IMASOY

(Isika Mitsabo tArimo ho an'ny SOa Iombonana)

A randomised, open-label controlled non-inferiority trial

comparing 10-day ciprofloxacin to three-day aminoglycoside followed by seven-day ciprofloxacin

for treating bubonic plague in Madagascar

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Collaborative partners:

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Plague ?

- First documented human infections 5000 years ago
- Caused 3 major pandemics (Justinian plague, Black Death, Modern plague) massive death toll and societal disruption throughout human history

- Causative agent *Y. pestis* only discovered 130 years ago (1894); Flea vector in 1898

- Bubonic, pneumonic, septicaemic

- Steady decline in the 20th century → WHO 2018 = 248 cases, 98% in Madagascar, DRC; Sporadic cases in Asia, North & South America, Africa

But epidemic potential

- widespread rodent reservoir
- dormancy
- deliberate release (1346 siege of Caffa!)

Plague treatment –why a clinical trial needed

- Treatment guidelines based on very **weak evidence** – **no conclusive RCT**
  (Mwengee et al 65 patients in Tanzania failure rates gentamicin 19% vs. doxycycline 17%)

- FDA approved based on '**animal rule**': streptomycin, doxycycline and other tetracyclines; fluoroquinolones (ciprofloxacin, levofloxacin, and moxifloxacin). Others, not FDA-approved, generally considered effective – gentamicin, chloramphenicol, and trimethoprim-sulfamethoxazole

- **Challenges**:
  - Clinical presentation poorly characterised A systematic review of the clinical profile of patients with bubonic plague and the outcome measures used in research settings | PLOS Neglected Tropical Diseases
  - No prior established clinical trial methodology, endpoints
  - Logistical challenges

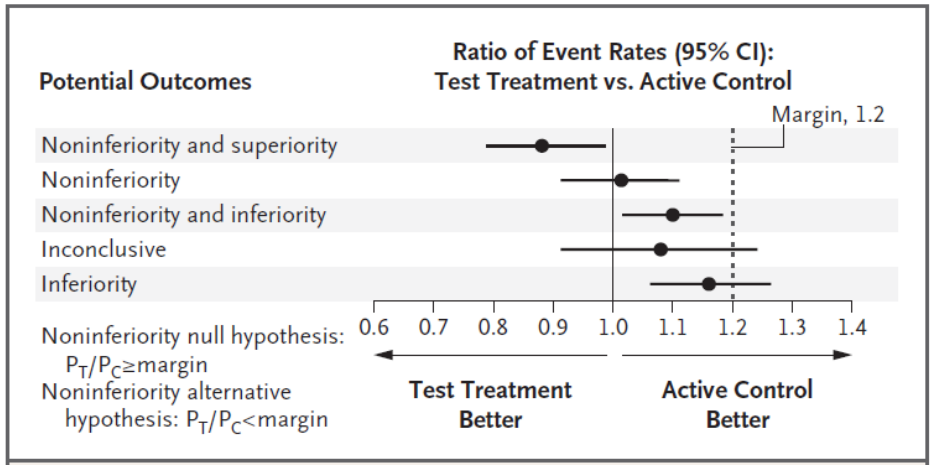
Plague in Madagascar

- First case 24th Nov **1898** – third Plague Pandemic (Modern Plague)
- Endemic in rural areas, annual peaks August-April
- **2017**: exceptionally large urban epidemic. **CFR in confirmed BP and PP = 24-25%**
- **2018-2025** = avg. ~160 suspected BP → avg. ~80 confirmed/probable BP cases/yr. **avg. CFR BP ~18%**

[CFR Bubonic Plague: WHO estimate 17-26%; Systematic review 5-17%; pre-antibiotic ~75%]

IMASOY (NCT04110340)

- Open-label, randomised controlled trial evaluating the **non-inferiority** of **10-d ciprofloxacin monotherapy vs. 3-d aminoglycoside + 7-d ciprofloxacin** for bubonic plague – both in WHO, CDC, Madagascar guidelines
- **NI margin 15%** = NI met if upper bound of 95% CI around the RD in D11 failure rates <15%



- Target sample size: >=190 confirmed/probable cases (assuming 10% failure rate in the control arm, 90% power, one-sided alpha 2.5%, allowing for 10% loss to follow-up)
- Protocol: An open-label, randomized, non-inferiority trial of the efficacy and safety of ciprofloxacin versus an aminoglycoside + ciprofloxacin in the treatment of bubonic plague (IMASOY): study protocol for a randomized control trial—an update to the published protocol | Trials | Full Text

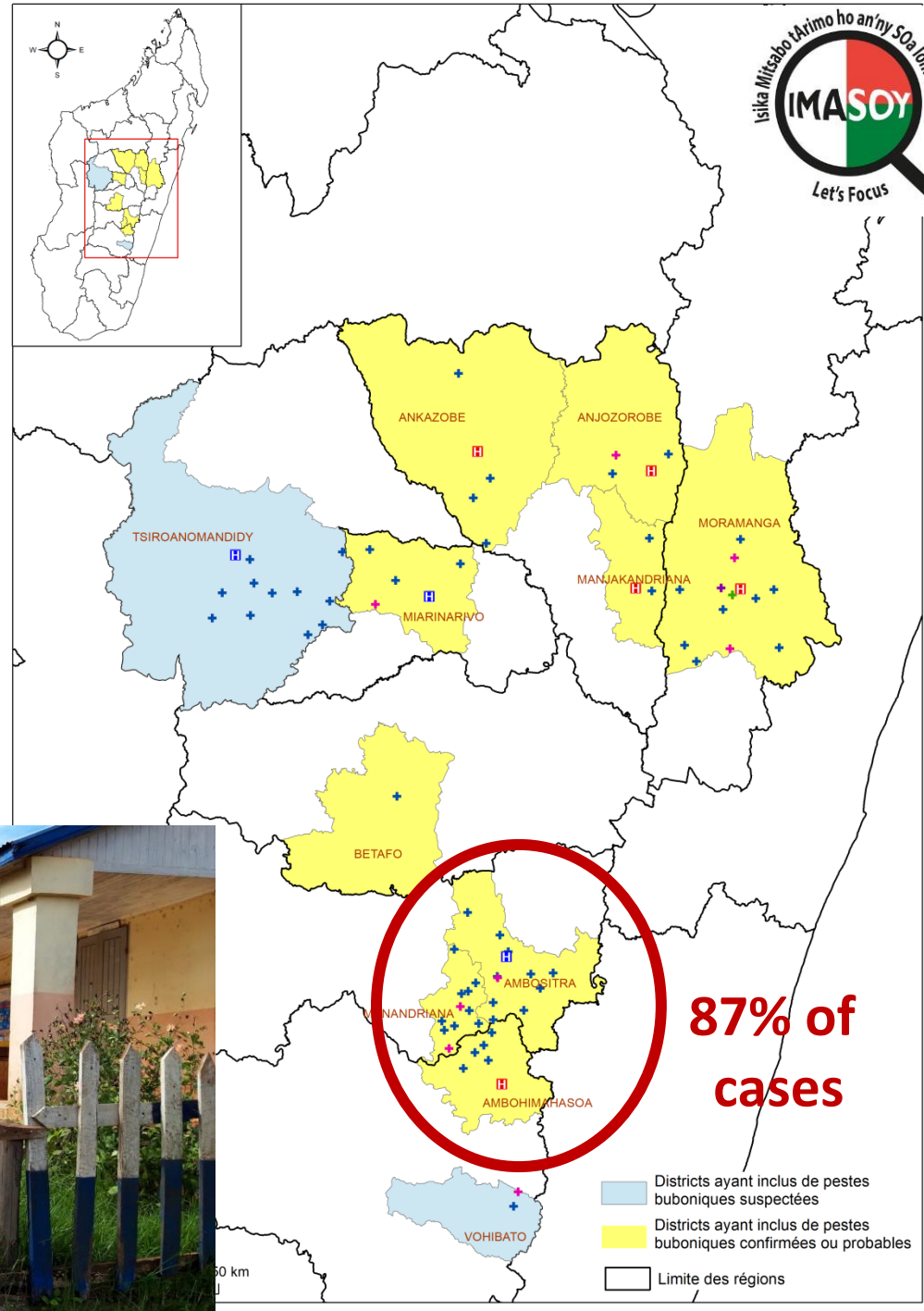
Massive operational achievement:

82 sites activated in 12 districts over 5 transmission seasons – including during covid-19 pandemic.

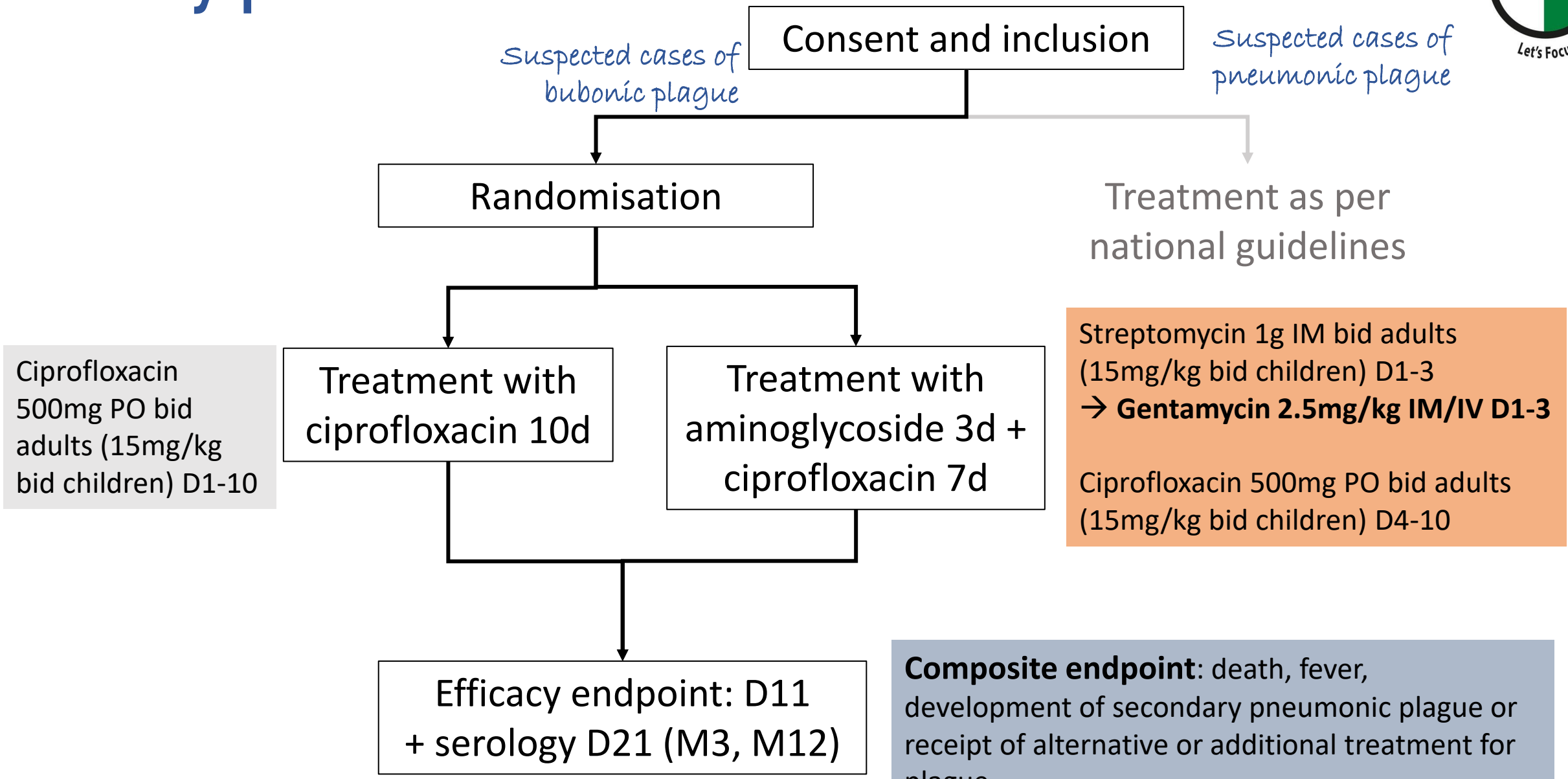
Trial embedded in public healthcare system from most peripheral dispensary to hospital

40 research team members deployed

>230 doctors, nurses trained; >1300 village health workers



Study procedures



Patient flow

Exclusions:

Refused consent n = 6
Known allergy to aminoglycosides or fluoroquinolones n = 0
Tendinitis n = 1
Theophylline or warfarin use n = 0
Treatment for plague in last 3 months n = 3
Pregnant n = 5
No fever or history of fever n = 40
Patient in critical condition n = 20
Trial enrolment suspended n = 13
Not resident in plague-endemic area n = 1
No suspicion of plague n = 257
Suspected of pneumonic plague n = 137

Suspected cases screened N = 933

Suspected bubonic randomised N = 450

Control: N = 229

Intervention: N = 221

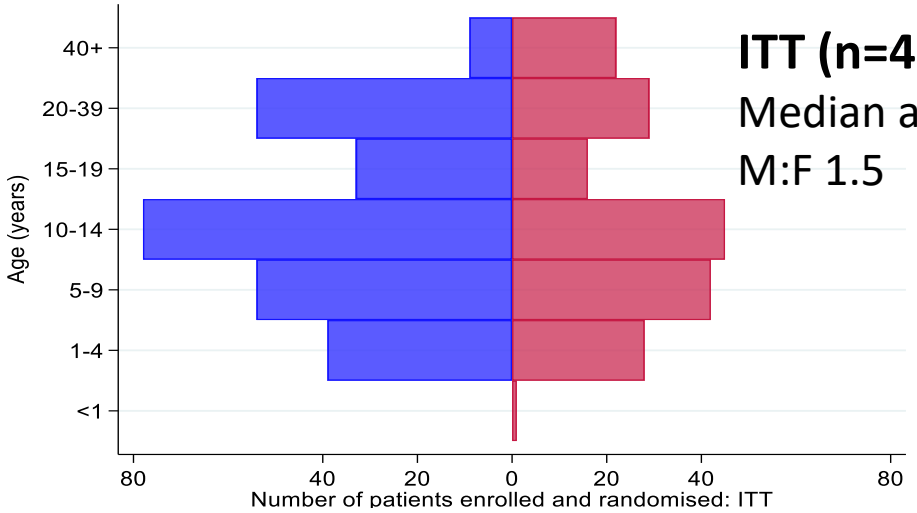
ITT population

Control arm (confirmed/probable) N = 111

ITTI population

Intervention arm (confirmed/probable) N = 111

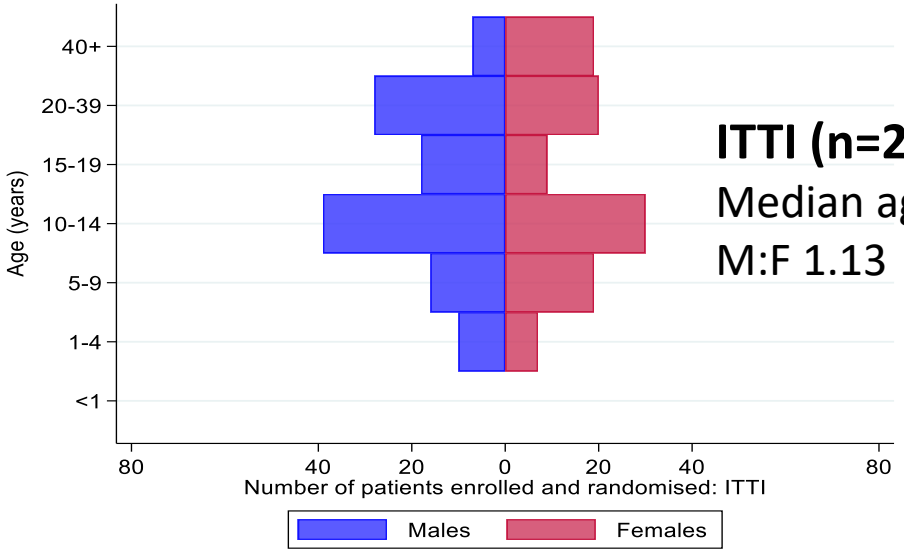
Confirmed case (n=220)
+ve D1 qPCR or culture OR
anti-F1 IgG seroconversion or a four-fold increase in antibody titre through D21
Probable case (n=2)
+ve D1 RDT at the central lab
OR
single D1 +ve anti-F1 serology



ITT (n=450)

Median age 12 (0-72) y

M:F 1.5



ITTI (n=222)

Median age 14 (2-72) y

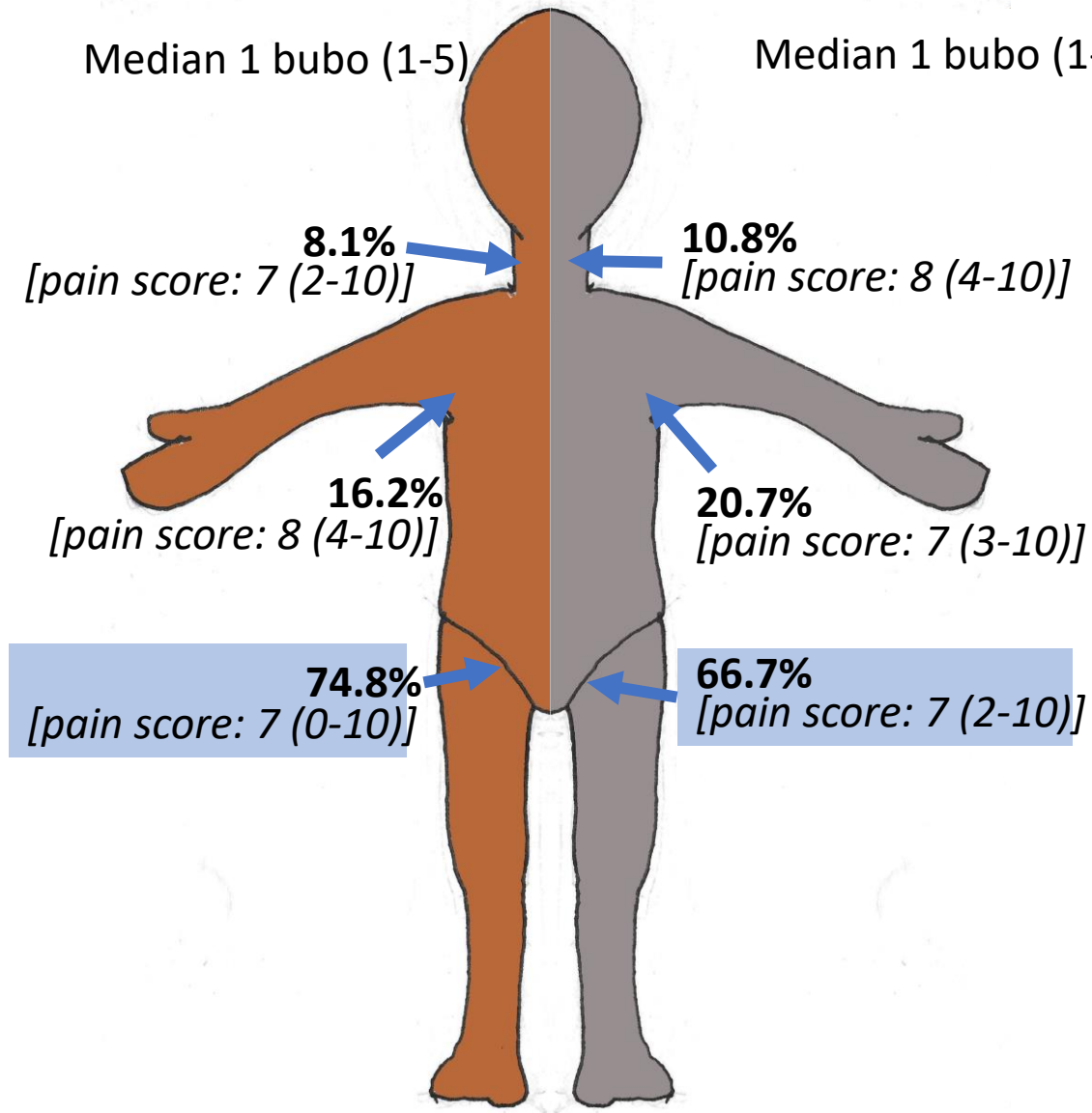
M:F 1.13

CONTROL

INTERVENTION

Median 1 bubo (1-5)

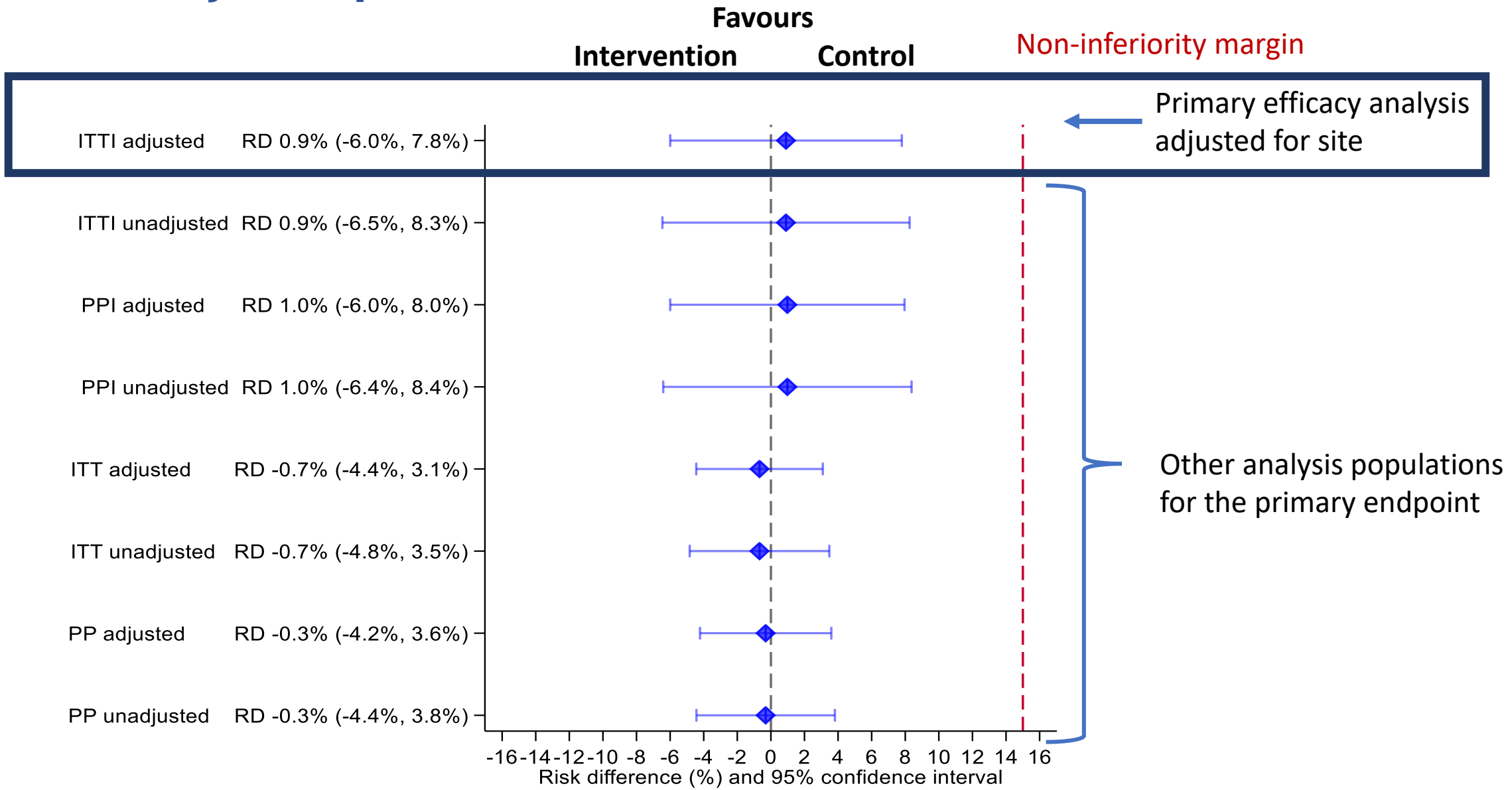
Median 1 bubo (1-3)



Primary efficacy analysis ITTI: Primary Endpoint

		Control	Intervention
	N	111	111
Died by D11	n (%)	4 (3.6)	5 (4.5)
Fever at D11	n (%)	1 (0.9)	2 (1.8)
Secondary pneumonic plague	n (%)	3 (2.7)	3 (2.7)
Extra-treatment before or at end of treatment	n (%)	2 (1.8)	2 (1.8)
Total Failures	**n (%, 95% CI)**	**9 (8.1% 3.8 - 14.8)**	**10 (9.0% 4.4 - 15.9)**
Unadjusted risk difference	% (95% CI)		**0.9 (-6.6 to 8.3)**
Adjusted risk difference	% (95% CI)		**0.9 (-6 to 7.8)**

Primary Endpoint



Safety

- Overall, 13.8% experienced ≥1 AE, 3.6% of patients experienced ≥1 SAE, and 2.7% experienced an ADR

- In both the ITT and ITTI analysis populations, similar percentages of patients in each arm experienced an SAE (none drug-related), AE, ADR.

- **SAEs**: death, pneumonic plague, septic shock, bubo rupture

- **most common AEs**: diarrhoea (5 patients), vomiting (3 patients). All ADRs were mild or moderate, except for one severe event of GI pain

A prospective assessment of the performance of diagnostic procedures for bubonic plague in Madagascar

- BP diagnostic relies on clinical evaluation and epidemiological context
- Routine confirmation includes PCR and culture (central reference laboratory)
- Plague treatment started promptly on clinical grounds
- Antigen F1-based RDT (F1RDT) routinely used in peripheral health centres (on-site F1RDT) and central reference laboratory (RL F1RDT) since 2002

Performance of F1-RDT on site and in central reference laboratory against all available gold standard and its utility in BP

Diagnostic value of culture, PCR (2-step protocol targeting *caf1* and *pla* genes) and serology (not routinely performed) in BP

Background

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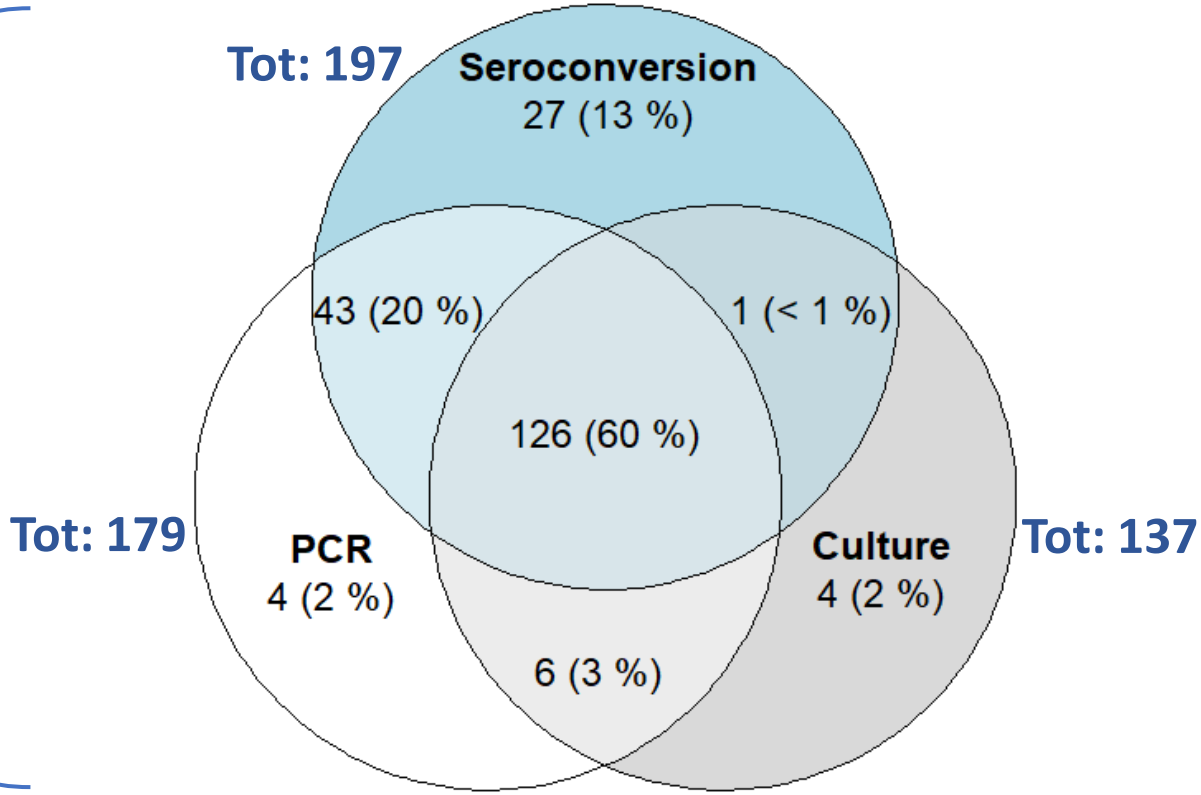
Performance of confirmatory tests at Central Reference Laboratory*

438 suspected bubonic plague

184 (42%) confirmed by culture or PCR (**Gold Standard 1**)

211 (48%) confirmed by GS1 + seroconversion (**Gold Standard 2**)



* Numbers slightly different from ITT analysis: 450 – [1 (withdrew) + 1 (missing serology) + 10 died before D11]

Performance of F1RDT

Reference	F1RDT	Sensitivity	Specificity
GS1	On-site	94% (95%CI: 89.6-97.0)	**74% (95%CI: 68.2-79.3)**
	Ref lab	91.8% (95%CI: 86.9-95.4)	97.6% (95%CI: 94.9-99.1)
GS2	On-site	89.1% (95%CI: 84.1-93)	89.1% (95%CI: 84.1-93)
	Ref lab	**82.0% (95%CI: 76.1-86.9)**	99.1% (95%CI: 96.9-99.9)

Between-F1RDT agreement 83.1%, Cohen's kappa 0.67 (= moderate agreement)

Performance of clinical diagnosis

Reference	Under-10s	10-17	18 and above
GS1	26.6% (42/158)	49.3% (75/152)	52.8% (67/127)
GS2	**31% (49/158)**	**54.6% (83/152)**	**62.2% (79/127)**

Conclusion for bubonic plague diagnosis

- For plague **surveillance**, we have a set of tests that, ideally combined, provide reliable data for plague surveillance – caveat: operational and financial sustainability
  - Serology requires multiple visits
  - PCR outperforms culture (previous gold standard)
  - F1RDT may be used at peripheral lab in resource-constraint settings for surveillance
- No reliable point-of-contact test for **case management** decision
  - A negative F1RDT does not conclusively exclude plague
- NB: conclusions based on data from setting where ~50% of suspected cases are confirmed – false detection rates will be higher and false omission rates lower in settings with lower incidence.

Overall conclusions

- IMASOY is the first RCT powered to produce conclusive results on treatment of bubonic plague
- Both gentamicin + ciprofloxacin and ciprofloxacin alone >90% effective; Ciprofloxacin non-inferior (from 7.8% worse to 6% better)
- **Mortality** 9/222 (**4%**) vs 26/138 (**19%**) non-IMASOY sites

High internal and external validity:

- Between 2020-2024, IMASOY enrolled 220/358 (**61%**) of confirmed/probable notified cases in the recruiting districts
- Conducted at all levels of health system, care provided by local doctors as per routine care
- [enhanced prescriber's and patient's adherence]

Implications for policy & practice:

- High-quality data to inform evidence-based treatment and diagnostic guidelines

Implications for research:

- WHA resolution 74.8 can be implemented even in challenging conditions in low-resource countries

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- This study would not have been possible without the dedication of research staff, doctors and nurses at level 1 and 2 health posts and hospitals, and community health workers over 5 transmission seasons, including during the COVID-19 pandemic
- We are grateful to all participating patients
- Outcomes have been reported to and discussed with MoH, and disseminated to the local healthcare providers and communities

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