

Inhaled Dry Powder Colistin:

**A novel approach for reducing M/XDR-TB
transmission in congregate settings
and in the community**

Edward A. Nardell, MD, (PI)

Anton Stoltz, MD, PhD, (on-site PI)

and the AIR Consortium: Brigham & Women's
Hospital, MRC, U. Pretoria, CSIR, and U. Groningen

Rationale: Global MDR-TB Treatment Scale Up

- Estimated 500,000 new MDR-TB cases per year
 - **More than half result from transmission**
 - 2008 - 29,423 cases reported
 - 7% of estimated cases
 - 1% treated with quality assured drugs
 - XDR is a by-product of MDR treatment and transmission
- Most are treated in hospitals for first 6 months – until culture conversion
 - HIV co-infection common
- **No effective infection control strategies for XDR TB in hospital or in the community**
 - No new TB IC interventions in decades
- Envision routine treatment with inhaled colistin until proven not to have drug resistance



XDR outbreak - KZN

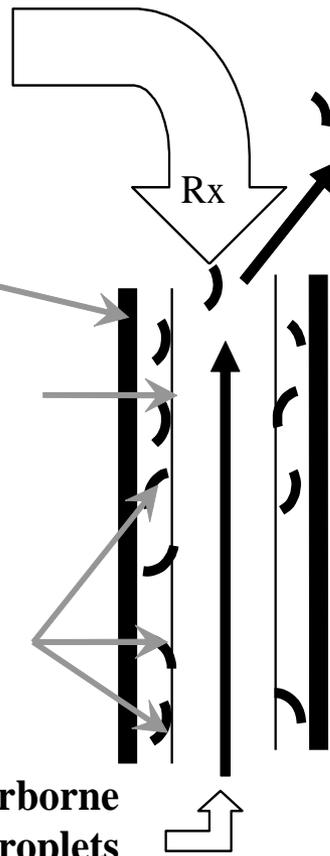
Inhaled antibiotic:
Nebulized kanamycin,
or *Dry powder capreomycin**
or dry power colistin

**Trachea and
large airways**

Antibiotic
concentration
1000-100,000 X MIC

Microbes in epithelial
fluid lining layer

**Cough generating airborne
infectious respiratory droplets**



**Airborne infectious
droplet nuclei**

**Measures of infection control
potential:**

- Mtb cultured in daily 12 hr sputum
- Mtb cultured in cough aerosol samples
- Infection rate of exposed guinea pigs*

Figure 1: Theoretical model and experimental approach to testing the inhaled antibiotics infection control hypothesis. (* indicates future planned studies)

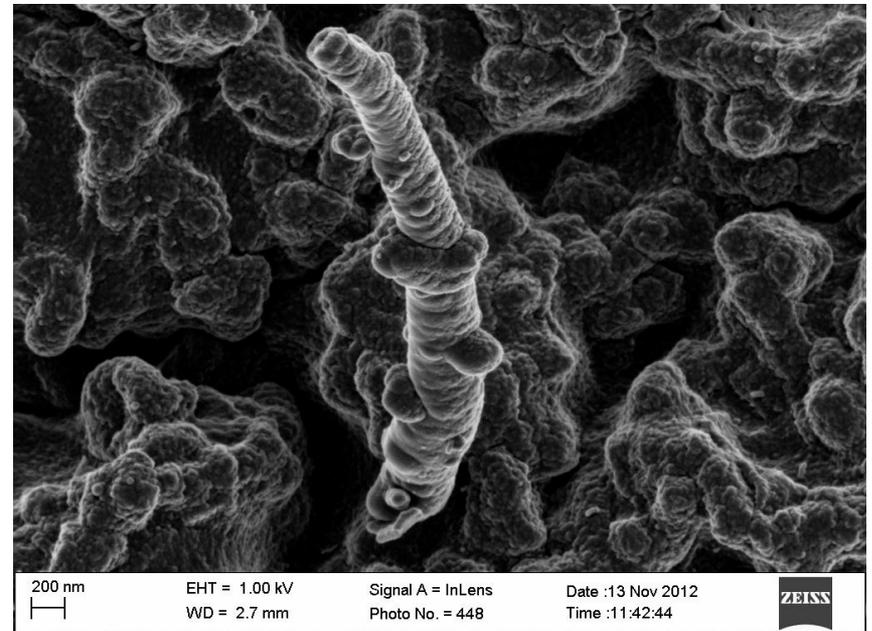
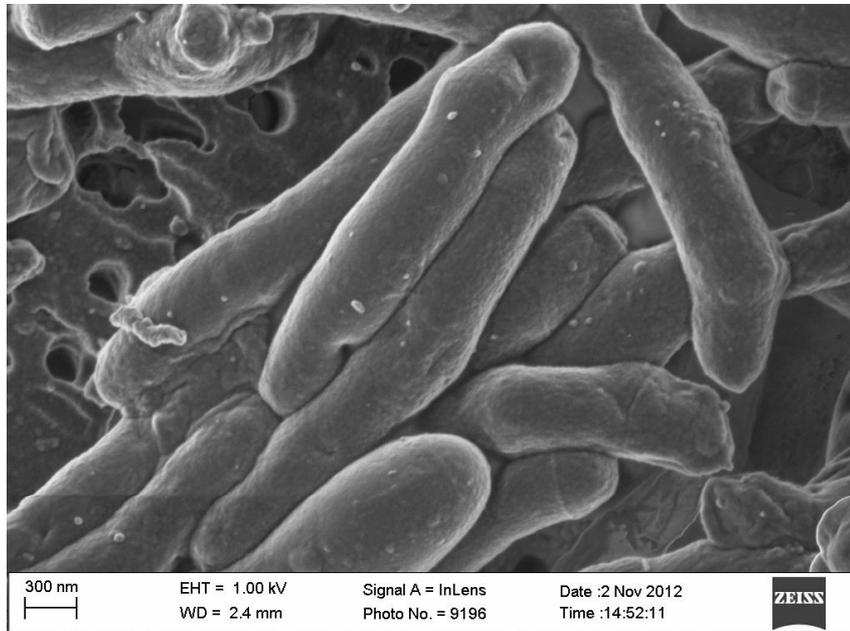
Hypothesis: A cohort of MDR-TB patients receiving systemic treatment for pulmonary TB plus inhaled dry powder colistin will be 75% less infectious for guinea pigs compared to the same cohort of MDR-TB patients receiving systemic treatment alone.

Inhaled Antimicrobials for TB:

- Among TB antimicrobials, only **kanamycin** is approved for inhalation by nebulization
 - But resistance to KM is common
- Only **capreomycin** has been developed specifically for dry powder inhalation (*Phase I clinical trial in Boston*)
 - Not yet available, and also growing drug resistance
- **Colistin** is active against a wide range of mycobacteria,
 - but not at an MIC or MBC achievable (**5 µg/ml and 50 µg/ml**) systemically without renal toxicity
 - Widely used systemically for resistant gram negative sepsis.
- **Inhaled colistin** has been safely used by nebulization in cystic fibrosis patients for 20 years
- A dry powder formulation of **colistin sulfomethate and delivery system** has been developed by the U. Groningen, Netherlands, and well tolerated by both human volunteers and CF patients
- **No clinical trials of any inhaled antibiotic specifically to reduce TB transmission**
 - **Potential therapeutic benefit – not this study (& synergy)**

Scanning EM images* of XDR culture, control and with 12.5 ug/ml colistin.

- Evidence of cell wall damage, deformation and bulging.
 - Potential synergy with other drugs (rifampin) – helps drug enter bacilli
- (*Courtesy of Shane Vontelin van Breda and Anton Stoltz. U. Pretoria)



**Colistin - non-specific detergent-like mechanism, poking holes in the cell wall.
Damaging the organism and increasing access to other drugs.**

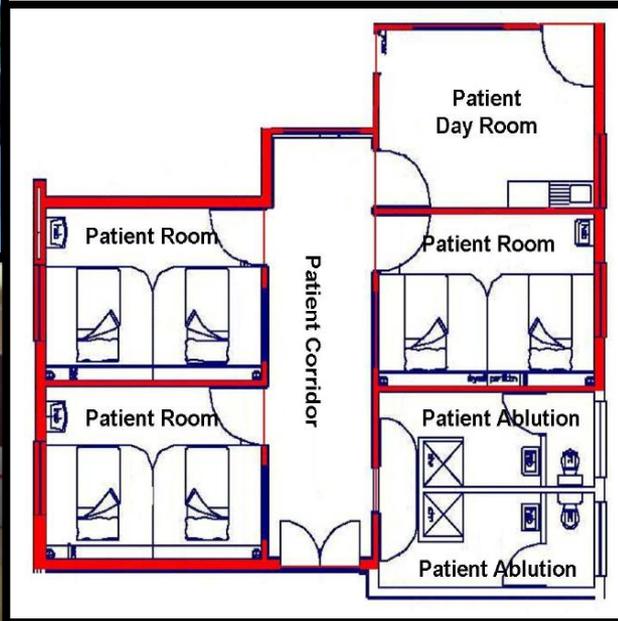
Twincer Dry Powder Inhaler

University of Groningen

- No nebulizer or electricity
- No sterile saline or mixing
- No toxic by-products
- Inexpensive
- Pre-loaded, foil sealed
- Good storage without refrigeration
- Regulatory approval for use in SA obtained



The Airborne Infections Research (AIR) Facility Witbank, Mpumalanga Province, SA

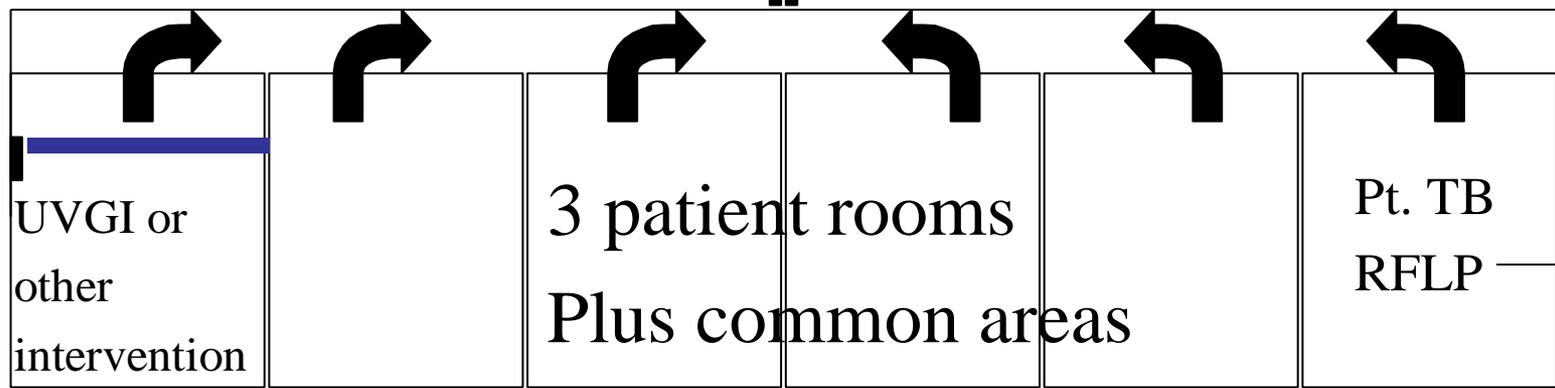
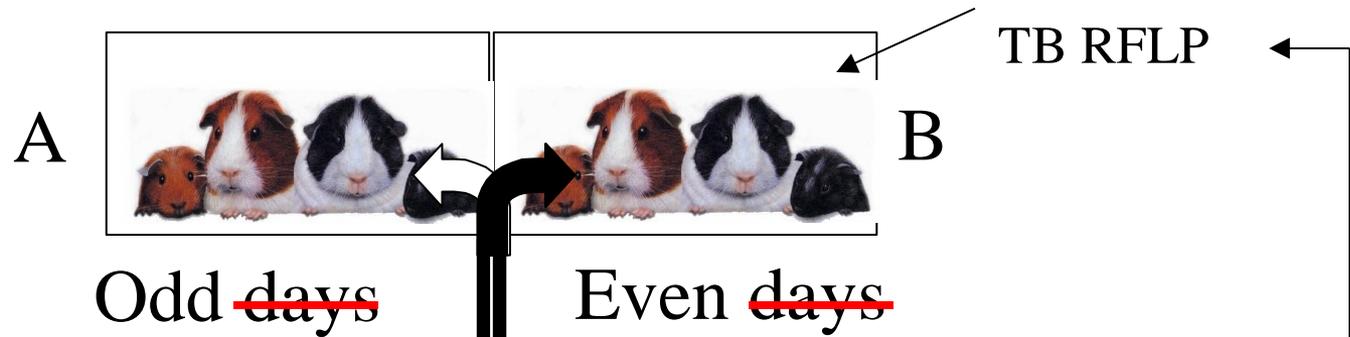


AIR, Experimental Plan

Guinea Pig Air Sampling

(Usual intervention studies)

Guinea Pig
TB RFLP



Intervention on/off on alternative ~~days~~

Colistin Experimental Plan

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | | | | |
|---|-----------------|---------|---------|---------|-----------------|---------|---------|---------|-----------------|---------|---------|---------|-----------------|---------|---------|---------|-------------------------------------|----|----|----|-------|--|--|--|
| Guinea Pig Cohort Receiving Aerosols from TB Ward | A | B | A | B | B | A | B | A | A | B | A | B | B | A | B | A | TB exposure stopped to Animal Rooms | | | | | | | |
| Inhaled Administration to TB Patients | ST only | ST + IA | ST only | ST + IA | ST + IA | ST only | ST + IA | ST only | ST only | ST + IA | ST only | ST + IA | ST + IA | ST only | ST + IA | ST only | | | | | | | | |
| Infectious Source | Patient Group 1 | | | | Patient Group 2 | | | | Patient Group 3 | | | | Patient Group 4 | | | | | | | | | | | |
| | TST-1 | | | | TST-2 | | | | TST-3 | | | | TST-4 | | | | TST-5 | | | | TST-6 | | | |

Table 1: A schematic of key events during the course of the proposed study. Six MDR-TB patients, forming a patient group, will provide the infectious aerosols to expose susceptible guinea pigs in the study. Each Patient Group is required to remain in the TB Ward of the AIR facility for four weeks, after which a new set of 6 patients will be admitted. There are at most 4 patient groups recruited over the course of four months. After the Patient Group 4 is discharged from the study, only activities regarding the guinea pigs are maintained. Tuberculin Skin Tests are administered to guinea pigs at six time points: before the start of the study, at 4, 8, 12, 16, and finally 20 weeks. Air from the ward is directed to Guinea Pig Cohort A when patients are on systemic therapy (ST) alone, while air is directed to Guinea Pig Cohort B when patients are receiving an inhaled antimicrobial (IA) on top of systemic therapy.

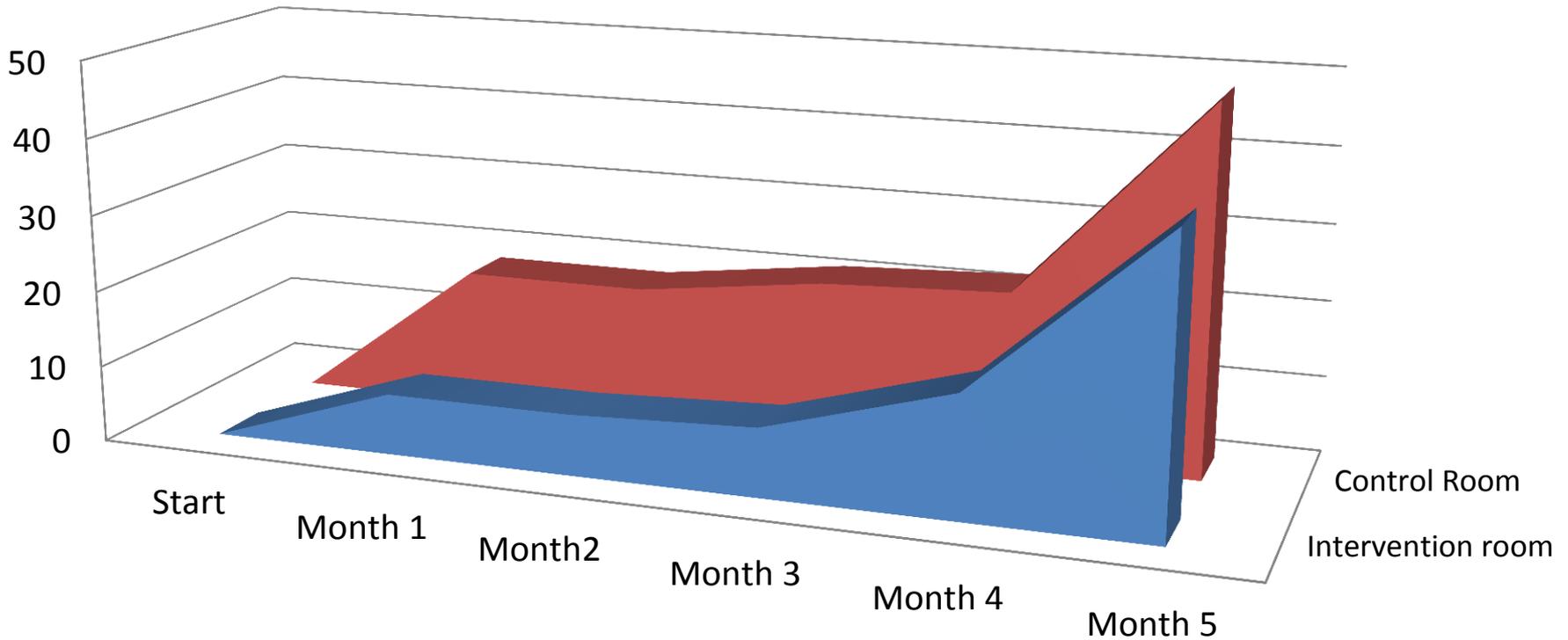
Notes:

1. Alternate **week** modification was introduced to prevent a carry-over antibiotic effect
2. **Numbers of subjects** (6 per group X 4 groups, plus replacement subjects) based on experience of the number needed to include enough infectious patients to generate enough transmission during control weeks to be able to measure a significant reduction with the intervention.
3. End point is **guinea pig infections**, not subject-related, per se. 90 guinea pigs in control and intervention chambers has proven effective in measuring 50-80% efficacy in previous trials.
4. Efficacy is for the **intervention against transmission of the entire cohort** of subjects, not for individual subjects. We cannot determine which patients caused infections.

Safety Concerns

- Clinical studies of 9 normal volunteers and total of 19 CF patients (FEV1 30-100%) showed minimal cough, and no significant change in FEV1.
 - Cmax in normals 90 µgm/L, and in CF patients 66.3 µgm/L with 25 mg dry powder dose; compared to 144 µgm/L nebulized. $T_{1/2} = 3$ hrs in CF patients
 - Note: iv dose 6-12 mg/kg colistimethate (300-600 mg for 50 kg patient) for systemic infection
 - Low dose of 25 mg every 8 hrs used (125 mg per day now approved for CF patients)
- Exclusion criteria:
 - room air oxygen saturation <90%
 - asthma (PEF < 50% predicted), or severe chronic obstructive lung disease (PEF < 50% predicted)
 - eGFR < 60 cc/min.
- Safety procedures:
 - PEF before and after first colistin dose both weeks,
 - Discharge from study > 20% fall in FEV1 without immediate response to bronchodilator
 - Oximetry at intake and once post dosing, and with any complaint
 - Weekly serum creatinine
- Adverse events logged and reported according to protocol
 - Acute management by hospital nurses and physicians
 - Investigation of all adverse events by Dr. Anton Stoltz, on-site PI

Results: Inhaled Colistin Study: infections added per month



| | Start | Month 1 | Month2 | Month 3 | Month 4 | Month 5 |
|-------------------|-------|---------|--------|---------|---------|---------|
| Intervention room | 0 | 8 | 8 | 9 | 16 | 38 |
| Control Room | 0 | 18 | 18 | 21 | 22 | 48 |

Secondary end point, sputum conversion: results pending

Conclusions:

1. Inhaled dry powder colistin used in advanced TB patients for the first time – well tolerated
2. Suggestion of early effect of topical antibiotics on transmission – confounded by study design that assumed no prolonged effect
 - *sputum conversion results pending*
3. Additional studies needed:
 - a. Repeat transmission study with different protocol
 - Higher dose (safe in CF patients) – 50 mg every 8 hrs.
 - Control-colistin sequence only
 - b. Therapeutic trial – but requires dose ranging study in animals first to arrive at rationale doses for humans
 - c. GP studies also needed to assess synergy with other TB drugs.