3 President's Malaria Initiative. Uganda malaria operational plan FY 2015. Washington DC: President's Malaria Initiative, 2015.
4 Besamusca J, Tijdens KG, Kahyarara G, Tingum EN. Wages in Uganda. Wage Indicator Survey 2012. Amsterdam: Wage Indicator Foundation, 2012
5 Uganda Bureau of Statistics (UBOS) and ICF International. Uganda Malaria Indicator Survey 2014–15. Kampala, Uganda, and Rockville, Maryland, USA: UBOS and ICF International, 2015.
6 WHO. Targeted subsidy strategies for national scaling up of insecticide-treated netting programmes. Geneva: World Health Organization, 2005.
7 Uganda Bureau of Statistics. National Population and Housing Census 2014. Kampala: Uganda Bureau of Statistics, 2016.
8 Clark S, Berrang-Ford L, Lwasa S, et al. A longitudinal analysis of mosquito net ownership and use in an Indigenous Batwa population after a targeted distribution. *PLoS One* 2016; **11:** e0154808.
9 Honjo K, Chaves LF, Satake A, Kaneko A, Minakawa N. When they don't bite, we smell money: understanding malaria bednet misuse. *Parasitology* 2013; **140:** 580–86.
10 Pettifor A, Taylor E, Nku D, et al. Bed net ownership, use and perceptions among women seeking antenatal care in Kinshasa, Democratic Republic of the Congo (DRC): opportunities for improved maternal and child health. *BMC Public Health* 2008; **8:** 331.
11 Kilian A, Lawford H, Ujuju CN, et al. The impact of behaviour change communication on the use of insecticide treated nets: a secondary analysis of ten post-campaign surveys from Nigeria. *Malar J* 2016; **15:** 422.
12 Curtis C, Maxwell C, Lemnge M, et al. Scaling-up coverage with insecticide-treated nets against malaria in Africa: who should pay? *Lancet Infect Dis* 2003; **3:** 304–07.
13 Lines J, Lengeler C, Cham K, et al. Scaling-up and sustaining insecticide-treated net coverage. *Lancet Infect Dis* 2003; **3:** 465–66.
14 Koenker H, Kilian A, Zegers de Beyl C, et al. What happens to lost nets: a multi-country analysis of reasons for LLIN attrition using 14 household surveys in four countries. *Malar J* 2014; **13:** 464.

Implications of intrapartum azithromycin on neonatal microbiota

A randomised controlled trial recently reported by Tita and colleagues[1] in the *New England Journal of Medicine* found that azithromycin, given in addition to a standard cephalosporin prophylaxis before incision for cesarean births, reduced maternal infections without affecting neonatal outcomes. However, the authors did not discuss potential neonatal dysbiosis from perinatal antibiotic exposure, the consequences of which might have long-lasting implications.

Tita and colleagues' conclusion—that there were no significant between-group differences in serious neonatal complications—was based on short-term observations unlikely to yield negative or positive results. Antibiotic exposure can cause significant, long-lasting effects on gut microbiota. Specifically, intrapartum antibiotics have been shown to cause infant gut dysbiosis. The CHILD study,[2] a prospective cohort study of Canadian infants followed up over a period of 2 years, found that infant gut microbiota differed significantly with intrapartum antibiotic prophylaxis exposure.[2] Moreover, antibiotic-induced alteration of physiological gut microflora has been shown to last into adulthood.[3]

Infant gut dysbiosis has been associated with various long-term negative and costly health consequences.[4] As antibiotics indiscreetly halt beneficial microbiota, opportunistic pathogens occupy previously unavailable ecological niches.[5] The long-term effects of this dysbiosis have been linked to increased susceptibility to autoimmune diseases such as type 1 diabetes, multiple sclerosis, and inflammatory bowel disease, as well as obesity and non-alcoholic steatohepatitis.[6] Dysbiosis-associated neonatal immune system dysregulation has also been associated with development of childhood allergies and asthma in industrialised countries.[6] Dysbiosis might be particularly relevant for preterm infants, especially very-low-birthweight infants, in whom gut microbiota imbalance between Gram-negative bacilli and anaerobic bacteria is associated with necrotising enterocolitis and sepsis, major causes of morbidity and mortality.[7]

Macrolide antibiotics in particular have a high potential for altering microbiota. In a large Finnish cohort study,[8] penicillin use in early life had only a small effect on intestinal microbiota, whereas macrolide use correlated with substantial, long-standing shifts from normally dominant Gram-positive phyla to Gram-negative species. This alteration was associated with asthma and obesity in children aged 2–7 years.[8]

These data suggest that use of expanded intrapartum surgical prophylaxis with azithromycin might cause long-term infant harm. Although the potential for infant harm should not overshadow proven benefit in maternal outcomes, the optimal timing of administration of azithromycin prophylaxis remains unknown and could reduce negative effects in infants. Earlier studies on expanded antibiotic prophylaxis for cesarean births showed reductions in postoperative endometritis and wound infection with azithromycin given after cord

clamp.[9,10] This dosing schedule might retain most, if not all, of the maternal benefit while reducing neonatal antibiotic exposure, because azithromycin is transported rapidly across the placenta, maintains high uterine concentrations, and has a 72 h half-life.[11]

Although surgical prophylaxis primarily reduces the bioburden sufficiently to allow the immune system to clear remaining bacteria contaminating surgical sites, treatment regimens eradicate already established infections.[12] Azithromycin targets genital tract microbes such as mycoplasma and ureaplasma that are commonly linked to post-partum infections.[1] The azithromycin prophylactic dose used by Tita and colleagues (500 mg given once intravenously) is equivalent to 1 g of oral therapy with respect to bioavailability, and is an effective treatment for almost all genital tract infections. By contrast, cefazolin, the standard prophylactic antibiotic for cesarean births, mainly targets skin flora, has a 2 h half-life, and requires a multiday and multidose regimen for wound infection treatment. Thus, the timing of surgical prophylaxis is crucial for cefazolin, which has a greater effect in reducing surgical site infections with dosing before incision than after cord clamp.[13] However, given azithromycin's unique pharmacokinetic and pharmacodynamic properties, in theory, maternal infectious outcomes related to the timing of azithromycin administration should not differ.

According to the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Surgical Infection Society, and the Society for Healthcare Epidemiology of America, antimicrobials used for surgical prophylaxis should ideally "have no adverse consequences for the microbial flora of the patient".[14] In the case of cesarean births, the effects of prophylactic antibiotics need to be considered on both the mother and the child. To date, no studies have compared azithromycin given at skin incision with azithromycin given after cord clamp, and none have compared various dosing strategies. Further research is needed on cesarean prophylactic antibiotic type, dose, and timing to maximise improvement in both maternal and infant, and short-term and long-term, outcomes.

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1 Tita AT, Szychowski JM, Boggess K, et al. Adjunctive azithromycin prophylaxis for cesarean delivery. *N Engl J Med* 2016; **375:** 1231–41.
2 Azad MB, Konya T, Persaud RR, et al. Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. *BJOG* 2016; **123:** 983–93.
3 Willing BP, Russell SL, Finaly BB. Shifting the balance: antibiotic effects on host-microbiota mutualism. *Nat Rev Microbiol* 2011; **9:** 233–43.
4 Faa G, Gerosa C, Fanni D, Nemolato S, van Eyken P, Fanos V. Factors influencing the development of a personal tailored microbiota in the neonate, with particular emphasis on antibiotic therapy. *J Matern Fetal Neonatal Med* 2013; **26:** 35–43.
5 Gorkiewicz G. Nosocomial and antibiotic-associated diarrhea caused by organisms other than *Clostridium difficile*. *Int J Antimicrob Agents* 2009; **33:** 37–41.
6 Bedford Russell AR, Murch SH. Could peripartum antibiotics have delayed health consequences for the infant? *BJOG* 2006; **113:** 758–65.
7 Warner BB, Deych E, Zhou Y, et al. Gut bacteria dysbiosis and necrotizing enterocolitis in very low birth weight infants: a prospective case-control study. *Lancet* 2016; **387:** 1928–36.
8 Korpela K, Salonen A, Virta LJ. Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children. *Nat Commun* 2016; **7:** 104–10.
9 Tita AT, Owen J, Stamm AM, Grimes A, Hauth JC, Andrews WW. Impact of extended-spectrum antibiotic prophylaxis on incidence of postcesarean surgical wound infection. *Am J Obstet Gynecol* 2008; **199:** 301–03.
10 Tita AT, Hauth JC, Grimes A, Owen J, Stamm AM, Andrews WW. Decreasing incidence of postcesarean endometritis with extended-spectrum antibiotic prophylaxis. *Obstet Gynecol* 2008; **111:** 51–56.
11 Sutton AL, Acosta EP, Larson KB, Kerstner-Wood CD, Tita AT, Biggio JR. Perinatal pharmacokinetics of azithromycin for caesarean prophylaxis. *Am J Obstet Gynecol* 2015; **212:** 812
12 Ehrenkranz NJ. Antimicrobial prophylaxis in surgery: mechanisms, misconceptions, and mischief. *Infect Control Hosp Epidemiol* 1993; **14:** 99–106.
13 Mackeen AD, Packard RE, Ota E, Berghella V, Baxter JK. Timing of intravenous prophylactic antibiotics for preventing postpartum infectious morbidity in women undergoing cesarean delivery. *Cochrane Database Syst Rev* 2014; **12:** CD009516.
14 Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health-Syst Pharm* 2013; **70:** 195–283.