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A Simulation Analysis of the Epidemiological Principles for Fungicide Resistance Management in Pathogen Populations

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ABSTRACT

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Three epidemiological principles governing the buildup of fungicide resistance in populations of plant pathogens were derived from a simple mathematical model. These principles are that resistance will build up more slowly if: 1) the initial frequency of resistance is reduced, 2) the apparent infection rates of both fungicide-resistant and fungicide-sensitive genotypes (r_R and r_S, respectively) are reduced, and 3) r_R is reduced relative to r_S. These principles can be used to define the basic strategies for managing fungicide resistance. To illustrate these principles, we used a model for potato late blight that included a subpopulation of *Phytophthora infestans* that was resistant to the fungicide metalaxyl. We simulated the effects of initial frequency of resistance, favorable and unfavorable weather for late blight development, protectant fungicides, cultivar resistance, frequency of metalaxyl applications, metalaxyl dose, metalaxyl weathering rates, fitness of metalaxyl-resistant genotypes, and levels of resistance to metalaxyl. All of the simulated treatments conformed to theoretical predictions, although the magnitudes of the effects were specific to the late blight system. Recommended tactics for management of metalaxyl resistance were also evaluated with the simulation model; most were shown to reduce the buildup of resistance in the pathogen population. Contrary to recommendations, eradicant use of metalaxyl resulted in the least buildup of resistance; however, eradicant use also resulted in unacceptably high levels of disease.

Recent review articles on fungicide resistance management (7,11,31) have identified some of the basic strategies and tactics for reducing the risk of resistance. Staub and Sozzi's (31) strategies for resistance management were to "reduce selection pressure by decreasing disease pressure," and to "reduce selection time," the time a pathogen population is exposed to an "at-risk" fungicide. In practice, these strategies translate into several different tactics. Among the tactics that have been considered are: mixtures and alternations with companion fungicides, fewer applications, use of resistant cultivars, use of cultural practices, and lower fungicide dose (7,8,11,24,31–33).

The efficacy of most of these tactics for preventing or delaying resistance problems has not been conclusively demonstrated. There are several anecdotal examples (4; other examples cited in 8,11) and two greenhouse studies (23,30) that support the use of mixtures to slow the increase in the frequency of fungicide resistance in pathogen populations. Lalancette et al (16) demonstrated in a field study that the proportion of benomyl-resistant lesions in a population of *Venturia inaequalis* on apple trees did not increase as quickly when lower benomyl doses were used. They also showed a significant effect of mancozeb in slowing the increase of benomyl resistance when it was used as a companion fungicide (16). Unfortunately, this is only one of a few field studies testing the effects of fungicide resistance management tactics. Other studies are difficult to interpret because of interference from exogenous inoculum (6,9) or reduced fitness of the fungicide-sensitive isolate used as inoculum (9).

Although there are very few experimental studies, there are numerous mathematical models that have identified some of the factors relevant to resistance dynamics in pathogen populations (8,14,15,17,18,27–29). Among the factors that have been considered are initial frequency of resistance (8,17), fungicide efficacy (15,27), fungicide coverage (15,17,18), fungicide

weathering (14,17,18), and various epidemiological factors, such as apparent infection rate and latent period (17,18,27,29). Although each model is quite different, their predictions concerning management are similar in that, in general, mixtures and alternations reduce the buildup of fungicide resistance. However, with few exceptions, other resistance management tactics have not been adequately tested with models.

An additional shortcoming of these models is the lack of a conceptual framework in which to understand how any particular factor affects the buildup of fungicide resistance. With the exception of Skylakakis's papers (27–29), the epidemiological mechanisms have not been fully examined. Skylakakis (27,29) does not generalize his model enough to derive comprehensive principles that explain how management strategies reduce the buildup of resistance. A need exists for a synthesis of the mechanisms that affect the buildup of resistance so that management strategies can be derived and understood in a clear theoretical context.

Management strategies derived from theory should ideally be tested before being adopted. We have approached the evaluation of strategies (and tactics) by simulation modeling because of the difficulty of conducting extensive field experiments. Our efforts differ from previous ones in that we have modeled a specific system: metalaxyl resistance in *Phytophthora infestans* (Mont.) de Bary on potatoes (*Solanum tuberosum* L.). Parameter estimates for this model are based mostly on experimental data (20) rather than on hypothetical values. This model has been shown to realistically simulate metalaxyl treatments on metalaxyl-sensitive isolates under field conditions (20).

Simulation is an especially appropriate approach where field experimentation is impossible. Metalaxyl resistance in *P. infestans* has developed in Europe (4,6,21) and elsewhere (5,13), but it has not yet been found in North America. Thus, field experimentation that requires deliberate release of resistant isolates is not yet possible in the United States. Although simulation modeling cannot replace field experimentation, it can be useful for evaluating management tactics relatively easily and inexpensively (2,10,25).

The first objective of this paper was to establish a comprehensive conceptual framework in which to understand the mechanisms of fungicide resistance management strategies. We identified the epidemiological principles involved in fungicide resistance dynamics by examining a simple mathematical model. The second objective was to apply these epidemiological principles to management by using a simulation model of potato late blight. Our final objective was to evaluate some of the tactics that apply specifically to metalaxyl resistance in *P. infestans*.

THEORY OF FUNGICIDE RESISTANCE BUILDUP

Several authors have used similar mathematical models to describe changes in the relative proportion of two asexually reproducing plant pathogen genotypes that are growing exponentially (1,12,19,26). A generalized model for an exponentially growing population with fungicide-resistant (R) and fungicide-sensitive (S) genotypes is:

$$x_t/y_t = (x_0/y_0)e^{(r_R - r_S)t}, \quad (1)$$

in which x_t and y_t are the proportions of plant tissue diseased at time t, x_0 and y_0 are the initial proportions of diseased tissue ($t = 0$) caused by R and S, respectively, and r_R and r_S are the apparent infection rates, for R and S, respectively. Assume that r_R and r_S are independent and apply to the population when it is being exposed to an at-risk fungicide, and that $t = 0$ when the population is first exposed to an at-risk fungicide. Using this simple model, the time it takes to get from x_0/y_0 to some fixed value of x/y can be found by solving for t in equation 1:

$$t = [1/(r_R - r_S)][\ln(x/y) - \ln(x_0/y_0)], \quad (2)$$

in which ln is the natural logarithm, and a fixed ratio x/y is substituted for x_t/y_t.

From this simple model (equations 1 and 2) we can derive a set of three general epidemiological principles that govern the dynamics of fungicide resistance. First, the time it takes to get to any fixed value of x/y, t, will increase if the initial ratio of R to S, x_0/y_0, decreases, other things being equal. Second, decreases of the same relative magnitude in both r_R and r_S will cause t to increase (e.g., if both are multiplied by the same constant between 0 and 1). And third, a decrease in r_R relative to r_S will increase t. This will happen, for example, if there is an increase in r_S while r_R remains constant, or, conversely, a decrease in r_R while r_S remains constant. These three principles can be used to explain how various factors, not just management tactics, affect the dynamics of resistance. They may also suggest strategies for fungicide resistance management, providing a context in which to understand the effects of each management tactic. For example, a cultivar with rate-reducing resistance reduces both r_R and r_S (second principle), or less frequent use of an at-risk fungicide increases r_S while r_R remains constant (third principle). Both of these tactics will increase t, thus delaying the buildup of R. It is important to note that these same principles could have been derived from more complex population models; for example, Skylakakis's (26) model for competing races that are increasing logistically.

MATERIALS AND METHODS

The model that we used to apply these principles incorporates the effects of weather, host cultivar resistance, protectant fungicides, and the systemic fungicide metalaxyl on late blight epidemics (2,20). Metalaxyl-resistant genotypes (R) have been incorporated into this model by assuming they are identical to metalaxyl-sensitive genotypes (S), except that metalaxyl has no effect on R. We also assumed that the efficacy of metalaxyl is independent of protectant fungicides (in contrast to the assumptions in [17]). Density-dependence is a feature of the original late blight model (2).

The model operates on a daily time-step and is driven by weather data (2). One simulation consists of a 50-day epidemic. Simulated epidemics were initiated by inoculating plants in 25-m^2 plots of fully grown potato plants. Simulations were done using 9 yr of weather data. Rainfall and temperature were taken from data recorded at Geneva, NY. The number of hours each day when relative humidity was greater than 90% was generated from the temperature and rainfall data using a stochastic model (3). The same weather data were used for all treatments, and results for each treatment are reported as means of nine simulations.

Simulations were done in two sets: to illustrate epidemiological principles and to evaluate specific tactics for metalaxyl resistance management. The first simulated fungicide treatment (treatment 1) was used as a baseline against which to compare treatments that illustrate epidemiological principles (treatments 2–14). In this treatment, metalaxyl was applied at field rates (0.22 kg/ha) on a 14-day schedule beginning 5 days after inoculation. The initial frequency of R was 10^{-5}, and the potato cultivar was susceptible. Treatments 2–14 were simulated under these same conditions except for the changes noted below and in Table 1.

To illustrate the effect of the initial frequency of resistance (first principle), we varied the frequency of resistant sporangia in the initial inoculum. The proportions we used were 10^{-3}, 10^{-7}, and 10^{-9} (treatments 2–4). To illustrate the effect of reducing both r_R and r_S (second principle), we simulated unfavorable weather conditions (treatment 5), protectant fungicide application (treatments 6 and 7), and cultivar resistance (treatments 8 and 9). The 9 yr of weather data were considered normal, favorable weather for late blight development. Unfavorable weather for late blight was derived from the favorable weather by subtracting 2 hr from each daily period of high relative humidity (10). Apparent infection rates were also reduced by applying protectant fungicides at full (treatment 6) and half (treatment 7) rates in mixtures with metalaxyl, and by simulating epidemics on cultivars with two different levels of rate-reducing resistance (treatments 8 and 9).

We illustrated the effect of reducing r_R relative to r_S (third principle) in two general ways. First, r_S was increased, while r_R was held constant. This was accomplished by applying metalaxyl less frequently, on a 28-day schedule (treatment 10), applying lower metalaxyl doses, 1/4 rate (0.055 kg/ha, treatment 11), and by increasing the rate at which metalaxyl residues declined in the potato foliage (treatment 12). Second, r_R was decreased while r_S was unchanged. This situation would arise if resistant genotypes were less fit, or if resistance was incomplete. To simulate reduced fitness of R (treatment 13), lesion establishment, sporulation, and lesion expansion were reduced by 20%, and latent period was increased by 1 day. Incomplete resistance was simulated (treatment 14) by allowing metalaxyl to inhibit R by 33% as much as it inhibited S.

A second set of simulations was done to evaluate some tactics recommended for metalaxyl resistance management (32). These tactics are: use metalaxyl only in a mixture with companion (protectant) fungicide; use high rates of companion fungicide; application interval for companion fungicide should not exceed 14 days; limit to two to four metalaxyl applications per season; no curative or eradicative applications of metalaxyl. To evaluate these tactics, we first simulated metalaxyl application on potatoes using all five of these recommended tactics. Mixtures of metalaxyl (0.22 kg a.i./ha) and full rates of protectant fungicides (equivalent to

TABLE 1. Simulation results of potato late blight epidemics, caused by *Phytophthora infestans*, when metalaxyl resistance is present in the pathogen population[a]

Treatment no.	Treatment description	x/y[b]	p[c]	t_1[d]	x[e]	$(x+y)$[f]	AUDPC[g]
Evaluation of three principles of fungicide resistance management[h]							
1.	Baseline for trts. 2–14[i]	6.289	0.720	31.9	0.285	0.341	2.62
A. Effects of initial frequency of resistance (first principle)							
2.	Initial frequency = 10^{-3}	49.285	0.961	18.1	0.812	0.842	9.25
3.	Initial frequency = 10^{-7}	0.187	0.126	44.9	0.010	0.078	1.37
4.	Initial frequency = 10^{-9}	0.002	0.002	>50.0[j]	<0.001	0.069	1.35
B. Effects of reducing f_R and r_s (second principle)							
5.	Unfavorable weather	3.439	0.390	41.0	0.114	0.138	1.22
6.	Mixtures (full rate protectant)	0.348	0.198	39.9	0.011	0.034	0.90
7.	Mixtures (half rate protectant)	0.652	0.288	38.4	0.022	0.047	0.96
8.	Resistant cultivar	0.995	0.399	37.4	0.009	0.015	0.28
9.	Moderately resistant cultivar	6.197	0.673	33.9	0.094	0.110	0.88
C. Effects of reducing r_R relative to r_s (third principle)							
10.	28-day schedule (2 metalaxyl applications)	3.190	0.528	34.1	0.207	0.330	3.22
11.	1/4 rate metalaxyl	0.116	0.083	46.2	0.029	0.524	9.02
12.	Rapid metalaxyl decay	1.371	0.308	37.4	0.141	0.442	5.08
13.	Reduced fitness of R	0.031	0.028	47.9	0.001	0.025	0.74
14.	Incomplete resistance of R to metalaxyl	0.084	0.067	44.3	0.003	0.027	0.74
Evaluation of specific metalaxyl resistance management tactics[k]							
15.	Baseline for trts. 16–20[l] Met. days: 5,33[m] Prot. days: 5, 19, 26, 33, 47[m]	0.079	0.068	44.1	0.003	0.030	0.94
16.	Alternations Met. days: 5, 33 Prot. days: 19, 26, 47	0.983	0.327	37.4	0.044	0.091	1.34
17.	Half-rate protectant Met. days: 5, 33 Prot. days: 5, 19, 26, 33, 47	0.179	0.133	40.8	0.008	0.040	1.03
18.	21-day schedule Met. days: 5, 26, 47 Prot. days: 5, 26, 47	0.947	0.377	37.9	0.035	0.063	1.06
19.	14-day schedule Met. days: 5, 19, 33, 47 Prot. days: 5, 19, 33, 47	0.379	0.207	39.9	0.011	0.035	0.90
20.	Eradicant use Met. days: 15, 43 Prot. days: 15, 29, 36, 43	0.002	0.002	>50.0[n]	<0.001	0.395	12.91

[a] Simulations were conducted to illustrate three general principles of fungicide resistance management, and to evaluate specific management tactics for reducing the buildup of metalaxyl resistance (see text). Treatments 2–14 illustrate the effects of various factors corresponding to each general principle; these treatments are to be compared to a baseline treatment (treatment 1). Treatments 16–20 evaluate the efficacy of specific tactics for managing metalaxyl resistance (32); these treatments are to be compared to a different baseline treatment (treatment 15). Results are from 50-day epidemics and are expressed as means of simulations from 9 yr of weather data.

[b] Mean ratio of the proportion of plant tissue affected by metalaxyl-resistant isolates (x) to the proportion of plant tissue affected by metalaxyl-sensitive isolates (y).

[c] Mean proportion of disease caused by the metalaxyl-resistant isolates.

[d] Mean time, in days after inoculation, for x/y to increase to 0.01. In all treatments, except for treatments 1, 2, 9, and 10, there was at least 1 yr in which x/y did not reach 0.01; therefore, these values of t_1 are underestimates.

[e] Mean proportion of plant tissue affected by metalaxyl-resistant isolates.

[f] Mean total proportion of diseased plant tissue.

[g] Mean area under the disease progress curve, calculated on proportions of diseased tissue.

[h] Treatments 2–14 are the same as the baseline (treatment 1) except for the changes listed under treatment description.

[i] Baseline treatment is a standard against which treatments 2–14 are compared. Metalaxyl (0.22 kg/ha) was applied four times to a susceptible cultivar every 14 days, without a companion fungicide, starting 5 days after inoculation. The initial frequency of metalaxyl resistance was 10^{-5}.

[j] t_1 is greater than 50 days because x/y never reached 0.01 in any of the 9 yr.

[k] Treatments 16–20 are the same as the baseline (treatment 15) except for the changes listed under treatment description.

[l] Baseline against which treatments 16–20 are compared. Simulations were done with a susceptible cultivar, and the initial frequency of metalaxyl resistance was 10^{-5}. Metalaxyl was applied at the rate of 0.22 kg/ha for all treatments. Protectant (prot.) fungicide was applied at full-rate except in treatment 17.

[m] Days after inoculation on which metalaxyl and protected fungicides were applied.

[n] Mean t_1 is greater than 50 because x/y only reached 0.01 in one of 9 yr; $t_1 = 44$ days for that 1 yr.

1.26 kg a.i./ha chlorothalonil) were applied twice during the season, 5 and 33 days after inoculation. Protectant fungicide was applied 19, 26, and 47 days after inoculation in addition to being applied with metalaxyl. This treatment is the baseline (treatment 15) against which other simulated tactics (treatments 16–20) are compared. We then changed each tactic individually to observe the effect. The treatments were: metalaxyl applications made without a protectant fungicide (this is, in effect, an alternation treatment, since protectant fungicide was applied 19, 26, and 47 days after inoculation) (treatment 16); half rates of protectant fungicide (treatment 17); 21-day intervals between mixture applications, without any intervening protectant sprays (treatment 18); mixtures applied on a 14-day schedule, for a total of four applications per season (treatment 19); eradicant use of metalaxyl was simulated (treatment 20) by beginning applications 15 days after inoculation. For all of these treatments (treatments 15–20), the initial frequency of R was 10^{-5}.

Student's t-tests were performed on differences between treatments, or contrasts among several treatments, within each year. Comparisons were made from data at the end of the 50-day epidemics for six variables: the ratio x/y; the proportion of disease caused by the resistant genotype (R), p, where $p = x/(x + y)$; the number of days after inoculation when x/y reached 0.01, denoted by t_1; the proportion of plant tissue diseased by R, x; the total final disease caused by both R and S combined, $(x + y)$; and the area under the disease progress curve for total disease caused by R and S combined, AUDPC. For differences among treatments 1–4, contrasts were used to test for linear trends with the logarithm (base 10) of the initial frequency of R. Analysis of variance was not used to analyze these data because the variances were not equal among treatments.

RESULTS

Simulation results of metalaxyl resistance using the potato late blight model conform to the theoretical predictions for all treatments (Table 1). The first simulations evaluated the influence of initial frequencies of the resistant genotype (R). The buildup of metalaxyl resistance was the least when initial frequency was lowest, and increased as the initial frequency of R increased. This trend was shown by x/y, p, and x ($P < 0.01$) (Table 1). Similarly, the time taken for x/y to reach a value of 0.01, t_1, was shortest for the treatment with the highest initial frequency (treatment 2) and became greater as initial frequency decreased ($P < 0.0001$, Table 1). Total final disease, $(x + y)$, and AUDPC also increased as the initial frequency of R increased ($P < 0.001$); these differences are caused almost entirely by the increase in disease caused by R (Table 1). When R increased to high levels, as in treatment 2, metalaxyl did not control disease very well (Table 1).

Theoretical predictions that reducing both r_S and r_R will result in slower buildup of R (second principle) are also supported by simulation results. Unfavorable weather (treatment 5), protectant fungicides (treatments 6 and 7), and resistant cultivars (treatments 8 and 9) all resulted in lower x/y, p, and x ($P < 0.01$) and greater t ($P < 0.0001$) compared with the baseline treatment (treatment 1, Table 1). The moderately resistant cultivar (treatment 9) was not different from the susceptible cultivar (treatment 1) in terms of x/y or p ($P > 0.15$), but had a significantly greater t_1 ($P < 0.05$); this is because the level of rate-reducing resistance is not very high. Nonetheless, even the small differences in cultivar resistance produced results consistent with theoretical predictions for t_1. The resistant cultivar (treatment 8) had a smaller x/y, p, and x ($P < 0.05$) and a greater t ($P < 0.005$) than the moderately resistant cultivar (Table 1). Similarly, full rates of protectant fungicides (treatment 6) had a greater effect than half rates (treatment 7) on slowing resistance buildup ($P < 0.05$ for x/y, p, and x; $P < 0.005$ for t_1, Table 1). Because each of these treatments (treatments 5–9) reduced both r_R and r_S, $(x + y)$ and AUDPC were lower in all treatments relative to the baseline ($P < 0.005$, Table 1).

Treatments in which r_S was increased relative to r_R showed slower buildup of R (third principle). When r_S was increased by metalaxyl applications on a 28-day schedule (treatment 10), in low doses (treatment 11), or when the metalaxyl decay rate was increased (treatment 12), x/y, p, and x were reduced ($P < 0.01$), and t_1 was increased ($P < 0.0001$) relative to the baseline treatment (treatment 1, Table 1). Similarly, reductions in r_R, while r_S was unchanged, resulted in slower increases in R. Treatments of reduced fitness of R (treatment 13) and incomplete resistance to metalaxyl in R (treatment 14) had smaller x/y, p, and x ($P < 0.01$) and greater t_1 ($P < 0.0001$) than the baseline treatment (treatment 1, Table 1). $(x + y)$ and AUDPC were greater than the baseline when r_S increased (treatments 10–12, $P < 0.025$), and less than the baseline when r_R was decreased (treatments 13 and 14, $P < 0.01$, Table 1).

Results of simulations for evaluating specific tactics for metalaxyl resistance management in the potato late blight system showed that four of the five proposed tactics were effective at reducing the buildup of R. Violations of these four tactics (treatments 16–19, Table 1) resulted in a greater increase in R than using all the tactics simultaneously (treatment 1, baseline for metalaxyl resistance management). Each of these treatments resulted in higher x/y, p, and x ($P < 0.05$ for each treatment) and smaller t_1 ($P < 0.01$ for each treatment) than the management baseline (treatment 15, Table 2). $(x + y)$ and AUDPC increased significantly ($P < 0.05$) for treatments 16–18 but did not increase for treatment 19 ($P < 0.10$). The simulation of an eradicant treatment (treatment 20) resulted in the least increase of R (smallest x/y, p, and x, $P < 0.05$; and greatest t_1, $P < 0.01$) (Table 2). However, this tactic resulted in the highest disease levels, reaching a mean $(x + y)$ of 0.395 compared with less than 0.100 for the other treatments (treatments 15–19); the eradicant treatment also had an AUDPC more than 12 times greater than the baseline (Table 1).

DISCUSSION

Simulations of metalaxyl resistance with the potato late blight model illustrate the epidemiological principles involved in fungicide resistance dynamics. The value of these principles is that they provide a conceptual framework for understanding how each factor important to resistance buildup affects the population dynamics. Most of the factors identified by previous models relate to the magnitude of the difference between r_R and r_S, and are therefore examples of the second and third principles. Skylakakis (27,29) recognized the importance of $(r_R - r_S)$ in determining the rate of resistance buildup, but did not clearly distinguish between reducing both r_R and r_S (second principle) and reducing r_R relative to r_S (third principle).

The second and third principles lead to two fundamentally different strategies for fungicide resistance management even though the effect of both strategies is to reduce $(r_R - r_S)$. The second principle, reducing both r_R and r_S simultaneously, corresponds to the strategy proposed by Staub and Sozzi (31): "reduce selection pressure by decreasing disease pressure." The mechanism by which this strategy works is to reduce $(r_R - r_S)$. The tactics necessary for implementing this strategy are the various disease control tactics that are alternatives to using an at-risk fungicide: protectant fungicides, resistant cultivars, and cultural control practices reduce both r_R and r_S. In contrast, tactics necessary for implementing the third principle relate directly to the use of at-risk fungicide, which affects r_S. Less frequent use or lower doses of at-risk fungicide increase r_S, thus reducing $(r_R - r_S)$ and, therefore, reducing selection for R.

Although our simulations were done with a model specific to metalaxyl resistance in *P. infestans*, they support our hypotheses that these principles, derived from theory, can be applied to any pathogen and fungicide. The value of the simulations is that, because they were developed independently, they provide independent corroboration (using a realistic model) of the theoretical principles. These principles can be invoked to evaluate proposed tactics for fungicide resistance management in any host:pathogen:fungicide system. For example, Wolfe (33) proposed treating seeds of only one component in a cultivar mixture of barley with fungicide as a tactic to reduce the increase of

triazole resistance in *Erysiphe graminis* f. sp. *hordei*. Because each component in the mixture has different race-specific resistance genes, the initial occurrence of triazole resistance must arise in a pathogen genotype with the corresponding pathogenicity genes for the triazole-treated cultivar in order to gain a selective advantage. If resistance is associated with a particular pathogen race, and a cultivar with resistance to that race is treated with fungicide, the net effect would be to reduce the initial frequency of R (first principle). If R does become established in a population it may not be able to spread to untreated plants because of the need for different pathogenicity genes (reducing r_R and r_S, second principle). Finally, because triazoles are used on fewer plants, r_S increases, reducing $(r_R - r_S)$, and selection for R is reduced (third principle). Thus, the tactics proposed by Wolfe (33) for slowing the increase in triazole resistance in barley powdery mildew are likely to succeed. Whether a set of tactics are sufficient to delay the buildup of resistance enough to be of practical value is a question that is specific to each system and must be addressed as such.

An additional value of these simulations is that they provide first approximations of the magnitude of effects of specific management tactics. The management tactics recommended specifically for the phenylamides (including metalaxyl) are generally valid for reducing the buildup of R. These tactics are based on both the second and third principles. Simulation results suggest that, for metalaxyl resistance management, frequent use of protectant fungicides is just as important as reducing the number of metalaxyl applications.

The least increase in the x/y ratio occurred when metalaxyl was applied as an eradicant treatment. Although this result appears to contradict the manufacturers' recommendations for phenylamide resistance management (32), it was predictable since the exposure time is 10 days less in this treatment than for any other because metalaxyl applications began 10 days later. The mathematical model used to derive the general epidemiological principles considers only the ratio x/y, not the absolute amount of disease. Even though the frequency of R increased more slowly in the eradicant treatment than in other treatments disease reached unacceptably high levels (see $[x + y]$ and AUDPC, Table 1). The recommendation not to use metalaxyl in an eradicant manner is valid, but not necessarily because of the risk of selecting for metalaxyl-resistant genotypes. Experimental studies on the eradicant use of metalaxyl for controlling late blight have shown that disease can still reach high levels even when metalaxyl resistance is not present in the population (22). The absolute amount of disease caused by R in the eradicant simulations was still less than that of the baseline treatment (treatment 15) when all the tactics were used simultaneously.

It is obvious from the simulations of eradicant use of metalaxyl that fungicide resistance management must be integrated into the overall disease management strategy. It is not sufficient to maintain a low frequency of R if the crop is being lost to high levels of disease. Balancing the potentially conflicting goals of keeping the frequency of R low while simultaneously controlling disease is a complex problem. The problem becomes even more complex if the economics of fungicide use are considered as an additional constraint on disease and resistance management. The model simulations we have conducted for evaluating management tactics are by no means exhaustive. An important next step in metalaxyl resistance management in the potato late blight system is to use this model to find optimal management tactics, which combine the potentially conflicting goals of maintaining a low frequency of R and low disease levels.

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