Impact of delays in diagnosis on healthcare costs associated with blastomycosis, coccidioidomycosis and histoplasmosis in a commercially insured population

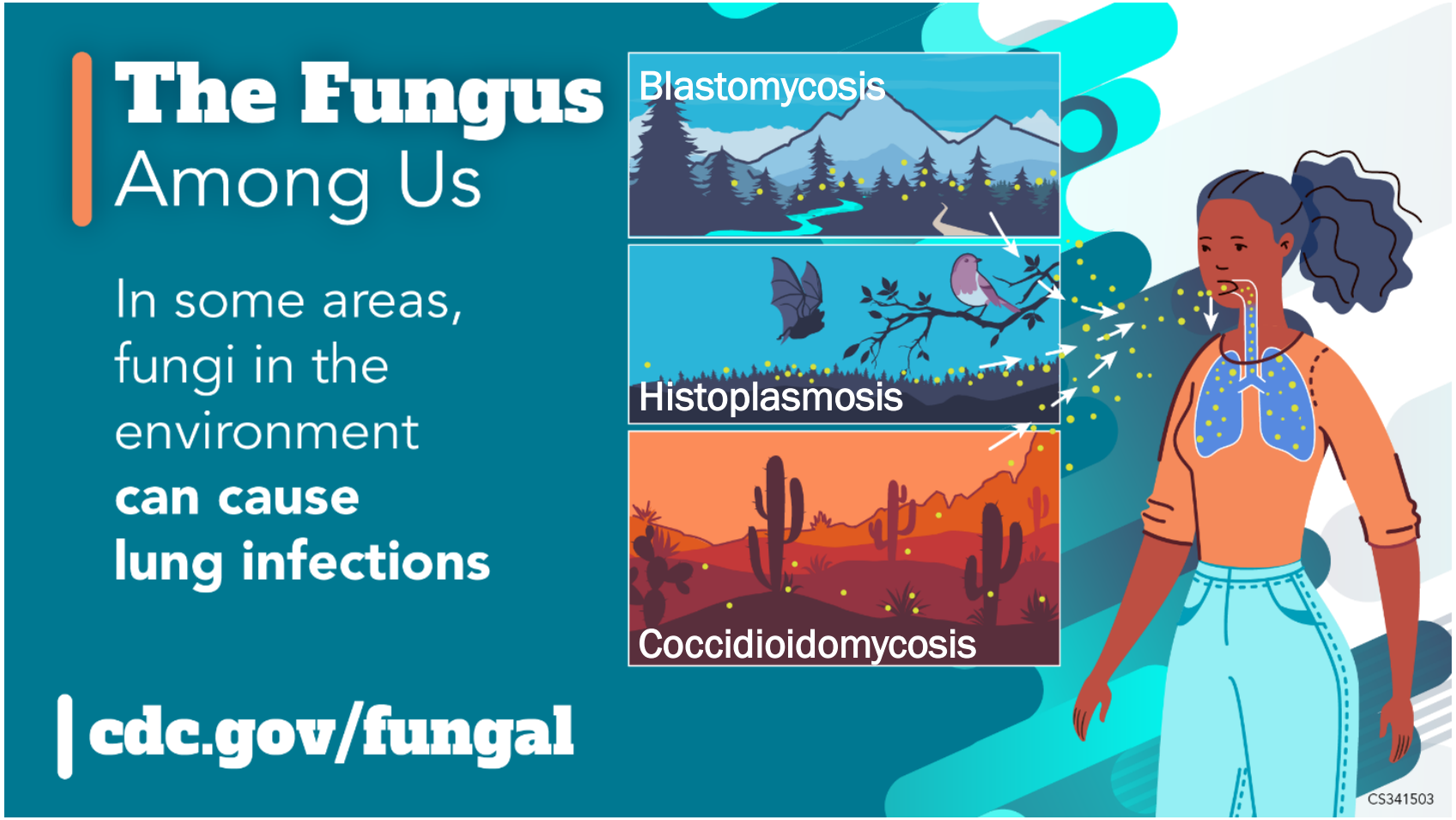
December 16th 2024

Authors:

(CDC/NCEZID/DFWED/MDB):
Kaitlin Benedict, Michelle Fearon Scales, Mitsuru Toda, Ian Hennessee, Sam Williams

(CDC/NCEZID/DFWED/OD):
Jason Massey

Blastomycosis, histoplasmosis, and coccidioidomycosis are environmentally acquired fungal pneumonias



Background: Symptoms

- Clinical signs and symptoms are nonspecific and often resemble those of other respiratory infections
- Often mistaken for bacterial or viral community-acquired pneumonia

Fever

Cough

Fatigue

Headache

Night sweats

Muscle aches

Background: Unresolved illness, repeat healthcare visits

23–38 days (median time between seeking healthcare and diagnosis)

56%–70% receive **another diagnosis** before being tested for an endemic fungal infection

54%–60% see provider **≥3 times** before tested for an endemic fungal infection

Benedict K, Ireland M, Weinberg MP, Gruninger R, Weigand J, Chen L, et al. Enhanced Surveillance for Coccidioidomycosis, 14 U.S. States, 2016. *Emerging Infectious Diseases*. 2018 Aug; 24(8).
Alpern JD, Bahr NC, Vazquez-Benitez G, Boulware DR, Sellman JS, Sarosi GA. Diagnostic Delay and Antibiotic Overuse in Acute Pulmonary Blastomycosis. *Open Forum Infect Dis*. 2016 Apr 19;3(2):ofw078.
Benedict K, McCracken S, Signs K, Ireland M, Amburgey V, et al. Enhanced Surveillance for Histoplasmosis–9 States, 2018–2019 . *Open Forum Infect Dis*. 2020 Sept; 7(9):ofaa343.

Background: Overuse of unnecessary antibiotics

>50% receive **antibiotics** before diagnosis of histoplasmosis or coccidioidomycosis

Most patients receive ≥2 rounds of **antibiotics** before being tested for an endemic fungal infection

Benedict K, Ireland M, Weinberg MP, Gruninger R, Weigand J, Chen L, et al. Enhanced Surveillance for Coccidioidomycosis, 14 U.S. States, 2016. *Emerging Infectious Diseases*. 2018 Aug; 24(8).
Alpern JD, Bahr NC, Vazquez-Benitez G, Boulware DR, Sellman JS, Sarosi GA. Diagnostic Delay and Antibiotic Overuse in Acute Pulmonary Blastomycosis. *Open Forum Infect Dis*. 2016 Apr 19;3(2):ofw078.
Benedict K, McCracken S, Signs K, Ireland M, Amburgey V, et al. Enhanced Surveillance for Histoplasmosis–9 States, 2018–2019 . *Open Forum Infect Dis*. 2020 Sept; 7(9):ofaa343.

Background: Increased healthcare costs

- A previous study reported that diagnostic delays in coccidioidomycosis were associated with >$500,000 increase in healthcare costs at a single center (n = 276 patients) in Tucson, Arizona.[1]
- However, this association has not been examined for coccidioidomycosis in other areas or for blastomycosis or histoplasmosis.
- Large-scale data are needed to guide public health action and policy.

1. Donovan et al 2019. *EID.* https://pmc.ncbi.nlm.nih.gov/articles/PMC6711243/

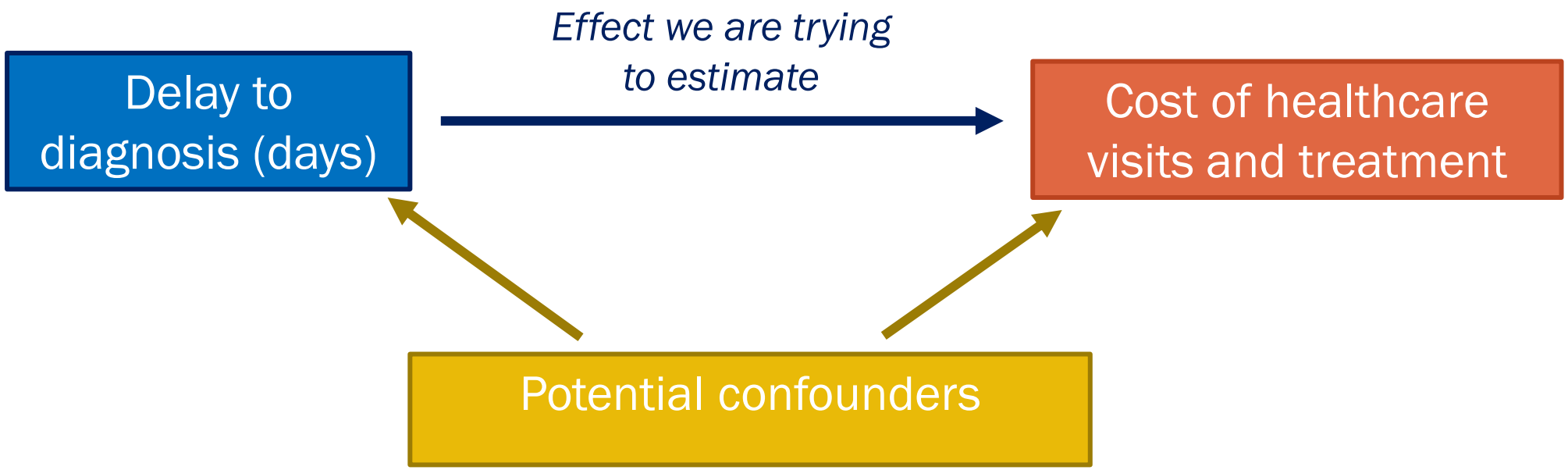
Project Objective and Hypothesis

- Project objective: Our goal is to model the impact of diagnostic delays on cost of treatment for endemic mycoses (coccidioidomycosis, blastomycosis, histoplasmosis).

- We hypothesize that diagnostic delays will significantly increase the cost of treatment.

- We are using a large commercial health insurance claims database to evaluate this question.

Causal Diagram



Confounders: Sex, age group, urbanicity, insurance status, antibiotics, antifungals, previous immune condition

Methods – Data

- Used MarketScan health insurance claims data to identify patients diagnosed with histoplasmosis, coccidioidomycosis, blastomycosis (based on ICD-10 codes) during 2017-2022
- Patients needed to be continuously enrolled in the 90 days before and 365 days after their diagnosis (index date)
- Identify compatible symptoms or respiratory illnesses that could be mistaken for fungal disease
- **Delay time**: the number of days between the first visit for compatible symptoms and the index date
- **Total costs (2024 USD) associated with disease**: outpatient visits, hospitalizations, antibiotics, and antifungals
- **Adjust for demographics**: sex, age, region, insurance type, urbanicity, and presence of underlying condition(s)

Methods – 2 issues

1. The association between delay in diagnosis and cost may be confounded by certain characteristics (e.g., patient age, underlying medical conditions, etc.). To address this, we needed to use **probability weights**.
2. The distribution of our exposure was heteroscedastic and zero-inflated, and the full outcome model was non-linear. This influenced both the type of **weights** and the type of **outcome models** we used.

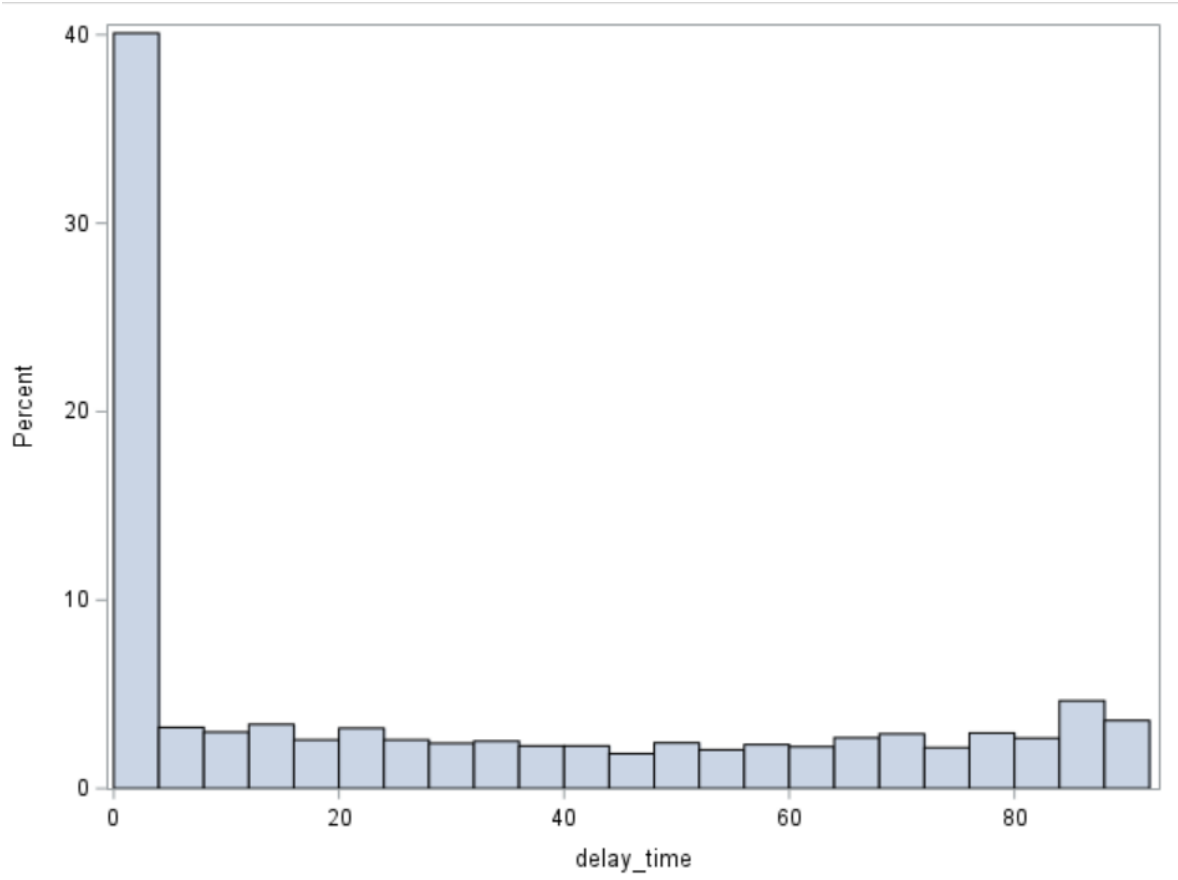
Methods – Resolving Causality Issue

- First, we used **quantile binning** to assign an equal number of observations to each of the five categories with delay times greater than zero. Zero delay time between the first visit for compatible symptoms and the index date received its own category.
- Second, we used **overlapping probability weighting** to balance out the populations within each delay-to-diagnosis time bin. This method ensures analysis of the effect of delayed diagnosis on costs, rather than impacts from confounding patient characteristics.
- Solving Simpson's Paradox with Inverse Probability Weighting | by Ehud Karavani | Towards Data Science

Exposure Issue (Weights)

Distribution of zero inflated exposure delay time

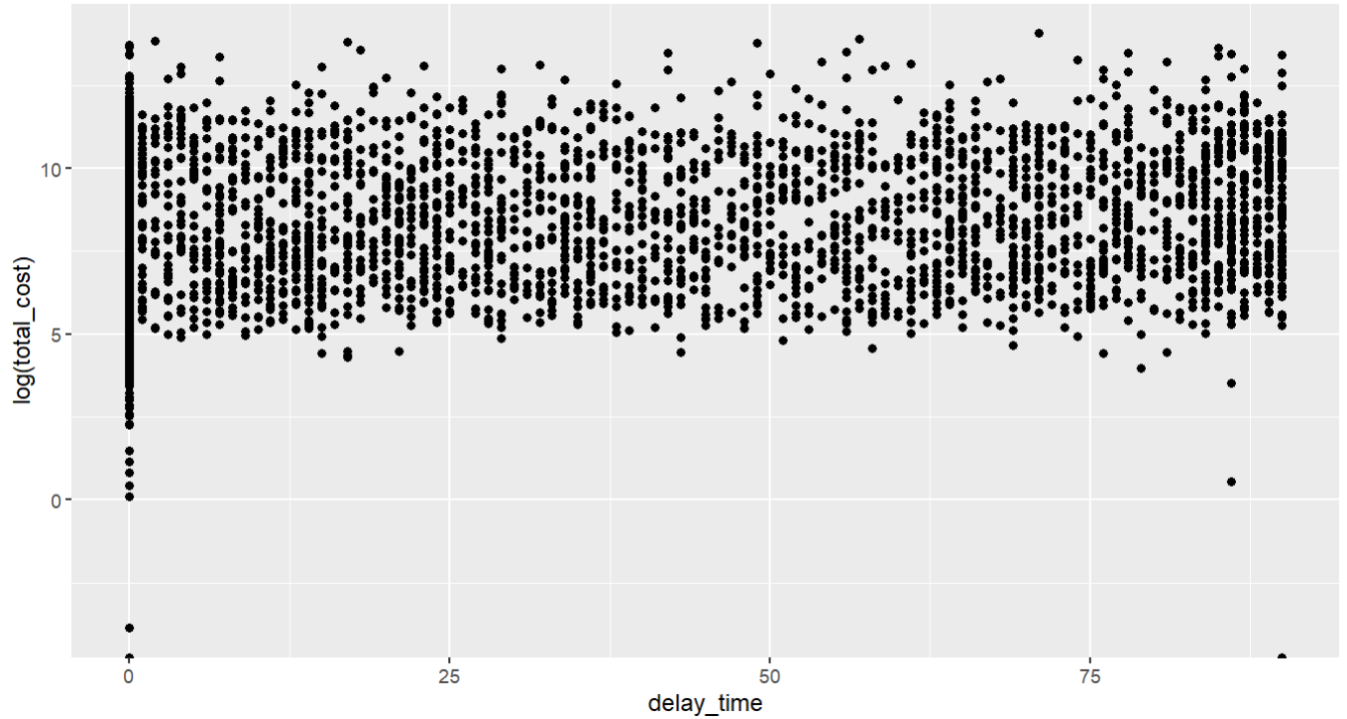
0 Delay time: N=1,654 (37.8%)
>0 Delay time: N=2,727 (62.2%)



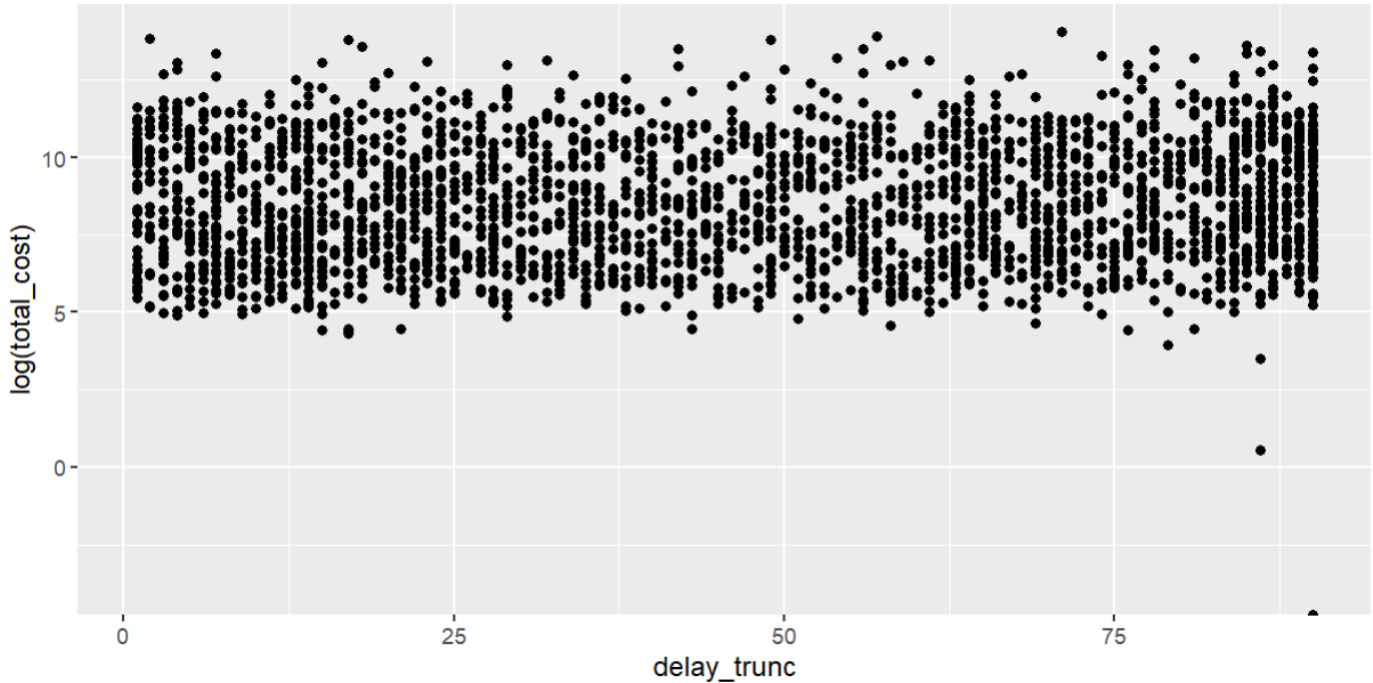
Exposure Issue (Outcome Models)

Scatterplots of the distribution of delay time by log(cost). The zero inflated exposure skewed the association when running linear regression

Non-truncated:



Truncated:



Methods – 2 Outcome Models

- **Truncated Linear Model** – Excluding those with no delay time, this model uses a subset of our dataset to show the change of USD per day of delay.
- **Categorical Regression Model** – Including the full analytic dataset, this model shows the mean extra costs accrued when comparing patients who experienced a delayed diagnosis within 3 subsequent 30-day time period categories to those who experienced no delay as our reference category.

Results (Truncated Linear Model)

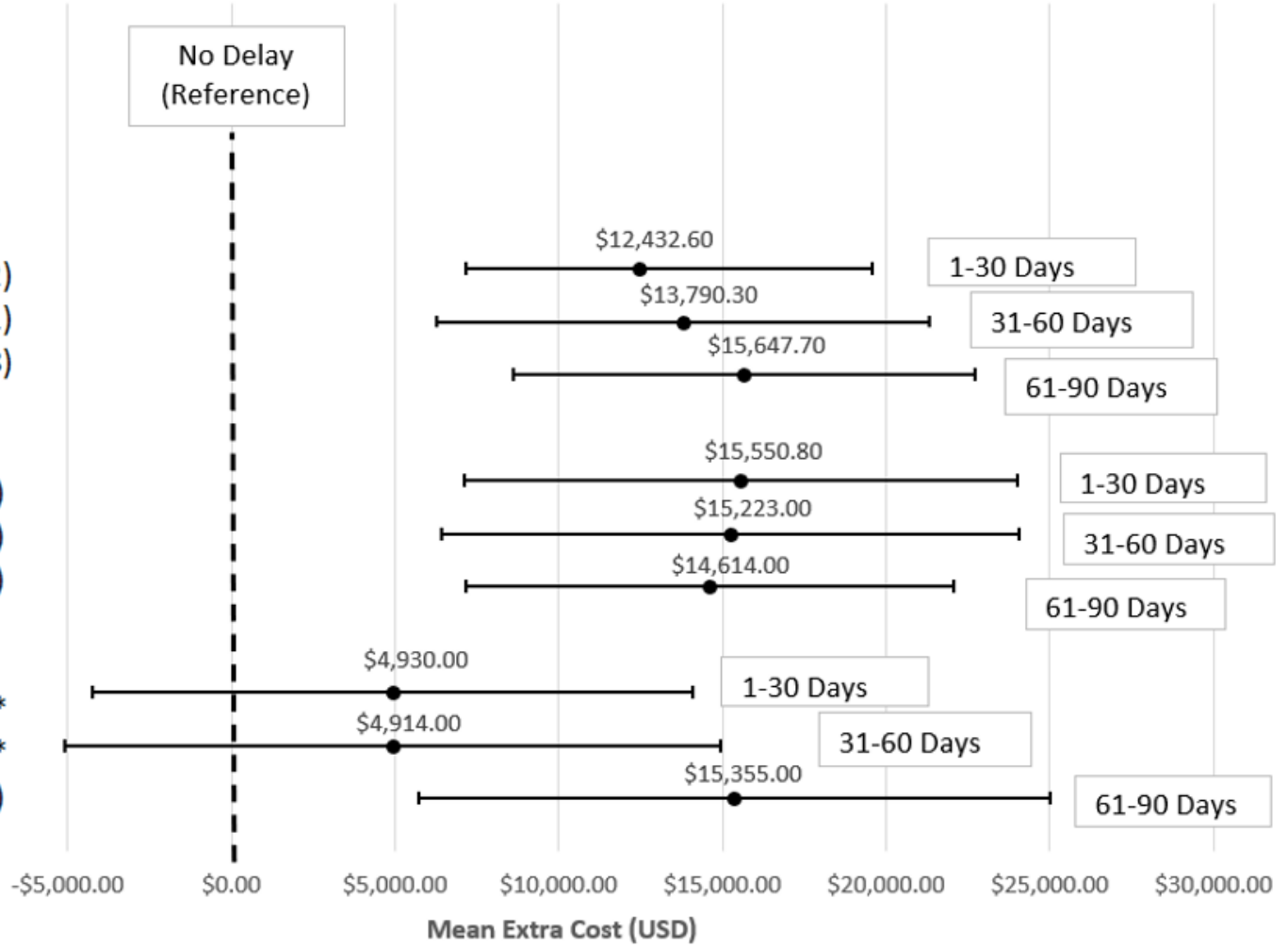
- **$131.00 ($54.67—$207.33)** increase of cost per day of delay time for blastomycosis, coccidioidomycosis, and histoplasmosis combined ($p<0.001$).

- **$174.86 ($35.68—$314.05)** increase of cost per day of delay time for coccidioidomycosis ($p=0.01$).

- **$38.00 (-$147.83—$223.83)** increase of per day of delay time for histoplasmosis ($p=0.69$).

Results (Categorical Model)

	Delay Days	N	95% Confidence Intervals
All 3 Diseases	**No delay**	1,654	Ref
	1-30	974	$12,432.60 ($7,147.12-$19,564.122)
	31-60	723	$13,790.30 ($6,267.25-$21,313.341)
	61-90	1,030	$15,647.70 ($8,600.48-$22,694.828)
Histoplasmosis	**No delay**	978	Ref
	1-30	350	$15,550.80 ($7,114.89-$23,985.75)
	31-60	319	$15,223.00 ($6,407.51-$24,038.73)
	61-90	533	$14,614.38 ($7,151.75-$22,076.83)
Coccidioidomycosis	**No delay**	552	Ref
	1-30	569	$4,930.78 ($-4,226.29-$14,085.40)*
	31-60	364	$4,914.74 ($-5,092.05-$14,919.17)*
	61-90	435	$15,355.03 ($5,728.31-$24,982.23)



Conclusions

- Healthcare costs for patients with blastomycosis, coccidioidomycosis and histoplasmosis and diagnostic delays were significantly higher than those without delays, similar to a previous study of patients with coccidioidomycosis from Tuscon, AZ.
- There were greater costs for patients with any delay that were diagnosed with histoplasmosis alone or greater than 60 days delay for those diagnosed with coccidioidomycosis.
- Costs increased with each day of delay, for coccidioidomycosis alone as well as for blastomycosis, coccidioidomycosis and histoplasmosis combined

Limitations

- Potential disease misclassification inherent in medical coding data.
- Patients who were never diagnosed or never sought care were not included.
- Our cost estimates only represent direct medical costs; indirect costs accounting for productivity loss are likely to be substantially higher.

Potential Impacts

- Encourage greater prioritization of early testing for fungal pathogens by demonstrating the costs of delays in time to diagnosis.
- Aim to reduce patient healthcare costs by improving early diagnosis and appropriate treatment, which also promotes antimicrobial stewardship by reducing inappropriate antibiotic use.
- Enhancing awareness in the medical and public health community about fungal community acquired pneumonia.
- In the future, our models may allow us to understand how different interventions that reduce diagnostic delays could reduce treatment costs.

Next Steps

- **Target journal and audience:** Planning to submit to *Clinical Infectious Diseases*. Aiming to reach a clinical, hospital administrator, and public health audiences.
- **Next steps:** Planning to conduct additional evaluations looking at proportion of costs from outpatient visit, hospitalization, and medication, and by disease type (pulmonary, disseminated, etc.).
    - Hope that this information will provide greater context for the burden of costs and interpeting out results.

Discussion Questions

- **Are there any other measures or information that we can provide from this analysis to further convince partners of the importance of early diagnosis?**
- **What other messaging do you think would be impactful to include in this paper and its promotion?**
    - How can we promote resources to help justify the need for earlier consideration of fungal etiology and help providers test for fungal infections to distinguish from other forms of CAP?
- **How can we use these findings to leverage policy changes? What scale of policy changes would be most impactful (e.g., health systems or insurance providers)?**
    - What systems-level changes can be made to help facilitate testing (e.g., prompts within EMR systems)?

Supplemental Slides

Methods - Weighting

1. Create N = 6 bins make sure zero is its own bin. Non-zero bins are broken into quintiles

2. Fit a multinomial logistic regression model to these categories to obtain the predicted probabilities of falling into the observed exposure category (this creates our PS variables)

3. Use inverse probability weighting/other weighting (overlap, etc.) to transform PS into a weight variable

4. Check balance of different weights

5. Now run regression models with weights

Weight Balance