Developing unit-level disease state and within-unit prevalence parameters for *NAADSM*

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Abstract

This report describes how a model of within-unit (*i.e.*, within-flock or within-herd) disease dynamics can be used to develop parameters for *NAADSM*, a model of between-unit spread and control of disease. In *NAADSM*, disease state transitions are represented at the unit level. We have developed a separate model of within-unit disease spread, called *WH*, which represents the dynamics of disease spread, progression, and immunity at the level of individual animals within a homogeneously mixing herd. Outcomes produced by WH can be used to develop several key parameters for *NAADSM*, including unit-level disease state durations and levels of within-unit prevalence of disease.

Document revision history

- 2012/10/01 – Initial public version released

Introduction

In all versions of *NAADSM* released to date, progression of disease is modeled at the level of an entire herd or flock: this level is often referred to as the "unit". Each unit in a population is treated as though it has one disease state, as shown in Table 1. This characteristic applies to *NAADSM* 3 (including versions 3.0, 3.1, and 3.2) as well as *NAADSM* 4.

Table 1. Disease and disease-like transition states used in *NAADSM* 3 and 4.
Adapted from Reeves *et al.* (2012a). See Reeves *et al.* (2012a, 2012b), Harvey *et al.* (2007), and (2010a, 2010b, 2012) for complete descriptions of disease states used in *NAADSM* 3 and 4.

Herd- or unit-level transition states in* NAADSM *3	***Description***
Susceptible	Healthy units without immunity to infection. Susceptible units become infected upon effective contact.
Latent	Units which are infected, but not yet shedding the disease agent.
Subclinical	Units which are infected and shedding the disease agent, but not yet showing clinical signs of disease.
Clinical	Units which are infected, shedding the disease agent, and showing clinical signs.
Naturally immune	Units which have progressed through the disease cycle and are immune to further infection.
Vaccine immune	Units which are immune to infection by virtue of vaccination.
Destroyed	Units which have been destroyed (depopulated) as part of a disease control strategy.
Dead from disease[1]	Units which have progressed through a cycle of a disease associated with a high degree or mortality. All or nearly all animals have died as a result of disease.

While this simplification of treating each entire unit as though it has a single disease state can be a useful abstraction for modeling purposes, it has several practical problems. First, in reality, infected units are composed of individuals in different stages of their disease cycles: this mix of individuals in different states can make it difficult to define a single disease state for the entire unit.

Second, it is very difficult to obtain reliable data regarding the duration of disease states at the unit level. When information about the durations of disease states is reported, it is almost always reported for individual animals rather than herds or flocks (*e.g.*, Bouma *et al.*, 2009; Mardones *et al.*, 2010).

Finally, the degree of infectiousness of a unit might be expected to be related to the proportion of the unit that is infected: a unit nearing its peak prevalence of infected individuals might reasonably be expected to

[1] The dead-from-disease state was introduced in *NAADSM* 4.0, and is not present in any release of *NAADSM* 3.

be more infectious than a unit nearing the end of its epidemic. This variability in infectiousness over time cannot be represented in a unit-based model that does not consider the disease states of individuals.

This report demonstrates how individual animal-level data can be used in conjunction with a model of within-unit spread of disease to partly overcome the difficulties identified above, and to produce disease parameters suitable for use in unit-based versions of *NAADSM*. The within-unit model of disease spread used here is *WH*, an open-source modeling framework available from *http://www.naadsm.org/wh* (Reeves, 2012; Reeves *et al.*, in preparation).

Overview of the individual-level model of disease spread in *WH*

This section provides a brief overview of the WH model. For more detail, please see Reeves *et al.* (in preparation) and Reeves (2012).

WH is a stochastic modeling framework for the simulation of disease spread and progression in randomly mixing populations. *WH* operates at the level of the individual animal. In this model, disease may be transmitted by subclinically and clinically infectious individuals to susceptible individuals in the population. Once infected, an individual undergoes the set of transitions between disease states as illustrated in Figure 1. This should be quite familiar to users of *NAADSM*: *NAADSM* uses a very similar set of disease states and transitions, except that, as discussed above, the states and transitions in *NAADSM* apply to entire units.

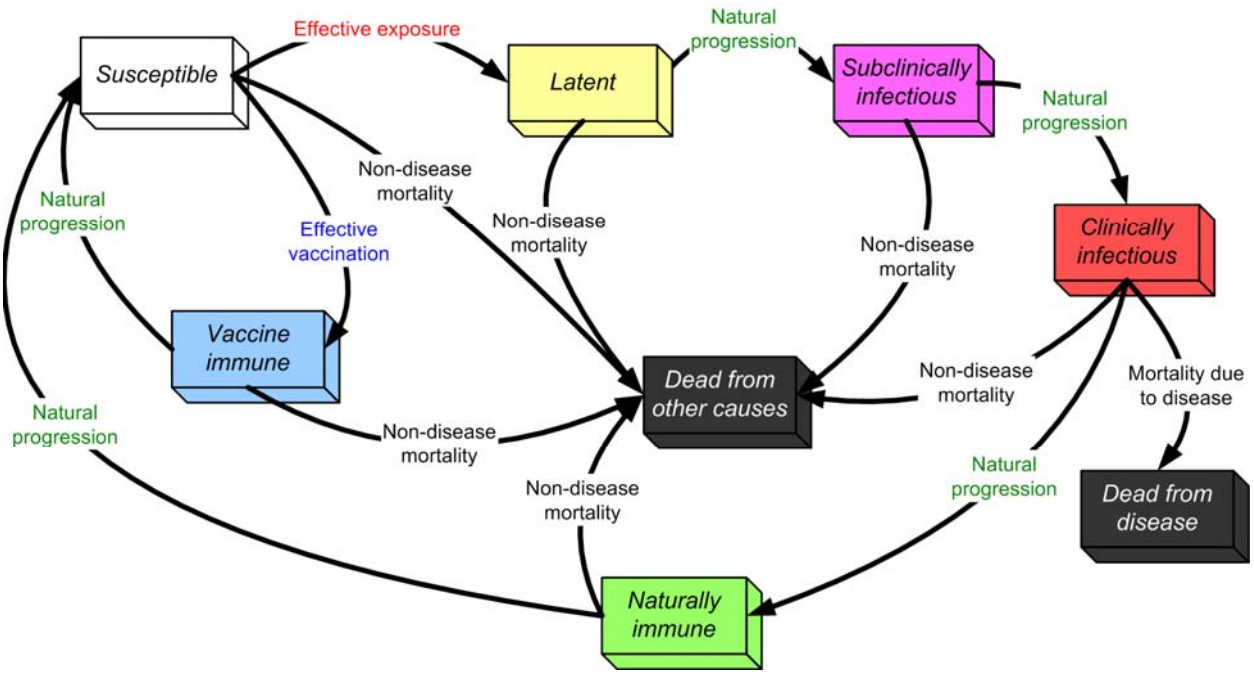


Figure 1. Possible disease states and transitions in *WH*, from Reeves (2012).

Similarly analogous to *NAADSM*, probability density functions in *WH* are used to represent the length of time (measured in discrete time steps) that an infected individual will spend in each disease state before progressing to a subsequent state.

The number of contacts (exposures) that each infectious individual will have with other individuals in the population in each time step is also determined with a probability density function. Because the population is assumed to undergo homogeneous mixing, a random process is used to determine sources and recipients for each of these exposures. Upon effective exposure (*i.e.*, an exposure that occurs

between an infectious and a susceptible individual), the susceptible individual will become infected, and will itself become infectious upon progressing past the latent state.

Each iteration of *WH* represents a complete simulated outbreak of disease within a randomly mixing population of individuals. Figure 2 illustrates four sample simulated outbreaks generated by *WH*. For each simulated outbreak, the prevalence of latent (yellow), subclinically infectious (pink) and clinically infectious (red) individuals is shown at each time step.

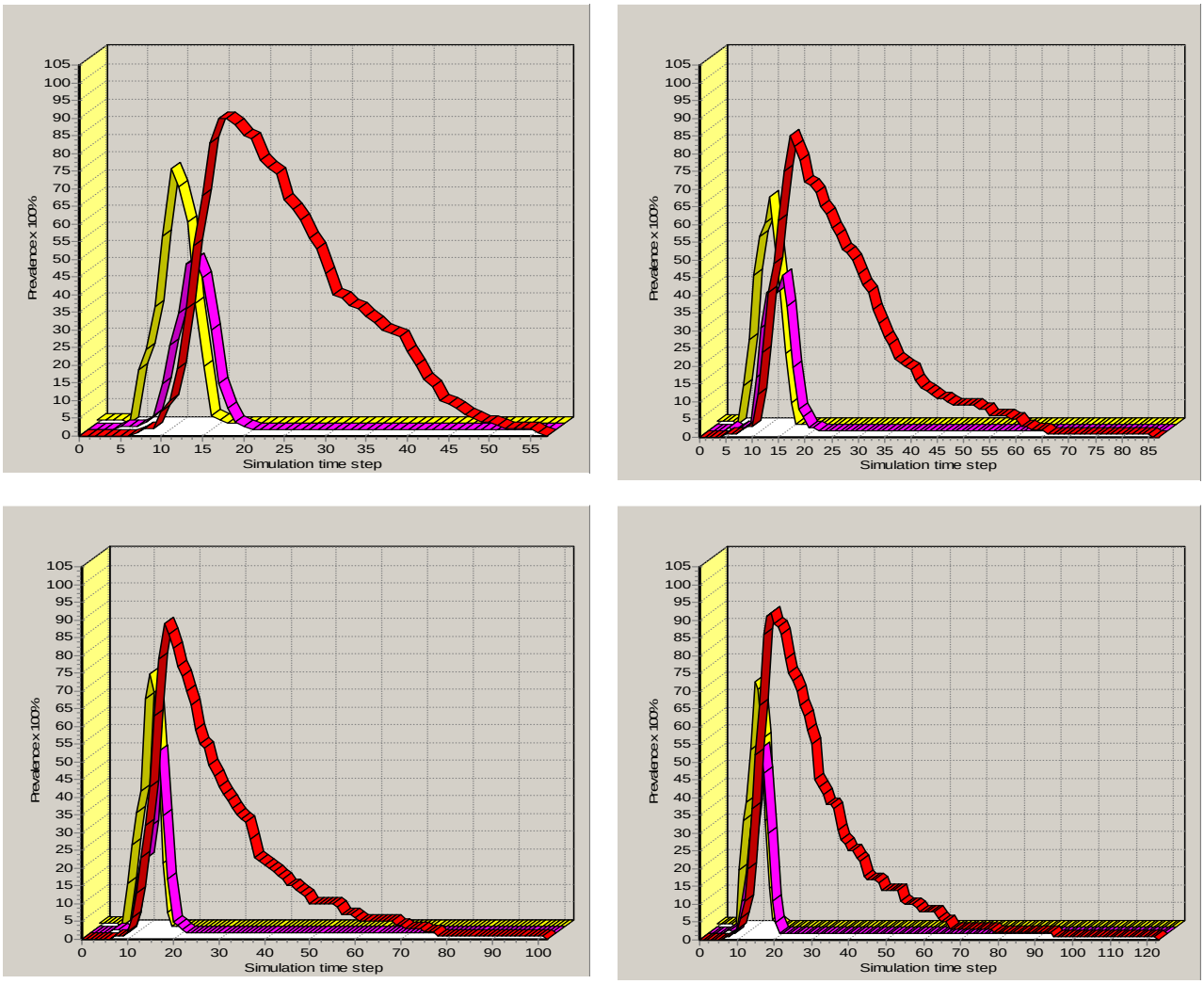


Figure 2. Results of four simulated within-unit outbreaks of foot-and-mouth disease (FMD), generated with *WH*. Parameters for this model were taken from a report by Carpenter *et al.* (2004). This simulation was carried out in daily time steps. Yellow: daily prevalence of latent individuals within the unit. Pink: daily prevalence of subclinical individuals within the unit. Red: daily prevalence of clinical individuals within the unit.

Using *WH* to produce distributions for unit-level disease state durations

In order to use output generated by *WH* to inform unit-level disease state parameters, it is first necessary to more precisely define several of the unit-level disease states shown in Table 1. As with all modeling, these definitions or assumptions should be explicitly stated. For purposes of the method described in this

paper, unit-level disease states could be defined as follows. Under this set of assumptions, the state of the animal in the most advanced infected stage determines the state of the entire unit.

- A unit is *latent* if there is *at least one* latent animal in the unit *and* if there are *no* subclinical or clinically infectious animals in the unit.
- A unit is *subclinical* if it contains *at least one* subclinically infectious animal *and* if it contains *no* clinically infectious animals.
- A unit is clinical if it contains *at least one* clinically infectious animal.

From these basic assumptions, definitions can also be determined for the unit-level durations of the different infected states:

- The duration of the latent period for a unit that is initially completely susceptible *(i.e.*, a unit composed entirely of susceptible animals) is the length of time from the first appearance of a latent animal to the first appearance of an animal in a more advanced infected state.
- The duration of the subclinical period for a newly infected unit is the length of time from the first appearance of a subclinical animal to the first appearance of a clinical animal.
- The duration of the clinical period is the length of time between the first appearance of a clinical animal to the time that the last remaining clinical animal either recovers or dies from disease.

As a consequence of these definitions, a unit-level latent state duration can be represented by exactly the same distribution that describes latent state durations for individual animals.

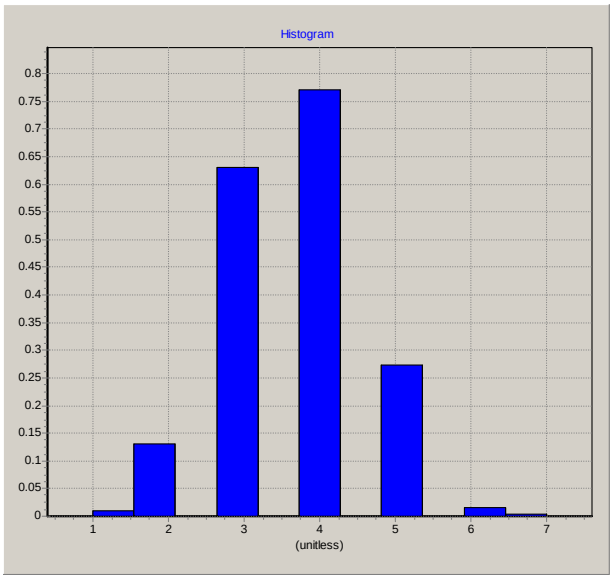
Slightly more effort is required to determine distributions for the subclinical and clinical state durations. Based on these definitions presented above, *WH* can track the durations of the subclinical and clinical phase of each unit-level outbreak. Table 2 shows the disease state durations calculated for the four simulated outbreaks illustrated in Figure 2.

Table 2. Unit-level disease state durations produced by *WH*, based on definitions presented above.

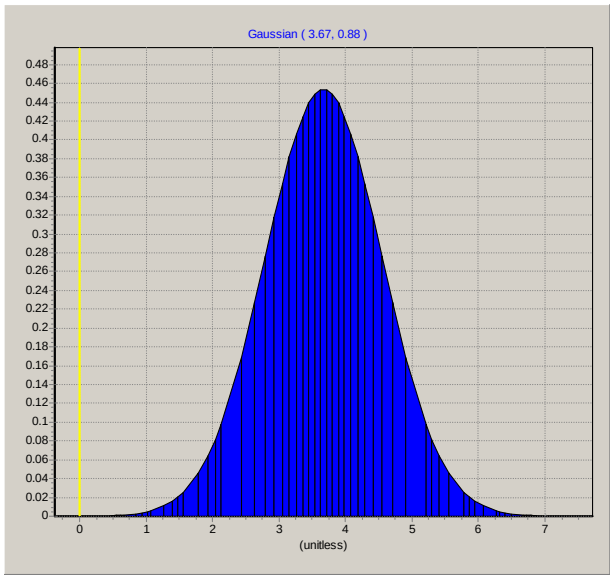
Simulated outbreak	***Latent period***	***Subclinical period***	***Clinical period***
A	4 days	3 days	50 days
B	4 days	1 days	81 days
C	5 days	2 days	95 days
D	5 days	2 days	116 days

Repeatedly running the model produces an empirical (histogram) distribution for each of these three unit-level disease state durations. These empirical distributions can be used directly in *NAADSM*, or can be used with distribution fitting software and techniques (Law, 2006; Palisade Corporation, 2008; Venables and Ripley, 2002; Vose, 2000) to determine theoretical distributions. Figure 3 shows histogram distributions and fitted theoretical distributions for data produced by 1000 iterations of the model in *WH*.

Unit-level latent state duration: Note the similarity of the fitted unit-level latent state Gaussian (3.67, 0.88) to the individual-animal-level state duration distribution of Gaussian (3.7, 0.8) (Carpenter *et al.*, 2004).

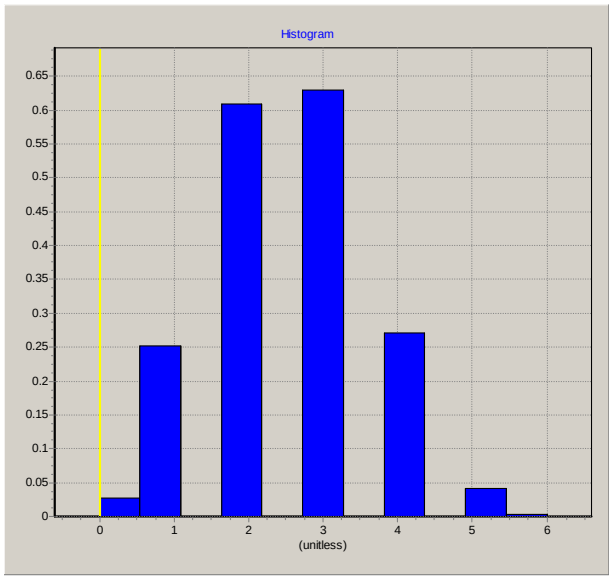


a) Histogram distribution for the latent state

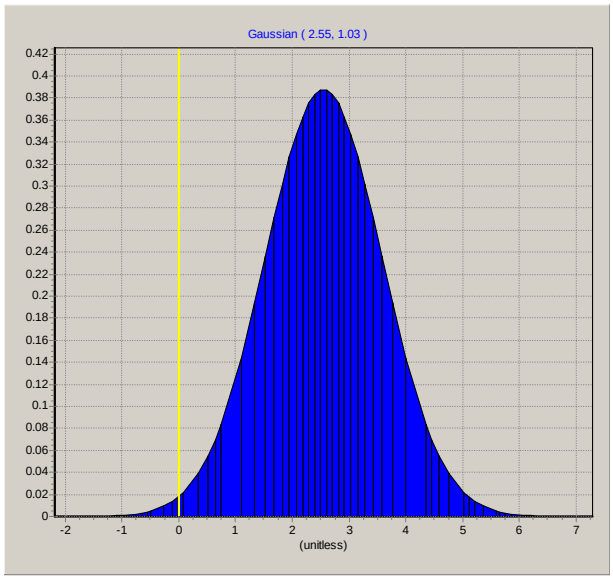


b) Fitted distribution for the latent state.

Unit-level subclinical state duration: Note the similarity of the fitted unit-level subclinical state Gaussian (2.55, 1.03) to the individual-animal-level state duration distribution of Gaussian (2.6, 1.05) (Carpenter *et al.*, 2004).



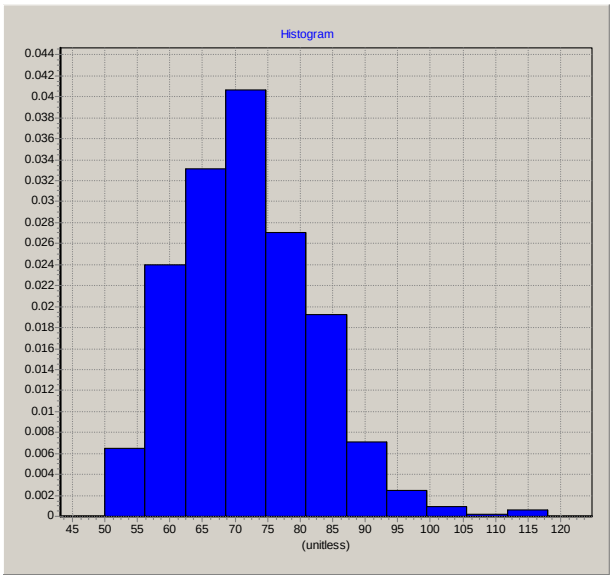
c) Histogram distribution for subclinical state



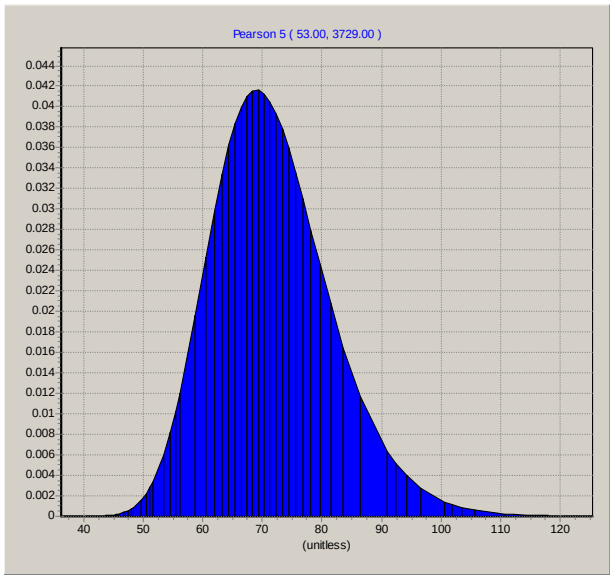
d) Fitted distribution for the subclinical state

Figure 3. Unit-level disease state durations for FMD, based on results from 1000 iterations of the *WH* model illustrated in Figure 2. Histogram distributions (a,c,e) were produced using *PDFCalc* 1.1.1 (Reeves, 2011). Distribution fitting (b,d,f) was carried out with *@Risk* 5.0.1 (Palisade Corporation, 2008).

Unit-level clinical state:



e) Histogram distribution for the clinical state



f) Fitted distribution for the clinical state.

Figure 3. (continued)

The technique described here has been applied in simulation modeling research. For example, Patyk *et al.* (in preparation) used the approach described here to product flock-level disease states for highly pathogenic avian influenza (HPAI) in nine commercial and backyard poultry production types. The authors ran separate simulations in WH for each of these production types, using an appropriate distribution of flock sizes for each type, together with information regarding the durations of individual bird-level disease states and rates of within-flock transmission of HPAI, to generate distributions for the flock-level clinical disease state.

Using *WH* to produce within-unit prevalence curves for use in *NAADSM*

Since version 3.1, *NAADSM* has had the capability to use simple curves to represent daily within-unit prevalence, which are then used to modulate the probabilities of disease spread by direct contact, local-area transmission, and airborne transmission (Reeves *et al.*, 2012a, 2012b). In addition to generating unit-level disease state durations, *WH* can also generate the data required to produce within-unit prevalence curves suitable for *NAADSM*.

For each time step of each iteration, *WH* records the prevalence of each of the various disease states (Reeves, 2012). Table 3 gives data generated by *WH* for the first 15 days of each of the first 5 iterations of the model of FMD illustrated in Figure 2. This table shows the prevalence of all infected animals (latent, subclinical, and clinical), expressed as a proportion of the total unit size.

Table 3. Daily prevalence of FMD-infected animals generated with *WH*. Parameters for this model were taken from a report by Carpenter *et al.* (2004).

Day	*Iteration 1*	*Iteration 2*	*Iteration 3*	*Iteration 4*	*Iteration 5*	*Median*
1	0.01	0.01	0.01	0.01	0.01	0.01
2	0.01	0.01	0.01	0.01	0.01	0.01
3	0.01	0.01	0.01	0.01	0.01	0.01
4	0.01	0.01	0.01	0.01	0.01	0.01
5	0.01	0.13	0.01	0.01	0.01	0.01
6	0.11	0.24	0.12	0.01	0.01	0.11
7	0.29	0.32	0.25	0.13	0.14	0.25
8	0.38	0.44	0.33	0.27	0.24	0.33
9	0.5	0.88	0.62	0.39	0.34	0.5
10	0.8	0.97	0.87	0.47	0.44	0.8
11	0.97	0.98	0.97	0.75	0.82	0.97
12	1	0.98	0.99	0.99	0.99	0.99
13	1	0.98	0.99	1	1	1
14	0.98	0.97	0.99	1	1	0.99
15	0.97	0.96	0.97	0.99	1	0.97

Recall that *NAADSM* uses curves that represents the average daily prevalence of infected or shedding animals for each production type (Reeves *et al.*, 2012a, 2012b). In order to produce curves suitable for use in *NAADSM*, an average (mean or median) prevalence for each day is calculated, as shown in Table 3. These values can then be used to produce relational functions suitable for application in *NAADSM* (Figure 4).

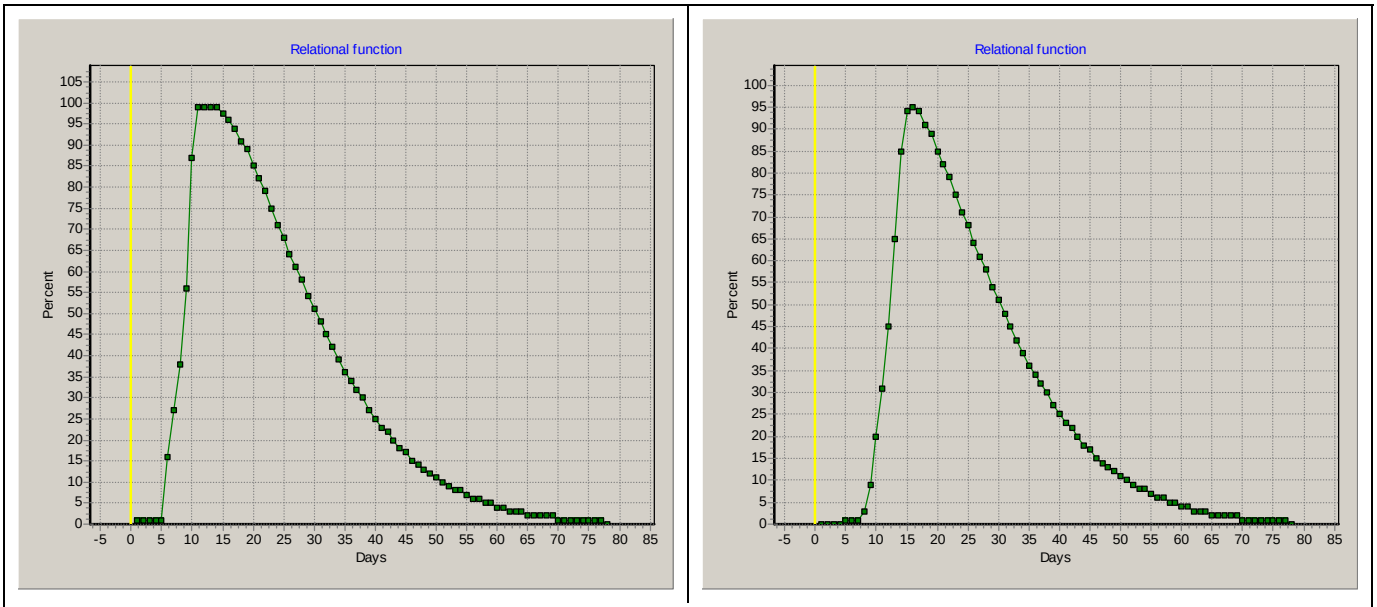


Figure 4. Within-unit prevalence functions for *NAADSM*, generated from output from the *WH* model of FMD illustrated in Figure 2. Left: median daily prevalence of all infected (latent, subclinical, and clinical) animals, expressed as a percentage of unit size. Right: median daily prevalence of all shedding (subclinical and clinical) animals, expressed as a percentage of unit size.

These relational functions were generated using *R* (R Development Core Team, 2012) and then imported into *NAADSM* 4.0, but any general-purpose statistical package should be sufficient to produce *NAADSM*-compatible relational functions. Appendix B of Reeves *et al.* (2012a) describes file formats for use with *NAADSM*.

Remaining difficulties

Handling unit-level immunity

Two additional transitional states in *NAADSM* are the unit-level immune states, which occur after infection (natural immunity) or vaccination (vaccine immunity). These states are binary conditions: a unit is either completely susceptible to disease, or completely immune.

WH does represent animal-level immune states. It would be possible, outside of *NAADSM* and *WH*, to establish a threshold prevalence of immunity below which it would be reasonable to treat a unit as though it were completely susceptible and above which it were completely immune to a particular disease of interest. Results from *WH* could then be used to determine when this threshold was reached after infection or vaccination.

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