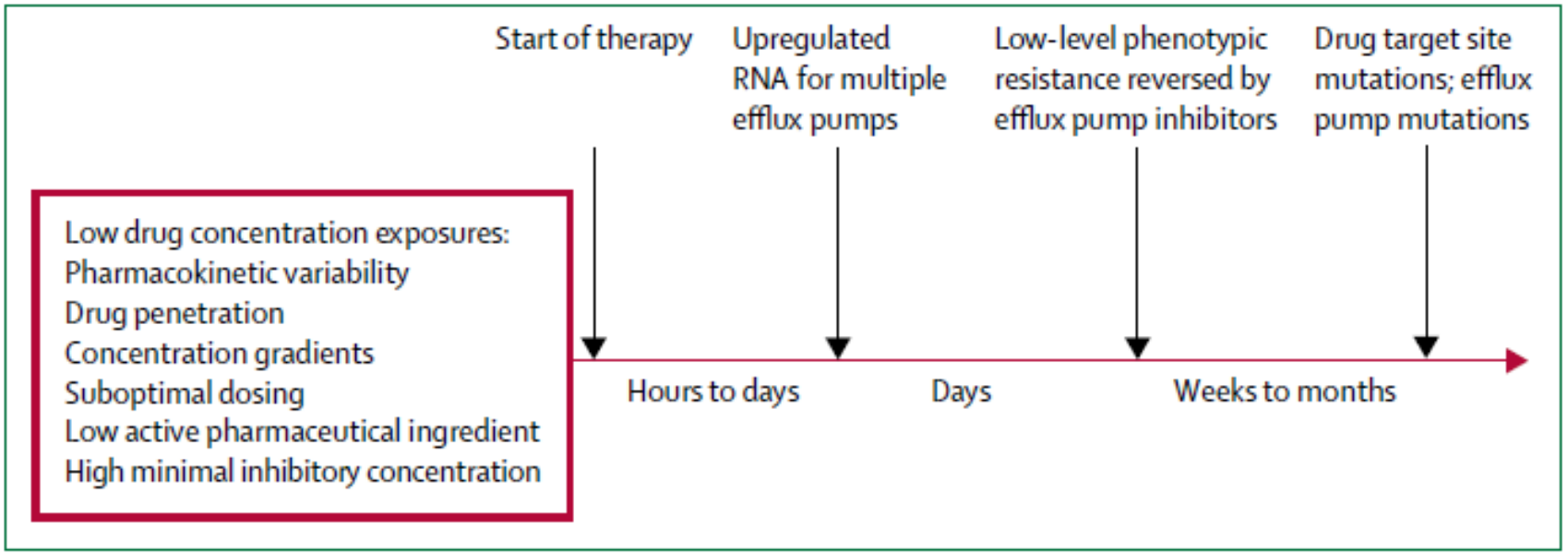
Multi drug-resistant tuberculosis

An example of the need for antimicrobial stewardship

Anna Ralph, Menzies & RDH

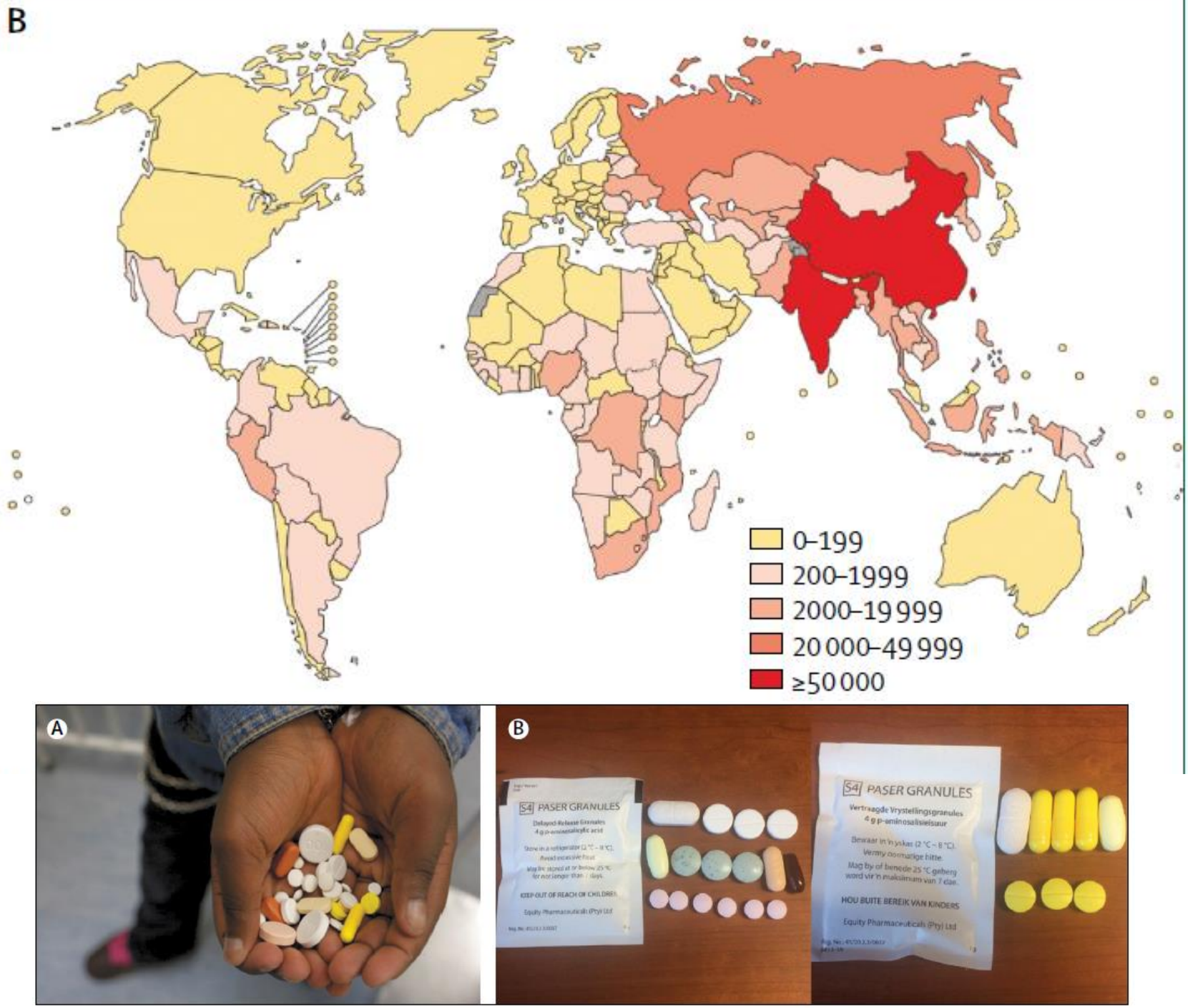
- What is MDR-TB?
- Why is MDR-TB relevant in northern Australia?
- What is HOT NORTH doing about it?

Acquired resistance development



Origins of MDR-TB

Dheda et al. Lancet Commission on DR-TB. 2017


B
0–199
200–1999
2000–19 999
20 000–49 999
≥50 000
A
B
S4 PASER GRANULES
KEEP OUT OF REACH OF CHILDREN
Equity Pharmaceuticals (Pty) Ltd
S4 PASER GRANULES
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Equity Pharmaceuticals (Pty) Ltd

Why is MDR-TB relevant in Northern Australia?

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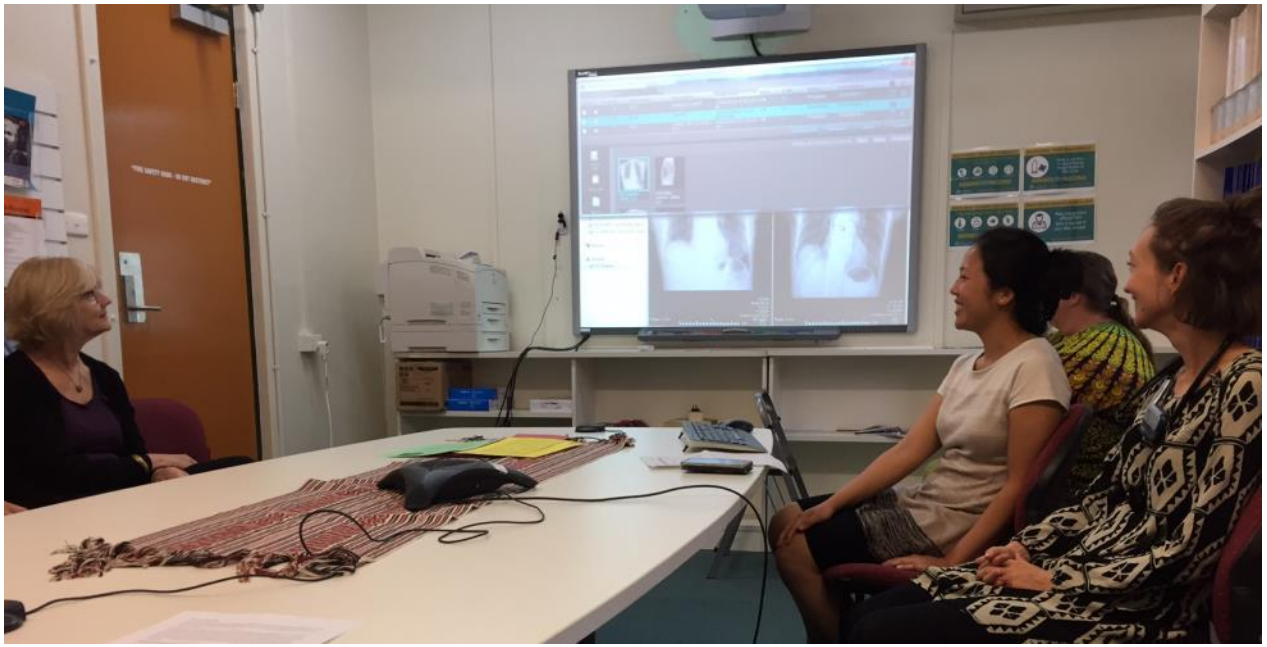
- Because of the clinical challenges it poses
- Because of the huge burden it poses to our near neighbours
- Because of the risk of transmission to northern Australia
- Because of the lessons it teaches and the new approaches it has generated

MDR-TB Clinical Case Conference, 2/8/2017, NT CDC



Local burden of active disease

- Western Australia
  - 16 cases in 14 years (0 to 3 per year)
    - 15 overseas-born
- Queensland
  - In 2015: 7 cases (out of total 157 culture+ TB)
    - 4 overseas-born (3 PNG); 3 Australian born
- Northern Territory
  - 7 cases in 23 years (1989-2017).
    - 6 overseas-born, 1 fatality

Multidrug-resistant tuberculosis in Western Australia, 1998–2012

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Multidrug-resistant tuberculosis (MDR-TB), defined by resistance to both isoniazid and rifampicin, has significant implications for individual patient management and TB control efforts. The current global situation is further complicated by the emergence of extensively drug-resistant TB (XDR-TB), defined by additional resistance to a fluoroquinolone and at least one second-line injectable drug (amikacin, kanamycin or capreomycin).[1] Drug resistance may develop in the context of TB treatment, but the majority of MDR-TB cases are contracted as primary infections.[2] As with drug-susceptible TB, household transmission is common, frequently affecting young children.[3,4] Treatment is resource-intensive and requires longer courses of less effective, more toxic and more expensive drugs compared with drug-susceptible TB.[5]

Global efforts to combat the threat of MDR-TB have been hampered by a paucity of data. Although progress has been made towards obtaining

Abstract

Objective: To describe the epidemiology, clinical features, health care resource use, treatment and outcomes of multidrug-resistant tuberculosis (MDR-TB) cases diagnosed in Western Australia, compared with matched controls with drug-susceptible TB.

Design, setting and patients: Retrospective case–control study of all MDR-TB cases notified in WA between 1 January 1998 and 31 December 2012, compared with matched controls. Cases were identified and managed through the Western Australia Tuberculosis Control Program, including specialist TB services, the Mycobacterium Reference Laboratory and affiliated secondary and tertiary outpatient and inpatient medical services in WA.

Main outcome measures: Demographic characteristics, clinical manifestations, treatment, outcomes and health care resource use.

Results: Sixteen MDR-TB cases were notified during the study period (1.2% of all TB notifications). The median age of patients with MDR-TB was 26 years, and 15 were born outside Australia. Patients with MDR-TB were more likely to have received previous treatment (25% v 2%; $P = 0.006$) and had longer delays to effective therapy (median, 48 v 21 days; $P = 0.002$) than controls. MDR-TB patients more frequently required hospitalisation (100% v 35%; $P < 0.001$) and were treated for longer (mean, 597 v 229 days). Adverse effects were more commonly reported in MDR-TB patients than controls (81% v 33%; $P < 0.001$). Treatment success was not significantly different between patients with MDR-TB and controls (75% v 84%; $P = 0.72$). No treatment failures or deaths were identified in either group.

Conclusion: MDR-TB remains uncommon in WA but its challenges are increasingly recognised. Despite delays in commencing effective therapy, MDR-TB is usually associated with treatment success. Adverse effects of medications are common, and treatment courses are long and complex. Specialist TB services should continue to be involved in management and prevention of all cases of MDR-TB.

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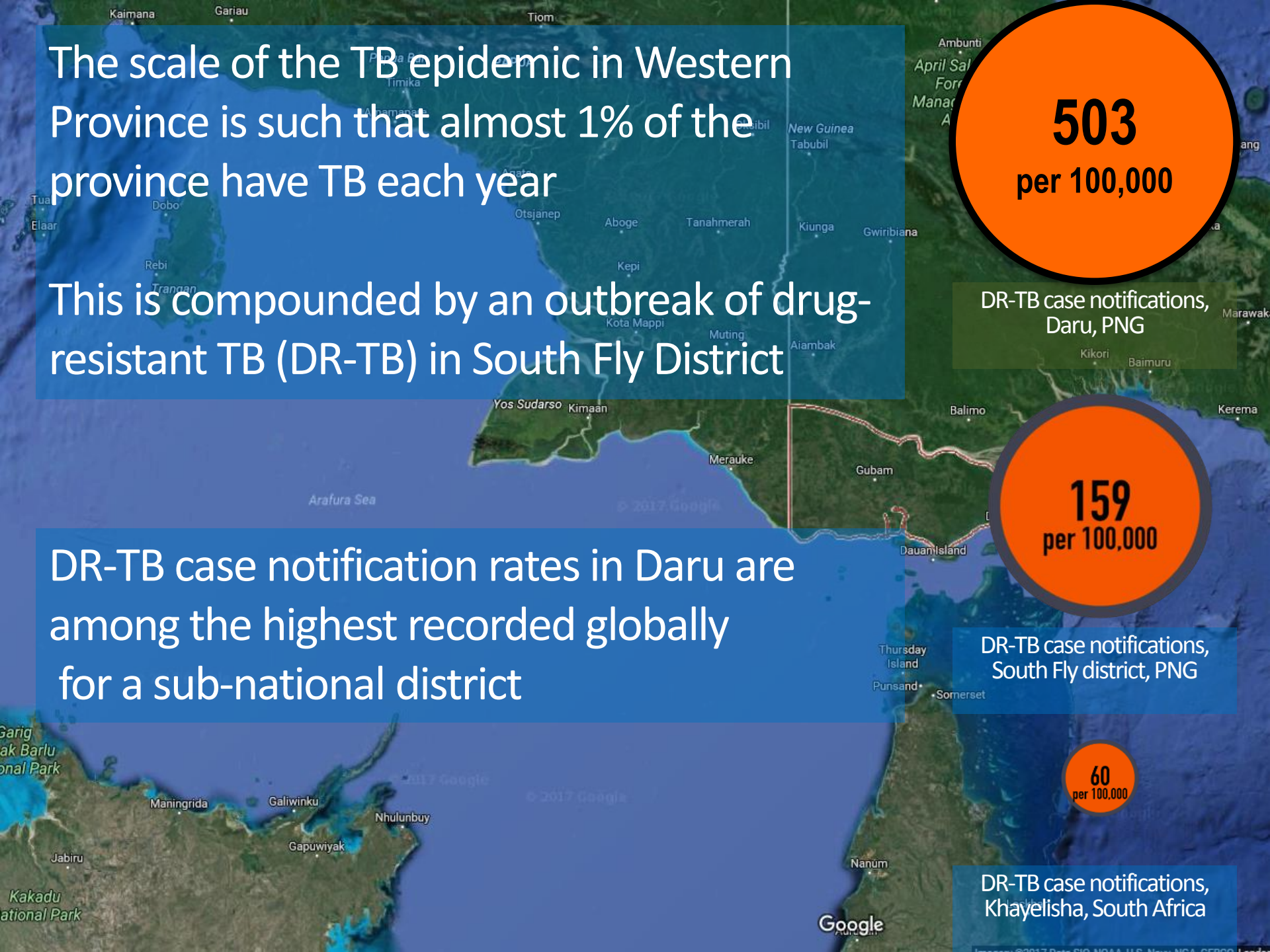
The scale of the TB epidemic in Western Province is such that almost 1% of the province have TB each year

This is compounded by an outbreak of drug-resistant TB (DR-TB) in South Fly District

DR-TB case notification rates in Daru are among the highest recorded globally for a sub-national district



DR-TB Response

- Declaration of DR-TB emergency in 3 hotspot areas in 2014: Gulf, Western Province and NCD
- Emergency response taskforce formed by NDoH to coordinate the response in the 3 hotspots

MDR-TB, potential national crisi

WHO official: Multi-drug resistant TB problem a priority

O'Neill fears rise in TB

Outbreak of multidrug-resistant tuberculosis on Daru Island

The growing crisis of multidrug-resistant tuberculosis (MDR-TB) is so serious that tuberculosis specialists have called it a "time bomb",[1] and multiple deadly explosions have already been reported globally.[2] On Daru Island in Papua New Guinea, an unprecedented outbreak of MDR-TB is occurring.[3]

The 6 km² island has a population of about 15000 individuals; in 2015, almost 200 people were being treated for MDR-TB. These numbers suggest that nearly 1% of the population is diagnosed with MDR-TB every year, and this is probably just the tip of the iceberg, because active case finding has yet to be implemented. Most patients with MDR-TB in Daru have never taken tuberculosis drugs, meaning primary transmission is occurring at an extraordinarily high level, which is especially concerning given that there are very few HIV cases in Papua New Guinea.[4] Whereas WHO estimates that roughly 1000 MDR-TB cases emerge across Papua New Guinea every year, isolated studies from different settings suggest a much higher burden.[5,6] Despite direct evidence of high rates of MDR-TB transmission from as early as 2008,[7] data remain scarce, mainly because Papua New Guinea has no facilities for tuberculosis culture or drug susceptibility testing. Access to MDR-TB treatment also remains poor, with the Australian government stepping in to procure emergency supplies of second-line medicines in 2013–14.[8]

The national and international response to the Daru outbreak has been inadequate. In January, 2015, the

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Acknowledgement: Suman Majumdar and Steve Graham, Burnet Institute

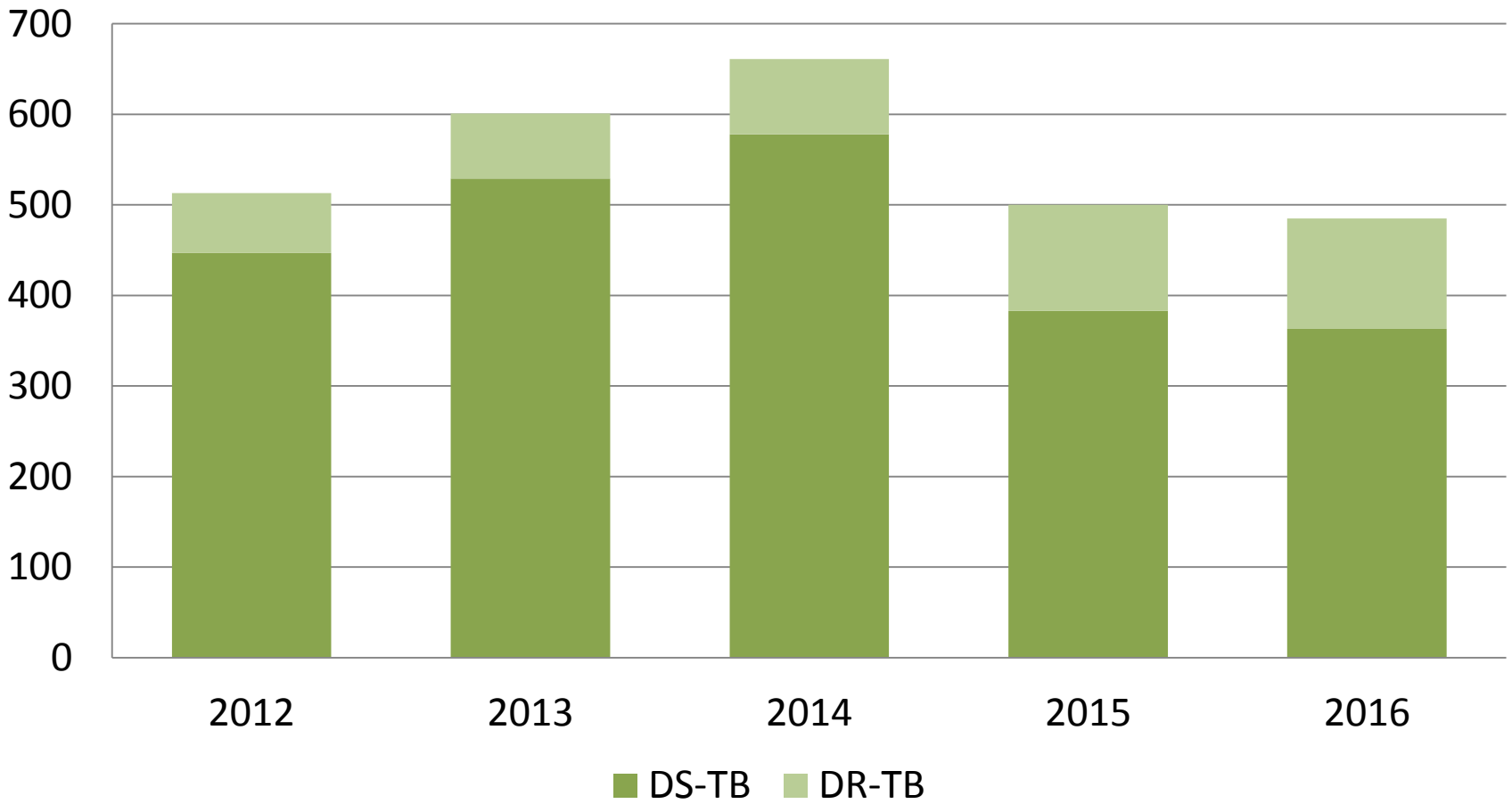
Responding to an outbreak of DR-TB in Papua New Guinea

Daru Island

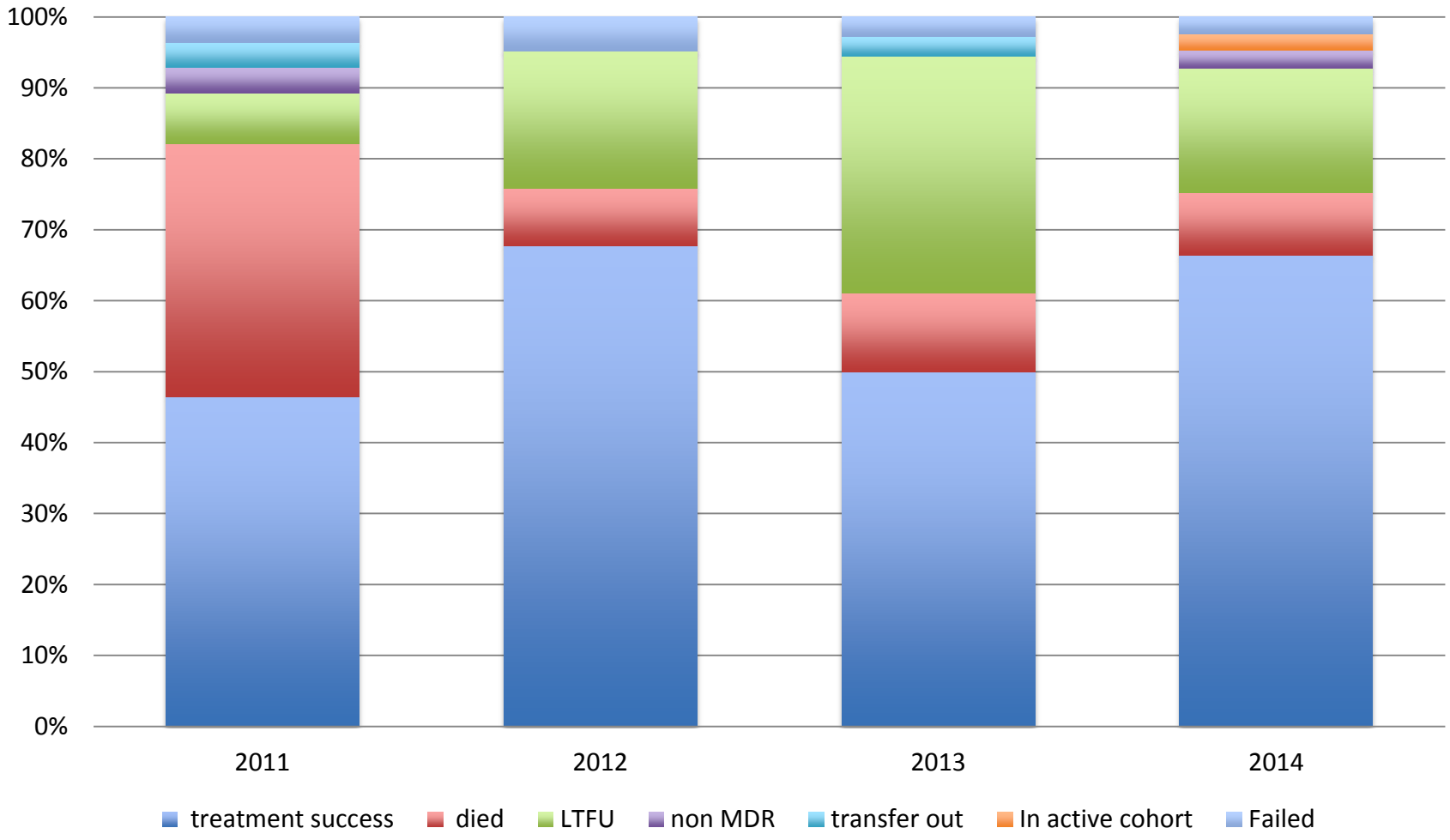
Population: 15,142
Area: 15km^2

DS & DR-TB Enrolments in Daru

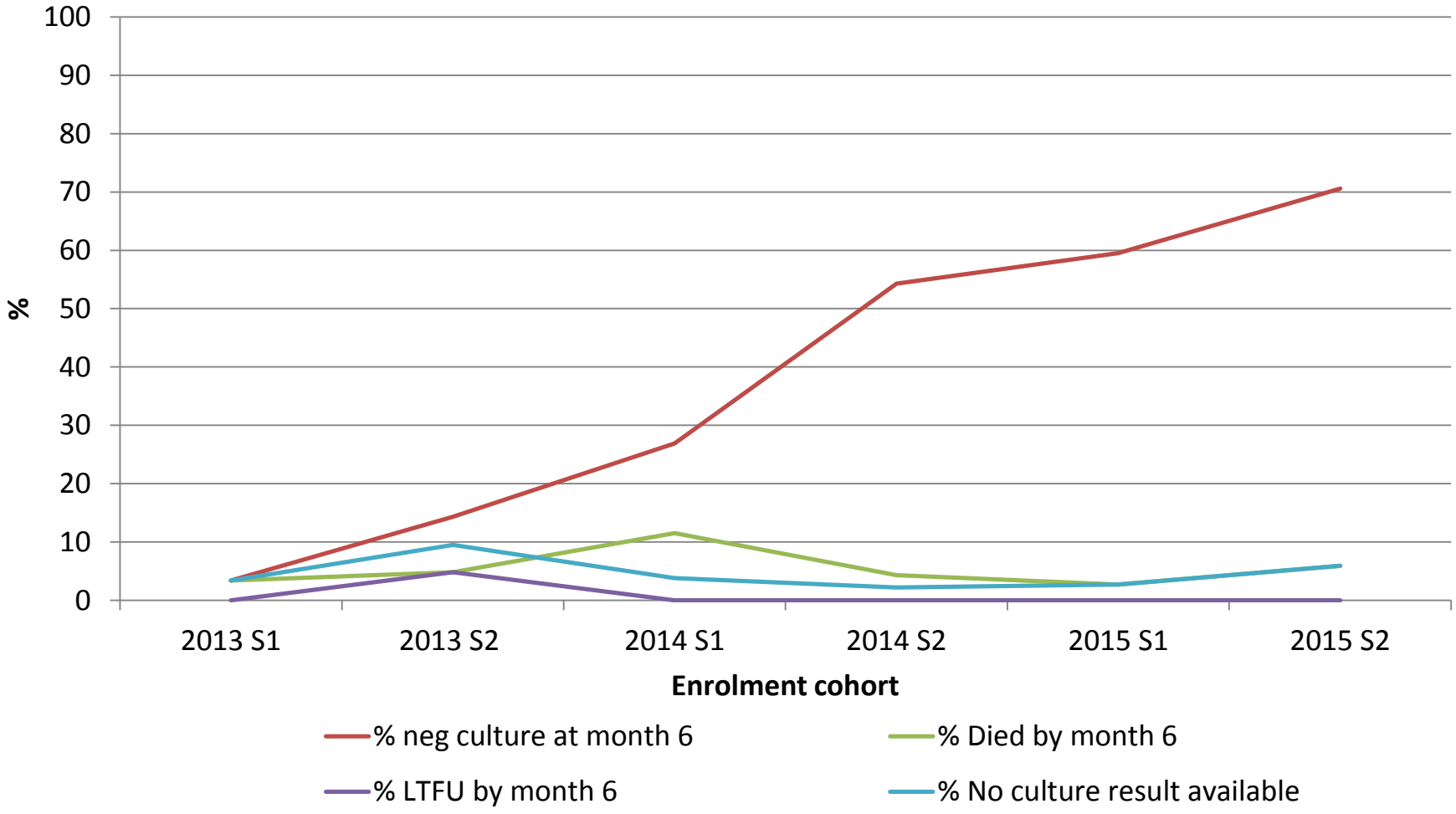
(total population: 15,000)



DR-TB Outcomes



DR-TB % Culture negative at 6 months



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MDR-TB been a driving force for development of:

- AMS programs internationally
  - Including high-quality operational research
- new diagnostics
  - Gene Xpert MTB/RIF
- new surveillance approaches
  - clinical & public health application of application of next-generation sequencing
- new drugs
  - bedaquiline, delaminid
- new drug formulations
  - dispersible child-friendly formulations

What is HOT NORTH doing about MDR-TB?

- Project support
  - Enhanced screening and preventive therapy for TB in Daru, South Fly District, Papua New Guinea (Suman Majumdar, Stephen Graham, Anna Ralph)
- Personnel support
  - Dr Trisasi Lestari, HOT NORTH CDU International PhD Scholarship: TB prevention in Indonesian Papua

Practical antimicrobial stewardship at Royal Darwin Hospital

Anna Ralph, Menzies & RDH

RDH AMS rounds

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- RDH is third leading user of antibiotics Australia-wide
- Daily ward list produced from electronic prescribing and pathology databases to identify:
  - Any prescription of a restricted antimicrobial
  - Any prescription of a broad spectrum antimicrobial
  - Drug-bug mismatch
  - Creatinine-dose mismatch
  - Antibiotic dose outside a standard range
  - Drug interaction
  - Presence of a potentially illogical combination of antibiotics (e.g. clindamycin and metronidazole)
  - IV antibiotic order continued for >3 days

Guidelines to assist with the assessment of appropriateness

Appropriateness			If endorsed guidelines are present	If endorsed guidelines are absent
Appropriate	1	Optimal[1]	Therapy follows either the Therapeutic Guidelines[2] or endorsed local guidelines optimally, including antimicrobial choice, dosage, route and duration[3], (including for surgical prophylaxis)	Therapy will cover the (likely) causative pathogens *and* there is not a narrower spectrum or more appropriate antimicrobial choice, dosage, route or duration[3] available, (including for surgical prophylaxis) **OR** The patient has been reviewed by an "expert", such as an infectious diseases physician or registrar, clinical microbiologist or registrar, or specialist pharmacist
	2	Adequate	Therapy does not optimally follow the Therapeutic Guidelines[2] or endorsed local guidelines, including antimicrobial choice, dosage, route or duration[3], however, is a ***reasonable*** alternative choice for the (likely) causative pathogens **OR** For surgical prophylaxis, as above *and* duration[3] is less than 24 hours	Therapy, including antimicrobial choice, dosage, route and duration[3] is not the most optimal, however, is a ***reasonable*** alternative choice for the (likely) causative pathogens **OR** For surgical prophylaxis, as above *and* duration[3] is less than 24 hours
Inappropriate	3	Suboptimal	Therapy, including antimicrobial choice, dosage, route and duration[3], is an ***unreasonable*** choice for the (likely) causative pathogens, including: • spectrum excessively broad or failure to appropriately de-escalate with microbiological results • unnecessary overlap in spectrum of activity • dosage excessively high/low • duration[3] excessively long **OR** There may be a mild or non-life-threatening allergy mismatch	
	4	Inadequate	Therapy, including antimicrobial choice, dosage, route or duration[3] is ***unlikely*** to treat the causative pathogens **OR** There may be a severe or possibly life-threatening allergy mismatch, or the potential risk of toxicity due to drug interaction **OR** For surgical prophylaxis, the duration[3] is greater than 24 hours (except where guidelines endorse this)	
	5	Not assessable	The indication is not documented and unable to be determined from the notes **OR** The notes are not comprehensive enough to assess appropriateness **OR** The patient is too complex, due to multiple co-morbidities, allergies or microbiology results, etc.	

[1] Taking into account acceptable changes due to the patient's age, weight, renal function (eGFR/CrCl), etc. or other prescribed medications, if any of this information is available

[2] Antibiotic Expert Group. Therapeutic Guidelines: Antibiotic. Version 14. Melbourne: Therapeutic Guidelines Limited; 2010. http://online.tg.org.au/ip/

[3] Duration should only be assessed if the guidelines state a recommended duration and the antimicrobial has already been dispensed for longer than this, or if there is a clear planned 'end date' documented

Adult Community Acquired Pneumonia in Top End of the NT RDH Guideline

Target Audience	All Clinical Employees
Jurisdiction **Jurisdiction Exclusions**	Royal Darwin Hospital Paediatric Patients
Document Owner	Catherine Marshall Infectious Diseases Physician RDH
Approval Authority	Catherine Marshall Consultant Physician Infectious Diseases RDH
Author	Josh Davis; Bart Currie; Krispin Hajkowicz

Purpose

The prime aim of treating community-acquired pneumonia (CAP) is to prevent death. We present the 2012 revised antibiotic protocol for adult CAP for use in all Top End communities and hospitals.

Procedure / Guideline (remove whichever not applicable)

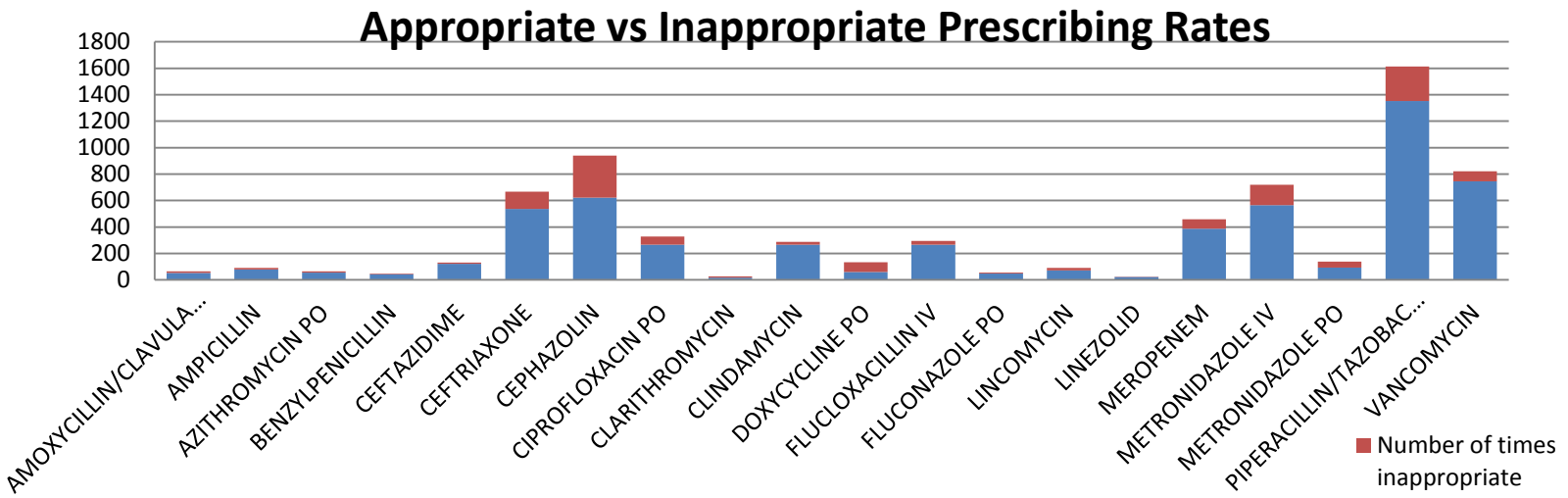
Table 1 Initial Therapy of Top End Adult Community-Acquired Pneumonia

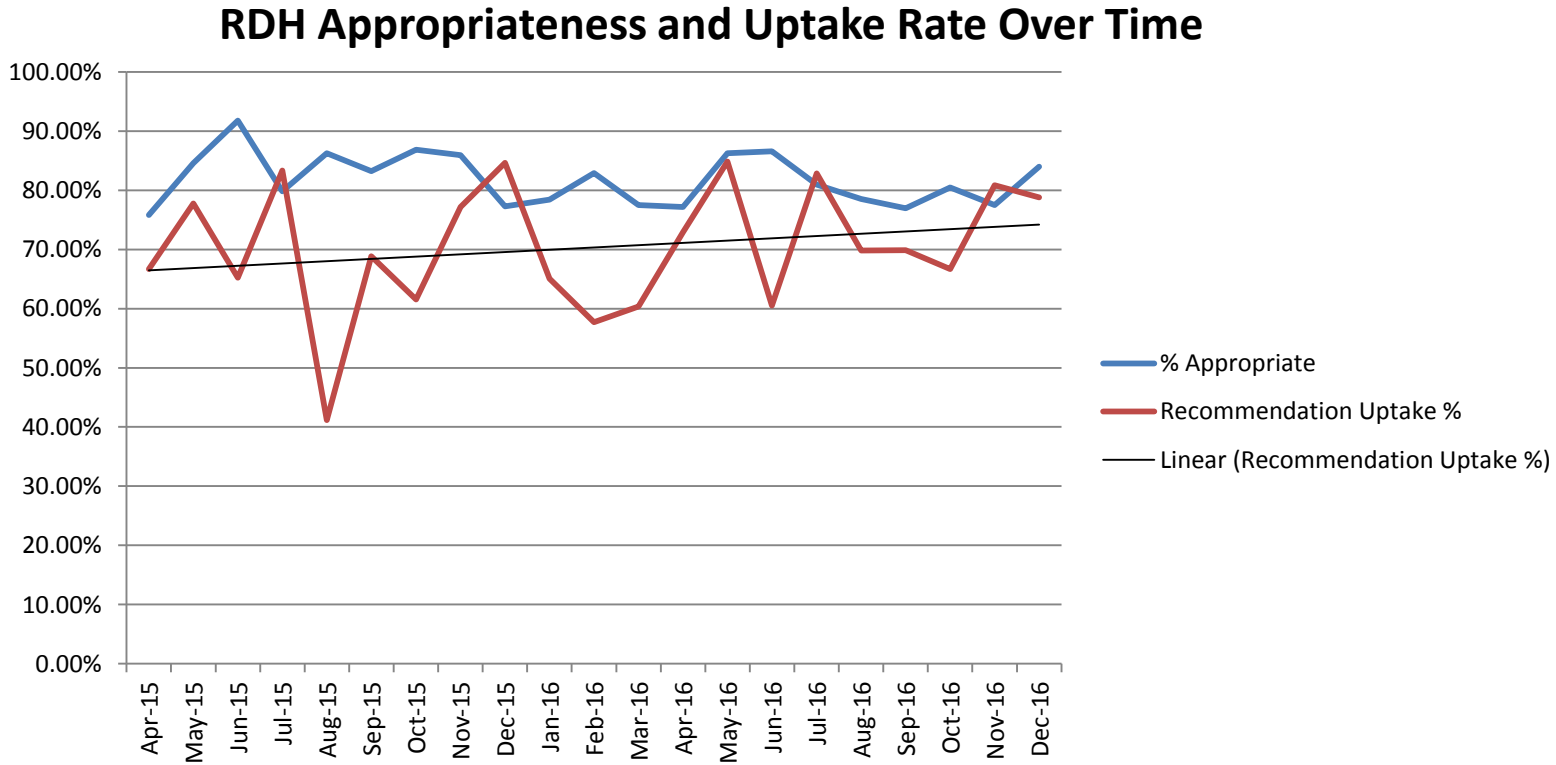
	MILD#	*MODERATE#*	*SEVERE (Non-ICU) #*	*SEVERE (ICU)*
Definition	**SMARTCOP score<3** *AND* clinical impression is mild	**SMARTCOP score<3** *AND* clinical impression is moderate	**SMARTCOP score >=3** (Irrespective of clinical impression) *OR* Clinical impression is severe (Of a consultant, irrespective of SMARTCOP score)	Any one of: i) Already in ICU OR ii) Accepted for ICU admission awaiting transfer OR iii) Meet criteria for severe sepsis protocol
First line treatment – No risk factors^	Amoxicillin 1g PO tds or Benzyl penicillin 1.2g IV q6h	Benzyl penicillin 1.2g IV 6hrly	Ceftriaxone 2g IV daily PLUS gentamicin 4-6mg/kg IV for 1-2 doses then review	meropenem (wet season) 1g IV 8hrly OR piperacillin/tazobactam (dry season) 4.5g IV 6hrly PLUS azithromycin 500mg IV daily
First line treatment – Risk factors^	Amoxicillin 1g PO tds or Benzyl penicillin 1.2g IV q6h	Ceftriaxone 2g IV daily PLUS gentamicin 4-6mg/kg IV for 1-2 doses then review	Ceftriaxone 2g IV daily PLUS gentamicin 4-6mg/kg IV for 1-2 doses then review	As for ICU, no risk factors

Antibiotic recommendations - surgical patients	Number
• Surgical prophylaxis course extending beyond 1 day in absence of infection. e.g. ongoing surgical prophylaxis beyond 24 hours after uncomplicated cholecystectomy	84
• Overly broad antimicrobial used . e.g. Tazocin used for shoulder carbuncle without anaerobes/pseudomonas on micro	77
• Drug - bug mismatch (e.g. pt on flucloxacillin but micro results returned as MRSA)	57
• Duplication of therapy (e.g. Augmentin prescribed with metronidazole without rationale provided)	38
• Dosage incorrect. e.g. metronidazole dosed as 400mg daily	29
• Over/underdosage for given renal function (e.g. pt dosed bd Tazocin despite normal renal function or vice versa)	27
• Vancomycin dose incorrect for given renal function	22
• Ceftriaxone/Metronidazole used first line for intra-abdominal infection without contraindication to penicillin or gentamicin	16
• Penicillin/cephalosporin not used despite minor reaction or no allergy present to other class. e.g. patient started on cephazolin for abscess when first line flucloxacillin with no allergy	11
• Metronidazole used when anaerobes unlikely or not present (e.g. for simple carbuncle)	10
• Antimicrobial discontinuation overlooked after planned stop date	2

Antibiotic Recommendations - medical patients	Number
Drug Interaction (e.g. doxy or ciprofloxacin with zinc/calcium/iron)	40
Change to PO Abx	31
Dosage incorrect in relation to renal function	15
Overly broad spectrum agent used	11
Drug-bug mismatch	9
Ceftriaxone used when ampicillin/gentamicin appropriate	8
Duplication of cover	12
Antibiotic not indicated	6
Patient dosed adult dose of antibiotics despite weight < 40Kg	2
Vancomycin/clindamycin used first line with only minor penicillin allergy	2

RDH Total Antimicrobial Prescribing Error Prevalence			
Type of Error	**Number of Occurances**	**Percentage of Orders**	**Percentage Changed Following Recommendation**
Surgical prophylaxis course extending beyond 1 day in absence of infection	214	2.98%	46.2%
Overly broad antimicrobial used	113	1.57%	73.7%
IV antibiotic treatment continuing long term for non-severe infection	172	2.39%	72.7%
Dosage incorrect	72	1.00%	33.3%
Duplication of therapy	73	1.02%	100.0%
Ceftriaxone/Metronidazole used first line for pancreatitis or intra-abdominal infection without	23	0.32%	28.6%
Vancomycin dose incorrect in respect to vancomycin level or renal function	40	0.56%	80.0%
Over/underdosage in respect to poor renal/hepatic function	53	0.74%	100.0%
Penicillin/cephalosporin not used despite minor reaction or no allergy present to other class	25	0.35%	50.0%
Drug - bug mismatch	84	1.17%	80.0%
Antimicrobial unlikely to treat causative organism	25	0.35%	100.0%
Antimicrobial treatment continuing after set stop date. No mention of antimicrobial to continue in notes	4	0.06%	Not recorded
Metronidazole used when anaerobes unlikely or not present	14	0.19%	0.0%
Ceftriaxone used first line for			


Appropriate vs Inappropriate Prescribing Rates
1800
1600
1400
1200
1000
800
600
400
200
0
AMOXYCILLIN/CLAVULA...
AMPICILLIN
AZITHROMYCIN PO
BENZYLPENICILLIN
CEFTAZIDIME
CEFTRIAXONE
CEPHAZOLIN
CIPROFLOXACIN PO
CLARITHROMYCIN
CLINDAMYCIN
DOXYCYCLINE PO
FLUCLOXACILLIN IV
FLUCONAZOLE PO
LINCOMYCIN
LINEZOLID
MEROPENEM
METRONIDAZOLE IV
METRONIDAZOLE PO
PIPERACILLIN/TAZOBAC...
VANCOMYCIN
Number of times inappropriate


RDH Appropriateness and Uptake Rate Over Time
100.00%
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
Apr-15
May-15
Jun-15
Jul-15
Aug-15
Sep-15
Oct-15
Nov-15
Dec-15
Jan-16
Feb-16
Mar-16
Apr-16
May-16
Jun-16
Jul-16
Aug-16
Sep-16
Oct-16
Nov-16
Dec-16
% Appropriate
Recommendation Uptake %
Linear (Recommendation Uptake %)