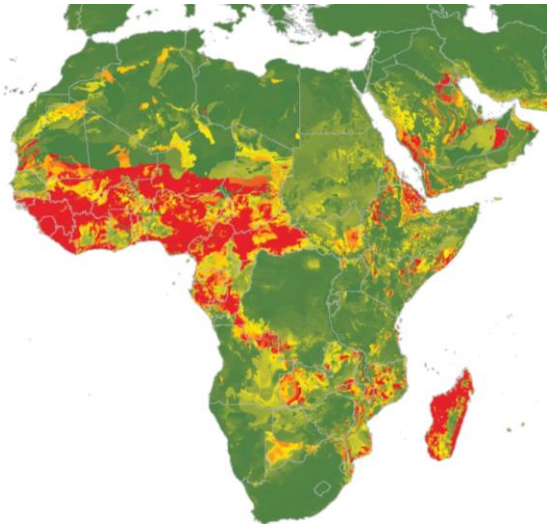


Newly discovered pediatric melioidosis in Mali: the tip of an African iceberg?

Lichtenegger, Sabine; Klugherz, Isabel; Wagner, Gabriel E; Michel, Justine; Mollo, Bastien; Sanogo, Adama; Diawara, Moussa Karim; Traore, Soumaila; Kodo, Hyacinthe Gatchimou; Mbangui, Max-Yvon; Koudika, Marie-Hortense; Sidibé, Youssouf Diam; Kohler, Christian; Becker, Karsten ; Assig, Karoline; Limmathurotsakul, Direk; Kohl, Matthias; Kanapathipillai, Rupa; Ousley, Janet; Steinmetz, Ivo

Conflicts of interest
All authors declare no competing interests.

Ethics
This study was approved by the Ethics Review Board of Médecins Sans Frontières and the Ethical Committee in the Ministry of Health in Bamako.

Melioidosis?
Never heard of it…

Deadly tropical infections that kill within 48 hours don't usually go unnoticed. But one killer has been largely ignored for decades. Now, thanks to worries about bioterror, it is being taken more seriously. Peter Aldhous reports.

Mention melioidosis in most circles — even those with a passing interest in tropical medicine — and you'll be met with blank stares. The infection is often misdiagnosed because the bacterium that causes it, the soil-dwelling *Burkholderia pseudomallei*, triggers multiple symptoms that mimic those of other diseases. In parts of Asia where *B. pseudomallei* is endemic, this serial killer often commits its crimes without even being identified as a suspect.

Not so in Ubon Ratchathani, a bustling provincial capital in northeast Thailand. For Wipada Chaowagul, a specialist in internal medicine at the city's Sappasitprasong Hospital, melioidosis is public enemy number one. Each year, the hospital admits about 200 people who test positive for *B. pseudomallei*. Up to half of them die.

Chaowagul's patients are mostly rice farmers. When the rains come each year, between May and October, *B. pseudomallei* threatens anyone paddling in the flooded paddy fields that surround Ubon — especially those already weakened by other conditions such as diabetes. Some develop internal abscesses or inflamed joints; others have difficulty breathing. Many are overwhelmed by the infection, and die from septic shock within 48 hours.

Chaowagul wants to run clinical trials of new antibiotics, to see if they can reduce this toll. But for Thailand's overstretched healthcare system, such drugs are prohibitively expensive. No pharmaceutical company has volunteered to donate its products, so Chaowagul's plans remain stalled. "If we use our own money, we have a problem," she says.

In from the cold

This tale is echoed for 'orphan' diseases across the developing world — unless pathogens afflict rich Westerners, they tend to attract little research money. But *B. pseudomallei* may soon lose its orphan status, thanks to fears that it might be used as a biological weapon. Through its richly funded biodefence initiative, the US National Institute of Allergy and Infectious Diseases (NIAID) is now encouraging microbiologists to begin working on the bacterium. "We're looking at building a research base," says Michael Schaefer, an official at the NIAID's headquarters in Bethesda, Maryland.

There are many puzzles to solve. *Burkholderia pseudomallei* is a resilient organism, able to hunker down in the soil or inside the cells of its human victims for years on end, only emerging when conditions favour its growth. One US Vietnam veteran, probably infected after breathing in aerosols of *B. pseudomallei* whipped up by helicopters, first became sick 26 years later. Vanaporn Wuthiekanun, who works on *B. pseudomallei* in the Wellcome Trust unit at Mahidol University in Bangkok, has cultured the bacterium from a sample kept in distilled water for a decade. "It's very tough," she observes.

For the most part, *B. pseudomallei* is thought to get its nutrition from rotting organic matter, and when the opportunity arises, by parasitizing soil-dwelling amoebae. Its ability to infect human cells may simply be an unhappy consequence of the mechanisms that allow it to do the latter. But these mechanisms are poorly understood, as are the ecological factors that influence *B. pseudomallei*'s distribution across the tropics. One mystery is why it is absent in central Thailand — where it is replaced by its cousin, the harmless *B. thailandensis*.

"It's probably something to do with the soil, but we haven't worked it out yet," says Nick Day, who heads the Wellcome Trust's Bangkok unit. As if the scientific challenges weren't enough, researchers out in the field also face obstacles imposed by southeast Asia's history of conflict. "We're keen to do soil surveys in Cambodia, but we're afraid of the landmines," says Wirongrong Chierakul, who works in Day's unit.

From the limited information available, it is clear that *B. pseudomallei* is present in the

J. MARSHALL/ASIA-IMAGES.COM

From **2005** to **2025**

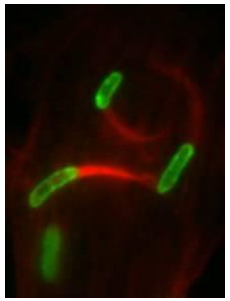
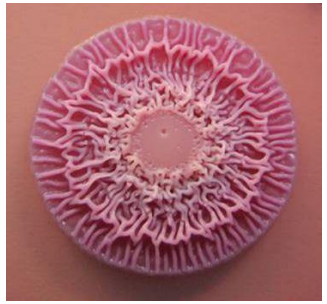
Knowledge and awareness increased ✓

.....but still we could do better!

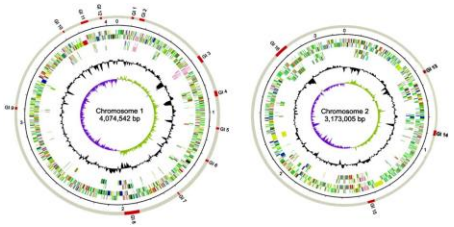
.....for populations at risk

Burkholderia pseudomallei – causative agent of melioidosis

- Gram negative ß-Proteobacterium


- environmental saprophyte
- facultative intracellular pathogen
- causative agent of melioidosis in <u>animals</u> and <u>humans</u>



B. pseudomallei genome

Proc Natl Acad Sci U S A. 2004 Sep 28;101(39):14240-5.

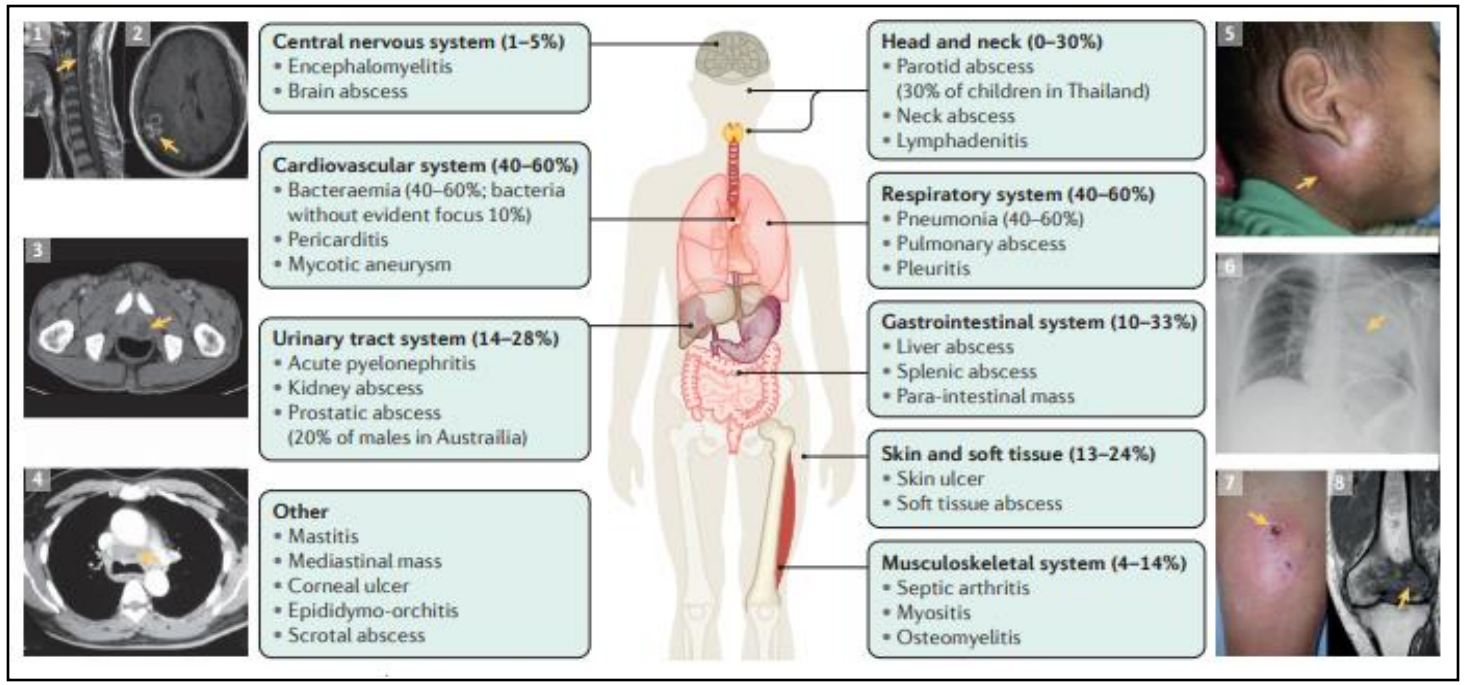
- melioidosis is associated with rain fall


- increasingly recognized in Asian and Pacific regions
- disease of the elderly (diabetes main risk factor)
- estimated global burden **165.000** and **89.000** deaths
- estimated mortality comparable to measles

Istockphoto; NATURE MICROBIOLOGY | VOL 1 | JANUARY 2016

.....an environmental infection

Clinical manifestations of melioidosis are extremely variable



Nat Rev Dis Primers. 2018 Feb 1;4:17107.

Mode of transmission

- Ingestion
- Inhalation
- Inoculation

(Human-to-human transmission is exceptionally rare)

Therapy

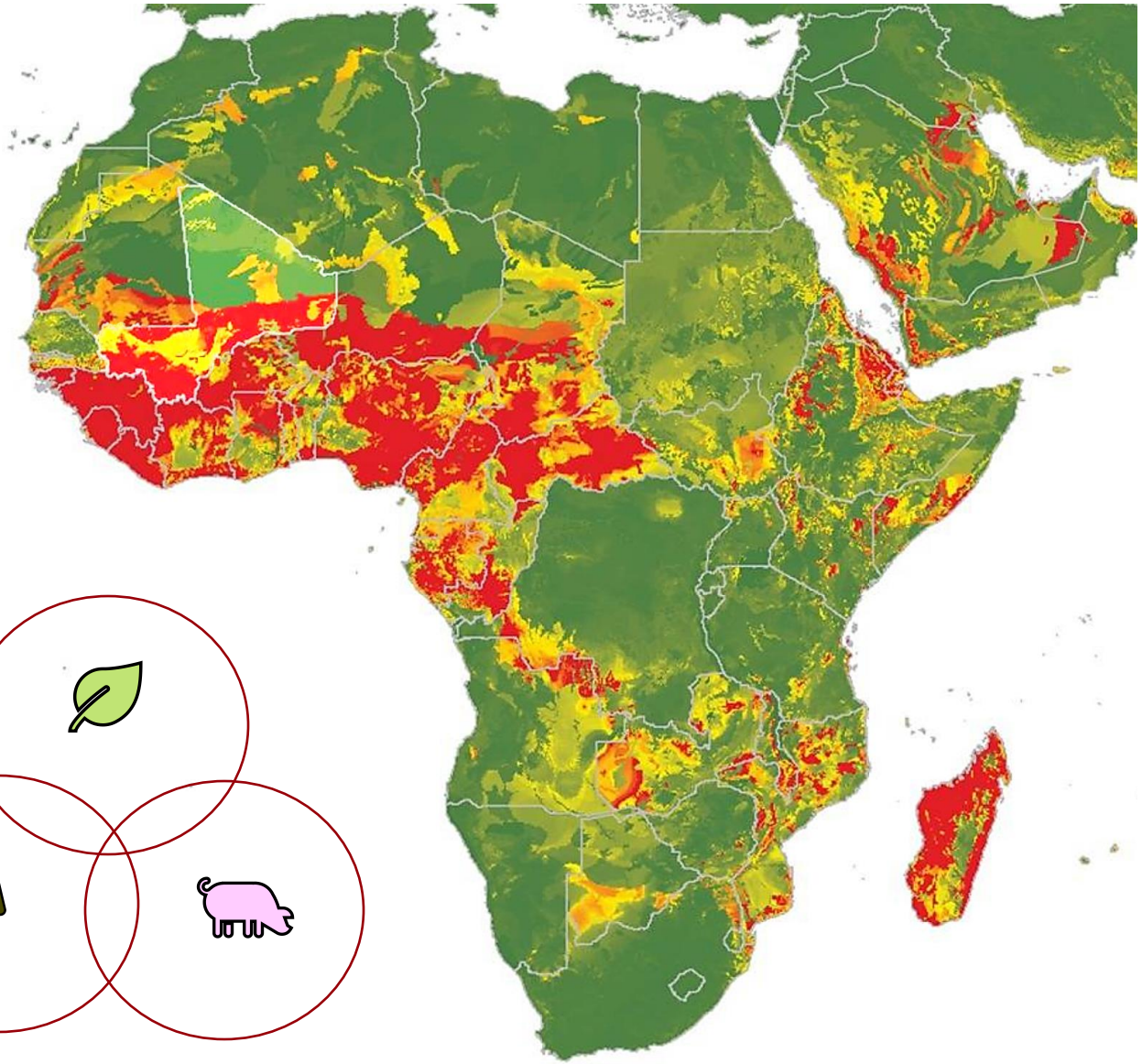
Intensive phase: **ceftazidime** or a **carbapenem** (meropenem or imipenem) ≥ 2 weeks with or without trimethoprim-sulfamethoxazole

Eradication phase: **trimethoprim-sulfamethoxazole** for 3-6 months

Mortality

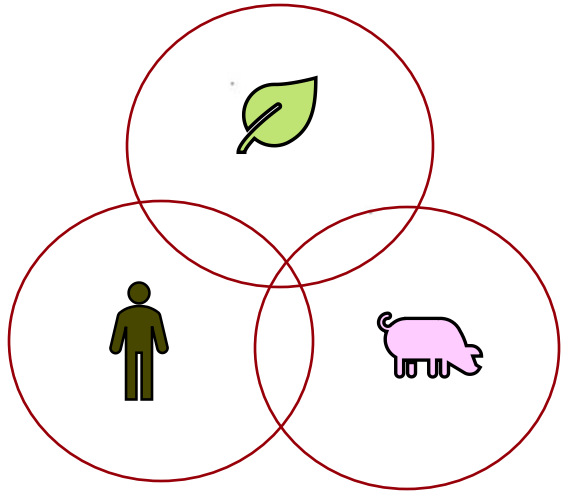
10 - 40 % or higher (with ineffective treatment >70%)

Predicted environmental suitability for *B. pseudomallei* in Africa

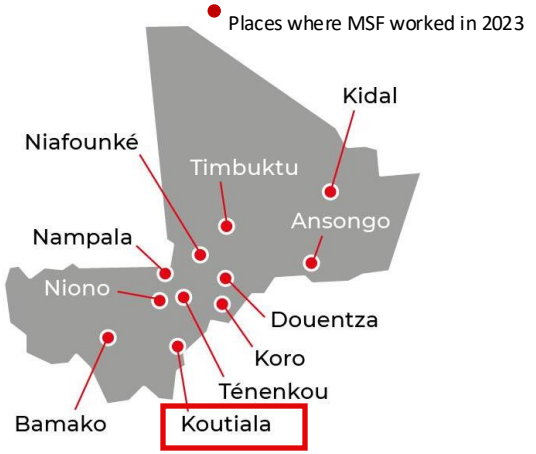


Current challenges

- Lack of epidemiological data on melioidosis in humans and animals
- only sporadic reports
- only few environmental studies



Background of the study



MSF Center in Koutiala, Mali

- Focus on child nutrition for ages 0-5
- High-quality microbiology laboratory

→ Biochemical characteristics (API20NE) of isolated strains suggested the presence of *B. pseudomallei* in clinical samples

Aims

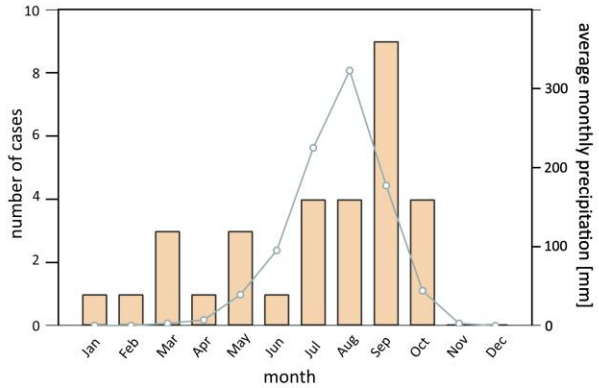
- To confirm and characterize putative *B. pseudomallei* strains collected from 2018 to 2021
- To conduct a retrospective analysis of the clinical data of confirmed melioidosis cases

Methods

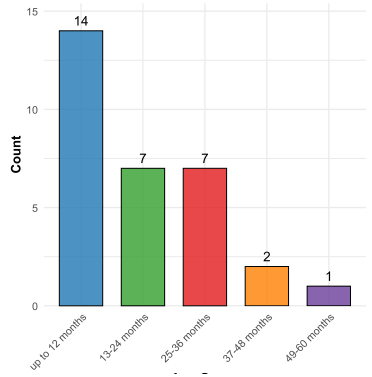
- Retrospective observational study (approved by the CNESS, Bamako, Mali as well as the MSF ERB)
- Suspicious bacterial isolates were investigated by PCR (recA and TTSS1)
- *B. pseudomallei* isolates were further characterized by whole genome sequence sequencing and antibiotic susceptibility testing
- Available clinical data of confirmed melioidosis cases were analyzed from the hospital records

Results

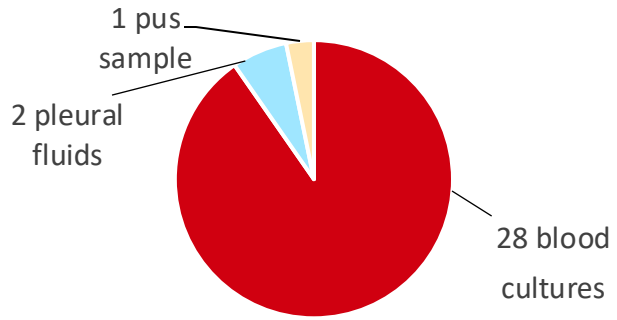
- 31 pediatric melioidosis cases were confirmed between 2018 and 2021.
- Out of 19 patients with available outcome data, **12 (63%) patients died.**



Most patients during the rainy and the malaria season



14 (45%) were aged 12 months or younger

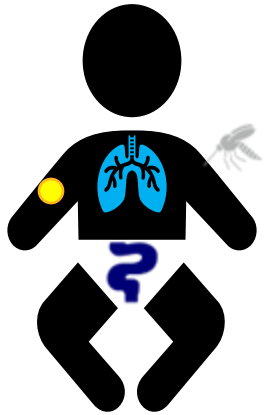


B. pseudomallei-positive clinical samples

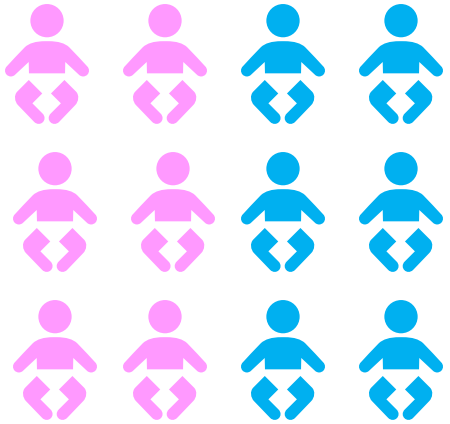
- Based on our cases and the Malian population structure **we estimated an annual incidence of 15·5 per 100.000** (95% CI 10-21·9)

Results

More detailed clinical information was available for **12 patients**



- Respiratory distress (10)
- Gastrointestinal syndroms (7)
- Malaria co-infection (5)
- Altered consciousness (4)
- Abscesses (2)

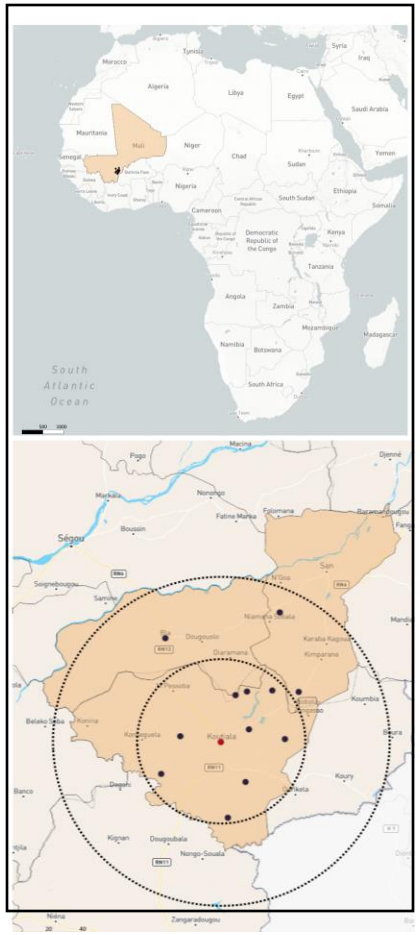


- The median time from symptom start to hospital admission was 4·5 days.
- Seven out of 12 children received antibiotic treatment with ceftazidime or a carbapenem
- All isolates were susceptible to drugs currently recommended for the treatment of melioidosis.

- Eight of 10 children with known nutritional status showed signs of **undernutrition**
- All children presented with moderate to severe **anemic hemoglobin levels** (11/11 with documented values).
- Apart from one child with Trisomy 21, no underlying medical conditions were noted.

Results

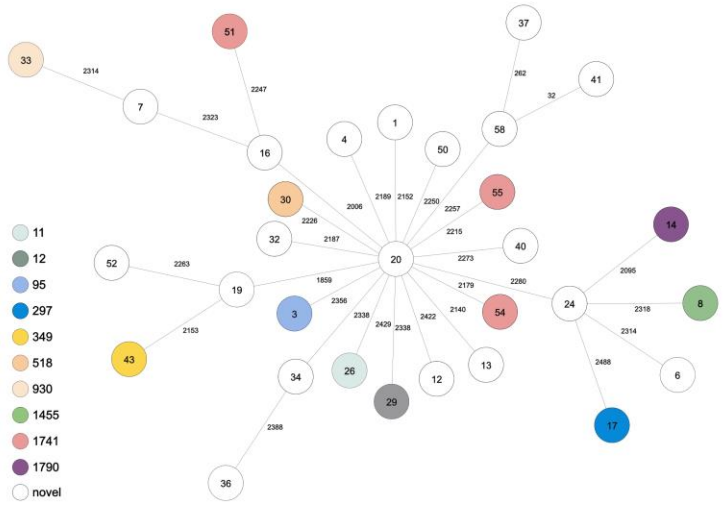
Origin of patients



High genetic diversity of the *B. pseudomallei* strains suggests long-standing persistence rather than recent introduction

Local phylogeny

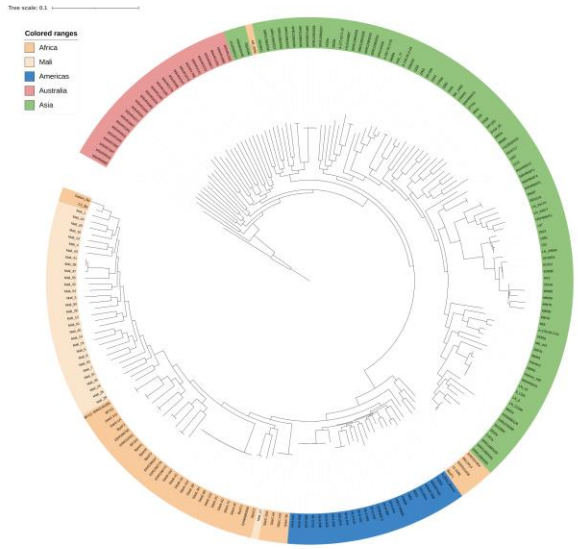
Koutiala strains represent several novel sequence types



Core genome MLST (cgMLST) minimum-spanning tree of pediatric isolates in Koutiala

Global phylogeny

Koutiala strains classify within the African clade



Core genome SNP-based maximum likelihood phylogeny of 218 global *B. pseudomallei* isolates

The cases in our study comprise approximately **half of all melioidosis cases ever reported from Africa**

Limitations of the study

- We have no information whether **hemoglobinopathies such as sickle cell disease or thalassemia** were present in our cohort, the latter being a known risk factor for pediatric melioidosis.

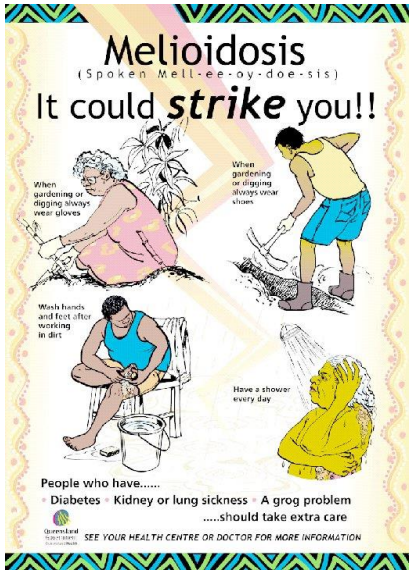
- Our clinic's **malnutrition focus may introduce bias** and therefore further observational studies are needed to clarify associated risk factors and the clinical presentation of pediatric melioidosis in this region.

- **Long distances between patients' homes and clinics** likely hindered access to diagnosis and treatment.

- It is therefore likely that the cases detected in our study are only the **tip of a melioidosis iceberg in Mali.**

Implications and impact

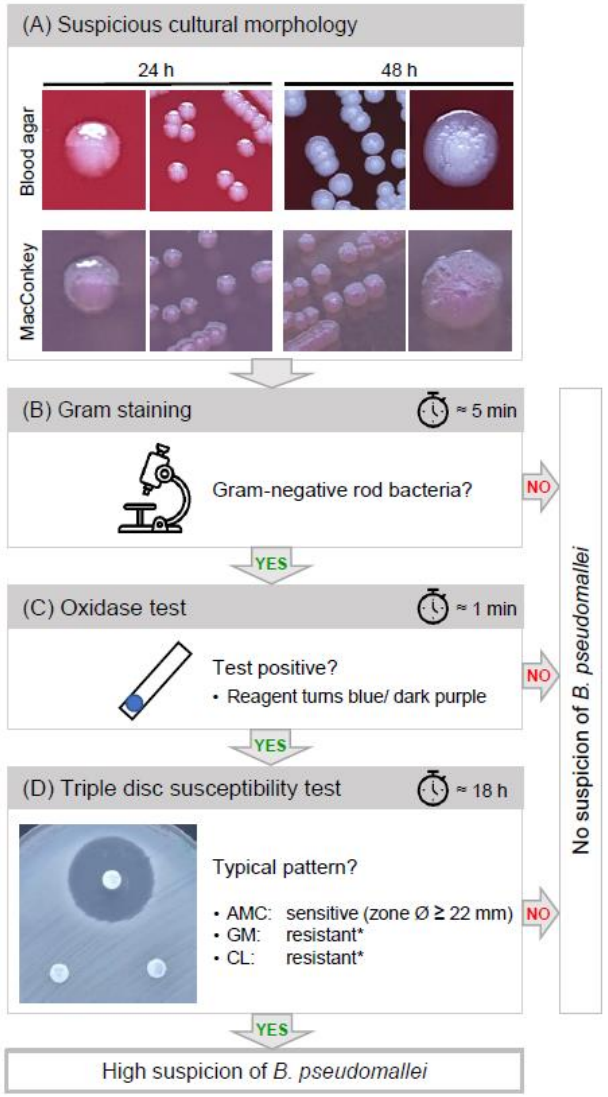
- This is, to our knowledge, the **largest cohort of melioidosis cases ever reported from Africa.**
- Our study clearly highlights the need for **improved diagnostics and observational studies** to learn more about the African melioidosis burden and risk factors.
- **Targeted awareness** raising e.g. in diabetic clinics to reach vulnerable individuals



https://www.melioidosis.info/

Search for melioidosis in potentially endemic African regions

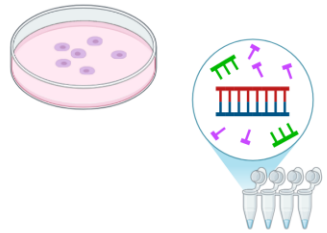
- introduce **simple but effective laboratory algorithms** to improve *B. pseudomallei* identification in resource-constrained African laboratories.
- A **positive triple-disk tests** can lead to adequate melioidosis therapy

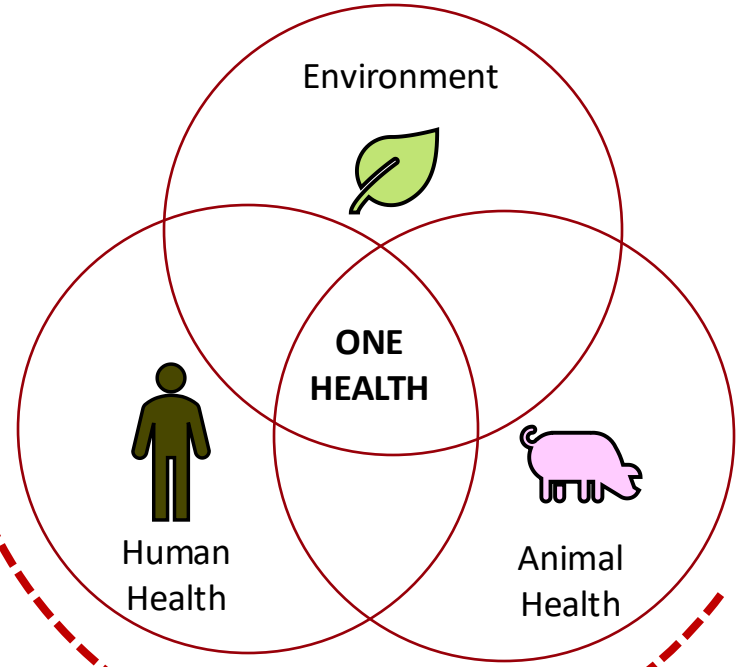


https://doi.org/10.1016/j.ijregi.2024.100377

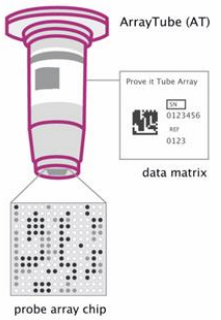
Further Research strategies to unravel so far unknown endemic regions

Search for
B. pseudomallei in the
environment





Population directed
serological screening
Is there exposure to
B. pseudomallei?



Patient directed

serological POC testing
to detect melioidosis in
„Fever of Unknown Origin“

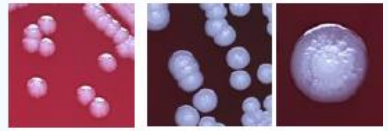
Acknowledgements

MSF team on the ground in Koutiala and in Bamako Ministry of Health

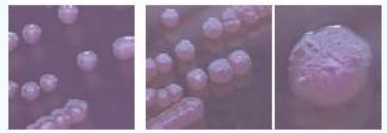
Med Uni Graz team

Are you unsure if you see melioidosis cases in your clinic?

Have you isolated strains suspected to be *Burkholderia pseudomallei* ?



Do you need confirmatory tests?



We are happy to support!

Contact:

ivo.steinmetz@medunigraz.at

Thank you!

MEDECINS SANS FRONTIERES

SCIENTIFIC DAYS