Effects of precipitation, heat, and drought on incidence and expansion of coccidioidomycosis in western USA: a longitudinal surveillance study

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Summary

Background Drought is an understudied driver of infectious disease dynamics. Amidst the ongoing southwestern North American megadrought, California (USA) is having the driest multi-decadal period since 800 CE, exacerbated by anthropogenic warming. In this study, we aimed to examine the influence of drought on coccidioidomycosis, an emerging infectious disease in southwestern USA.

Methods We analysed California census tract-level surveillance data from 2000 to 2020 using generalised additive models and distributed monthly lags on precipitation and temperature. We then developed an ensemble prediction algorithm of incident cases of coccidioidomycosis per census tract to estimate the counterfactual incidence that would have occurred in the absence of drought.

Findings Between April 1, 2000, and March 31, 2020, there were 81 448 reported cases of coccidioidomycosis throughout California. An estimated 1467 excess cases of coccidioidomycosis were observed in California in the 2 years following the drought that occurred between 2007 and 2009, and an excess 2649 drought-attributable cases of coccidioidomycosis were observed in the 2 years following the drought that occurred between 2012 and 2015. These increased numbers of cases more than offset the declines in cases that occurred during drought. An IQR increase in summer temperatures was associated with 2·02 (95% CI 1·84–2·22) times higher incidence in the following autumn (September to November), and an IQR increase in precipitation in the winter was associated with 1·45 (1·36–1·55) times higher incidence in the autumn. The effect of winter precipitation was 36% (25–48) stronger when preceded by two dry, rather than average, winters. Incidence in arid counties was most sensitive to precipitation fluctuations, while incidence in wetter counties was most sensitive to temperature.

Interpretation In California, multi-year cycles of dry conditions followed by a wet winter increases transmission of coccidioidomycosis, especially in historically wetter areas. With anticipated increasing frequency of drought in southwestern USA, continued expansion of coccidioidomycosis, along with more intense seasons, is expected. Our results motivate the need for heightened precautions against coccidioidomycosis in seasons that follow major droughts.

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Introduction

Coccidioidomycosis is an emerging infectious disease caused by the inhalation of spores of the soil dwelling fungal pathogen belonging to the *Coccidioides* genus, which can become airborne through wind erosion or soil disturbance.[1] Infection can lead to a primarily respiratory illness that can last months or might progress to a chronic state in 5–10% of individuals.[1] In California (USA), age-adjusted incidence rates of coccidioidomycosis increased by nearly 8 times from 2000 to 2018, and more than tripled between 2014 and 2018.[2] The highest incidence of coccidioidomycosis in California occurs in the hot and arid southern area of the San Joaquin Valley, but the largest increases in incidence rates (>15 times increase from 2000 to 2018) have been observed in cooler, wetter regions along the coast and in the northern area of the San Joaquin Valley.[2] Changing climatic factors that influence the distribution of suitable *Coccidioides* habitat could have a major role in the expansion and rise of coccidioidomycosis in California.[3]

The emerging southwestern North American megadrought is intensifying, with the period 2000–21 ranking as the driest 22-year period in California since at least 800 CE.[4] Continued increases in drought frequency and severity are likely to continue under anthropogenic warming.[5] Between May, 2012, and October, 2015, California had one of its most severe droughts in recorded history, receiving less precipitation in 2013 than in any previous calendar year since records began.[5,6] The drought was exacerbated by record high temperatures[7]

Research in context

Evidence before this study

Coccidioidomycosis is a major cause of community-acquired pneumonia in the southwestern USA caused by inhalation of fungal spores of the *Coccidioides* genus. Since the 2000s, the incidence of coccidioidomycosis has increased more than 8 times and has undergone an expansion in geographical range, with the largest increases occurring in areas that have historically wetter and cooler conditions than those thought to be most suitable for *Coccidioides*. Among the most concerning climatic changes observed in the southwestern USA is the increase in drought frequency and severity, a trend that is likely to continue under anthropogenic warming. We searched for studies published in English up to February 21, 2022, with the terms "coccidioidomycosis AND drought" in PubMed and identified ten results, published between 1994 and 2021. Two of these studies examined drought as a predictor of coccidioidomycosis in multivariate models. One study hypothesised that the sharp increases in case counts observed between 1991 and 1993 (2·7–10·0 times higher than average annual counts observed from the beginning of 1980 to the end of 1990) was due to anomalously high precipitation in 1991–92 that followed over 5 years of drought. No studies that were identified attempted to determine the causal effect of drought on cases of coccidioidomycosis. We then searched for "coccidioidomycosis AND climate AND (precipitation OR rain OR temperature)" in PubMed, which identified 25 results. Although previous studies generally support the theory that alternating wet and dry periods enhance transmission, the role of these wet and dry periods (eg, the timing and duration for which they are associated with increased risk, and the magnitude of this effect) are inconsistent by model structures, geographical foci, and approaches to disaggregate seasonal trends and account for lagged effects of climate. The prevailing use of traditional linear models in previous studies prevents the generalisation of results to geographies with differing climates.

Added value of this study

In this study, we examined the relationships between temperature, precipitation, and incidence of coccidioidomycosis, including how the relationships varied across time periods and geographical areas, and the degree to which the effects of intra-annual climatic factors were modified by inter-annual climatic factors. We further estimated the causal effect of the droughts that occurred in California (USA) between 2007 and 2009, and 2012 and 2015, on the incidence of coccidioidomycosis across geographical areas, applying a non-parametric substitution-estimator (G-computation) approach to simultaneously describe space-varying, delayed, and non-linear effects. We found that wet winters followed by hot, dry summers increased transmission, with the largest increases occurring when multi-year cycles of dry conditions are followed by a wet winter. Incidence in arid counties was most sensitive to precipitation fluctuations, while incidence in wetter, coastal counties was most sensitive to temperature fluctuations. We found that drought temporarily displaced the transmission of coccidioidomycosis, suppressing cases in years that were characterised by drought conditions but increasing cases in years immediately following drought. Nearly 2650 excess cases of coccidioidomycosis were observed after the 2012–15 drought, which were attributable to the effect of drought on transmission. These excess cases more than offset the 2323 cases of coccidioidomycosis that were estimated to be averted during the drought period.

Implications of all the available evidence

This study provides the first evidence of a causal association between drought and an emerging infectious disease, and offers a comprehensive mechanistic examination of the role of meteorological factors and drought in the emergence and transmission of coccidioidomycosis in California. Our results are consistent with precipitation during winter and spring supporting the hyphal growth of *Coccidioides immitis*, and hot and dry summer and autumn (September to November) periods facilitating lysis of hyphae into singular spores that are amenable to wind dispersion. Our findings suggest the presence of limiting factors in the lifecycle of *Coccidioides* that vary by region. In arid regions, low amounts of precipitation could restrict growth. By contrast, in cooler and wetter regions, the limiting factors include insufficient heat to lyse the mycelia into individual arthroconidia or desiccate soils to facilitate dust emissions. Anthropogenic climate change is expected, with medium-high confidence, to increase the duration, intensity, and frequency of temperature-driven drought in California and other western states. Accordingly, incidence of coccidioidomycosis might continue to expand into historically wetter and cooler regions, such as coastal counties and northern San Joaquin counties in California. Beyond expansion, more intense seasonal increases in disease might be apparent following drought. Our results motivate the need to include drought monitoring for coccidioidomycosis surveillance and prediction. Health-care providers and people living in endemic regions should be aware of the heightened risk for coccidioidomycosis following drought. Future analyses should consider how the associations resolved in this study can inform predictions of the spatiotemporal distribution and seasonality of coccidioidomycosis under anticipated climate regimes in the decades to come.

See Online for appendix

and was preceded by a less severe drought spanning March, 2007, to November, 2009 (appendix p 12).[8] Although public records from as early as 1980 showed that statewide incidence of coccidioidomycosis was lowest during periods of drought and highest in years immediately following periods of drought,[9,10] the causal effect of drought on the incidence of coccidioidomycosis has yet to be estimated.

Precipitation and temperature are both factors driving drought occurrence that co-vary with the geographical range of *Coccidioides* spp.[3] Periods of precipitation are thought to facilitate the hyphal growth and sporulation of *Coccidioides*,[11,12] and hot and dry periods cause the hyphae to autolyse, releasing infectious, heat-tolerant spores termed arthroconidia, and permitting dispersal of spores from desiccated soils.[13–15] Previous studies have reported that the associations between antecedent precipitation and transmission of *Coccidioides posadasii* in Arizona are delayed by as much as 2–3 years,[13] but no studies have examined whether antecedent conditions modify the influence of more recent meteorological effects in the months leading up to transmission. In this study, we aimed to estimate the immediate and delayed effects of temperature, precipitation, and drought on the incidence of coccidioidomycosis. We compared these effects by region to arrive at new insights as to why California has observed substantial increases and geographical expansion in incidence of coccidioidomycosis since the 2000s.

Methods

Data

We obtained data on coccidioidomycosis cases among California residents with an estimated date of disease onset between April 1, 2000, and March 31, 2020, from the California Department of Public Health reportable disease surveillance system. We matched 95% of patients to a census tract on the basis of reported residence. For each census tract, we aggregated the total number of cases reported each month, assigning patients to the month indicated in the surveillance record for estimated disease onset. We also summarised information for total precipitation, average temperature, soil texture, proportion of ground surface that is impervious, and elevation at the census tract and monthly scale (appendix pp 2–3). We linked aggregated case counts to climate data by census tract and month.

To minimise exposure misclassification bias associated with the assignment of cases to their census tract of residence, we restricted the study region to areas of known endemic transmission, limiting misclassification from travel-associated cases. We defined the study region to include 14 counties or sub-counties (herein after referred to as counties) where cumulative cases exceeded 500 over the study period and mean annual incidence exceeded ten cases per 100 000 residents (figure 1A; appendix p 10). Because the Sierra Nevada and San Emigdio-Tehachapi mountains produce strong climate gradients within the endemic counties of Kern, Fresno, Madera, Tulare, and Los Angeles, we split each into two sub-counties along a 500-metre elevation isocline and applied our inclusion criteria to each of the sub-counties. Both the areas on the low and high elevation side of the isocline in Kern County met the inclusion criteria, whereas only the lower elevation, western area of Fresno, Madera, and Tulare Counties, and the higher elevation, northern area of Los Angeles County, met the inclusion criteria.

Distributed-lag non-linear regression models

Associations between the incidence of coccidioidomycosis and temperature and precipitation were estimated using a meta-analytic approach for estimating non-linear, delayed effects across spatial locations.[16] We restricted this stage of our analysis to patients with an estimated disease onset between September and November, when most cases (33%) are typically reported in California. As the effect of seasonal and lagged climatic factors might vary by season of disease onset,[9,13] restricting the analysis to these months enables a clearer identification of the effect of climate in distinct seasons while improving comparability of our results with previous results.

We first estimated county-specific associations between lagged monthly average temperature and total precipitation and monthly incidence using distributed-lag generalised additive models.[16] Model details are included in the appendix (pp 3–4). We used monthly cases per census tract as the outcome variable and the log of each census tract's population as an offset term so that model coefficients reflected logged incidence rate ratios (IRRs). The primary exposure variables were lagged total precipitation and mean temperature. These variables were modelled with natural cubic spline functions of smoothed 3-month averages, with lags spanning 1–36 months before the estimated date of onset. We included a natural cubic spline for soil type (percent sand) and year, the latter of which enabled our exploration of shorter-term climate associations by controlling for reporting and other long-term secular trends not due to climate.[17]

We pooled estimates of county-specific IRRs using a fixed-effects meta-analysis.[16] We examined the overall shape of the spline representing the exposure–response relationship between precipitation and temperature with incidence at each of the 36 monthly lags. We identified the 25th and 75th percentiles of precipitation or temperature for the lagged months included in a 12-month cycle (eg, a lag of 1 month corresponds to the period between August and October), and calculated the IRR per IQR increase in temperature or precipitation, keeping other factors fixed. We assessed factors explaining heterogeneity in the temperature-incidence and precipitation-incidence relationships across counties by extending the fixed-effects meta-analysis to include meta-predictors of county-level information (eg, median county mean daily temperature). To examine the potential modification of the effect of recent (ie, within the past year) precipitation by antecedent conditions (lagged by over 1 year), we multiplied the basis function for the cubic spline on precipitation by a binary indicator for whether or not the census tract had a drier than average winter in the 2 years before the estimated date of disease onset, 3 years before the date of disease onset, or both. All statistical analyses were done in R (version 3.3.1) using the splines and dlnm package for fitting distributed-lag generalised additive models and the mvmeta package for doing fixed-effect meta-regression modelling.[16]

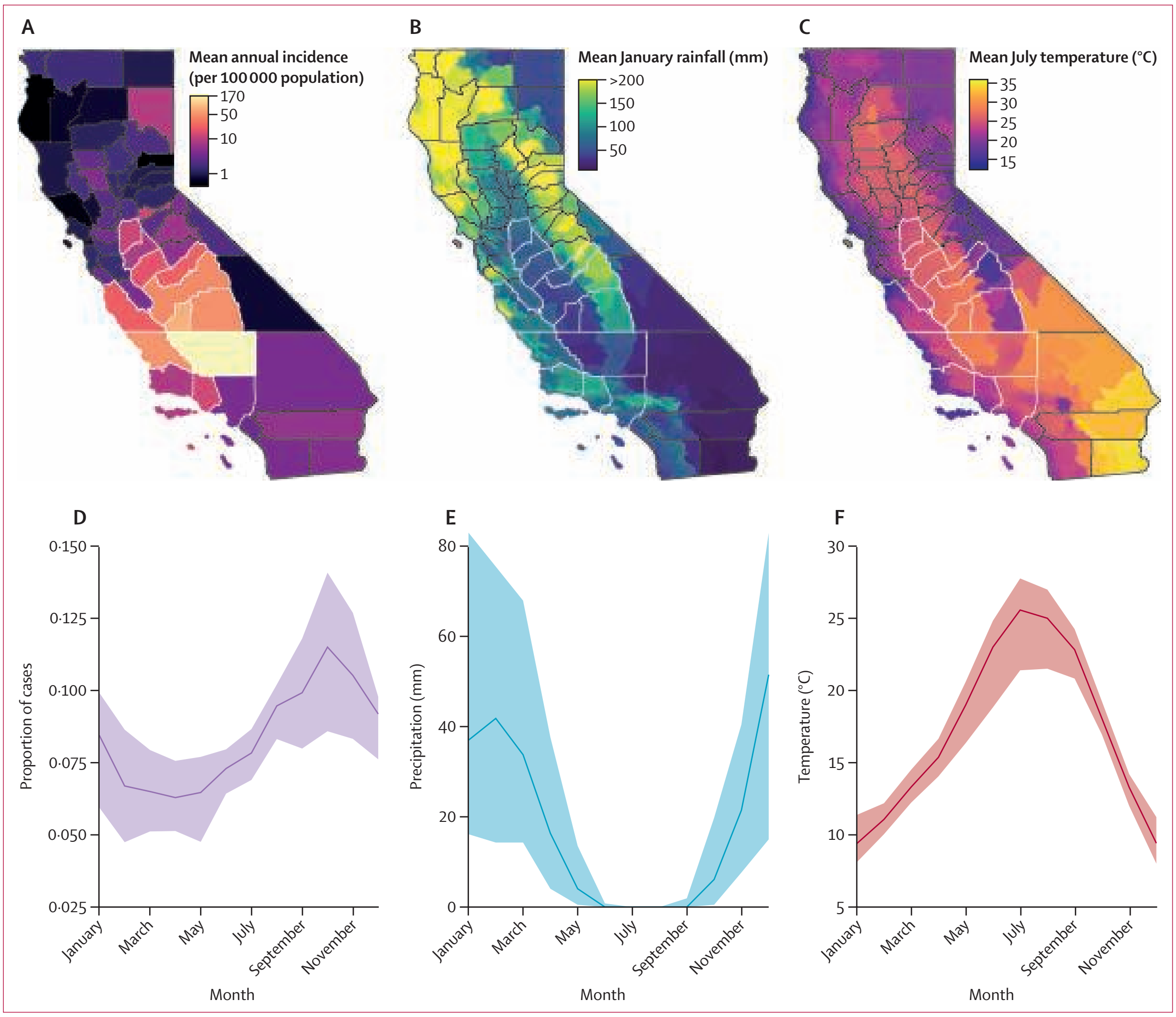

Figure 1: **Spatial and seasonal trends in coccidioidomycosis incidence, precipitation, and temperature**

(A) Mean annual incidence of coccidioidomycosis between the years 2000 and 2020. Counties outlined in white were included in our analyses. (B) Mean total monthly precipitation during January between the years 2000 and 2020. Counties outlined in white were included in our analyses. (C) Mean daily temperature during July between the years 2000 and 2020. Counties outlined in white were included in our analyses. (D) The mean (dark line) and IQR (shaded area) of the proportion of annual cases with an estimated date of onset per month between the years 2000 and 2020 in the study region. The median (dark line) and IQR (shaded area) of monthly total precipitation (E) and mean daily temperature (F) between the years 2000 and 2020 in the study region.

Ensemble model

We estimated cases of coccidioidomycosis attributable to, or averted because of, major droughts in California between April 1, 2000, and March 31, 2020, using an ensemble modelling approach to predict incidence under counterfactual scenarios reflecting the absence of drought.[18,19] Because our target parameter was total estimated cases attributable to drought (rather than IRRs; appendix p 2), for this stage of the analysis we examined incidence throughout the entire year, rather than restricting incident cases from September to November. For each county, we modelled monthly cases per census tract using multiple candidate prediction algorithms that included: generalised linear models with increasing complexity with respect to variables and interaction terms; generalised additive models; and random forest[20] (appendix pp 4–7). Predictors varied by algorithm, but could include season, year, soil texture, elevation, percent impervious surface, total lagged monthly precipitation, and lagged mean temperature. We calculated the sum of squared errors for each algorithm using leave-out-one-year cross-validation. We then generated an ensemble prediction by generating a weighted average of candidate model predictions in which the weights were derived using non-negative least squares and were inversely associated with their out-of-sample prediction error.

Agricultural drought is defined by lack of soil moisture, attributable to low precipitation or high temperature.[21] We used a simple substitution estimator (G-computation)[19] to calculate the expected incident cases in census tract i in month t with observed covariates, $W_{i,t}$, and the primary exposure, $A_{i,t}$, set to either observed or counterfactual values for lagged rainfall and temperature. For the counterfactual scenario that reflected the absence of drought, we deterministically set any monthly average temperature higher than the historical average and any total monthly precipitation below the historical average to their monthly county-level means during the two droughts. We summed across specific time periods and across all census tracts in a county to estimate the number of expected cases in a county over a time period.

$$\hat{E}(Y) = \sum_{t=t0}^{t=T} \sum_{i=1}^{N} \hat{E}(Y_{i,t} \mid A_{i,t} = a_{i,t}, W_{i,t})$$

The incident cases attributable to, or averted by, the drought ($\hat{\psi}$) were estimated as the difference between predicted cases under the observed conditions, $\hat{E}(Y)$, and those predicted under the counterfactual scenario that reflected the absence of drought, $\hat{E}(Y_0)$.

$$\hat{\psi} = \hat{E}(Y) - \hat{E}(Y_0)$$

Because antecedent conditions as far back as 3 years might have carried influence, we examined the attributable incidence separately for the 2007–09 drought and 2012–15 drought in the 2 years following the end of each drought. Because seasonal incidence is lowest between March and April, we considered the change in incident cases during drought to include the period starting at the onset of the drought and extending until the end of the transmission season following the droughts. The 2 years after the drought encompassed the full epidemiological seasons following the drought (eg, April 1, 2010–March 31, 2012; April 1, 2016–March 31, 2018).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between April 1, 2000, and March 31, 2020, there were 81 448 reported cases of coccidioidomycosis throughout California. There were 62 002 (76·1%) cases among residents of the examined counties (figure 1A), of which 33% of patients had an estimated onset between September and November (figure 1D). The counties of Kern (170 cases per 100 000 individuals), Kings (104 cases), and San Luis Obispo (43 cases) had the highest average annual incidence rates (figure 1A). Among the counties analysed, precipitation and temperature exhibited strong seasonal patterns. Precipitation was lowest in summer and highest in winter (figure 1E), while air temperature typically peaked in July (figure 1F). Counties in the southern San Joaquin Valley had among the lowest precipitation and highest temperatures, while northern and coastal counties were wetter and cooler (figure 1B, C).

When analysing data for cases with an estimated onset between September and November, IQR increases in precipitation in the 1–4 months before the estimated date of disease onset (ie, during the typically dry summer and early autumn) were negatively associated with autumn incidence (IRRs by lag: 1 month before the estimated date of disease onset: 0·87 [95% CI 0·80–0·94]; 2 months: 0·89 [0·85–0·94]; 3 months: 0·95 [0·92–0·98]; 4 months: 0·87 [0·81–0·94]; figure 2A; appendix p 9). Increasing precipitation in the month before estimated disease onset from the 25th percentile to the 75th percentile was associated with a 13% reduction in incidence rates between September and November. Exposure–response relationships for lags are shown in the appendix (pp 13–14).

Average daily mean temperature in the 1 to 3 months before the estimated disease onset (during the typically hot summer months) was positively associated with incidence of coccidioidomycosis (IRRs by lag: 1 month [1·29 (95% CI 1·16–1·44)]; 2 months [1·55 (1·32–1·82)]; 3 months: [2·02 (1·84–2·22)]; figure 2B; appendix p 9). The exposure–response relationship at a 3-month lag (appendix p 13) showed that the incidence in autumn increased with increasing summer temperature monotonically, with no apparent maximum beyond which temperatures are too hot. Exposure–response relationships for all lags are shown in the appendix (pp 13–15).

Positive, significant pooled associations were detected between precipitation (lagged 5–10 months) and incidence of coccidioidomycosis between September and November. The association peaked for precipitation in the winter before the estimated date of disease onset (ie, precipitation lagged 9 months; figure 2A; appendix p 9). An increase of total monthly winter precipitation from the 25th percentile (27·1 mm) to the 75th percentile (73·2 mm) in the 9 months preceding disease onset was associated with a 45% (IRR 1·45 [95% CI 1·36–1·55]) increase in coccidioidomycosis incidence between September and November. Pooled exposure–response relationships for both winter and spring precipitation showed a unimodal response, whereby an increase in the incidence of coccidioidomycosis was observed with incremental increases in precipitation until an optimal value was achieved (around 40–65 mm during spring and 80–105 mm during winter; appendix p 13), after which additional precipitation was associated with lower incidence than the optimal.

Higher temperatures in the winter and spring before the estimated date of disease onset (ie, 5–10 months before disease onset) were associated with suppressed incidence. In pooled analyses, an increase of 1 IQR in average monthly temperature in the winter before the estimated date of disease onset (from 9·5°C to 12·0°C) was associated with a 26% (IRR 0·74 [95% CI 0·69–79]) decrease in incidence rates between September and November.

Although total monthly precipitation in the winter immediately before the estimated date of disease onset

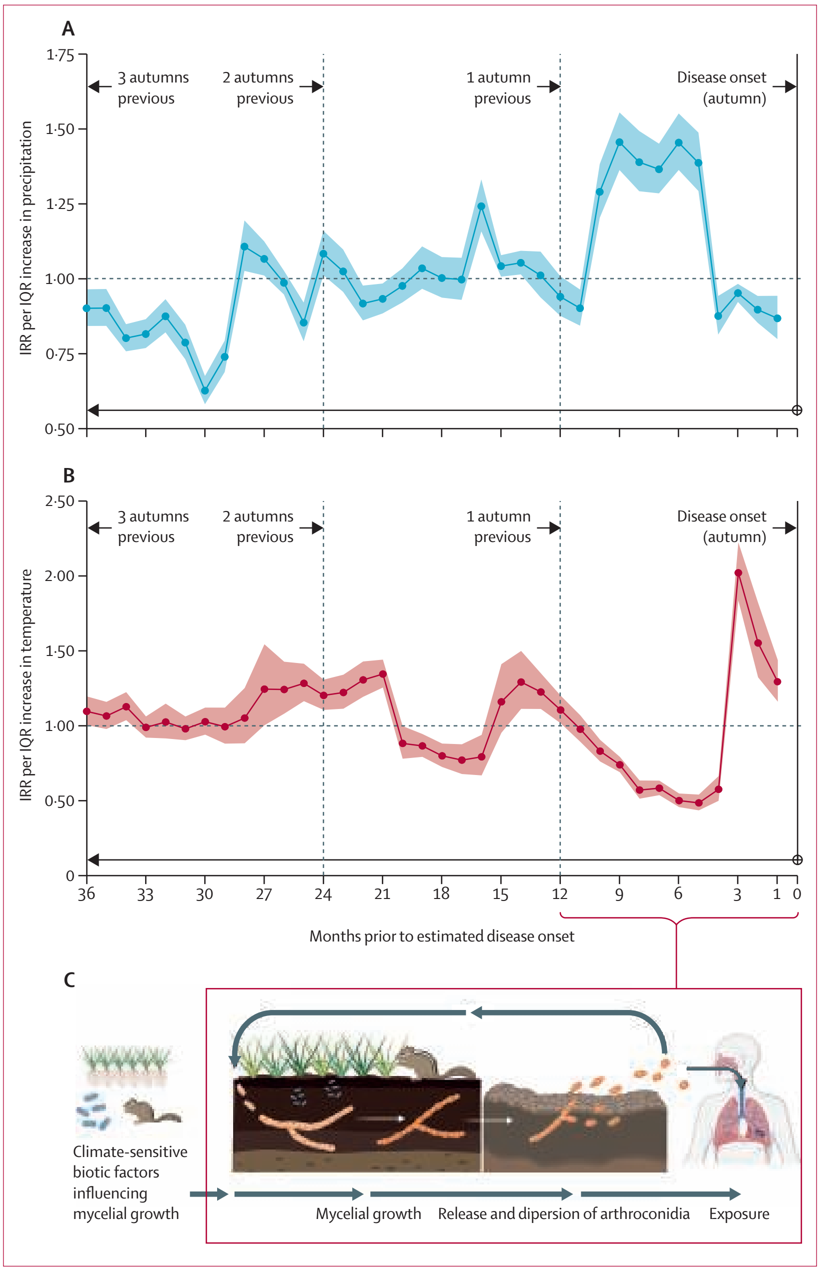

Figure 2: **Incidence rate ratios obtained from distributed-lag non-linear model testing for the association between incidence of coccidioidomycosis during autumn (September to November) and lagged meteorological variables**

Incidence rate ratios (IRRs) express the effect of an IQR increase in precipitation (A) or temperature (B) in the months before the estimated date of disease onset, with CIs shown by shading. The horizontal line at one indicates null association (IRR=1). (C) The saprobic lifecycle of Coccidioides and the hypothesised grow and blow cycle to the intra-annual wet–dry patterns. Inter-annual influences affecting mycelial growth might include biota, small mammals, and soil dwelling microbial competitors (shown in blue). These factors could be influenced by climate across inter-annual time scales.

was positively associated with incidence, precipitation in the winters 2–3 years before the estimated date of disease onset were negatively associated with incidence (figure 2A). For temperature, warmer summers and cooler springs occurring 2–3 years before disease onset were associated with higher incidence, with a dampening of this association seen as the lag increased (figure 2B).

Antecedent conditions modified the effect of more recent meteorological conditions. Low precipitation in the winters 2–3 years before increased the positive association between precipitation in the most recent winter and coccidioidomycosis. When following a year with low winter precipitation (ie, a year with winter precipitation falling below the 50th percentile), an IQR increase in the current year's winter precipitation was associated with an IRR 1·19 (95% CI 1·10–1·30) times larger than the IRR when the same IQR increase in the current year's winter precipitation was experienced following a year with high winter precipitation (ie, a year with winter precipitation above the 50th percentile). When following 2 years of precipitation below the median levels, the effect of a 1 IQR increase in the current year's winter precipitation was 1·36 (1·25–1·48) times the effect of the same increase in winter precipitation following 2 years in which precipitation for both years was not drier than average.

In multivariate meta-regression models, we found that median winter precipitation in counties explained a significant amount of heterogeneity in county-specific IRRs that express the effect of winter precipitation on incidence (figure 3A). The effect of a 1 IQR increase in winter precipitation (from 27 mm to 73 mm) was most pronounced among counties with low median monthly winter precipitation (figure 3A). For instance, in western Kern, which has only 22·7 mm of total precipitation in a typical winter month, an increase from 27 mm to 73 mm of precipitation was associated with an IRR of 1·67 (95% CI 1·42–1·96). Precipitation in the wettest counties, such as Monterey County, which typically receives 70 mm of precipitation in a single winter month, had a non-significant negative effect on incidence. Thus, spatial variation in winter precipitation drove heterogeneity in the delayed effect of precipitation on the incidence of coccidioidomycosis, with dry counties most sensitive to fluctuations.

Similarly, spatial variation in median summer temperature drove heterogeneity in the delayed effect of temperature on the incidence of coccidioidomycosis, with cooler counties most sensitive to fluctuations (figure 3B). The effect of a 1 IQR increase in summer temperature (from 20·3°C to 25·8°C) was most pronounced among counties where the median summer temperature was coolest. For instance, in Monterey County, which had a mean daily temperature of 16·2°C in a typical summer month, an increase from 20·3°C to 25·8°C in temperature was associated with an IRR of 12·7 (95% CI 3·07–53·3). An increase in mean summer temperature in the hottest four of 14 counties, such as western Kern County, which has a mean monthly temperature of 27·0°C, was non-significant.

Ensemble models explained over 90% of the variation in incidence of coccidioidomycosis (figure 4A). In ten of the

14 counties examined, the drought that occurred between 2012 and 2015 was associated with lower than expected cases during the drought, followed by higher than expected cases in the 2 years following the drought (figure 5; appendix pp 10, 16). Because of the importance of winter precipitation on incidence in the following autumn, the aversion of cases due to drought continued past the end of the drought, lasting until the end of the coccidioidomycosis transmission season (March 31). Across the study region and period, we estimated that drought averted 2323 cases of coccidioidomycosis between May 1, 2012, and March 31, 2016, and caused 2649 excess cases between April 1, 2016, and March 31, 2018 (figure 4C; appendix pp 17–23).

The shorter drought that occurred between 2007 and 2009 followed similar patterns to the drought that occurred between 2012 and 2015 but was associated with fewer averted cases during the drought. Across all counties examined, this drought was associated with 1234 fewer cases between March 1, 2007, and March 31, 2010, and 1467 excess cases between April 1, 2010, and March 31, 2012, in the study region (figure 4B; appendix p 10). For both droughts, >85% of estimated excess cases occurred between September and November, and nearly all estimated excess cases occurred between August and November.

Kern County, west of the Sierras, has the highest incidence rates of coccidioidomycosis in California and is among the hottest and driest regions (figure 1A–C). For both droughts, the decline in cases during the drought was most prominent in western Kern County and least pronounced in the counties in the northern San Joaquin Valley, while the increase following the drought was most prominent among the coastal counties and those in the northern San Joaquin Valley (figure 5; appendix p 16). Over the 47 months spanning the drought period between May 1, 2012, and March 31, 2016, 3390 cases of coccidioidomycosis were reported among residents of western Kern County. We estimated that drought conditions were associated with an estimated 29·4% reduction from expected (counterfactual) incidence between May 1, 2012, and March 31, 2016, in Kern County and a 9·6% increase from expected incidence in the 24 months following the drought in Kern County. By comparison, we estimated that drought conditions were associated with an estimated 13% reduction in cases in the wetter San Luis Obispo county, which lies west of Kern County along the coast, and an increase of 65% after the drought.

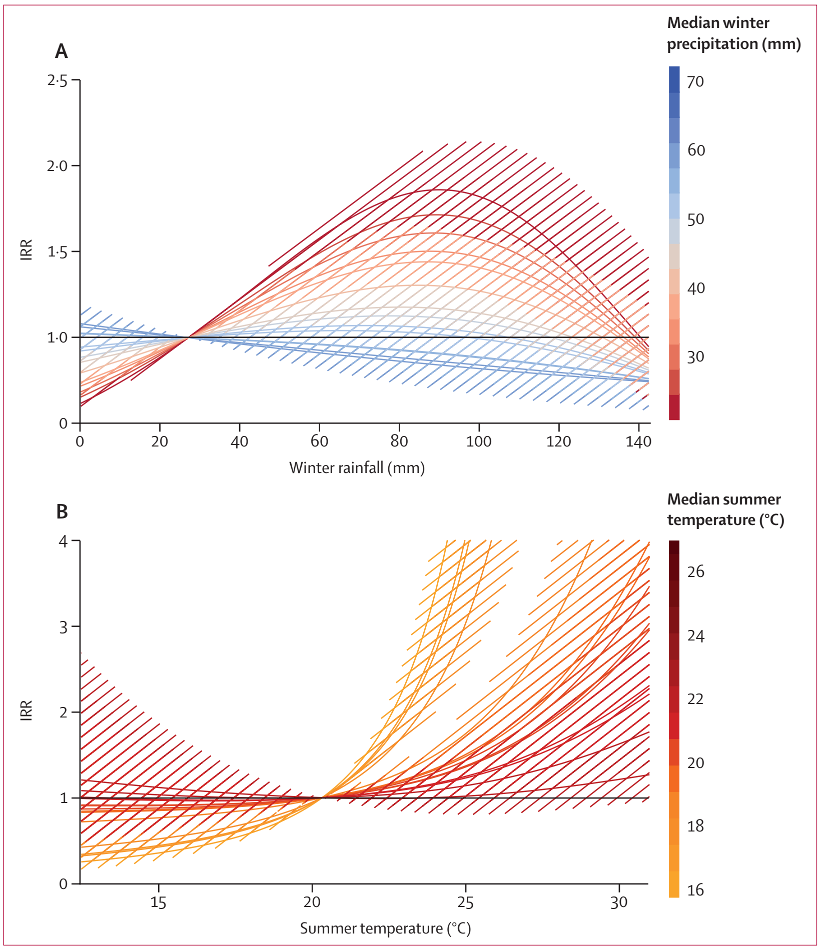

Figure 3: **County-level exposure-response relationships between winter precipitation, summer temperature, and incidence rate of coccidioidomycosis**

Increases in winter precipitation had the greatest effect on the incidence rate ratios (IRRs) of coccidioidomycosis in regions where rain was scarce, and increases in summer temperature had the greatest effect on the IRRs of coccidioidomycosis where temperatures were low. Estimated exposure-response relationships expressed as IRRs (shown by coloured lines), corresponding to the effect of changing winter precipitation (A) and summer temperature (B) from a reference level to the value shown. The reference level for the IRR was the 25th percentile for the study region (for which the IRR=1). Each line indicates an exposure-response relationship expressed as the IRR for a given temperature or precipitation value compared with the incidence rate at the 25th percentile condition for a given county, based on the county's median total monthly winter precipitation (A) or median mean daily summer temperature (B). Dashed regions around the solid lines indicate 95% CIs.

Discussion

In our study, we provide evidence to show that drought displaces the transmission of coccidioidomycosis, suppressing incidence in years characterised by drought conditions but increasing incidence and seasonal peaks in the 2 years following drought conditions. These findings show a previously unknown linkage between drought and transmission of an infectious disease. We found that incidence of coccidioidomycosis increased following wetter than average winters and hotter than average summers, and the magnitude of these effects was mediated by the underlying average climate regime of the region. The results provide evidence for the inclusion of drought monitoring and seasonal climate forecasts in surveillance and prediction of coccidioidomycosis.

The so-called grow and blow hypothesis is among the most widely accepted mechanistic theories linking transmission of coccidioidomycosis to climate conditions,[13,14,22,23] and hypotheses that transmission of coccidioidomycosis is highest following wet periods after drought have circulated for at least three decades.[10] Our findings

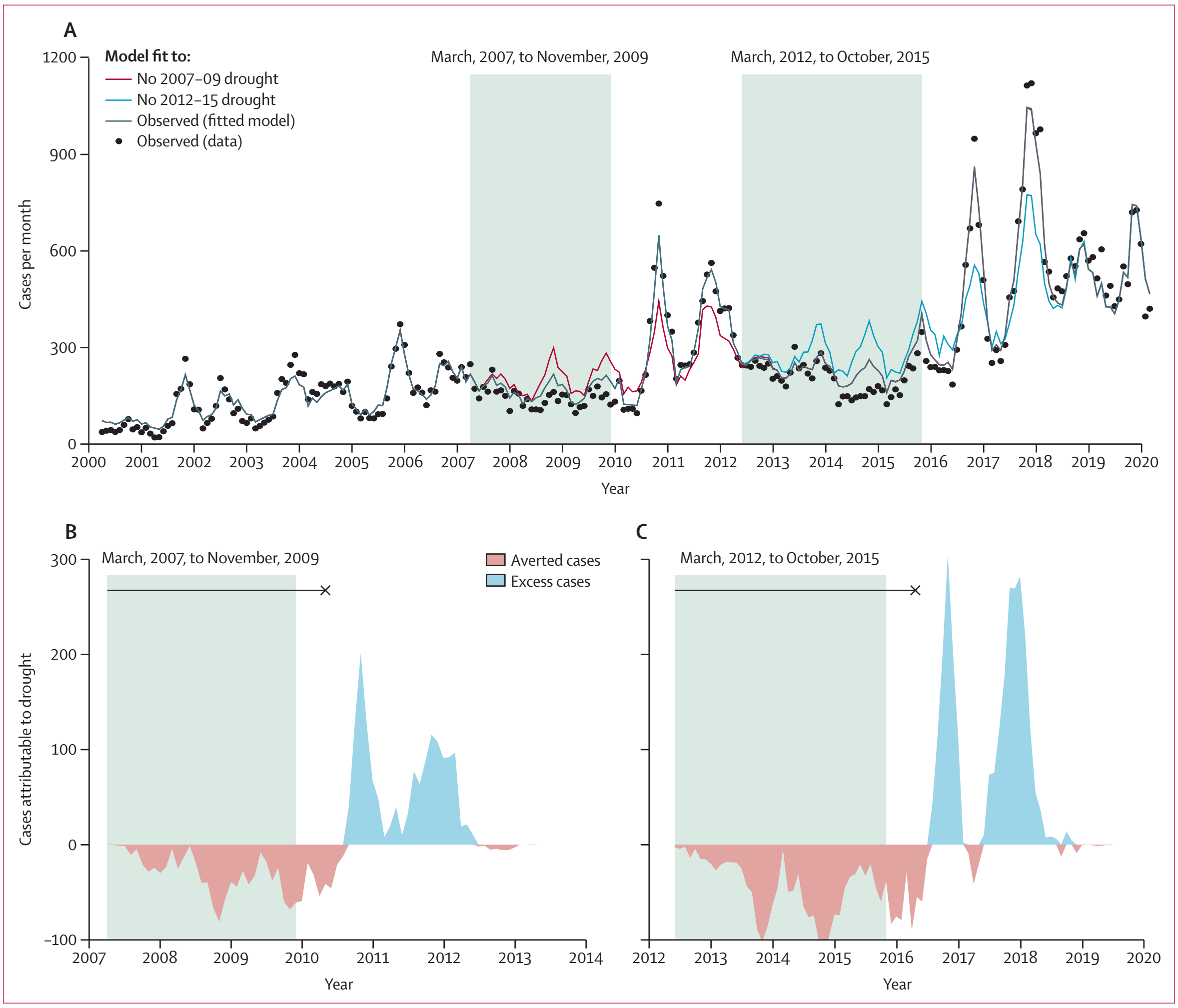

Figure 4: **Incidence of coccidioidomycosis during and after drought**
Droughts were associated with reduced incidence of coccidioidomycosis during the drought, and excess incidence following the drought. (A) Observed incidence (shown by black dots) by month within the study region. The grey line is the model fit under the observed environmental conditions. Coloured lines represent the expected incidence under the counterfactual intervention if the drought that occurred from 2007 to 2009 did not occur (shown in cyan) or the drought that occurred from 2012 to 2015 did not occur (shown in red). Counterfactual scenarios were generated by setting temperatures observed to be higher than historical averages (and precipitation values observed to be below historical averages) deterministically to their average values. Green boxes indicate the drought period. Differences between expected cases of coccidioidomycosis and counterfactual cases if the droughts that occurred between 2007 and 2009 (B) and 2012 and 2015 (C) had not occurred. In panels B and C, the line symbol "——x" indicates the period that encompasses the drought and lasts until the end of the transmission season (March 31).

support and enhance our understanding of this hypothesis (figure 2C; appendix p 11) by suggesting that, within a transmission season, hyphal growth for *Coccidioides immitis* could be most important during winter and spring months when there is adequate rainfall to promote growth.[12] Meanwhile, higher temperatures and lower precipitation during summer and autumn was associated with increased incidence of coccidioidomycosis, suggesting that lysis of hyphae into spores and wind dispersion of spores is most important in the summer and autumn. Furthermore, we found that increasing summer temperatures were associated with especially pronounced relative increases in incidence among cooler counties than already hot counties, while increases in winter precipitation were associated with greatly increased incidence in very dry counties. This finding, along with our estimates of drought-attributable cases across counties, suggests the presence of limiting factors in the lifecycle of *Coccidioides* that vary by region. In arid regions, low levels of precipitation might restrict growth. By contrast, in cooler and wetter regions, the limiting factors might be insufficient heat to lyse the mycelia into individual arthroconidia or to desiccate the soil to facilitate dust emissions, or excessive moisture for growth. This hypothesis could explain why rates of incidence have increased most sharply in wetter and cooler counties, like the central coast counties, compared with the arid southern San Joaquin Valley counties.[2]

The associations detected between incidence of coccidioidomycosis and climatic conditions that occurred more than a year before might involve the influence of upstream factors on pathogen proliferation, such as nutrient availability and the presence of other soil microbes (figure 2C; appendix p 11). Both our ensemble model and regression results suggested that an increase in the mycelial growth that occurs during wet periods is induced by previous dry conditions, supporting hypotheses from as early as 1994 that abundant rains after drought increases transmission.[10] There are several hypotheses that could explain these acyclical inter-annual patterns. First, the so-called soil sterilisation hypothesis posits that extreme hot or dry periods might suppress the relative fitness of microbial competitors in the soil,[13,23] allowing *Coccidioides* populations to grow uninhibited by competition when more favourable conditions (ie, moisture) return. *Coccidioides* spp are poor competitors for nutrients compared with other soil fungi and bacteria,[24] but are resilient and can survive climatological extremes.[25] Another hypothesis is that small mammals harbour inactive *Coccidioides* granulomas that transform into hyphae following host death, using the hosts' keratin as nutrients.[26] Rodent death rate is highest during drought,[27] which could lead to an accumulation of keratin in the soil.

This analysis was subject to exposure misclassification from assignment of cases to the month of their estimated date of onset, which was estimated either by the patient's own report or, if a report was absent, as the date of specimen collection. Therefore, the lag between a change in a climatic factor and its associated change in disease incidence includes the incubation period for coccidioidomycosis, which varies between 7 and 21 days. For some patients, a lag between symptom onset and health-care seeking is reported to be a median of 22 days,[28] and there is also a lag between health-care seeking and diagnostic testing. Exposure misclassification could bias the associations towards the null. Our focus on incident cases that occurred between September and November enabled us to parse out the influence of specific timing of wet and dry periods, but reduced our ability to draw conclusions about how precipitation and temperature affect incidence of coccidioidomycosis at other times of the year. Our ensemble models examined incidence throughout the entire year, and the findings align qualitatively with regression results from September to November; both analyses found that incidence is suppressed during years with low precipitation, and a dry period before a wet period increased the transmission-enhancing effect of the wet period. When modelling associations between climate variability and disease incidence, we did not control for factors that might lie on the causal pathway between temperature and incidence, such as near-surface winds or vegetation, preventing our ability to examine their role in spore dispersal. The small mammal, endozoan-based lifecycle of *Coccidioides* introduced by Taylor and Barker[26] postulates that precipitation could enhance *Coccidioides* growth indirectly

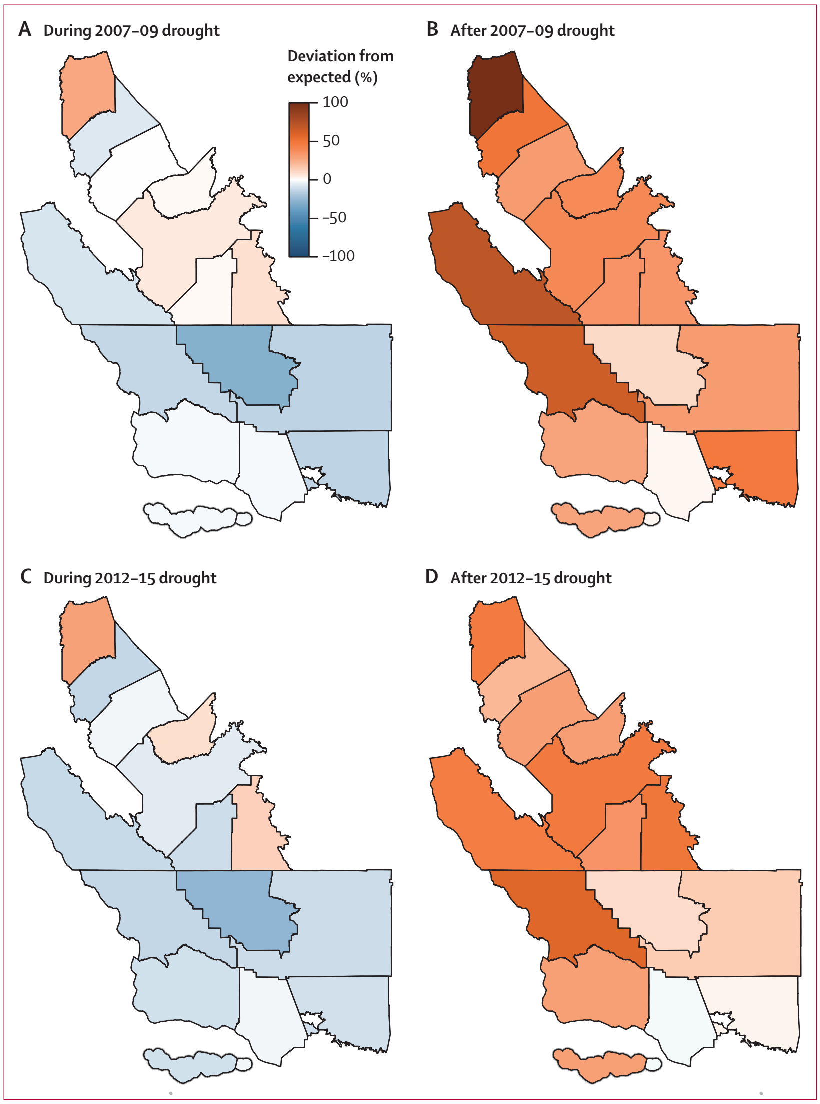

Figure 5: **Deviation in observed incidence of coccidioidomycosis during and after drought compared to the incidence expected in the absence of drought**
Estimated deviation in observed incident cases of coccidioidomycosis compared with the number expected in the absence of drought during (A, C) and in the 2 years following (B, D) the 2007–09 (A, B) and 2012–15 (C, D) droughts across the 14 counties in the study region.

by increasing food sources for small mammal populations that might be associated with the fungus. Although these indirect effects could contribute to delays in the effect of precipitation on transmission, our study was unable to distinguish direct effects from indirect effects. Finally, our results pertain to California, where *C immitis* dominates, and might not be reliably extrapolated to other endemic areas where *C posadasii* prevails. The geographical distributions of *C immitis* and *C posadasii* have little spatial overlap, and adaption to distinct environmental and climate factors within their habitats could have led to differences in thermotolerance or response to other climate stressors. For instance, laboratory studies demonstrate that the growth rate of

C immitis slows under high temperatures (37°C), while the growth rate of *C posadasii* does not.[29]

With climate change, average winter precipitation is projected to see a modest increase in California,[30] while precipitation in autumn and spring is projected to decrease,[6,31] which could enhance conditions favourable for growth and dispersion of *Coccidioides* in the state. At the same time, anthropogenic climate change is expected, with medium–high confidence, to increase the duration, intensity, and frequency of temperature-driven drought in California and other western states.[5,32] Accordingly, we expect that incidence of coccidioidomycosis is likely to continue to expand into historically wetter and cooler regions, such as coastal counties and northern San Joaquin Valley counties in California. Beyond expansion, the seasonality of transmission, particularly following drought, could become more pronounced. Future analyses should consider how the associations resolved in this study can inform projections of the spatiotemporal distribution and seasonality of coccidioidomycosis under anticipated climate regimes in the decades to come.

Contributors

JRH, GS-C, AKH, ATY, DJV, SJ, and JVR conceptualised the research. GS-C, ATY, DJV, and SJ assisted with the curation of the surveillance data and GS-C and JRH validated the data. AB, SKC, SP, NK, GSO, and DPL assisted with curation and validation of environmental data. All authors had access to environmental data, and JRH, GS-C, ATY, SJ, DJV, SKC, IJ, and AKH had access to the raw health data. JRH, AKH, SKC, IJ, EE, JVR, and AH assisted with statistical methods. AB, GSO, DPL, and IJ assisted with methods pertaining to drought characterisation. JT, RW, and WM assisted with methods pertaining to *Coccidioides* environmental lifecycle. JVR, JT, EE, AH, DPL, and GSO acquired the funding. JVR, JT, EE, AH, DPL, GSO, SJ, and DJV supervised the work. WM helped develop figure 2. JRH conducted the formal analysis and wrote the original draft. All authors reviewed and edited the final draft. JVR had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The R script used to conduct the data analysis is available in a publicly available GitHub repository (https://github.com/jrhead/ValleyFever_and_Drought). Human case data are protected health information with access restricted to authorised California Department of Public Health (CDPH) staff. More complete human disease data can be obtained by submitting a formal request to the CDPH, Infectious Disease Branch, Surveillance and Statistics Section. All environmental predictors are publicly available.

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