Landscape Analysis to Identify Effective Drug Repurposing Candidates for the Treatment of Implantation Mycoses: Comparison of World Health Organization Survey Treatment Data and Published Case Reports on CURE ID

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Introduction

A group of pathogenic fungi that gain access in a mammalian host through various types of cutaneous or mucosal wounds or by contact are categorized as implantation or inoculation mycoses. These constitute a group of unrelated fungal diseases where causative fungi are transferred from their sapronotic or zoonotic niche to the cutaneous or mucosal teguments. The most widespread implantation mycosis is sporotrichosis. Chromoblastomycosis, eumycetoma, coccidioidomycosis, and some clinical forms of phaeohyphomycosis are amongst the other fungal diseases that begin at the site of multiple transcutaneous or transmucosal traumas.

These are geographically confined mainly to tropical and subtropical areas, and are associated with significant morbidity due to long-term sequelae, incapacity to work and decreased quality of life, mostly associated with severe clinical forms.

Due to the high cost of drugs, long treatment durations, and difficulty in early diagnosis, they can be recalcitrant and very difficult to treat. They are identified as areas of high unmet needs and merit a systematic approach towards identifying cost-effective and efficacious drug candidates.

Materials and Methods

World Health Organization (WHO) in collaboration with the U.S. Food and Drug Administration (US FDA) and CURE Drug Repurposing Collaboratory (CDRC) developed an online survey in early 2022 to capture treatment data on implantation mycoses from around the world. The survey aimed to collect information on diagnostic capacities and treatment practices in different settings in various countries on four implantation mycoses: eumycetoma (n=114), actinomycetoma (n=102), cutaneous sporotrichosis (n=97) and chromoblastomycosis (n=101). This global online survey captured real-world data (RWD) on the use of repurposed drugs and non-pharmacological interventions in the treatment of these mycoses.

The WHO global online survey collected information from a total of 142 respondents from 47 countries. Majority of the respondents of the survey were clinicians (39%), followed by dual professional profile of laboratory and clinical experts (36%), laboratory technicians/specialists (9%), public health specialists (7%), and others (9%).

CURE ID is an internet-based repository developed by the US FDA and the National Center for Advancing Translational Sciences (NCATS), part of the National Institutes of Health (NIH) to gather RWD on the novel uses of existing drugs for difficult-to-treat infectious diseases from clinicians, patients and now through Electronic Health Records (EHRs). It can be accessed on the web, smartphone or other mobile devices. The platform enables crowdsourcing of medical information to gather RWD on the off-label use for a new indication, especially for neglected diseases.

The CURE ID Team performed a systematic literature review on all published case reports from PubMed. In total, we did data entry on 656 published implantation mycoses case reports, that included sporotrichosis (n=255), chromoblastomycosis (n=198), coccidioidomycosis (n=157), and eumycetoma (n=46). We excluded reports that did not have drug treatment, were not in English, and those that were not full text articles.

Disclaimer: This poster reflects the views of the authors and should not be construed to represent NIH or FDA's views or policies.

Results and Discussion

In the CURE ID database, sixty-four percent of patients are males, and females constitute thirty-five percent of reports on implantation mycoses. CURE ID case reports are reported from 48 countries, with majority of cases being reported from Brazil (29%), as highlighted in figure 1. Clinical features/visual inspection (86%) was reported most frequently as a diagnostic tool in the WHO survey. While in CURE ID database, clinical assessment was reported in 52% of published reports, with culture (bacterial/fungal) being the most reported (63%) diagnostic modality, as depicted in figure 2.

The WHO survey confirms a widespread use of repurposed drugs, with respondents outlining a few medicines that were not included in the survey list. For eumycetoma, chromoblastomycosis and cutaneous sporotrichosis, itraconazole was reported as the first choice (85-90%) and terbinafine for refractory cases (44-56%) in the WHO survey. Newer generation azoles (posaconazole and voriconazole) were also reported (27-41%) for chromoblastomycosis and eumycetoma. Older generation azoles were also reported for eumycetoma (ketoconazole at 30%). Amphotericin B was considerably reported for eumycetoma (36%). For chromoblastomycosis, there is a lower but consistent use of flucytosine (14%) and imiquimod(11%)

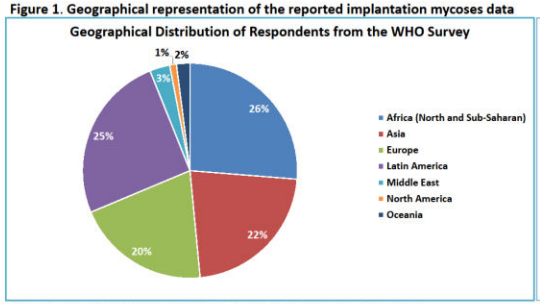
For cutaneous sporotrichosis, we noted a considerable use of potassium iodide (44%).

For actinomycetoma, several antibiotics from several classes were reported in the WHO survey, suggesting a high level of drug repurposing. Dapsone (30%), rifampicin (27%), carbapenems (23%) and fosfomycin (10%) were amongst the other drugs reported in the WHO survey.

Analyzing treatment data from published case reports on CURE ID from 2015 onwards, itraconazole was also the most frequently used drug across all implantation mycoses. It was used in 95% reports on sporotrichosis, while for eumycetoma and chromoblastomycosis, its use was reported at 64 and 55% respectively. Terbinafine has been reported in 7% cases of eumycetoma and 37% for chromoblastomycosis, while it was used sparingly in just 3% of cases of sporotrichosis. While newer generation azoles were reported for chromoblastomycosis and eumycetoma, they were used less frequently (9-29%) in published reports, as compared to the WHO survey. Use of ketoconazole was reported sparingly (1%) for chromoblastomycosis in case reports published from 2015 onwards, while it is reported more consistently for chromoblastomycosis (6%) and eumycetoma (7%) from all the published reports in CURE ID dating back to the 1980s.

Use of imiquimod was reported in 9% of cases of chromoblastomycosis. Three percent of reports from CURE ID on sporotrichosis used potassium iodide. Antidulafungin (2%) is another drug in the outliers that was reported for sporotrichosis in CURE ID. For chromoblastomycosis, griseofulvin (6%) and naftifine (3%) were also reported.

Figure 1. Geographical representation of the reported implantation mycoses data



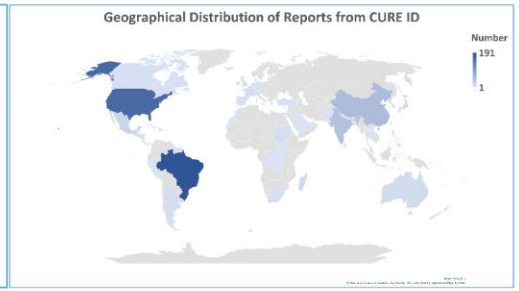
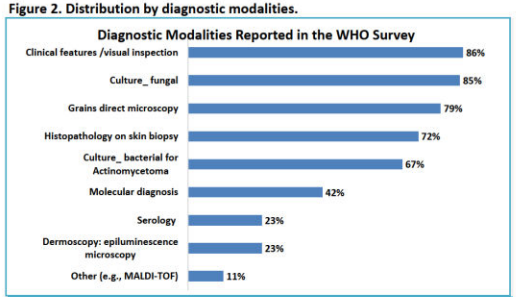


Figure 2. Distribution by diagnostic modalities.



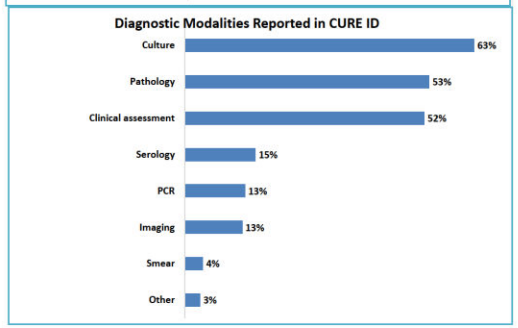
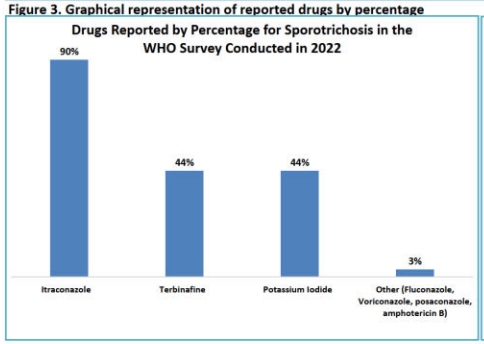
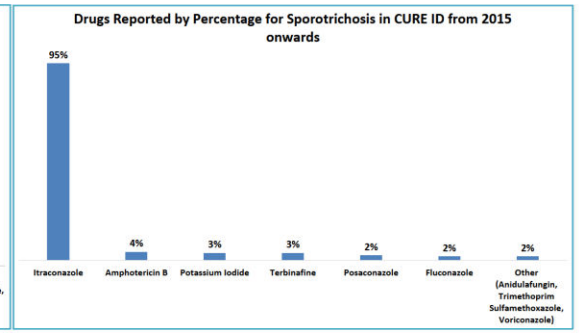


Figure 3. Graphical representation of reported drugs by percentage





Conclusions

Implantation mycoses affects a significant percentage of the world's population. Severe clinical forms are associated with significant morbidity due to long-term sequelae and decreased quality of life. This is further complicated by the lack of effective therapies and increased cost and limited availability of medications.

Analysis of existing data from both the WHO online survey and the CURE ID database identified itraconazole as the most frequently used drug across the studied implantation mycoses. While itraconazole is used worldwide as a standard of care in the treatment of implantation mycoses, it is not yet approved by the FDA for use in most of these conditions of interest. This effort should be further facilitated by capturing large volumes of RWD for hypothesis generation and informing clinical trials about efficacy signals to support regulatory decisions, especially for neglected diseases.

Medical Imaging Working Group

PRESENTER: **Paul Nagy, Seng Chan You**

INTRO:

Medical Imaging plays an essential part of medical care in diagnosing and measuring disease as well as the response to medical interventions. The OHDSI medical imaging WG has developed an extension to the Observational Medical Outcomes Partnership (OMOP) common data model (CDM) to support incorporating medical imaging studies as well as measurements derived from medical imaging.

METHODS

The steps taken to create this extension were

1. Create use cases of this data model is intended to be able to answer for observational research
2. Identify the vocabularies needed to support clinical findings. RadLex is employed as a comprehensive vocabulary of radiologic terminology which has been developed and maintained by the RSNA
3. Create data models required to be able to support the use case questions

1. Primary Use Case

The primary use case we created was tracking of pulmonary nodules over time that require treatment. This is a good example as patients can have multiple clinical findings within any given imaging study and each clinical findings can have multiple features that describe that finding.

An imaging study includes a collection of medical images, and each study can have multiple clinical findings (nodules). Each imaging finding can have multiple imaging features (attribute size, composition, location). An example Pulmonary Nodule is a 55-year-old patient that quit smoking 8 years ago. It is able to see the use case tables through the QR code in the middle of this poster.

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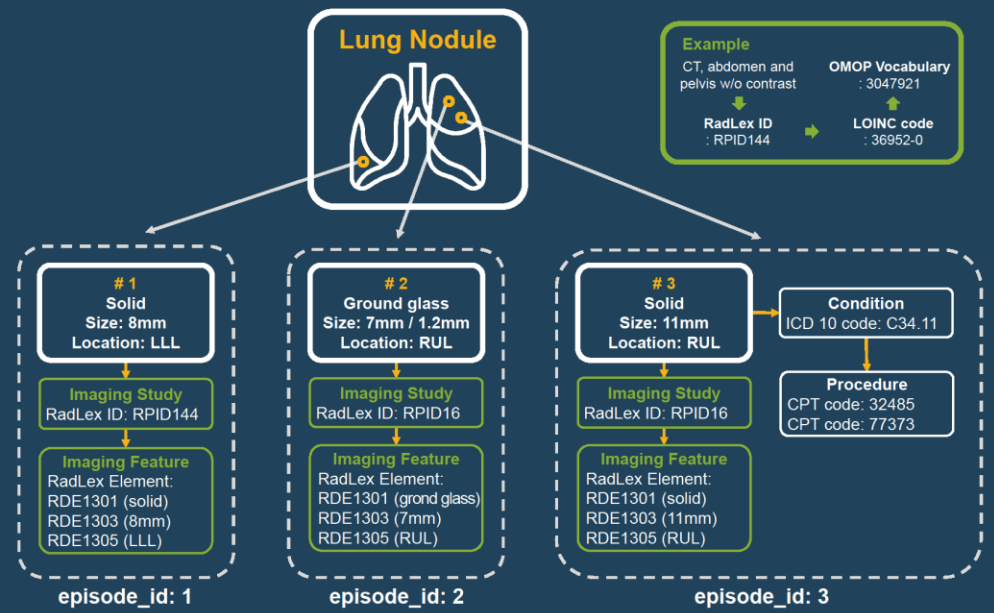
Development of the Medical Imaging Extension



We aim to harmonize and standardize information for medical images to overcome current challenges in interoperability and reproducibility in medical image research. From pixels to Phenotypes.

Scan QR code link to
use case tables of lung nodule

2. Proposed Additional Vocabulary

RADLEX was developed by the RSNA to add radiological findings not present in SNOMED and is available via the NCBO Bioportal.bioontology.org. The Radlex playbook is a lexicon of standardized procedure descriptions which is linked to CPT as LOINC codes.

3. Proposed Data Model

The data model includes two tables.

Imaging Study table. The goal of this table is to provide the provenance to the imaging study performed in a DICOM format stored on a PACS (Picture Archiving and Communication System) or a VNA (Vendor Neutral Archive). Imaging Studies are stored in a DICOM format as a series of files in a Study – Series – Image style. The second goal of the table is to provide a link to procedure_occurrence entries. In the DICOMweb standard there is the ability to provide a Uniform Resource Identifier (URI). The intention of this table is to point to the origin source image pixel data.

Imaging Feature table. It is to take features derived from medical images and link to the measurement domain while providing provenance of those features back to the imaging pixel data in the imaging study. The Imaging Feature table has groupers that enables imaging features to be grouped into imaging findings with multiple unique imaging findings allowable for a given imaging study. The Imaging Feature table also allows for the features to be identified by the algorithm and to enable reconstruction of features from computer algorithms.

Conclusion

We the OHDSI medical imaging WG propose medical imaging extension to standardize features and provenance of medical images in OMOP CDM. With further development, we hope that medical image extension provides essential infrastructure for robust, scalable, and reproducible medical image study.

Protocol for finding supplemental oxygen data in electronic health record (EHR) flowsheets for inclusion in the OMOP ETL

PRESENTER: Tanner Zhang MD,MS

INTRO:

- Incorporating flowsheet data from EHRs into the OMOP ETL has been a challenge due to the high volume of entries and high variability of facility-specific customization.
- We propose a standardized and reproducible protocol to identify the flowsheet elements of interest, map them to their appropriate OMOP concept IDs, and load them into the OMOP Common Data Model (CDM)

METHODS

1. **Flowsheet Identification**
   - **Wildcard search for candidates**
   - **Manually identified nonintuitive flowsheet names**
   - **Manually identify anesthesia records**
   - **List template and flowsheet measurement identification numbers**
   - **Extract based on included template, measurement numbers**
2. **Semantic Mappings**
   - **Semantic mappings were created by clinicians, then reviewed by informaticians, terminologists**
   - **Proposed custom OMOP concept ids for BiPAP, CPAP & NIPPV**
3. **Utilization of OMOP CDM Tables**
   - **Measurement/Observation tables are used to persist respiratory device settings (e.g., flow rate)**
   - **Device_exposure table is used to persist ventilator records**
   - **Linkage is kept between the tables, through time stamps – anesthesia records are excluded, sequential ventilator records are merged for straightforward understanding.**

Raw Patient Data, dates obfuscated

Patient ID	Flowsheet value	Flowsheet field name	Flowsheet time
9302	None-room air	O2 Device	10/6/19 12:00 AM
9302	6	O2 Flow Rate (L/min)	10/6/19 12:12 AM
9302	Nasal cannula	O2 Device	10/6/19 12:12 AM
9302	Nasal cannula	O2 Device	10/6/19 12:16 AM
9302	6	O2 Flow Rate (L/min)	10/6/19 12:16 AM
9302	6	O2 Flow Rate (L/min)	10/6/19 2:21 AM
9302	Nasal cannula	O2 Device	10/6/19 2:21 AM
9302	6	O2 Flow Rate (L/min)	10/6/19 3:10 AM
9302	Nasal cannula	O2 Device	10/6/19 3:10 AM
9302	6	O2 Flow Rate (L/min)	10/6/19 4:25 AM
9302	Nasal cannula	O2 Device	10/6/19 4:25 AM
9302	Non-rebreather mask	O2 Device	10/6/19 4:32 AM
9302	60	FiO2 (%)	10/6/19 5:23 AM
9302	60	Oxygen Therapy FiO2 (%)	10/6/19 5:23 AM
9302	40	Flow Rate (L/min)	10/6/19 5:23 AM
9302	40	O2 Therapy Flow Rate (L/min)	10/6/19 5:23 AM
9302	Heated High Flow	O2 Device	10/6/19 5:23 AM
9302	60	FiO2	10/6/19 6:38 AM
9302	High flow nasal cannula	O2 Device	10/6/19 6:38 AM
9302	40	O2 Flow Rate (L/min)	10/6/19 6:38 AM
9302	60	FiO2	10/6/19 8:29 AM
9302	High flow nasal cannula	O2 Device	10/6/19 8:29 AM
9302	40	O2 Flow Rate (L/min)	10/6/19 8:29 AM
9302	40	Flow Rate (L/min)	10/6/19 11:41 AM
9302	Heated High Flow	O2 Device	10/6/19 11:41 AM
9302	40	O2 Therapy Flow Rate (L/min)	10/6/19 11:41 AM
9302	50	Oxygen Therapy FiO2 (%)	10/6/19 11:41 AM
9302	50	FiO2 (%)	10/6/19 11:41 AM
9302	40	O2 Flow Rate (L/min)	10/6/19 11:52 AM
9302	60	FiO2	10/6/19 11:52 AM
9302	High flow nasal cannula	O2 Device	10/6/19 11:52 AM
9302	High flow nasal cannula	O2 Device	10/6/19 12:34 PM
9302	40	O2 Flow Rate (L/min)	10/6/19 12:34 PM
9302	60	FiO2	10/6/19 12:34 PM
9302	60	FiO2 (%)	10/6/19 1:56 PM
9302	Heated High Flow	O2 Device	10/6/19 1:56 PM
9302	40	Flow Rate (L/min)	10/6/19 1:56 PM
...	...	...	...
9302	100	FiO2 (%)	10/7/19 9:12 AM
9302	50	Flow Rate (L/min)	10/7/19 9:12 AM
9302	Ventilator	O2 Device	10/7/19 10:10 AM
9302	60	FiO2	10/7/19 10:10 AM
9302	60	Vent FiO2 (%)	10/7/19 10:11 AM
9302	50	Vent FiO2 (%)	10/7/19 11:19 AM
9302	50	FiO2	10/7/19 11:26 AM
9302	Ventilator	O2 Device	10/7/19 11:26 AM
9302	60	Vent FiO2 (%)	10/7/19 11:33 AM

Measurement table, partial view

person_id	measurement_concept_id	measurement_concept_name	value_as_number	measurement_datetime	unit_concept_id_etc.
9302	4141684	Delivered oxygen flow rate	6	10/6/19 12:12 AM	...
9302	4141684	Delivered oxygen flow rate	6	10/6/19 12:16 AM	...
9302	4141684	Delivered oxygen flow rate	6	10/6/19 2:21 AM	...
9302	4141684	Delivered oxygen flow rate	6	10/6/19 3:10 AM	...
9302	4141684	Delivered oxygen flow rate	6	10/6/19 4:25 AM	...
9302	4353936	Inspired oxygen concentration	60	10/6/19 5:23 AM	...
9302	4353936	Inspired oxygen concentration	60	10/6/19 5:23 AM	...
9302	4141684	Delivered oxygen flow rate	40	10/6/19 5:23 AM	...
9302	4141684	Delivered oxygen flow rate	40	10/6/19 5:23 AM	...
9302	4353936	Inspired oxygen concentration	60	10/6/19 6:38 AM	...
9302	4141684	Delivered oxygen flow rate	40	10/6/19 6:38 AM	...
9302	4353936	Inspired oxygen concentration	60	10/6/19 8:29 AM	...
9302	4141684	Delivered oxygen flow rate	40	10/6/19 8:29 AM	...
9302	4141684	Delivered oxygen flow rate	40	10/6/19 11:41 AM	...
9302	4141684	Delivered oxygen flow rate	40	10/6/19 11:41 AM	...
9302	4353936	Inspired oxygen concentration	50	10/6/19 11:41 AM	...
9302	4353936	Inspired oxygen concentration	50	10/6/19 11:41 AM	...
9302	4141684	Delivered oxygen flow rate	40	10/6/19 11:52 AM	...
9302	4353936	Inspired oxygen concentration	60	10/6/19 11:52 AM	...
9302	4141684	Delivered oxygen flow rate	40	10/6/19 12:34 PM	...
9302	4353936	Inspired oxygen concentration	60	10/6/19 12:34 PM	...
9302	4353936	Inspired oxygen concentration	60	10/6/19 1:56 PM	...
9302	4141684	Delivered oxygen flow rate	40	10/6/19 1:56 PM	...
...	...	...	...	...	...
9302	4141684	Delivered oxygen flow rate	50	10/7/19 9:12 AM	...
9302	4353936	Inspired oxygen concentration	100	10/7/19 9:12 AM	...
9302	4353936	Inspired oxygen concentration	60	10/7/19 10:10 AM	...
9302	4353936	Inspired oxygen concentration	60	10/7/19 10:11 AM	...
9302	4353936	Inspired oxygen concentration	50	10/7/19 11:19 AM	...

Device_exposure table, partial view

person_id	device_concept_id	device_exposure_start_datetime	device_exposure_end_datetime	concept_name	...
9302	2004208005	10/6/19 12:00 AM	10/6/19 12:12 AM	Room air (in the context of a device)	...
9302	45760842	10/6/19 12:12 AM	10/6/19 4:25 AM	Basic nasal oxygen cannula	...
9302	4145528	10/6/19 4:32 AM	10/6/19 5:23 AM	Nonrebreather oxygen mask	...
9302	4139525	10/6/19 5:23 AM	10/6/19 6:58 PM	High flow oxygen nasal cannula	...
9302	45768197	10/7/19 10:10 AM	10/7/19 11:33 AM	Ventilator	...

Features:

1. Measurement/Observation tables are used for respiratory device settings, and device_exposure table is used for respiratory device information.
2. Linkage is kept by the time stamps. The datasets for analysis could be curated by the analysts' needs for different use cases.
3. Current pilot sites are mainly Epic sites. Thus the scripts and mappings are curated for Epic templates and internal measurement ids. We welcome other EHR-vendor sites to join the forces.
4. We have designed flowsheet-specialized data quality checks and this may potentially be an add-on to the DQD 2.0 version.

Semantic mappings for flowsheet data, and statistics among patients hospitalized with COVID-19 at JHU

Oxygen support device	Other raw entries	n	total	Perc (%)	OMOP Concept ID	OMOP Concept
none-room air	none/room air, none (room air)	505033	1246633	41	2004208005	Room air (in the context of a device)
nasal cannula		295793	1246633	24	45760842	Basic nasal oxygen cannula
ventilator	venitaltor - hfov, endotracheal tube	243858	1246633	20	45768197	Ventilator
high flow nasal cannula	heated high flow	101590	1246633	8	4139525	High flow oxygen nasal cannula
tracheostomy mask/collar	trach mask, trach collar	57755	1246633	5	45760219	Tracheostomy mask, oxygen
nippv		14733	1246633	1	2004208008	NIPPV (non-invasive positive pressure ventilation or nasal intermittent positive pressure ventilation)
non-rebreather mask		12684	1246633	1	4145528	Nonrebreather oxygen mask
simple facemask		4880	1246633	0	4222966	Oxygen mask
other		3272	1246633	0	2004208004	Other oxygen device
venturi mask		3119	1246633	0	4188570	T piece without bag
t-piece		1543	1246633	0	4322904	Venturi mask
Total		1244260	1246633	99.8		

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RESULTS

- The semantic mappings for respiratory devices and the associated settings were designed by a group of clinicians and reviewed by informaticians and terminologists.
- In addition to the custom codes proposed by N3C, we have proposed three more to complete the respiratory device mapping. See below.
- We are working with OHDSI to finalize the related vocabulary table changes (in concept and in concept_relationship and etc.).

2004208004	**Other oxygen device**
2004208005	**Room air (in the context of a device)**
2004208006	**CPAP (continuous positive airway pressure)**
2004208007	**BiPAP (bilevel positive airway pressure)**
2004208008	**NIPPV (non-invasive positive pressure ventilation or nasal intermittent positive pressure ventilation)**

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JOHNS HOPKINS MEDICINE

OHDSI

Lowering the OMOP ETL Barrier for Clinical Registries

PRESENTER: **Smith Heavner**

INTRODUCTION

Goal: To systematically collect anecdotal data of how clinicians use existing drugs in new ways to treat diseases with limited or no treatment options.

Aim: To simplify ETL process and create pathway for real-world data to be made available in CURE ID

Method: Data harmonization using OMOP CDM

Impact: Secure deidentified data elements for assessing the effectiveness of repurposed treatments for diseases of high unmet clinical need.

METHODS

With funding from HHS Assistant Secretary for Planning and Evaluation:

1. Developed tools and resources to disseminate harmonization methods developed by Johns Hopkins University
2. Expand CURE ID from physician entered reports to automated EHR data collection
3. Promote conversion of non-common data model EHR systems to OMOP standards
4. Developed minimal dataset for drug repurposing research in COVID-19 as a use case

RESULTS

- Possible to lower OMOP ETL barrier
  - Default configuration transformations
  - Support and feedback from experienced site
- Project continues with site implementing OMOP using Perseus

Pilot site implemented OMOP in less than 200 hours

DataQualityDashboard Version: 1.4.1
Results generated at 2022-07-07 21:20:09 in 11 mins

	Verification				Validation				Total			
	Pass	Fail	Total	% Pass	Pass	Fail	Total	% Pass	Pass	Fail	Total	% Pass
Plausibility	1982	31	2013	98%	287	0	287	100%	2269	31	2300	99%
Conformance	656	23	679	97%	104	0	104	100%	760	23	783	97%
Completeness	381	5	386	99%	11	4	15	73%	392	9	401	98%
Total	3019	59	3078	98%	402	4	406	99%	3421	63	3484	**98%**

- **Streamlined process for future sites**

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CONCLUSION:

It is feasible to reduce the ETL implementation time by providing default configuration transformations along with assistance and feedback on the process. Further reduction in the person-hours required to perform an OMOP ETL will be evaluated with the Perseus web based OHDSI ETL project and cloud provider deployments of Atlas and the DQD. Our goal is to increase the adoption of OMOP in sites with fewer resources and enable wider participation in high-quality clinical registries with sufficient patient numbers and data variables to perform appropriate observational research techniques to control for potential confounders (e.g., propensity score matching).

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Building organizational capacity for observational research within a health system

PRESENTERS: **Paul Nagy, Mary Grace Bowring**

INTRODUCTION The Johns Hopkins OHDSI research community was formed to help clinical researchers take advantage of this opportunity. We approached the institutional adoption of OHDSI as a socio-technical endeavor benefiting from social solutions and providing new technical methods.

We leverage the work of Patterson et al. to highlight the sources of influence necessary to enact effective change within an institution and enable adoption of OHDSI practices.

APPROACH Patterson describes sources of influence using the main categories of motivation and ability:

Motivation: 'Will this be worth it?'
Ability: 'Can I do this?'

These categories are subdivided into **organizational, team, and individual** levels that encompass the **six sources of influence**. Organizational ability refers to changes in the environment that allow for organizational change. Team or social ability refers to the need to find strength in numbers to enact change. Individual ability refers to the need to surpass your current skill level and develop proficiency. Organizational motivation refers to extrinsic rewards and incentives that are built into the environment or organization. Team motivation refers to peer pressure and how we can harness that for change. Individual motivation refers to making the behavior desirable.

We delineated activities implemented at one institution to support researchers in their use of OHDSI through an application of the six sources of influence model.

One institution's approach to **empowering** researchers **to learn and conduct observational research**

JH OHDSI adoption strategy

ORGANIZATIONAL ABILITY	TEAM ABILITY	INDIVIDUAL ABILITY
Data: Up-to-date EHR data available **Tools**: OHDSI tools **Tools**: R/Python/SQL **Support**: Clinical research core data service team	**Team science:** Teams channel with interdisciplinary group **Networking**: Partner with OHDSI institutions **Registry creation:** OMOP sub-setting	**Online training:** EHDEN Academy, office hours **Graduate courses**: Observational research, data science
ORGANIZATIONAL MOTIVATION	**TEAM MOTIVATION**	**INDIVIDUAL MOTIVATION**
Awareness: Institutional website **Leadership:** Support for OHDSI **Support**: Grant letters of support **IRB**: Enable easier process	**Peer Mentoring**: Weekly calls **Networking**: Participation in OHDSI working groups **Data Science**: Graduate student project partnering	**Data:** Get data faster **Publications**: Produce robust, reproducible publications **Grants**: Grant template library **Data**: Get multi-institutional data

We aim to accelerate the use of OHDSI by creating value for our researchers and our organization. This framework can be adopted to support clinicians and researchers as they incorporate OHDSI into their research efforts.

Mary Grace Bowring, Michael Cook, Star Lui, Khyzer Aziz, Aki Nishimura, Paul Nagy
Johns Hopkins University School of Medicine, Baltimore, US

CURE Pregnancy Treatment Repository: Prioritizing Systematic Collection of Real-World Data to Identify Effective Treatments in a Special Population

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Abstract

Historically, pregnant patients have been excluded from conventional clinical trials due to safety and ethical concerns. As a result, very little is known about the efficacy of drugs used off-label for conditions affecting pregnant individuals. FDA and NCATS/NIH built a mobile application and website called CURE ID to capture the experiences of clinicians around the globe, prescribing FDA-approved drugs for new indications to treat infectious diseases, emerging threats, and multidrug resistant organisms.
The purpose of this project was to expand CURE ID to collect data on drugs used during pregnancy. We collected 174 case reports from the published literature and clinicians on drugs used to treat Trichomoniasis (6) Listeriosis (9), Group B Streptococcus (13), Toxoplasmosis (20), Gonorrhea (13), Cytomegalovirus (19), and COVID-19 (94) in pregnant patients. We also added a new case report form to collect treatment information of pregnant patients in CURE ID. For drug repurposing to be successful for pregnant patients, data collection on off-label drug use is one of the first steps in identifying drug candidates that can be later studied in a formal setting.

Materials and Methods

We identified seven high impact infectious diseases that lack FDA approved drugs in the pregnant population, namely, Trichomoniasis, Listeriosis, Group B Streptococcus, Toxoplasmosis, Gonorrhea, Cytomegalovirus (CMV), and COVID-19 . A group of maternal health experts from within and outside FDA was convened to consult on this topic. We updated the case report form in CURE ID to include additional data points to gather information on pregnancy-related details, such as, gestational age at the time of treatment and delivery, and pregnancy outcome.
Published literature reviews were conducted to retrieve case reports of the above-mentioned diseases, where the patient was pregnant and was treated with a drug that is not approved for that indication (or for use in pregnancy). We included articles pulled from PubMed using pregnancy and disease specific keywords and Medical Subject Headings (MeSH) terms. One hundred and seventy four cases were included after applying the exclusion criteria (Figure 1). After aggregating the data, we looked at the drug labels of the drugs used most frequently for the treatment of each disease to review the pregnancy related information.

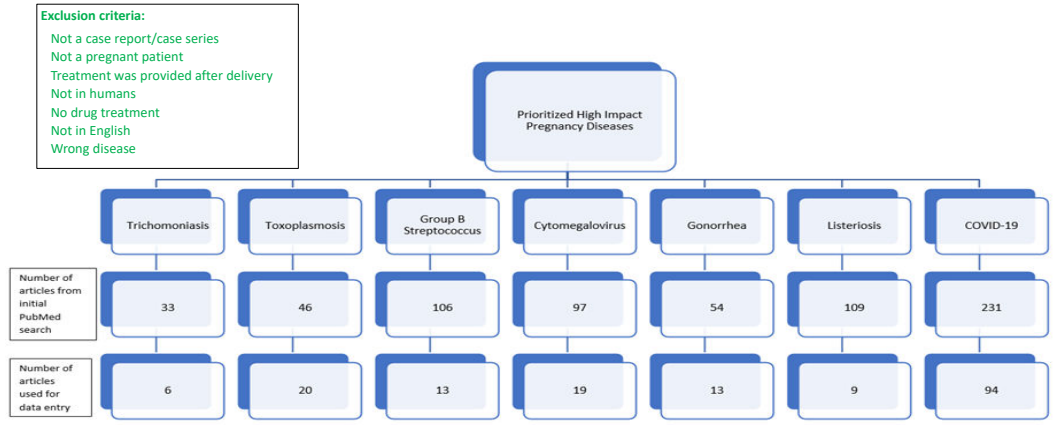

Figure 1: Flowchart of inclusion and exclusion criteria of relevant articles

Disease n-(Number of cases)	Mean gestational age at the time of treatment (Weeks), IQR	No. of patients treated with monotherapy/combination therapy	Outcome	Most frequently used drug
Trichomoniasis 6	21 Range: 10 -28 weeks	3/3	Improved 6/6 (100%)	Metronidazole (2/6) Tinidazole (2/6)
Listeriosis 9	24 Range: 11 – 35 weeks	1/8	Improved 9/9 (100%)	Ampicillin (6/9) Gentamicin (6/9)
Group B Streptococcus 13	26 Range: 9 – 37 weeks	3/10	Improved 13/13 (100%)	Clindamycin (4/13)
Toxoplasmosis 20	20 Range: 6 -36 weeks	9/11	Improved 12/20)60%) Unknown 5/20 (25%) Deteriorated 3/20 (15%)	Spiramycin (10/20)
Gonorrhea 13	30 Range: 20 – 36 weeks	3/10	Improved 13/13 (100%)	Ceftriaxone (4/13)
Cytomegalovirus (CMV) 19	21 Range: 10 -31 weeks	17/2	Improved 19/19 (100%)	Immunoglobulins (14/19)
COVID-19 94	28 Range: 9 – 39 weeks	23/71	Improved 80/94 (85%) Died 13/94 (14%) Unchanged 1/94 (1%)	Hydroxychloroquine (36/94)

Table 1. Aggregated data depicting patient outcomes from CURE Pregnancy Treatment Repository

Drug (Disease for which the drug was used most frequently)	Is the drug approved for the indication/s it was used for	Does the label follow the PLLR?	Does the label include any reproductive black-box warning?	Does the label include any human data related to pregnancy?	Does the label include any animal data related to pregnancy?	Does the label include information for females and males of reproductive potential?	Does the label include pregnancy registry information?
Metronidazole (Trichomoniasis)	Yes	No	No	No	Yes	Yes	No
Tinidazole (Trichomoniasis)	Yes	Yes	No	No	Yes	Yes	No
Ampicillin (Listeriosis)	Yes	No	No	No	Yes	No	No
Gentamicin (Listeriosis)	No	No	Yes	No	Yes	Yes	No
Clindamycin (Group B Strep)	Yes	No	No	Yes	Yes	Yes	No
Ceftriaxone (Gonorrhea)	Yes	No	No	No	Yes	Yes	No
Hydroxychloroquine (COVID-19)	No	Yes	No	Yes	No	No	Yes

Table 2. Evaluation of FDA labels of drugs used most frequently in CURE Pregnancy Treatment Repository

Results and Discussion

The mean gestational age at the time of treatment across all diseases in the Pregnancy Repository was 27 weeks (range: 6 – 39 weeks). More than 75% of cases of Listeriosis, Group B Streptococcus, Gonorrhea, and COVID-19 were treated with a combination of drugs. More than 89% of CMV cases were treated with a single drug. Fifty percent of cases of Trichomoniasis and 55% cases of Toxoplasmosis were treated with monotherapy. Eighty-seven percent of patients were reported to improve after the treatment in our Repository. The high number of cases with a positive outcome may be attributed to a reporting bias where practitioners are more motivated to report a case when it is a positive outcome compared to a negative outcome. Most drugs (except Gentamicin, Spiramycin, and Hydroxychloroquine) that are being used to treat patients have been approved for that particular indication; however, with limited or no human data related to their use in pregnancy.

Conclusion

The aim of the CURE Pregnancy Treatment Repository was to create a digital platform for clinicians across the world to submit information on repurposed drugs used in pregnant individuals who are diagnosed with an infectious disease. The case report form was updated with additional data points for the purpose of this project. The Repository now provides free access to users wishing to view de-identified, aggregated data of pregnant patients and allows reporting of cases involving pregnant patients. All published cases of pregnant patients that met the inclusion criteria were extracted and included in the Repository. Despite our best efforts to collect data directly from clinicians, we did not see much engagement from clinicians in reporting their cases or using the discussion forum in the mobile app for queries regarding challenging cases. In both formal and informal discussion with clinicians, we found that there is a hesitation among obstetric care professionals in reporting the use of off-label drugs, especially if the outcome is negative. For drug repurposing to be successful for pregnant patients, collection of large quantities of real-world data (RWD) on off-label drug use is the first stage in discovering therapeutic candidates that can be subsequently examined in a more formal setting.

This work was supported by the FDA Office of Women's Health. This project was supported in part by an appointment to the ORSIE Research Participation Program at Office of Medical Policy (OMP), CDER, US Food and Drug Administration, administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and FDA/Center.

Deploying the Edge Tool Suite to Extract Real-World Data: an Implementation Science Approach

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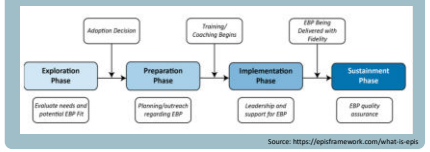
What is EPIS?

- The EPIS framework is an implementation science approach to the implementation of evidence based practices (EBPs)
- The framework is made up of four main phases: exploration, preparation, implementation, and sustainment
- EPIS also includes four groups of factors that impact the implementation: inner context, outer context, bridging factors, and innovation factors



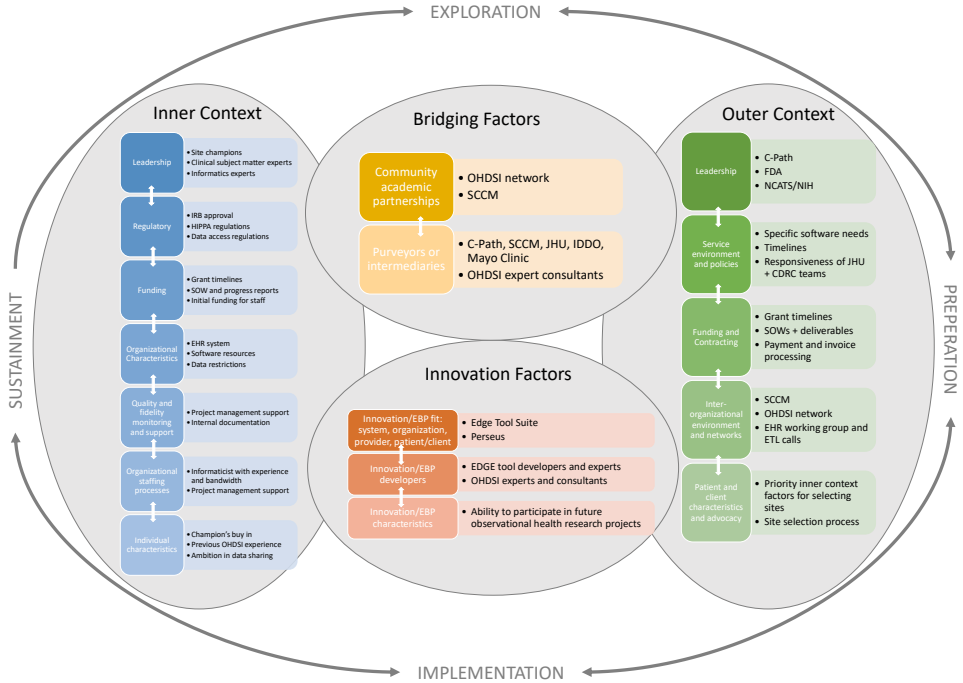
Source: https://episframework.com/what-is-epis

Introduction to CURE ID:

- Public private partnership between the FDA, National Center for Advancing Translational Sciences, and the Critical Path Institute
- Aims to collect real-world data (RWD) on drug repurposing
- Funded by a grant from HHS ASPE's Patient Centered Outcomes Research Trust Fund
- Expanded to build a tool that automates the collection of case reports directly from the electronic health record (EHR)
- The EHR collection project is a collaboration with Johns Hopkins, the Society of Critical Care Medicine, Emory, and the Infectious Disease Data Observatory at Oxford

Background

- The CURE ID project has developed relationships with over a dozen clinical sites in conjunction with SCCM
- In exchange for a small grant, clinical sites agree to work with OMOP experts to implement the EDGE tool suite and extract their inpatient COVID cases in the OMOP common data model
- These cases will eventually be sent to SCCM, IDDO, and finally NCATS for inclusion in the CURE ID app
- Guiding sites through the process has been challenging due to time, resource, and regulatory constraints
- This project sought to complete a comprehensive, multi-stakeholder review of site-based implementation
- Although the EPIS framework is often used as a prospective planning tool, we use it here to review an on-going effort and make recommendations for new practices



Methods

- Our team looked at all aspects of the CURE ID project and mapped them to the EPIS framework
- Analyzed stake-holder feedback received in weekly stake-holder meetings held over the two-year project
- Specific stakeholder groups included:
  - Regulators
  - Providers
  - Informaticists
  - Data analysts
  - Health researchers
  - Patients/patient advocates
  - Compliance professionals
  - Health care system leaders
- Implementation team engaged in concept mapping activities to organize feedback

- By identifying the inner context, outer context, bridging factors, and individual factors, we are able to find where main roadblocks have developed

Funding Statements

- The CURE ID EHR Program was supported by the Office of the Secretary Patient-Centered Outcomes Research Trust Fund under Interagency Agreement #75F40121S35006.
- This project was supported in part by an appointment to the ORISE Research Participation Program at the Center for Drug Evaluation and Research, U.S. Food and Drug Administration, administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and FDA/CDER.

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Recommendations, Future Directions:

- Emphasize the benefits of the Edge Tool Suite (the "innovation factor," in the EPIS framework) to sites early in the process to encourage engagement and buy-in.
- Ensure a complete, thorough, and well-documented technological and regulatory factor review with each site prior to contracting and beginning the ETL process. This should include examining the expertise of the informaticist, the availability of the necessary software and other tools, the informaticist's access to the data, the ability of a site to get an IRB and DUA approved, and the availability of resources to initiate the project before contracting with the site is finalized.
- Establish and document a timeline for sites based on the grant timeline. Ensure this timeline is well communicated and able to be met before initiating work with a site.

Repurposing in RASopathies

This data was collected from published literature during background research to inform the pilot for the rare disease expansion of the CURE ID app, a joint project between the FDA and NCATS/NIH, but is not a representation of the views of either agency.

Overview

There are over 7,000 rare diseases with more being discovered everyday. Somewhere between 92-95% of rare disease patients lack FDA approved therapies, leading clinicians and patients to rely on off-label drug usage, also known as “repurposing” for treatment. There is a lack of drug development in the rare disease space due to lack of funding and the challenges that having small patient populations provide for conducting a randomized clinical trial (RCT) along with the ethical implications of doing a controlled study in certain rare diseases with deadly outcomes without medical intervention.

This poster explores repurposing in the group of rare diseases known as the RASopathies as a case study.

The RASopathies

The RASopathies are a group of disorders including NF1, Noonan Syndrome, Costello Syndrome, and more that are caused by changes in genes in the Ras/mitogen-activated protein kinase (Ras/MAPK) pathway, which is responsible for a variety of essential bodily functions, including growth and inflammatory responses. No two RASopathy syndromes present in the same, way, however, there are many overlaps including hypertrophic cardiomyopathy (HCM), failure to thrive, lymphatic associated symptoms, and bleeding disorders.(8,9) Because of this, there is not necessarily a “one size fits all” treatment available for the RASopathies, however, therapeutics targeting the underlying pathway has potential to benefit patients unilaterally despite unique presentations.

Figure 1: RASopathy Pathway (1)

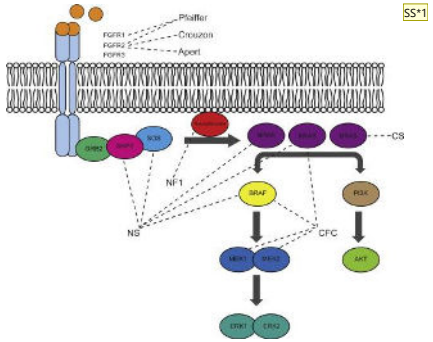


Figure 2: MEKi Pathway (6)

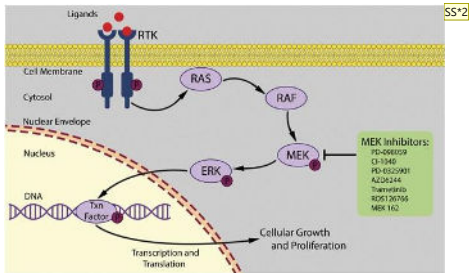
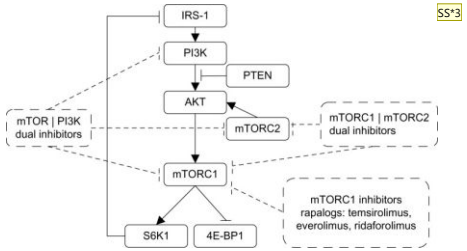


Figure 3: MTOR Inhibitor Pathway (7)



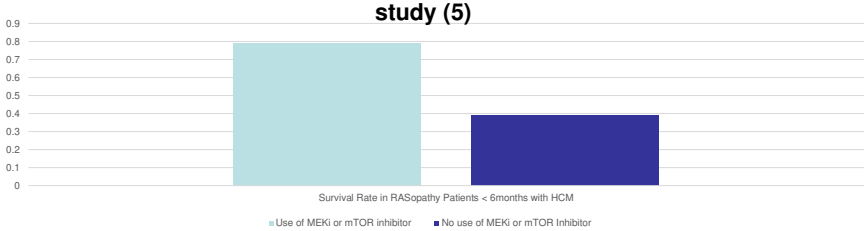
Potential of MEKi’s and MTOR Inhibitors

Pre-clinical data suggested the possible efficacy of mitogen-activated protein kinase inhibitors (MEKi) and drugs that inhibit the mechanistic target of rapamycin (mTOR) in treating the various symptoms of the RASopathies. MEKi’s directly impact the MAPK pathway and are often FDA-approved for cancers that occur as a result of this being deregulated, which accounts from approximately one-third of cancers. Deregulation of the MAPK pathway is also involved in the RASopathies. mTOR inhibitors work by blocking a protein causing cell-division and is also FDA-approved to treat different types of cancers. This is also what makes it potentially effective in treating the RASopathies. (2, 3, 4, 5)

Conclusions

Clinicians began to use these medications in their practice, based upon the mouse model data that showed decrease and even reversal in HCM. In human patients, clinicians also noted anecdotal improvement in HCM, along with other unexpected outcome measures, such as less need for growth hormones, lessened supplemental nutrition, and even improved cognitive function. Patients and care-partners have been critical in obtaining this data on both unexpected positive and negative effects of these repurposed medications. (2, 3, 4, 5)

Figure 4: Results from “MAPK and AKT/MTOR Inhibition Improves Childhood RASopathy-Associated Cardiomyopathy” study (5)



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Landscape Analysis of Drug Treatments for PEComa

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Introduction

Perivascular epithelioid cell neoplasms (PEComas) are rare tumors formed by epithelioid cells. As with other rare cancers, funding, trial recruitment, and other concerns pose a significant barrier to obtaining Food and Drug Administration (FDA) approval for treatments. To date, the FDA has approved only one agent, Nab-Sirolimus, for the treatment of PEComa. However, there is a lack of research that systematically addresses the current landscape of available drug treatments for PEComas.

Aim

Our research aims to identify repurposed pharmacological treatments for PEComas and their associated subtypes.

Methods

- We first conducted a PubMed search with this search string
- In the first pass of our review, we screened the titles and abstracts for inclusion.
- All study types were included.
- Articles that were not in English were excluded.
- Data entry and analysis are still underway using Rayyan software.
- Data entry will be done on Excel workbook containing predefined data variables in the form of a case report form

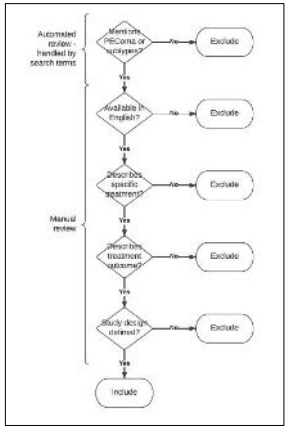

Figure 1. Flow diagram of inclusion and exclusion criteria.

Results

A total of 1267 articles were retrieved from PubMed and uploaded in Rayyan database for review. After the first pass, a total of 197 articles were included for full-text screening in the second pass. Of these articles, 153 were included in the data entry and analysis. Results show that the majority of research for PEComa treatment focuses on the mTOR inhibitors, with the FDA approved agent, Sirolimus, accounting for 78 articles.

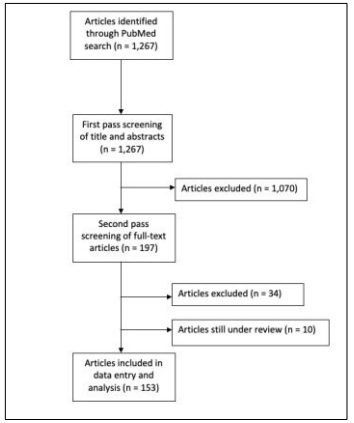

Figure 2. PRISMA flow diagram of the screening process. All the articles that were obtained from the initial PubMed search were first screened by title and abstract (n = 1,267). Articles were excluded from the review based on the inclusion and exclusion criteria (n = 1,070). Full-text articles were screened under the same criteria. The second pass is currently underway. Data entry and analysis will be completed for all of the included articles (n = 153).

Results

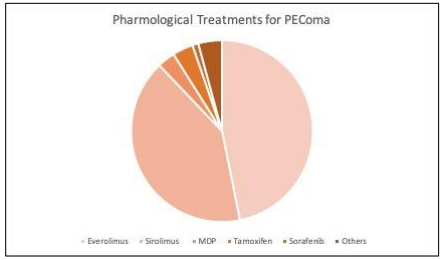

Figure 3. The results of our research show that Everolimus and Sirolimus were the two most studied treatments, with 89 articles and 78 articles, respectively. There were 7 articles about Tamoxifen treatment, 6 articles about Medroxyprogesterone (MDP) treatment, and 2 articles about Sorafenib treatment. Metformin, Prednisone, Imatinib, Buserelin, Letrozole, AICAR, Nivolab, and Cannabidiol (CBD) were each found to be studied for PEComa treatment in one article.

Conclusion

These findings demonstrate the extensive availability of research on PEComa treatment. Our review offers a comprehensive analysis of the current pharmaceutical treatment options for PEComas including FDA approved (i.e., Nab-Sirolimus) and repurposed agents. Our analysis can provide useful information for further research identifying potential targets for repurposed pharmaceutical treatments.

The Landscape of Rare Infectious Diseases – A Proof of Concept with Rare Bacterial Infections

Authors Tahsin Farid, Reema Charles, Keyla Tumas, Heather Stone, Raghav Tirupathi
Location: Cure Drug Repurposing Collaboratory (CDRC) Annual Meeting, 2023

❖ This project was supported in part by an appointment to the ORISE Research Participation Program at the Center for Drug Evaluation and Research, U.S. Food and Drug Administration, administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and FDA/Center.
❖ The views and opinions presented here represent those of the authors and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

Abstract

Here the landscape of rare bacterial infections (RBIs) is reviewed. 22 established RBIs were identified and information regarding their transmission, incidence, and therapy were recorded. Zoonosis was the most common mode of transmission (10), with a worldwide pattern of incidence (8). The observed transmission and incidence patterns are likely influenced by low endemicity, outbreaks in different regions, and socioeconomic, demographic, and/or climate change. Very few RBIs had approved therapy (7). The intention of this group is to expand the scope of the research to all rare infectious diseases and propose the use of real-world data to better inform therapy.

Introduction

Rare infectious diseases (RIDs) collectively represent a significant source of morbidity and mortality around the world[1]. However, most lack approved medications. Due to their sporadic nature and often, distribution in resource limited settings, it has been difficult to perform comprehensive trials on therapeutic efficacy[2]. Additionally, there is little monetary incentive in drug development for these diseases[3]. RIDs therefore represent an area of high unmet medical need. The aim is to review the landscape of RIDs and to highlight those constituting the most urgent medical needs. This poster is a pilot project that focuses on rare bacterial infections (RBIs).

Materials and Methods

A list of bacterial infections was curated by combining reportable infections from health agencies[4-7] with the CURE ID[8] database of diseases. This list was independently reviewed by two experts in infectious diseases to identify potential rare bacterial diseases. A literature review was then conducted to identify which of these bacteria met the inclusion criteria of a global incidence of less than or equal to 10,000 cases per year. Table 1 outlines the data that was collected for each RBI that met the inclusion criteria. This data was then analyzed

Discussion

It was hypothesized that a majority of RIDs occur through zoonoses, while environmental and commensal organisms primarily caused opportunistic infections in immunocompromised patients. Perhaps surprisingly, the majority of zoonoses, had a worldwide distribution. This does not imply higher incidence, rather it may indicate that these RBIs have no sustained endemicity and cause outbreaks in varied geographic areas when animal to human spillover occurs. Transmission patterns may also be related to socioeconomic conditions, climate change, and population growth. The intention of this group is to explore these possibilities and expand the scope to all RIDs. Only a few RBIs had FDA-approved therapies because the paucity of cases makes it difficult to conduct efficacy trials and there is little financial incentive for traditional pharmaceutical development. It is imperative to adopt a rare disease approach to these conditions and to

Results

From the comprehensive list of 163 bacterial infections, 22 met the final inclusion criteria. The workflow process is depicted in Figure 1. The distribution of the RIB by the World Health Organization (WHO) Region where they have the highest incidence is displayed in Figure 2. The frequency with which each mode of transmission was noted for these RBIs are shown in Figure 3. Table 2 plots the distribution of RBIs that have commonly used standard of care and/or FDA approved therapy. Figure 4 breaks down the transmission mode of infections according to the WHO region where they are most frequent.

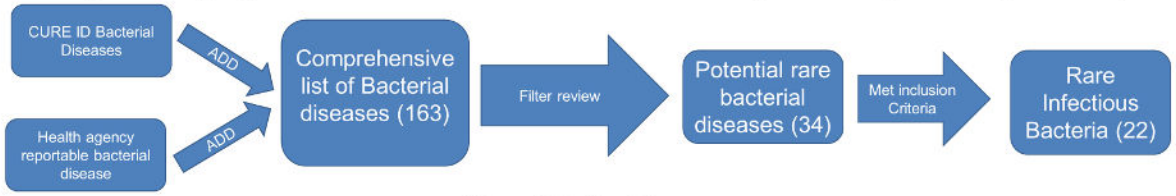

Figure 1. Data Flow Diagram

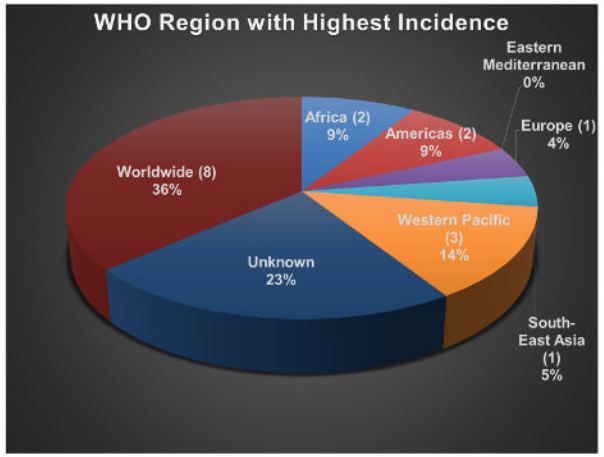

Figure 2: Distribution of RBIs by WHO Region with Highest Incidence

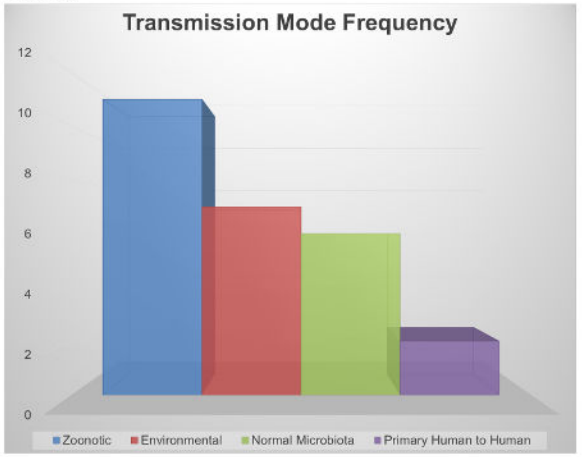

Figure 3: Frequency of transmission mode of RBIs

FDA Approved Therapy	Standard of Care	
	Yes	No
Yes	7	0
No	13	2

Table 2: Standard of care availability plotted against FDA approved therapy availability

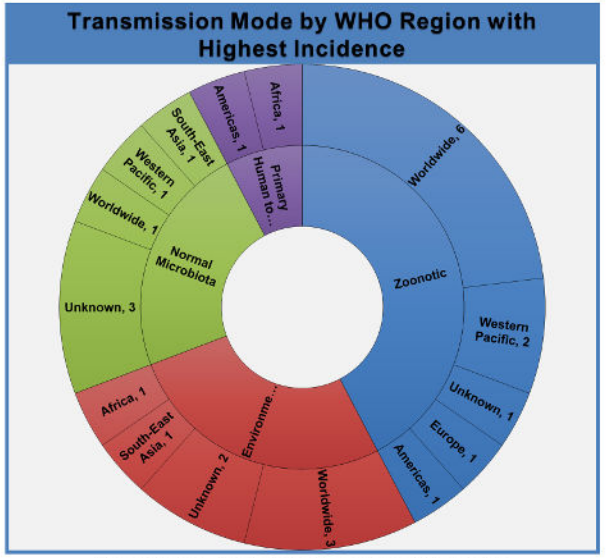

Figure 4: Plot of transmission mode by WHO region

Disease	WHO Region w Highest Incidence	Transmission	Standard of care data available	FDA-approved therapy?
Actinomycosis, Respiratory tract	South-East Asia	Normal microbiota, Environmental	Yes	None
Aerococcus Infective Endocarditis	Unknown	Environmental	Yes	None
HACEK Infective Endocarditis	Western Pacific	Normal microbiota	Yes	None
Bartonellosis	Americas	Zoonotic	Yes	Yes
Glanders	Worldwide	Zoonotic	Yes	None
Capnocytophaga infection	Unknown	Zoonotic	Yes	None
Clostridium butyricum infection	Unknown	Normal Microbiota, Environmental	No	None
Elizabethkingia infections	Worldwide	Environmental	Yes	None
Erysipeloid	Worldwide	Zoonotic, Environmental	Yes	Yes
Eubacterium infections	Unknown	Normal Microbiota	No	None
Epidemic Typhus	Worldwide	Zoonotic	Yes	Yes
Murine Typhus	Worldwide	Zoonotic	Yes	Yes
Buruli Ulcer	Africa	Environmental	Yes	None
Rhodococcus equi infection	Worldwide	Zoonotic, Normal Microbiota	Yes	None
Mediterranean spotted fever (MSF)	Europe	Zoonotic	Yes	Yes
Japanese spotted fever	Western Pacific	Zoonotic	Yes	None
North Asian Tick-Borne Rickettsiosis	Western Pacific	Zoonotic	Yes	Yes
Rothia mucilaginosa infection	Unknown	Normal Microbiota	Yes	None
Vancomycin-resistant Staphylococcus aureus (VRSA) infection	Worldwide	Environmental	Yes	None