MAJOR ARTICLE

Projected Benefits of Active Surveillance for Vancomycin-Resistant Enterococci in Intensive Care Units

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(See the editorial commentary by Farr on pages 1116–8)

Hospitals use many strategies to control nosocomial transmission of vancomycin-resistant enterococci (VRE). Strategies include "passive surveillance," with isolation of patients with known previous or current VRE colonization or infection, and "active surveillance," which uses admission cultures, with subsequent isolation of patients who are found to be colonized with VRE. We created a mathematical model of VRE transmission in an intensive care unit (ICU) using data from an existing active surveillance program; we used the model to generate the estimated benefits associated with active surveillance. Simulations predicted that active surveillance in a 10-bed ICU would result in a 39% reduction in the annual incidence of VRE colonization when compared with no surveillance. Initial isolation of all patients, with withdrawal of isolation if the results of surveillance cultures are negative, was predicted to result in a 65% reduction. Passive surveillance was minimally effective. Using the best available data, active surveillance is projected to be effective for reducing VRE transmission in ICU settings.

Vancomycin-resistant enterococci (VRE) are now a major cause of nosocomial infections and are endemic in many hospital settings in the United States [1]. Hospitals use many strategies to detect and control VRE. Possible strategies include standard infection-control practices (unless outbreaks are identified); passive surveillance, with isolation of all patients with known previous or current VRE colonization or infection; and active surveillance for VRE using rectal or perirectal culture, with isolation of patients who are found to be colonized with VRE. In 1995, the Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee published guidelines for the prevention and control of vancomycin resistance, which advocated the latter strategy [2]. Active surveillance may be preferred because a large number of VRE-colonized patients can be detected who would otherwise remain a reservoir for continued patient-to-patient transmission [3–6]. Recently, the Society for Healthcare Epidemiology of America (SHEA) released guidelines for the control of nosocomial VRE transmission and recommended the implementation of active surveillance for VRE at admission for patients at high risk for colonization [7].

However, only a minority of hospitals have implemented active surveillance programs to date, and some do not isolate VRE-positive patients at all [8]. Possible

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reasons for lack of active surveillance might include limited evidence supporting its implementation, concerns about the generalizability of benefits of active surveillance outside large tertiary care centers, and beliefs related to the potential costs of active surveillance programs.

We created a mathematical model of VRE transmission in an intensive care unit (ICU) using data available from an existing active surveillance program, to provide plausible estimates of the potential benefits associated with active surveillance for VRE. By varying model parameters, we sought to identify factors that would alter the projected impact of active surveillance and to assess whether such surveillance would be projected to be as beneficial in community hospitals as it is in tertiary care centers, where prevalence of VRE is highest. To our knowledge, this is the first model to assess the benefits of an active VRE surveillance program.

METHODS

The model. To compare the spread of VRE in an ICU under various hypothetical conditions, we created a stochastic mathematical model (appendix A), in which patients were categorized as being either colonized or uncolonized. The risk of transmission to an uncolonized host was proportional to the number of colonized patients, and a colonized patient's contribution to transmission risk was reduced by a fixed proportion if he or she was isolated.

Infection control strategies. We assessed 3 competing scenarios: (1) standard precautions are used in the ICU, with no active surveillance program in place and no isolation of persons who were previously known to be VRE positive; (2) passive surveillance is used, whereby only those who were previously known to be VRE positive on the basis of a clinical culture from a previous admission were isolated; and (3) active surveillance is used for all patients at ICU entry using standard perirectal culture detection methods [9], with isolation of all patients found to be colonized with VRE. The active surveillance scenario was further subdivided into (A) the base case, a strategy in which individuals were not isolated until culture positivity was confirmed; and (B) a strategy in which individuals were immediately isolated from the time of ICU admission until culture results were available, with discontinuation of isolation after a negative culture result was obtained. Repeated testing of patients whose cultures were initially negative for VRE was not analyzed, because the mean length of ICU stay was 4 days, which was far shorter than the duration for weekly repeated testing. We assumed that isolation precautions would include the requirement of gown and glove use for all patient contact and that dedicated equipment, such as stethoscopes, would be present in each room.

Study population. The hypothetical population we evaluated consisted of patients admitted to a medical ICU with diverse medical conditions. The mean length of ICU stay was 4 days. The index hospital used to estimate the parameters in the model simulations was the University of Maryland Medical Center, a 656-bed tertiary care academic medical center in Baltimore with a 10-bed medical ICU. The length-of-stay estimates were drawn from this hospital's medical ICU demographic database and were quite similar to those published in a large database study covering 285 ICUs and >38,000 patients [10]. In the initial base case analysis of the model before any sensitivity analysis, ICU size was 10 beds, with 96% occupancy of beds on average, as was the case in the University of Maryland Medical Center's medical ICU during the calendar year 2002.

Parameter estimates. Parameters used in the base case analysis are listed in table 1. The majority of parameters were

Table 1. Variables included in the base case active surveillance mathematical model.

Variable	Parameter	Base case initial value
N	Size of ICU	10 beds[a]
L	Length of ICU stay	4 days[a]
s	Sensitivity of perirectal culture test	100%
p	Specificity of perirectal culture test	100%
E	Effectiveness of isolation	70%[b]
f	VRE prevalence at ICU admission	20%[a]
q	Compliance with obtaining active surveillance cultures	90%[a]
ϕ	Fraction of empty beds filled	90%[a,c]
β	Contact rate/transmission probability	0.025 patient-to-patient contacts/day[a]
ψ	Return time for tests	1 day[a]

NOTE. ICU, intensive care unit; VRE, vancomycin-resistant enterococci.

[a] Variable obtained from index hospital active surveillance program database.

[b] From [28, 29].

[c] Projects to a daily average of 96% of ICU beds filled.

derived from the index hospital's existing medical ICU active surveillance database, which includes demographic data, length of stay, and results of active surveillance cultures. The medical ICU has conducted active surveillance culturing for VRE at admission, weekly during admission, and at discharge, in accordance with the current SHEA guidelines, since 1999. During the study period (calendar years 2001 and 2002), all patients had perirectal specimens sent for culture and processed within 24 h after admission to the ICU, in accordance with NCCLS guidelines. Samples were also obtained for culture once per week on a set single day of the week and at the time of discharge from the unit. Patients who were found to have positive results of the initial culture or of any subsequent culture underwent contact isolation for the duration of hospitalization. Acquisition of VRE was defined as the recovery of VRE after a negative admission culture result was obtained. Patients who had positive admission culture results were excluded from the calculation of VRE acquisition but were used to determine the prevalence of VRE colonization and/or infection at ICU admission. During the study period, active surveillance samples were also obtained for culture in the surgical ICU, but such samples were not obtained in the general surgical or medical wards.

The transmission probability (β) was calculated using the index hospital's screening data by fitting the model to the size and demographic characteristics of the teaching hospital's ICU under the condition of active surveillance with 90% compliance. We fit the transmission parameter (β) by simulating iteratively until equilibrium (i.e., when the discharge VRE prevalence matched the teaching hospital screening data). We assumed that the ICU population was in steady state, with the number of admissions equaling the number of discharges, and that patients could be colonized with only 1 strain of VRE at a time. The length of stay of a colonized patient was set equal to that of an uncolonized patient, because we assumed that the presence of VRE alone in the colon should not, in and of itself, increase length of stay. Increased length of stay would result from VRE infection, but this would occur in only a small fraction of colonized patients [5, 11]. Thus, we assumed that all patients had the same length of ICU stay, on average. In addition, it was assumed that there was no latent period, meaning that patients were immediately infectious when they became colonized.

Additional parameter estimates that were not available in the index hospital database were obtained from a formal review of the literature (table 1). A search of the MEDLINE database with the phrase "vancomycin resistant enterococcus," combined with "rectal culture" "active surveillance," "outcomes," "colonization," "infection," "isolation," and "cohorting," identified studies published during the period of January 1986 through May 2003. Additional studies were identified through manual search of references and abstracts from major scientific meetings. Passive surveillance (i.e., isolation of newly admitted patients on the basis of previously positive clinical cultures as a way of detecting current VRE colonization) was assumed to have a sensitivity of 11.4% [6]. Perirectal swab culture was assumed to be a perfect test (i.e., sensitivity and specificity of 100%) [12]. These values were chosen, because we found little in the literature to suggest at what threshold of detectability VRE becomes transmissible. All parameter values were further analyzed using sensitivity analysis (table 2). This allowed us to analyze how variation in each parameter would affect the outcome of reduced VRE acquisition in the condition of active surveillance, compared with no active surveillance.

RESULTS

Primary analysis. The estimated benefits of the competing active surveillance strategies are displayed in table 2. One thousand model simulations predicted that, in a typical 10-bed ICU,

Table 2. Estimated number of incident vancomycin-resistant enterococci (VRE) acquisitions and absolute number and proportion of cases prevented in 1 year with 3 competing infection-control strategies, after 1000 model simulations.

Infection control strategy	Average no. of incident VRE acquisitions	Estimated no. of incident cases of VRE colonization/infection prevented, compared with no surveillance strategy	Reduction of cases of VRE colonization/infection, compared with no surveillance strategy, %
No surveillance	118	…	…
Passive surveillance only	113	5	4.2
Active surveillance			
Patients isolated after culture results are determined to be positive	72.2	45.8	39
Immediate isolation and removal of patient after culture results are determined to be negative	41.1	76.9	65

NOTE. Each strategy is compared with a setting where no surveillance is in place.

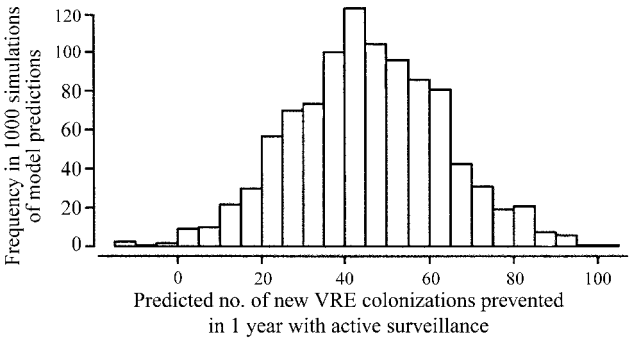

Figure 1. Results of 1000 model simulations comparing 1 year without active surveillance with 1 year with active surveillance. Bars represent an improvement, with reduced rates of vancomycin-resistant enterococci (VRE) after the implementation of an active surveillance program.

institution of an active surveillance culture and isolation program after return of culture results for VRE would, on average, prevent ~46 cases of new incident VRE colonization in 1 year, compared with no surveillance. This represented a 39% reduction, compared with no surveillance. Fewer cases of colonization were seen during 99.4% of the simulations when the active surveillance strategy was in place, as demonstrated by the distribution of the 1000 model simulations in figure 1. The average number of new incident cases of VRE colonization went from 118, when no active surveillance was in place, to 72, when an active surveillance program had been implemented. When compared with a strategy of no surveillance, passive surveillance (i.e., isolation of only those patients known to be VRE positive by previous clinical culture) was estimated to prevent, on average, only 5 cases (4.2%) of new VRE patient colonizations per year. Alternatively, if patients were immediately isolated when admitted to the ICU and only removed from isolation if the results of perirectal surveillance cultures were negative, then active surveillance was predicted to prevent 77 new VRE cases per year, representing a 65% reduction. Thus, immediate isolation of patients in an active surveillance program, instead of waiting for confirmation of positive test results, was estimated to prevent 68% more VRE incident colonizations per year in a 10-bed ICU than would delayed isolation.

Sensitivity analysis. Base case results for the active surveillance strategy (i.e., patients are isolated only after culture results are determined to be positive) and selected univariate sensitivity analyses are displayed in table 3. Sensitivity analyses suggested that active surveillance may be less effective in preventing new VRE acquisitions when the length of ICU stay was short, with 18.5 new cases (29%) prevented in an ICU with an mean length of stay of 2 days. When the length of stay was 8 days, 41 cases (27%) were prevented, which suggests that, as the time from admission to the determination of culture results becomes prolonged, the benefits of reduced transmission associated with isolating patients may also be reduced.

The benefit of active surveillance also appeared to be sensitive to changes in the prevalence of VRE colonization at ICU admission. In general, as the prevalence of VRE colonization at ICU admission increased, active surveillance was found to prevent more cases of VRE acquisition per year. Of note, even though the absolute number of new cases of VRE prevented with an active surveillance program increased with the admission prevalence of VRE, the proportion of total cases consistently decreased as the admission prevalence of VRE prevalence increased. As ICU occupancy decreased, the absolute number of VRE cases prevented by an active surveillance program also decreased, but the proportion of prevented cases remained ~40%.

To understand the impact that an active surveillance program would have in various hospital types such as community hospitals and tertiary care centers, a 2-way sensitivity analysis was conducted (figure 2). Five differing average admission VRE prevalence rates (range, 2.5%–40%) were modeled with varying mean lengths of ICU stay (range, 2–10 days). Thus, we estimated numerous possible combinations of the 2 factors that frequently differ between large urban tertiary care centers and community hospitals. In general, the 2-way sensitivity analysis predicted that hospitals with lower admission prevalences of VRE would see less absolute benefit in terms of the number of VRE cases prevented from an active surveillance program given a fixed length of stay (e.g., 3 days). However, if the length of ICU stay was long in hospitals with a low admission prevalence of VRE, a significant number of cases would be prevented with active surveillance (e.g., >20 cases prevented in an ICU with admission prevalence of VRE colonization of 2.5% and an 8-day mean length of ICU stay).

DISCUSSION

Using a mathematical model with parameters based on the best available data, we projected that the use of active surveillance would markedly reduce VRE transmission in the ICU setting. The benefits of an active surveillance appeared to vary depending on the ICU population, as evidenced by the 2-way sensitivity analysis, but they were found to be significant, with the exception of ICUs with a low admission prevalence of VRE and extremely short length of stays. These findings are compatible with existing recommendations by the CDC [2] and SHEA, which recently released guidelines recommending active surveillance for VRE using perirectal or rectal swab cultures [7]. These projections are also compatible with the results of existing clinical studies, most of which have found that active surveillance can reduce VRE transmission in a variety of ICU environments and patient populations [13–18]. In addition,

Table 3. Selected univariate sensitivity analyses using the base case strategy of active surveillance (AS) with isolation after confirmation of positive culture results, compared with a strategy of no surveillance.

Variable name and value	Estimated no. of incident cases of VRE colonization/infection prevented with AS compared to no surveillance	Reduction of cases of VRE colonization/infection with AS, %
Base case AS benefits if patient is isolated after culture results are determined to be positive	45.8	39
ICU occupancy, %		
90	40.0	40
80	30.8	40
Transmission probability		
0.0125	23.2	44
0.05	61.9	25
Length of ICU stay, mean days		
2	18.5	29
8	40.8	27
Prevalence of VRE colonization at admission, %		
5	9.9	44
10	34.2	42
30	49.4	37
50	43.1	35
Effectiveness of isolation, %		
20	11.1	9.5
90	61.5	52
Test sensitivity, %		
70	31.8	29
50	20.9	18
Test specificity, %		
70	61.3	52
50	70.9	60

NOTE. ICU, intensive care unit; VRE, vancomycin-resistant enterococci.

they are consistent with our previous findings showing that active surveillance reduced incident rates of positive clinical cultures for VRE in high-risk settings and that isolation of all patients in the ICU, irrespective of colonization status, significantly lowered VRE acquisition rates [19, 20].

Despite such data, active surveillance for VRE has not been adopted by most health care institutions, and the rate of isolation of VRE has continued to increase as a percentage of all enterococcal clinical isolates [21]. Controversy regarding the benefits of active surveillance is partly the result of the lack of supporting data from randomized, controlled trials, which are logisitically difficult and expensive to perform in the field of hospital infection control. Furthermore, active surveillance, even in a limited population during a short outbreak, can emphasize available infection-control and laboratory resources [22].

In the absence of randomized, controlled trials, mathematical models can be helpful to decision-makers who must formulate policy despite persisting uncertainty. Models can serve to quantify the projected impact of proposed interventions and to identify parameters, which may strongly influence intervention effectiveness, and they may provide insights into potential strengths and weaknesses of competing clinical strategies. Others have used a mathematical model to show reduced VRE cross-transmission with improved compliance with hand washing protocols, cohorting of nursing staff, and antibiotic restriction [23].

We projected that active surveillance would be particularly beneficial if tested patients were isolated immediately at the time of ICU admission and were removed from isolation only after culture results were determined to be negative for VRE. In our simulation, this strategy led to a greater reduction in

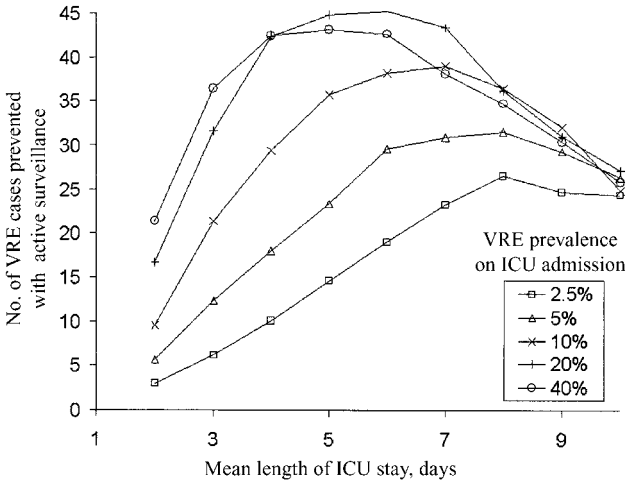

Figure 2. Results of a 2-way sensitivity analysis comparing the impact of varying mean lengths of stay in the intensive care unit (ICU) and mean prevalence of vancomycin-resistant enterococci (VRE) at admission on the estimated number of VRE cases prevented by an active surveillance program during a 1-year period. Analysis assumes that patients were isolated only after culture results were determined to be positive in the active surveillance program.

the number of VRE colonizations, compared with a strategy in which patients were not isolated until culture results were determined to be positive. To our knowledge, we are the first persons to suggest that such a strategy may be beneficial. However, although such a practice might result in gains in infection control, it may also be resisted by health care workers who are already operating under time and resource constraints. The practicability of such a strategy warrants further exploration.

It is important to note that our model demonstrated that the use of passive surveillance (i.e., isolation of only persons who are known to be VRE positive on the basis of previously obtained clinical cultures) is of little benefit. Passive surveillance alone is known to have a low sensitivity for detection of current VRE colonization at ICU admission [6]. Thus, it is not surprising that passive surveillance was projected to prevent so few cases of VRE colonization. Despite this, many hospitals currently use this method to control VRE transmission in high-risk populations.

In addition, we found that the effectiveness of active surveillance was influenced by admission prevalence of VRE. The projected number of colonizations averted via active surveillance increased until the admission prevalence was >30%, after which point the number of averted colonizations decreased slightly, depending on the average admission VRE prevalence (table 2 and figure 2). This occurred as a result of decreasing opportunities for transmission with a fixed ICU population; as the absolute number of patients already colonized upon admission increases, opportunities for transmission diminish. Mean length of stay also influenced the effectiveness of surveillance: with very brief length of stay, relatively few transmissions occurred, regardless of whether active surveillance was used, whereas, with an extremely long mean length of stay, the effectiveness of active surveillance was diminished by persisting low-level transmission that occurred despite the use of precautions. When analyzed together in a 2-way sensitivity analysis (figure 2), the understanding of the interaction of both mean ICU length of stay and average admission VRE prevalence can have important policy implications with regard to where VRE active surveillance programs would be most beneficial and cost-effective. Community hospitals, which may have lower prevalences of VRE and shorter length of ICU stays, would expect to prevent fewer cases of VRE colonization if they introduced an active surveillance program, and urban tertiary care centers in the United States would be expected to see large benefits.

Our analysis had several limitations. We assumed in the primary analysis before the sensitivity analysis that perirectal culture for VRE had 100% sensitivity and specificity. This was done because we lacked a good estimate of the accuracy of the perirectal culture as it relates to transmissibility of VRE from patient to patient. Any biases resulting from such an assumption may be attenuated by the fact that individuals with low-level colonization that might be missed during screening may have less infectious potential than do individuals with higher levels of colonization [24]. We also assumed the length of ICU stay for a VRE-colonized patient would equal that of an uncolonized patient. We acknowledge that VRE colonization may be a marker of a more severely ill patient and, thus, a longer length of stay, and it would be ideal for a variable length of stay to be built into future models. Furthermore, we did not take into account the potential impact of antibiotic prescribing patterns on VRE colonization and transmission [25, 26]. Of note, others have found that, when the colonization pressure (i.e., the proportion of patients colonized in the ICU) was high, it became the dominant risk factor for VRE acquisition relative to other risk factors, including antibiotic use [27].

In summary, active surveillance for VRE in ICUs, with isolation of persons who are found to be colonized with the organism, is projected to be a highly effective strategy for VRE control across a diverse range of possible ICU populations. Isolation of patients purely on the basis of history of previous detection of VRE on clinical cultures seems to be of little benefit. Future research might include clinical trials and formal estimates of cost-effectiveness to further our understanding of where active surveillance might best be implemented.

APPENDIX

We developed a stochastic simulation. Patients were considered to be either VRE colonized or not and undergoing isolation or not. In addition, recently admitted patients were considered to

be in a separate class while they were awaiting test results, and they may have been isolated or not. We let U denote the number of patients who were uncolonized with VRE yet who were isolated (false positives), X denote the number of patients who were colonized with VRE and isolated (true positives), V denote the number of patients who were uncolonized and not isolated (true negatives), and Y denote the number of patients who were colonized with VRE and not isolated (false negatives). W and Z represent the number of uncolonized and colonized patients, respectively, who have been tested and are awaiting test results. Each simulated day, the stochastic simulator performs the following operations in order.

1. We assume that the unit has N beds and that each empty bed is filled with probability ϕ. We draw a random variate to determine the number of patients admitted to the hospital, A = binomial [ϕ,N − U − X − V − Y − W − Z].

2. We let f denote the proportion of patients who are colonized at the time of ICU admission. We draw a random variate to determine the number of patients who are colonized with VRE on ICU admission, B = binomial [f,A].

3. We let q denote the proportion of patients who are tested. We draw a random variate to determine which patients are tested. The number of VRE-colonized patients who are tested is C = binomial [q,B]; the number of uncolonized patients who are tested is D = binomial [q,A − B].

4. We let s denote the sensitivity of the of the active surveillance perirectal culture. We draw a random variate to determine the number of patients who are VRE positive who test positive, binomial [s,C].

5. We let p denote the specificity of the active surveillance perirectal culture. We draw a random variate to determine the number of uncolonized patients who test positive, binomial [1 − p,D].

6. Recently admitted patients who tested positive could be isolated or not, depending on the policy being simulated. We let ψ denote the isolation state of these individuals; if they were isolated, then $\psi = 1 - E$; otherwise, $\psi = 1$.

7. Each day, a random number is drawn to determine whether an uncolonized patient became colonized. The proportion that become colonized is a function of the number of patients who were colonized and isolated and colonized and not isolated. We assume that, for each uncolonized patient, the daily probability of an infectious contact is β from each colonized patient in the ICU who is not isolated and $(1 - E)\ \beta$ from each isolated patient. Thus, the rate of contacts for isolated patients is further reduced by the factor $(1 - E)$, where E is the effectiveness of isolation in reducing VRE transmission. The probability of remaining uncolonized is the fraction who receive zero contacts from colonized patients, computed using the Poisson distribution. The probability of becoming colonized is different for each of the 3 subpopulations: for those who were isolated, $\Lambda_I = 1 - \exp(-\beta(1 - E)\ [X_t + (1 - E)\ Y_t + \psi\ Z_t])$; for those who were not isolated, $\Lambda_N = 1 - \exp(-\beta[X_t + (1 - E)\ Y_t + \psi\ Z_t])$; for those who were awaiting test results, $\Lambda_A = 1 - \exp(-\beta\ \psi\ [X_t + (1 - E)\ Y_t + \psi\ Z_t])$.

8. We let 1/L denote the average length of stay; $r = 1 - 1/L$ denotes the proportion of patients that remain hospitalized. At the end of each day, we draw a random variate to determine the proportion of each class that remained hospitalized in the ICU, binomial [r, *].

9. The day after admission, the test results were returned, and patients who remained hospitalized were moved. If patients had been isolated while awaiting test results, those who tested negative were removed from isolation. If the patients had not been isolated, those who tested positive were isolated.

10. Repeat.

A deterministic approximation in which each variable takes its expected value in the next time step is the following: The variable A denotes the number of new admissions to empty beds.

$$U_{t+1} = r\ [\ (1 - \Lambda_{I,t})\ U_t + (1 - p)\ (1 - \Lambda_{A,t})\ W_t\ ] \quad (1)$$

$$X_{t+1} = r\ [\ X_t + \Lambda_{I,t}\ U_t + s\ Z_t + (1 - p)\ \Lambda_{A,t}\ W_t\ ] \quad (2)$$

$$V_{t+1} = r\ [\ (1 - \Lambda_{N,t})\ V_t + p\ (1 - \Lambda_{A,t})\ W_t\ ] + (1 - q)(1 - f)\ A_{t+1} \quad (3)$$

$$Y_{t+1} = r\ [\ Y_t + \Lambda_{N,t}\ V_t + (1 - s)\ Z_t + p\ \Lambda_{A,t}\ W_t\ ] + (1 - q)\ f\ A_{t+1} \quad (4)$$

$$W_{t+1} = q\ (1 - f)\ A_{t+1} \quad (5)$$

$$Z_{t+1} = q\ f\ A_{t+1} \quad (6)$$

$$A_{t+1} = \phi[N - r\ (U_t + X_t + V_t + Y_t + W_t + Z_t)] \quad (7)$$

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