We thank Benjamin Teh , Werner C Albrich and respective colleagues for their comments. This randomised multi-centre placebo-controlled trial found levofloxacin reduced fever or death at 12 weeks and also reduced deaths by 64%1. This survival benefit was not maintained at 12 months, but this may be obscured by later events. Alternatively, it could be that prophylaxis was stopped too early. The early divergence of the Kaplan-Meier curves is compatible with the known infectious risk being highest at the start of treatment2.

The difference in deaths with active myeloma in 29/40 levofloxacin versus 15/39 placebo patients should be treated with caution as the attribution of cause of death can be inaccurate in 41% of cases3: Consequently we read no further into these data especially as overall survival of both groups was similar at 12 months. Data on how antibiotics affect the microbiome during cancer treatment is conflicting with reports of enhanced and reduced efficacy4. Firm conclusions on the influence of the microbiome await prospective randomised trials.

The FDA alert on fluoroquinolones outlines risks of toxicity, although the data on which the report is based is from retrospective surveillance with little information on the denominator. The FDA recommends quinolones should be used where benefits outweigh risks. It is large randomised studies such as TEAMM that can provide the evidence to integrate concerns about the risks of levofloxacin and the prevention of infections and deaths[5].

Concerns about overuse of antibiotics and risk of emergence of resistance were not confirmed in this study. Not only was there no increase in carriage of resistant organisms, but concerns about resistance in invasive organisms needs to be taken within the context of total reductions in invasive Gram negative isolates in our study (6 for levofloxacin versus 27 for placebo p<0.01): In this context we detected 3/489 invasive fluoroquinolone-resistant isolates in the levofloxacin group versus 1/488 for placebo which does not indicate emergence of resistance.

Co-trimoxazole has a higher incidence of side effects and higher subsequent resistance than fluoroquinolones5. 663 patients did not take Co-trimoxazole as non-randomised prophylaxis against *pneumocystis* and with only 2 patients developing *pneumocystis* we suggest that routine use of co-trimoxazole may be unnecessary.

Important questions remain concerning the use of prophylaxis in myeloma including the optimal duration of prophylaxis, effect on bacterial resistance and the microbiome. However, these questions must be answered with further large randomised studies and speculations from observational studies should be guarded. Currently we show a benefit for survival and reduced febrile episodes from levofloxaicn prophylaxis with little toxicity and no increase in carriage of resistant organisms. Prophylaxis should be considered during the early treatment of newly diagnosed myeloma, with due consideration for risks and benefits in the individual.

Word count – 449

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