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MAJOR ARTICLE

# Clinical and Economic Burden of Valley Fever in Arizona: An Incidence-Based Cost-of-Illness Analysis

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***Background.*** Coccidioidomycosis, ie, Valley fever, is an important fungal infection in the Southwest, with half to two thirds of all cases occurring in Arizona. This endemic respiratory disease can range from primary uncomplicated pneumonia to disseminated infection such as meningitis with chronic pulmonary complications. Valley fever diagnoses have risen over recent years and cause substantial morbidity and economic burden in Arizona.

***Methods.*** We estimated the lifetime cost-of-illness associated with all cases of Valley fever diagnosed in 2019 in Arizona. Natural history of the disease was determined from literature and expert opinion and assigned costs from national data sources to determine lifetime direct and indirect costs (work loss).

***Results.*** Total lifetime costs of $736 million were estimated for the 10 359 cases of Valley fever diagnosed in Arizona in 2019. Direct costs of $671 million accounted for over 90% of expenditures, with $65 million in indirect costs. Disseminated infection produces the highest economic burden at $1.26 million direct and $137 400 indirect costs per person. The lowest Valley fever lifetime costs were for cases of primary uncomplicated pneumonia with $23 200 in direct costs and $1300 in lost wages. The average lifetime direct costs across all Valley fever manifestations are $64 800 per person diagnosed in Arizona in 2019 and $6300 for indirect costs.

***Conclusions.*** Valley fever is responsible for substantial economic burden in Arizona. Our estimates underscore the value of supporting research into developing more rapid diagnostic tests, better therapies, and ultimately a preventative vaccine to address this important public health problem in Arizona.

**Keywords:** Arizona; coccidioidomycosis; cost-of-illness; economic analysis; Valley fever.

Coccidioidomycosis (also known as Valley fever) is an incurable infection caused by the fungi, *Coccidioides immitis* and *Coccidioides posadasii*, which are endemic to regions in the Southwestern United States and parts of Mexico and the rest of the Western Hemisphere [1, 2]. Arizona has more cases than any other state, with half to two thirds of all US diagnosed cases [3]. Valley fever manifests as respiratory illness [4, 19] and causes 15%–30% of community-acquired pneumonias in Arizona [6, 7]. Clinical presentation varies widely, with approximately 60% of cases being asymptomatic, and, therefore, typically not diagnosed [8]. When illness does occur, it is most frequently that of a community-acquired pneumonia that lasts weeks or months. Costs of diagnosis and initial treatment can be substantial, with costs rapidly increasing for more severe infections requiring lifetime antifungal treatment and recurrent hospitalization. Occasionally, the pulmonary infection becomes chronic or the fungus spreads to other parts of the body, most typically to the skin, bones, and brain (ie, disseminated infection), leading to significant morbidity and economic burden. As cases of Valley fever increased in recent years, from 5624 cases diagnosed in 2014 (84.4/100 000) to 10 359 cases in 2019 (144.1/100 000), so also has morbidity, mortality, and costs [9].

Although Valley fever is very common within its endemic regions, these are relatively small geographic areas, and nationally it is considered an uncommon problem. There has been little commercial incentive to develop new more sensitive and rapid diagnostic tests [10], curative therapies [4], or preventative vaccines [11]. Even within the endemic regions, standard medical practice results in surprisingly frequent delays in diagnosis, which also contributes to the impact of the disease [12, 13, 14].

The purpose of this analysis is to estimate lifetime costs (direct and indirect) associated with new (incident) cases of Valley fever in Arizona in the year 2019. Understanding the economic burden that Valley fever places on Arizona will help illuminate the need to direct more resources to solving this

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costly problem, through efforts such as prevention, accurate diagnosis, access to care, and vaccine and antifungal drug development.

## METHODS

An incidence-based lifetime cost model was developed for Arizona patients newly diagnosed in 2019. We used a societal approach, including both direct and indirect costs. The direct costs of Valley fever include those that the healthcare system is expected to incur over a patient's lifetime for the diagnosis, treatment, and follow up of the disease. Indirect costs of Valley fever represent those associated with work loss (absenteeism) and lost earnings due to premature mortality.

We adopted most of the disease frequency distribution and resource use outlined in a recent lifetime cost analysis for Valley fever in California [15]. Using natural history of the disease along with treatment guidelines and expert opinion, Wilson et al [15] estimated costs for 5 manifestations of Valley fever: (1) primary uncomplicated pneumonia, (2) chronic pneumonia, (3) disseminated infection, (4) other pulmonary changes such as pulmonary nodules, and (5) other pulmonary changes such as pulmonary cavities. The California analysis based several model inputs on estimates obtained from a 5-member expert panel. For each of the 5 disease manifestations, the panel confirmed and/or modified published estimates of resource utilization regarding prediagnosis, diagnosis, and medication treatment. They also provided expert opinion for nonpublished resource use such as follow-up testing, x-rays, hospitalizations, and home care/nursing home care.

Several California estimates were adjusted to reflect treatment patterns in Arizona; most prominently to reflect higher incidence rates in Arizona. In addition, the California analysis used a 7-day treatment with levofloxacin for primary uncomplicated pneumonia. In Arizona, the current standard is 5 days for nonsevere community-acquired pneumonia caused by typical pathogens. Mortality rates were also adjusted to better reflect age at diagnosis and natural history of Valley fever in Arizona.

### Study Population

A total of 10 359 new Valley fever cases were recorded in Arizona in 2019 [9], with an overall rate of 144.1/100 000 population. The highest rates were in those 55 years and older. The mean age at diagnosis was 50 years and females comprised approximately 55% of cases. The majority (85%) of reported cases are assumed to include primary uncomplicated pneumonia [7, 15]. Chronic pneumonia is estimated to occur in 2.5%, and 2.5% developed disseminated infection with or without pulmonary complications. The remaining 10% of Valley fever patients experience "other pulmonary changes." Of these, 70% involve pulmonary nodules and 30% pulmonary cavities without associated symptoms. Most deaths occur in the disseminated infection group; therefore, normal life expectancy is anticipated for all other patients.

### Time Horizon

A 40-year lifetime model was estimated using normal life expectancy for a 50 year-old (mean of 83 years) and included annual mortality probabilities out to age 90 from the Social Security Administration's 2017 Actuarial Life Table [16].

### Costs

All costs were measured in 2019 dollars, and a 3% discount rate was applied to future costs to reflect present values. Inflation adjustments for selected costs from Wilson et al [15] were made using the percentage change in US healthcare costs from 2017 to 2019 as measured by the Medical Care and Physician Services components of the Consumer Price Index for All Urban Consumers, Bureau of Labor Statistics [17].

Direct costs of healthcare resource use were obtained from Wilson et al [15] and included physician visits, diagnostic procedures such as chest x-rays, antifungal medications, hospitalization, home care, and skilled nursing facility (Table 1). The Centers for Medicare and Medicaid Services CPT (Current Procedural Terminology) codes were used to estimate costs for diagnosis, office visits, and procedures [15]. Medication costs were estimated using 2019 average wholesale price (AWP) minus 17% using Red Book Online [18]. Hospitalization costs were estimated using *International Classification of Diseases, Tenth Revision* codes via the Healthcare Cost and Utilization Project (HCUP) [15]. United States Bureau of Labor and Statistics data were used for home care costs [15], and nursing home costs were estimated from the US Department of Health and Human Services [15].

Indirect costs were calculated using expert panel estimates [15] of the short-term work loss associated with each of the 5 disease manifestations. Mortality rates associated with Valley fever were used to estimate lost earnings due to premature death. The mean employee compensation in 2018 for a 50-year-old (the average age at diagnosis in 2019) was $87 179 (Bureau of Economic Analysis, 2018). Bureau of Labor Statistics data (2018) [19] were used to estimate the percentage of population employed by age group. Annual wages were adjusted for employment-to-population ratios and accounted for age-related growth, economy-wide growth, and age-related changes in labor force participation (ie, numbers of individuals employed decreased with aging, going to zero after age 69) [20].

Lifetime costs were the sum of per-person direct and indirect costs for each of the 5 disease manifestation categories. These costs were then multiplied by the number of patients experiencing each of the 5 disease manifestations.

**Table 1. Direct Lifetime Costs per Person Diagnosed in 2019 in Arizona by Valley Fever Disease Manifestation[a]**

| Disease and Cost Type | Item | Healthcare Utilization | Average per Person Lifetime Cost |
|---|---|---|---|
| Primary Uncomplicated Pneumonia | | | |
| Pre-Valley Fever Diagnosis | | | |
| Physician visit | | 100% had 3 physician visits | $491 |
| ER visit | | 23% first sought care in ER | $18[a] |
| Medication | Azithromycin/levofloxacin | 100% (50% require 2nd course) | $106 |
| Diagnosis | Immunodiffusion and titer | 100% (25% require repeat testing) | |
| | Chest x-ray | 100% | $338 |
| | Chest CT | 25% | |
| | Others, HIV testing | 100% | |
| Post-Valley fever diagnosis | | | |
| Hospitalization | Requiring hospitalization | 40% | |
| | 1 lifetime hospitalization | 90% | $14 868 |
| | 2 lifetime hospitalizations | 7% | |
| | >2 lifetime hospitalizations | 3% | |
| Medication | Fluconazole (400 mg/day) | 90% (6 months) | |
| | Itraconazole (200 mg twice/day) | 3% (6 months) | $6134 |
| | Liposomal amphotericin B (5 mg/kg per day) | 2% (for pregnant women, 6 months) | |
| | Voriconazole (200 mg twice/day) | 5% (after failing fluconazole/ voriconazole, 6 months) | |
| Follow-up | Immunodiffusion and titer | 100% every 3 months for 12 months | |
| | Chest x-ray | (expected compliance 50%–80%) | $1238 |
| Home care/nursing home | | None | $0 |
| Total | | | $23 192 |
| Chronic Pneumonia | | | |
| Pre-Valley fever diagnosis | | Same as for primary uncomplicated pneumonia | $615 |
| Other medication | 4-drug regimen for tuberculosis (rifampin 600 mg/day, isoniazid 300 mg/day, pyrazinamide 1500 mg/day, ethambutol 1200 mg/day) | 10% (1 month) | $53 |
| Diagnosis | Immunodiffusion and titer | 100% (25% require repeat testing) | |
| | Chest x-ray | 50% have 2 x-rays/year outside of hospital | $337 |
| | Chest CT | 30% have chest CT outside of hospital | |
| Post-Valley Fever Diagnosis | | | |
| Hospitalization | 1st hospitalization in year 1 | 75% | |
| | 2nd hospitalization in year 1 | 65% (of those with 1st hospitalization) | $73 600 |
| | 1 future lifetime hospitalization | 100% | |
| Medication | Fluconazole (800 mg/day) | 75% (36 months) | $47 443 |
| | Itraconazole (200 mg twice/day) | 25% (36 months) | |
| Follow-up | Immunodiffusion and titer | 100% every 3 months for 12 months | |
| | | (expected compliance 50%–80%) | $1642 |
| | Chest x-ray and chest CT | 100% (at discharge, expected compliance 50%–80%) | |
| Home care | | 100% (3 days a week for 3 months) | $2569 |
| Rehabilitation facility | | 100% (30 days) | $3774 |
| Total | | | $130 033 |
| Disseminated Infection | | | |
| Pre-Valley fever diagnosis | | Same as for primary uncomplicated pneumonia | $614 |
| Diagnosis | | | |
| Immunodiffusion/titer/chest x-ray/chest CT | | Same as for chronic pneumonia | |
| Lumbar puncture | | 50% | |
| MRI | | 15%–20% | |
| Aspirates of joint effusions | | 10% | |
| Skin biopsy | | 10% | $773 |
| Bone marrow biopsy | | 5% | |
| Lung biopsy | | 20% | |

**Table 1. Continued**

| Disease and Cost Type | Item | Healthcare Utilization | Average per Person Lifetime Cost |
|---|---|---|---|
| Lymph node biopsy | | 20% | |
| Liver biopsy | | 5% | |
| Post-Valley Fever Diagnosis | | | |
| Hospitalization | 1st hospitalization in year 1 | 100% | |
| | 2nd hospitalization in year 1 | 65% (of those with 1st hospitalization) | $915 959 |
| | Hospitalization in year 2 | 100% hospitalized once a year for life | |
| Medication | Fluconazole (800 mg/day) | 98% (lifelong) | $315 975 |
| | Liposomal amphotericin B (5 mg/kg per day) | 2% (lifelong) | |
| Other treatment considerations | Ventriculoperitoneal shunt placement | 15% of those with meningitis | $864 |
| | Ventriculoperitoneal shunt replacement | 100% of shunts replaced once in lifetime | |
| Follow-up | Immunodiffusion and titer | | |
| | Chest x-ray | 100% (every 3 months in year 1, every 6 months for life; MRI every 6 months for life; lumbar puncture 2 times in year 1, times in lifetime; expected compliance 50%–80%) | $17 697 |
| | Chest CT | | |
| | Liver function test | | |
| | Renal function test | | |
| | MRI | | |
| | Lumbar puncture | | |
| Home care | | 100% (3 days a week for 3 months) | $2569 |
| Nursing home | Temporary stay | 10% (2 months) | $763 |
| Total | | | $1 262 414 |
| Other Pulmonary Changes: Pulmonary Nodules | | | |
| Pre-Valley fever diagnosis | | Same as for primary uncomplicated pneumonia | $614 |
| Diagnosis | Immunodiffusion and titer | 100% (25% require repeat testing) | $80 352 |
| | Chest x-ray | 100% | |
| | Chest CT | 25% | |
| | Diagnostic workup for lung cancer (CT scan, and biopsy if indeterminate) | 90% | |
| Post-Valley Fever Diagnosis | | | |
| Hospitalization | | Same as for primary uncomplicated pneumonia | $14 868 |
| Medication | Requiring medication | 25% | |
| | Fluconazole (400 mg/day) | 90% (6 months) | $1198 |
| | Itraconazole (200 mg twice/day | 5% (6 months) | |
| | Voriconazole (200 mg twice/day) | 5% (after failing fluconazole/voriconazole, 6 months) | |
| Follow-up | Immunodiffusion and titer | 100% every 3 months for 12 months, then every 6 months for 1 year (expected compliance 50%–80%) | $3735 |
| | Chest x-ray | | |
| Home care/nursing home | | None | $0 |
| Total | | | $100 768 |
| Other Pulmonary Changes: Pulmonary Cavities | | | |
| Pre-Valley Fever Diagnosis | | | |
| Diagnosis | | Same as for pulmonary nodule | $100 768 |
| Post-Valley Fever Diagnosis | | | |
| Additional Hospitalization | | | |
| Cavity complications | | 5% | $2936 |
| Hemoptysis/chest pain | | 5%–10% | $2467 |
| Home care/nursing home | | None | $0 |
| Total | | | $106 171 |

Abbreviations: CT, computed tomography; ER, emergency room; HIV, human immunodeficency virus; MRI, magnetic resonance imaging.

[a]Pre-Valley fever ER costs do not represent the associated medical doctor fees, which are included in the physician visit costs.

NOTE: Inflation of costs from Wilson et al [15] made using the percentage change in US healthcare costs from 2017 to 2019 as measured by the Medical Care component or Physician Services component of the Consumer Price Index for All Urban Consumers, Bureau of Labor Statistics [17].

## RESULTS

Total lifetime costs for Valley fever cases (n = 10 359) diagnosed in Arizona in 2019 were estimated at $736 million (Table 3). Just over 91% of expenditures were direct costs ($671 million) and $65 million were indirect costs. The average lifetime direct costs across all 5 Valley fever manifestations is $64 800 per

**Table 2. Indirect Lifetime Costs per Person Diagnosed With Valley Fever in 2019 in Arizona by Disease Manifestation.**

| Disease and Cost Type | Duration of Loss | Average per Person Lifetime Cost |
|---|---|---|
| Primary Uncomplicated Pneumonia | | |
| Work loss | 7 days | $1299 |
| Mortality | Normal life expectancy | $0 |
| Total | | $1299 |
| Chronic Pneumonia | | |
| Work loss | 90 days | $16 703 |
| Mortality | 2% in first year, 0.2% each year thereafter | $24 410 |
| Total | | $41 113 |
| Disseminated Infection | | |
| Work loss | 120 days | $22 270 |
| Mortality | 5% in year 1, 4% in year 2, 3% in year 3, 2% in year 4, and 1% each year thereafter | $115 109 |
| Total | | $137 379 |
| Other Pulmonary Changes: Pulmonary Nodules | | |
| Work loss | 7 days | $1299 |
| Mortality | 0.2% each year | $6172 |
| Total | | $7471 |
| Other Pulmonary Changes: Pulmonary Cavities | | |
| Work loss | 7 days | $1299 |
| Mortality | 0.2% each year | $6172 |
| Total | | $7471 |

NOTE: Mortality rates from Wilson et al [15] and adjusted for Arizona by Dr. John Galgiani, Director, Valley Fever Center for Excellence, College of Medicine Tucson, The University of Arizona Health Sciences.

person diagnosed in Arizona in 2019 and $6300 for indirect costs. Of the 5 disease manifestations, disseminated infection has the highest economic burden at $1.26 million direct and $137 400 indirect costs per person. Work loss during the initial diagnosis was much higher for those with disseminated infection (120 days) compared with those without dissemination (90 days) or those with primary uncomplicated pneumonia, or either pulmonary complication (7 days each). Loss of earnings due to premature mortality was also highest in the disseminated infection group ($115 100 per person), with 15% of these individuals dying during the first 5 years and 1% more than normal population-based rates each year afterward.

#### Primary Uncomplicated Pneumonia

Eighty-five percent of newly diagnosed Valley fever patients have primary uncomplicated pneumonia. The estimated average per-person lifetime direct costs for this group is $23 200, the lowest of all the disease manifestations (Table 3). Direct costs included diagnostic workup with physician visits, antibiotics, testing, and chest x-ray for all patients, and a subset receiving emergency department (ED) care, additional testing, including a chest computerized tomography (CT), hospitalization, and antifungal medication (Table 1). Valley fever patients presenting with primary uncomplicated pneumonia have normal life expectancy; therefore, indirect costs are simply the value of an estimated 7 workdays lost during the initial period of treatment, which is estimated to total $1300 per person (Table 2).

#### Chronic Pneumonia

Diagnostic workup costs are similar to those with primary uncomplicated pneumonia (Table 1). However, patients with chronic pneumonia, even without disseminated infection, require antifungal medication for 3 years, additional testing, and likely hospitalization during the first 2 years after diagnosis. Surgery is needed in approximately 25% of patients as part of the management for fibrocavitary complications and is included in the hospitalization estimates. In addition, all hospitalized patients receive home nursing care or spend 1 month in a rehabilitation facility. The lifetime direct costs for these patients are estimated to be $130 000 per person (Table 3). Indirect costs are not trivial for Valley fever patients presenting with chronic pneumonia with approximately 90 workdays lost ($16 700) per person (Table 2). With 2% mortality in the first year of diagnosis, followed by a 0.2% marginal mortality rate thereafter, the cost of premature mortality equals $24 400 per person. These figures bring the lifetime indirect costs to an estimated $41 100 per person.

#### Disseminated Infection

Healthcare costs are the highest for patients diagnosed with disseminated infection, especially when meningitis is involved. A higher percentage than for chronic pneumonia present to the emergency room, require procedures such as magnetic resonance imaging, CT scans, lumbar punctures, and biopsies, and require home nursing care and skilled nursing facility care. All patients with serious disseminated infection require lifelong antifungal medication, periodic testing, and recurring hospitalization (Table 1). The lifetime direct costs for cases with disseminated infection are estimated to be $1.26 million per person (Table 3). Work loss during their initial period of treatment (120 days) is substantial ($22 270), and the marginal mortality rate of 15% in the first 5 years and 1% each year thereafter results in premature mortality costs of $115 109 per person (Table 2). Total indirect costs are estimated at $137 379 per person for those with disseminated infection.

#### Other Pulmonary Changes: Pulmonary Nodules or Cavities

Approximately 7% of Valley fever patients experience other pulmonary changes involving pulmonary nodule plus another 3% involving pulmonary cavity. These patients require expensive diagnostic workup to rule out lung cancer, 6 months of antifungal treatment, and approximately 40% require hospitalization (Table 1). The direct costs estimated for these cases are $101 000 per person for pulmonary nodule and $106 000 per person for pulmonary cavity (Table 3). These patients are assumed to lose 7 days of work during their initial period of

Table 3. Estimated Total Direct and Indirect Lifetime Costs for Newly Diagnosed Valley Fever Cases in Arizona in 2019

| Costs | Patients (N = 10 359) | Avg Per Person Lifetime Cost | Total Lifetime Cost for Arizona |
|---|---|---|---|
| Direct Costs | | | |
| Primary uncomplicated pneumonia | 8805 | $23 192 | $204 209 262 |
| Chronic pneumonia | 259 | $130 033 | $33 675 245 |
| Disseminated infection | 259 | $1 262 414 | $326 933 779 |
| Other pulmonary changes: pulmonary nodules | 725 | $100 768 | $73 069 735 |
| Other pulmonary changes: pulmonary cavities | 311 | $106 171 | $32 994 839 |
| Indirect Costs | | | |
| Primary uncomplicated pneumonia | 8805 | $1299 | $11 437 890 |
| Chronic pneumonia | 259 | $41 113 | $10 647 198 |
| Disseminated infection | 259 | $137 379 | $35 577 694 |
| Other pulmonary changes: pulmonary nodules | 725 | $7471 | $5 417 535 |
| Other pulmonary changes: pulmonary cavities | 311 | $7 471 | $2 321 801 |
| Total Costs of Valley Fever | | | |
| Direct costs | | | $670 882 860 |
| Indirect costs | | | $65 402 119 |
| Work loss | | | $22 876 440 |
| Mortality | | | $42 525 679 |
| Total direct + indirect costs | | $71 077 | $736 284 978 |

Abbreviations: Avg, average.

treatment and have increased mortality rates that are 0.2% higher than normal population-based rates each year for the remainder of their lives, leading to indirect costs of approximately $7500 per person (Table 2).

## DISCUSSION

We estimated the lifetime costs of a 2019 diagnosis of Valley fever in Arizona at approximately $736 million, with the majority (91%) being direct costs. We based much of the methodology on that used by Wilson et al [15], who recently estimated the lifetime costs of Valley fever diagnoses in California in 2017. Many of their resource use estimates derived from an expert panel, so we adjusted some of the estimates to better reflect treatment in Arizona. Despite criticisms of expert panels as a source for model inputs, there are no publicly available databases to obtain variables to estimate lifetime costs associated with Valley fever, which makes expert opinion the only viable data source.

Table 4. Arizona and California Estimates for Direct and Indirect Lifetime Costs per Person by Valley Fever Disease Manifestation

| Disease Manifestation | Arizona Mean per Person Estimate 2019 Dollars | California Mean per Person Estimate 2017 Dollars |
|---|---|---|
| Primary Uncomplicated Pneumonia | | |
| Direct costs | $23 192 | $22 039 |
| Indirect costs | $1299 | $931 |
| Chronic Pneumonia | | |
| Direct costs | $130 033 | $132 416 |
| Indirect costs | $41 113 | $350 063 |
| Disseminated Infection | | |
| Direct costs | $1 262 414 | $1 023 730 |
| Indirect costs | $137 379 | $562 291 |
| Other Pulmonary Changes: Pulmonary Nodules | | |
| Direct costs | $100 768 | $95 399 |
| Indirect costs | $7471 | $126 883 |
| Other Pulmonary Changes: Pulmonary Cavities | | |
| Direct costs | $106 171 | $101 748 |
| Indirect costs | $7471 | $126 883 |
| Total direct costs | $670 882 860 | $428 648 626 |
| Total indirect costs | $65 402 119 | $271 173 042 |
| Total direct + indirect costs | $736 284 978 | $699 821 668 |

The total lifetime costs for Valley fever in California ($700 million) differed in some ways from our estimate of $736 million (Table 4). Arizona experienced more annual cases of Valley fever than California with 10 359 versus 7466, respectively, and had a slightly older population at diagnosis (age 50 vs 46). The proportion of direct costs were higher for Arizona (91% of total costs) with an estimated $671 million compared with the $429 million (61% of total costs) in the California analysis. Because of lower mortality rates used in the Arizona analysis, more people incurred long-term hospitalization and medication costs than in the California study, which translated to higher direct costs. The overall per-person direct costs of approximately $65 000 for all diagnoses in Arizona compared with $57 000 for the California study.

The largest difference between the studies emanated from indirect costs with $65 million for Arizona compared to $271 million for California (Table 4). We used the same estimates for work days lost, but we varied the mortality rates used to calculate lost wages due to premature death. We adjusted mortality rates to reflect what our investigators have experienced locally in Arizona. Mortality for chronic pneumonia in the California

**Table 5. Results of Varying Discount Rate From 3% to 1% for Future Costs by Valley Fever Disease Manifestation**

| Parameters | n | 3% | 1% | Per Patient Difference | Total Difference |
|---|---|---|---|---|---|
| Chronic Pneumonia | | | | | |
| Lost wages | 259 | $24 410 | $29 175 | $4765 | $1 234 135 |
| Disseminated Infection | | | | | |
| Hospital costs | 259 | $915 959 | $1 176 221 | $260 262 | $67 407 858 |
| Medication | 259 | $315 975 | $409 432 | $93 457 | $24 205 363 |
| Lost wages | 259 | $115 109 | $138 060 | $22 951 | $5 944 309 |
| Other Pulmonary Changes: Pulmonary Nodules | | | | | |
| Lost wages | 725 | $6172 | $7336 | $1164 | $843 811 |
| Other Pulmonary Changes: Pulmonary Cavities | | | | | |
| Lost wages | 311 | $6172 | $7336 | $1164 | $361 966 |
| Total | | | | | $99 997 442 |

model was estimated at 7.5% per year in the first 3 years and 4.3% annually thereafter, resulting in lost wages due to premature death of over $330 000 per person. The Arizona estimate of just over $24 000 per person was based on a mortality rate of 2% for the first year, followed by 0.2% each year after. For disseminated infection, Wilson et al [15] used a mortality rate of 30% per year for the first 5 years followed by 8.6% for the next 5 years, bringing the estimate for lost wages due to premature death to almost $532 000 per person. For Arizona, we used a mortality rate of 15% spread across the first 5 years and 1% each year thereafter for a total of $115 000 per person (Table 2). For California patients with other pulmonary changes, lost wages totaling approximately $126 000 per person were estimated based on mortality of 1% per year for the first 5 years followed by normal life expectancy. Arizona estimates (approximately $6200 per person) were lower with mortality estimates of 0.2% annually throughout the duration of the model. It is difficult to estimate mortality rates associated with complications of Valley fever. The expert clinical opinions differed between our 2 studies, but it is not likely that the 2 states differ in their overall statistics if precise estimates were known. Mortality estimates made from death certificates between 1990 and 2008 found rates of 1.89 and 2.19 Valley fever deaths per 100 000 person years in California and Arizona, respectively [21]. If we had relied on the higher mortality estimates from the California analysis, the Arizona indirect costs associated with premature death would have been higher.

Another factor accounting for the difference in indirect costs between the 2 analyses was the inclusion of both short- and long-term disability payments in the California study, which totaled approximately $4.2 million. We chose not to include disability payments in our estimates because these could be considered transfer payments from taxpayers to patients, without a true societal cost.

Finally, we applied a 3% discount rate to estimate the present value of Valley fever costs that occur in the future. This rate is recommended by the Second Panel on Cost-Effectiveness in Health and Medicine [22] and supported by ISPOR (the International Society for Pharmacoeconomics and Outcomes Research) [23]. To examine the impact of a lower discount rate, we reanalyzed the data using a 1% rate, which was used in Wilson et al [15]. A change in the discount rate would increase the overall cost-of-illness estimate by almost $100 000 000 (Table 5). The majority of this increase comes from individuals with disseminated infection who, in addition to lost wages, accrue future costs for hospitalization and medication. Using the 3% discount rate may underestimate the economic burden to society for both direct and indirect costs of Valley fever compared with the 1% rate used in the California study findings, which was calculated during the recession.

Our calculations were based on 10 359 Arizona Valley fever cases reported in 2019. Like others, we believe that a significant number of patients with primary coccidioidal pneumonia are not diagnosed by current clinical practice [24, 25]. Moreover, recent studies demonstrate significant delays in diagnosis, which lead to increased costs [12, 13, 14]. Valley fever-related charges for patients with any delay (≥1 day) were significantly greater than for those diagnosed on the day they presented with symptoms [13]. Although the workup costs in our study included some rule-out testing, it is likely our results underestimate the additional costs associated with delayed diagnosis.

Disseminated coccidioidomycosis is associated with an average per-person lifetime cost 10 times higher than chronic pneumonia and 54 times higher than primary uncomplicated pneumonia. Although the advent of lifelong oral azole therapy makes meningitis (a common manifestation of disseminated disease) manageable in many patients, complications such as hydrocephalus, lumbar arachnoiditis, cognitive defects, and cranial neuropathy are common [26]. In addition to meningitis, patients with disseminated disease present with spinal involvement with osteomyelitis, diskitis, and risk of spinal cord compression, which requires extensive surgery [27]. Valley fever presenting as disseminated disease is an extremely serious and costly condition that warrants prevention if at all possible.

### Limitations

Our study relied on assumptions made by the California expert panel as well as our investigators, and it may not be representative of actual treatment practices for Valley fever in all of Arizona. In addition, patients within each disease manifestation were assumed to utilize the same resources. Economic modeling relies on average patient experiences, but undoubtedly there are variations in severity of these disease manifestations among a cohort of Valley fever patients. National cost sources used such as CMS for physician visits and procedures, HCUP for hospitalization, and AWP minus 17% for drug costs may not be representative of the US payer perspective as a whole. Further studies are needed to accurately assess the resource use and costs associated with the various manifestations of the disease, as well as the intangible costs associated with the patients' quality of life.

A few assumptions that were appropriate in California may differ in Arizona. We outline several areas where patients may be managed differently in Arizona, based on the clinical experience of our authors. Because there is a lack of empirical evidence to support treatment pattern differences, we maintained the assumptions developed in the California study. The analysis assumed that 100% of patients were treated with an antifungal drug for 6 months. Physicians that are most experienced in managing coccidioidomycosis will often withhold antifungal treatment in patients with uncomplicated pulmonary infection unless risk factors for complications are present. In Arizona, patients who need an alternative to fluconazole may receive posaconazole, which is more expensive than itraconazole or voriconazole. Along with the diagnostic testing and 4-drug antitubercular regimen for patients with chronic pulmonary lesions included in the California analysis, patients may require isolation with associated costs. The cost assumed for diagnosis of chronic pneumonia was similar to that of uncomplicated pneumonia, but it is likely higher due to a greater number of chest CT scans used in these patients. We included a daily dose of 800 mg of fluconazole for chronic pneumonia, although 40-mg doses are often used in Arizona patients. The California model assumed that 2% of patients with disseminated disease would receive lifelong treatment with liposomal amphotericin B. Our experience in Arizona is that patients would likely transition to intermittent administration of once or twice a week. We did not have specific data sources to incorporate these potential differences from the California analysis. Had we incorporated these changes, some costs would increase and some would decrease. The differences are unlikely to have a significant effect on the overall costs. Further research is needed to confirm possible treatment pattern differences in Arizona.

## CONCLUSIONS

Valley fever represents a substantial economic burden to Arizona. Although there is currently no vaccine, the concept is clearly feasible given that individuals who recover from Valley fever seem to acquire lifelong immunity [28]. Extensive research is underway to develop an effective vaccine, which would have a substantial impact on morbidity, mortality, and costs associated with Valley fever in Arizona as well as other endemic regions [29]. Although the ultimate goal is to prevent Valley fever, there is also a need for earlier diagnosis as well as safer and more effective antifungals. Considerable advances in medications with novel mechanisms and formulations to improve both safety and effectiveness are also underway [29]. From a public health perspective, there is an urgent need for the availability of both vaccines and improved therapeutic options. With rates of Valley fever continuing to rise in Arizona and other locations in the Southwest, and the substantial cost burden of the disease ($736 million in Arizona in 2019 and $700 million in California in 2017), now is the time to push forward to solve this public health issue.


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