LIST OF CORRECTIONS:

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MONO- AND POLYRESISTANT TUBERCULOSIS AT TB FOCAL POINT, HELEN JOSEPH HOSPITAL.

Thank you to the examiners for reviewing my MMed, and for their comments and assistance.

The following changes have been made as requested:

Examiner 1:

1. Literature review:

- Page 16 and 17 includes information on Xpert MTB/RIF® Test and GenoTypeMTBDR*plus* HAIN Lifescience:
  "Xpert MTB/RIF® Test (Xpert) is a test used to identify TB DNA. In a study conducted in Johannesburg, the sensitivity of the Xpert test was 86%, comparing favourably with smear microscopy (59%), and in HIV positive individuals, the sensitivity only dropped to 84% for the Xpert. The specificity was more than 97% (Scott et al., 2011). Xpert was introduced in the TB Focal Point at HJH in an experimental capacity on extra pulmonary fine needle aspirate specimens from July 2010, and HJH began performing Xpert on sputum specimens in March 2011. As such, not all the patients in the cohort had access to the test.
  A molecular assay for the detection of Mycobacterium tuberculosis complex, GenoTypeMTBDR*plus* HAIN Lifescience (HAIN) was also used in this study population. The HAIN test identifies the rpoB genetic mutation for RIF resistance, and either the katG or the inhA genetic mutation for INH resistance. The sensitivity of the HAIN test is 98.1% for RIF resistance, and 90.2% for INH resistance, with specificities of 97.8% for RIF and 100% for INH resistance (Hillemann, Rusch-Gerdes, & Richter, 2007). "

2. Clarification:

- Page 20: 2.2: Sentence inserted to clarify categories of patients attending TB Focal Point. "TB Focal point deals specifically with drug resistant TB and with difficult to treat TB."
- Page 20: 2.3: The group of 'sensitive TB' was better defined as "genotypically resistant, phenotypically sensitive". This change was carried through the rest of the MMed.
- Page 31: Added information to explain the graph better, and rearranged the bars in the graph to assist in the explanation. "Graph 3 indicates the results from the HAIN testing, where 76.8% of the samples underwent a HAIN test. Of those samples that underwent the test, the proportion of resistance is shown in the graph. The total adds up to more than 100% as some samples could have both INH and RIF resistance."
- Page 40: Clarified the TB treatment in the genotypically resistant, phenotypically sensitive group. "These patients had been initiated on drug resistant TB therapy initially according to Xpert or HAIN results, but DST for first line TB drugs later proved phenotypically sensitive TB."
- Page 43: Rationale for serum albumin cut-off: Unfortunately this was an arbitrary cut-off. However, the serum albumin was not significant as a predictor at other cut-off levels.
- Page 44: Rationale for serum haemoglobin cut-off: Added to page 13: "Data gathered includes laboratory findings of haemoglobin and serum albumin. The value used as cut-offs in this study for haemoglobin is according to WHO, with severe anaemia defined as a serum haemoglobin of less than 8g/dL (World Health Organisation, 2011). The serum albumin cut-off of 2.0g/L was arbitrary."

3. Corrections required:

- Page 14: Reference regarding Chakroborty was misquoted, and has been corrected. . "Mutations in the rpoB region are associated with RIF resistance (Chakroborty, 2011), although true RIF monoresistance has previously been documented as being relatively uncommon and is often used as a marker for MDR TB (Evans, Stead, Nicol, & Segal, 2009)."
- Page 14: Error regarding RIF and INH resistance was misplaced, moved to paragraph regarding INH on page 15. " Different mutations are known to confer differing levels of resistance, for example, katG confers high level resistance, whilst inhA confers only low level resistance (Gillespie, 2002)."
- Page 17: TB is a major concern, placing third, is clarified to "third globally"
- Page 24: CD_4 is now described in quartiles. "The lower quartile is 30.5 and upper quartile is 145.5, with an interquartile range of 115."
- Pages 43, 47: the unit for serum albumin levels has been changed from g/dL to g/L

4. Phraseology:

- Pages 28-30: "There were 137 patients with data available for CD_4 count."," A total number of 193 cases out of the 194 cases in the sample population were valid for analysis for Xpert MTB/RIF® Test (Xpert), representing 99.5% of the total sample.", "A total of 194 cases were valid for analysis, representing 100% of the sample population."

5. Typographical Errors:

- Mono resistant/resistance was changed to monoresistant/monoresistance, poly resistant/resistance was changed to polyresistant/polyresistance.
- Page 20: 2.3: g/dL was deleted
- Page 27: "table" has been omitted from the first sentence
- Pages 30, 31, 40: 'GenoTypeMTDR*plus* HAIN Lifescience' was changed to 'GenoType MTBDR*plus* Hain Lifescience'
- Pages 46: Fluoroquinilone was changed to fluoroquinolone
- Page 50: RIF mono was changed to RIF monoresistance
- Page 51: This paragraph has been changed and moved to page 52. "The phenotypically sensitive group had rpoB mutations, or were missing the wild type, and had no katG nor inhA mutations. This group was genotypically resistant, but tested phenotypically sensitive on DST. It is possible that this group represents subclinical RIF resistance, and is an area of further research and attention."
- Page 55: INH poly has been changed to INH polyresistance, and RIF poly has been changed to RIF polyresistance

Examiner 2:

1. The sensitive group in the study has been clarified as " genotypically resistant, phenotypically sensitive"
2. Unavailability of treatment regimens, initial treatment and treatment changes after resistance profiles was highlighted in the limitation section on page 52. "These facilities tasked with managing mono- and polyresistant TB did not have access to all drugs, did not have guidance on treatment or protocols, and there was no standardization of regimen or follow-up. This resulted in the non-uniformity of treatment, including drug choice and duration, making studies such as this one difficult to compare with other centers. Information regarding the initial drug treatment, and the potentially revised treatment after resistance result was not available to the study investigator."
3. Bootstrapping was performed in order to detect any differences between groups with small numbers, but there was no clinical significance found, so this was omitted.

4. RIF and ART interactions are better expressed on page 14. “Rif monoresistance has been associated with co-infection with HIV. Sandman et al suggest that there is potential for drug interactions with anti-retroviral therapy (ART) and anti TB treatment, creating selective drug pressures (Sandman et al., 1999). However, there are as yet no reports of decreases in TB treatment efficacy when administered with ART. The particular interactions described are those between RIF and protease inhibitors, and RIF and non-nucleoside reverse-transcriptase inhibitors (McIlleron, Meintjes, Burman, & Maartens, 2007). “
5. Page 14, 15: RIF resistance is associated with rpoB mutations, and INH resistance is associated with inhA and katG mutations. These statements have been separated into paragraphs describing INH resistance and RIF resistance.
6. Factually incorrect, changed to “Ethambutol (EMB) is another first line drug, and resistance to it is often associated with resistance to INH (A. Jain et al., 2008). This is associated with inhA mutations, where a mutation in the RNA polymerase gene confers INH and EMB resistance (Chakroborty, 2011).”
7. HAIN testing was not yet introduced as standard practice at the time of the study, and this is clarified on page 30. “At the time of the study, there was no protocol in place for the routine use of HAIN, and as such, specimens would undergo HAIN testing as an initial test if specifically requested by the treating doctor, otherwise, the HAIN was performed on culture positive specimens.”
8. A paragraph and small table were added to show improved outcomes, after removal of cases with unknown outcomes. “If one removes the cases where the files were not retrievable, lost to follow up cases, and the cases that were transferred out, where the outcomes are not known, and are not necessarily poor, the new denominator total would be 39. In this case, the outcome for RIF monoresistance would be as follows. Table 5: RIF monoresistant TB outcomes excluding cases with unknown outcomes”.
9. The Levines test was removed.
10. The polyresistant group was described on page 39 “. In the group of polyresistant TB, 3.6% had INH and EMB resistance; 2.6% had RIF and EMB resistance; 1.5% had RIF and streptomycin resistance; 0.5% had one of the following groups of resistance each: INH, streptomycin, EMB, ofloxacin, kanamycin; INH, EMB, ethionamide, streptomycin, PZA; INH, streptomycin, ethionamide; INH, streptomycin, PZA; RIF, ethionamide; or INH, EMB, ethionamide, and streptomycin resistance.”
11. See point 2.
12. See point 1.
13. Page 44: Paired T Test done, this is included now.
14. Table 14 became table 15, and the following explanation was included: “Unfortunately, the majority of the cases had outcomes that were not quantifiable, in that they were not necessarily poor outcomes, (ie, death or treatment failure), but neither could they count as a good outcome (ie cure, treatment completed), making statistical analysis non-significant, as total numbers were too small.”
15. Added “However, the Turkish cohort was not HIV positive, so a direct comparison is not reliable”.
16. Spearman correlation not included as no significant findings.