# Using Real World Data from CURE ID to Identify Drug Repurposing Opportunities in Mycology: Impact of Climate Change

Marco Schito[1], Reema Charles[2], Barbara Milani[3], Daniel Argaw Dagne[3], Pam Dasher[1], Heather Stone[2]

Critical Path Institute[1], U.S. Food and Drug Administration[2], World Health Organization[3]

CDRC
CURE DRUG REPURPOSING COLLABORATORY

CURE ID
Challenging cases... New approaches

# Agenda

- Introduction to CDRC
- CURE ID: U.S. FDA vision for a public resource and WHO partnership
- WHO survey on subcutaneous mycoses
- CURE ID data on implantation mycoses and next steps
- Impact of climate change on coccidioidomycoses
- Summary

# Problem statement

- A significant percentage of the world's population suffers from diseases where no approved therapy exists

- For regulatory drug approval, a sponsor must submit a new drug application to ensure marketing of safe and effective drugs (for all indications)

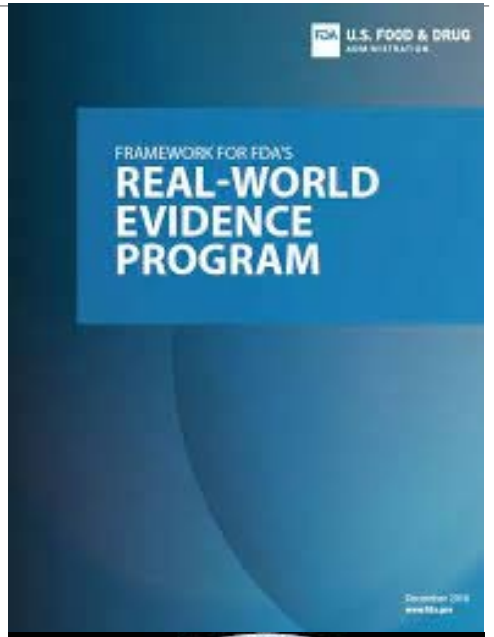
- The commercial incentives for drug development may not work for all diseases and in all places…
  - Diseases are often neglected
  - No ROI despite evidence of drug efficacy
  - Unlikely to pursue additional indications for generic drugs

## Question

- Can the collection of real-world data regarding off-label prescriptions be used to advance drug repurposing?

# Using real-world data to advance drug repurposing

- Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.
- There is considerable interest in using RWD to generate Real-World Evidence (RWE) to support regulatory decisions about the efficacy of drug products.
- Regulators have used RWD primarily in its evaluation of safety and only in limited circumstances to inform decisions about efficacy.
- How can the scientific community move from the non-systematic collection of anecdotal reports to informing clinical trials, and potentially drug labeling?

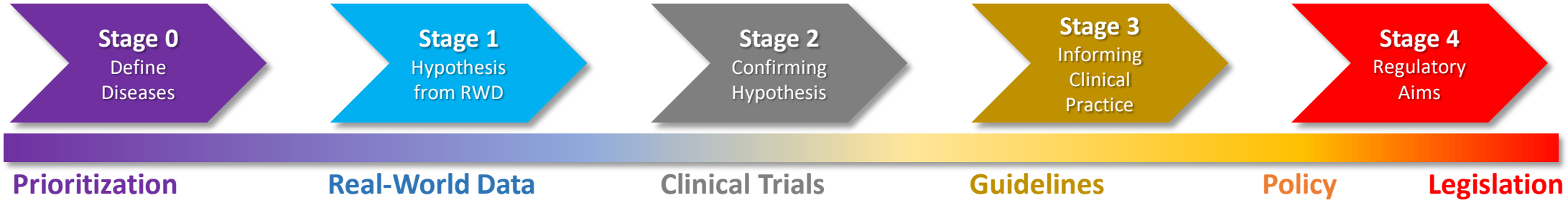



# CURE Drug Repurposing Collaboratory

C-Path launched a public-private partnership with U.S. FDA and National Center for Advancing Translational Science (NCATS/NIH) in June 2020 to bring stakeholders together and address how drug repurposing can be accelerated

## Mission

- Become the global, public source of validated real-world data to advance drug repurposing for diseases with the highest levels of unmet medical need
- On-patent to generic drugs (lack of commercial incentives & regulatory paths)
- Provide a forum for reviewing real-world data and building consensus
- Promote, where feasible, randomized controlled trials to confirm/refute the initial hypothesis
- Generate clinical evidence to influence clinical practice



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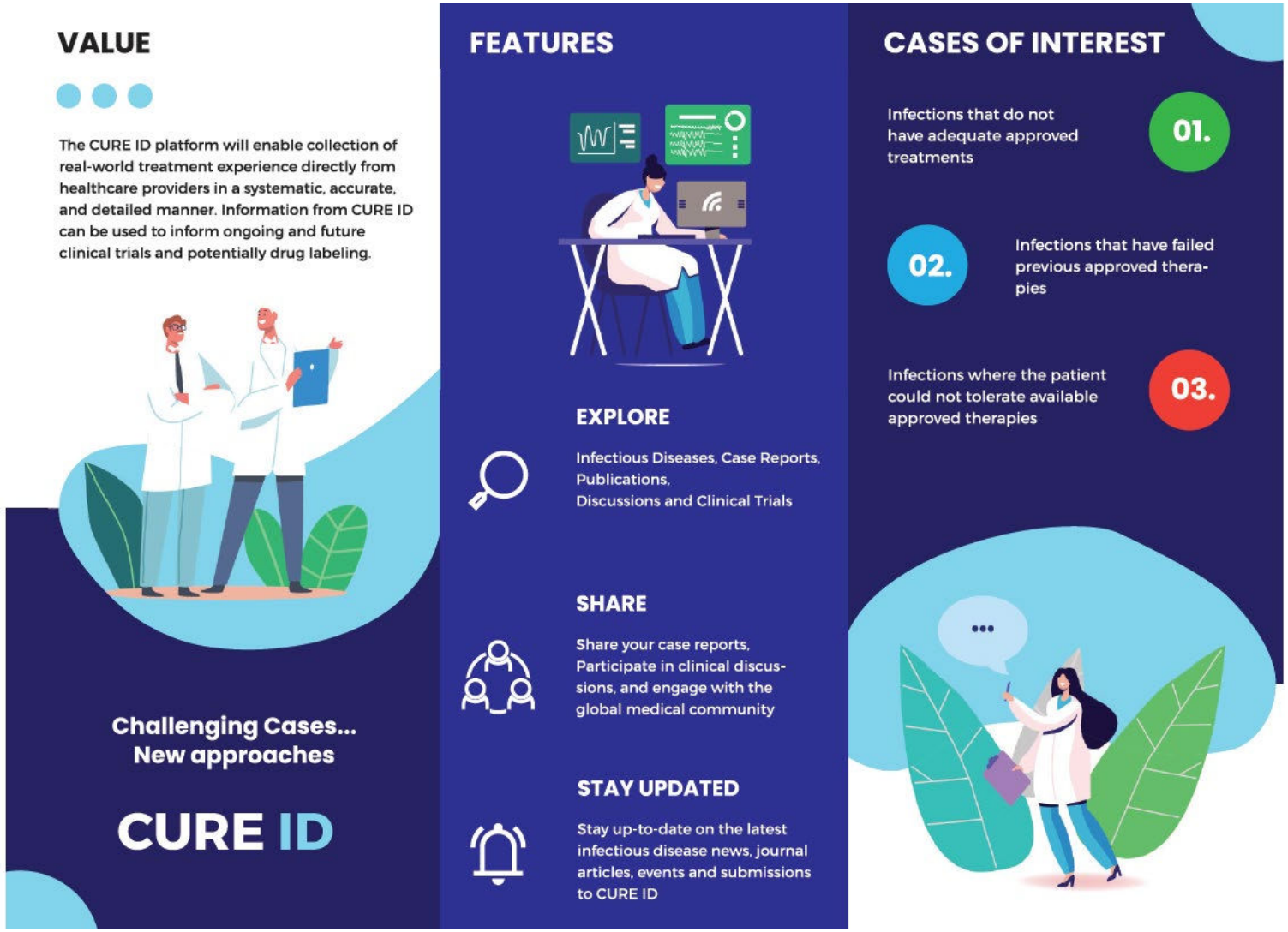
**Heather Stone (FDA)**

# A platform to capture novel uses of existing drugs

- Web-based tool
  - Computer, smartphone or mobile device
- Capture and share real-world experiences treating patients through a simple online case report form
- All data collected is HIPAA compliant and contains no PII
- Newsfeed
- Link to [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

https://cure.ncats.io



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**Barbara Milani (WHO consult)**

# World Health Organization (WHO) partnership

- WHO is collaborating with U.S. FDA and CDRC with the aim of collecting real world clinical data which can inform drug repurposing/clinical research

- Since 2019, WHO has been conducting a **landscape analysis to identify diseases** for which CURE ID may have the greatest utility

- Among the diseases to be investigated, WHO jointly with U.S. FDA and CDRC identified several **implantation infections**
  - Eumycetoma
  - Chromoblastomycosis
  - Sporotrichosis
  - (Actinomycetoma)

# Initial work to engage global experts

- Initial inquiry with 10–12 key informants
  - International and national experts on implantation mycoses

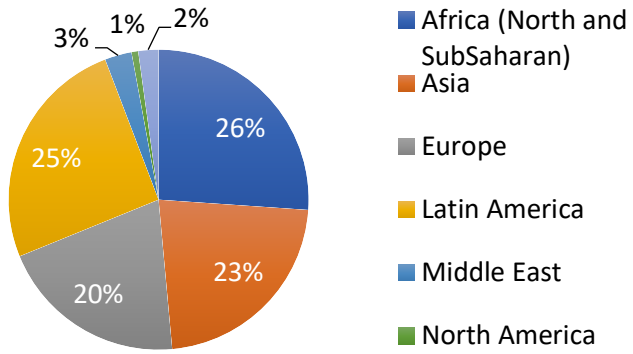
- WHO online survey on implantation mycoses January 7th to March 15th, 2022
  - Of 318 people who approached the survey, 142 provided complete answers and 138 respondents declared their country. There were respondents from 47 countries, from all continents

- Extensive dissemination of the survey

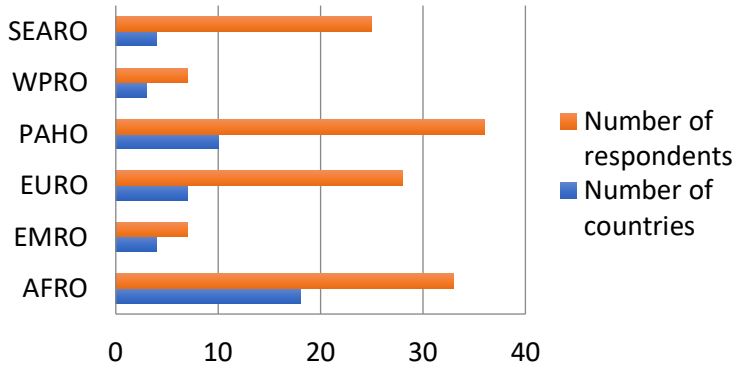
- ISNTD webinars
  - The launch of the WHO survey with 6 speakers (4 country experiences: Madagascar, Brazil, Mexico, India) https://www.youtube.com/watch?v=aKhmkWbvp_4
  - Innovation in Data Collaborations for Future NTD Treatments https://www.youtube.com/watch?v=v7GRiKpXmIY

# WHO survey respondent profiles

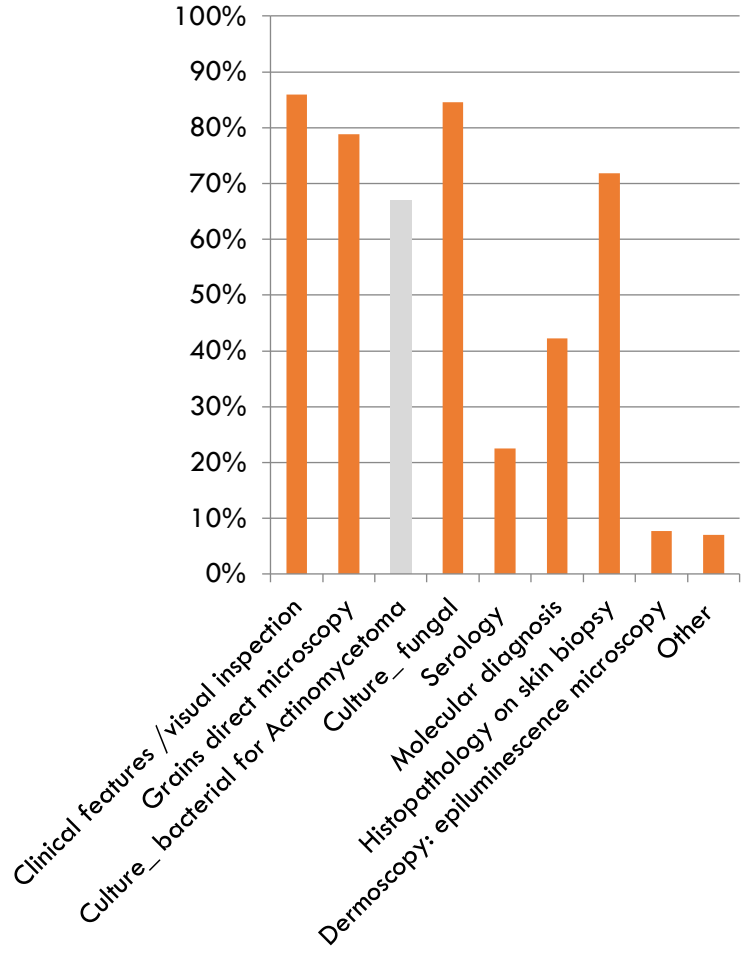
### Geographical distribution of respondents



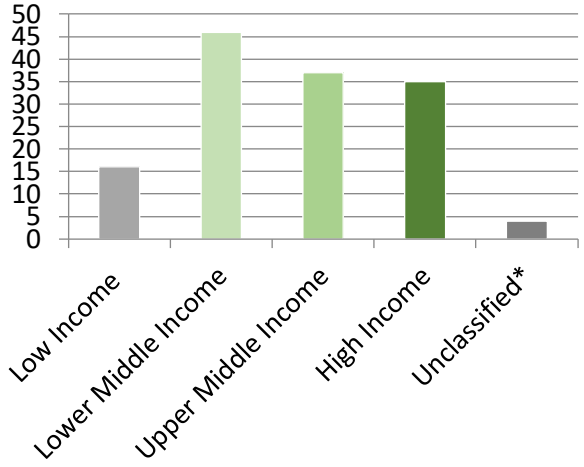

### Analysis of countries and respondents by WHO region



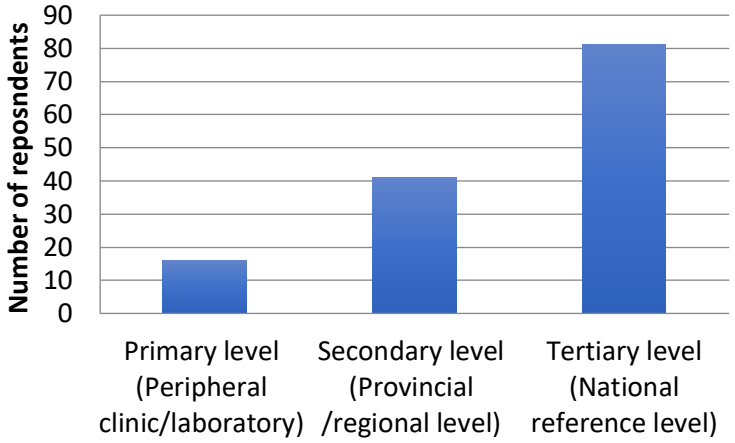

### Diagnostic methods available for implantation mycoses (Percentage)



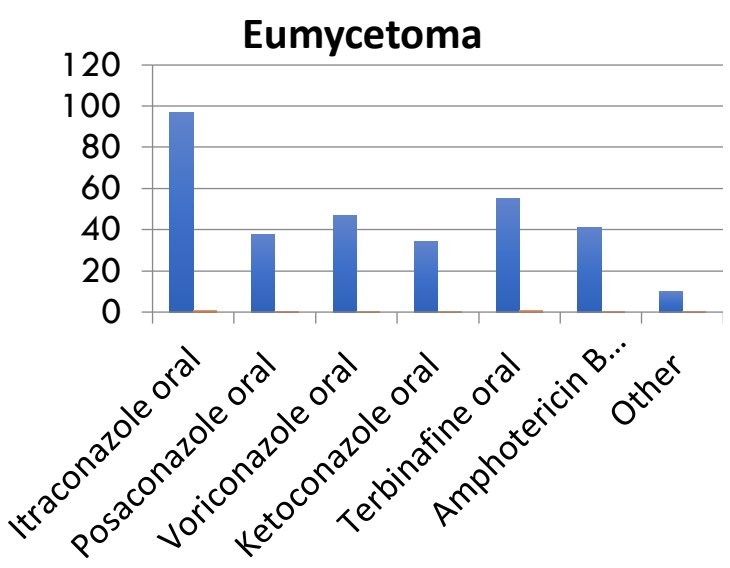

### Respondents by economic country classification

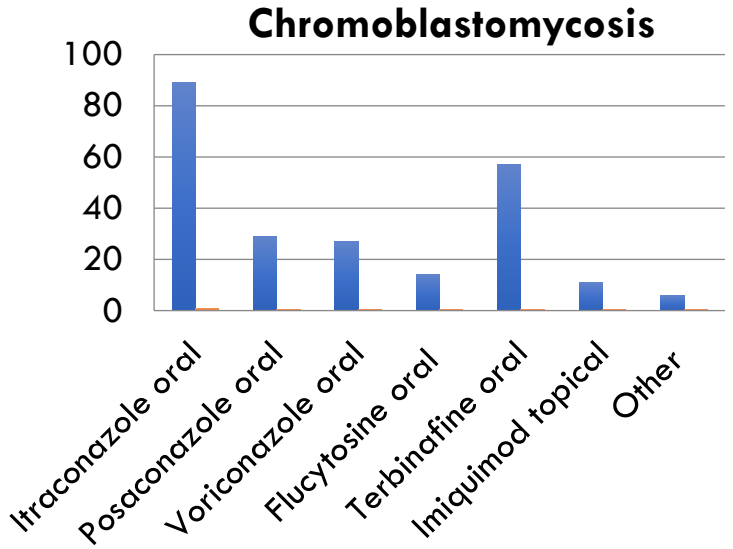


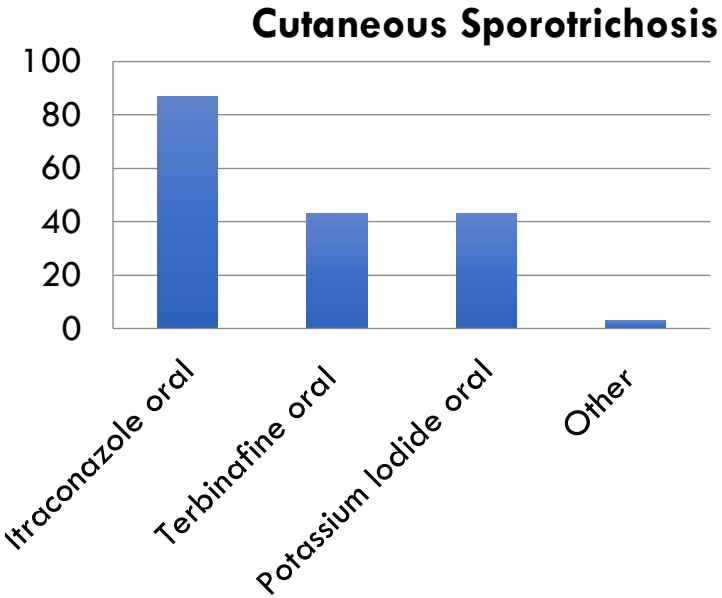

### Respondents by health system setting

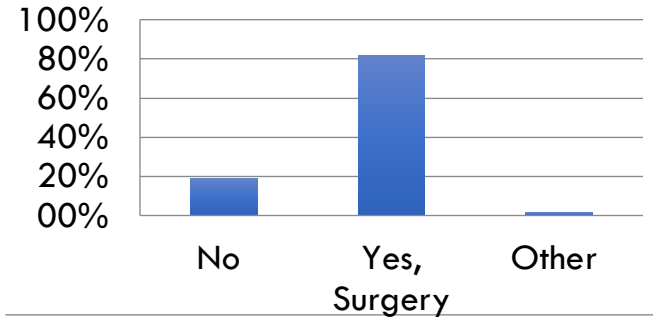


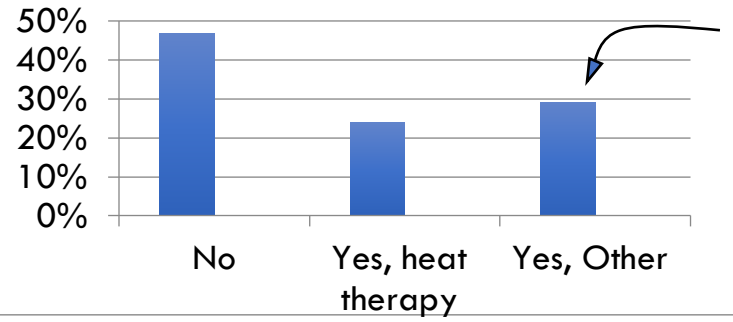
# Drug treatment practices for implantation mycoses



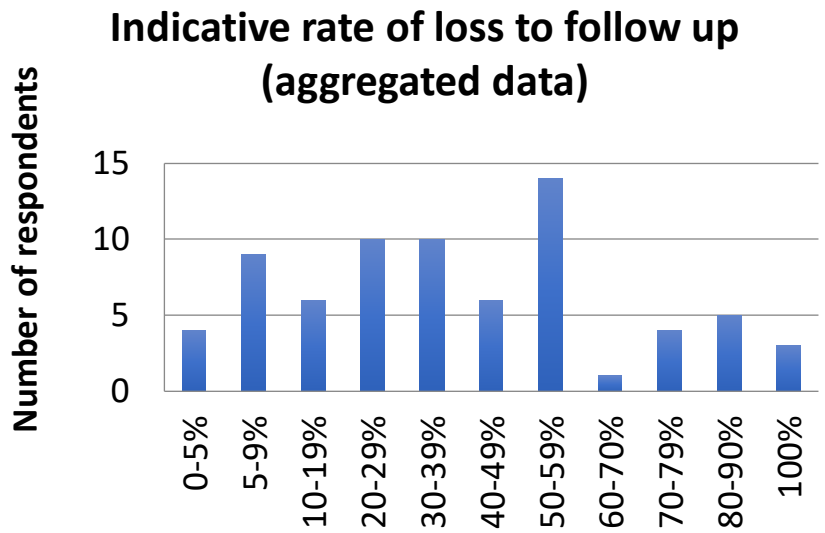




- Cryotherapy/cryosurgery (14%)
- Surgery/surgical excision (15%)

# Drug repurposing driven by lack of drug availability, affordability, and loss to follow up

| Answer | Indicated use by respondent (135) | Percentage |
|---|---|---|
| Yes (Available and affordable) | 75 | 56% |
| No | 60 | 44% |




| Medicine indicated as unavailable and/or unaffordable (* for Actinomycetoma) | Number of respondents |
|---|---|
| Itraconazole oral | 17 |
| Posaconazole oral | 24 |
| Voriconazole oral | 23 |
| Terbinafine oral | 4 |
| Potassium iodide oral | 2 |
| Flucytosine oral | 7 |
| Dapsone* | 5 |
| Rifampicin* | 1 |
| Amphotericin B IV | 5 |
| Liposomal amphotericin B | 7 |
| Streptomycin IV* | 3 |
| Amikacin IV* | 4 |
| Carbapenems IV* | 1 |
| Imiquimod topical | 1 |

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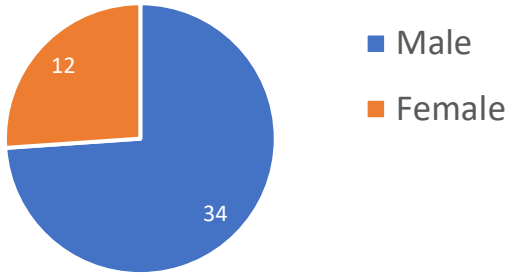
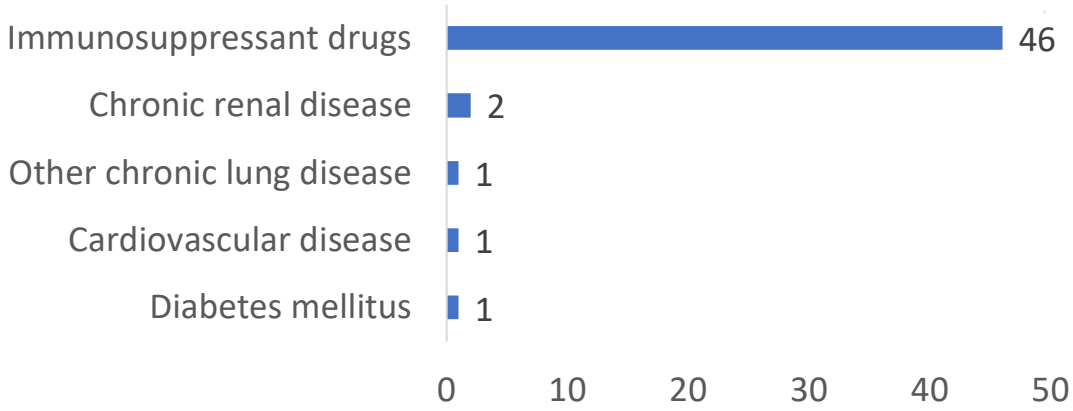
**Reema Charles (FDA)**

# CURE ID: Eumycetoma literature extracted case report profiles

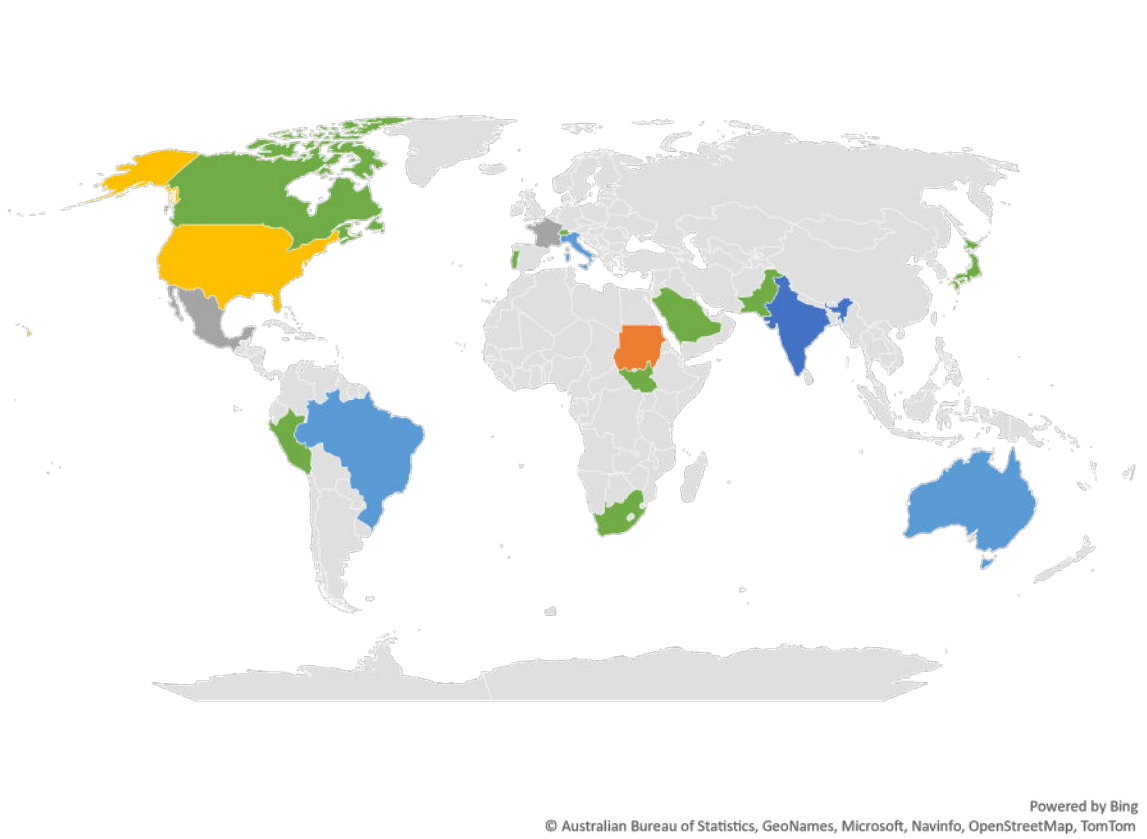
## Distribution by Gender



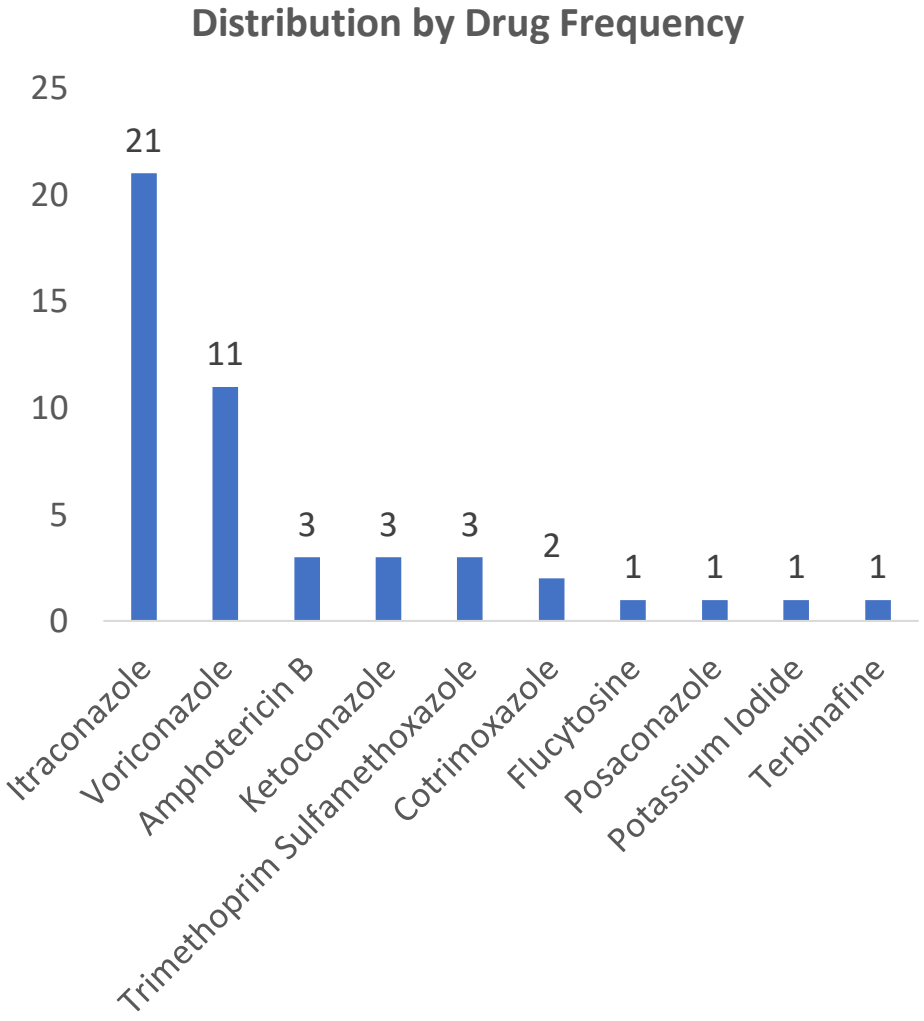

## Distribution by Co-morbidities

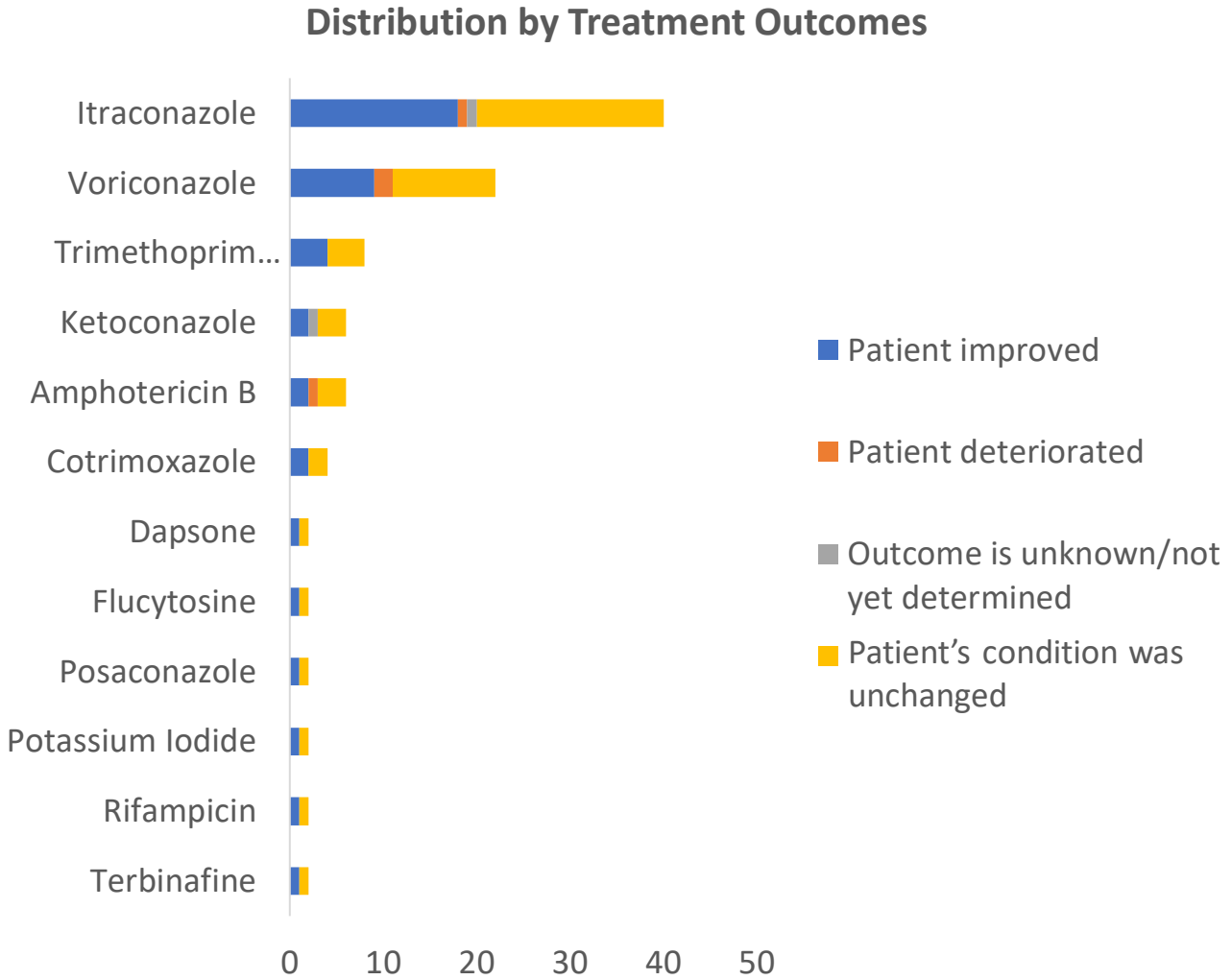



## Geographical Distribution



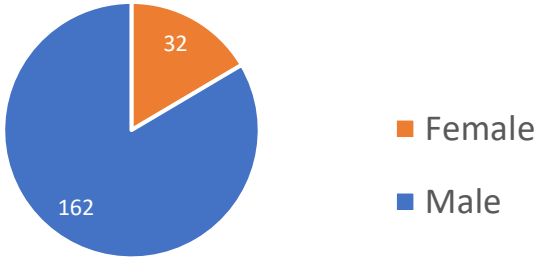
# CURE ID: Eumycetoma literature extracted case report treatment practice and outcomes



# CURE ID: Chromoblastomycosis literature extracted case report profiles

## Distribution by Gender

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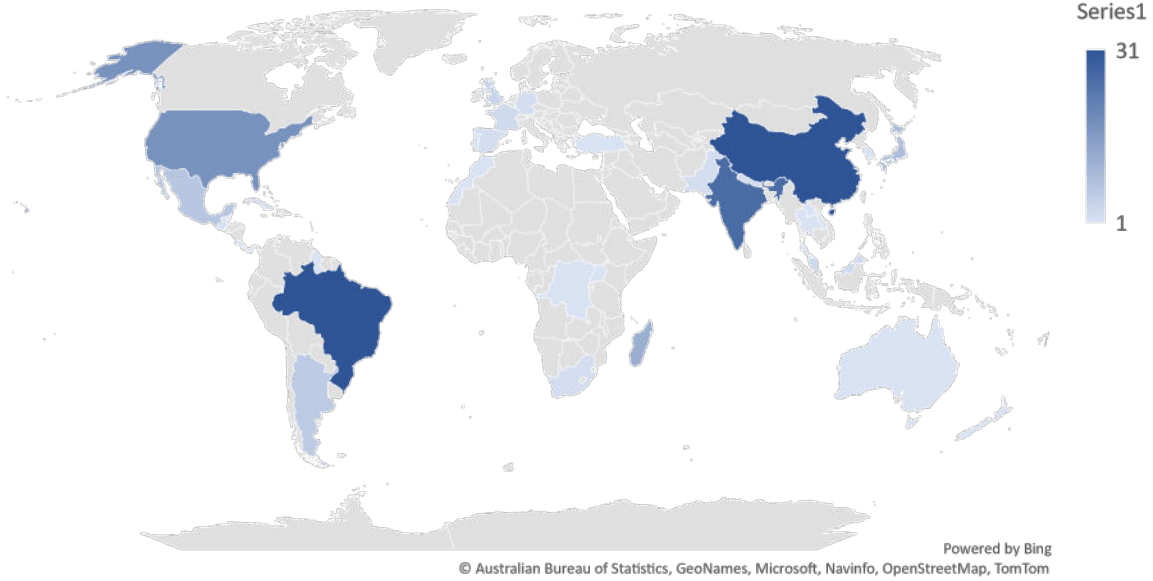


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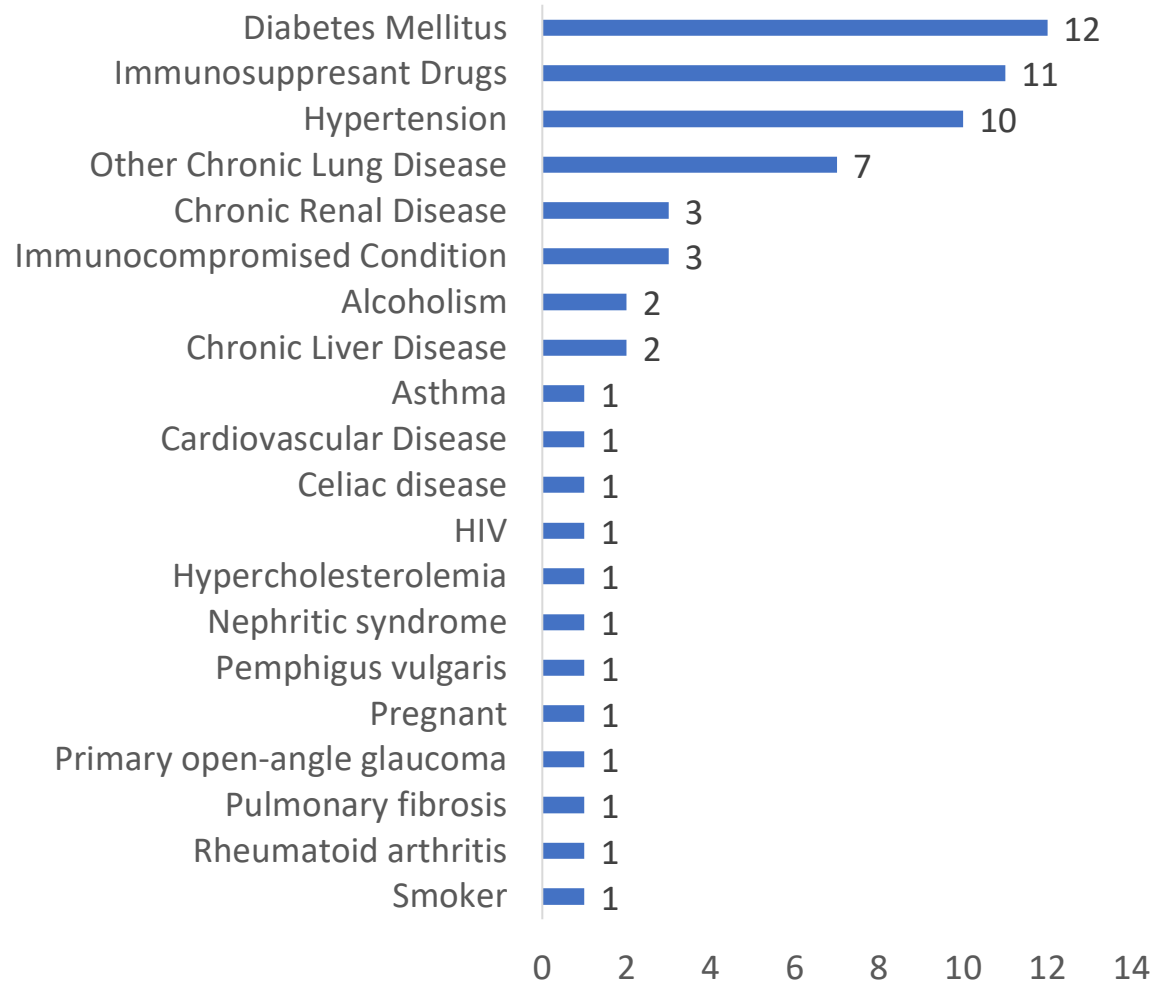

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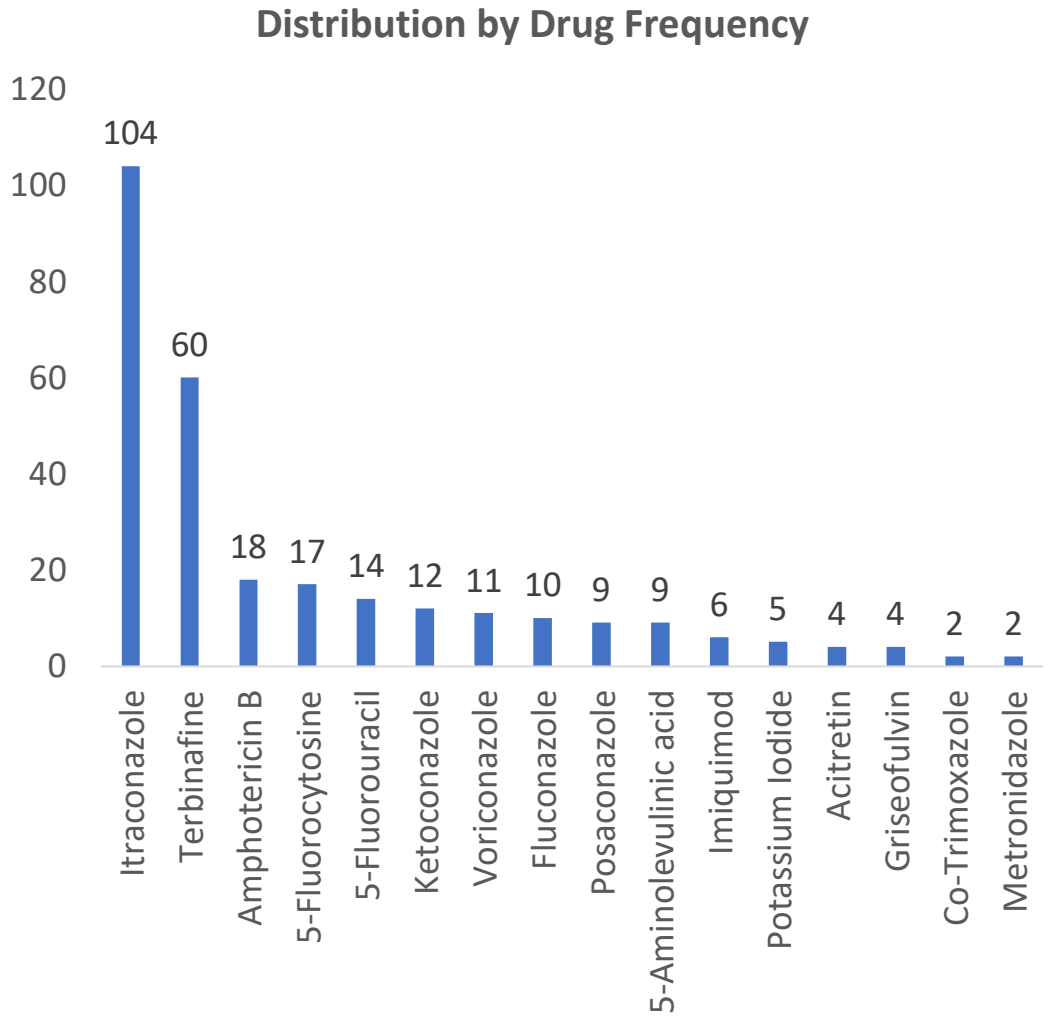
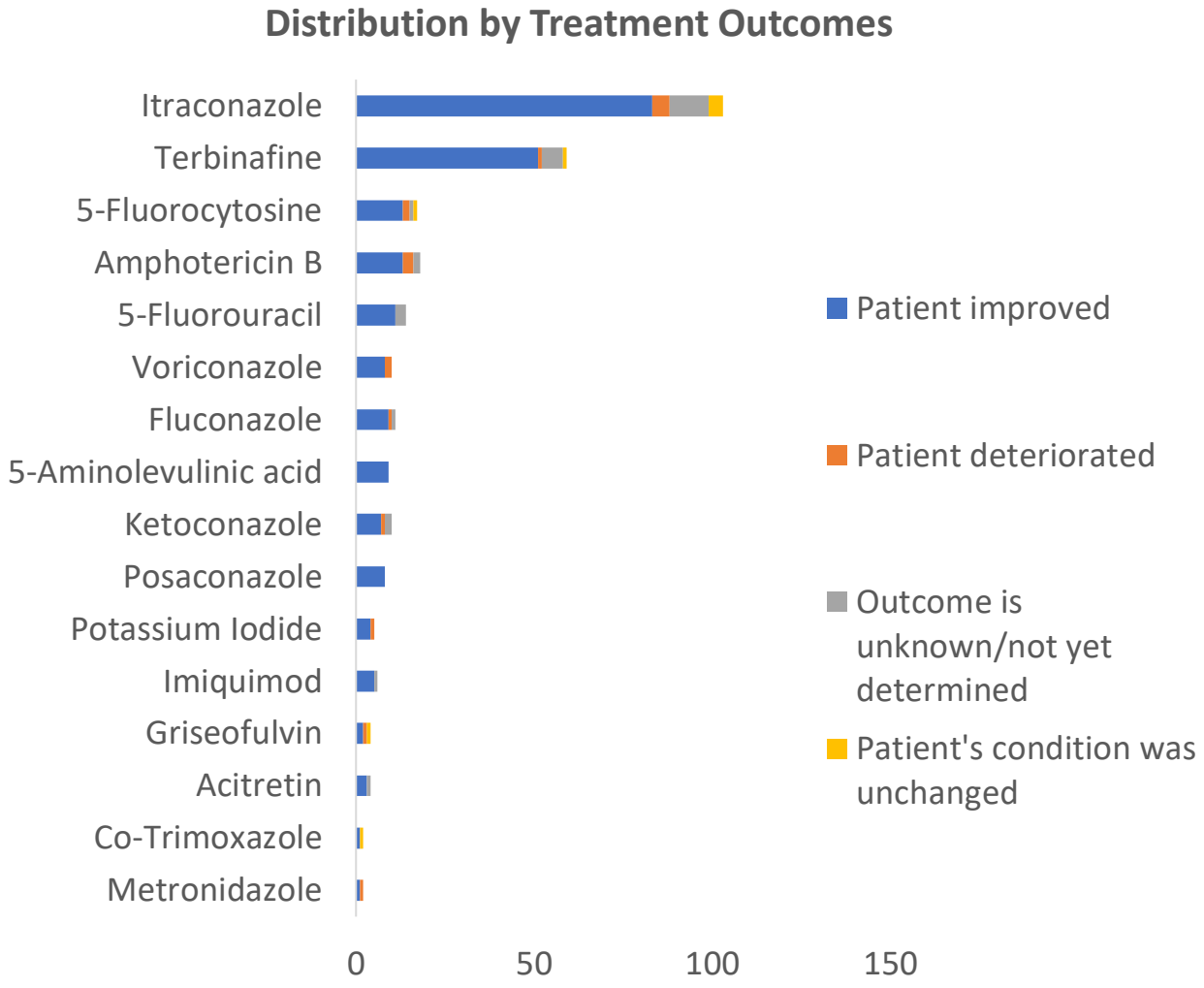
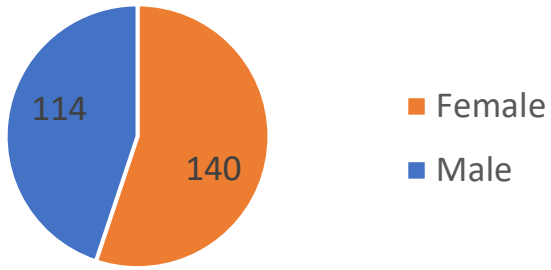


# CURE ID: Sporotrichosis literature extracted case report profiles

### Distribution by Gender

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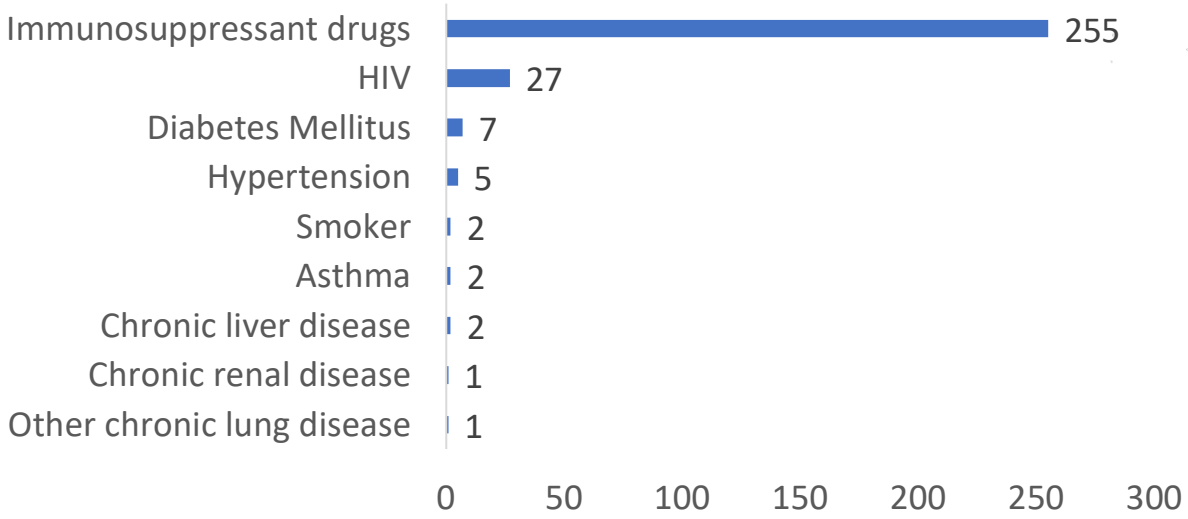


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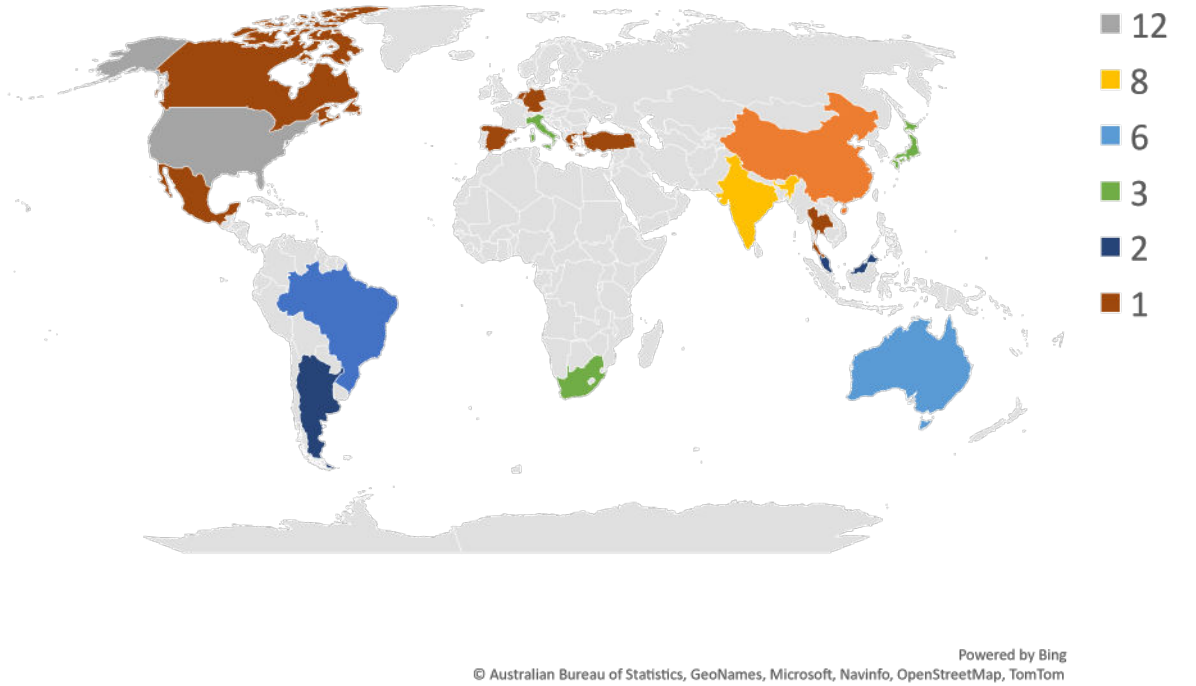

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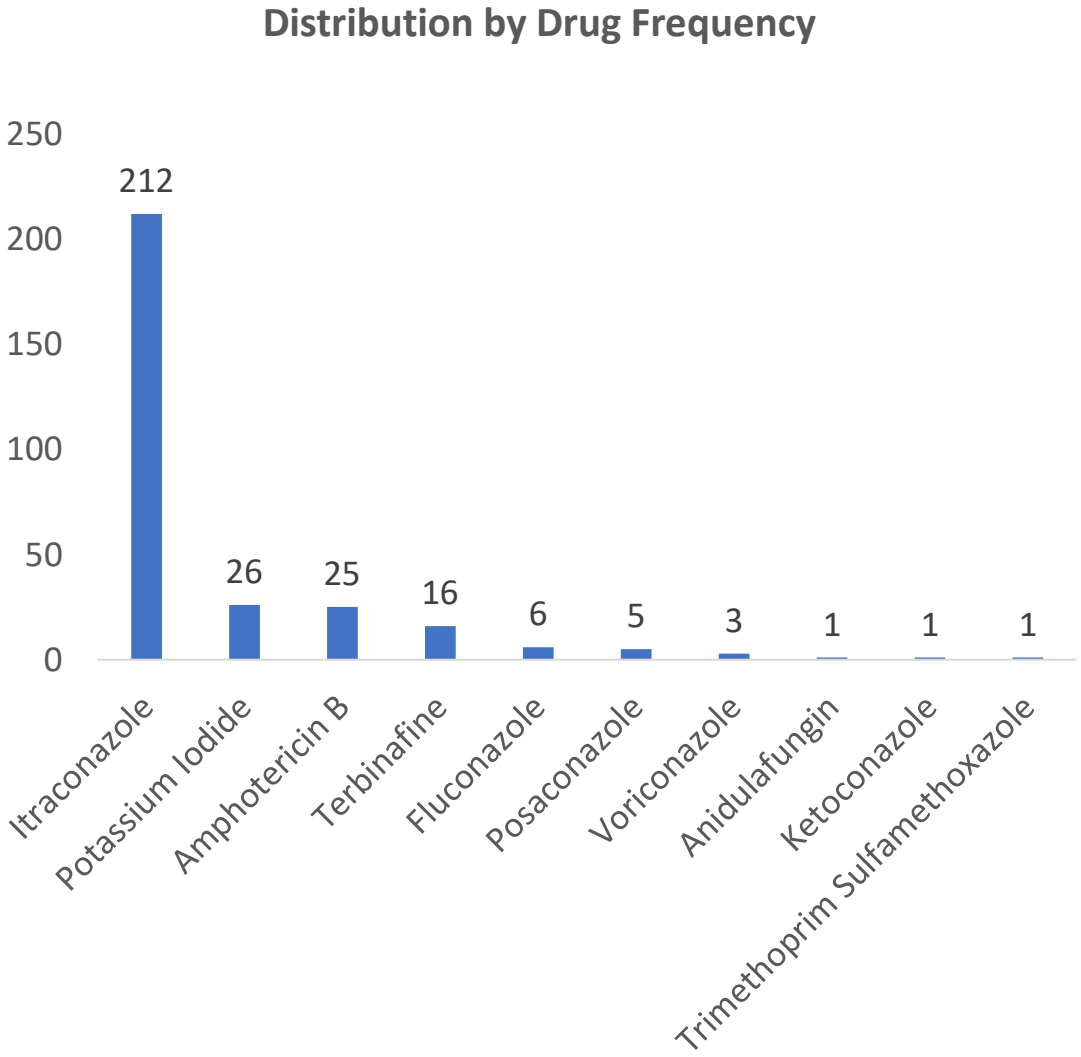
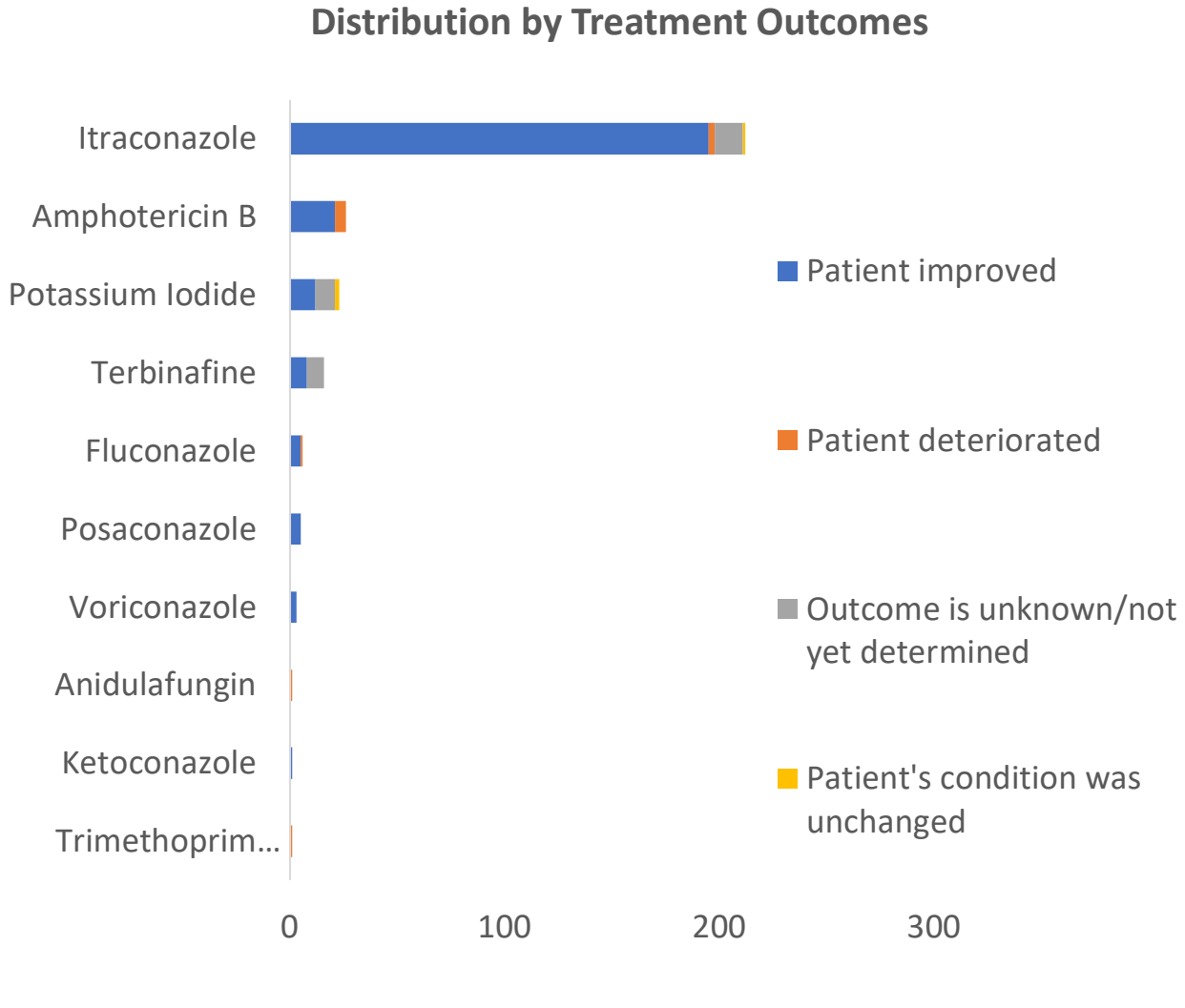


# Do prospectively collected treatment outcomes from patients align with literature?

**Next steps:**

- WHO, U.S. FDA and CDRC are engaging in bilateral discussions with several groups which could contribute data to CURE ID
- Publication of the collected data to inform:
  - Diagnostic capacity/techniques, level of drug repurposing, non-pharmacological interventions with this group of diseases
- Implantation mycosis sub-group under the auspices of CDRC
  - Identification of experts/groups which can act as ambassadors
  - Evaluate covariates (disease severity, contemporaneous,…)

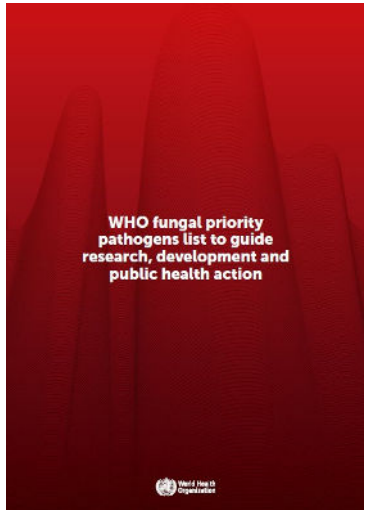
**Challenges**:

- No well-established networks for implantation mycoses: CURE ID as an opportunity to create such networks & collect treatment and epidemiological data

# WHO fungal priority pathogen list

- Exploring whether CURE ID could have value for other fungal diseases identified by WHO with the priority pathogen list
- Implantation, deep, and subcutaneous mycoses


| Critical group | High group | Medium group |
|---|---|---|
| *Cryptococcus neoformans* | *Nakaseomyces glabrata (Candida glabrata)* | *Scedosporium* spp. |
| *Candida auris* | *Histoplasma* spp. | *Lomentospora prolificans* |
| *Aspergillus fumigatus* | Eumycetoma causative agents | *Coccidioides* spp. |
| *Candida albicans* | Mucorales | *Pichia kudriavzeveii (Candida krusei)* |
| | *Fusarium* spp. | *Cryptococcus gattii* |
| | *Candida tropicalis* | *Talaromyces marneffei* |
| | *Candida parapsilosis* | *Pneumocystis jirovecii* |
| | | *Paracoccidioides* spp. |



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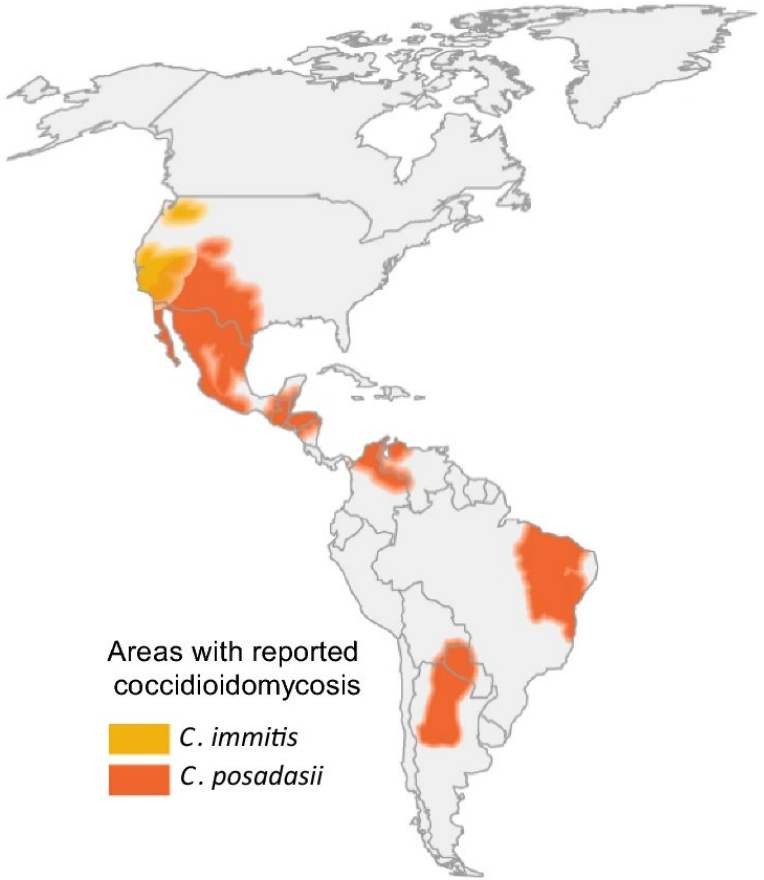
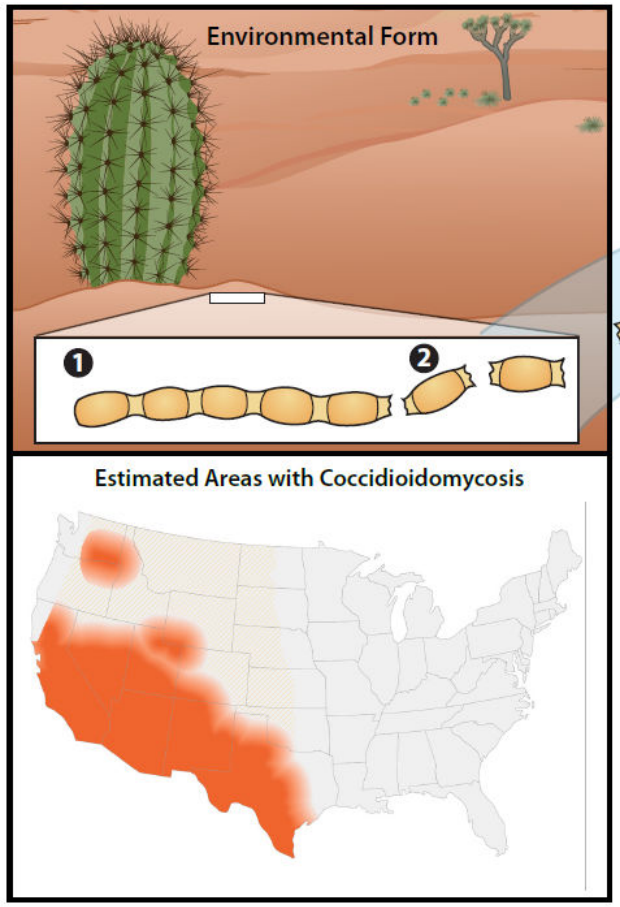
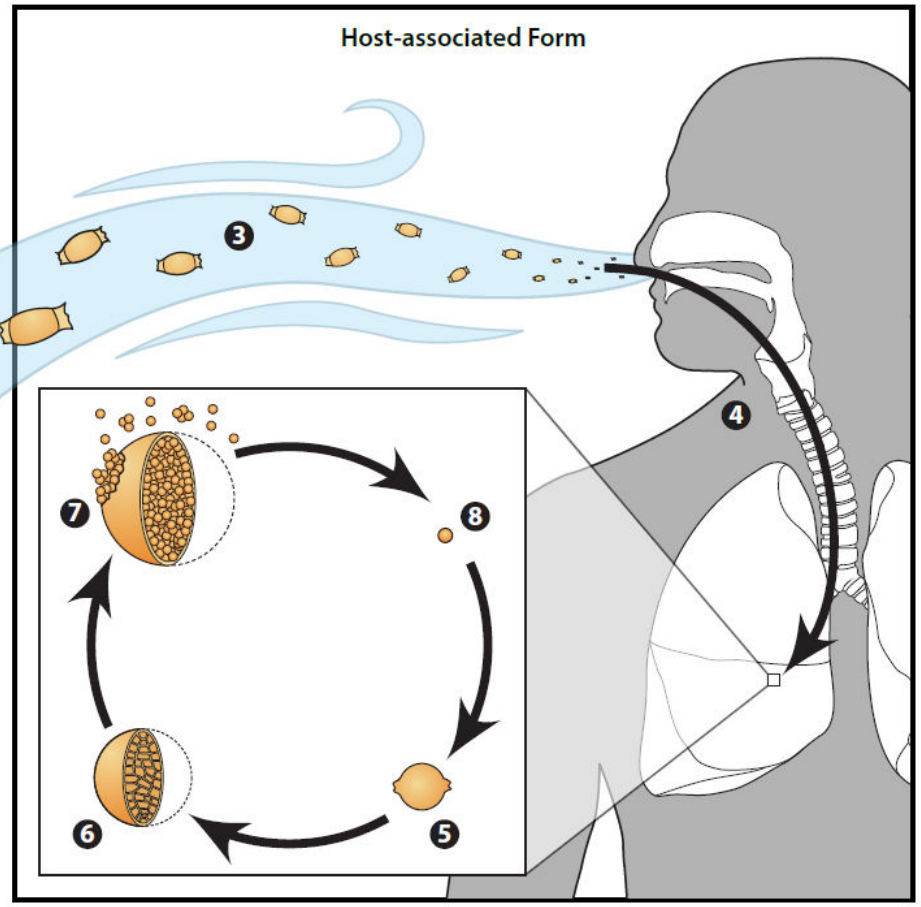
# Valley fever and the link to climate change



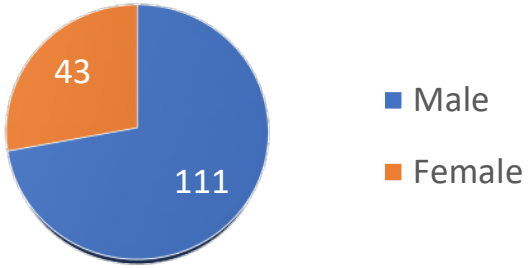




Ashraf et al. 2020. Mycopathologia 185, 843–865

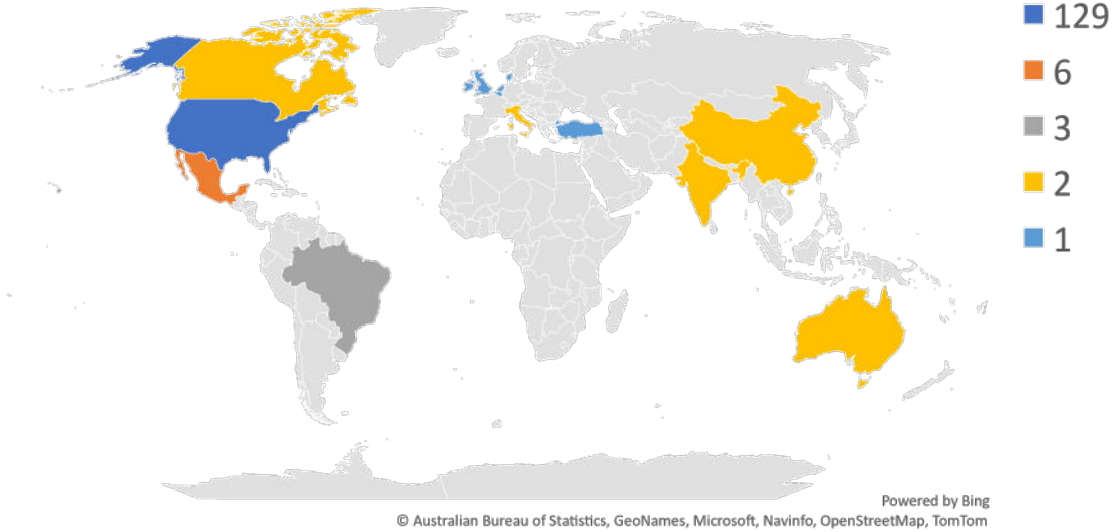
https://www.cdc.gov/fungal/diseases/coccidioidomycosis/causes.html

# CDRC data: Coccidioidomycosis literature extracted case report treatment practice and outcomes

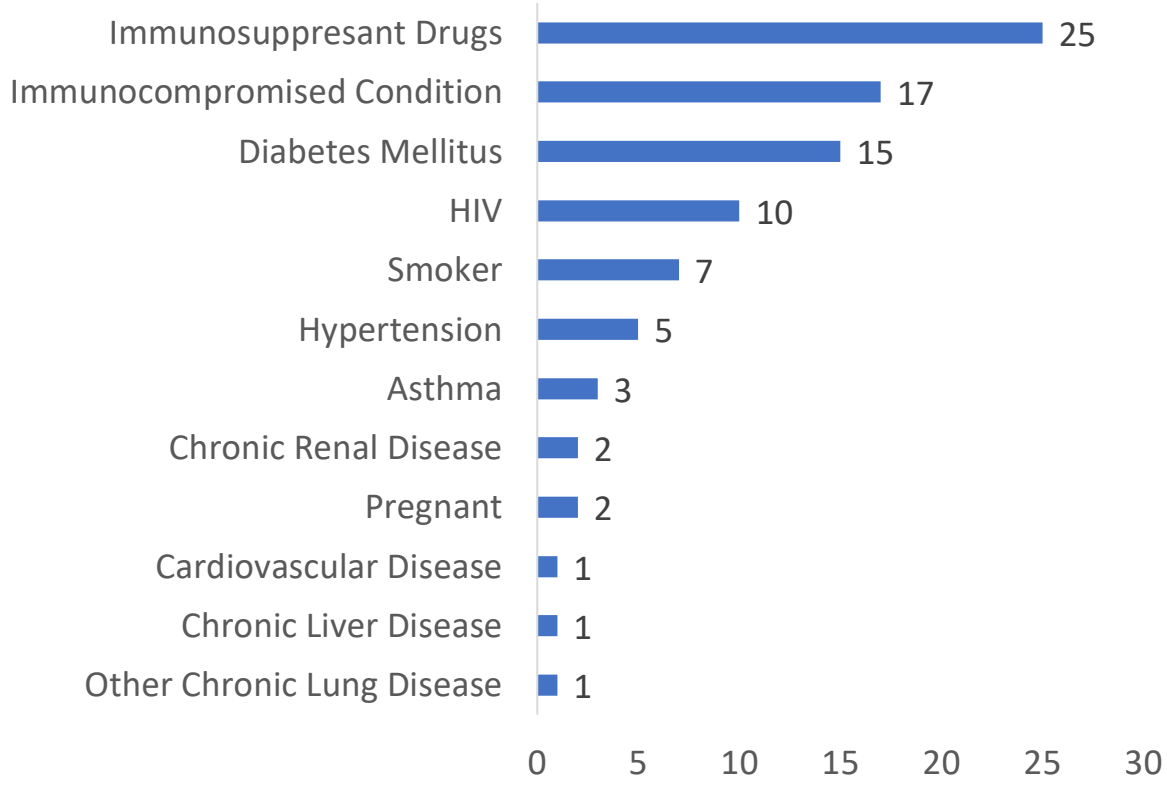
## Distribution by Gender




## Geographical Distribution




## Distribution by Co-morbidities



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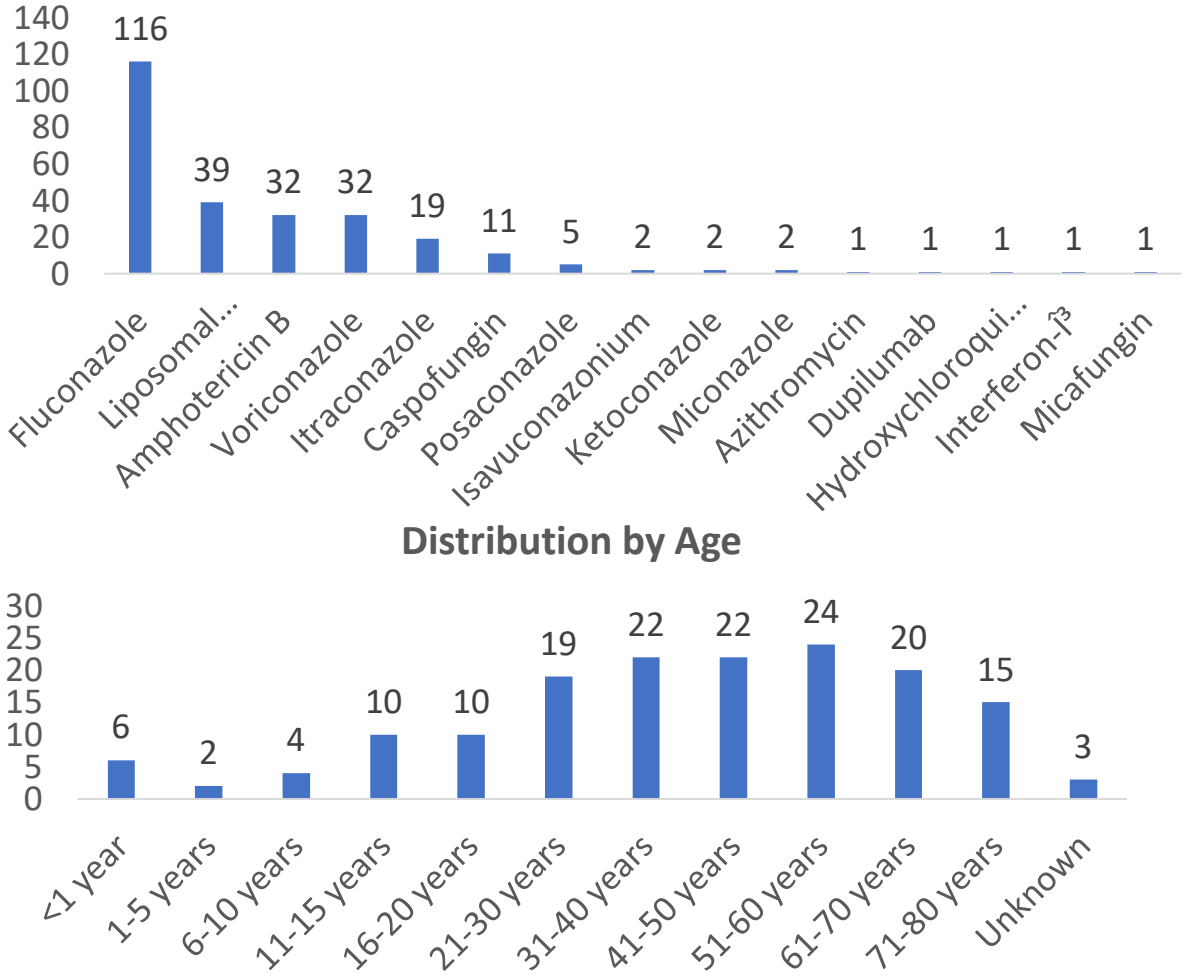
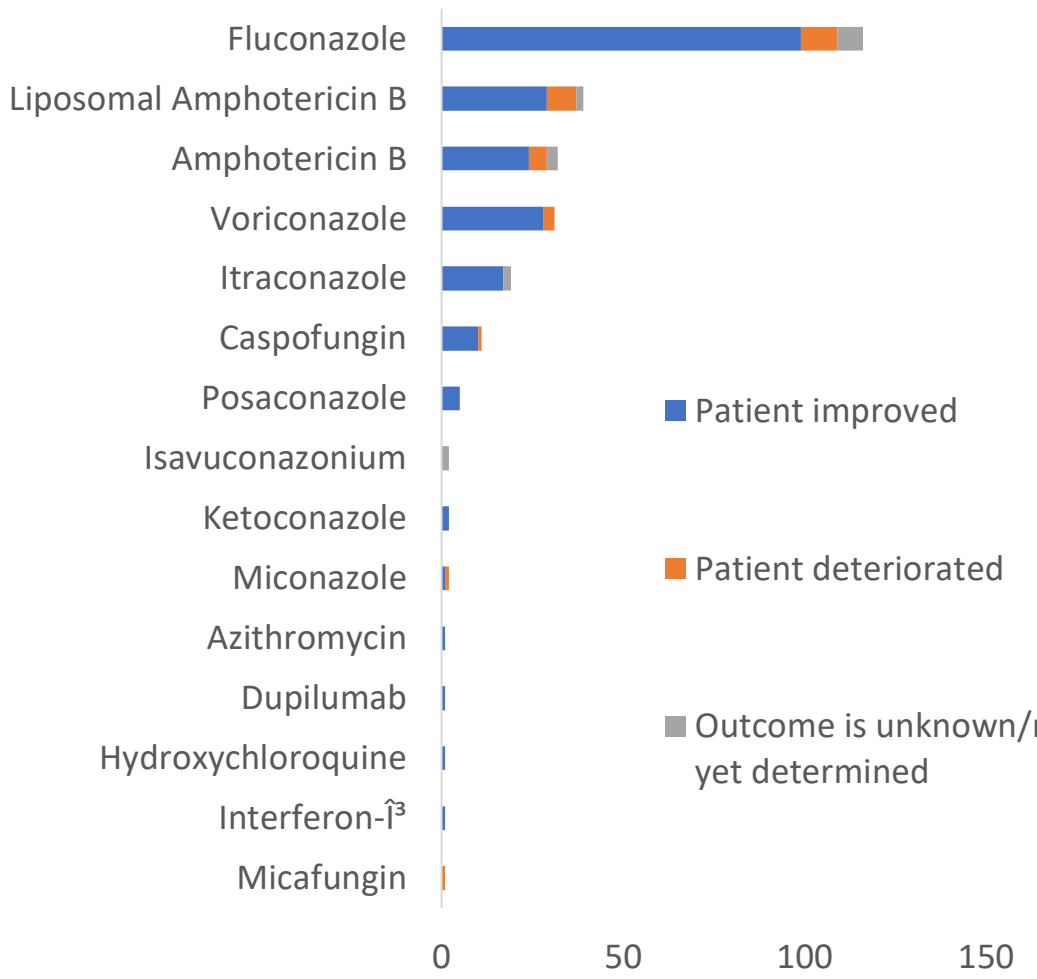


# Patient susceptible population due to increasing prevalence of inflammatory diseases

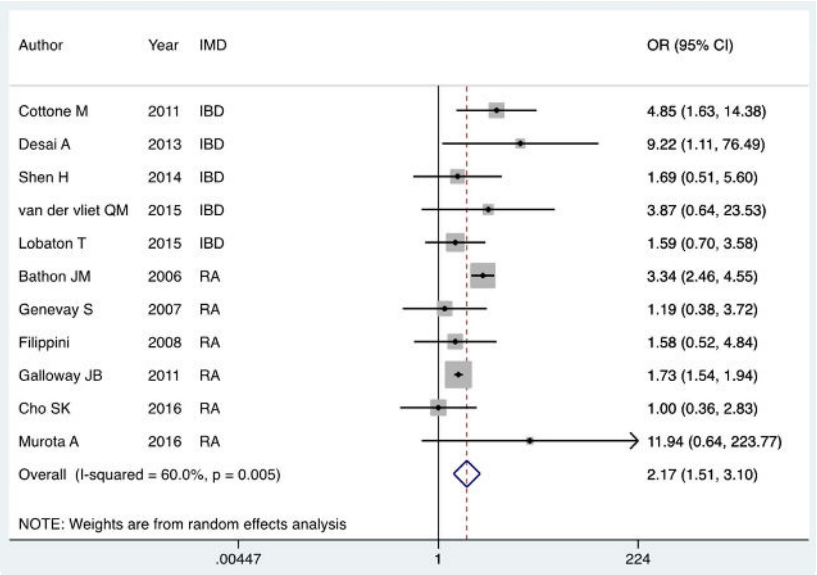
Published in final edited form as:
*Clin Gastroenterol Hepatol*. 2019 August ; 17(9): 1736–1743.e4. doi:10.1016/j.cgh.2018.12.032.

## Safety of Biologic Therapy in Older Patients with Immune-Mediated Diseases: A Systematic Review and Meta-Analysis

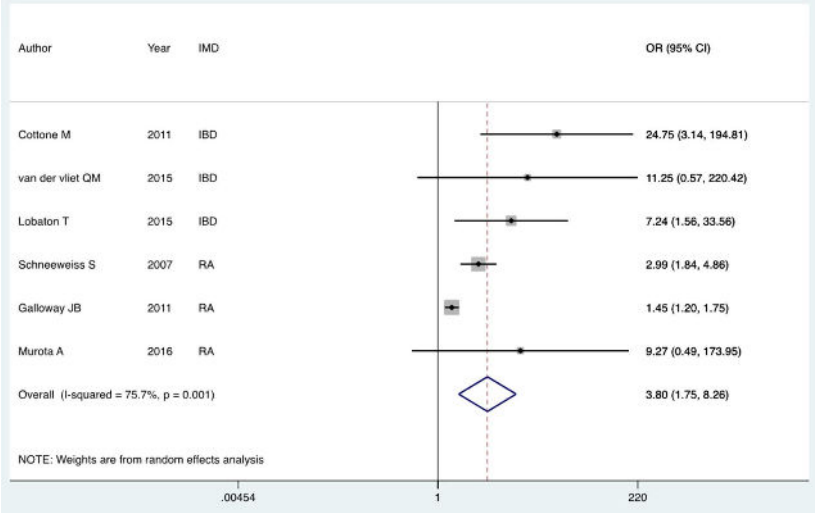
Nienke Z Borren, MDAshwin N Ananthakrishnan, MD, MPH
Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School

Conclusion: In a systematic review and meta-analysis of studies on the safety of biologic therapies in older patients with inflammatory diseases, we found that older users of biologic agents have an increased risk of infections compared with younger users or older patients who do not use biologics. Large, prospective cohort studies are needed to examine safety of biologic therapy in older patients with immune-mediated diseases

Old vs. Young on biologics




Old on biologics vs. controls



# FDA warning labels on existing biologics used to treat IBD, psoriasis, and rheumatoid arthritis

**INFLIXIMAB for injection, for intravenous use**
**Initial U.S. Approval: 1998**

**WARNING: SERIOUS INFECTIONS and MALIGNANCY**
***See full prescribing information for complete boxed warning.***

- **Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis) and infections due to other opportunistic pathogens. (5.1)**
- **Discontinue Infliximab if a patient develops a serious infection.**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting Infliximab. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)**
- **Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor (TNF) blockers, including Infliximab. (5.2)**
- **Postmarketing cases of fatal hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF blockers including Infliximab. Almost all had received azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. The majority of Infliximab cases were reported in patients with Crohn's disease or ulcerative colitis, most of whom were adolescent or young adult males. (5.2)**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use HUMIRA safely and effectively. See full prescribing information for HUMIRA.**
**HUMIRA (adalimumab) Injection, Solution for Subcutaneous use**
**Initial U.S. Approval: 2002**

**WARNINGS:**
***See full prescribing information for complete boxed warning.***

**SERIOUS INFECTIONS (5.1, 6.1)**

- **Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.**
- **HUMIRA should be discontinued if a patient develops a serious infection or sepsis during treatment.**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting HUMIRA.**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative.**

**MALIGNANCY (5.2)**

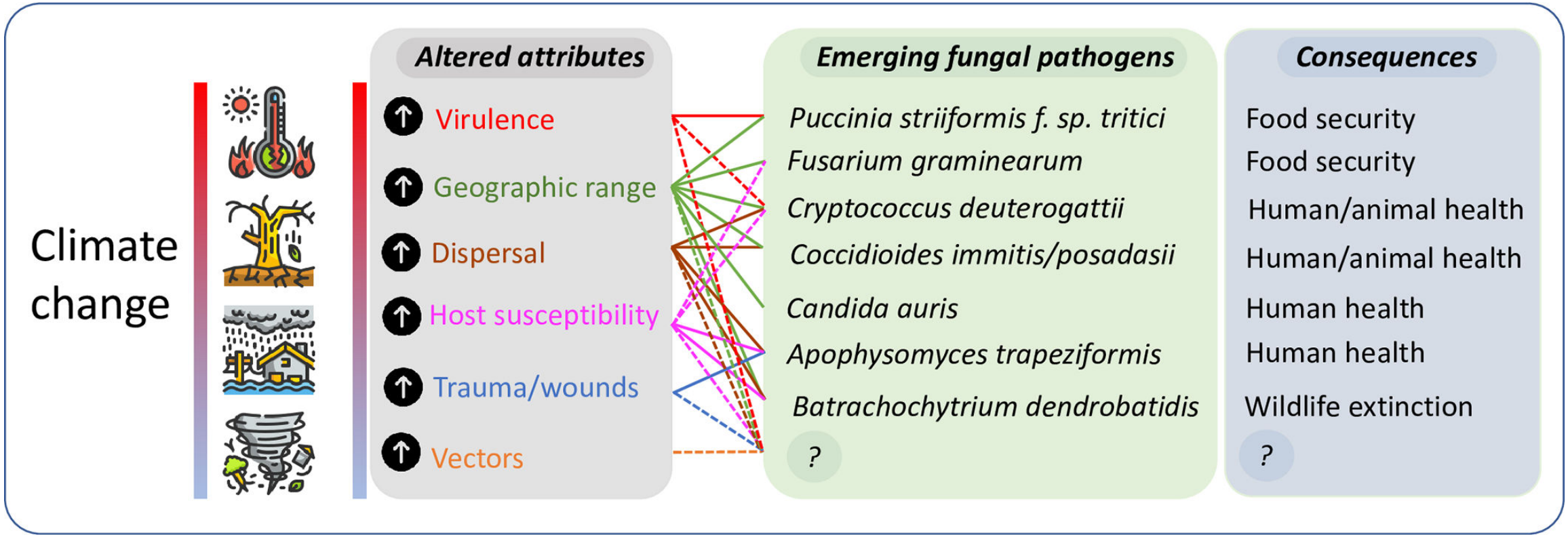
- **Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which HUMIRA is a member.**
- **Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in adolescent and young adults with inflammatory bowel disease treated with TNF blockers including HUMIRA.**

# Biologic drug pipeline: Beyond TNF inhibitors

CRITICAL PATH INSTITUTE

| Company | Drug Name | Target | Drug Class | Phase of Development | Notes |
|---|---|---|---|---|---|
| Galapagos NV | Filgotinib | JAK1 | JAK1 | Phase 3 | |
| AbbVie | Upadacitinib | JAK1 | JAK1 | Phase 3 | |
| Theravance | TD-1473 (izencitinib) | gut-selective oral pan-JAK inhibitor | JAK1 | Phase 3, Phase 2 | Failed in Phase IIb |
| Roche | Etrolizumab | β7 subunit of α4β7 and αEβ7 integrin heterodims | Anti-integrin molecules | Phase 3 | |
| Takeda | Ontamalimab | MADCAM1 | Anti-integrin molecules | Phase 3 | |
| EA Pharma Co | AMJ300 | α4 integrin subunit | Anti-integrin molecules | Phase 3 | |
| BMS | Ozanimod (Zeposia) | | S1P receptor | Phase 3 | |
| Arena Pharma | Etrasimod | | S1P receptor | Phase 3, Phase 2 | |
| Eli Lilly | Mirikizumab | IL-23 | anti-interleukin | Phase 3 | |
| AbbVie | Risankizumab | IL-23 | anti-interleukin | Phase 3 | |
| AstraZeneca | Brazikumab | IL-23 | anti-interleukin | Phase 3, Phase 2 | |
| J&J | Guselkumab (Tremfya) | IL-23 | anti-interleukin | Phase 3, Phase 2 | |
| Boehringer Ingelheim | Spesolimab | IL-36R | anti-interleukin | Phase 3, Phase 2 | |
| BMS | BMS-986165 | JAK1 | JAK1 | Phase 2 | |
| Seres | SER-287 | Microbiome | Microbial Therapy | Phase 2 | |
| InDex Pharmaceuticals | Cobitolimod | TLR9 oligo | Toll-Like Receptors | Phase 2 | |
| Applied Molecular Transport | AMT-101 | IL-10 and a carrier protein | Fusion Therapies | Phase 2, Phase 1 | |
| AstraZeneca | Abrilumab | Adhesion molecule α4β7 | Anti-integrin molecules | Phase 2 | *MedImmune, Amgen |
| Pfizer | PF-04236921 | IL-6 | anti-interleukin | Phase 2 | |
| GlaxoSmithKline | GSK1070806 | IL-18 | anti-interleukin | Phase 1 | |
| Assembly Biosciences | ABI-M201 | Microbiome | Microbial Therapy | Phase 1 | |
| Bausch Health Americas, Inc. | Amiselimod (MT-1303) | | S1P receptor | Phase 1 | |

# The effect of climate change on the emergence of fungal pathogens

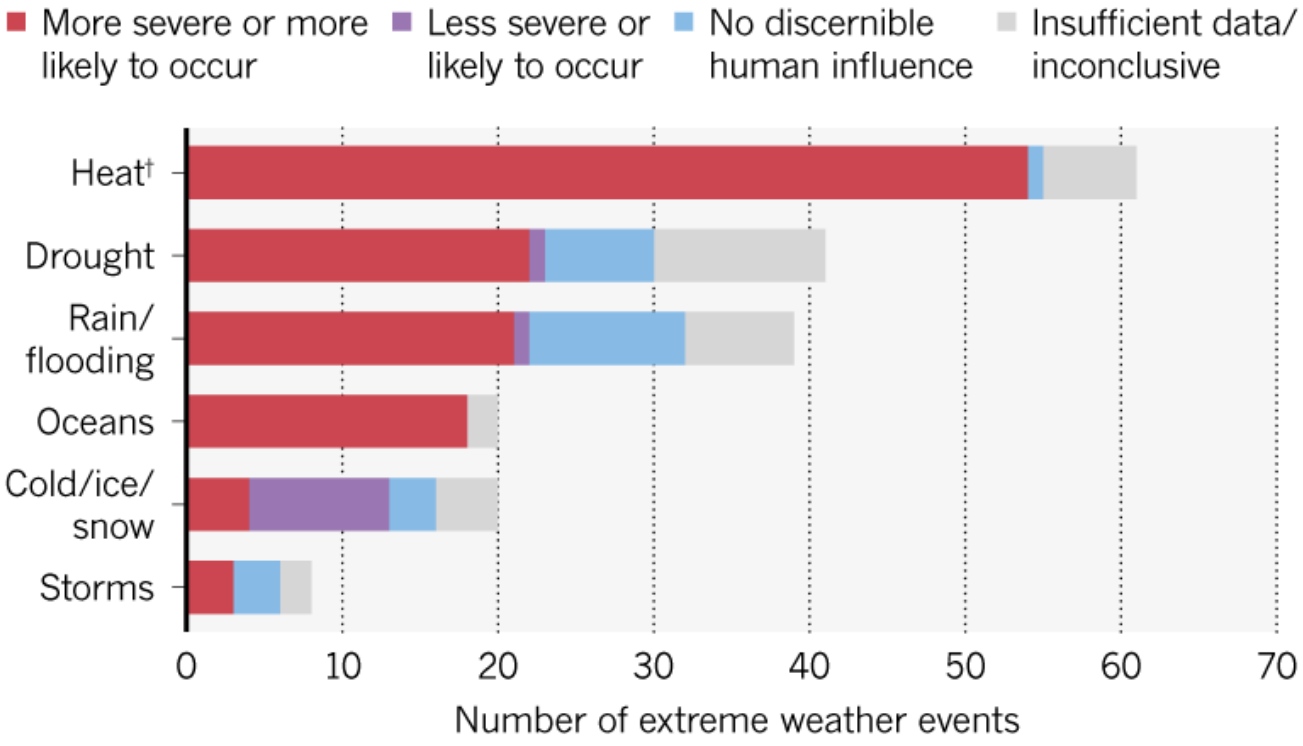



Nnadi NE, Carter DA (2021) Climate change and the emergence of fungal pathogens. PLOS Pathogens 17(4): e1009503. https://doi.org/10.1371/journal.ppat.1009503
https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1009503

# More people living in areas of excess heat, wildfires, and drought

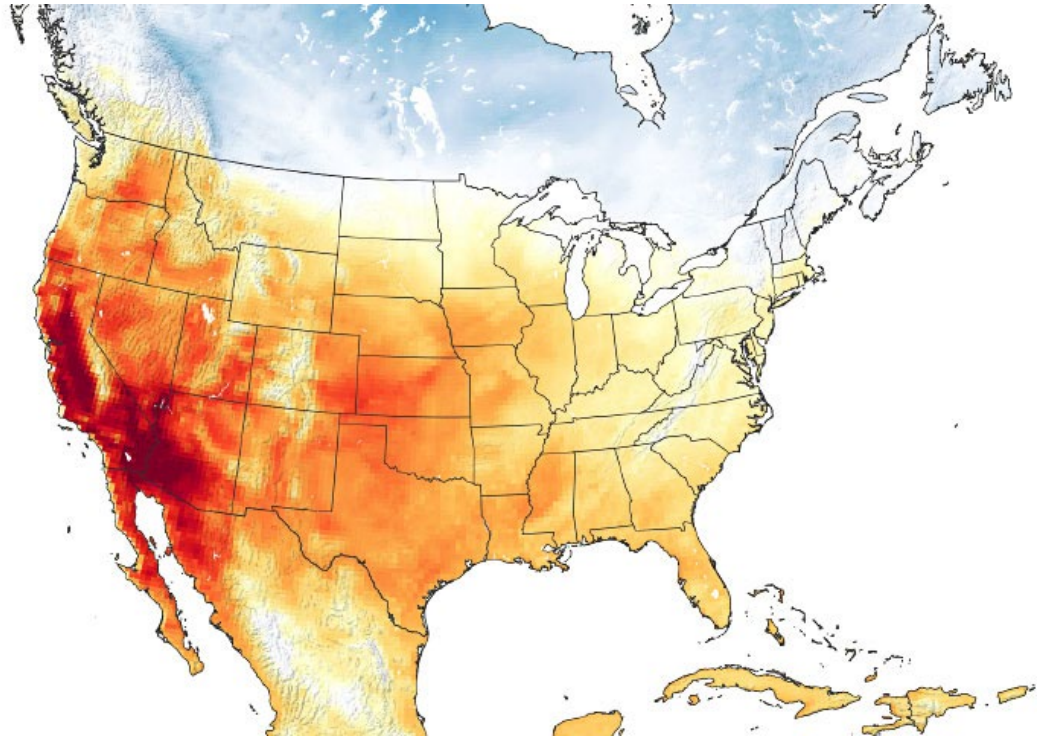
## Attribution science

Researchers have published more than 170 studies* examining the role of human-induced climate change in 190 extreme weather events.

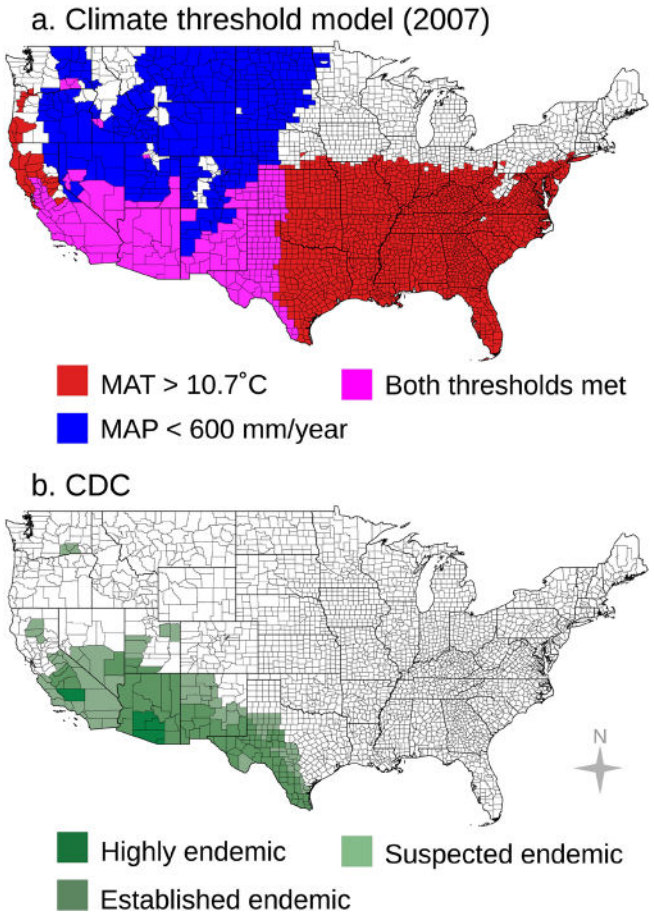


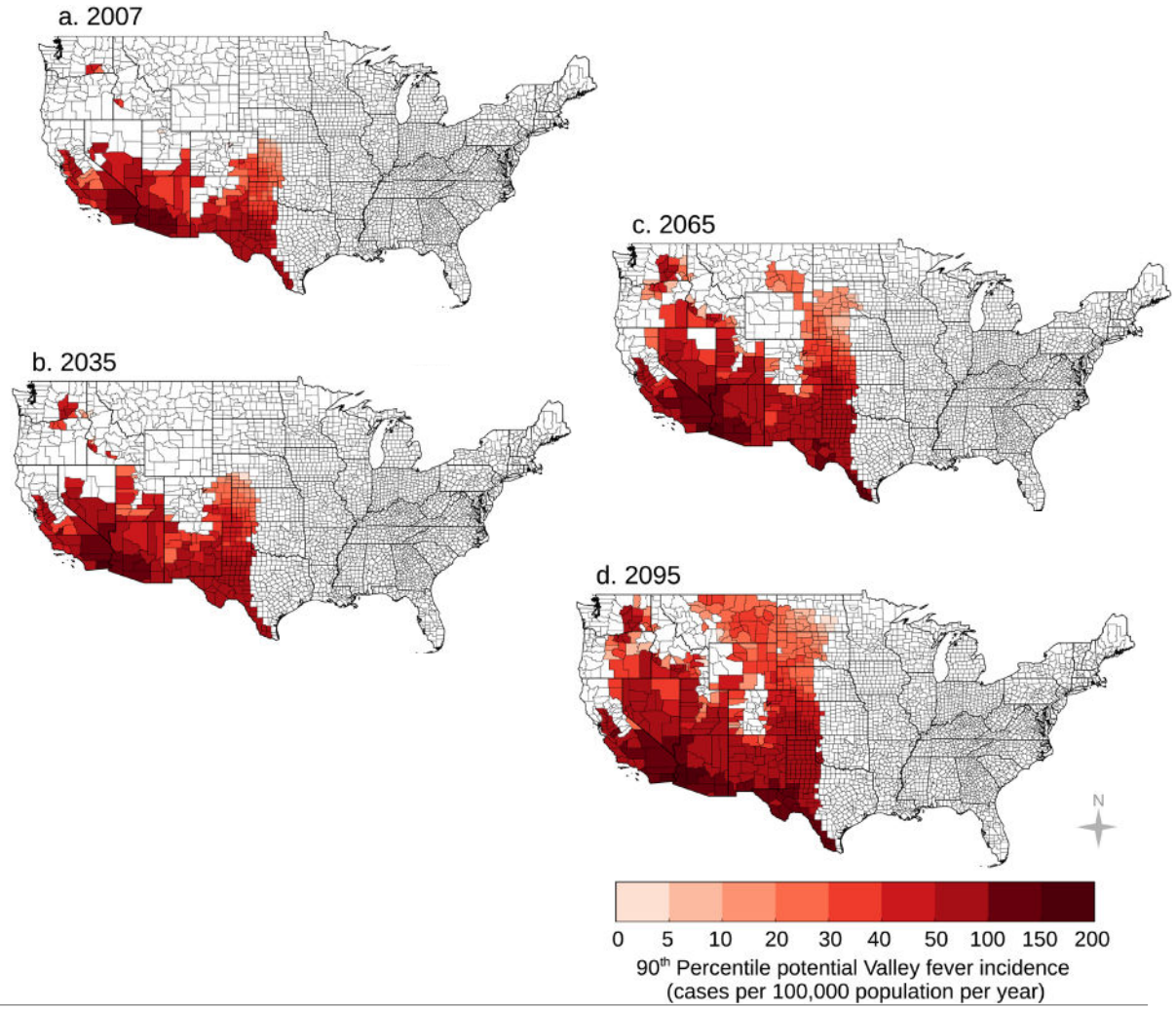

©nature

*Studies from 2004–18 collated by *Nature* and CarbonBrief. †Heat includes heatwaves and wildfires; Oceans includes studies on marine heat, coral bleaching and marine-ecosystem disruption.



# Expansion of Coccidioidomycosis endemic regions in response to climate change




Gorris et al. GeoHealth, Volume: 3, Issue: 10, Pages: 308-327,
First published: 30 August 2019, DOI: (10.1029/2019GH000209)

# Haboob: Mechanism for dispersing Coccidioidomycosis spores

Image from Jason Ferguson: August 2018 Phoenix Arizona

# Agenda

- Introduction to CDRC
- CURE ID: U.S. FDA vision for a public resource and WHO partnership
- WHO survey on subcutaneous mycoses
- CURE ID CDRC data on implantation mycoses and next steps
- Impact of climate change on coccidioidomycoses
- Summary

# Take home messages

1. CDRC to maximize utility of existing drugs for indications not on label
   - Tools to systematically capture real-world data, generate hypothesis, and confirm using randomized controlled trials
2. Repurposing is being used to treat implantation mycoses
   - In literature and in survey
   - Does not appear that any treatment is better than the other
3. Opportunity to capture data being generated every day globally on treatment and outcomes
   - Pilot program to align on CRF and capture prospective contemporaneous data
   - Evaluate treatments to generate evidence on effectiveness
4. Disseminate information to change clinical practice
   - Generic drugs that have no pharma interest due to lack of financial incentives
5. Climate change will increase human and animal exposure to fungal pathogens
   - Increasing the need to identify effective treatments from the existing arsenal of approved products

# Thank you

Dr. Marco Schito (mschito@c-path.org)

https://c-path.org/programs/cdrc/

cdrc@c-path.org

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