Off-target Health Impacts of Azithromycin Mass Drug Administration

Session Date: Saturday, October 27

Session Time: 1:00pm – 4:00pm

Session Location: Frontenac, 3rd Floor

Session Description: The overall aims of this session are to present the most recent research on the impact of MDA on health outcomes other than NTDs, and to discuss how program planning and evaluation can be developed to better address these impacts. Azithromycin MDA has been highly effective in the control of trachoma, and is being extended to yaws control. As a broad-spectrum antibiotic, azithromycin has the potential to control a range of other infection-related conditions, but its overuse may also lead to resistance that could limit its value. There has not yet been a comprehensive approach to these non-target outcomes of azithromycin MDA programs, despite interest over many years. Observations from trachoma programs of reduced child mortality were confirmed in a recent cluster randomised trial in African countries. There have also been observations on the impact of azithromycin MDA on skin, gastrointestinal tract, respiratory and sexually transmitted infections, and some investigation of resistance in organisms that are normally susceptible to azithromycin. In this context, the session will involve (i) presentation of the latest research findings on non-target impacts of azithromycin MDA, including resistance; (ii) strategies for monitoring these impacts; (iii) discussion of how program monitoring could be adapted to capture non-target impacts, whether through special surveys or routine health facility data and (iv) proposals for modelling and health economic analyses of non-target impacts.

Session Chairs: Sheila West, Johns Hopkins University
Nebiyu Negussu, Federal Ministry of Health, Ethiopia

Session Rapporteur: Laura Senyonjo

KEY DISCUSSION POINTS

Mortality (Caitie Oldenburg, University of California, San Francisco)
There is a growing body of evidence suggesting that azithromycin mass drug administration has an impact on reducing under-five (U5) mortality, in some settings. MORDOR was an randomized controlled trial designed to specifically address this question across three study sites in Niger, Malawi, and Tanzania. The study showed an overall reduction in U5 mortality of 13.5% in those children that received azithromycin as compared to a placebo. The impact was largely driven by the results in Niger, where the reduction on U5 mortality was the greatest. Further planned studies in this area include understanding the mechanism of action for azithromycin on reducing U5 mortality, evaluating alternative delivery platforms, further evaluation of resistance markers, and efficacy in other geographic regions and time periods.

Antimicrobial resistance (AMR) is an important consideration if the strategy is to be scaled up as a child survival tool. To date, there is no evidence of AMR in *C. trachomatis* following azithromycin mass drug administration (MDA), although there have been reports of an increase in resistance in *S. pneumoniae*, *E. coli*, and *S. aureus*, however resistance reverts back to baseline levels once the selection pressure has been removed. The reversion may take much longer depending on the number of rounds of mass drug administration.

Impact monitoring (Oliver Sokana, Solomon Islands Ministry of Health)
Under the AIM study, in the Solomon Islands, the feasibility of using routine health information systems to evaluate the impact of azithromycin on alternative targets (other than trachoma) was presented. This included tracking of disease prevalence using patient health facility attendance records and sentinel surveillance of notifiable diseases. The AIM study is evaluating the feasibility and safety of ivermectin and azithromycin co-administration for control of scabies (and impetigo). Co-administration of the drugs has proven feasible with no extra time and field cost implications.

Paediatrics (Andrew Steer, Murdoch Children's Research Institute)
A number of examples was also provided regarding the impact of azithromycin on paediatric infections. Azithromycin is a first- or second-line therapy for a broad spectrum of pathogens and also has anti-inflammatory properties. A rare but serious adverse effect is pyloric stenosis in infants. Azithromycin has been shown to have an effect on reducing incidence of respiratory, diarrhoeal, and skin diseases, but the effect has been shown to be short lived (matter of months). Reductions in U5 mortality are found to be greatest in the first three months post-MDA and this coincides with the timing in relation to disease benefits.

STIs (John Kaldor, The Kirby Institute, University of New South Wales)
The final presentation was on the impact of azithromycin MDA on bacterial sexually transmitted infections (STIs). Azithromycin is a first-line treatment for a number of STIs including chlamydia, gonnorhoea (in conjunction with IM ceftriaxone), *Mycoplasma genitalium*, and syphilis. There is a paucity of data regarding the prevalence of STIs worldwide and very little published data on trachoma MDA and impacts on STIs. Methods for assessment of STI infections (pelvic examination) and costs of tests have been major barriers to studies in the past.

KNOWLEDGE GAPS IDENTIFIED

Current knowledge gaps regarding azithromycin as a child survival tool include:

- Which populations exact most benefit (and offset any potential risk)
- Optimal target age group. Which age group has the most significant reduction in mortality?
- Frequency of azithromycin MDA and the impact on mortality
- Duration of beneficial effect
- Optimal platforms to reach target groups
- Mechanisms of action eliciting effects observed
- Impact of seasonal transmission (specific disease entities) and timing of MDA
- The efficacy and utility of azithromycin MDA through delivery of azithromycin to mothers in labour, or children where no trachoma or yaws MDA indicated
- Impact on gut microbiome of young children given azithromycin

Current knowledge gaps related to the impact of azithromycin MDA on STIs include:

- The impact of azithromycin MDA on STIs

- Duration of any effect
- The relationship between multiple rounds of azithromycin MDA and STIs

RECOMMENDED NEXT STEPS

Operational research required

- Further studies on azithromycin and U5 mortality from across a wide range of settings (underlying mortality rates and disease profiles) are needed, including (but not exclusive to) understanding the optimal target age group, the duration of the beneficial effect and any negative consequences including AMR.
- Evaluation of the long-term risk of azithromycin on young children through a longitudinal study evaluating the gut microbiome and possibly cardiovascular health
- Studies to evaluate the impact of azithromycin MDA on STIs
- A cost-benefit analysis of azithromycin MDA beyond trachoma; this should also take into account any potential long-term negative risks
- Azithromycin impacts on quality of life
- AMR studies across a broader range of gram negative bacteria (e.g., shigella, salmonellosis, and gonococcus)

Programmatic next steps required

- Further evaluation of routinely collected data through the health information system in countries in order to determine the feasibility of use for monitoring off-target impacts
- Need for broad guidance on what indicators would be useful for health systems to measure in regards to off-targets for azithromycin
- Support to data managers on how to analyze that data in real time or in a short timeframe