TITLE PAGE

The adverse effects and choice of injectable agents in MDR-TB: amikacin or capreomycin

Running title: Adverse events of injectable agents in MDR-TB

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Abstract

Background: The prolonged use of injectable agents in an MDR-TB regimen is recommended by the WHO despite association with ototoxicity and nephrotoxicity.

Objective: We undertook this study to look at the relative adverse effects of capreomycin and amikacin.

Methods: We reviewed the case notes of 100 consecutive patients treated at 4 MDR-TB treatment centres in the UK.

Results: The median total duration of treatment with an injectable agent was 178 (IQR 109-192, n=73) days for those with MDR-TB, 179 (104-192, n=12) days for those with MDR-TB plus fluoroquinolone resistance and 558 (324-735, n=8) days for those with XDR-TB. Injectable use was longer for those started with capreomycin at 183 (IQR 123-197) days compared to 119 (IQR 83-177) days with amikacin (p=0.002). Excluding XDR-TB, 51 (51/85, 60%) patients were treated with an injectable for over 6 months and 12 (12/85, 14%) for over 8 months. 40 % of all patients discontinued the injectable due to hearing loss. 55% of patients experienced ototoxicity: 5 times (hazard ratio (HR) 5.2, CI 1.2-22.6, p=0.03) more likely in those started on amikacin compared to treatment with capreomycin only. Amikacin was associated with less hypokalemia than capreomycin (Odds ratios: 0.28 (0.11-0.72)), with 5 (5/37, 14%) patients stopping capreomycin due to recurrent electrolyte loss. There was no difference in the number experiencing a creatinine rise of > 1.5 times baseline.

Conclusion: Hearing loss is frequent in this cohort, though significantly lower in those starting capreomycin which should be given greater consideration as a first line agent.

Main Text

Introduction

Treatment of multidrug resistant tuberculosis (MDR-TB) is challenging requiring extensive multidrug combinations for up to two years associated with significant adverse effects(1) Current treatment for MDR-TB is largely dependent on the World Health Organisation (WHO) guidelines(2-4) which are based on cohort, meta-analysis data and expert opinion. These recommend that all patients should be initially (intensive phase) treated with an injectable agent in the form of an aminoglycoside (kanamycin/amikacin) or polypeptide (capreomycin). The duration of the intensive phase recommended by the WHO rose from a minimum of 6 months to 8 months in 2011(3, 4) with even longer durations recommended for cases with more extensive resistance. The recommendation was based on a large meta-analysis of patient outcomes and did not take into account the side effects or other costs of these drugs.(5)

The injectable agents have significant side effects in the form of permanent and potentially progressive post cessation ototoxicity and usually reversible nephrotoxicity. (6-9) The frequency of ototoxicity and nephrotoxicity experienced by patients varies between studies, and most focus on the side effects of the aminoglycosides rather than the polypeptide,

capreomycin. Limited evidence suggests that capreomycin may be less ototoxic than amikacin.(10)

No randomised controlled trial of different injectable agents has been performed but better data is needed to inform policy. We performed a detailed service evaluation cohort study within four specialist UK MDR-TB treatment centres to compare the outcomes with different injectable agents in a real world setting.

Methods

Setting

Retrospective data were collected through clinical records and hospital database review at 4 tuberculosis (TB) treatment centres; St Mary's Hospital, Imperial College NHS Trust, London (centre 1), Heartlands Hospital, Birmingham (centre 2), the Royal Free Hospital, London (centre 3), St George's Hospital, London (centre 4). These centres act as regional referral hubs for MDR-TB treatment . Data were also collected at referring hospitals if patients were treated under a shared care model. Standard definitions were used for MDR-TB and extensively drug resistant tuberculosis (XDR-TB), pulmonary (PTB), extra pulmonary tuberculosis (EPTB)(11) and treatment was based on the WHO guidelines.(2, 3) At sites 1-2 amikacin is the preferred injectable agent, site 3 uses a mix and site 4 predominantly uses capreomycin (all intravenous). All sites switched injectable at the physician's discretion. All injectable agents are dosed initially at 15mg/kg once a day with trough drugs levels for amikacin at least weekly.

Reduced frequency of dosing is used if side effects occur. Duration of 6 months or more was defined as over 160 days and duration of 8 months was defined as over 220 days.

Study population and eligibility criteria

The first 100 consecutive patients, over 14 years of age, with a diagnosis of MDR-TB made in the UK, initiating MDR-TB treatment at the four sites between 2008 and 2014, were reviewed. Seven patients were excluded due to: lack of injectable agent use (2), streptomycin use at start (2), and over three initiations on MDR-TB medications (n=3). The cohort was split into two according to date of treatment start (the 51st patient started treatment in spring 2011) which corresponded to the change in WHO advice regarding injectable duration.

Renal function monitoring

To be included in analysis of renal function patients required at least weekly blood results available for review. Renal impairment was defined as mild at 1.5 times baseline creatinine and severe at over 3 times baseline(12). Hypokalaemia was defined as any drop below 3.5mmol/L.(13) Hypomagnesaemia was defined as any measurement below 0.7mmol/L.(12)

Audiological monitoring

All patients underwent pure tone audiometry (PTA) performed to the standards of the British Society of audiology (14) at the start of the injectable therapy. All sites performed PTA if hearing loss/change symptoms/any concern about hearing arose on treatment and sites 1, 2 and 3 had a policy of monthly PTA in addition (limited by patient adherence to protocol). Centre 3 performed audiograms at frequencies above 9- 20khz for a proportion of the study period. Significant deterioration between audiograms was determined by the American

speech and hearing association (ASHA) criteria which were as follows for frequencies tested between 250-8khz: (i) 20dB decrease ay any one test frequency, (ii) 10 dB decrease at any two adjacent frequencies, (iii). Loss of response at any three adjacent frequencies where responses were previously obtained .(15) Two end points relating to hearing were chosen: an audiogram definition (ototoxicity) and a composite definition encompassing audiogram results and clinically reported hearing loss (hearing loss (composite)) (**Table 1)**. Patient reported 'hearing impairment' was defined as any report by the patient of a negative change in hearing while on injectable agents or after stopping the injectable as documented by a nurse or doctor. 'Tinnitus' was defined as any symptoms reported by the patient that were interpreted as tinnitus by a doctor or nurse and documented in the records. Reasons for stopping injectable agents were collated from the medical notes according to what was written by the consultant in charge of treatment.

Statistics

Patients were grouped according to the injectable agent they were exposed to: 1. capreomycin only, 2. amikacin start (includes those only treated with amikacin and those treated with amikacin and switched to capreomycin or streptomycin because hearing loss was the main driver of this switch), 3. capreomycin then switch to amikacin (none switched due to hearing loss). Hearing loss was analysed within survival settings using Cox proportional hazard models, modelling the time since treatment start to point of hearing loss. Raised creatinine and hypokalaemia were investigated using logistic regression. Univariate analyses were initially undertaken which included all variables collected *(age, gender, baseline*

creatinine, baseline creatinine clearance (Cockroft Gault equation), dose of drug, MDR-TB type, number of amikacin troughs, centre, and amikacin and capreomycin group). Associations with resulting p-values less than 0.1 were further considered to form a multivariable/adjusted models based on similar numbers of complete observations. Model selection was undertaken by choosing the most parsimonious model using Akaike information criteria (AIC) and Bayesian information criteria (BIC). The final models were further refined using multiple imputation methodologies assuming missing at random model to account for approximately 15% of the original data that was missing (16). Further details on statistical methodologies are given in appendix 1. STATA software was employed for data analyses (StataCorp.2015 S*tata Statistical Software: Release 14. College Station,* TX:StataCorp LP).

Ethics

The study was deemed to be a service evaluation at the NHS ethics board (NRES committee London- City and East). Consent was given by the Confidentiality Advisory Group (GAG) for access to clinical records review. The data were anonymised onsite for off sites analyses.

Results

Fifty-four patients were started on amikacin and 39 were started on capreomycin (total, n=93). Nineteen patients switched injectable agent for the reasons stated in **Figure 1.** Background demographics and tuberculosis characteristics can be seen in **Table 2.**

Total duration of treatment with an injectable agent

The median total duration of treatment with an injectable agent was 178 (IQR 109-192, n=73) days for those with MDR-TB, 179 (104-192, n=12) days for those with MDR-TB plus fluroquinolone resistance (MDR-TB +FLQ) and 558 (324-735, n=8) for those with XDR-TB.

Excluding those with XDR-TB, 51 (51/60, 60%) patients were treated for 6 months or more and 12 (12/85, 14%) for 8 months or more. In the early cohort the median duration of treatment was 165 (107-187, n=42) days, of which 23 (23/42, 55%) achieved the target of 6 months and 3 (3/42, 7%) were treated for 8 months plus. In the latter cohort the median duration of treatment was 183 (109-210, n=43) days, of which 28 (28/43, 65%) were treated for 6 months or more and 9 (9/43, 21%) achieved the target of 8 months or more. There was no statistical difference in duration between the early and late cohort (p=0.19).

Seven (7/8, 87%) patients with XDR-TB were treated for 6 months or more and 6 (6/8, 75%) for 8 months or more.

The reasons for not achieving 6 months of treatment or more for all groups of patients were hearing loss (composite) 14 (14/35, 40%), physician choice 8 (8/35, 23%), resistance 4 (4/35, 11%), compliance concerns 3 (3/35, 9%) other 6 (6/35, 17%).

The median duration of the first line injectable agent was 160 (IQR 91-186) days for all patients. The median total duration was 183 (IQR 123-197) days for those started on capreomycin and 119 (IQR 83-177) days for those started on amikacin (p=0.002).

Ototoxicity

The proportion of cases that met the criteria for ototoxicity assessment was 55 (55/93, 59%) (Table 1) of whom 39 were started on amikacin and 16 started on capreomycin. Clinical notes were available for all 55 patients. Ototoxicity occurred in 30 patients (30/55, 55%), at a median duration of 112.5 days (IQR 91-177) and 18 (18/55, 60%) had bilateral changes. Deterioration was seen at the frequencies 6 -8 kHz only in 19 (19/55, 63%) cases, in the frequencies 4-8kHz only in 3 (3/55, 10%) cases, in frequencies 2-8kHz only in 6 (6/55, 20%) cases and across all frequencies tested (250Hz-8kHz) in 2 (2/55, 7%) cases. The median maximum change from baseline hearing at the worst effected frequency was 40 dB (IQR 25-55). At the time that ototoxicity was detected 8 (8/55, 27%) patients reported new onset hearing disturbance and tinnitus, 8 (8/55, 27%) reported tinnitus only, 3 (3/55, 10%) reported hearing disturbance only and 11 (11/55, 37%) did not report any symptoms.

Ototoxicity occurring on Amikacin

Twenty-eight cases of ototoxicity occurred while on treatment with amikacin (n=23) or after stopping treatment with amikacin (n=5). The median total number of amikacin trough levels did not differ between those with ototoxicity (1.03 IQR 0.77-1.28) and those without (1.21 IQR 1-1.43) (p=0.10). The proportion of one or more amikacin trough levels above 2.5 was 12/28 (40%) for those with ototoxicity and 5/14 (36%) for those treated with amikacin and no ototoxicity (P=0.66).

3 cases experienced ototoxicity on amikacin and had initially been treated with capreomycin. They had been switched to amikacin due to electrolyte disturbance (n=2) or resistance (n=1).

Two of the patients had normal audiograms (and same as their baseline) at the time of switch (174 and 164 days) and the third had a normal audiogram at the start of capreomycin followed by an abnormal audiogram after 282 days of amikacin treatment when newly reported tinnitus lead to testing. Fifteen (15/28, 54%) patients had sufficient audiograms to assess deterioration after stopping amikacin; 10 (10/15, 67%) progressed, 1 (1/28, 7%) improved and 4 (4/15, 27%) did not change.

Ototoxicity occurring on Capreomycin

Two cases of ototoxicity occurred on capreomycin. Both were in patients with XDR-TB in whom stopping the regimen would have reduced the number of active drugs below 4 and so despite early detection, treatment was continued with monitoring. Neither case experienced any permanent symptoms. Both cases had normal audiograms on first assessment and sensorineural hearing loss was identified on the second audiogram to be performed after the baseline which was at day 33 (performed due to vague symptoms of muffled hearing which went away) and day 112 (performed for screening no symptoms) of treatment respectively. Changes were seen bilaterally in both cases at the 6KHz and 8KHz frequency. There was a drop of 10-20db in case 1 and a drop of 30-55db in case 2. A further 3 and 4 audiograms were performed until days 434 (case 1) and 447 (case 2) of treatment and no further deterioration was seen. Both patients continued treatment after this period of monitoring with no change in symptoms but no further audiograms were performed.

Multivariable analysis using only the patients who fitted the ototoxicity criteria showed that ototoxicity was five times more likely for patients started on amikacin than for those treated with only capreomycin (HR 5.2, CI 1.2-22.6, p=0.03).

Hearing loss (composite)

Three patients (3/93) did not have sufficient medical notes (n=1) or could not express loss of hearing (psychosis n=1, intubated n=1) to be included in this analysis. Thirty-four (34/90, 38%) of those meeting criteria for inclusion experienced hearing loss (composite). The multivariable analysis showed that the likelihood of hearing loss (composite) was 14 times greater for patients started on amikacin compared to those treated with capreomycin only (Hazard ratio 13.9 CI 3.25-59, P<0.001) **(Table 3) .** Predicted survival analysis also showed that the probability of not developing hearing loss beyond 90 days was 0.99 (0.95- 1.00) in those on capreomycin only compared to 0.85 (0.73-0.92) for those starting amikacin. Furthermore the probability of surviving without hearing loss beyond 180 days was 0.97 (0.86-0.99) for those on capreomycin only compared to 0.58 (0.41, 0.72) for those started on amikacin **(Figure 2).**

Nephrotoxicity

Over the first 3 months renal function monitoring was performed a median of 19 times (IQR: 14-25) and over months 4-6, 9 times (IQR: 4-15).

Raised creatinine

Eighty-five cases had complete set of creatinine blood results. 25% (21/85) had a rise of 1.5 times or more from baseline of which 3 (3.5% =3/85) had a rise of 3 times baseline. The creatinine returned to baseline (under 1.5 times normal) in 19 (19/21) cases, 16 before the end of the injectable and 3 before the end of MDR-TB treatment. In patients where the creatinine did not return to baseline; one required haemodialysis after the amikacin was stopped (he already had chronic kidney disease at the start of therapy for MDR-TB and a baseline creatinine of 313 µmol/L which peaked at 846µmol/L) and the other due to death from advanced HIV (CD4=5). A multivariable model including baseline creatinine, duration on injectable agent and choice of injectable agent at start showed that there was no significant difference in the odds of raised creatinine between the two injectable agents chosen at the start (p=0.178) when adjusted for the total duration of the treatment. However, some evidence suggests that increasing duration may increase the odds of raised creatinine, i.e. 30 days increase is associated with 15% (95%CI(25, 32%)) raise in the odds of raised creatinine (p=0.04) (Table 4).

Electrolyte disturbance

Eighty-six patients had a complete set of potassium results, 37 started on capreomycin and 49 amikacin. Hypokalaemia was found in 38 (38/86, 44%) patients while on an injectable agent: 23 (23/38, 61%) were on capreomycin and 15 (15/38, 39%) amikacin.Eighteen cases (18/38) resolved alone without potassium replacement. Seventeen required replacement with oral potassium (13/17 on capreomycin), 7 required replacement with intravenous

potassium (all capreomycin), 4 had their dose reduced to 3 times per week (all capreomycin) and 3 required a switch in injectable agent (all capreomycin to amikacin). A multivariable model including duration of injectable agent and initial injectable agent indicated that the odds of hypokalaemia were approximately 4 times lower in those starting amikacin than for those starting capreomycin (Odds ratios: 0.28 (0.11-0.72). **(Table 4)**

Regular magnesium testing was performed for 15 of the capreomycin and none of the amikacin patients. Thirteen (13/15) were hypomagnesemic (11/13 with a reading below 0.5 mmol/L) of which 10 were treated with oral replacement, 9 with intravenous replacement and 4 required a switch to amikacin (3 of these also had reduced potassium and are inclusive of the 3 above). One stopped injectable earlier than planned due to hypomagnesaemia.

Switching from capreomycin to amikacin or stopping capreomycin early for electrolyte disturbance occurred in 5 patients (5/37) at a median of 132 (range 53-207, n=5) days. Of the four cases switched from capreomycin to amikacin one subsequently suffered ototoxicity on amikacin.

Discussion

We present data showing that ototoxicity is very frequent and that in England a third of patients do not reach the original 2008 WHO treatment guideline advising at least 6 months of an injectable agent. Even fewer reach the newer target of 8 months for the intensive phase. In a sub-cohort analysis capreomycin is associated with less ototoxicity and/or hearing loss

than amikacin though its use is sometimes limited by electrolyte disturbance. Those starting capreomycin were also able to tolerate injectable treatment for much longer.

Hearing loss during MDR-TB treatment is reported to be anywhere between 4.4% (1, 17)and 62% (18) (19) dependent on duration, drug choice, dose(6) and type of monitoring. Studies with a clinical definition (patient reporting symptoms) show lower levels than those with an audiogram based definition (20) and the majority of studies have been performed in the presence of the aminoglycosides, amikacin or the more commonly used worldwide and closely related kanamycin (15mg/kg/day). Our level of 55% ototoxicity is similar to the findings of others using intense monitoring and aminoglycosides at 15mg/kg, (15) (7, 18, 19, 21) Retrospective cohort analysis suggests that Kanamycin use is associated with less ototoxicity than amikacin. (21)

There are few recent MDR-TB studies investigating hearing loss associated with capreomycin possibly as its cost and need for electrolyte monitoring put it out of reach for many low income countries. However, although clearly defined methods for monitoring are not always described, there is a suggestion that levels of hearing loss are lower for capreomycin with proportions affected ranging from 0.7%-25%.(6, 22-25) Studies comparing amikacin to capreomycin are limited to a small retrospective study by this group which showed in univariate analysis that hearing loss was associated with amikacin use over capreomycin(10) and a pharmacovigilance reporting study showing spontaneous reports of deafness were disproportionately associated with amikacin followed by kanamycin compared to capromycin. (26) Our study has larger numbers than our earlier study and is not limited by

reporting bias and other issues inherent in pharmacovigilance reporting. The main limitation of our study arises from the differing audiogram policies at the sites. In the hearing loss (composite) analysis there is the possibility of underestimating hearing loss caused by capreomycin due to asymptomatic cases with ototoxicity being less likely to be identified (ascertainment bias) than those in the amikacin group who had more routine audiograms. However, to counter this possible bias we performed the ototoxicity analysis including in the denominators only those who had had an audiogram within a month of ending the injectable agent. Although the numbers of patients is smaller, in this analysis, the possible bias works in the opposite direction because patients at capreomycin sites who had audiograms were more likely to be those with a perceived risk of ototoxicity. These issues probably account for the difference between the hazard ratio for the ototoxicity outcome (5 times more likely with amikacin) compared to 15 times more likely for the composite hearing loss outcome with amikacin, and the real value may lie between the two numbers. We also consider that the character as well as the likelihood of occurrence of hearing loss can differ with capreomycin. The evidence for this suggestion is that the audiograms of the two patients who experienced ototoxicity on capreomycin did not display progressive hearing loss despite on-going exposure (lack of alternative drugs) which would be extremely unlikely for amikacin. (8) However, further investigations on the type of and degree of hearing loss caused by capreomycin in a randomised controlled trial is required. Reducing the proportions of patients experiencing hearing loss treated with amikacin may be possible with lower doses (7.5mg/kg) and AUC monitoring. (27) However the efficacy of this dose is unclear and it is not currently recommended. Other possibilities include the co-administration of N-acetyl cysteine or other

antioxidants,(28) and genetic testing for mutations in the mitochondrial gene encoding 12S rRNA (*MT-RNR1*) and avoiding aminoglycosides in these cases, (29-31) though the prevalence of these mutations is low.

However, our findings support the initial use of capreomycin over amikacin as a means of reducing hearing loss. Capreomycin use first line has also been advocated for, when onwards resistance patterns are considered; amikacin activity is often spared after the evolution of capreomycin resistance but not the other way round.(32, 33) The disadvantage of capreomycin is the associated electrolyte disturbance which led to discontinuation/switch in 14% of patients treated with it in our study. Of note, however, electrolyte abnormalities were managed effectively in all patients with no long term consequences. The association of capreomycin with electrolyte disturbance and renal impairment during treatment for TB is well reported. (13, 34, 35) In settings where regular rapid and reliable blood monitoring is not feasible, the nephrotoxicity of capreomycin may lead to deaths due to hypokalaemia and renal failure.(13, 23) Our data demonstrate that this is not the case in a well-resourced setting.

In summary we provide retrospective cohort evidence of high levels of ototoxicity and hearing loss in a UK MDR-TB cohort. Hearing loss was 14 times more likely with amikacin than capreomycin, while capreomycin was associated with electrolyte disturbance leading to cessation of the drug in 14% of those treated with it. Given the significance and irreversibility of hearing loss, in settings where blood monitoring is possible, we would favour starting with

capreomycin rather than amikacin, until such time as short course and injectable drug -free regimens incorporating the newer drugs have been shown to be effective .(17)

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Ethics

The study was deemed to be a service evaluation at the NHS ethics board (NRES committee London- City and East). Consent was given by the Confidentiality Advisory Group (GAG) for access to clinical records review. The data were anonymised onsite for off sites analyses. Data sharing with public health was according to Caldicott principles.

Contributorship statement

AA, TSH, MD, GSC, OMK, AL, PDB contributed to the design of the work. The acquisition of data was undertaken by AA, MD, OMK, ML, AL and acknowledged persons MM, VP, MOD and AS. ICS undertook statistical analysis with AA and TSH. All authors contributed to data interpretation, drafting and are responsible for content.

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Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.	All Authors

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Table 1: Ototoxicity and Hearing loss (composite) definitions

	Hearing loss	No hearing loss	Unable to classify
Ototoxicity	A significant deterioration (as determined by ASHA criteria) between an audiogram performed before or during therapy and one performed later during therapy or after completing therapy in the presence of normal tympanograms.*	A normal audiogram in the last month or after completing injectable therapy.*	An abnormal audiogram without an earlier audiogram for comparison*

		No significant deterioration (ASHA criteria) between an audiogram performed in the last month or after injectable therapy stopped and one performed within the first month of therapy.*	A normal final audiogram before the last month of therapy (unless performed after 365 days on therapy).
		No significant deterioration (ASHA criteria) between an audiogram performed after 365 days of injectable therapy and one performed within the first month of therapy.	
Hearing loss (composite)	As for ototoxicity	No report of 'hearing impairment' or 'tinnitus' and does not fit the criteria for ototoxicity.	Unable to report symptoms (intubated, extreme psychosis) or full set of medical or nursing notes missing.
	A clinical report of new 'hearing impairment' or 'tinnitus' during or after therapy with an injectable agent in association with an abnormal audiogram. No prior audiogram required.	A clinical report of new 'hearing impairment' or 'tinnitus' during or after therapy with an injectable agent in association with a normal audiogram or no deterioration in audiograms performed within a month of starting and at the time or after the onset of symptoms.	
	A clinical report of new 'hearing impairment' or 'tinnitus' during or after therapy with an injectable agent in association with a significant deterioration (ASHA criteria) between an audiogram performed before or during therapy and one performed later during therapy or after completing therapy above 8khz range.		
Worsening ototoxicity after stopping injectable agent	A significant deterioration (as determined by ASHA criteria) between an audiogram performed 30 days or more after the end of injectable therapy to one performed in the month before the end of therapy or on the stop date.	No significant deterioration (as determined by ASHA criteria) between an audiogram performed 30 days or more after the end of injectable therapy to one performed in the month before the end of therapy or on the stop date.	Any case not fitting either of the definitions.

PTA= pure tone audiometry, Normal audiogram=all frequencies better than 25 dB, abnormal audiogram = ASHA criteria, ASHA=American speech and Hearing Association. *based on definitions of hearing loss proposed by Seddon et al 2012[9]

Table 2: Background characteristics and demographics of patients (n=93)

Characteristic		Number (% unless otherwise indicated)
Median age in months (IQR*) (n=93)		28 (24-38)
Male gender (n=93)		64 (68)
HIV infected (n=93)		5 (5)
Country of birth (n=93)	UK	9 (10)
	Western and Northern Europe other	1 (1)
	Chinese subcontinent	10 (10)
	Indian subcontinent	36 (38)
	Africa	15 (16)
	Eastern Europe + Russia	22 (24)
Type of TB (n=93)	MDR-TB	73 (78)
	MDR-TB +FLQr**	12 (13)
	XDR-TB	8 (9)
Location of TB (n=93)	Pulmonary	41 (44)
	Extra-pulmonary only	31 (33)
	Both pulmonary and extra-pulmonary	21 (23)
Injectable agent (n=93)	Capreomycin	31 (33)
	Amikacin	43 (46)
	Amikacin and capreomycin (sequentially, either order)	18 (19)
	Amikacin followed by streptomycin	1 (1)
Baseline creatinine µmol/L (n=87)(IQR)		66 (58-75)
Creatinine clearance (n=81, median/IQR)		116.2 (75.7, 179.1)
Median initial dose of injectable agent (mg/kg) (n=82) (IQR)		14.81 (14.06-16.13)
Median number of Amikacin troughs/week (those on amikacin) (n=58) (IQR)		1.01 (0.76-1.29)

*IQR-interquartile range, FLQr=fluroquinolone resistance.

Table 3: Multivariable (adjusted) analysis investigating the predictors of hearing loss (composite)

				Univariate analysis		Multivariable analysis	
VARIABLES		**Hearing loss (%) n=34 (38%)**	**No hearing loss (%) n=56 (62%)**	**Hazard ratio**	**p**	**Hazard ratio**	**p**
Choice at start:	Amikacin (n=53) versus Capreomycin (n=37)	29 (55) 5* (14)	24 (45) 32 (86)	5.80(2.23-15.04)	<0.001		
Grouping	Starting amikacin (n=53) versus Capreomycin only (n=30)	29 (55) 2 (7)	24 (45) 28 (93)	11.70 (2.78-49.20)	0.001	13.85 (3.25-58.99)	<0.001
	Capreomycin followed by amikacin (n=7) versus Capreomycin only (n=30)	3 (43) 2 (7)	4 (57) 28 (93)	6.29 (1.05-37.65)	0.044	4.03 (0.66-24.63)	0.13
	Starting amikacin (n=53) versus Capreomycin followed by amikacin (n=7)	29 (55) 3 (43)	24 (45) 4 (57)	1.86 (0.56-6.13)	0.307	3.44 (0.97-12.18)	0.06
MDR-TB Type	MDR+ FLQ-TB (n=12) versus MDR-TB (n=70)	8 (67) 22 (31)	4 (33) 48 (69)	3.26(1.44-7.36)	0.005		
	XDR-TB (n=8) versus MDR TB (n=70)	4 (50) 22 (31)	4 (50) 48 (69)	1.62 (0.55-4.73)	0.378		
	XDR-TB (n=8) versus MDR+FLQ-TB (n=12)	4 (50) 8 (67)	4 (50) 4 (33)	0.55 (0.17-1.83)	0.331		
	FLQ resistance (n=20) versus MDR TB (n=70)	12 (60) 22 (31)	8 (40) 48 (69)	2.43 (1.20-4.93)	0.013	3.15(1.45-6.88)	0.004
Median dose of injectable at start (mg/kg) (IQR)		14.58 (13.82-15.51)	14.94 (14.07-16.63)	0.84 (0.71-1.00)	0.047		
Median creatinine baseline µmol/L (log scale)		4.25(4.13, 4.30)	4.17 (4.04, 4.32)	4.37 (1.12-17.11)	0.034		
Median creatinine clearance		114.1 (99.5, 122.9)	119.3 (105.8-134.5)	0.98 (0.97, 1.00)	0.055	0.99 (0.97-1.00)	0.11
Median Age (1 year effect) (IQR)		28.5 (25-39)	27.5 (22.5-33.5)	1.03 (0.99-1.07)	0.127		

*Only two of these cases occurred on capreomycin. The other three occurred on amikacin after they had been switched off capreomycin for other reasons. 2 had normal pure tone audiograms (PTA) at the start of amikacin.

Table 4: Multivariable model for creatinine rise to over 1.5 times baseline and hypokalaemia

	MV model for cratinine rise > 1.5x baseline		MV model for hypokalaemia	
variable	Odds Ratios	P value	Odds ratios	P value
Creatinine baseline	1.02 (0.99-1.05)	0.145		
Amikacin verses capreomycin at start	0.44 (0.14-1.45)	0.178	0.28 (0.11-0.72)	0.008
Total duration (30 days effect)	1.15 (1.02-1.32)	0.040	1.00 (0.91-1.08)	0.869

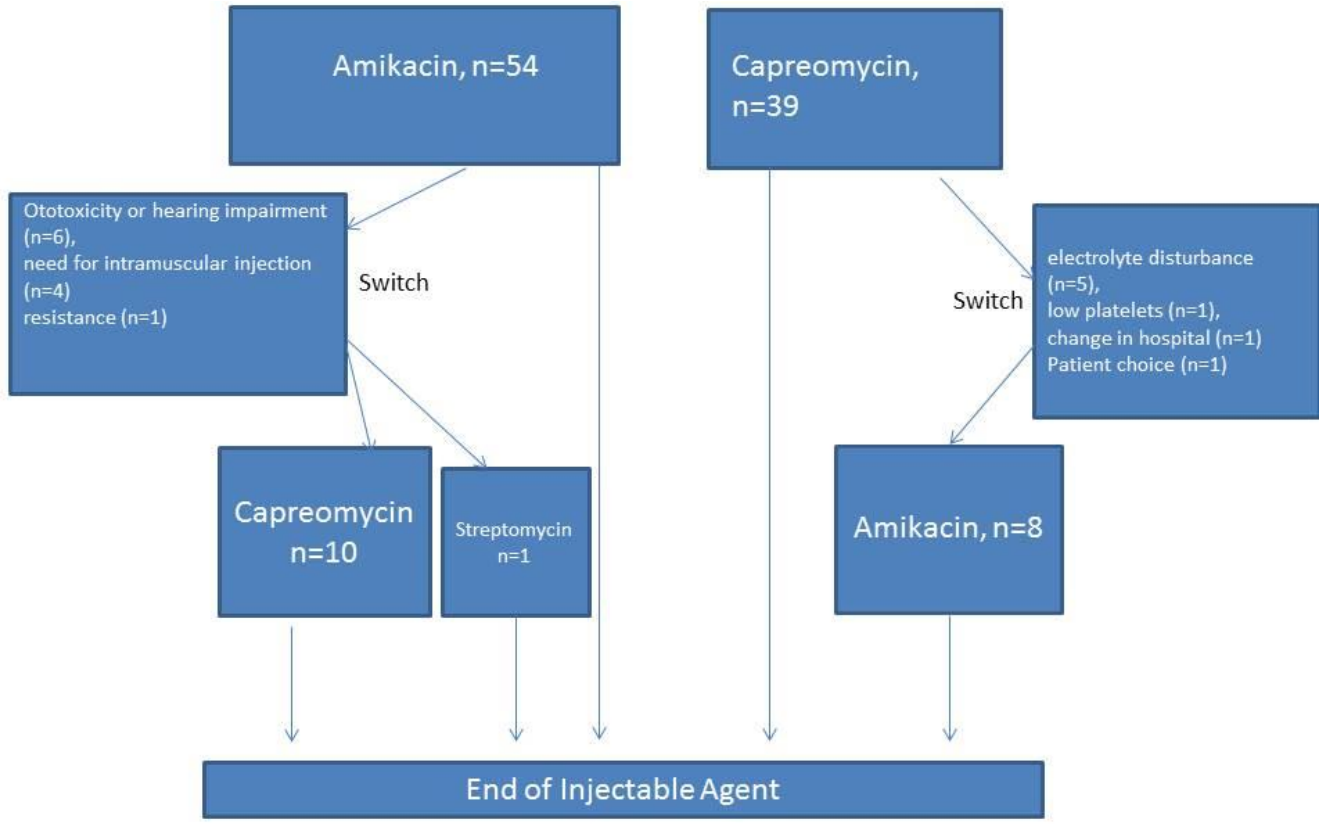

Figure 1: Flow diagram showing injectable agent use in cohort

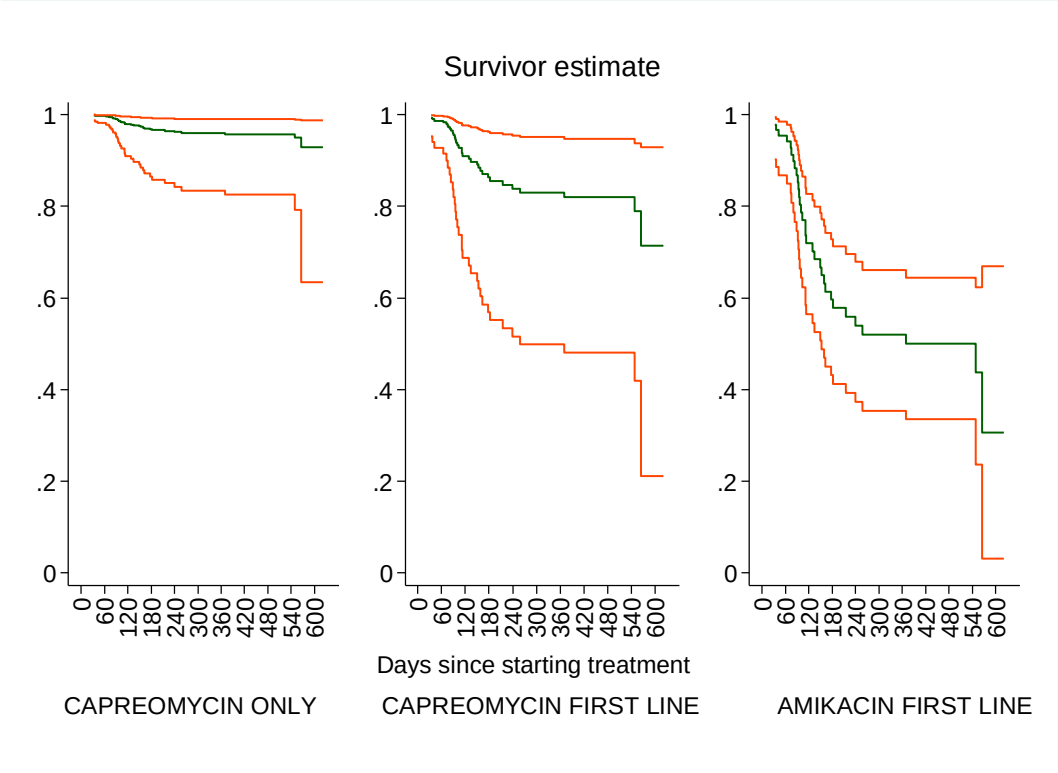

Figure 2: Predicted proportion surviving without hearing loss by initial choice of injectable agent. Middle line (black) represents the predicted proportion and outer lines represent 95% confidence intervals (red).