists in discussions about both research priorities and possible interventions. Consider the bottom row. As this contains the parameter values not currently known, it offers an agenda for future work, a proposal for research priorities. Consider the right hand column. Parameters in this column speak to the core interest of this study. These are the parameters that do not stand fixed, that can in principle be altered. These therefore indicate candidates for intervention. Not all would necessarily change the time evolutionary behaviour of the system appreciably[22] and it is clear that many would be very difficult intervene in and alter. However, they offer a start to the question at the centre of this work: where could FSA target its efforts in support of its 'Foodborne Disease Strategy'? Moreover, the model would directly support experimentation on the consequences of altering these parameters.
For these reasons, the matrix is now used to organise the parameters in the 'FSA NoV Model' developed for this report.

7.2 Categorising Model Parameters

The following tables apply the matrix in Table 7.1 to the sectors of the model. In each case they can be read as giving information on the values needing further research (bottom row) and on the values that might be discussed as possible intervention points (right hand column).

22. It would be necessary to perform sensitivity analysis on the model to determine in the case of each parameter whether it does so, and could therefore be referred to as a 'policy parameter' in the system dynamics modelling usage [51].

	Fixed Value	**Alterable Value**
Known Value	Fixed, Known Daily Excreta Mass per Person Genome Copies per gram of Infected Stool	Alterable, Known Sewage Treatment Reduction in NVGC Purification Parameter Shellfish Meals Eaten per Day Avg Shellfish Eaten per Meal
Unknown Value	Fixed, Unknown Proportion of Treated Sewage Discharging Near Estuary Farm Areas Filter Concentration Effect Dissipation Time NVGCs Required per Potential Infection	Alterable, Unknown

Table 7.2: Categorised parameters employed in the 'Bivalve Shellfish' sector of the 'FSA NoV Model'.

	Fixed Value	**Alterable Value**
Known Value	Fixed, Known Total Sewage Volume per Day	Alterable, Known
Unknown Value	Fixed, Unknown Sludge Separation Effect Sludge MAD Treatment Dilution Effect * NVGC to Contamination Prob Conversion Harvesting Dilution Effect *	Alterable, Unknown Sludge Decay in Soil Dilution Effect * Washing Dilution Effect * BFLV Food Portions Grown per Lt Sludge Used

*Table 7.3: Categorised parameters employed in the 'Sludge Contamination' sector of the 'FSA NoV Model'. For the parameters marked *, although their values are unknown, related values are available for Giardia cysts and could be used as proxies.*

	Fixed Value	**Alterable Value**
Known Value	Fixed, Known BFLV Food Portions Harvested Daily Avg Time before Food Processing Avg Time before Food Use in Home & Catering Proportion BFLV Used in Catering	Alterable, Known
Unknown Value	Fixed, Unknown Base Probability of Food Portion Contamination via Harvesting by Infectious Individual Base Probability of Food Portion Contamination via Processing by Infectious Individual Base Probability of Food Portion Contamination via Catering by Infectious Individual Probability of Infection via Contact with BFLV Food Portion Infected by Catering Base Probability of Food Portion Contamination via Home Preparation by Infectious Individual Probability of Infection via Contact with BFLV Food Portion Infected by Home Use	Alterable, Unknown Proportion of BFLV Food Portions Produced from Land Using Sludge Proportion of Food Harvesters Infectious Hygiene Reduction Effect on Food Harvester Infectivity Proportion of Food Processors Infectious Hygiene Reduction Effect on Food Processor Infectivity Proportion of Food Caterers Infectious Hygiene Reduction Effect on Food Caterer Infectivity Proportion of Home Preparers Infectious Hygiene Reduction Effect on Home Preparers Infectivity

Table 7.4: Categorised parameters employed in the 'Berry Fruit & Leafy Vegetable Supply Chain' sector of the 'FSA NoV Model' .

	Fixed Value	**Alterable Value**
Known Value	Fixed, Known Proportion All Other Food Portions Used in Catering Proportion All Other Food Portions Used in Home	Alterable, Known
Unknown Value	Fixed, Unknown Probability of Infection via Contact with All Other Food Portion Infected by Catering Probability of Infection via Contact with All Other Food Portion Infected by Home Use	Alterable, Unknown (Catering Contamination Fraction) (Home Contamination Fraction)

Table 7.5: Categorised parameters employed in the 'Other Foods Contamination' sector of the 'FSA NoV Model'. The elements in brackets are calculated in a different model sector, from other parameter values (see Figs. 5.4 & 5.5). They are included here to record the important influence of those constitutive parameters on this sector.

Part 2 Scoping the Foodborne Effects

8 Recalibration and Analysis of the Extended Person-to-Person Model

The following three chapters describe a different approach to the central concern of the research: the wish to understand the contribution of the foodborne mechanisms of norovirus transmission. Using new data, the person-to-person model is used to explore – scope - the scale and sensitivity of both person-to-person infectivity and the foodborne effect on overall incidence of norovirus.

This analysis is based on a re-calibrated version of the extended person-to-person model described in Chapter 2. That new version of the model is the focus of this chapter. The first section reports newly established parameters for incidence, foodborne percentage and asymptomatic carriage. Section 8.2 then describes how this data is used within the model, first to calculate parameters for person-to-person infectivity and the foodborne effect, and then to calculate the overall 'footprint' of norovirus in the population. Section 8.3 reports model simulations which reproduce the 'footprint' results. Finally, Section 8.4 outlines how the parameters for person-to-person infectivity and the foodborne effect and the norovirus footprint can all be calculated analytically – directly – from any assumptions about incidence and foodborne percentage.

8.1 New Data on Norovirus

Three new parameter values are used in the analysis contained in this part of the report. These concern incidence, the foodborne percentage and the fraction of asymptomatic carriage.

The first parameter is an updated estimate for the observed annual incidence of norovirus and was generated by the second IID study, or 'IID2' [57]. Figures from IID2 show the total number of cases in the UK, inferred from a study conducted between April 2008 and August 2009. Using a 95% "credible interval", a range of [2,418,208 - 3,490,451] is given, with a best estimate value of 2,905,278.[23] This parameter, becoming 7,960 as it is converted to a daily basis, will be referred to as the 'Observed Incidence Rate'. In model terms it equates to the variable 'Infection Development Rate Is' - see Fig. 2.2 - and so the symbol Φ is used for it.

The second parameter relates to the percentage of cases attributable to foodborne mechanisms. An early version of results from the 'IID2 Extension Study' was made available during the project [56]. In this study the number of cases from outbreaks and their sources

23. These data can be found in Table 3, p. 75 of [57].

were used to determine whether the cases were foodborne. The resulting figures lie in a 95% "credible interval" of [50,320 - 104,000] for cases per year, whilst the best estimate value is 73,420.

At the inception of this project the cautiously held view for the fraction of cases attributable to foodborne mechanisms was 10.7% [1]. Combining the data from the previous two paragraphs gives a new, sharply reduced, estimate for the fraction of cases attributable to foodborne mechanisms: 2.527%.[24] This proportion will be referred to as the 'Foodborne Proportion of Incidence Rate' and the symbol π used for it. In algebraic terms it proves useful to define a related variable, the ratio of foodborne cases to person-to-person cases. The symbol ρ is used for this and it should be noted that $\rho = \pi/(1-\pi)$.

The third and final parameter value is the 'Asymptomatic Carriage Proportion'. This is the proportion of all those exposed to norovirus who show no signs of infection and have no symptoms but may still shed the virus. This parameter was represented by the symbol κ and in the Lawrence *et al.* work [36] it had the value 0.003, or 0.3%.[25]

FSA staff advising DCL discussed this point at some length in November 2012. Some difficulty was experienced regarding exactly which parameters were being considered in the literature.[26] The conclusion was that the value of 0.003 was a serious underestimate and that 0.12 was a better estimate. This value was used in the following analysis.

This significant increase in the proportion of those exposed to norovirus who are asymptomatic – up from 0.3% to 12% - leads to comment on a fourth model parameter. As mentioned in Chapter 2, the model discussed in this report has been extended from the version in [36] via the introduction of differential infectivity of asymptomatic infective individuals. In the equations presented in Section 2.2 this is accomplished by introducing a new parameter, 'Weighting for Infectious Asymptomatics' designated by the symbol ϖ. This new parameter merits comment.

The parameter was introduced in this work to address the fact that the extent to which asymptomatic viral shedders are infectious is not known [5]. This parameter allows their infectivity to be set at a proportion of the infectivity of symptomatic individuals. The reasons for the uncertainty are many. Symptomatic carriers are likely to exhibit vomiting, an important transmission route; this does not occur with asymptomatic people. The stools of

24. The 2.527% is calculated as 100x73,420/2,905,278. Note that use of the CI extrema for the foodborne cases, still with the 2,905,278 total cases figure, gives a range for this percentage: of [1.732% - 3.580%].
25. The authors state, "Asymptomatic carriage in the English population has been estimated to be from 0.1 to 0.5%, based on the positivity rates of controls in the two components of the IID study (62). However it is not known whether asymptomatic viral shedders are infectious" [36] p. 7. The citation (62) here is [60] in this report.
26. Some sources seemed to be describing the proportion of the whole population that is asymptomatic, others the proportion of asymptomatic individuals found (using PCR techniques) to be carrying Norovirus.

asymptomatic tend to be more solid, which may also reduce the infectivity of those individuals. Moreover, these stools may be associated with antibodies that prevent symptoms. Finally, without quantifying the effect, research suggests that viral loads tend to be lower in asymptomatic individuals than symptomatic ones. Of course, these effects which all hint at a reduced infectivity for asymptomatic infectives must be placed in the balance with the fact that asymptomatics are likely to have a higher social mixing rate than symptomatics, for the simple reason that they are not debilitated as a result of the symptoms of norovirus. It is currently impossible to calculate the overall balance of these effects. As [49] states, "more work is needed to understand whether asymptomatic infections are important for norovirus transmission leading to sporadic illness and outbreaks" (p. 1454).

This uncertainty was very much less likely to be important when only 0.3% of those exposed to norovirus became asymptomatic but 12% must give pause for thought. Hence the inclusion of ϖ, the parameter that serves as a platform for this uncertainty.

The work in [36] can be interpreted as having set the value of this parameter to one. FSA staff have cautiously suggested that it could be 1/10, 1/100 or even zero. In the specific calculations that follow in this and the next chapters the value of one is used. However, all of the general, algebraic results include ϖ as a parameter, thereby allowing sensitivity analysis around this assumption to be conducted. Section 9.5 contains a comment on the consequences of changing this parameter.

8.2 Calculating Infectivity and 'Footprint'

The parameter values discussed in the previous section can be combined with the extended version of the person-to-person model to calculate both the transmission parameters and the prevalence of norovirus in the population. This section documents the process of doing this and reports the results.

In conceptual terms, the following calculations are straightforward. What is sought is the steady state solution to the model equations, the values of all of the stocks that keep the system in permanent balance.

The new parameters from IID2 and the Extension Study must be reflected. Any model must generate a value of the 'Observed Incidence Rate' that is equal to the value of Φ put forward by IID2. Any model must be consistent with the value of 'Foodborne Proportion of Incidence Rate' – and hence π (or its associated parameter ρ) - advanced by the Extension Study. Consistency with these two parameters is a requirement to lock the model to reality.

These requirements are then 'processed' through the assumptions represented by the extended person-to-person model. This model consists of assumptions on the set of structures representing the causal mechanisms believed to be operating, and the values of the other parameters. Combining all of this information it is possible simultaneously to calculate two sets of outputs (see Fig. 8.1).

First, parameters for the person-to-person infectivity, β_0 and for the foodborne effect, θ_0 can be deduced. These values represent current best estimates of the 'state of the world as is', in that they are consistent with other observed data.[27] Second, the steady state values of all of the key population groups can be calculated, giving a measure of the overall prevalence, or 'footprint' of in the population.

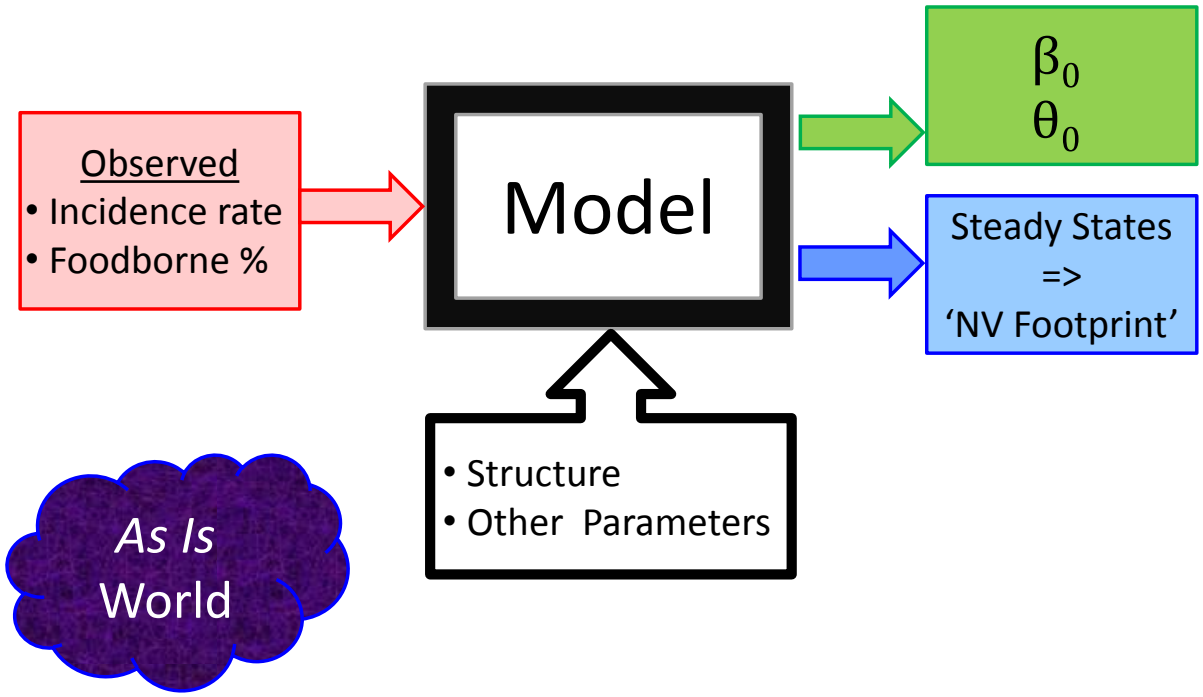


Figure 8.1: Representation of how the extended person-to-person model and improved parameter values are used to calculate infectivity parameters and prevalence of norovirus.

To provide a complete record of the calculations, listed below are the ODEs for the extended person-to-person model.

$$\frac{dS}{dt} = -\left(\frac{\beta}{N}\{Is + \varpi Ia\} + \theta\right)S + \delta R + \mu(\{1-\chi\}N - S) \quad [1]$$

$$\frac{dE}{dt} = \left(\frac{\beta}{N}\{Is + \varpi Ia\} + \theta\right)S - (\mu + \alpha)E \quad [2]$$

27. Given the 'scoping' experiments done in the following chapter it is useful also to think of them as baseline values, so these specific numerical results are subsequently referred to as β0 and θ0.

$$\frac{dIs}{dt} = \alpha(1-\kappa)E - (\gamma+\mu)Is \quad [3]$$

$$\frac{dIa}{dt} = \alpha\kappa E - (\gamma+\mu)Ia \quad [4]$$

$$\frac{dR}{dt} = \gamma(Ia+Is) - (\mu+\delta)R \quad [5]$$

$$\Phi = \alpha(1-\kappa)\bar{E} \quad [6]$$

$$\theta = \rho\frac{\beta}{N}(\bar{Is} + \varpi\bar{Ia}) \quad [7]$$

Equation [6] merits comment. It is consistent with the idea that the 'Observed Incidence Rate' can only be a measure of those individuals who, having been exposed to norovirus, go on to develop symptoms. Hence Φ is set equal to the flow into the 'Infectious Symptomatic Is' stock. Note also that, consistent with the nature of the reported data, both equations [6] and [7] are written in terms of the steady state values of some of the population categories, indicated by $\overline{\text{Name}}$, the standard notation.

To ensure reproducibility of the results, Table 8.1 (below) displays all of the parameters that are inputs to the model (as opposed to those derived from it).

Parameter in Model	**Value**	**Symbol**
Population Size N	61,792,000	N
Asymptomatic Carriage Proportion	0.12	κ
Weighting for Infectious Asymptomatics	1	ϖ
Proportion of Pop Non Susceptible to NV Chi	0.2	χ
1/Latent Period	0.5	α
1/Infectious Period	0.5	γ
1/Period of Immunity	2/365	δ
1/Life Expectancy	1/(78*365)	μ
Observed Incidence Rate	7,960	Φ
Foodborne Proportion of Incidence Rate	0.02527	π
$\pi/(1-\pi)$	0.02593	ρ

Table 8.1: Parameters that are inputs to the model, listed with their associated name, respective value, and symbol in the ODEs. The time period used is [days].

Following the approach outlined earlier in this section – and detailed in algebraic form in Section 8.4 – the results in Table 8.2 are obtained for the steady state values of all of the key population groups (the 'footprint' of norovirus) and for the parameters for the person-to-person infectivity and for the foodborne effect.

Parameters Derived from Model	**Value**	**Symbol**
Deduced Footprint		
Susceptible Individuals	47,757,324	$\bar{S}$
Exposed Individuals	18,090	$\bar{E}$
Infectious Symptomatic Is	15,918	$\bar{I}s$
Infectious Asymptomatic Ia	2,171	$\bar{I}a$
Recovered Immune	1,640,097	$\bar{R}$
Deduced Infection Effects		
Forcing term for the foodborne effect	4.78662E-06	θ_0
Person-to-person infectivity	0.630677102	β_0

Table 8.2: Values derived from the extended person-to-person model and updated parameter values for: the prevalence, or 'footprint', of norovirus; the forcing term for the foodborne effect; and the person-to-person infectivity.

These outputs can be seen as logical deductions from the parameters used and the model that is hypothesised as capturing the mechanisms in play. They imply, for example, that in the UK at any time there are 1.6 million individuals who are temporarily immune from norovirus, having been exposed to it, and that there 18,000 people who have been exposed to norovirus. It is also worth commenting that the output implies that norovirus is sustained in the population even though the individuals carrying it make up less than 1/1000 of the total population.

8.3 Simulation using the System Dynamics Model

The system dynamics model built as part of this work will reproduce the values shown in the top segment of Table 8.2. The model is parameterised using Table 8.1 and the values of β_0 and θ_0 shown in Table 8.2. It must then be run for sufficient time to settle down to a 'steady state'. A choice is available regarding the initial values used. A standard option is to include a number of initial carriers to start the presence. In this case, a non-zero value of I_s was specified. An alternative is to leave the whole population in the 'Susceptible Individuals' stock and allow the θ_0 forcing term alone to pull the system to a steady state in which the

prevalence of norovirus is established. Model output using both is shown in Fig. 8.2.

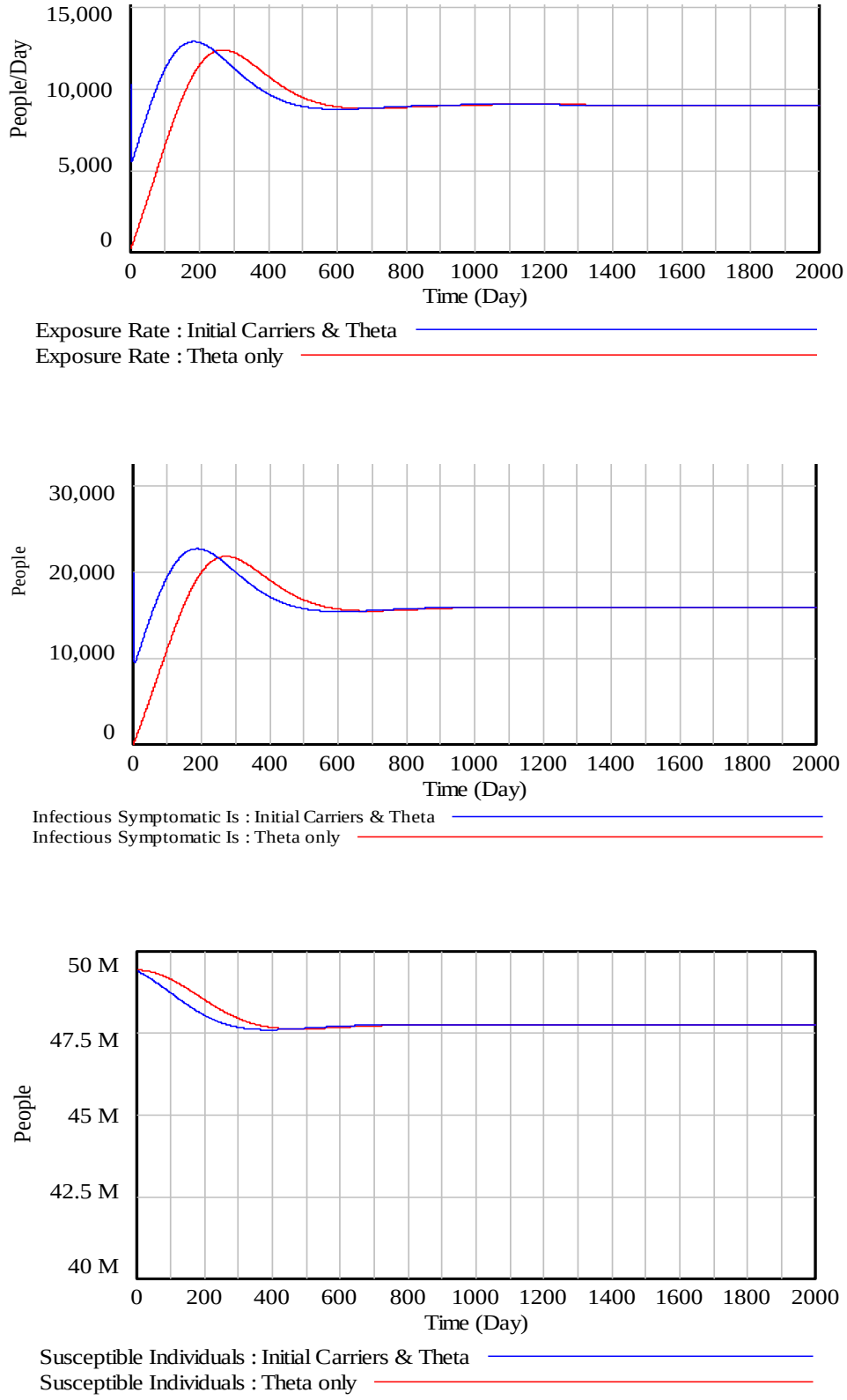


Figure 8.2: A sample of outputs from the system dynamics simulation model showing the effects of the two different initial values approaches.

As the model output in Fig. 8.2 reveals, there is very little difference between the two initialisation approaches; in both cases the model needs ~1000 simulated days to settle down to steady state. Unless stated, in the simulations that follow the Theta term is the sole initiator for the onset.

(Note that the transient response can be thought of as a realistic simulation of the consequence of norovirus appearing in a previously infection-free environment - either as a result of foodborne infections or as a result of this effect and the arrival of a number of human carriers. However, it is no less valid to interpret them merely as 'initialisation transients', the result of a 'warm-up period' which produces simulation artefacts as a system homes in on its steady state [59].)

Naturally, the model can produce all of the state variable results shown in the upper segment of Table 8.2. Simulation results are shown overleaf in Fig. 8.3. The upper panel shows values for the three stocks of individuals having the norovirus: individuals who are exposed and individuals who are infectious – either symptomatically or asymptomatically. The lower panel shows the larger-scale stocks in the model, including the constant 20% of the population who are not susceptible to norovirus – the 'Permanently Protected'. The value for 'Infectious Symptomatics Is' is included for scale comparison purposes. Note that the topmost black line sums all of the stocks in the model. That it is constant, at the value 61,792,000 (the specified value of 'Population Size N'), serves as one check on the correct functioning of the model.

In fact, the steady state values to which these plots converge can, in the general case, be obtained analytically. Their derivation is discussed in the following section.

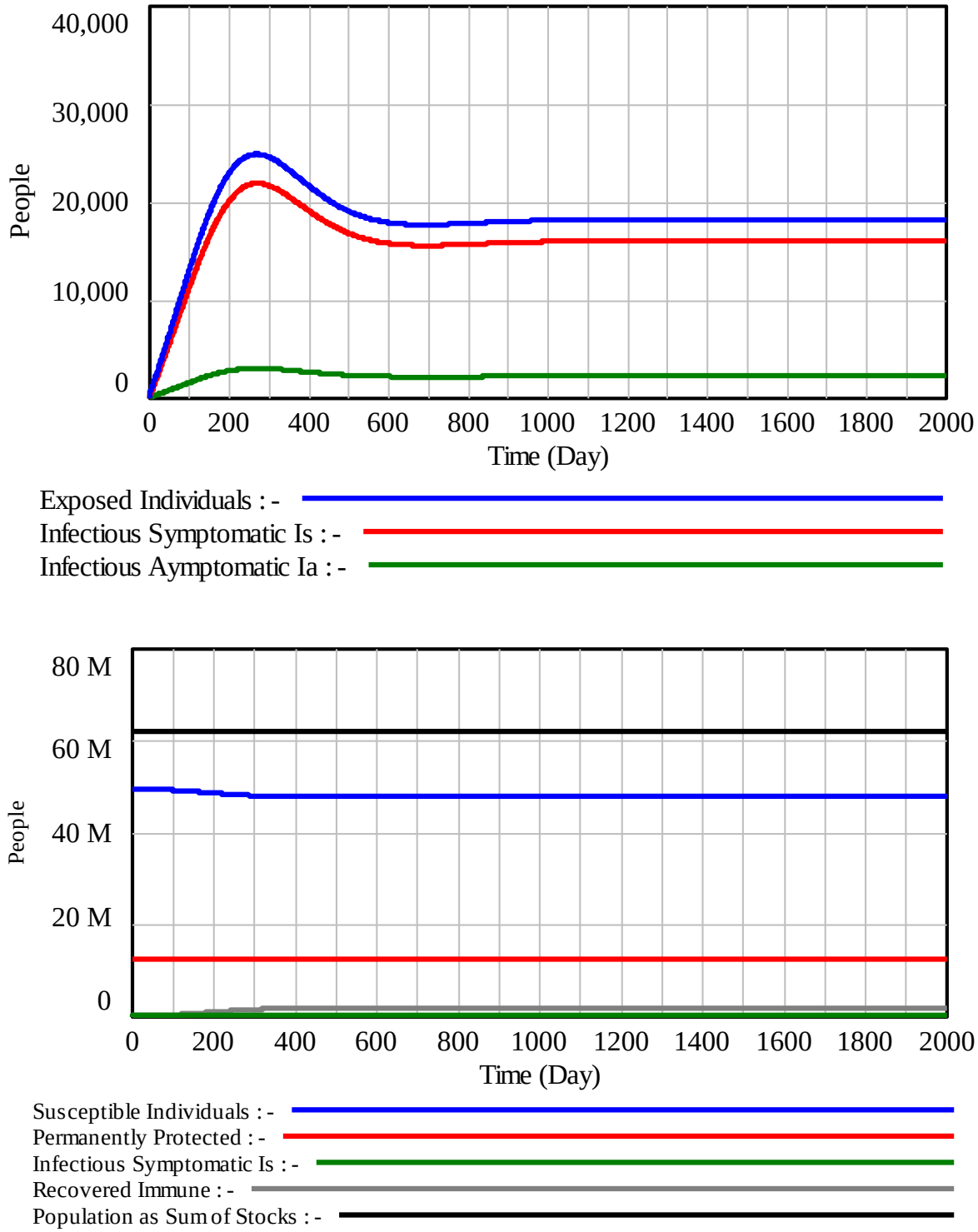


Figure 8.3: Output from the system dynamics simulation model showing the recreation of the steady state values of Table 8.2

8.4 General Form for Model Steady States ('World As Is')

The specific results discussed in Section 8.2 (and reproduced via simulation in Section 8.3) were calculated analytically by solving the system of equations to find their steady state. The mathematical tractability of the extended person-to-person model is useful because it allows the calculations to be done again, either in the light of future data availability, or as part of sensitivity analysis. This section therefore lists the algebraic results for the footprint and for the parameters for person-to-person infectivity and the foodborne effect.

$$\bar{S} = (1-\chi)N + \frac{\Phi}{\alpha\mu(1-\kappa)}\left(\frac{\alpha\gamma\mu}{(\mu+\delta)(\gamma+\mu)} - (\alpha+\mu)\right)$$

$$\bar{E} = \frac{\Phi}{\alpha(1-\kappa)}$$

$$\bar{Is} = \frac{\Phi}{(\gamma+\mu)}$$

$$\bar{Ia} = \frac{\Phi}{(\gamma+\mu)}\frac{\kappa}{(1-\kappa)}$$

$$\bar{R} = \frac{\Phi}{(\mu+\delta)}\frac{\gamma}{(1-\kappa)(\gamma+\mu)}$$

$$\beta = \frac{\frac{N(\alpha+\mu)(\mu+\gamma)}{(1+\rho)(1+(\varpi-1)\kappa)}}{\alpha(1-\chi)N + \frac{\Phi}{\mu(1-\kappa)}\left(\frac{\alpha\gamma\mu}{(\mu+\delta)(\gamma+\mu)} - (\alpha+\mu)\right)}$$

$$\theta = \frac{\frac{\rho(\alpha+\mu)\Phi}{(1+\rho)(1-\kappa)}}{\alpha(1-\chi)N + \frac{\Phi}{\mu(1-\kappa)}\left(\frac{\alpha\gamma\mu}{(\mu+\delta)(\gamma+\mu)} - (\alpha+\mu)\right)}$$

9 Scoping the Sensitivity of the Person-to-Person Model

This chapter builds on the work in Chapter 8 to address directly the question of how the foodborne effect influence overall incidence of cases. The mathematical approach that is used is outlined in Section 9.1. In Section 9.2 this approach is then used to 'scope out' the effect on prevalence of changing the strength of the foodborne effect. Both simulation and mathematical approaches are used. In Section 9.3 the consequences of changing the person-to-person infectivity are considered – again, using two approaches. The equations that are needed to generate the results of the earlier sections are then presented. The chapter then closes with Section 9.5, which comments briefly on the (in)sensitivity of the previous results to changes in the new parameter describing the role of asymptomatic infective individuals.

9.1 Approach to Scoping Parameter Sensitivity

The aim is no longer to fit the model to data representing the 'world as is' (the 'Observed Incidence Rate', Φ and the 'Foodborne Proportion of Incidence Rate', π) and then use this to calculate the footprint and parameter values for foodborne transmission and person-to-person infectivity. Instead, the approach aims to consider scenarios, or 'worlds' in which the parameters governing the two infectivity effects are inputs (see Fig. 9.1).

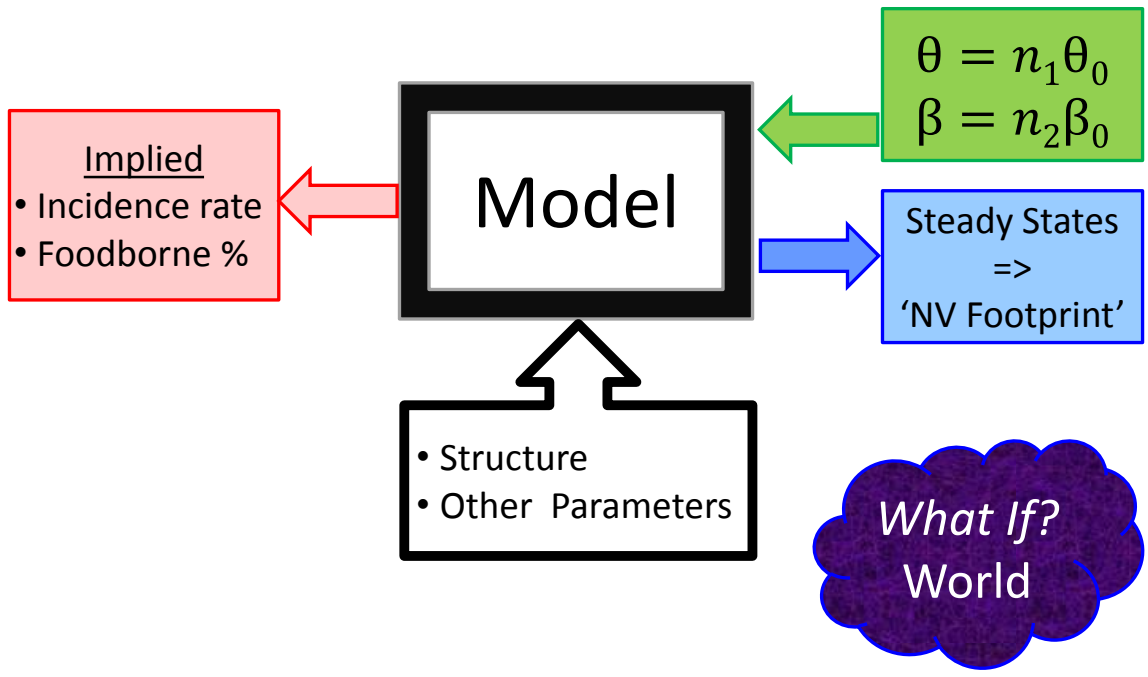


Figure 9.1: Representation of how the extended model can be used to take alternative assumptions about foodborne infection and person-to-person effects and calculate the resulting incidence rate and prevalence of norovirus.

The model can then be used to take these assumed values of θ or β and deduce the consequent prevalence, or footprint, along with the new observed incidence rate of norovirus. The ratio of foodborne cases is also an output of these calculations.

The model equations remain the same; the issue is the use of parameters. Any values for θ or β can be used. However, as indicated in Fig. 9.1, the values calculated in the last chapter are used as a baseline, with multiples of these values used in the model to ask 'What If?' questions. Table 9.1 shows the parameters that are inputs to the model.

Parameter in Model	**Value**	**Symbol**
Population Size N	61,792,000	N
Asymptomatic Carriage Proportion	0.12	κ
Weighting for Infectious Asymptomatics	1	ϖ
Proportion of Pop Non Susceptible to NV Chi	0.2	χ
1/Latent Period	0.5	α
1/Infectious Period	0.5	γ
1/Period of Immunity	2/365	δ
1/Life Expectancy	1/(78*365)	μ
Base Value of Forcing term for the foodborne effect	4.78662E-06	θ_0
Base Value of Person-to-person infectivity	0.630677102	β_0
'What if?' values		
Forcing term for the foodborne effect	$n_1\theta_0$	θ
Person-to-person infectivity	$n_2\beta_0$	β

Table 9.1: Parameters that are inputs to the model for the purpose of scoping the sensitivity of prevalence to foodborne infectivity and person-to-person effects.

Following the approach just outlined, numerical values can be obtained for the variables in Table 9.2, that is, for the steady state values of all of the key population groups (the 'footprint' of norovirus).

Note that there are two methods for doing this calculation. Simulation can be used and values read off when the system has converged (reasonably close) to the steady state. Additionally, the state equations can be solved analytically using the algebraic solutions described in Section 9.4. In the following sections both methods are used.

Values Derived from Model	Symbol
Deduced Footprint	
Susceptible Individuals	$\bar{S}$
Exposed Individuals	$\bar{E}$
Infectious Symptomatic Is	$\bar{Is}$
Infectious Asymptomatic Ia	$\bar{Ia}$
Recovered Immune	$\bar{R}$
Deduced Incidence of norovirus	
Observed Incidence Rate	Φ
Foodborne Proportion of Incidence Rate	π
$\pi/(1-\pi)$	ρ

Table 9.2: Values derived from explorations using the extended person-to-person model and alternative parameter values for the forcing term for the foodborne effect and the person-to-person infectivity.

The following section applies this approach to changes in θ (the forcing term for the foodborne effect). Changes in β (the person-to-person infectivity effect) are considered in Section 9.3.

9.2 Scoping the Sensitivity of the Foodborne Effect

This section explores the sensitivity of prevalence to changes in θ, the parameter controlling the forcing term for the foodborne effect. This is done in two ways. First the system dynamics model based on the extended person-to-person model is simulated and the steady state values examined for a sample of model variables.[28] Second, closed form solutions of the model's underlying equations are used to generate results for the steady states.

A sample of simulation results is shown in Fig. 9.2 (overleaf).

28. Note that for these runs some initial carriers are introduced. This is necessary to cope with the experiment in which n1 = 0, since this completely removes foodborne infection and, in the absence of any carriers, thereby introduces a steady state in which there is no Norovirus.

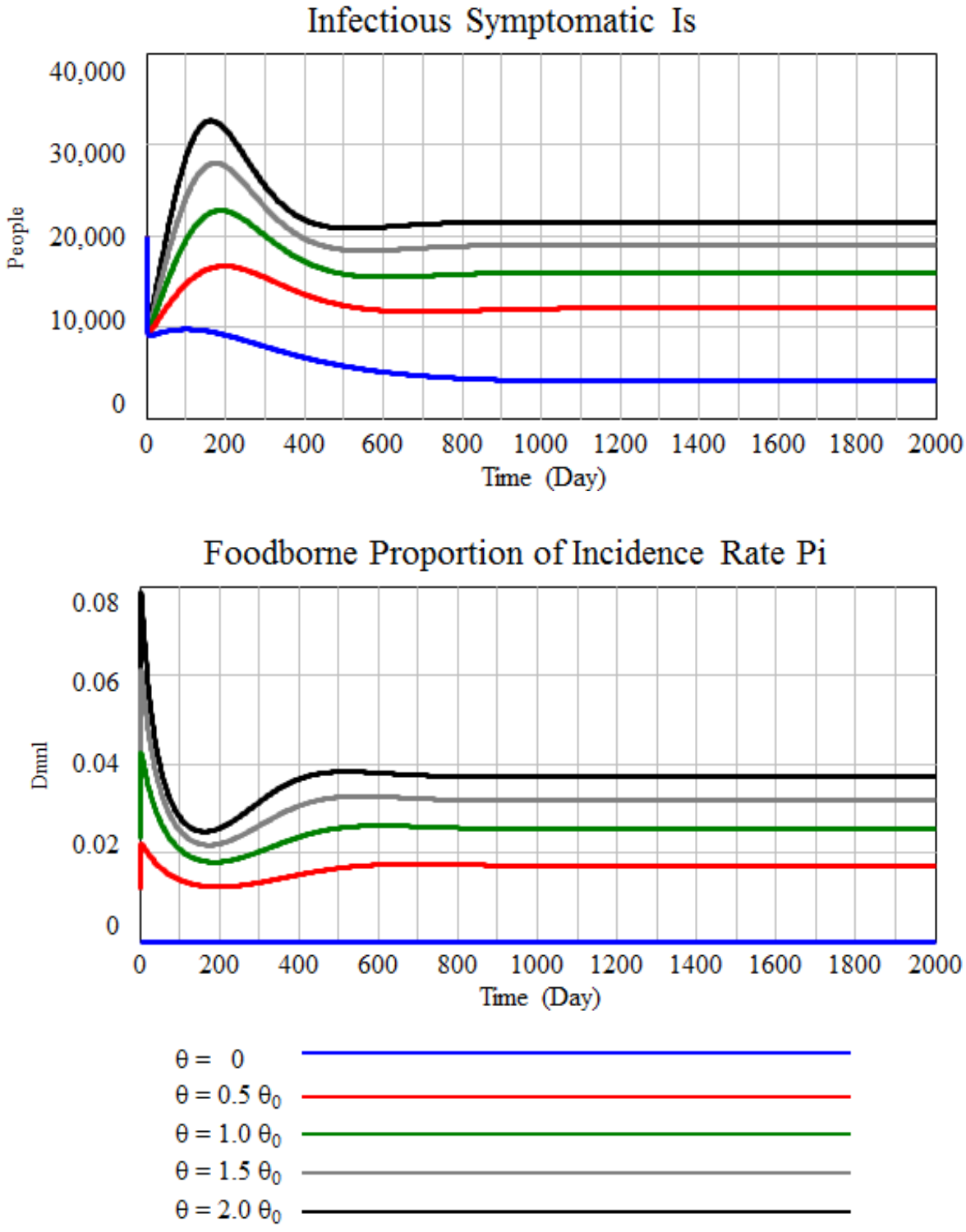


Figure 9.2: Sample results from scoping experiments directed towards θ, the forcing term for the foodborne effect. To illustrate the data obtainable by simulation, an example of a state variable is shown, Is, and the value of the proportion of incidence rate that results from foodborne effects, π. The base case value, θ_0 is indicated by the green line. N.B. The initialisation transient in the left-hand 1/3 of these runs is of less importance than the final values on the right.

The response is simple to intuit: as the foodborne effect becomes strong so the number of infectious individuals increases (Top panel). Similarly, as the foodborne effect increases so the proportion of all infections that are due to foodborne mechanisms increases (bottom panel). When the foodborne effect has zero magnitude such cases are a zero proportion of the total; the blue line. Additionally, in these two cases the changes in the values produced are of the same order of magnitude as the changes in the values of θ that produce them.

One of the key indicators of norovirus is the observed number of cases. In the base case this was roughly 2.9 million per year. Model output for this variable - converted back to annual data - is shown in Fig. 9.3. Again, the responses are intuitively correct: as the foodborne effect becomes strong so the observed incidence rate rises. Again, in these scoping experiments the differences in values produced are of the same order of magnitude as the differences in the values of θ that produced them.

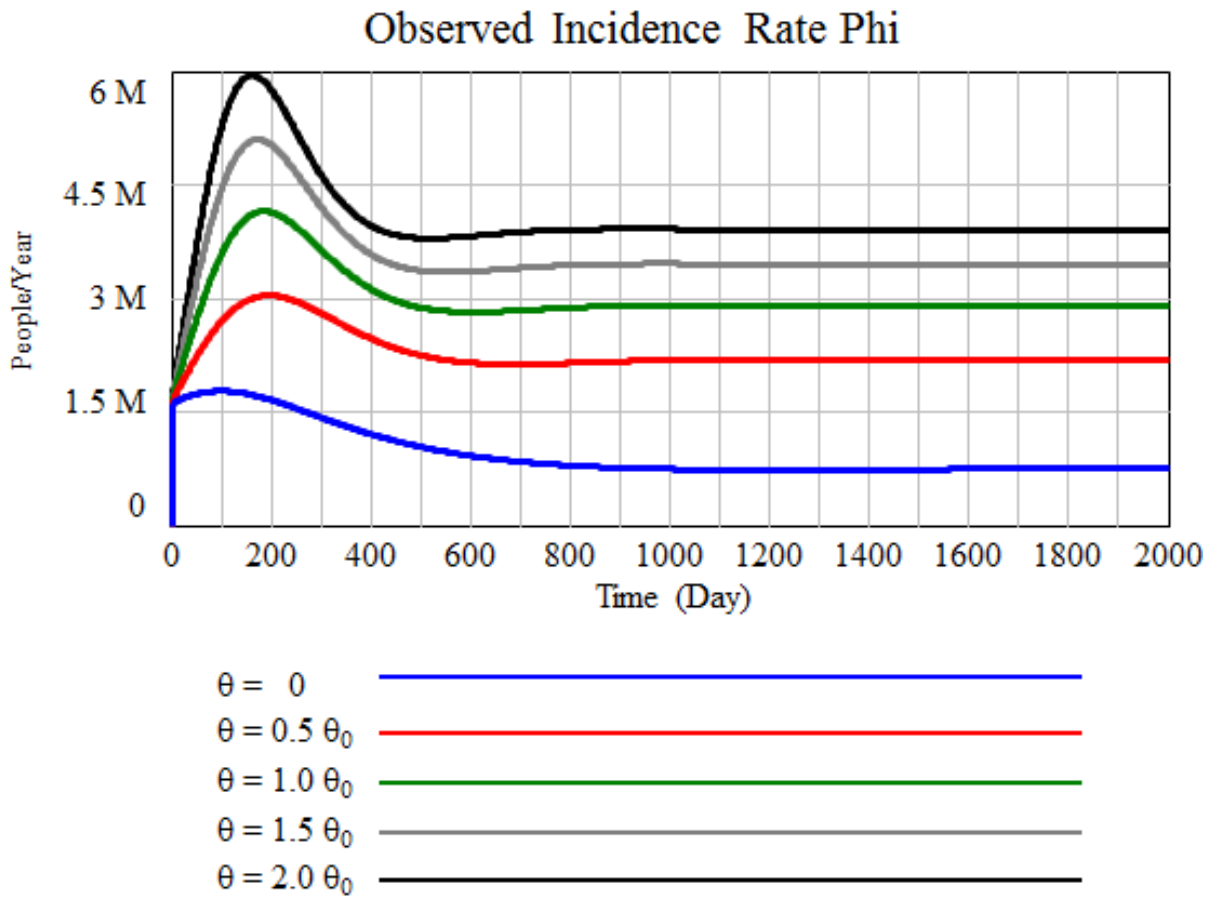


Figure 9.3: Simulation results from scoping experiments directed towards θ, the forcing term for the foodborne effect. Displayed are values of the 'Observed Incidence Rate', Φ. The base case value, θ_0 is indicated by the green line. Note that the initialisation transient in the left-hand 1/3 of these runs is of less importance than the final values on the right.

Self-evidently, it is expected that the model reproduces the base case and it is helpful that it can be used to generate outputs for the other scoping experiments. However, it is possible to move straight to the steady state values of the system via the analytical solution of the model equations. This allows the nature of the sensitivity of norovirus prevalence to the foodborne forcing term to be displayed as a 'spiderplot' [10].

As a 'scoping' device this is useful. The approach is to plot values of one output measure against the value of the parameter that is being changed. In the case of both the output measure and the parameter, the data is indexed against the base case value of that variable. In other words, it is ratios of current to base values that are plotted. The resulting plot can be made up from many more experiments and reveals the slope and shape of the relationship. Any of the model variables can be used as an output measure and the analytical solution to the model equations can generate values of all variables. The results are shown in Fig. 9.4 below, using the 'Observed Incidence Rate' as the output measure.

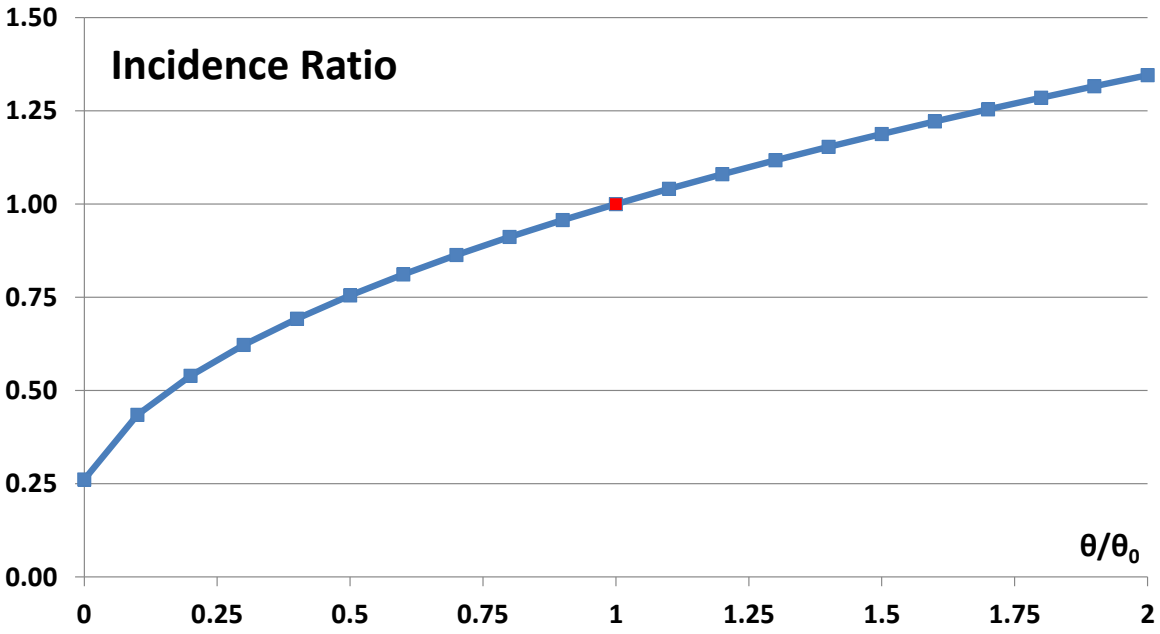


Figure 9.4: Spiderplot of scoping experiments directed towards θ, the forcing term for the foodborne effect. Displayed are values of the 'Observed Incidence Rate' (divided by the base case value of 2,905,278). These are plotted against the value of θ used in each experiment (divided by θ_0, or 4.79E-06). The red data point at (1,1) therefore indicates the base case. Note that the range of the vertical (response) scale – zero to 1½ - is of the same order of magnitude as that of the horizontal (stimulus) scale – zero to two.

This plot is consistent with the results shown in Fig. 9.3. Clearly being able to reduce the foodborne effect could be effective for reducing the prevalence of norovirus. Indeed, the plot suggests that removing all foodborne cases would produce a significant reduction in

norovirus. However, before interpreting these results further it is useful to conduct the same scoping exercise on the person-to-person effect. Both responses are then considered in Chapter 10.

9.3 Scoping the Sensitivity of the Person-to-person Effect

To offer a comparison with the results of Section 9.2, this section explores the sensitivity of prevalence to changes in β, the parameter controlling the person-to-person infectivity effect. Again, this is done in two ways: using the system dynamics model to generate output for a sample of model variables; and by using closed form solutions of the model's underlying equations.[29]

The same sample of simulation results is shown in Fig. 9.5. The most striking feature is the scale of the response, particularly in the 'Infectious Symptomatics Is' panel. The time series are a mixture of very large excursions and, less obviously, very small output values. It is particularly important here not to focus on the transient effects but even the steady state values show the same remarkable scale of responses. The values of π are also more dispersed than those of Fig. 9.2, albeit constrained by the fact that this parameter can only lie between zero and one. These outputs give an immediate indication that the model is much more sensitive to values of β than it is to values of θ.

Having observed the scale of the responses, the general direction is simple to intuit: as the person-to-person infectivity effect becomes strong so the number of infectious individuals increases (top panel). Similarly, as the person-to-person infectivity effect increases, so the proportion of all infections that are due to foodborne mechanisms decreases (bottom panel). Note that when the person-to-person infectivity effect has zero magnitude, foodborne cases make up the entire total; the blue line. But when person-to-person infectivity is merely doubled the proportion of foodborne infection in the total is reduced to a sliver; the black line. In these two cases the changes in the values produced are of a quite different order of magnitude than the changes in the values of β that produce them.

29. Note that for these runs also it is useful to introduce non-zero initial values for a number of the state variables. However, here it is necessary because of the scale of the response in some of these experiments: with only the θ term, unrealistic and distractingly large values of the stocks are otherwise explored during the warm-up period before the system stabilises.

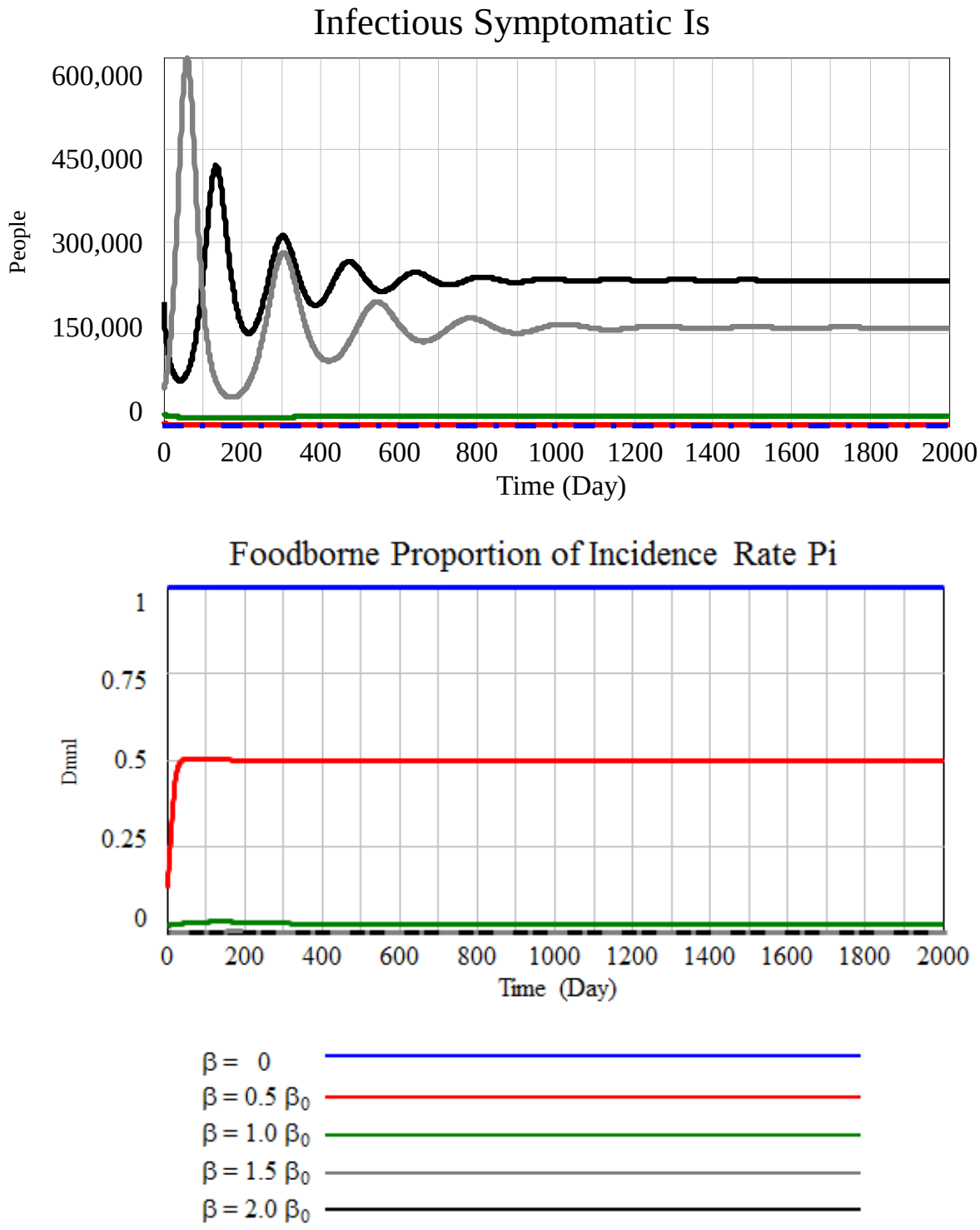


Figure 9.5: Sample results from scoping experiments directed towards β, the parameter controlling the person-to-person infectivity effect. To illustrate the data obtainable by simulation, an example of a state variable is shown, Is, and the value of the proportion of incidence rate that results from foodborne effects, π . The base case value, β_0 is indicated by the green line. N.B. The initialisation transient in the left-hand 1/3 of these runs is of less importance than the final values on the right.

Model output for the observed number of cases (base case value ~2.9 million per year) is shown in Fig. 9.6 – again, converted back to annual data. Once more, the responses are intuitively correct: as the person-to-person infectivity effect becomes stronger so the observed incidence rate rises. However, in these scoping experiments the differences in values produced are of a different order of magnitude than the differences in the values of β that produced them. This gives a further indication that the model is much more sensitive to values of β than it is to values of θ.

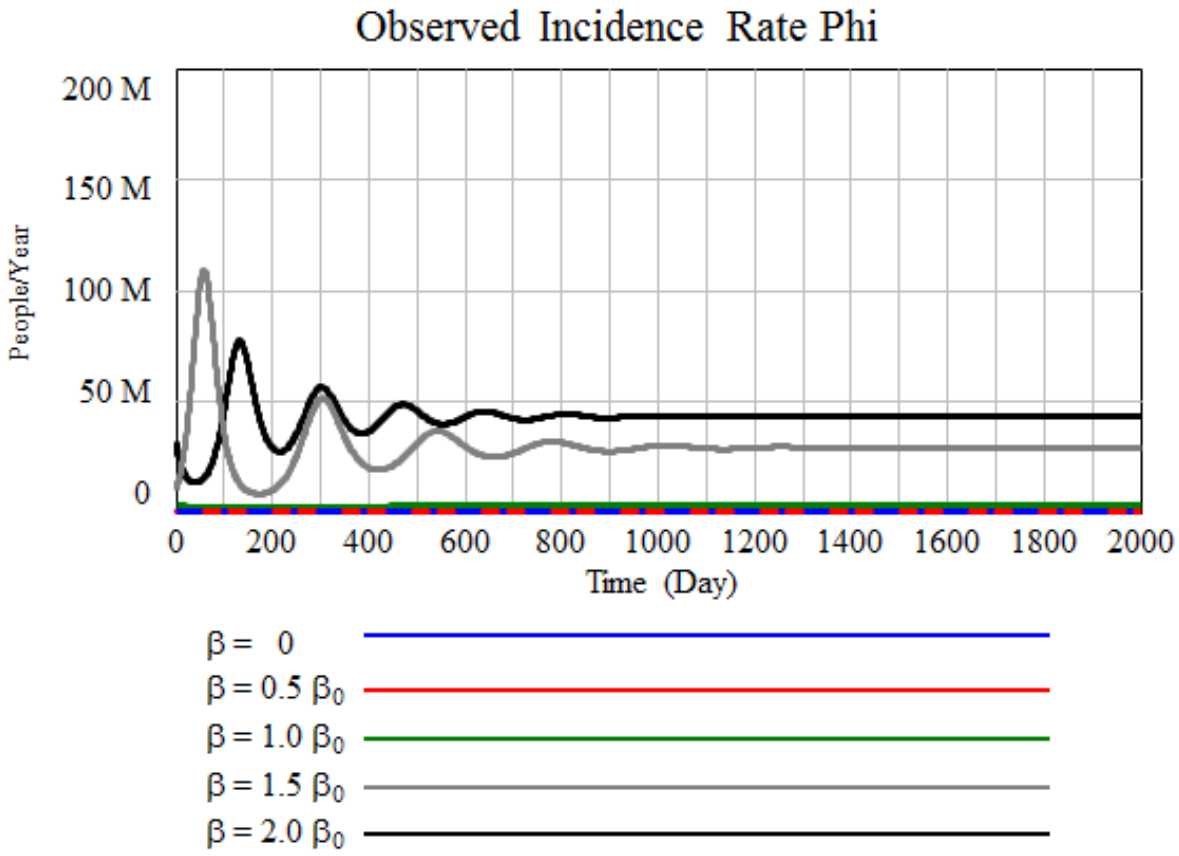


Figure 9.6: Simulation results from scoping experiments directed towards β, the parameter controlling the person-to-person infectivity effect. Displayed are values of the 'Observed Incidence Rate', Φ. The base case value, β_0 is indicated by the green line, roughly 2.9 million. Note that the initialisation transient in the left-hand 1/3 of these runs is of less importance than the final values on the right.

The results of using the spiderplot approach to present the results of scoping experiments with the person-to-person infectivity parameter are shown in Fig. 9.7. This plot is completely consistent with the results shown in Fig. 9.6. Clearly the person-to-person infectivity effect is very important in explaining prevalence.

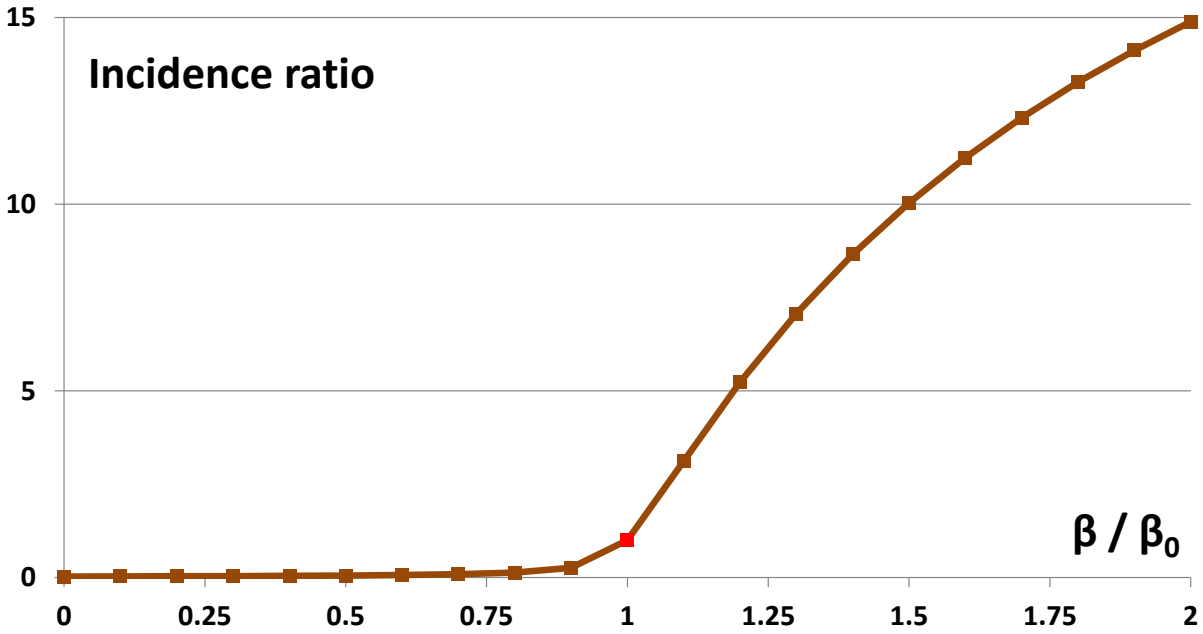


Figure 9.7: Spiderplot of scoping experiments directed towards β, the parameter controlling the person-to-person infectivity effect. Displayed are values of the 'Observed Incidence Rate' (divided by the base case value of 2,905,278). These are plotted against the value of β used in each experiment (divided by β_0, or 0.630677102). The red data point at (1,1) therefore indicates the base case. Note that the range of the vertical (response) scale – zero to 16 - is now an order of magnitude greater than that of the horizontal (stimulus) scale – zero to two.

9.4 Model Steady State Equations ('What If World')

The specific results discussed in Sections 9.2 & 9.3 were calculated analytically by solving the system of equations to find their steady state. The solutions are rather more complex but the mathematical tractability of the extended person-to-person model is useful because of the generality and adaptability that they afford. This section therefore lists the algebraic results which assume given values for parameters for person-to-person infectivity and the foodborne effect and then produce relationships for the footprint and for the observed incidence rate.

Define:

$$T_1 = \frac{\alpha\beta}{N(\gamma+\mu)}(1 + \kappa(\varpi - 1))$$

$$T_2 = 1 + \frac{\alpha}{(\gamma+\mu)} + \frac{\alpha\gamma}{(\gamma+\mu)(\delta+\mu)}$$

$$A = T_1 T_2$$

$$B = \alpha + \mu + \theta T_2 - N(1-\chi)T_1$$

$$C = -N(1-\chi)\theta$$

Then:

$$\bar{E} = \frac{-B + \sqrt{B^2 - 4AC}}{2A}$$

$$\bar{S} = \frac{(\alpha+\mu)\bar{E}}{\left(\frac{\alpha\beta}{N(\gamma+\mu)}\right)(1 + \kappa(\varpi-1))\bar{E} + \theta}$$

$$\bar{Is} = \frac{\alpha(1-\kappa)}{(\gamma+\mu)}\bar{E}$$

$$\bar{Ia} = \frac{\alpha\kappa}{(\gamma+\mu)}\bar{E}$$

$$\bar{R} = \frac{\alpha\gamma}{(\gamma+\mu)(\mu+\delta)}\bar{E}$$

$$\Phi = \alpha(1-\kappa)\bar{E}$$

$$\pi = \frac{\theta}{\beta(\bar{Is} + \varpi\bar{Ia})/N + \theta}$$

9.5 Changing 'Weighting for Infectious Asymptomatics' Parameter

As an addition to the original scope of the project, DCL was asked to add to the system dynamics simulation model a parameter representing the current state of uncertainty about the role of asymptomatic infective individuals. The point was discussed further in Section 8.1 and the extended model described in Section 8.2 includes the new parameter, 'Weighting for Infectious Asymptomatics' designated by the symbol ϖ. In addition, the author was asked to consider the effect of this parameter on the sensitivity of the model. In closing this chapter, and before considering further the scoping results represented in, for example, Figs. 9.4 & 9.7, it is worth discussing this point briefly.

Stated simply, changes to the parameter ϖ have no effect on the scoping results discussed in Sections 9.2 & 9.3.

Changing this parameter certainly effects some changes to the outcome of the approach discussed in Chapter 8. For the extended model to be consistent with the data described in Section 8.2, if the infection effect of the asymptomatics is altered then it is clear that the parameter β_0 will change. Generally, it is the case that $\beta_0 = \beta_0(\varpi)$; the functional relationship is shown in Section 8.4, and some specific results are shown in Fig. 9.8.

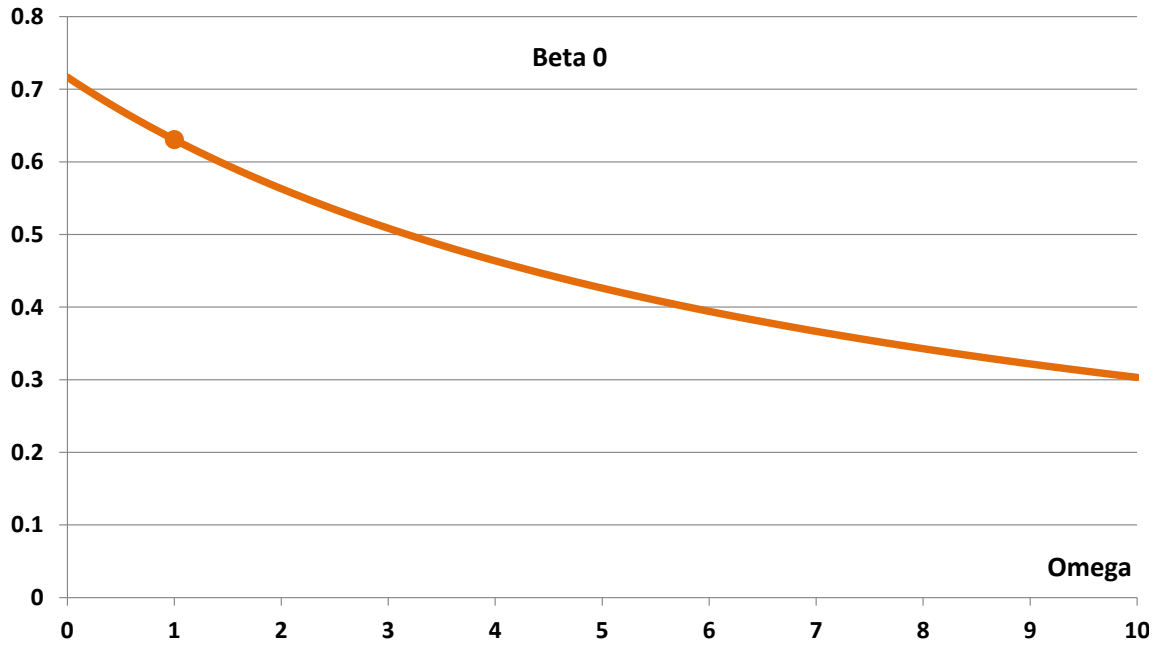


Figure 9.8: The value of the person-to-person infectivity parameter, β_0 changes as the parameter representing the proportionate infectivity of asymptomatic individuals, ϖ changes. This results from the need of the extended model still to reproduce the observed incidence rate. The highlighted point represents the case when $\varpi = 1$.

The relationship matches intuition. If ϖ falls below one then this indicates that the asymptomatic infectious individuals are, via the various mechanisms described in Section 8.2, less infective than the symptomatic ones. Since the same observed infection rate must be generated, if follows that the value of β_0 must rise to compensate for the effective reduction in infectious individuals. In fact, β_0 increases from is base case value of 0.6307 to a maximum of 0.707 if ϖ falls to zero, thereby compensating for the effective 'loss' of 12% of the total infected individuals. Similarly, if ϖ increases (perhaps because asymptomatic individuals retain a higher social mixing rate than those suffering the effect of norovirus, so β_0 falls away. It falls to 0.5631 when ϖ=2 and to 0.3032 in the case (included here to fully to explore this sensitivity) when ϖ=10.

However, whilst it is true that $\beta_0 = \beta_0(\varpi)$, the parameter ϖ still has no influence on the value of θ_0. Changing ϖ does not change θ_0 because this term must still produce a set fraction of a set number of observable cases. The same holds for the footprint; the equations for the steady state values of the stocks of people in the system are independent of ϖ, as is reflected in the equations in Section 8.4. This is the result of calibrating the extended person-to-person model to the 'World As Is'. However, recall that this only serves to give a base value for the approach used in the scoping experiments described in Section 9.1 . If the approach is used to explore 'What If Worlds', to scope out the effect of changing θ or β then, if ϖ is varied, and multiples of θ or β are explored around the calculated values of $\beta_0(\varpi)$, there is still no change in the resulting incidence rate or state variables. Put another way, applying ϖ= 10, 1, 0.1, 0.01 or 0 and creating the equivalents of the spiderplots in Figs. 9.4 & 9.7 produces exactly the same lines. Such a scoping exercise produces precisely the same results, an effect that derives from the functional forms in Section 9.4. The sensitivity of the model to θ or β is independent of ϖ.

Adding a parameter representing a distinct weighting for the infectiousness of infectious asymptomatic individuals makes for a better model, a better representation of the causal mechanisms hypothesised as operating in reality. That representation is open to reflecting improved understanding of the role of ϖ. It is therefore an improved model. However, when it comes to calibrating this extended person-to-person model with respect to the IID2 study and the IID2 Extension study, the role of ϖ is fairly minor. When it comes to scoping the effects of changing θ or β, the value of ϖ is irrelevant.

It follows that changes to the parameter ϖ also have no effect on the discussion in the following chapter.

10 Interpretation of the Scoping Analysis

This chapter applies the work of the previous two chapters and explores the central concern of the research: the wish to understand the contribution of the foodborne mechanisms of transmission. Using the person-to-person model it is possible to comment on the scale and sensitivity of any changes to overall incidence of norovirus that might be produced by altering the foodborne effect. The same comment can be offered for changes to the person-to-person infectivity. These two are discussed in Sections 10.1 and 10.2 respectively; policy implications are considered in Section 10.3.

10.1 Interpreting the Foodborne Sensitivity

The sensitivity of norovirus prevalence to the foodborne effect was shown in Fig. 9.4. This reveals that changing the size of the foodborne forcing term θ across the interval illustrated generally produces changes in norovirus incidence of the same order of magnitude. However, reducing θ towards zero has striking non-linear consequences. This response is illustrated in more detail in Fig. 10.1, which shows the observable effect of such parameter changes: the actual annual incidence of norovirus.

Of particular interest to the FSA is what this graph says about the effects of existing food production and hygiene legislation and guidelines. Because it is not known what value of θ would be implied, it is not possible to create a 'counterfactual', that is a simulation of a world in which there are no requirements whatsoever of food production.[30] However, this figure does give some indication of the value of existing legislation guidelines. It indicates that a 'dirtier' world, one in which the foodborne effect was twice as strong, would produce an increase in cases of more than 1/3; some 3.9 million cases annually, compared with the current figure of 2.9 million[31] This is surprising given that foodborne cases constitute only 2½% of current cases. One possible interpretation is that it indicates that considerable 'value' has resulted from the wide range of activities undertaken over time by FSA and other agencies to bring foodborne infections down to their present value.

The consequences of further reducing the foodborne effect are indicated by the left-hand side of Fig. 10.1. Here the model can be used to scope out the benefits of improving food production and hygiene legislation and guidelines. For example, it indicates that a 'cleaner' world, one in which the foodborne effect is halved, would experience ~25% fewer cases of norovirus, 2.2 million cases rather than 2.9 million. Whilst it would probably take

30. This 'counterfactual' approach is used by the National Audit Office to consider the value for money of hospital cleaning activities by considering the case in which no attempt is made to respond to the appearance of a healthcare associated infection [3].
31. It is straightforward to calculate that if the foodborne was three times as strong as currently believed then a ~60% increase in Norovirus prevalence would result, implying almost 4.7 million cases annually.

considerable effort to produce this response, it is noteworthy that some 700,000 people annually would be spared a bout of norovirus in the UK.

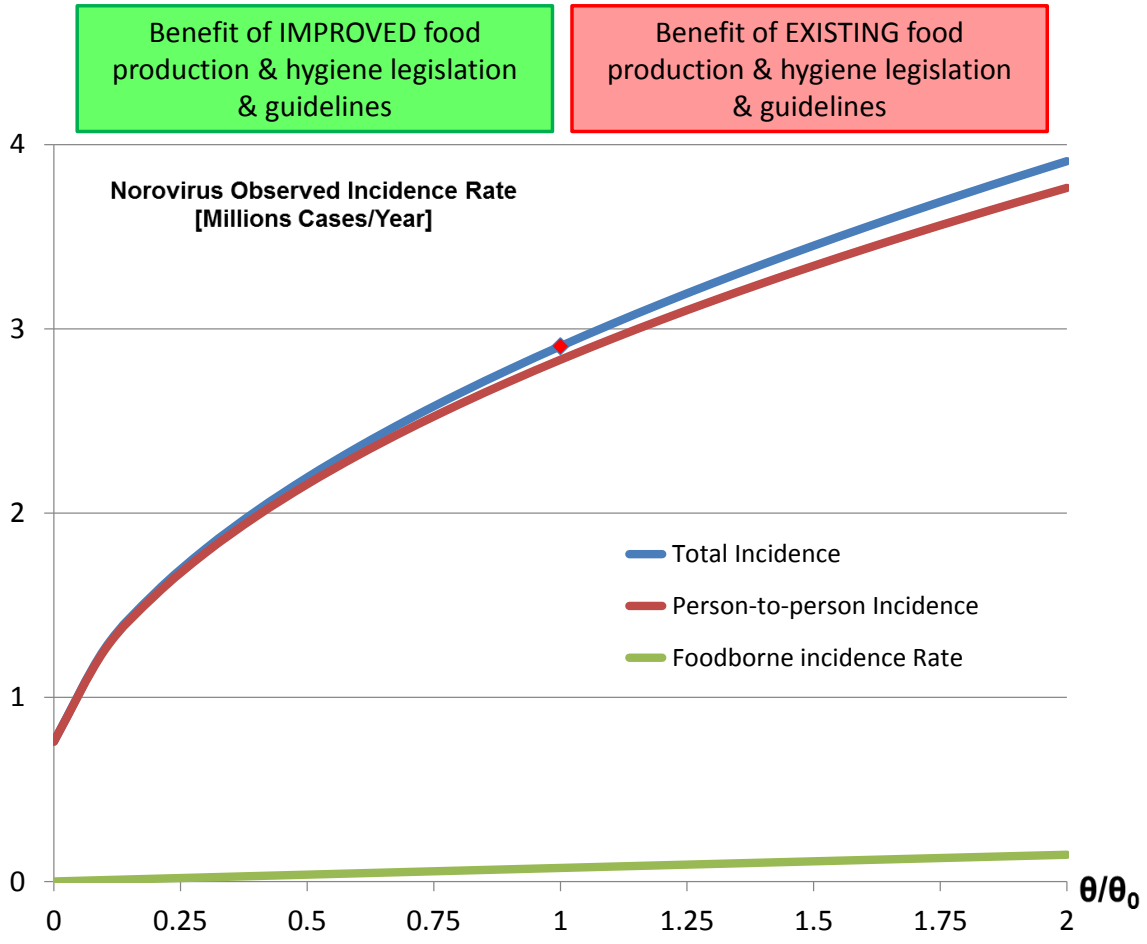


Figure 10.1: Plot of the annual incidence rate of as a function of the size of the foodborne effect. Displayed are values of the 'Observed Incidence Rate', broken down into cases produced by person-to-person effects and those resulting from foodborne effects. These are plotted against the value of θ used in each experiment (divided by θ_0, or 4.79E-06). The red data point at (1, 2,905,278) therefore indicates the base case for 'Total incidence'.

This modelling can be used to explore an even more striking scenario. The plot suggests that removing all foodborne cases would produce a 75% reduction in norovirus, that cases would fall from 2.9 million to 750,000 annually. This is somewhat surprising given that only 2.527% are currently considered to be foodborne.

The effect can be illustrated using the system dynamics simulation model. In Fig. 10.2 the model is started in the steady state implied by the base case parameters. After 400

simulated days the value of θ is dropped from the base case value of 4.78662E-06 shown in Table 8.2 to zero. After roughly a simulated year the observed incidence rate does indeed fall to ~25% its previous value, undershooting this steady state and then settling down.

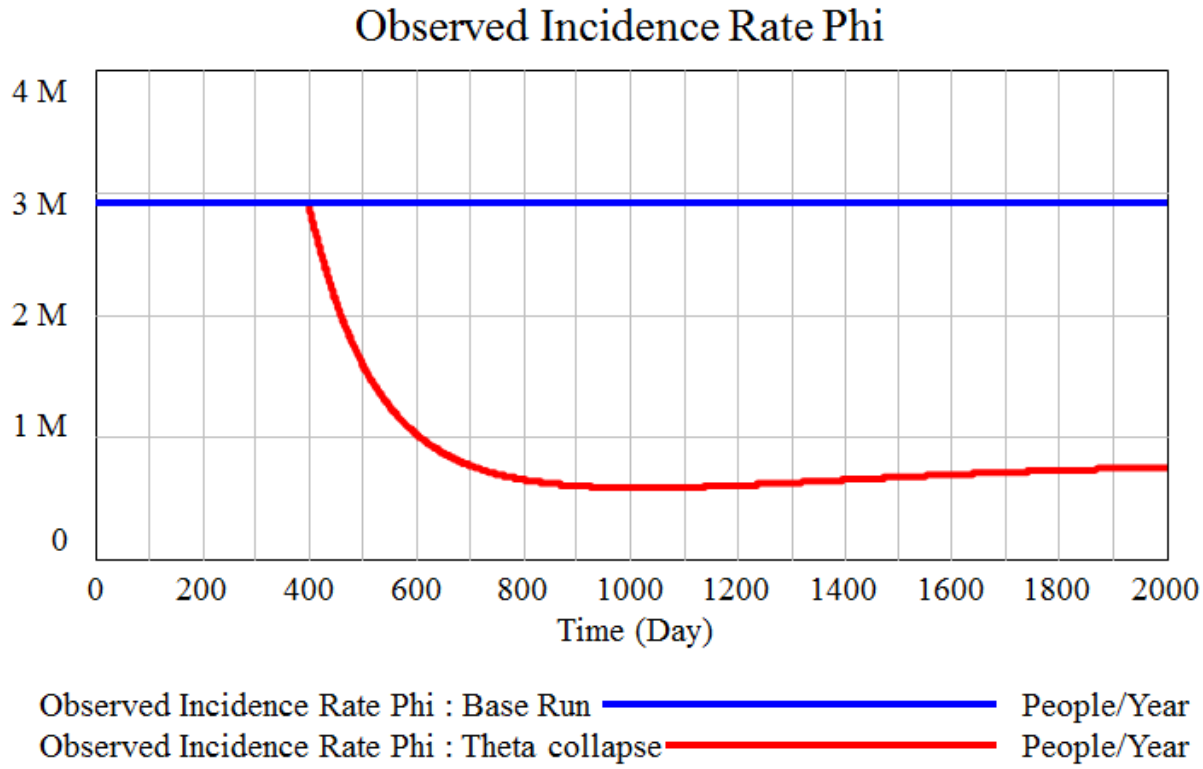


Figure 10.2: Simulation showing the effect of removing all foodborne infections. The model starts at the stable steady state indicated by Tables 8.1 and 8.2. At t= 400 the value of θ is dropped to zero and incidence falls to ~25% its previous value.

What this counter-intuitive effect reveals is that foodborne infections do indeed have a very powerful 'forcing effect' on the system. They cause incidence to be lifted to much higher levels. The response can be thought of in this way. In the absence of any foodborne cases there are only ~750,000 cases per year. The introduction of only 73,000 foodborne cases[32] – 10% of the number of person-to-person cases in this prelapsarian world – has the effect of boosting the presence of amongst the population so that total incidence quadruples to 2.9 million.

The aim of totally eradicating foodborne transmission of norovirus may not be a plausible

32. This is 2.527% of the total cases of 2.9 million in the base case.

one but a result of this scoping work is the understanding that there are gains to be made on the foodborne front that are – happily - out of proportion to the current low level of foodborne cases. Even though they only constitute some 2.5% of cases, this area – one clearly in the purview of the FSA – is a potentially fruitful one to explore.
However, before interpreting these results further it is useful to conduct the same scoping exercise on the person-to-person effect.

10.2 Interpreting the Person-to-Person Sensitivity

The sensitivity of prevalence to the parameter β, which controls the person-to-person effect, was shown in Fig. 9.7. As was observed in Chapter 9, this spiderplot reveals a highly non-linear relationship between the value of β and the incidence of norovirus. The response is illustrated again in Fig. 10.3, now in terms of the actual annual incidence of norovirus.

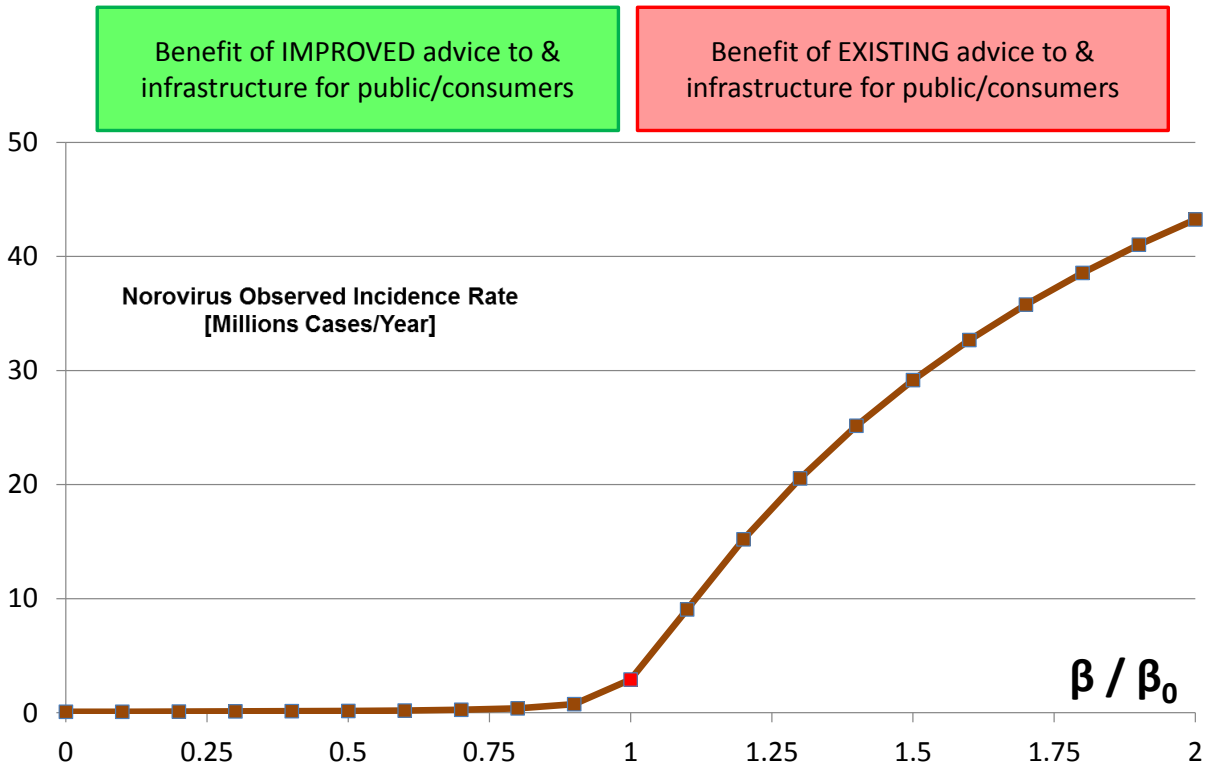


Figure 10.3: Plot of the total annual incidence rate of as a function of the size of the person-to-person infectivity effect. Displayed are values of the 'Observed Incidence Rate' plotted against the value of β used in each experiment (divided by β_0, or 0.630677102). The red data point at (1, 2,905,278) therefore indicates the base case. Note that on the scale used here the foodborne incidence rate of 70,000, or 0.07 million, would appear as a line along the x-axis, so small is that value in comparison.

The parameter β represents aspect of human behaviour that do not normally fall within the interests of FSA: hand washing behaviour of the general population, cleanliness of lavatories beyond food production facilities etc. However, it is worth scoping this parameter because it does reveal information about norovirus prevalence and the potential to reduce this prevalence – particularly in light of the sensitivity of incidence to foodborne effect effects discussion in Section 10.1.

As was done in the previous section, Fig. 10.3 can be considered in two parts, the data falling to the right and to the left of the x=1 point.

To the right can be seen the effects of worsening the behaviours underlying person-to-person transmission. The effects are powerfully non-linear. Consider the case in which behaviour worsens to the extent that person-to-person infectivity doubles. Then prevalence increases by 1400%, that is, it increases almost 15-fold, from 2.9 million to 43 million. An increase of only 10% in infectivity more than triples the annual incidence to 9 million. Indeed, so non-linear is this effect that a 1% increase in annual incidence is produced by an increase of only 0.06% in the value of β. These figures put the sensitivity of foodborne infectivity into context. They also serve to indicate the scale of the benefits that have been achieved in getting the public to behave in the way that they do now. It remains true that not everyone displays good cleanliness habits, in toilets, around sick individuals, on public transport etc. It is also true that the physical infrastructure that makes it easy – sometimes even possible – to attend to hygiene is not always ideal.[33] However, the steps that have been taken, in terms of advice given to the public and the quality of infrastructure currently in place, have, on the basis of the model's sensitivity, produced considerable benefit.

The potential benefits of improving person-to-person infectivity effects are shown on the left of Fig. 10.3. Reducing this effect by relatively small amounts could be very effective for reducing the prevalence of norovirus. Indeed, the plot suggests that a reduction of only 25% would cause incidence to collapse to ~300,000 per year, about 10% its current value, regardless of the presence of foodborne infections.[34]

Clearly the person-to-person infectivity effect is very important in explaining norovirus prevalence. It is perhaps this half of the graph that raises the sharpest questions about the benefit of activities aimed at reducing foodborne effects. However, the graph affords

33. A talk on the research reported here was given at the FSA Foodborne Viruses Research Conference in mid-January 2013 where a delegate reported in open session that his visit to the toilets had involved his having to physically turn a tap and still only produce a stream of water of slowly increasing temperature. This, he observed, was despite the existence of movement-sensitive taps which produce water at a set temperature. The conference was held in a hotel in central London – though the same story could have arisen almost anywhere in the industrialised world.
34. For completeness, the model indicates that a complete absence of person-to-person infections produces an annual incidence of around 70,000. This consists entirely of foodborne effects, calibrated as 2.527% of the total cases of 2.9 million in the base case.

another insight, concerning seasonality.

As discussed in Section 1.1 and illustrated in Fig. 1.1, norovirus exhibits strong seasonality: incidence rates vary greatly across any given year. The shape of the plot in Fig. 10.3 gives some insight into this. If small (but permanent) changes in β produce such large changes in incidence, then might the real world variability be explainable in terms of a combination of random and also seasonal changes in person-to-person effects? This is a question that can be explored using the system dynamics simulation model.

The question of what external input to use to stimulate the model to reproduce the observed behaviour of norovirus incidence rate is a complex one [37]. For this report we construct the input in two steps, using 'pink noise' for random changes in β and combining this with a multiplicative seasonality model [29].

The first step in simulating the effect in question is to use values of β which vary randomly over time - taking the base value, β_0, and applying a stochastic variability around that value. It is possible to use a purely random series for this, or 'white noise'. However, this would be a poor model of the effect in question. What is being modelled is human behaviour, consisting of habits, responses to weather, time of year, even mood. These are not purely capricious effects in which what is done now is unrelated to what was done in the recent past. Rather, such effects are best seen as having a limited, enduring quality; if one value of β falls below the mean β_0 then it is more likely to be followed by another value below the mean. To produce such an auto-correlated effect it is best to use 'pink noise', with a correlation time constant that expresses the degree of history, or inertia, in the system.

The model was therefore run with values of β produced using 'pink noise' of a set standard deviation and a set correlation time.[35] The results are shown in Fig. 10.4. The figure shows one specific, though long, random time series displaying peaks and troughs of ~±15%. This response is consistent with the sensitivity relationship shown in Fig. 10.3, overleaf.

35. The process used was to generate uniformly distributed, uncorrelated white noise and then pass this through a first-order exponential smoothing formulation to produce a series which is auto-correlated and asymptotically Normal, with mean zero and a given standard deviation. A correlation time of 10 days was used. Note that the formulation used means that the model must be solved using Euler integration.

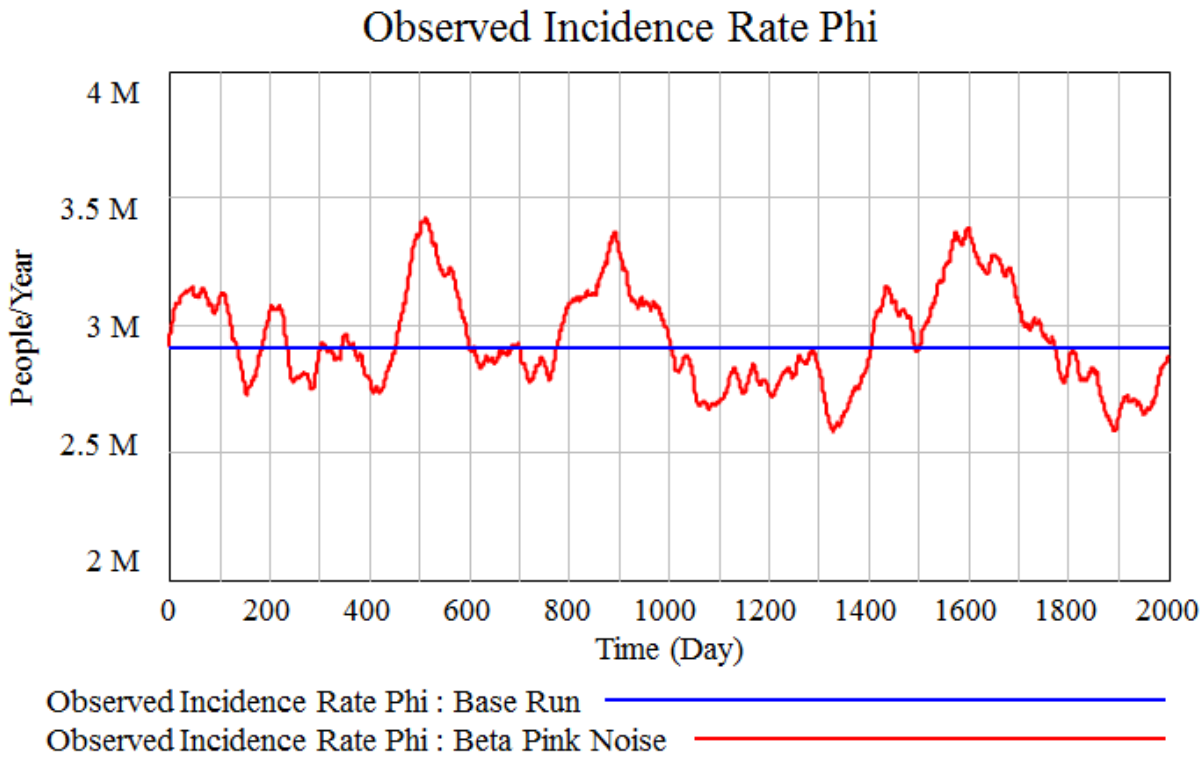


Figure 10.4: Simulated annual incidence rate of norovirus using stochastic values of β. The red line shows the result of realising β using 'pink noise', asymptotically distributed Normally around a mean β_0, with standard deviation of 1% of that mean value. The blue line has $\beta = \beta_0$ throughout the run.

The effect of increasing the standard deviation of the 'Pink Noise' to 2% of the mean value is shown in Fig. 10.5 (overleaf). The effect seems also to have roughly doubled in size, displaying peaks and troughs of ~±30%.[36]

36. Note that the same 'seed' has been used in the runs in Fig. 10.5, which is why the plots are so similar. The series used is still random, it is simply that the same one has been used in both cases, to aid comparison.

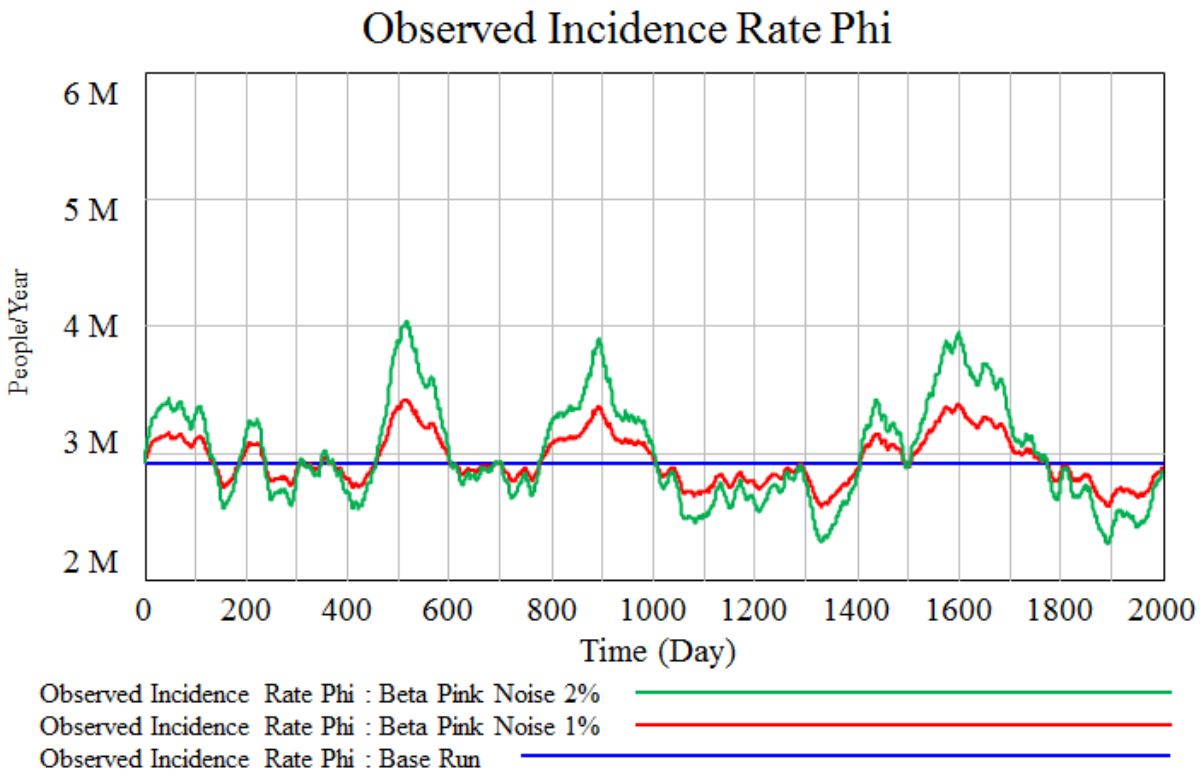


Figure 10.5: Simulated annual incidence rate of using stochastic values of β. The red and green lines shows the result of realising β using 'pink noise', asymptotically distributed Normally around a mean β_0, with standard deviation of 1% (red) and 2% (green) of that mean value. The blue line has $\beta = \beta_0$ throughout the run.

The results shown above are robust to changes in the correlation time[37] and so begin to offer an explanation for the observed variation in norovirus incidence.

To explore this particular phenomenon further it is necessary to include seasonality explicitly in the model. Using the observed data shown in Fig. 1.1 it is possible to specify a seasonal effect for the person-to-person infectivity. A quartic polynomial is fitted to the observed incidence data. This aims to capture the annually repeating pattern and can then be used as a multiplier to the mean value. The result is shown in Fig. 10.6. Note that this rises to a peak of $2^1/_3$ times the mean and falls to a low of only $^1/_5$ this value.

37. Experiments with correlation time of 3 and 30 – so 1/3 and three times the value of 10 used in Figs. 10.4 and 10.5 – produced broadly similar output.

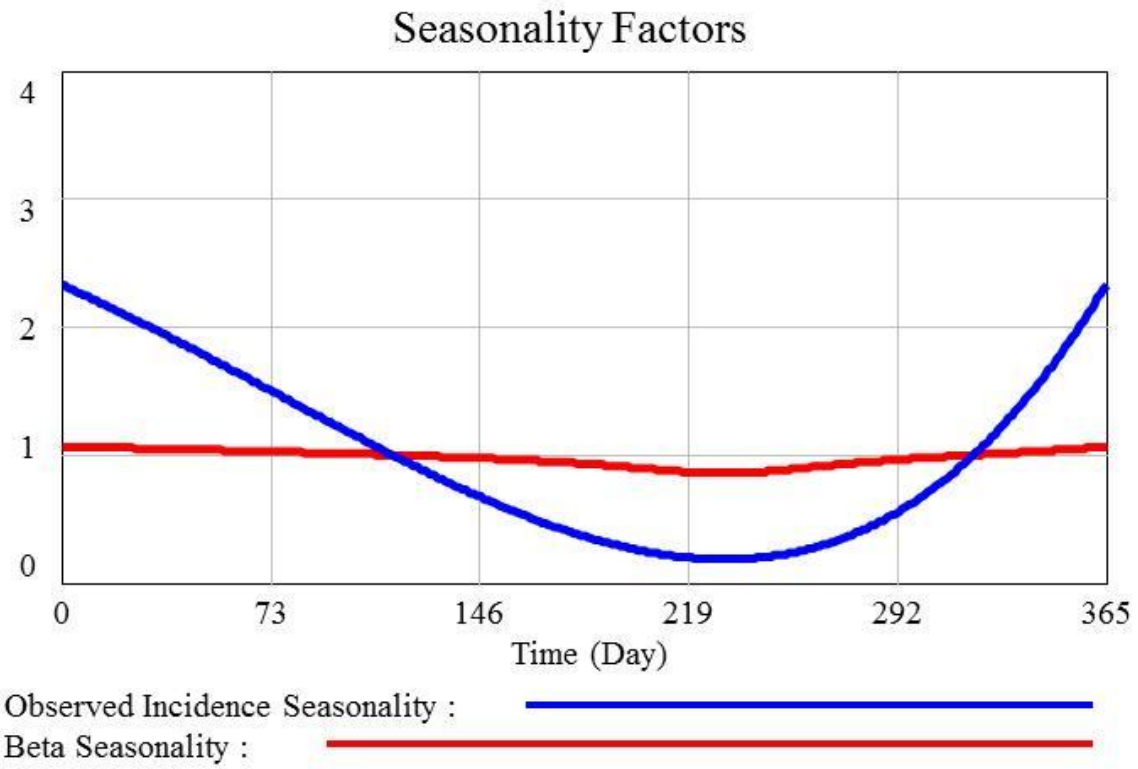


Figure 10.6: Seasonality factors for the norovirus model. The blue line shows the proportionate changes in the underlying trend of observed norovirus incidence. The red line shows the changes in person-to-person infectivity, β consistent with this pattern of incidence. Note the difference in the variation of the two lines.

It is then possible to calculate the values of β that are instantaneously consistent with the observed incidence rate. This is done using a variation of the analysis used in Chapter 8. In essence, for a given foodborne infectivity effect θ_0 and a given observed incidence rate, Φ, it is possible to calculate the value of β which, in steady state terms, is consistent.[38] Hence, putting aside the other parameters that must be employed, the approach involves setting $\beta=\beta(\theta_0,\Phi)$, where Φ is driven by the seasonal factor shown in Fig. 10.6.

It is important to note that any actual simulation output will not be identical to the input seasonal effect. This is because the $\beta=\beta(\theta_0,\Phi)$ linkage only holds in the steady state. Using that linkage is a good method for calculating values of β consistent with the seasonally varying values of Φ. However, when the model's assumptions are calculated over time the dynamic nature of the relationships creates transient effects which result in some divergence from the perfect, steady state output.

38. The key difference is that rather than π (Foodborne Proportion of Incidence Rate) being treated as a given value, the actual value of θ is taken to be fixed at $\theta 0$, the value in Table 8.2.

A striking aspect of the values of β calculated in this way is the reduction in variation. A peak in β of only 6½% above the base case value β_0 should be sufficient to generate (in steady state terms) a peak in observed incidence $2^1/_3$ times the mean incidence value, whilst a trough in β of only 14% below the mean is sufficient to produce an incidence rate only $^1/_5$ the mean incidence value. This effect is, of course, in line with the sensitivity of the relationship between Φ and β illustrated in Fig. 10.3: it is clear from that figure that one would expect small horizontal (=input) variations to produce considerable vertical (=output) variations

Whilst the fitted seasonal effect for Φ captures much of the variation over time there is still variability around this seasonal trend. This can be modelled by combining multiplicatively the seasonal effect with pink noise random variation. After fitting the seasonal effect to the incidence data the residuals still have a standard deviation of 27%. This seems large. However, again, the steepness of the relationship between Φ and β suggests that using noise in β with a lower standard deviation would be appropriate. In principle the relationship between the standard deviation of Φ and that of β relationship changes as one moves along the β/β_0 axis in Fig. 10.3. However, a figure calculated around the β/β_0=1 point is a reasonable first approximation and so a standard deviation in β of only 2% should be sufficient to represent the observed variation.

The results are shown overleaf in Fig. 10.7, alongside the empirical data for roughly 2½ years. Note that the empirical data has been converted from laboratory reports into the best estimate of actual cases, using the factor given in [57].

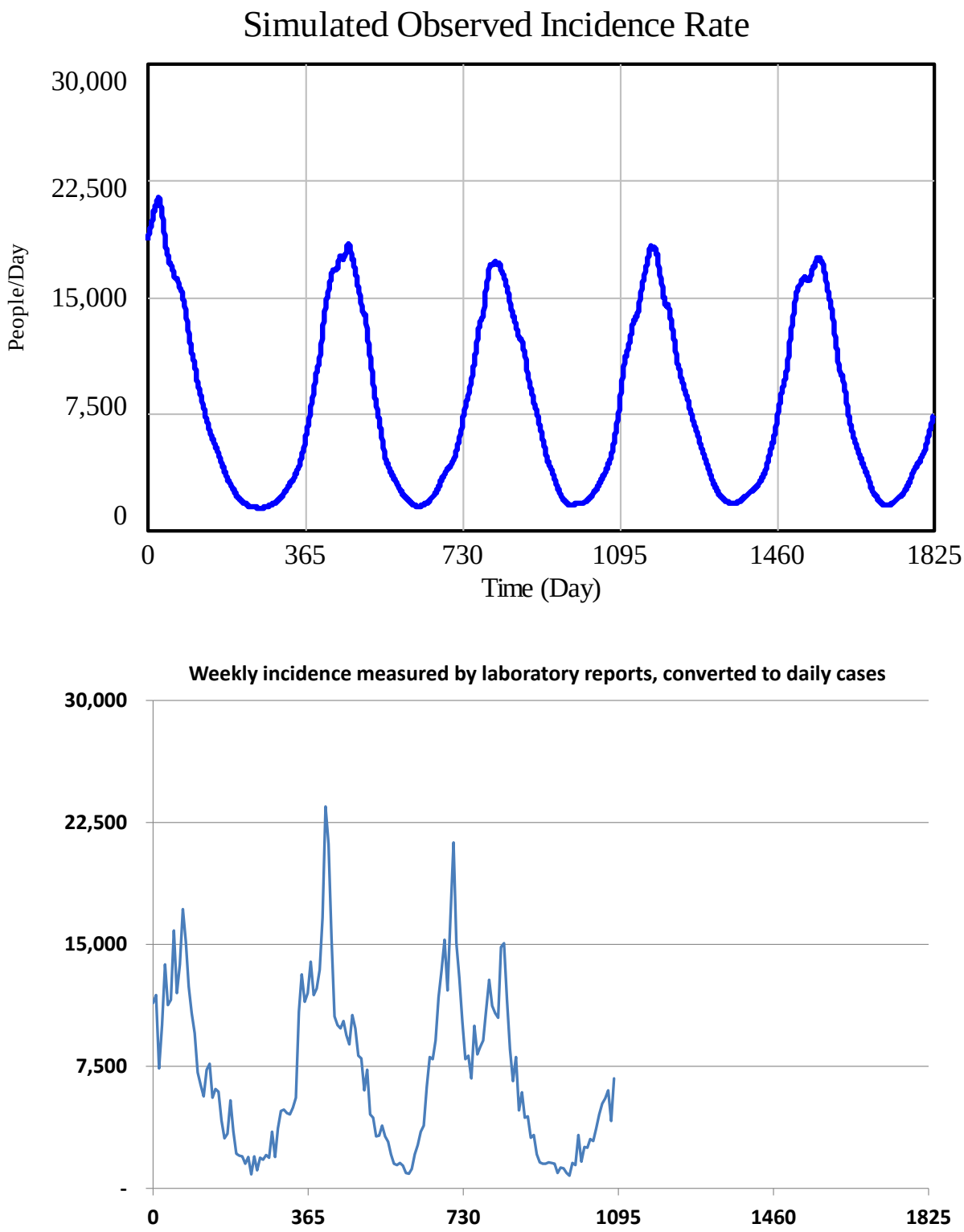


Figure 10.7: Reproducing observed norovirus incidence data. The top panel shows output from the system dynamics simulation model. The lower panel reproduces the empirical data of Fig. 1.1 but presented now as one time series and scaled up from laboratory reports to actual daily cases.

It is important to recall the comment made above about the difference between steady state solutions and dynamic output. For example, examination of the simulation output shows that the underlying trend does not, other than at the start, reach the peak of $2^1/_3$ its mean value. The simulation output in the top panel of Fig. 10.7 should therefore be seen as a low estimate of seasonality effects. However, the precise nature of the fit is not the issue, rather it is a comparison of the modes, the general shapes of the two curves, that are relevant. On this basis the comparison holds: as indicated by Figs. 10.3 and 10.6, surprisingly small seasonal variations in β can produce large changes in the observed incidence rate.

Further care must be taken in interpreting this model output. Extracting a seasonality and variability pattern from real world data, simulating the model with it and showing that the model reproduces that data is not surprising. Indeed, it borders on tautology. However, it has two useful features.

First, in system dynamics terms this is an example of one of the tests that should be conducted on model behaviour to test its consistency with reality [19, 51]. Such tests are performed on a model to build confidence in its credibility. The model passes this test very well indeed.

Second, and more importantly, it does suggest a more complete explanation for the observed variation in norovirus incidence. Changes in β indicate changes in human behaviour. For example, regarding the winter increases, people who go out less because of unwelcomingly cold weather are, it follows, staying indoors more and are therefore likely to be mixing more with other people. One possible explanation is therefore that the system is so sensitive to the value of β that quite small seasonal changes in human behaviour, combined with even smaller random variations, are quite capable of producing the characteristic variation in observed cases of the virus. Of course there must also be seasonal effects in the foodborne mechanisms – though the model's sensitivity to values of θ is much less than to values of β. So although this analysis is not exhaustive it does provide a compelling hypothesis regarding the source of the large seasonal variations in observed norovirus incidence. What is needed, therefore, and what this modelling work suggests, is empirical research that tests whether the human behavioural effects contained within β could indeed vary in this way, producing a 6½% increase and a trough of only 86%, as shown by the red line in Fig. 10.6. Such a line of research – motivated by this modelling – would then provide a standalone explanation for the high seasonal variation.

10.3 Implications for Policy

The usefulness of the 'scoping' analysis in Chapters 8 - 10 is that, in the absence of a parameterisation of the detailed model of the foodborne mechanisms, it does allow an assessment of the effects of changing the foodborne incidence rate - thus linking back to the project's goals. The analysis indicates that reducing foodborne infections by 10% should reduce total norovirus incidence by 4%, whilst a 20% reduction in foodborne infections

causes total incidence to drop by 9%. A 9% reduction in nearly 3 million cases is a significant reduction in morbidity and lost work – a gain worth having - whilst reducing the foodborne effect by 1/5 is a goal that could be contemplated.

However, the difficulty with this view is twofold. First, no account is taken of costs and benefits. Chapter 7 gives an indication of the number of parameters that could, in principle, be targeted by FSA in an attempt to reduce foodborne incidence. But there is no firm data to call on to measure the plausibility of targeting any of these, or on measures of the cost and/or difficulty of reducing these foodborne effects. Similarly, some measures – economic in the case of lost work and perhaps judgemental for the misery of being ill – are needed for the benefit of reducing foodborne incidence. Any attempt to move from modelling, into the policy formulation realm and hence into the world of implementation and action necessitates the use of calculations such as these.

The second difficulty is the need to compare actions taken to target foodborne incidence with those which seek to influence normal person-to-person effects. The examples given above can be reworked: reducing person-to-person infectivity by 10% should reduce total incidence by 75%, whilst a 20% reduction in person-to-person infectivity causes total incidence to drop by almost 90%. It is perhaps worth returning to Figs. 10.1 and 10.3 and plotting the incidence rates on the same scale. The result is shown in Fig. 10.6 and this illustrates just how different the sensitivities are. Again, costs and benefits of targeting person-to-person effects would need to be considered – along with the fact that policies aimed at producing changes in person-to-person infectivity probably fall outside the scope of the FSA's work. Nevertheless, if the mathematical modelling presented here does offer a useful framework for thinking about UK incidence then it indicates that it is not foodborne incidence that should be targeted simply because it fits with the FSA's aspirations. Rather, norovirus needs to be considered in a manner which stands above such organisational silos and considers the virus in the large, with the benefits of targeting person-to-person effects being judged on the same basis as the benefits for reducing foodborne effects would be. That insight is perhaps a leading product of this research.

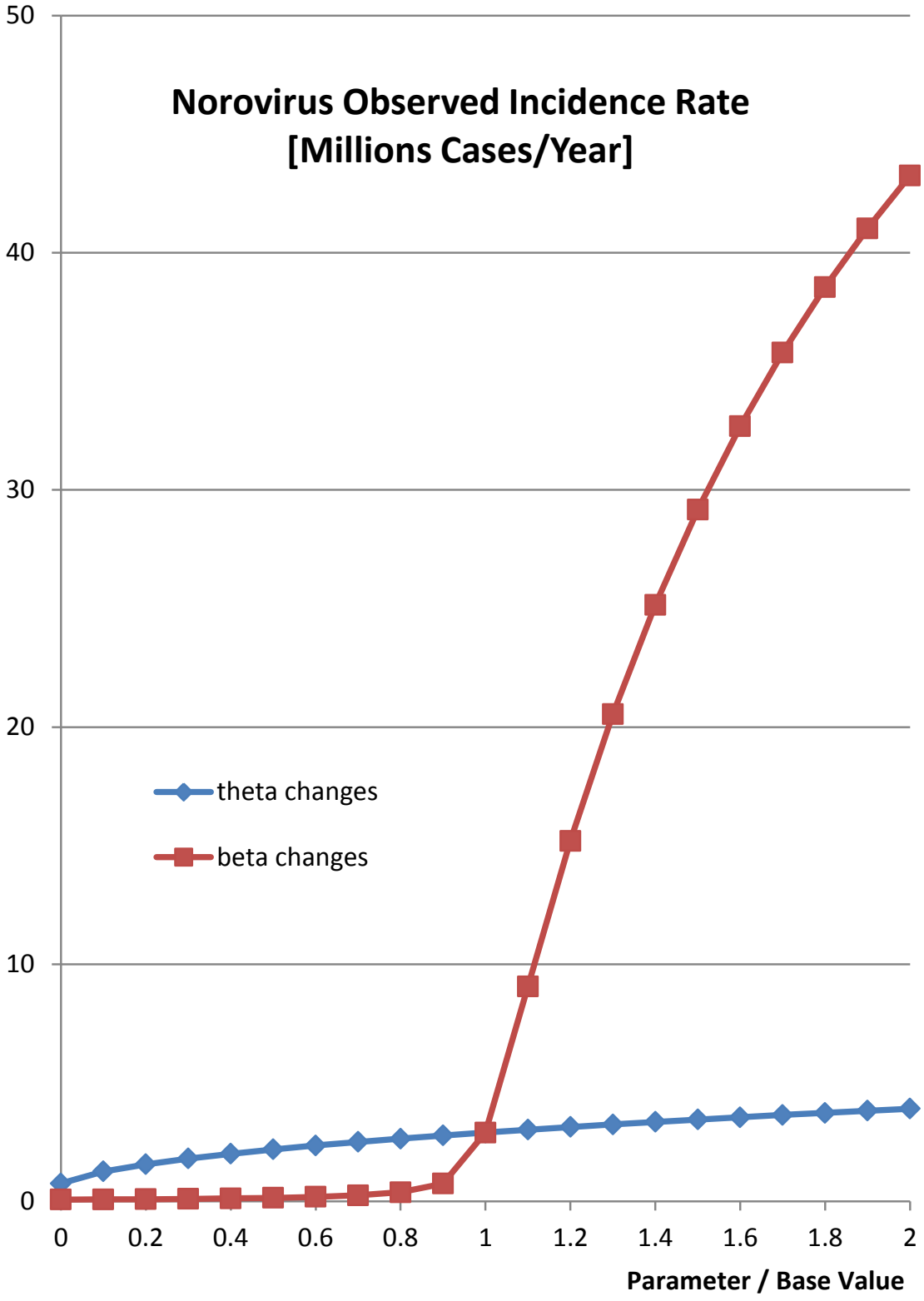


Figure 10.6: Plot of the total annual incidence rate of norovirus as a function of the size of both the foodborne infectivity effect and person-to-person infectivity effect. This figure combines the results of Figs. 10.1 and 10.3 to compare the sensitivity of the model to both θ and β.

11 Conclusions

The conclusions of the work are discussed here. Section 11.1 contains those conclusions derived from the work in Part 1, whilst Section 11.2 outlines an important caveat on that style of modelling work. Section 11.3 acknowledges that caveat and discusses the conclusions of Part 2 of the work.

11.1 Endogenised Model of the Foodborne Mechanisms

The most important conclusion of the system dynamics modelling work is that disaggregation of the foodborne routes into plausible causal mechanisms and the modelling of those mechanisms are indeed possible. The contents of Chapters 3-6 constitute a detailed, explicit and visual set of hypotheses about how the mechanisms work, a representation of current thinking about how those mechanisms are thought to be operating. At the November 2012 workshop members of the expert team were of the view that the modelling was useful for them in improving understanding of the mechanisms. Moreover, the representation can contribute to more general understanding of current thinking on how these transmission routes work.

The conceptualisation and formulation of the system dynamics model is complete. Each and all of the foodborne transmission processes is endogenised, looping from the person-to-person sector eventually back into that sector.

Extension of this model is eminently possible. By making the assumptions of the model explicit it becomes, in the best scientific sense, easier to criticise and to offer alternative assumptions about the mechanisms thought to be operating. Including other, or alternative, mechanisms in the system dynamics model should itself be a straightforward matter.

Notwithstanding the above, the model cannot be simulated. Disaggregating a single parameter – the forcing term θ, representing foodborne effects – into the multiplicity of its constituent elements was always going to produce a 'data hungry' model. In line with good system dynamics practice [51], care has been taken to ensure that all model variables are conceptually meaningful, that is, can be related to real world entities that can, at least in principle, be measured. The model also consists of equations in which parameters are used in a manner which accords with current understanding. However, putting aside the conceptualisation and formulation phases of modelling, parameterisation of the model is only partial. As had been anticipated by the FSA, the detail of the model inevitably meant the inclusions of parameters whose values were unknown and could not reasonably be estimated.

However, the model is still able to contribute to understanding of foodborne transmission processes. By offering an explicit account of the mechanisms it reveals with some precision what is and what is not known. In this way it generates a list of parameters which cannot currently be established and so creates an agenda for future research. Participants at the

November 2012 workshop were also of this view.

Lastly, the model provides structure to the question arising from the FSA's 'Foodborne Disease Strategy'; where could FSA target its efforts with respect to foodborne transmission. As presented in Chapter 7, the model generates a second list of parameters, those which can in principle be altered. These are therefore the candidates for intervention. Most would be difficult to change, some very difficult. However, the modelling work has identified them as specific, measurable entities that can be considered for intervention.

11.2 The 'Imported Strawberries Problem'

Lack of necessary parameters is the obvious reason why the modelling work in Part 1 could not be completed. However, there is more profound difficulty that must be acknowledged.

Late in 2012 a large outbreak of acute gastroenteritis occurred amongst children and adolescents in five Länder in Germany. Indications were that there was a high probability that norovirus was the causative agent via the consumption of fruit yoghurts which had been produced using frozen strawberries from China which had been contaminated [52].

Chinese strawberries are not grown in German soil that might have been fertilised by sludge derived from the faeces of German citizens. Chinese strawberries are not picked by people based in Germany, people who are part of the German mixing population in the system dynamics model. Yet, as this example serves to illustrate, the German population – like the UK population - frequently consumes food grown outside Germany. The term the 'imported strawberries problem' is therefore used to convey the fact that for virtually any county or region in the industrialised world foodborne infections of people in the country or region can be produced by contaminated foodstuffs drawn from the global food network and therefore originating outside the country or region.[39] Of course, a similar problem arises with the person-to-person element of any model; people can become infected overseas and then return to the UK to join that mixing population. However, the focus here is foodborne transmission. Therefore, it must be noted that the 'imported strawberries problem' is a fundamental problem for any modelling attempt which aims to move from an artificial, exogenous θ forcing term to a fully endogenised representation of foodborne norovirus transmission.[40]

Any attempt fully to endogenise the foodborne effects of norovirus therefore has two options. Option 1 is to construct an aggregated model for the whole world. This certainly ensures that all effects arise within the model boundary. However, a model which pools together the population, as well as all production of the various foodstuffs of interest to

39. This is but one example of a common situation which extends as far beyond Chinese products as it does beyond strawberries. See, for example, [11].
40. The point is also illustrated by looking again at the FSA strategic objective to "Reduce foodborne disease using a targeted approach"; this statement appears under the heading "Food produced or sold in the UK is safe to eat" [14].

norovirus transmission clearly operates at a low level of model granularity. The significance of that is that national (or possibly regional) granularity is necessary if the model is to be used for meaningful policy analysis and for intervention planning. Option 2 is therefore to create a model which is greatly disaggregated, possibly into individual countries, possibly into major food source sectors. Foodborne transmission still falls entirely within the boundary of such a model. However, this would be huge model and would be even harder to parameterise: as well as detailed global food production and supply data, all of the norovirus-related parameters that proved unknown for the UK would be required for all geographical areas and for all crops.

The UK model presented in Part 1 sits at something of a mid-point to these two. This is a credible position in policy analysis terms since the FSA plausibly has influence over the UK population and its food production protocols.[41] However, lack of parameters aside, it still leaves out very large volumes of food produced outside the UK: it faces the 'imported strawberries problem'.

This raises serious questions about how such detailed modelling might add to the policy process. A conclusion of this research is therefore that, in the light of the work reported here, a critical re-evaluation of the role of detailed, mechanism-based endogenised modelling work is called for.

An alternative approach is described in Part 2. This steps back both from over-aggregation and from over-disaggregating, acknowledges the 'imported strawberries problem' and instead takes an enhanced person-to-person model and uses it to address the core interest of this work by producing a sense of the individual and relative numerical sensitivities of the two different transmission effects. Conclusions for this work are discussed in the next section.

11.3 Scoping the Foodborne Effects

New data and a conceptual re-framing allow a new person-to-person model to be used in a fundamentally different way than previously. This model is a set of ODEs and a system dynamics simulation model. Both support the following conclusions, the first via closed-form solutions, the second via simulation runs. The model has been extended to address uncertainty regarding the role of asymptomatic carriers. As such, it is a better representation of our understanding of incidence. The foodborne effect is present as a straightforward 'forcing term'. The work makes it possible to do two things. Both give insights into the central concern of the research: the wish to understand the contribution of the foodborne mechanisms of transmission.

First, the model can be calibrated to be consistent with new research on the observed incidence rate of norovirus and the percentage of exposures thought to be foodborne

41. The same argument might be applicable to an EU-level model.

effects. By locating the model in the 'As Is World' it is possible to assess the prevalence - the foot print - of norovirus. The mathematical tractability of the steady state equations, or the easy simulation of the system dynamics model, allow the calculation of the number of individuals who at any time are in the population categories (susceptible, exposed, recovered immune etc.), as well as the rates of flow of people between these categories.

Second, the model proves to be a powerful tool for scoping out the contribution that foodborne effects – and person-to-person effects - have on norovirus prevalence. By exploring scenarios in these 'What If Worlds' the model generates some striking results.

For example, were the foodborne infection rate to double, observed infections would rise by 1/3. Were it to reduce by half then a 25% reduction in total incidence would result. These are noteworthy effects considering that foodborne infections currently make up only 2½ % of the total observed incidence rate. Furthermore, there is an even more remarkable scenario: removing all foodborne cases - albeit a very tall order - produces a 75% reduction in norovirus. Cases fall from 2.9 million to 750,000 annually. These non-linear effects indicate two things: that significant benefit has already been obtained by actions which have reduced foodborne infections to their current level; that there are still benefits to be gained by policies and actions which reduce this effect further.

However, these conclusions must be interpreted in the context of the model's much greater sensitivity to the human behaviour effects expressed in the parameter representing person-to-person infectivity. This can also be explored mathematically or by simulation. Increasing the person-to-person infectivity only 10% triples the incidence rate. A decrease of only 25% causes incidence to collapse to about 10% its current value - regardless of the continued presence of foodborne infections.

The same mathematical analysis can be used to explore uncertainties in the assumptions of the modelling. A conclusion is that the above results are robust to changes in a parameter representing uncertainty regarding the behaviour and infectivity of asymptomatic infective individuals.

The high sensitivity to person-to-person infectivity leads to two conclusions. First, that the observed variation in incidence over time may be explicable in terms of small changes in human behaviour. Simulation demonstrates this.

The second conclusion is that it is not just foodborne incidence that should be targeted for policy intervention. Notwithstanding the purview and leverage of the FSA, norovirus needs to be considered in an holistic manner, with the benefits of targeting person-to-person effects being judged on the same basis as the benefits for reducing foodborne effects. Of course, for both types of intervention detailed work would be needed on the character that such interventions might take, the practicality of such interventions and - a crucial attribute for assessing any benefits that might flow - the costs of different types of interventions. However, for all such work, the modelling acts as an organizing, or prioritising framework for discussions on interventions.

12 Recommendations

A series of recommendations follow from the research reported here. Any recommendations must, however, be made in the context of what the research has not considered. Hence, prior to discussing specific recommendations, clear reminders are called for regarding the notable assumptions made in this research.

12.1 Notable Assumptions of the Present Research

The very act of modelling makes clear the assumptions made and hence ; the limits of the applicability of the findings of the modelling work. This is a strength of any modelling approach. Four notable areas of those assumptions are recorded and discussed here.

First, the modelling work does not consider the role of different norovirus variant strains [31]. Yet the existence of such strains is believed to play a role in manifestations of norovirus [6, 21, 62, 63] and may also be significant because of the different transmission routes considered. For example, person-to-person transmission probably involves the transmission of the specific strain(s) to which the infectious person has been exposed. In contrast, foodborne routes involving faeces derived from the broad population are likely to involve the transmission of a suite of norovirus strains. How these different strains are transmitted, how they survive in different channels and what differential effects they have on humans is not modelled at all here. However, such effects are currently not known – therefore making the exclusions from modelling not unreasonable at present.

Second, throughout the research the approach to transmission has excluded any measure of 'viral load', or 'dose response'; the idea that a certain amount of norovirus (i.e. a certain number of genome copies) might be necessary for the next stage in any transmission process to become relevant. Research indicates that viral load is a factor [48, 58]. However, considering the complexity of the causal mechanisms included in the model, the absence of so many parameters and the fact that knowledge viral load and dose response effects is by no means complete, it would not have been possible to include this effect at this stage. Moreover, norovirus seems to operate at very low concentrations [7, 27]. However, it should be noted that inclusion of this effect is perfectly possible using the model reported here. Epidemiology offers a standard approach [45] and such models – when fully parameterised - can be simulated to produce results. However, it should be said that such models have an integro-differential form and would be unlikely to produce the sort of closed-form solutions developed in this work.

Third, the analysis has only begun to treat seasonality effects. Of course, Section 10.2 of the report considers seasonal changes to person-to-person effects but those changes were

inferred from observed norovirus incidence data, rather than from explicit analysis of the effects implicitly being modelled. Hence, there has been no causal mechanism-based consideration of seasonality effects resulting from, say, changes to person-to-person behaviour resulting from school holidays and/or weather. No analysis of any nature has been offered regarding foodborne seasonality effects. There has been no consideration of seasonality effects resulting from, say, farming seasons for different crops.

It will be clear from the work in Section 10.2 that these could be represented very straightforwardly as time-varying values on both θ and β which exogenously stimulate the model. From the results of Chapters 9 and 10 it seems likely that much of the observed variation in norovirus incidence could be reproduced in this way. However, the challenge would be twofold. First, it would be necessary to clarify quite which real world effects are represented by such external stimuli. Returning to the example in Section 10.2, it is useful to see the effects of increasing β by 6½ % and decreasing it by 14% in a seasonal pattern. However, the challenge is to disaggregate such effects into behavioural mechanisms which can be researched and which then generate such numbers and such patterns. The same comment applies to foodborne effects. The second challenge, having understood the source of seasonal effects, would then be to identify what interventions might be appropriate for dealing with them.

Lastly, the modelling is deterministic, in that it does not consider uncertainties at great length and the results discussed in Part 2 need to be seen in that light. Care is needed here to distinguish between two reasons for taking a non-deterministic approach, for considering uncertainty. In order to understand the deterministic stance of the work reported here, comment is necessary on each of these two reasons.[42]

One reason is that there are uncertainties about model formulation and parameter values. One can be uncertain about the presence of a causal link, or about the actual value of a parameter but still take the view that, in principle the link is present or not, or that, in principle, the parameter has a single value. More research would reduce such uncertainties. Alternatively, sensitivity analysis can be used to explore whether such uncertainties matter for the policy lessons of the model. As this report shows, the models can be used for the latter purpose; the work on the 'Weighting for Infectious Asymptomatics' in Section 9.5 is one example. Sensitivity analysis across a much wider range of model assumptions is perfectly possible – a consequence of building a model in the first place.

The second reason for a non-deterministic approach is fundamentally different. One may wish to specify a parameter in an uncertain, or stochastic, manner, because there is believed to be natural variation in that parameter as it operates in the world. Having a parameter take on a range of values may therefore be necessary in order to represent

42. This point is discussed further in Section 12.2, in paragraphs (6) and (7) respectively.

natural heterogeneity. Again, the modelling here can support experiments which explore the explanatory power of stochastic effects, ones in which parameters are treated as stochastic variables; the work on seasonality effects in Section 10.2 is one example.

The inclusion of stochastic effects can be insightful, whether applied to epidemic [28] or to other phenomena [33]. However, generally the approach taken in this report is not to look to stochastic effects for the source of complex behaviour. What the work in this report does is explore whether a set of highly interconnected causal mechanisms may plausibly be seen as the source of complex behaviour. The results in Part 2 show that they may. Having established this, it may be worth then introducing stochastic effects to see what they might contribute to the model's explanatory power. However, it merits repeating that the FSA had anticipated that the detail of the model in Part 1 would mean including parameters whose values were unknown and could not reasonably be estimated. Clearly, that work is not at a stage at which stochastic effects could be introduced. Even for the fully specified model discussed in Part 2, to consider stochastic effects one needs to specify, or hypothesis, considerable information about a value; specifically, its probability density function. This is now quite possible - but it is worth pointing out that such additional work only arises as a result of there being a model which represents the mechanisms thought to be operating, that is, a model is successful when it provokes questions and explorations of this nature.

12.2 Recommendations for Future Work

Given the above caveats, it is possible to present recommendations for how the contents of this report could be used and extended. These arise in the following areas.

1) Causal Mechanisms for Transmission

Part 1 of this report - Chapters 2 to 6 - contains model diagrams that express current thinking on the mechanisms underlying norovirus transmission. These are visual hypotheses, statements that could aid communication regarding what is currently believed to be taking place. Moreover, particularly when combined with the model equations, because the work here on foodborne transmission is expressed in a clear and unambiguous way, it becomes easier to critique and challenge the thinking using new experimental results and to put forward alternative hypotheses. The recommendation is therefore that this modelling work be made available to norovirus researchers.

2) Interventions in Foodborne Transmission

From the scoping analysis of Section 9.2 it is known that observed norovirus incidence can be influenced considerably by altering the strength of the foodborne effects. The modelling work of Part 1 gives rise to the parameter tables in Chapter 7. The right-hand columns of these tables list parameters which relate to the core interest of this study. These are

parameters that can in principle be altered and are candidates for intervention. This set therefore offers an indication of where the FSA could target its efforts in support of the FSA's 'Foodborne Disease Strategy'. The recommendation is that analysis be conducted on the practicality and cost of intervening to change these parameters.

3) Foodborne Transmission Parameters

The modelling work of Part 1 and the contents of in Chapter 7 also offer further structure to current knowledge of the specific parameters underlying foodborne transmission. The bottoms rows of the tables in this chapter contain parameter values not currently known. The recommendation is therefore that this analysis be made more broadly available with the aim of contributing to agenda setting for future work and discussion on future research priorities.

4) Endogenising the Foodborne Mechanisms

The modelling task at the core of Part 1 proved impossible to complete at present because of the absence of data. This does not mean that it will never be possible, rather that even the high quality research that has been done is only starting to get a purchase on how norovirus works in the foodborne realm. This problem may look very different in a decade. However, the modelling work also suffers at a conceptual level from the 'imported strawberries problem' discussed in Section 11.2. This raises very serious questions about the practicality of creating a detailed and truly endogenous model of norovirus foodborne transmission and equally series questions about what such a model might add to the policy process. The recommendation is therefore that, in the light of the experience of the study reported here, the aims of this modelling should be critically re-evaluated.

5) Interventions in Person-to-person Transmission Effects

Although such effects were not the focus of this research, a key benefit of Part 2 of this report is that it allows the effects of the two types of interventions (foodborne and person-to-person) to be compared. The scoping analysis of Chapter 9, along with the comparisons offered in Chapter 10, show that norovirus incidence is highly sensitive to changes in the parameter representing person-to-person interactions, more so than to foodborne effects. Looking at norovirus in this holistic fashion leads to the recommendation that appropriate agencies should consider person-to-person style interventions in the light of the results in this report. This would involve work on what character such interventions might take as well as analysis of the practicality and cost of intervening.

6) Alternative Model Formulations and Parameterisations

As stated throughout the report, uncertainty remains about aspects of the formulation and parameter values of the model explored in Part 2. Uncertainty about model formulation

implies that there may be additional or different causal mechanisms not represented in the model. For example, it is believed that partially immune people exposed again to norovirus may experience a boost in their level of immunity [43]. No such effect is represented in the structure of the model. Uncertainty about parameter values implies that the current numerical values used in the model may not be the correct ones. Examples are easy to find: there is uncertainty about the degree of infectivity of asymptomatics in spreading norovirus [2] and uncertainty about the period of immunity [55]. The only way to test whether such uncertainties matter is to try creating and running different models, models which explore alternative formulations and parameter values. If concern about such questions persists, or if new information comes to light, then the recommendation would be that these alternative models are built and their output explored.

7) Modelling Stochastic Variation

Some parameters in the model of Part 2 represent aggregated effects, effects where there is actually natural variation, or heterogeneity operating in the world. For example, the period during which infectious people shed norovirus, i.e. are infectious, appears to vary considerably across different person types [44]. This is different from the seasonal variations already explored but the approach is technically similar: simulation is performed with some parameters specified as stochastic values. If parameters representing such potential heterogeneities can be identified and sufficient information on them obtained then the recommendation would be that the model is simulated with fully specified stochastic variation effects to see what the consequences are for model output.

8) Further Modelling of Foodborne Effects

The work in Part 2 indicates a number of fairly simple but potentially quite fruitful modelling extensions that focus interest back onto foodborne effects. First, in the style of the simulation in Section 10.2 regarding β, it would be straightforward to explore the sensitivity of norovirus prevalence to stochastic changes in foodborne incidence, θ. Second, it would be useful to use the model to understand the effect of sudden, temporary 'shocks' in the value of θ. These would represent the introduction of infected foodstuffs. The model could be used to examine the speed with which norovirus prevalence responds, the extent of that response and how long it takes the system to settle down to its previous state. These two ideas involve simulation modelling rather than mathematical analysis but they are not insuperable tasks using the simulation approach.

A third and final thought is that an attempt could be made to create a version of the θ foodborne forcing term which is, to a limited extent, endogenised, thereby allowing its reservoir role to be studied further. This would not be done in the style of Part 1 here. Rather, it should be possible to formulate a model which disaggregates θ into the parts produced inside and outside the UK, and which then represents the timescales on which the

different effects operate. This would, obviously, be better model in terms of representing the causal mechanisms in place. However, it is also important, both for the new experiments suggested here and the sensitivity work presented in this report, because such a formulation would create new positive feedback loops which, though probably not changing the steady state of the system, could influence the system's response to shocks, random changes and seasonality. The evaluation of any interventions would have to be done with an idea of how the system would respond over time to changes such as these. This modelling could contribute further to policy making and to discussions concerning appropriate targets for intervention. Both simulation and eigenvalue-based analysis of structural dominance could be applied to give useful policy insights in this area. The recommendation is that this work is undertaken.

13 Acknowledgements

I would like to thank two groups of individuals for their support and contributions to this report.

First, staff at the Food Standards Agency: Darren Holland (Operational Research, Analysis & Research Division); Paul Cook (Head, Microbiological Food Safety Branch, Hygiene & Microbiology Division); Kara Thomas (Microbiological Food Safety Branch, Hygiene & Microbiology Division) and Abdul Khaled (Operational Research, Analysis & Research Division).

Second, the members of the expert team: Paul Gale (Animal Health & Veterinary Laboratories Agency); David Lees (Centre for Environment, Fisheries & Aquaculture Science); Nigel Cook (Food & Environment Research Agency); David Brown (Health Protection Agency) and Sarah J O'Brien (School of Translational Medicine, University of Manchester and Manchester Academic Health Science Centre). The work presented here has benefited immeasurably from their contributions. However, responsibility for any errors in the model lies solely with me and my FSA colleagues.

14 References

1. Adak, G. K., S. M. Long and S. J. O'Brien. 2002. Trends in indigenous foodborne disease and deaths, England and Wales: 1992 to 2000. *Gut* **51**: 832–841.

2. Amar, C., E. CL, J. Gray, M. Iturriza-Gomara, E. Maclure and J. McLauchlin. 2007. Detection by PCR of eight groups of enteric pathogens in 4,627 faecal samples: re-examination of the English case-control Infectious Intestinal Disease Study (1993-1996). *European Journal of Clinical Microbiology & Infectious Diseases* **26**: 311-323.

3. Bechberger, E., D. C. Lane, T. McBride, A. Morton, D. Quintas and C. H. Wong. 2011. The National Audit Office uses OR to assess the Value for Money of public services. *Interfaces* **41**: 365–374.

4. Bertrand, I., J. F. Schijven, G. Sánchez, P. Wyn-Jones, J. Ottoson, T. Morin, M. Muscillo, M. V. Nasser, A. M. de Roda Husman, M. Myrmel, J. Sellwood, N. Cook and C. Gantzer. 2012. The impact of temperature on the inactivation of enteric viruses in food and water: a review. *Journal of Applied Microbiology* doi:10.1111/j.1365-2672.2012.05267.x.

5. Bull, R. A., J.-S. Eden, F. Luciani, K. McElroy, W. D. Rawlinson and P. A. White. 2012. Contribution of Intra- and Interhost Dynamics to Norovirus Evolution. *Journal of Virology* **86**: 3219–3229.

6. Bull, R. A., E. T. Tu, C. J. McIver, W. D. Rawlinson and P. A. White. 2006. Emergence of a new norovirus genotype II.4 variant associated with global outbreaks of gastroenteritis. *J Clinical Microbiology* **44**: 327-33.

7. Caul, E. O. 1996. Viral gastroenteritis: small round structured viruses, caliciviruses and astroviruses. Part II. The epidemiological perspective. *Journal of Clinical Pathology* **49**: 959-64.

8. David, S. T., L. McIntyre, L. MacDougall, D. Kelly, S. Liem, K. Schallié, A. McNabb, A. Houde, P. Mueller, P. Ward, Y.-L. Trottier and J. Brassard. 2007. An Outbreak of Norovirus Caused by Consumption of Oysters from Geographically Dispersed Harvest Sites, British Columbia, Canada, 2004. *Foodborne Pathogens and Disease* **4**: 349-358.

9. Eberlein, R., J. Melhuish and D. Peterson. 1991. *Vensim: The Ventana simulation environment reference manual* Ventana Systems: Harvard.

10. Eschenbach, T. G. 1992. Spiderplots versus tornado diagrams for sensitivity analysis. *Interfaces* **22**: 40-46.

11. Falkenhorst, G., L. Krusell, M. Lisby, S. Madsen, B. Böttiger and K. Mølbak. 2005. Imported frozen raspberries cause a series of norovirus outbreaks in Denmark. *Euro Surveill.* **10**: E050922.2.

12. Fankhauser, R. L., M. S. S., J. S. Noel, Humphrey CD, J. S. Bresee, U. D. Parashar, Ando T and R. I. Glass. 2002. Epidemiologic and molecular trends of "Norwalk-like viruses" associated with outbreaks of gastroenteritis in the United States. *Journal of Infectious*

Diseases **186**: 1-7.

13. Food Standards Agency, "Request for Quotation - System Dynamics Model for Norovirus" 2011.

14. Food Standards Agency. 2011. *Safer food for the nation: Our strategic objective to 2015.* FSA/1677/0413: London. Downloadable from: http://food.gov.uk/news-updates/news/2011/mar/strategyto2015#.UfpYX23AEUU.

15. Forrester, J. W. 1975. *Collected Papers of Jay W. Forrester* Wright-Allen Press: Cambridge, MA.

16. Forrester, J. W. 1961. *Industrial Dynamics* MIT Press: Cambridge, MA.

17. Forrester, J. W. 1968. Market growth as influenced by capital investment. *Industrial Management Review (now the Sloan Management Review)* **9**: 83-105.

18. Forrester, J. W. 1968. *Principles of Systems* MIT Press: Cambridge, MA.

19. Forrester, J. W. and P. M. Senge. 1980. *Tests for Building Confidence in System Dynamics Models*. In System Dynamics: TIMS Studies in the Management Sciences ed. A. A. Lagasto, J. W. Forrester and J. M. Lyneis, North-Holland: Oxford; pp. 209-228.

20. Gale, P. 2005. Land application of treated sewage sludge: quantifying pathogen risks from consumption of crops. *Journal of Applied Microbiology* **98**: 380–396, doi:10.1111/j.1365-2672.2004.02482.x.

21. Gallimore, C. I., A. F. Richards and J. J. Gray. 2003. Molecular diversity of noroviruses associated with outbreaks on cruise ships: comparison with strains circulating within the UK. *Communicable disease and public health* **6**: 285-293.

22. Glass, R. I. 2013. Beyond Discovering the Viral Agents of Acute Gastroenteritis. *Emerging Infectious Diseases* **19**: 1190-1191.

23. Hall, A. J., B. A. Lopman, D. C. Payne, M. M. Patel, P. A. Gastañaduy, J. Vinjé and U. D. Parashar. 2013. Norovirus Disease in the United States. *Emerging Infectious Diseases* **19**: 1198-1205.

24. Health Protection Agency. 2009. *Foodborne illness at The Fat Duck restaurant: Report of an investigation of a foodborne outbreak of norovirus among diners at The Fat Duck restaurant, Bray, Berkshire in January and February 2009* HPA: London.

25. Health Protection Agency. 2012. *Guidelines for the management of norovirus outbreaks in acute and community health and social care settings* HPA: London.

26. Kapikan, A. Z. 1994. *Norwalk and Norwalk-like viruses*. In Viral infections of the gastrointestinal tract, 2nd ed. ed. A. Z. Kapikan, Marcel Dekker: New York, NY; pp. 471-519.

27. Kapikian, A. Z. 1996. Overview of viral gastroenteritis. *Arch. Virol. Suppl.* **12**: 7-19.

28. Keeling, M. J., M. E. J. Woolhouse, D. J. Shaw, L. Matthews, M. Chase-Topplng, D. T.

Haydon, S. J. Cornell, J. Kappey, J. Wilesmith and B. T. Grenfell. 2001. Dynamics of the 2001 UK Foot and Mouth Epidemic: Stochastic Dispersal in a Heterogeneous Landscape. *Science* **294**: 813-817.

29. Kendall, M. G. 1973. *Time-series* Griffin: London.

30. Koopmans, M. 2009. Noroviruses in healthcare settings: a challenging problem. *Journal of Hospital Infection* **73**: 331-337.

31. Koopmans, M. 2008. Progress in understanding norovirus epidemiology. *Current Opinion in Infectious Diseases* **21**: 544–552.

32. Lane, D. C. 2008. The Emergence and Use of Diagramming in System Dynamics: A critical account. *Systems Research and Behavioral Science* **25**: 3-23.

33. Lane, D. C. 2008. Formal Theory Building for the Avalanche Game: Explaining counter-intuitive behaviour of a complex system using geometrical and human behavioural/physiological effects. *Systems Research and Behavioral Science* **25**: 521-542.

34. Lane, D. C. 2007. The Power of the Bond Between Cause and Effect: Jay Wright Forrester and the field of system dynamics. *System Dynamics Review* **23**: 95-118.

35. Lane, D. C. and E. Husemann. 2009. *What Does The Arrow Mean? Observations on system dynamics mapping and the potential for experimentation with other methods*. In Strategisches und operatives Produktionsmanagement - Empirie und Simulation ed. J. Strohhecker and A. Größler, Gabler: Wiesbaden; pp. 327-350.

36. Lawrence, L., E. Kerrod, R. Gani and S. Leach. 2004. *Microbiological risk assessment for Norovirus infection – Contribution to the overall burden afforded by foodborne infections* Food Standards Agency: London.

37. Leemis, L. M. 2004. *Building Credible Input Models*. In Proceedings of the 2004 Winter Simulation Conference, Vol. 1 ed. R. G. Ingalls, M. D. Rossetti, J. S. Smith and B. A. Peters, Institute of Electrical and Electronics Engineers: Piscataway, NJ; pp. 29-40.

38. Lees, D. 2000. Viruses and bivalve shellfish. *Int. J. Food Microbiol* **59**: 81-116.

39. Lopman, B. A., G. K. Adak, M. H. Reacher and D. W. Brown. 2003. Two epidemiologic patterns of norovirus outbreaks: surveillance in England and Wales, 1992-2000. *Emerging Infectious Diseases* **9**: 71–77.

40. Marks, P. J., I. B. Vipond, F. M. Regan, K. Wedgwood, R. E. Fey, and E. O. Caul. 2003. A school outbreak of Norwalk-like virus: evidence for airborne transmission. *Epidemiol. Infect.* **131**: 727–736.

41. Meakins, S. M., G. K. Adak, B. A. Lopman and S. J. O'Brien. 2003. General outbreaks of infectious intestinal disease (IID) in hospitals, England and Wales, 1992-2000. *J Hosp Infect.* **53**: 1-5.

42. Meikle, J. 2014. *Heston Blumenthal's Dinner closed temporarily due to norovirus*

outbreak The Guardian newspaper, 2nd February.

43. Menon, V. K., S. George, F. Aladin, S. Nawaz, R. Sarkar, B. Lopman, J. J. Gray, M. I. Gomara and G. Kang. 2013. Comparison of Age-Stratified Seroprevalence of Antibodies against Norovirus GII in India and the United Kingdom. *PLoS ONE* **8**: e56239. doi:10.1371/journal.pone.0056239.

44. Milbraith, M. O., I. H. Spicknall, J. L. Zelner, C. L. Moe and J. N. S. Eisenberg. 2013. Heterogeneity in norovirus shedding duration affects community risk. *Epidemiology and Infection* **141**: 1572–1584.

45. Murray, J. D. 1989. *Mathematical Biology* Springer-Verlag: Berlin.

46. Neri, A. J., E. H. Cramer, G. H. Vaughan, J. Vinjé and H. M. Mainzer. 2008. Passenger Behaviors During Norovirus Outbreaks on Cruise Ships. *Journal of Travel Medicine* **15**: 172–176.

47. O'Neill, H. J., C. McCaughey, P. V. Coyle, D. E. Wyatt, and F. Mitchell. 2002. Clinical utility of nested multiplex RT-PCR for group F adenovirus, rotavirus and Norwalk-like viruses in acute viral gastroenteritis in children and adults. *J. Clin. Virol.* **25**: 335-343.

48. Phillips, G., B. Lopman, C. C. Tam, M. Iturriza-Gomara, D. Brown and J. J. Gray. 2009. Diagnosing Norovirus-associated infectious disease using viral load. *BMC Infectious Diseases* **63**: Doi: 10.1186/1471-2334/9/63.

49. Phillips, G., C. C. Tam, L. C. Rodrigues and B. Lopman. 2010. Prevalence and characteristics of asymptomatic norovirus infection in the community in England. *Epidemiol. Infect.* **138**: 1454- 1458.

50. Richardson, G. P. 1991. *Feedback Thought in Social Science and Systems Theory* Univ. Pennsylvania: Philadelphia.

51. Richardson, G. P. and A. L. Pugh. 1981. *Introduction to System Dynamics Modelling with DYNAMO (republished edition)* Productivity: Cambridge, MA.

52. Robert Koch Institut. 2012. Epidemiologisches Bulletin 15. Oktober. **41**: 409-420.

53. Rzezutka, A. and N. Cook. 2004. Survival of human enteric viruses in the environment and food. *FEMS Microbiology Reviews* **28**: 441–453.

54. Saupe, A. A., D. Kaehler, E. A. Cebelinski, Brian Nefzger, A. J. Hall and K. E. Smith. 2013. Surveillance among Callers to Foodborne Illness Complaint Hotline,Minnesota, USA, 2011–2013. *Emerging Infectious Diseases* **19**: 1293-1296.

55. Simmons, K., M. Gambhir, J. Leon and B. Lopman. 2013. Duration of Immunity to Norovirus Gastroenteritis. *Emerging Infectious Diseases* **19**: 1260-1267.

56. Tam, C. C., T. Larose and S. J. O'Brien. 2014. *Costed extension of the Second Study of Infectious Intestinal Disease in the Community: Identifying the proportion of foodborne disease in the UK and attributing foodborne disease by food commodity*. Food Standards Agency: London,

http://www.foodbase.org.uk//admintools/reportdocuments/866-11609_IID2_extension_report_-_FINAL_25_March_2014.pdf

57. Tam, C. C., L. C. Rodrigues, L. Viviani, J. P. Dodds, M. R. Evans, P. R. Hunter, J. J. Gray, L. H. Letley, G. Rait, D. S. Tompkins and S. J. O'Brien. 2012. Longitudinal study of infectious intestinal disease in the UK (IID2 study): incidence in the community and presenting to general practice. *Gut* **61**: 69-77.

58. Thebaulta, A., P. F. M. Teunisb, J. Le Pendud, F. S. Le Guyaderg and J.-B. Denish. 2013. Infectivity of GI and GII noroviruses established from oyster related outbreaks. *Epidemics* **5**: 98–110.

59. Tocher, K. D. 1963. *The Art of Simulation* Hodder and Stoughton: London.

60. Tompkins, D. S., M. J. Hudson, H. R. Smith, R. P. Eglin, J. G. Wheeler, M. M. Brett, R. J. Owen, J. S. Brazier, P. Cumberland, V. King and P. E. Cook. 1999. A study of infectious intestinal disease in England: microbiological findings in cases and controls. *Commun Dis Public Health* **2**: 108-13.

61. Tuladhar, E., M. Bouwknegt, M. H. Zwietering, M. Koopmans and E. Duizer. 2012. Thermal stability of structurally different viruses with proven or potential relevance to food safety. *Journal of Applied Microbiology* doi:10.1111/j.1365-2672.2012.05282.x.

62. Verhoef, L., E. Depoortere, I. Boxman, E. Duizer, Y. van Duynhoven, J. Harris, C. Johnsen, A. Kroneman, S. Le Guyader, W. Lim, L. Maunula, H. Meldal, R. Ratcliff, G. Reuter, E. Schreier, J. Siebenga, K. Vainio, C. Varela, H. Vennema and M. Koopmans. 2008. Emergence of New Norovirus Variants on Spring Cruise Ships and Prediction of Winter Epidemics. *Emerging Infectious Diseases* **14**: 238-243.

63. Widdowson, M.-A., E. H. Cramer, L. Hadley, J. S. Bresee, R. S. Beard, S. N. Bulens, Myrna Charles, W. Chege, E. Isakbaeva, J. G. Wright, E. Mintz, D. Forney, J. Massey, R. I. Glass and S. S. Monroe. 2004. Outbreaks of Acute Gastroenteritis on Cruise Ships and on Land: Identification of a Predominant Circulating Strain of Norovirus—United States, 2002. *J Infect Dis.* **190**: 27-36.