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Citation	Ojiambo, P. S., Gent, D. H., Quesada-Ocampo, L. M., Hausbeck, M. K., & Holmes, G. J. (2015). Epidemiology and Population Biology of Pseudoperonospora cubensis: A Model System for Management of Downy Mildews. Annual Review of Phytopathology, 53, 223-246. doi:10.1146/annurev-phyto-080614-120048
DOI	10.1146/annurev-phyto-080614-120048
Publisher	Annual Reviews
Version	Version of Record
Terms of Use	http://cdss.library.oregonstate.edu/sa-termsofuse

Epidemiology and Population Biology of *Pseudoperonospora cubensis*: A Model System for Management of Downy Mildews

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Annu. Rev. Phytopathol. 2015. 53:223–46

First published online as a Review in Advance on May 18, 2015

The *Annual Review of Phytopathology* is online at phyto.annualreviews.org

This article's doi: 10.1146/annurev-phyto-080614-120048

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Keywords

Bayesian prediction, disease management, genomics, mating type, pathotype, risk assessment

Abstract

The resurgence of cucurbit downy mildew has dramatically influenced production of cucurbits and disease management systems at multiple scales. Long-distance dispersal is a fundamental aspect of epidemic development that influences the timing and extent of outbreaks of cucurbit downy mildew. The dispersal potential of *Pseudoperonospora cubensis* appears to be limited primarily by sporangia production in source fields and availability of susceptible hosts and less by sporangia survival during transport. Uncertainty remains regarding the role of locally produced inoculum in disease outbreaks, but evidence suggests multiple sources of primary inoculum could be important. Understanding pathogen diversity and population differentiation is a critical aspect of disease management and an active research area. Underpinning advances in our understanding of pathogen biology and disease management has been the research capacity and coordination of stakeholders, scientists, and extension personnel. Concepts and approaches developed in this pathosystem can guide future efforts when responding to incursions of new or reemerging downy mildew pathogens.

INTRODUCTION

Cucurbit downy mildew (CDM), caused by the oomycete *Pseudoperonospora cubensis* (Berk. & M.A. Curtis) Rostovzev, is an important disease of cucurbits worldwide. Under conducive conditions, the disease is highly destructive and the pathogen spreads rapidly within a field and on a regional scale. The pathogen is known to overcome host plant resistance and to develop resistance to fungicides. Indeed, *P. cubensis* was the first pathogen to be reported as resistant to the fungicide metalaxyl (85). In North America, breeding efforts in the 1950s and 1960s led to the release of cucumber cultivars with high levels of resistance to CDM (9, 10). This host plant resistance typically allowed for field production of cucumbers without the use of fungicides.

Long-distance dispersal: the aerial dissemination of disease-causing propagules in time and space on a regional or continental scale

Disease wave front: velocity with which epidemics of a plant pathogen spread through space and time at different spatial scales

This situation changed dramatically in 2004 when the cucumber crop in several southeastern and mid-Atlantic states was destroyed by CDM. Growers were caught by surprise when the disease appeared in North Carolina in early June and later spread northward to Virginia, Maryland, Delaware, and New Jersey (46). Wherever the disease struck it was aggressive on cucumber and was not controlled by mefenoxam- or strobilurin-based fungicides. In the subsequent couple of years, the disease was observed farther north with similar levels of damage. Consequently, for more than a decade, growers in the eastern United States have had to apply fungicides prophylactically and at regular intervals to protect their crops from CDM.

The epidemic of 2004 and its annual reoccurrence spawned research on many aspects of the disease and the pathogen. Consequently, much has been learned about the ecology and biology of *P. cubensis* and the epidemiology of CDM. This article builds on recent reviews (47, 57, 95) and describes our current understanding of the pathogen and the disease as well as directions for future research efforts. More broadly, we describe aspects of the population biology and ecology of the pathogen and dynamics of CDM at different temporal and spatial scales that can serve as a framework to advance concepts and management for other downy mildews.

EPIDEMIOLOGY

Temporal Progress of Cucurbit Downy Mildew

Passive atmospheric transport of *P. cubensis* sporangia on a regional scale has long been thought to play a major role in long-distance spread of CDM (72). The pathogen is an obligate biotroph (104) and requires its host for survival. In North America, *P. cubensis* is not known to overwinter in the field in areas approximately north of the 30° latitude, where hard frost occurs annually, killing the cucurbit host plants. Thus, CDM outbreaks in northern latitudes rely on the annual dispersion of *P. cubensis* sporangia from overwintering sources in the south (72, 74) or from protected cultivation due to the presumed absence of overwintering oosporic inoculum. The absence of local initial inoculum, herein defined as inoculum that originates at the mesoscale (farm or county level), accentuates the role of long-distance dispersal in the seasonal dynamics of CDM. The annual extinction-colonization cycles of *P. cubensis* make it possible to quantify disease dynamics and risk of CDM outbreaks in northern latitudes on the basis of epidemic conditions and dispersal from overwintering habitats. Knowledge of early temporal dynamics of the annual introduction of a pathogen is important to predict future spread and damage potential of diseases (43). Such knowledge is also essential in forecasting the risk of initial outbreaks of CDM in cucurbit fields.

The advance of a disease wave front caused by an obligate pathogen is usually constrained by the availability of susceptible hosts. Thus, the rate of spread of the disease wave front in spring-planted annual crops is limited by the seasonal advance of host planting (6). As with other airborne pathogens, long-distance transport of *P. cubensis* sporangia in the United States can be inferred from the northward, seasonal progression of CDM. In 2008, disease monitoring plots (sentinel

plots) were established across 24 states in the eastern United States, from Florida to Connecticut, as part of the CDM ipmPIPE program (74), to quantify the temporal and spatial dynamics of CDM and establish the rates of northward spread of the epidemic. This was the first effort to directly establish the effective long-distance dispersal of the pathogen. Reports of first disease onset were used to determine the rate of advance of the epidemic front, which is based on the assumption that the time lag between pathogen arrival and disease detection is about the same in all sentinel plots. The first onset of CDM was reported on February 18, 2008, and March 16, 2009 (73). Reports of first disease onset increased exponentially in early to late June and the epidemics entered the stationary phase in September or early October. On the basis of the total number of first reports and the duration of the epidemic, the season-long rate of temporal progress was estimated to be approximately two new disease reports per day. In addition, disease onset in southern states in the two years was observed approximately one to two months earlier in the sentinel plots compared with commercial fields, where the disease was not monitored regularly. This lag period, attributable to enhanced monitoring in sentinel plots, is sufficiently long enough to provide an early warning for commercial fields in southern states and underpins the role of sentinel plots in disease risk assessment. The time from first detection in sentinel plots compared with commercial cucurbit fields appears to vary geographically, and in more northern states (e.g., Michigan or New York) the lag period is less pronounced or nonexistent. Nonetheless, regular monitoring of cucurbit fields and sentinel plots has been instrumental in forecasting and predicting the risk of disease outbreaks in the eastern United States and is currently the basis for the CDM forecasting system (74).

CDM ipmPIPE: cucurbit downy mildew integrated pest management pest information platform for extension and education

Space-time clustering: aggregation of events relatively close in space and in time of occurrence

Spatial Spread of Cucurbit Downy Mildew

Although CDM occurs annually in the eastern United States (74), the timing of its spread from overwintering sources in the south to fields in northern latitudes is the most uncertain feature within the prediction framework (73, 74). This uncertainty is expected because regional spread of disease tends to be curtailed by limited opportunities for pathogen establishment (i.e., susceptible host tissue) rather than by atmospheric transport of inoculum (7). The spatial spread of CDM can be estimated by dividing the maximum spatial extent of the epidemic (i.e., the largest linear distance between two outbreaks) and the epidemic duration (i.e., time between the first and last outbreak). Using this calculation along with disease records, the spatial spread of CDM was estimated to be approximately 11 km/day (73). Disease outbreaks were found to be spatially aggregated and disease development was most likely at a distance of 120 km or less. However, the extent of spatial dependence, which is a measure of the mean distance of spread, was found to be up to 1,000 km. Two key conclusions can be inferred from these spatial analyses. First, overwintering sources in southern Florida contribute initial inoculum for outbreaks above the 30° latitude up to North Carolina. Second, disease outbreaks in the Great Lakes and mid-Atlantic regions may be due to the spread of inoculum from disease outbreaks around North Carolina rather than from overwintering sites in the south. It is also possible that disease outbreaks in the Great Lakes region could be due to other inoculum sources, such as greenhouses within the region (47). Spatiotemporal studies also indicate that a risk window is associated with CDM outbreaks in the eastern United States. This space-time clustering risk window is fairly large, being 3 to 5 months after the first outbreak with a distance >300 km (73). These findings suggest that infection of cucurbits by *P. cubensis* is an outcome of a contagion (26), and factors such as host planting patterns and spore dispersal that occur on a large spatial scale facilitate the disease development on a regional scale.

The infection-threshold finite-leap dispersal model (7) is a useful analytical tool to evaluate the consistency of the spatial extent of CDM derived above from statistical analyses of records of

disease outbreaks. The finite-leap model can be expressed as:

$$D_{crit} = (v_T\, f_e\, Q_{\lim}) \exp(-\Delta x/\lambda) G_n \Delta x^{-B}, \quad 1.$$

where D_{crit} is the critical probability for the pathogen to leap a gap of host plants of distance Δx, v_T is the local deposition velocity, f_e is the fraction of the standing crop of spores that escape the canopy, and $Q_{\lim}$ is the maximum number of spores that can be produced in a region. The parameter λ is the length scale ($=U/\gamma$), where U is the wind speed and γ is the reciprocal time scale, and G_n and B are functions of atmospheric stability. We can estimate Δx by expressing Equation 1 as a function of Δx. Given that Δx is in the exponent and also multiplies with the exponential, Equation 1 does not have an elementary solution that is expressible in terms of simple functions. However, Equation 1 can be solved by defining a function that solves a related equation. If we assume that $B = 1$ as suggested by Aylor (7), Equation 1 can be expressed as

$$\Delta x = \lambda \cdot \text{Lambert}\, W[(v_T\, f_e\, Q_{\lim} G_n)/\lambda D_{\text{crit}}], \quad 2.$$

where the function Lambert W (24) is the inverse of the related equation

$$z = (v_T\, f_e\, Q_{\lim} G_n/\lambda D_{\text{crit}}) \exp(v_T\, f_e\, Q_{\lim} G_n/\lambda D_{\text{crit}}). \quad 3.$$

In this form, Equation 2 can now be used to estimate the critical gap distance for pathogen transmission and disease development. If we assume dry conditions along the trajectory of spore transport and wet deposition at a target site and the following set of parameters, $v_T = 0.14$ km/h for wet deposition at target site (7), $G_n = 0.000318$ and $\gamma = 1.0\ \text{h}^{-1}$ assuming exposure to full sun (7), $f_e = 0.17$ and $Q_{\lim} = 2 \times 10^8$ spores/ha for *P. cubensis* (70), then the critical gap widths for $D_{crit} = 1$, 0.1, and 0.01 spores/m^2 (7) are approximately 100, 140, and 180 km, respectively. If spore transport is assumed to occur under cloudy conditions, where $\gamma = 0.12\ \text{h}^{-1}$ (7), then critical gaps are approximately 520, 820, and 1,150 km for $D_{crit} = 1$, 0.1, and 0.01, respectively. These estimates are fairly consistent with those obtained from statistical analyses of disease records. Further, these critical gaps are comparatively lower than those reported for *Peronospora tabacina*. The parameter f_e is similar for both pathogens (6, 70), but $Q_{\lim}$ is 2×10^8 for *P. cubensis* (70) compared with 1.3×10^{11} for *P. tabacina* (5). Thus, the critical gaps for these two pathogens might be explained in part by differences in spore production at the source region.

Direct measurement of pathogen dispersal over long distances is exceedingly difficult because of inoculum dilution during transport, and effective dispersal is usually inferred from the appearance of disease symptoms in a field. Thus, there is always uncertainty in the exact source of overwintering inoculum that may initiate epidemics. The uncertainty surrounding the role of overwintering sources in southern Florida in CDM outbreaks in the continental United States can, however, be clarified by examining trajectories in distance-time space of the northward spread of disease fronts (6). The gradients of these trajectories represent the rate of progression of the disease front. From the 2008 and 2009 epidemics, the distance of disease advance was significantly ($P < 0.001$; $R^2 > 73\%$) linearly related to the date of first occurrence of disease (**Figure 1**). The gradients of the regression lines were 0.10 and 0.12 in 2008 and 2009, respectively. With 1° latitude being equivalent to 111 km over this range of latitudes (7), these gradients translated to a rate of spread of approximately 11.1 and 13.3 km/day in 2008 and 2009, respectively. These rates of spatial spread are highly similar to those estimated using the simple ratio of maximum spatial extent of the epidemic and epidemic duration. The rate of the northward advance of the CDM wave front is comparable to the mean rates reported for the spread of tobacco blue mold in the eastern United States, which was approximately 13.9 km/day from 1996 to 2000 (7). Plant pathogens that exhibit long-distance dispersal appear to spread on average at approximately the same rate as the seasonal advance of the green wave of available susceptible host (6). On the basis of the regression graphs

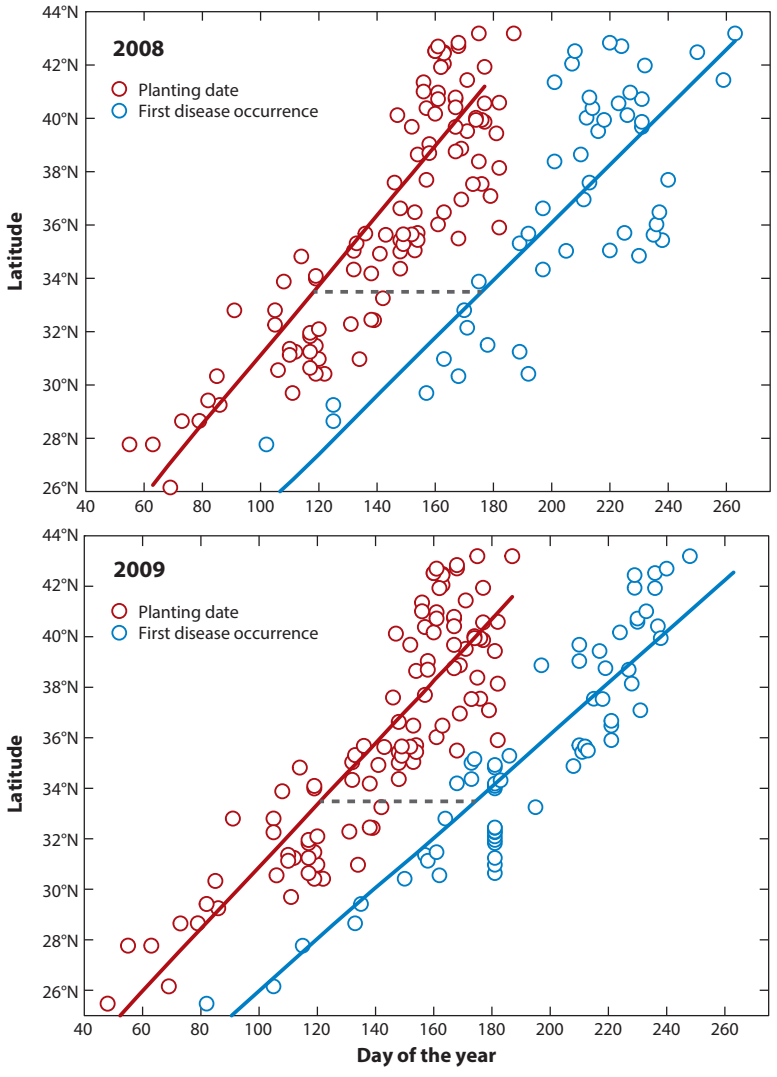

Figure 1

Northward spread of cucurbit downy mildew in cucurbit fields in the eastern United States during the epidemics in 2008 and 2009. The data display the location (as the latitude in degrees north of the equator) of the first report of the disease versus the first occurrence of disease in the sentinel plots and the planting date of each sentinel plot as the disease progressed up along the Atlantic coast from southern to northern states. The solid lines represent the regression of the latitude of the sentinel plots versus time of disease occurrence (*blue*) or planting date (*red*), with the blue line representing the average rate of northward progression of the epidemic front. The horizontal dashed line depicts the average difference in time between planting and first occurrence of the disease.

of planting date of the sentinel plots and their latitudinal locations, the gradient of the cucurbit planting line is approximately 11.9 and 13.9 km/day in 2008 and 2009 (**Figure 1**), similar to the rate of spread of the advancing disease wave front. This suggests that the spread of CDM over long distances may be constrained mainly by host availability rather than by dispersal of inoculum. As suggested by Aylor (6), the green wave of planting also presents a landscape barrier to potential

MODELS FOR RISK OF DISEASE OUTBREAK ON A REGIONAL SCALE

The spread of downy mildew is an ecological process that exhibits a complicated behavior over space and time. Prediction of such a process requires incorporation of available scientific insight, data, and theory into a structure that accounts for inexactitudes (119). Bayesian hierarchical models provide a useful framework to predict multiphasic processes by accounting for uncertainty in model parameters. This framework was applied to cucurbit downy mildew to obtain some sense of uncertainty in the risk of disease outbreak in the eastern United States (75). Time to disease outbreak in a field was the observed data and was represented as a Weibull proportional hazards model. The process model was defined as a spatial process in which unobserved heterogeneity among cucurbit fields was defined by a conditional autoregressive structure. The parameter model was specified by assigning uniform prior distributions for the data and process models. Bayesian hierarchical modeling indicated a high risk of disease in states in the mid-Atlantic region. This relatively large clustering of disease outbreaks is consistent with the relatively large transmission risk window identified from space-time analysis (73). However, Bayesian analysis also reveals uncertainty in disease outbreaks and suggests other factors that can aid in explaining the risk of CDM outbreak.

long-distance dispersal events that reduce the random variability and the rate of disease spread. Similarly, the disease wave is curtailed toward the end of the growing season by the golden wave (7) as cucurbits mature and are destroyed, resulting in a reduction or absence of susceptible hosts. With a critical gap of 180 km over which *P. cubensis* can disperse northward under clear skies, a rate of spread of 11 km/day suggests that it would take approximately 3 weeks for infection at a source to bridge this gap, and this can occur well before the crop is harvested in the target region. Prediction of the risk of CDM outbreak over a large spatial and temporal scale is often difficult. This is further complicated by the uncertainty in the parameters that describe various factors that influence disease outbreak at such scales. However, Bayesian hierarchical models (75, 119) have been instrumental and useful in quantifying the risk of CDM outbreak in the eastern United States (see sidebar, Models for Risk of Disease Outbreak on a Regional Scale).

Bayesian hierarchical model: a model formulated in multiple levels to estimate parameters of a posterior distribution using the Bayesian theorem

Fat-tailed dispersal: dispersal in which a high proportion of propagules are dispersed with increasing distance from the source over long distances

Isopleth: a line on a map connecting areas in which positive disease outbreaks occurred at the leading edge of the epidemic

Association of Initial Epidemic Area with Final Extent of the Disease

Disease expansion in epidemics caused by plant pathogens, such as *P. cubensis*, that exhibit substantial long-distance dispersal can be described by the power law relationships and fat-tailed dispersal kernels that are not exponentially bound. Thus, such pathogens result in accelerating dispersal wave fronts (30, 40). In addition, the spread of epidemic fronts for accelerating epidemics is multiplicatively related to the initial epidemic area (60, 67). Consequently, the area of the initial disease outbreak is expected to be strongly related to the final extent of the disease epidemic. Using records from the CDM ipmPIPE program, isopleth maps were constructed to calculate the cumulative extent of epidemic spread based on counties where CDM was detected. The epidemic front expanded slowly from March through May and rapidly thereafter from May to July, with the majority of expansion occurring from July to October (**Figure 2**). Preliminary work based on cumulative county-level disease outbreaks to delineate the extent of the epidemic showed that the initial epidemic area was variable from 2008 to 2010. For example, the initial epidemic area in March was 0.015, 0.005, and 0.013 million km^2 in 2008, 2009, and 2010, respectively, with a corresponding final epidemic area of 2.479, 2.674, and 2.564 million km^2, respectively. Final epidemic areas regressed against epidemic areas recorded in March during this time frame resulted in a significant ($R^2 = 0.71$; $P < 0.001$) linear relationship (P.S. Ojiambo & D.H. Gent, unpublished results). Although these results are based on a very small sample size, they suggest that the size of

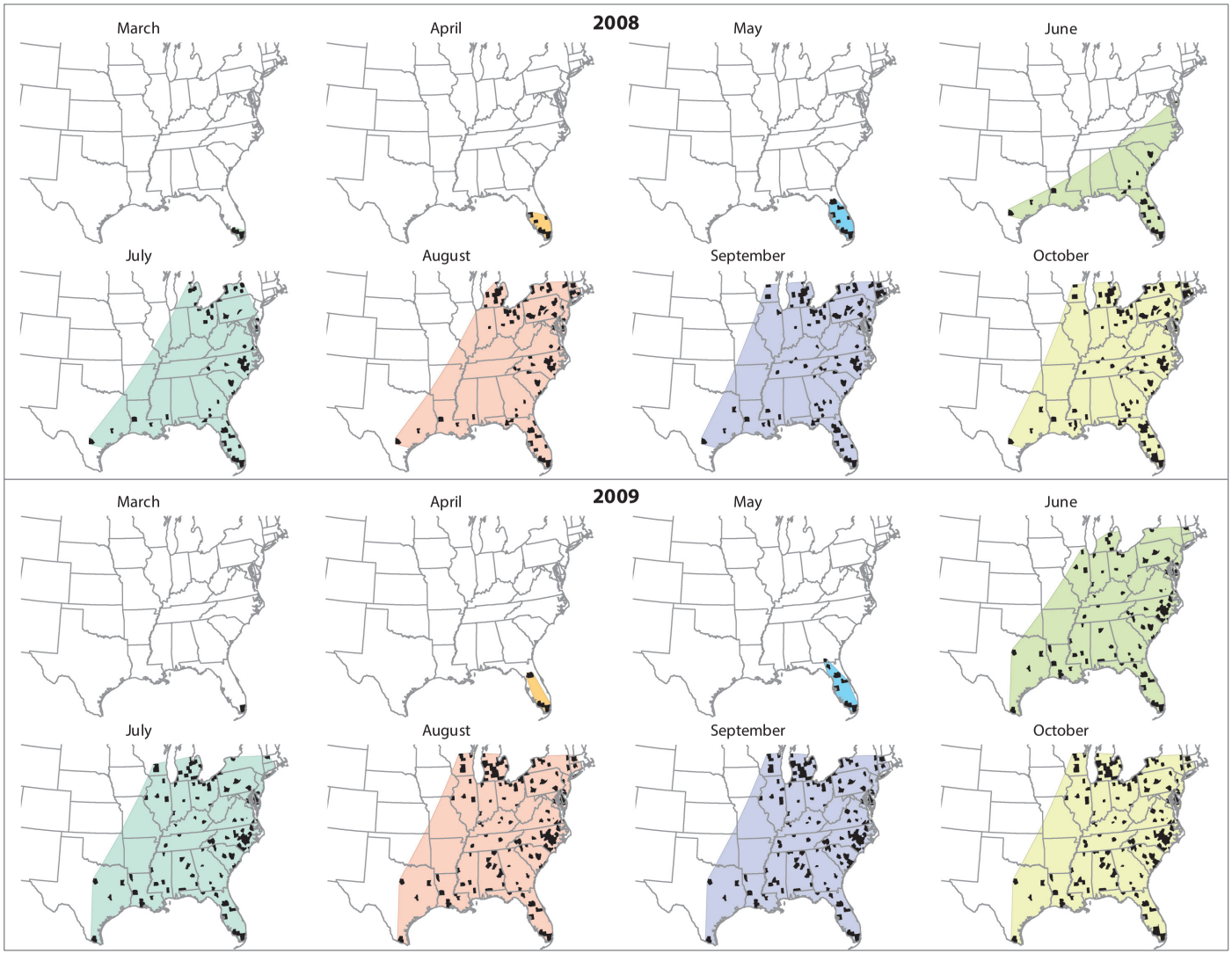

Figure 2

Isopleth maps depicting the spatial spread of cucurbit downy mildew in the United States during the 2008 and 2009 epidemics. The black fills represent the cumulative county-level disease reports in each year. Reports of the disease at leading edges of the epidemics were connected with straight lines each month and the resulting areas (*color shaded*) were used to calculate the area and extent of the epidemic.

the initial epidemic area is an important variable in determining the extent of subsequent spread of CDM as reported for other plant pathogens that exhibit long-distance dispersal (68). It is expected that reducing the size of initial CDM outbreaks in overwintering areas and implementing control measures immediately after inoculum incursion in non-overwintering locations should substantially limit the subsequent spread of the disease. Data from multiple years need to be analyzed to support the role of initial epidemic area in subsequent spread of CDM.

Models for Infection and Sporulation of *Pseudoperonospora cubensis*

Understanding environmental factors that influence infection and sporulation of the pathogen is the basis for timing CDM control measures such as fungicide applications (122). This is particularly important for CDM, where presently host resistance alone is insufficient and disease control relies heavily on fungicides. The optimum temperature for infection of cucurbits by *P. cubensis* ranges from 15 to 20°C (17), with a minimum leaf wetness duration of 2 h required for infection to occur (16). In the absence of moisture, the effect of other weather variables on disease development is limited (78). In recent studies, germination and infection of *P. cubensis* were reported to occur between 30 and 35°C (3, 71), which is a substantially higher range than previously reported. Highly aggressive strains of *P. cubensis* have also been associated with the resurgence of CDM in the United States. (23). These strains may have a higher cardinal temperature range than those strains prevalent prior to 2004. Strains of *P. cubensis* adapted to warmer temperatures can cause disease for a longer time during the growing season and thereby result in higher yield losses. Vanderplank (113) stated that increased aggressiveness would likely lead to increased fitness to survive. Thus, these recent strains might be expected to eventually replace most of the old strains. However, differences in latent period, lesion growth, and sporulation among these strains have not been determined.

Temperature and leaf wetness interact to affect the degree and extent of infection and sporulation of *P. cubensis*. Qualitative descriptions of this interaction have been proposed to describe disease development under field conditions (17). However, qualitative descriptions may not be accurate or useful over a wide range of temperature and leaf wetness combinations, and in most cases quantitative analyses are required. Quantitative models show that the effect of temperature on germination and infection is unimodal, with optimums of 15 to 17°C and 20 to 22°C, respectively (3), and the two variables increase in a sigmoidal fashion with increasing leaf wetness duration. These interactive effects have been described by a Weibull model, and in the presence of moisture temperature determines the rate and extent of infection by *P. cubensis* (3, 71). The interactive effects are also dependent on the cucurbit host, with the effect being characterized mainly by the level of host susceptibility to *P. cubensis* (71). As with other pathosystems (121), longer periods of wetness are required to achieve a specific level of disease severity on less susceptible compared with more susceptible hosts (71). Risk prediction charts based on the Weibull model have been generated to estimate the potential risk of infection of cucurbits by *P. cubensis* based on prevailing or forecasted temperature and leaf wetness duration (71). When inoculum is present, the prediction charts can be used in conjunction with spore dispersal models to identify locations of high risk for disease development based on forecasted temperature and leaf wetness duration along trajectories of sporangia transport. These charts would predict a high risk for cucumber but low risk for squash under the same combination of temperature and leaf wetness duration. In this case, a fungicide spray might be recommended only for cucumber but not squash. Given that growers tend to be risk averse, it is uncertain how crop-specific disease hazard warnings would be acted upon. It may be that disease forecasts based on the most susceptible hosts are a more practical decision support tool to control CDM.

AEROBIOLOGY

The probability that CDM will occur in a given field away from a source is directly proportional to the aerial concentration of viable spores in a field of susceptible hosts. This likelihood is determined by the dissemination of sporangia away from the source, a process that comprises three main parts: (*a*) reproductive rate of *P. cubensis* and carrying capacity of the source, (*b*) atmospheric turbulent transport and dilution, *T*, and (*c*) spore survival during transport, *S*. Thus, the concentration of viable spores, C_v, at a location away from the source can be summarized as follows (7):

$$C_v = Q_0 \times T \times S = P \times E \times T \times S, \quad 4.$$

where Q_0 is the amount of spores released in the air, which is a product of daily spore production, *P*, and the escape fraction *E*, which is the amount of spores that escape the canopy [daily total flux (F_D)] expressed as a fraction of *P*. The effects of *T* on atmospheric transport of spores have been reviewed extensively (e.g., see 5–7). Determinants of dissemination of *P. cubensis* sporangia, which are described in detail below, have been systematically incorporated in spore transport models to improve the efficiency of the CDM forecasting system (P.S. Ojiambo, unpublished results).

Sporangia Production and Escape

Spore production in a field varies widely during the day and depends on the weather, age of spore-producing lesions, and disease severity. Typical of most downy mildew organisms, aerial concentration of *P. cubensis* spores above the crop canopy exhibits a diurnal periodicity (**Figure 3**) with peak concentrations occurring between 0800 and 1000 h (36, 70). The pathogen is a prolific producer of spores and can produce up to 2×10^8 spores/ha in a day (70). Values of *P* are highest close to the canopy and decrease with increasing height above the canopy (**Figure 4**). The rapid decrease of *P* with increasing height above the canopy is due to an increase in wind shear and

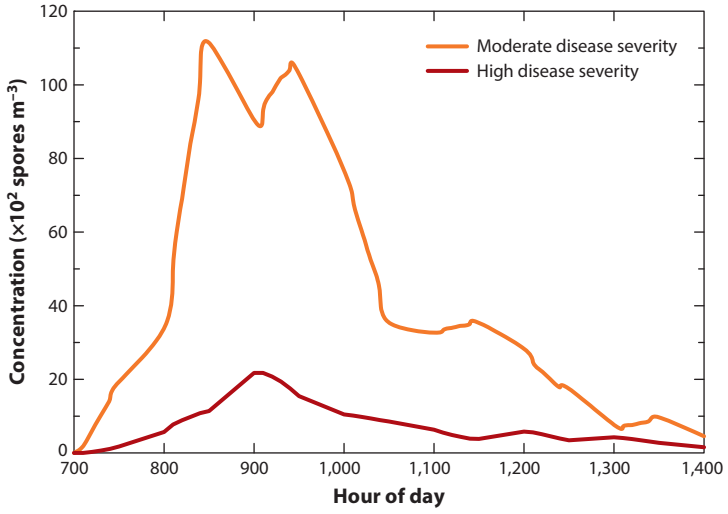

Figure 3

Diurnal pattern of release of *Pseudoperonospora cubensis* spores from a cucumber canopy during downy mildew epidemics. Spore concentrations were measured at 0.5 m above the canopy on August 25 and August 29, 2011 for moderate and high disease severity, respectively, at Clayton, North Carolina. Moderate and high disease severities represent 12% and 37% leaf area infected, respectively.

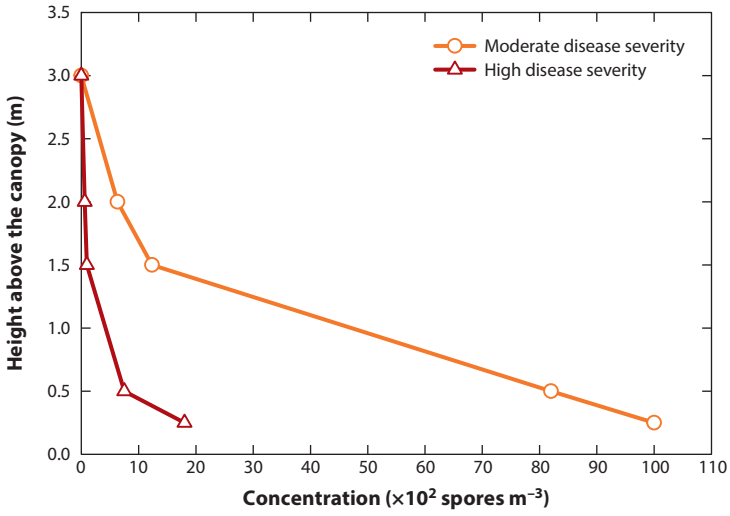

Figure 4

Vertical profiles of *Pseudoperonospora cubensis* spore concentration measured above a cucumber canopy during downy mildew epidemics. These profiles were measured on August 25 and August 29, 2011 for moderate and high disease severity, respectively, at Clayton, North Carolina, from 0700 to 1400 h. Moderate and high disease severity represent 12% and 37% leaf area infected, respectively.

turbulent diffusion (25), which reduce gravitational settling of spores. Similar dynamics in the vertical profiles of P above the canopy have also been reported for other oomycetes (8). The similarities in the general shape of P reflect an underlying generality in the physical laws that govern transport and dilution of airborne spores. Like with P, the variable F_D also follows a diurnal pattern (**Figure 5**), with maximum values at around 0900 h, which coincides with peak periods of P (70). Estimates of E range between 1% and 17%, indicating that a majority of spores produced in the canopy do not escape into the air above the crop. When the wind speed is at its peak, P is the main determinant of F_D, and hence E, and wind speeds of up to 3.6 m/s are sufficient enough to lift a large quantity of *P. cubensis* spores from the crop canopy (70).

Effect of Disease Severity on Sporangia Production and Escape

Disease severity at the source influences the source strength of *P. cubensis*, which directly affects the likelihood of pathogen transmission from a source to a neighboring field. For obligate plant pathogens such as *P. cubensis*, P and F_D increase with disease severity up to a certain threshold and decrease thereafter due to a reduction in healthy leaf tissue. Although the latter observation has been widely acknowledged, the relationship between disease severity and P or F_D was just recently quantified. Disease severity significantly affects P and E (70), with the two variables being high at moderate (~12%) disease severity (**Figure 3**). Variations in P and F_D are well described by a log-normal model (**Figure 5**) with 15% as the threshold above which P and F_D decrease with increasing disease severity (70). Most regional models use daily measurements of P at a source as the measure of inoculum source strength (50). Daily measurements of P are time consuming, labor intensive, and impractical for regional forecasting programs that rely on field surveys to delineate the geographic extent and the source strength. The predictable relationship between disease severity and P can improve the efficiency of region-wide aerobiology models, such as the CDM ipmPIPE model, which are highly dependent on knowledge of the geographic distribution

Source strength: the amount of spores produced in a field that is potentially available for transport to a neighboring field

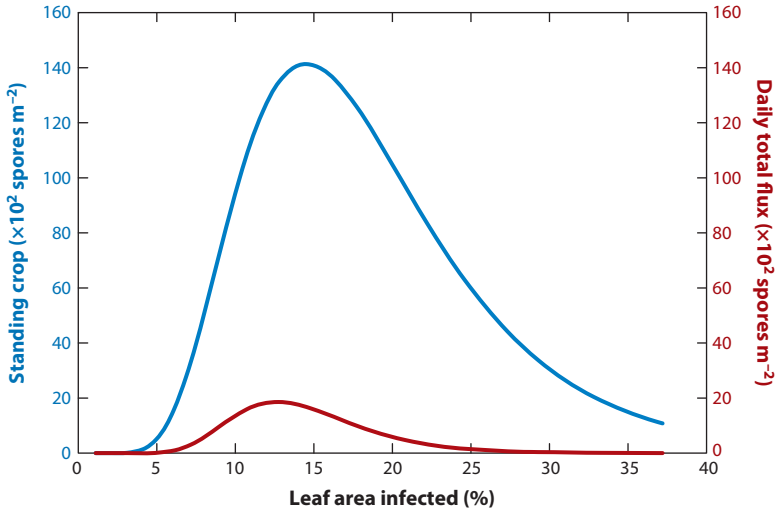

Figure 5

Relationship between disease severity and the number of *Pseudoperonospora cubensis* spores produced in a cucumber field (i.e., standing crop) and number of spores that escape the canopy (i.e., daily flux). These curves represent predicted values generated by fitting a three-parameter log-normal model to field data collected between August 12 and September 1, 2011 at Clayton and Clinton, North Carolina.

and intensity of P and F_D from infected canopies. Disease severity can also be a useful input variable in physical spore transport models, such as FLEXPART (102) or HYSPLIT (28), that are used to estimate F_D from a source.

Survival of *Pseudoperonospora cubensis* Sporangia

Sporangia are exposed to weather factors during transport from a source field to neighboring fields. For infection to occur in a field away from the source, spores must survive in the atmosphere for several hours during overcast or sunny skies. Solar radiation, temperature, and relative humidity can influence survival of oomycete sporangia (53). Studies conducted with *P. cubensis* indicate that temperature and relative humidity have a lesser effect, with solar radiation being the most important variable that affects sporangia survival (54). These results are similar to those reported for potato late blight, where solar radiation is the most important variable in survival of *Phytophthora infestans* sporangia (64). Deleterious effects of solar radiation on spores are primarily due to the UV-B spectrum (112). Total solar radiation has been found to explain the same degree of variation in survival of *P. cubensis* sporangia as does UV radiation (54). In *P. cubensis*, an exponential decay model best describes the effect of solar radiation on spore survival and survival is reduced by up to five-fold on sunny compared with cloudy days. For reasons that are not yet apparent, the same solar radiation dose on a cloudy day has a different effect on the viability of sporangia than on a sunny day. A working hypothesis is that the amount of active irradiance may be proportionally less on cloudy days than on sunny days (64).

The fraction of a cohort of spores (E_f) that survive after exposure to a given dose of solar radiation is usually estimated using an exponential decay function of the form

$$E_f = \exp(-1/I_c), \qquad 5.$$

where I_c is the critical dose that kills a fraction 1-e^{-1} (=63.2%) of the spores (5, 51). The variable I_c is equivalent to the lethal dose for chemicals and is a useful measure for comparing the effects of solar radiation on spore survival. Wide variations in I_c can indicate the likelihood of different dispersal distances for aerially transmitted plant pathogens. Among oomycetes, estimated values of I_c are 0.9 MJ/m^2 for *P. infestans* (64) and 2.4 MJ/m^2 for *P. tabacina* (86). In contrast, I_c for *P. cubensis* is estimated as 9.5 MJ/m^2 (54). Thus, if all factors are held constant, *P. cubensis* spores are expected to disperse and cause disease over a longer distance than are those of *P. infestans*. Pigmentation of spores is thought to be one factor that influences spore survival following exposure to solar radiation (103). Unlike sporangia of *P. infestans*, which are hyaline with thin walls, *P. cubensis* sporangia are dark brown and relatively thicker (118). Spores of *P. cubensis* are thus less sensitive to desiccation and solar radiation and survive longer than those of *P. infestans*, thereby increasing the potential for long-distance dispersal. Although tolerance to solar irradiance is greater in *P. cubensis* than *P. tabacina*, the overall dispersal potential is greater in *P. tabacina*, as described above, and this is due to other factors that influence the probability of long-distance dispersal and pathogen establishment.

POPULATION BIOLOGY

Pathogenic Variation

P. cubensis possesses a high degree of pathogenic and genetic plasticity. Reported hosts of the pathogen span 20 genera, with the genera *Cucumis*, *Cucurbita*, *Citrullus*, *Lagenaria*, *Benincasa*, and *Luffa* being among the most economically important (47, 89, 95, 116). Specificity among host species varies within *P. cubensis*, and pathotypes have been defined to distinguish host preference (59, 107, 108). Strains within a pathotype also vary in their level of aggressiveness. In the United States and Europe, variation is extremely high in populations in central and southern production regions (23, 58, 107). An extensive characterization of pathogenic variation has also shown a shift toward a higher number of virulence factors over time (58). Processes that drive variation are not well understood but may reflect local adaptation due to climatic factors that influence effective population size, heterogeneity of hosts at multiple spatial scales, and migration via long-distance dispersal (58, 81, 109).

Populations of *P. cubensis* are dominated by relatively few genetic clusters, many of which are shared among separate production regions, and states such as North Carolina and Florida have highly diverse pathogen populations (84). A recent study that evaluated the susceptibility of melon cultivars to *P. cubensis* reported that when disease severity differed between isolates from Michigan and South Carolina, higher levels of disease severity were more frequently associated with isolates from South Carolina (14). This observation tends to support the observation of greater diversity of *P. cubensis* in the southern United States (84). Diversity may be driven, in part, by host availability and more frequent incursion of inoculum from overwintering habitats. Generally, more diverse cucurbit hosts are present in the southern United States, which is also a presumed source of initial inoculum for more northern production regions in the United States. Pathogenic and genotypic diversity have important implications in the development of diagnostics and disease management strategies. Implementation of effective control measures for highly diverse pathogens like *P. cubensis* will require robust detection assays, as control is best achieved when implemented preventively or immediately after the first disease symptoms develop.

The downy mildew pathogen of hop *Pseudoperonospora humuli* is closely related to *P. cubensis*, and it is instructive to compare aspects of their biology. Unlike *P. cubensis*, pathotypes and races have not been described in *P. humuli* despite multiple attempts to delineate races (44, 87). In hop,

susceptibility to downy mildew is variable and resistance appears to be polygenic (42; reviewed in 87). Consequently, resistance to hop downy mildew seems to be durable, as evidenced by the stability of resistance in cultivars that have been produced in multiple environments in the United States and Europe for nearly a century. Given that physiological specialization in *P. cubensis* is manifested among species and genera within the Cucurbitaceae, an intriguing but unexplored area is whether physiological specialization similarly occurs in *P. humuli* beyond *Humulus lupulus*. If confirmed, this could in part explain conflicting reports of *P. humuli* infection of cucurbit species (63, 91).

Lineages and Mating System

The proposal by Choi et al. (15) to reduce *P. humuli* to a taxonomic synonym of *P. cubensis* based on morphological traits and internal transcribed spacer (ITS) sequences has been largely rejected. The ITS region offers too little resolution of species boundaries (115) and does not consistently differentiate the two species, particularly among isolates derived from Asia (61, 63, 94). Several of the morphological traits used by Choi et al. (15) are also questionable for phylogenetic inference within the genus, given the inability to disentangle morphological divergence from variation due to the host matrix (88, 90).

The resurgence of CDM in the United States suggests a possible introduction of a new pathogen genotype into the country (23), possibly from Asia (88). Recently, it was shown that *P. cubensis* can infect cucurbit seed (20), raising the possibility of dissemination of novel strains via seed. It is possible, therefore, that the pathogen may have been introduced in the United States or Europe via infected seed even though seed transmission appears to be rare (20). Populations infecting cucurbits have been characterized and the pathogen genetic structure is shaped mainly by host and geographical location, with some overlap of genetic clusters among these factors (84). There is also significant diversity within *P. cubensis*, and strains frequently associated with cucumber are genetically different from those infecting other hosts (84). The presence of two lineages in the United States, with one being more frequently associated with cucumber, has been confirmed using whole-genome analyses (107). These findings are consistent with suggestions by Runge & Thines (90) that a possible cryptic species or subspecies exists within *P. cubensis*. However, caution is needed when inferring new species from available data due to geographic and host-level population differentiation. Species boundaries are further complicated because mating types of *P. cubensis* appear to have distinct host preferences (19, 107), which can also result in sampling bias due to divergence of lineages among cucurbit hosts.

Phylogenetic analyses conducted by Runge et al. (88) may point toward a recent host jump from hop to cucurbits, possibly via an ancestral pathogen on *Humulus japonicas*. Host range studies have been variable when hop and cucurbits are challenged with *P. cubensis* and *P. humuli*, respectively (44, 63, 91). In two studies, *P. cubensis* was able to cause limited infection on hop under controlled conditions (63, 91), but no symptoms or signs of infection were observed on Japanese hop (61). Although these studies suggest that *P. cubensis* can potentially infect hop, low levels of compatibility in cross-inoculations suggest that each species is best adapted to its primary host. Further, evidence based on genetic markers does not indicate occurrence of either species on the other host (63). Inference of gene flow between the two species will require a large number of loci and more powerful tools for genetic analysis (38).

Reports of oospore formation in nature are available (57), but until recently these reports were rare. Cohen & Rubin (18) reported *P. cubensis* as heterothallic and observed fertile oospores in *Cucumis sativus* and *Cucumis melo*, but very few or no oospores were observed in other cucurbits. This suggests that host matrix is an important factor in oospore formation (19). Recent reports

(19, 107) in which the A1 mating type was observed to be exclusively associated with cucumber, whereas the A2 with other cucurbits support the role of host matrix in oospore formation. It is plausible that the A1 mating type may also have been responsible for the resurgence of CDM in the United States in 2004 given that epidemics during the resurgence were primarily associated with the breakdown of resistance in cucumber (46, 47).

The A2 mating type has been reported in China (21) and the United States (106). Viable oospores of *P. cubensis* have been reported in China, and they appear to be epidemiologically important (124). This finding, if verified in other regions, has very important implications for disease management. Current CDM management approaches in Europe and North America presume that the pathogen can survive only in living host tissues. Oospores have been considered to be of limited importance, and most attention in disease prediction and management is given to long-distance dispersal of inoculum from overwintering sources. Indeed, the basic premise of the CDM forecast system rests on this assumption (74). The role of oospores in CDM epidemiology needs to be determined because of their potential to significantly complicate disease management efforts. Although oospores may be of local importance, they have the potential to disseminate new or virulent pathotypes. It is believed that sexually reproducing pathogens have greater potential to overcome host resistance because of variability generated by recombination (62). Even in the apparent absence of the sexual stage, lifestyle characteristics of *P. cubensis* enable the pathogen to quickly generate new genotypes (e.g., 58). Greater diversity and persistence of novel genotypes may further hasten breakdown of host resistance, resulting in difficulties in controlling CDM.

Mating studies with *P. cubensis* and *P. humuli* could be helpful in deducing whether sexual recombination and gene flow may occur between these pathogens. In *P. humuli*, oospores are routinely observed in diseased host tissue, especially hop cones (12, 22, 87). Rybáček (93) stated that *P. humuli* is heterothallic, although to our knowledge, no studies on mating system exist in primary literature to support this observation. Recent work indicates that the mating system of *P. humuli* is more complicated than simple heterothallism. Inoculations conducted with single-sporangium isolates of *P. humuli* yield copious oospores (D.H. Gent, unpublished results), although the viability and infectivity of oospores still remains unknown. There have been some reports of successful germination and infection by oospores of *P. humuli* (4, 12), although direct evidence for their role in disease development in the field is lacking (87).

GENOMICS

Significant advances in understanding the population biology of *P. cubensis* have been possible due to the sequencing of the pathogen's genome (96). Polymorphic simple sequence repeats markers have been developed from the genome (117) and used to quantify temporal dynamics of populations in Michigan and Ontario, Canada (69). In Michigan, one genotype was predominant in some counties throughout the growing season, whereas shifts in predominant genotypes were observed in other counties. Temporal shifts in the genetic structure could be due to dispersal of new genotypes during the season from the southern United States or from greenhouses in Canada. Diversity of genetic clusters was also high in Michigan and all genetic clusters found in Canada were present in Michigan (69, 84).

The *P. cubensis* genome has allowed for gene expression analyses to characterize host-pathogen interactions (2, 97). Preliminary work identified 61 sequences containing RXLR or QXLR motifs, characteristic of oomycete effectors (110). Further analysis identified 271 effectors containing the RXLR or QXLR motif (96), and 2,383 genes that are differentially expressed in sporangia versus lesions in cucumber leaves (97). Differential gene expression is also evident in infected versus healthy leaves (2). These studies have provided a foundation in understanding

RxLR: oomycete effector protein that shares a common N-terminal amino acid motif; represents arginine, any amino acid, leucine, or arginine

QxLR: oomycete effector protein that shares a common N-terminal amino acid motif; represents glutamine, any amino acid, leucine, or arginine

P. cubensis–cucumber interactions. Given the wide host range, whole-genome sequencing of additional strains will be vital in characterizing pathogen diversity and host-pathogen interactions (107). Efforts to sequence more strains from diverse cucurbit hosts and the sister species *P. humuli* are underway (120) and will provide a rich resource to address questions about host specificity, adaptation, and breeding for durable resistance. An immediate outcome of this work has been the identification of genetic markers conserved in the species that may be useful in diagnostic assays and inoculum detection systems (33, 120). Preliminary analyses indicate bifurcation of *P. cubensis* and *P. humuli* based on mitochondrial DNA and transcriptome data from their primary hosts, providing further evidence of population differentiation by host (87, 88, 107).

Species closely related to *P. cubensis* can complicate species-specific molecular detection of inoculum from the environment (e.g., spore traps), especially in regions where crops affected by related pathogens are produced. Cucurbits and hop are grown in the same regions in the eastern United States, and *Plasmopara australis* also causes downy mildew in wild cucurbits in some states in the United States (79, 82). Although reports of *P. australis* in the United States are limited, the wild hosts it can infect are weeds common in the southern United States. Nonetheless, the phylogenetic relationship between *P. australis*, *P. cubensis*, and *P. humuli* and its impact on developing species-specific molecular detection of *P. cubensis* are unclear. These phylogenetic relationships will need to be clarified to facilitate the development of species-specific diagnostics (105, 120).

ASPECTS OF DISEASE MANAGEMENT

Host Resistance

Efforts to manage CDM using host resistance began shortly after the pathogen was described on cucumber (11). Gains have been achieved over the years, with the notable form of resistance associated with introgression of the *dm* gene from PI 197087 into the cultivar Poinsett (114). The *dm* gene was broadly deployed in cucumber and provided high levels of CDM resistance for nearly four decades. However, *dm* is no longer able to confer sufficiently high levels of resistance but can contribute to disease reduction when deployed with other resistance factors (13). This suggests that *dm* may have some residual effects on host susceptibility to virulent strains of the pathogen or that other genes may be associated with CDM resistance (123). Other resistance loci have also been introgressed into cucumber cultivars (45), but their ability to control CDM to levels equal to those observed before the resurgence of the disease is unknown (see sidebar, Durable Resistance to Downy Mildews).

DURABLE RESISTANCE TO DOWNY MILDEWS

Durable resistance is the ultimate sustainable disease management approach; however, identifying and then incorporating this trait into cultivars remains a complex process. Inheritance studies indicate that multiple recessive loci confer resistance to downy mildew in cucumber, whereas others control susceptibility (27). Advancing our understanding about pathogen genetic diversity, population dynamics, and genetic determinants of virulence and pathogenicity is imperative to enable durable resistance in the future. It seems likely, but not necessarily required, that durable resistance will involve multiple genetic factors and perhaps loss of genes that confer susceptibility. Breeding for lack of susceptibility has been postulated to confer more durable resistance than breeding for resistance (80). Concepts related to pathogen fitness penalty and loss of effectors essential for virulence need to be more fully explored in the downy mildews to better predict durability of resistance.

Cucurbit genomic resources are steadily becoming available and when combined with an improved understanding of determinants of pathogenicity and virulence may significantly accelerate breeding efforts. In recent years, reference genomes of cucumber (48), melon (31), and watermelon (39) have been published, and other cucurbit genomes are being sequenced. In addition to cultivars used to generate reference genomes, other cucumber (83) and watermelon (39) cultivars have been resequenced. The latter has increased our understanding of host genetic diversity and allowed for identification of markers for genomics-assisted breeding. However, the challenge of combining desirable horticultural traits with CDM resistance still persists (45). New genome-editing technologies such as clustered regularly interspaced short palindromic repeats (CRISPRs) (100) could provide a way to transfer resistance to preferred cultivars. However, limited public acceptance of genetically modified crops implies that resistant cultivars will likely be developed only through traditional breeding methods in the near-term.

Detection and Elimination of Primary Inoculum

Given the importance of source strength in the dispersal potential and epidemic extent of *P. cubensis*, prediction of conditions favorable for inoculum dispersal is critical for effective disease management. The CDM ipmPIPE has been instrumental in predicting disease onset (74). The structure and information content of disease hazard warnings issued by the CDM ipmPIPE are characteristic of predictive systems that typically have sustained use in disease management (32). At the field scale, direct detection and estimation of airborne inoculum have also found a role in disease hazard warnings and scheduling of fungicide applications (33, 36, 37). In Michigan, sporangia characteristic of *P. cubensis* have been detected within days of field plantings (37). There are several potential explanations for this observation. It is possible that inoculum dispersal does not limit epidemic development but rather that host availability may be the limiting factor, and inoculum levels increase once host tissue is available. Alternatively, it is also plausible that local sources of inoculum are broadly dispersed and contribute to early outbreaks. Disentangling the relative contribution of various sources of primary inoculum is an active area in CDM research.

Wild cucurbits and weedy hosts of *P. cubensis* that may facilitate overwintering of the pathogen have also been identified in the United States (116) and Europe (89). Greenhouses with year-round cucurbit production could be important reservoirs of the pathogen by providing a green bridge for overwintering and early infection of field-grown crops (95). Perennation of *P. cubensis* in greenhouse crops may significantly affect disease control in the field because the overwintering of the pathogen would be almost certain and there is potential to spread strains with complex virulence and fungicide resistance patterns as new crops are planted. Although seed transmission of *P. cubensis* is rare (20), seed testing and treatment should be encouraged to limit potential introduction of the pathogen through seed.

Scaling Disease Management Systems

Disease management can be integrated and scaled at multiple, nested levels, from individual fields to farms, landscapes, and ecoregions (49). Given the potential for long-distance dispersal, scaling CDM management to the highest level in the hierarchy (regional and even continental scales) may be necessary for effective disease control at lower spatial scales (66, 99). In the United States, host types and their susceptibility to *P. cubensis* populations varies on a regional scale (14). Cucumber, squash, and pumpkin are the primary cultivated hosts in the northeast, whereas pumpkin, melon, cucumber, squash, watermelon, and gourds are common hosts in the southeast. Pathogen populations affecting different hosts may differ because of differences in crop diversity

(14, 55, 84), and more field research and simulation studies are needed to quantify the impact of landscape heterogeneity and host diversity on CDM management strategies.

The size and population structure of the initial outbreaks of *P. cubensis* CDM in southern latitudes are predicted to be important in the subsequent development of CDM and the extent of the epidemic. Thus, reduction of overwintering inoculum at the very early stages of disease outbreak could substantially reduce disease development at the landscape level (29, 99). This concept of scaling and its impact on disease management has largely been neglected in botanical epidemiology but is gaining considerable interest (98). The fundamental challenge to scaling IPM may be the cooperation among growers and other organizations with disparate disease management goals. For instance, growers in southern latitudes may have little incentive to alter their planting times, deploy different fungicides, or make more fungicide applications simply to limit pathogen dispersal potential. Nonetheless, fungicide use, host resistance deployment and fungicide resistance management likely have a scalar relationship that is manifested at multiple levels.

Chemical Control of Downy Mildew

Fungicides remain integral to the control of CDM due to the lack of sufficient resistance in cultivars or effective cultural strategies. Early and frequent fungicide applications are required to protect the crop when environmental conditions favor disease development (95). In 2006, the global sales volume of fungicides for oomycete control was approximately $1.2 billion, with 12% being the proportion for *P. cubensis* on cucurbits (35). During periods of weather favorable for disease development, growers can apply up to 11 sprays in a growing season in an effort to control CDM (76).

Timing of the first and subsequent sprays is critical in limiting disease progress. Late season plantings can be exposed to inoculum at the cotyledon stage and a delay in fungicide application can result in complete crop loss (47). Growers must continuously weigh the threat of sporangia influx into their region, assess weather conditions suitable for disease development, and estimate the cost of fungicide sprays. To support their decision-making process, the CDM ipmPIPE system allows growers to track in near real time where CDM has developed and, indirectly, the movement of *P. cubensis* in the eastern United States (74). Linking disease hazard warnings from the CDM ipmPIPE system with current and forecasted disease risks and sporangia measurements within individual fields would be desirable.

Resistance of *P. cubensis* to phenylamide and strobilurin fungicides had been noted in other countries (34, 52, 85) prior to CDM resurgence in the United States. The pathogen was reported to be resistant to mefenoxam in the United States in 1987 (65), and strobilurin and carboxylic acid amide fungicides are no longer recommended for CDM in the United States (77). Most recently, a reduction in the field efficacy of fluopicolide, a pyridinylmethyl-benzamide fungicide, was reported (1, 41, 56). Previously, fluopicolide had been considered the most effective product for CDM control (76).

The high potential of *P. cubensis* to develop resistance to fungicides requires a continuous introduction of products with new modes of action (92). However, as the pathogen develops resistance to labeled products, fewer fungicides become available for inclusion in a spray program, which could further increase the likelihood that the pathogen will develop resistance. As a result, chemical control may be unsustainable as a stand-alone practice, particularly in cucumber, which is particularly susceptible to CDM. In the long-term, disease management will likely be achieved through a combination of host resistance and well-timed fungicide applications driven by real-time pathogen detection to ensure durability of fungicide activity and genetic resistance (47).

Monitoring fungicide resistance in major production regions is critical in providing real-time warnings if a fungicide is no longer effective, thereby averting a potential disease control failure (47,

95). Further, stopping the use of fungicides that are ineffective due to resistance reduces selection pressure. This might allow for reintroduction of the fungicide once pathogen populations return to sensitivity due to resistance's cost to pathogen fitness.

CONCLUSION AND APPLICATION OF CONCEPTS TO OTHER DOWNY MILDEWS

Considerable progress has been made in understanding the biology, epidemiology, and management of CDM in the past decade, but much more remains to be learned. For example, what are the genetic determinants of pathogenicity and host range in *P. cubensis*? How can a basic understanding of pathogenicity practically inform and influence breeding approaches for durable resistance? What is the contribution of locally produced inoculum to epidemic development relative to inoculum introduced via long-distance dispersal? When and how should chemical control measures for disease control and fungicide resistance management be best deployed? How can host resistance and other control measures be deployed most effectively on an area-wide basis? And, ultimately, can we develop sustainable disease management approaches?

Beyond the immediate impacts for the CDM pathosystem, possibly one of the most significant accomplishments from the recent body of research and extension work has been the scaling of research at multiple levels. The concept of ecological scale is important but somewhat underappreciated in plant pathology (98, 111). Life-cycle characteristics of *P. cubensis* lead to scaling of epidemic processes and therefore, necessitate understanding and integration of processes at the molecular, field, and landscape levels to make informed management decisions. These processes influence successful use of host resistance, the timing and extent of disease outbreaks, turnover of pathogen genotypes in a population, and dissemination of strains that are resistant to fungicides. The availability of long-term data sets collected at a geographic scale appropriate to capture these processes has been essential to predict and efficiently limit disease outbreaks. A similar need exists in other downy mildew pathosystems. A salient point from the CDM system is that conditions of the initial outbreak can have substantial impacts on epidemic development, a concept that could help shape management efforts in other downy mildews.

The CDM ipmPIPE has provided a platform to demonstrate the importance of research and extension capacity and the integration of human resources needed to effectively address downy mildew problems (74). The urgency of the CDM pandemic and the scope of problems to be solved extend well beyond what can be accomplished by one or a few laboratories, as is lucidly illustrated in the CDM ipmPIPE system (47). The essential requirement for this system is the wide deployment of standardized sentinel plots and commercial fields that match the scale of dispersal of the pathogen. The entire system rests on research and extension capacity because without a network of people the system is defunct. At the most basic level then, successful management of CDM and other downy mildews depends on the capacity of established research and extension programs and their relationships with growers and other clientele (47, 101).

SUMMARY POINTS

1. CDM is an important disease of cucurbits worldwide. In North America, breeding efforts in the 1950s and 1960s were foundational for successful management of the disease over multiple decades. Epidemics of CDM in 2004 and thereafter have occurred on previously resistant cultivars and have fundamentally changed disease management efforts and cucurbit production.

2. As *P. cubensis* is not known to survive in the field in temperate climates, annual introduction of the pathogen by means of long-distance dispersal is a key attribute of epidemic development. A network of sentinel plots and/or regular monitoring of commercial fields have been crucial aspects of the CDM ipmPIPE system. This system has been instrumental in predicting the risk of disease outbreaks in the eastern United States.
3. Prediction of pathogen dispersion is the most uncertain feature within the CDM ipmPIPE prediction framework and is influenced primarily by inoculum density in source regions, sporangia survival during transport, and host availability. Spatiotemporal studies suggest that infection of cucurbits by *P. cubensis* is an outcome of a contagion process, and factors such as host planting patterns and spore dispersal that occur on a large spatial scale facilitate disease spread on a regional scale. The size and population structure of initial outbreaks of *P. cubensis* in southern latitudes are predicted to be primary determinants of disease development and epidemic extent.
4. CDM outbreaks in northern latitudes, such as Michigan, could be due to other inoculum sources like greenhouses within the region. The epidemiological significance of local sources of inoculum warrants further investigation.
5. *P. cubensis* possesses a high degree of pathogenic and genetic plasticity, which complicates disease prediction, breeding efforts, and development of durable disease management systems. Whole-genome sequencing of additional strains will be vital in characterizing pathogen diversity and host-pathogen interactions, as well as in developing new detection and management tools.
6. Life-cycle characteristics of *P. cubensis* lead to scaling of epidemic processes and necessitate understanding and integration of processes at the molecular, field, and landscape level to make informed management decisions. At present, disease management relies heavily on regular use of fungicides, which may be unsustainable. Long-term management efforts likely will involve integration of limited use of fungicides, host resistance, and novel decision aids.
7. The past decade of research and progress made toward management of CDM demonstrates the utmost importance of research and extension capacity, and of the integration of human resources to effectively address downy mildew problems.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review. The use of trade, firm, or corporation names in this publication is for the information and convenience of the reader. Such use does not constitute an official endorsement or approval by the United States Department of Agriculture or the Agricultural Research Service of any product or service to the exclusion of others that may be suitable.

ACKNOWLEDGMENTS

We thank David Christie and Roger Magarey from the NSF Center for Integrated Pest Management at North Carolina State University for their help with generating the isopleth maps for cucurbit downy mildew epidemics. We also thank Chris Smart (Cornell University) and Walter

Mahaffee (US Department of Agriculture) for a critical review of this article prior to submission. We thank the collaborators of the Cucurbit Downy Mildew ipmPIPE project for their efforts in monitoring and reporting of disease outbreaks within their states.

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Annual Review of Phytopathology

Volume 53, 2015

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Errata

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