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CLINICAL PHARMACOLOGY OF AZITHROMYCIN IN INFANTS AND CHILDREN

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ABSTRACT

Azithromycin is the most active macrolide antibiotic. It is an azalide antibiotic. Azithromycin inhibits protein synthesis by binding reversibly to 50S ribosomal subunity. Azithromycin is bacteriastatic, but may be bactericidal, at high concentrations. This antibiotic is used for treating respiratory tract infections caused by common pathogens of community-acquired pneumoniae. Azithromycin is active against streptococci, gram-positive bacilli, Clostridium perfringens, Corynebacterium diphtheria, Listeria monocytogenes, Haemophilus influenzae, Neisseria meningitis, Neisseria gonorrhoea, Bordetella pertussis, Campylobacter jejuni, Mycoplasma pneumoniae, Legionella pneumophila, and Vibrio cholera. In infants, azithromycin dose is 10 mg/kg for treating and preventing diseases. In children, azithromycin dose ranges from 10 to 30 mg/kg. A loading dose of 500 mg is given on the first treatment day, and then 250 mg once-daily is given for days 2 through 5 for the treatment of community-acquired pneumoniae, pharyngitis, and sinusitis. Azithromycin has a long half-life, of approximately 80 hours, and thus it is administered once-daily. Much of azithromycin undergoes biliary excretion, and the rest is inactivated in the liver. This antibiotic is efficacy and safety in infants and children, and has limited side-effects in this population. Azithromycin reduces the mortality rate, and prevents illness in infants and children. Azithromycin pharmacokinetics has been extensively performed in infants and children. After azithromycin intravenous administration, the mean clearance and distribution volume are 0.15 L/h/kg, and 13 L/kg, respectively, in infants. After oral administration, Tmax is 2 hours, and the mean Cmax, $AUC_{0-24\ hours}$ and, clearance are 230 ng/ml, 1,841 ng.h/ml, and 3.03 L/h/kg, respectively, in children. Azithromycin trials have been extensively investigated in infants and children. The aim of this study is to review the published data of azithromycin effects, metabolism, pharmacokinetics, and bacteria-resistance in infants and children.

INTRODUCTION

Azithromycin is a macrolide antibiotic related to erythromycin and clarithromycin that is increasingly used to treat neonatal Chlamydia, Mycoplasma and, Ureaplasma infections and to reduce whooping cough cross infection. A single-dose can also speed up recovery in children with severe cholera (Vibrio cholera infection). Azithromycin is an azalide antibiotic developed in 1988 by structurally modifying erythromycin molecule. It works by interfering with bacterial protein synthesis. Although it is slightly less potent against gram-positive organisms, it demonstrates superior in-vitro activity against a wide variety of gram-negative bacilli, including Haemophilus influenzae. A single-dose is the more effective way of treating childhood cholera than a 3-day course of erythromycin and probably as effective as a single-dose of ciprofloxacin. Azithromycin is moderately well absorbed when taken by mouth (40% bioavailability) and better tolerated than erythromycin because it triggers fewer gastrointestinal side-effects. It has very low peak serum levels and a very high distribution volume (about 23 L/kg) consistent with data showing extensive tissue distribution and intracellular accumulation. This antibiotic makes it particularly effective against intracellular microorganisms such as Chlamydia and Legionella. Azithromycin cerebrospinal fluid concentrations are low but there is substantial penetration into brain tissue. Much of azithromycin undergoes biliary excretion (terminal half-life is about 5 days), and the rest is inactivated in the liver, that makes once-daily treatment more adequate, but can also make it important to give a first loading dose. Azithromycin has been used to treat Ureaplasma urealyticum infection in the hope that it would reduce bronchopulmonary dysplasia in

preterm infants. Organisms appear to respond very well to azithromycin, and this antibiotic is safe and well tolerated. There is limited published information relating the use in pregnancy, but the macrolide antibiotics are not, as a class, considered teratogenic. Less than 3% of azithromycin crosses the placenta, and no adverse-effects have been reported in human foetus. A breastfed infant only ingests about 5% of the weight-adjusted maternal dose [1]. Azithromycin is primarily excreted unchanged in the bile, with some hepatic metabolism to inactive metabolites. Azithromycin prolonged terminal half-life (approximately 80 hours) is thought to be due to extensive uptake and subsequent release from tissues [2]. Macrolide antibiotics are widely used agents for treatment of respiratory tract infections caused by common pathogens of community-acquired pneumonia. Azithromycin is the most active macrolide antibiotic. Azithromycin inhibits protein synthesis by binding reversibly to 50S ribosomal subunity of susceptible microorganisms at, or very near, the site that binds chloramphenicol. Azithromycin is usually bacteriastatic, but may be bactericidal in high concentrations, against susceptible organisms. This antibiotic has reasonable good activity against streptococci, isoniazid resistance among Streptococcus pneumoniae often coexist with penicillin resistance. Staphylococci are not reliably sensitive to azithromycin and macrolide-resistant strains of Staphylococcus aureus are potentially cross-resistant to clindamycin and streptogramin B (quinupristin). Gram-positive bacilli are also frequently sensitive to azithromycin, including Clostridium perfringens, Corynebacterium diphtheria, and Listeria monocytogenes. Azithromycin is inactive against most aerobic enteric gram-negative bacilli. It has modest activity in-vitro against Haemophilus influenzae and Neisseria meningitis and good activity against most strains of Neisseria gonorrhoea. Useful antibacterial activity is also observed against Borrelia species and Bordetella pertussis. Macrolides are usually active against Campylobacter jejuni. Azithromycin is active against Mycoplasma pneumoniae and Legionella pneumophila [3].

Azithromycin should be given 1 hour before or 2 hours after meals when administered orally. For outpatients therapy of community-acquired pneumoniae, pharyngitis, and sinusitis, a loading dose of 500 mg is given on the first day, and then 250 mg once-daily is given for days 2 through 5. Treatment of Mycobacterium avium intracellular infection in HIV-infected patients requires higher doses: 500 to 600 mg once-daily in combination with one or more other antibiotics for treatment or 1,200 mg once-weekly for primary prevention. Azithromycin is useful in treatment of sexually transmitted diseases, especially during pregnancy when tetracycline antibiotics are contraindicated (Centers for Disease Control and Prevention, 2015). The treatment of uncomplicated non-gonococcal urethritis, presumed to be caused by Chlamydia trachomatis, consists of an azithromycin 1 gram-single-dose, which is also effective for chancroid. In children, the recommended dose of azithromycin oral suspension for treatment of acute otitis media and pneumoniae is 10 mg/kg on the first day (maximum 500 mg) and 5 mg/kg (maximum 250 mg once-daily) on days 2 through 5. A single-oral-dose of 30 mg/kg is approved as an alternative for otitis media [3]. Macrolides are suitable antibiotics for treatment of a number of respiratory tract infections. Azithromycin is a suitable choice for treatment of mild-to-moderate community-acquired pneumoniae among ambulatory patients. In hospitalized patients, a macrolide is commonly added to an anti-pneumococcal β-lactam, for coverage of atypical respiratory

pathogens. Because of excellent in-vitro activity, superior tissue concentration, the ease of administration as a single once-daily dose, and better tolerability, azithromycin (or a fluoroquinolone) has supplanted erythromycin as the first-line agent for treatment of legionellosis. Macrolides are also appropriate alternative agents for the treatment of acute exacerbations of chronic bronchitis, acute otitis media, acute streptococcal pharyngitis, and acute bacterial sinusitis. Azithromycin is generally preferred to erythromycin due to its broader spectrum and superior tolerability [3].

Literature search

The literature search was performed electronically using PubMed database as search engine, the cut-off point was July 2019. The following key words: "azithromycin infants effects", "azithromycin children effects", "azithromycin infants metabolism", "azithromycin children metabolism", "azithromycin infants pharmacokinetics", "azithromycin children pharmacokinetics", "azithromycin infants resistance", and "azithromycin children resistance" were used. In addition, the books Neonatal Formulary [1] and NEOFAX by Young and Mangum [2] were consulted. The manuscript is prepared according to the "Instructions for Authors".

RESULTS

Azithromycin administration schedule in infants and children

Azithromycin trachoma prophylaxis: endemic disease can be much reduced in the whole community by giving all children aged < 11 years a single 20 mg/kg azithromycin oral dose once every 3 months [1].

Azithromycin pertussis prophylaxis: infants and young children should be treated with 10 mg/kg azithromycin orally once-daily for 3 days [1].

Azithromycin bacterial infection treatment: infants should receive a single 10 mg/kg oral dose once-daily for 3 consecutive days or 5 consecutive days (US) [1].

Azithromycin conjunctivitis treatment: infants should be treated with a single 20 mg/kg azithromycin oral-dose. This treatment is effective for chlamydial conjunctivitis, including chronic follicular trachoma. Alternatively, infants should be treated with 1.5% azithromycin eye drops twice- or once-daily for 3 consecutive days, this administration route is very active [1].

Azithromycin ophthalmia prophylaxis: infants should be treated with 1 to 2 drops of 1% azithromycin ophthalmic solution instilled in each conjunctival sac for 3 days [2].

Azithromycin efficacy and safety in infants and children: Oldenburg *et al*. [4] compared the distribution of adverse-events reported after treatment among azithromycin-treated versus placebo-treated infants. Approximately one-third of caregivers reported at least one adverse event (azithromycin: 26.9%, placebo 34.3%, P-value = 0.23). Azithromycin given to infants, aged 1 to 5 months, appeared to be safe. Hassan *et al*. [5] characterised the pharmacokinetics, safety, and biological effects of an azithromycin single intravenous dose of 10 mg/kg in preterm neonates (N = 12) at 24 to 28 weeks gestation at

risk for Ureaplasma infection. There were no serious adverse-events attributed to azithromycin.

Azithromycin is safe in infants and children: Harris *et al*. [6] compared the efficacy and safety of azithromycin with amoxicillin-clavulanate or erythromycin for treatment of community-acquired pneumoniae caused by Mycoplasma pneumoniae and Chlamydia pneumoniae. Multicenter, parallel group, double-blind trial in which children, aged 6 to 16 years, with community-acquired pneumoniae, were randomized 2:1 to receive either azithromycin for 5 consecutive days or conventional therapy for 10 consecutive days (amoxicillin-clavulanate if aged ≤ 5 years or erythromycin if aged > 5 years). Children, from 23 geographically diverse sites, were evaluated for clinical outcomes and/or adverse-events at days 3 to 5, days 15 to 19, and 4 to 6 weeks post-therapy. Of 456 children enrolled during 17 consecutive months, 420 were evaluable (95.1%). Clinical success at study days 15 to 19 was 94.6% in the azithromycin group and 96.2% in the comparative treatment group (P-value = 0.735) and at 4 to 6 weeks post-therapy 90.6% and 87.1% (P-value = 0.330), respectively. Treatment-related adverse-events occurred in 11.3% in the azithromycin group and 31.0% in the comparator group (P-value < 0.05). Azithromycin administered for 5 consecutive days produced a satisfactory therapeutic outcome similar to those of amoxicillin-clavulanate or erythromycin given 3-times a day for 10 days for treatment of community-acquired pneumoniae. Azithromycin had significantly fewer side-effects than the comparator drugs.

Azithromycin tolerability was investigated in 1,213 children, aged ≤ 18 years, who were treated with an oral suspension of 10 mg/kg azithromycin [7]. A total of 1,212 children received standard regimens of amoxicillin-clavulanic acid, cefaclor, cefixime, ceftriaxone, clarithromycin, erythromycin, or penicillin V. The incidence of treatment-related adverse-events was significantly lower in children receiving azithromycin than comparators (7.9% versus 11.5%, P-value = 0.003). Azithromycin paediatric oral suspension is well tolerated in children and associated with significantly fewer adverse-events than comparators. Hopkins [8] compared azithromycin with standard regimens of various comparators agents: co-amoxiclav, amoxicillin, penicillin V, erythromycin, dicloxacillin, and flucloxacillin, in treatment of otitis media, pharyngitis, and skin infections. Side-effects were assessed within 35 days of therapy. The total number of side-effects was significantly lower in azithromycin-treated children (46 of 606, 7.6%) than in the comparator-treated children (72 of 523, 13.8%, P-value = 0.001). Azithromycin was well tolerated in children of all ages. Treadway and Pontani [9] assessed azithromycin efficacy and comparators antimicrobial agents in children, aged 6 months to 16 years. Oral azithromycin suspension was administered to children at a dose of 10 mg/kg once-daily for 3 consecutive days. The comparators agents were: co-amoxiclav, cefepime, cefaclor, clarithromycin, erythromycin, penicillin V, cloxacillin, or roxithromycin. Adverse-events were recorded in 232 children (8.7%) treated with azithromycin and in 180 of 1,844 children (9.8%) who received comparator antibiotics. The present results confirm that azithromycin can be safely used to treat bacterial infections in children of all ages.

Bremond-Gignac *et al*. [10, 11] determined azithromycin efficacy and safety of 1.5% eye drops twice once-daily in a paediatric population with purulent bacteria conjunctivitis.

Azithromycin treatment eradicated causative pathogens, including resistant species. Azithromycin 1.5% eye drops was effective and safe in children, and provided a more rapid clinical cure than tobramycin 0.3% eye drops in the treatment of purulent bacterial conjunctivitis in children. In addition, this azithromycin treatment is convenient because requires only twice-once-daily dosing regimen. No adverse-effects were noted on the ocular surface. Cochereau *et al*. [12] determined azithromycin efficacy and safety of a short duration-treatment of azithromycin 1.5% eye drops versus oral azithromycin to treat active trachoma. Children (N = 670), aged 1 to 10 years, received either: azithromycin 1.5% eye drops twice-once-daily for 2 or 3 consecutive days, or azithromycin single-oral dose of 20 mg/kg. Cure rate in per protocol set was as follows: 93.0%, 96.3%, and 96.6%, respectively. Azithromycin 1.5% groups were non-inferior to oral azithromycin. In active trachoma, azithromycin eye drops twice or once-daily for 2 or 3 consecutive days, are as efficient as the reference treatment and represent an innovative alternative to oral azithromycin. Islam *et al*. [13] determined azithromycin efficacy and safety in 50 children with typhoid fever. Azithromycin oral dose was 10 mg/kg once-daily for 7 consecutive days. Clinical cure rate was 94% and no serious adverse effects were observed. Azithromycin oral administration for 7 consecutive days in the treatment of uncomplicated typhoid fever was effective and safe.

Different azithromycin doses, different azithromycin treatment lengths, and different azithromycin administration routes in children

The rationale for azithromycin single and high dose treatment regimen was reported by Gordon and Blumer [14]. The rationale for azithromycin use of single-dose and shorter course treatment regimens is based on azithromycin pharmacokinetics properties. This antibiotic has a long elimination half-life (> 50 hours), which enables short course 1- or 3-day dose regimens to be clinically effective. Azithromycin is concentrated within phagocytic cells and tissues and it achieves targeted delivery by these cells to infection sites. In-vitro and in-vivo models have demonstrated that azithromycin is taken up, transported and released at sites of infection, by phagocytic cells such as polymorphonuclear neutrophils and macrophages. Very little of azithromycin dose replace resides in plasma. Thus the neutrophil, laden with this drug, can potentially transport large amounts of active azithromycin to tissue infection foci, even when azithromycin plasma concentration is quite low. Uptake is not saturable; therefore, delivery of total azithromycin as a 1- or 3-day regimens should lead to increased uptake and delivery of azithromycin to infection sites. Soley and Arguedas [15] evaluated the clinical success rate, safety, and compliance of azithromycin single-dose of 30 mg/kg. This azithromycin dose had (in 498 out of 610) 81.6% clinical success at the end of treatment. After azithromycin oral administration, adverse-events were uncommon, mostly mild and transitory, in the gastrointestinal tract. Azithromycin single-dose of 30 mg/kg represents an alternative for the treatment of paediatric patients with uncomplicated acute otitis media, particularly in those geographic regions where high-level of Streptococcus pneumoniae macrolide resistance is uncommon, and for those children that require directly observed therapy or when compliance may be a problem. Azithromycin single oral dose is underway to eliminate trachoma worldwide. Schachterle *et al*. [16] examined the effect of azithromycin single oral dose

on prevalent malaria infection in a large prospective cohort of children, and quantified the temporal prevalence of malaria parasitemia, by PCR for 6 months after azithromycin single oral dose was administered. In the first month, but not in subsequent months, Plasmodium falciparum infections were reduced by 73.0%. Azithromycin single-oral-dose cause a transient, 1-month antimalarial effect without selecting for Plasmodium falciparum ribosomal L4 resistance mutations, in a region with 10-year history of treating trachoma with this antibiotic. Frenck *et al*. [17] studied 149 children and adolescents, aged 3 to 17 years, with clinical typhoid fever who were treated with either oral azithromycin (20 mg/kg once-daily, maximum dose, 1,000 mg once-daily) or intravenous ceftriaxone (75 mg once-daily, maximum dose 2.5 gram per day). Cure rate was achieved in 30 of 32 patients (93.7%) who were treated with azithromycin, and in 35 of 36 patients (97.2%) who received ceftriaxone. No child who received azithromycin had relapse, compared to 6 children who were treated with ceftriaxone. Azithromycin single oral dose 5-day course was found to be an effective treatment for uncomplicated typhoid fever in children and adolescents. Macrolides are commonly prescribed for respiratory infections and asthma-like episodes in children. While their clinical benefits have been proved, concerns regarding the side-effects of their therapeutic use have been raised. Wei *et al*. [18] assessed azithromycin short- and long-term impacts on the gut microbiota in children aged, 12 to 36 month, diagnosed with recurrent asthma-like symptoms. Each acute asthma-like episode was randomized to a 3-day azithromycin course of 10 mg/kg oral solution once-daily or placebo. Azithromycin reduced episode duration by half.

The assessment of gut microbiota after treatment was investigated in 59 children (short-term) and again at age 4 years in 49 children (long-term) and 18 children received placebo. The 16S rRNA gene amplicon sequencing was investigated. Azithromycin caused a 23.0% reduction in observed richness and 13.0% reduction in Shannon diversity. Microbiota composition was primarily shifted in the Actinobacteria phylum, especially a reduction of abundance in the genus Bifid bacterium. Long-term (13 to 39 months after treatment), these authors did not observe any difference between azithromycin and placebo recipients in their gut microbiota composition. Azithromycin treatment induced a perturbation in the gut microbiota 14 days after randomization but did not have long-lasting effects on the gut microbiota composition. Campbell *et al*. [19] determined whether azithromycin 2-day dosing may improve azithromycin efficacy in children with severe trachoma. Fifty children, with severe trachoma, were enrolled from 5 villages in Kongwa, Tanzania. Enrollment occurred within 1 month, and within the same district, as the historical control population of 99 children with severe trachoma, all of whom, received azithromycin 1-day treatment. Swabs for determination of Chlamydia trachomatis infection were taken. All 50 children received 20 mg/kg oral azithromycin once-daily for 2 consecutive days (short-term), which was directly observed. Children were followed-up at 6 weeks for trachoma and infection. Baseline characteristics were similar between the treatment group and the control-group. One of 46 children (2.2%) in the treatment group were PCR-positive at 6 weeks, a 96.3% reduction from baseline, compared to 13 of 96 (13.5%) in the historical control-group, an 89.4% reduction. This difference was statistically significant. However, when modelled using logistic regression and accounting for age, gender, weight, and baseline percent

PCR positivity, the difference was not significant. Prevalence of clinical trachoma did not differ between the groups at 6 weeks. For children with severe trachoma, a randomized controlled trial of 2-day versus 1-day treatment may be warranted. A total of 371 children, aged 6 months to 12 years, with acute otitis media, acute sinusitis, streptococcal tonsillitis/pharyngitis, or pneumoniae were included in an open multicenter study [20]. Among them, 192 children (51.7%) were randomized to receive oral azithromycin dose of 10 mg/kg once-daily, for 3 consecutive days and 179 children (48.2%) for 5 consecutive days (10 mg/kg on day 1 and 5 mg/kg on days 2. The overall clinical cure rate was 95.7% and 96.1%, and bacteriological eradication rate was 90.1% and 94.2% in the 3 day- and 5-day groups, respectively. Side-effects, mostly mild gastrointestinal disturbances, were observed in 5.3% of children from day 3, and 6.7% in day 5 groups. Only one child (0.3%) had therapy discontinued due to vomiting. These results demonstrate that 3-day and 5-day azithromycin courses have comparable efficacy and tolerability in children with respiratory infections.

A total of 41 children with cystic fibrosis, aged 8 to 18 years, and with a median forced expiratory volume in 1 s (FEV1) of 61% (range, 33% to 80%) participated in a 15-month randomized double-blind, placebo-controlled crossover trial [21]. They received either azithromycin (body-weight $\leq$ 40 kg: 250 mg once-daily, > 40 kg: 500 mg) or placebo for 6 months (long-term). After 2 months of washout, the treatments were crossed over. Median relative difference in FEV1 between azithromycin and placebo was 5.4%. Forced vital capacity and mid-expiratory flow did not significantly change overall. Seventeen of 41 children (41.5%) had fewer oral antibiotic courses when azithromycin was taken than when placebo and 5 children had extra courses (P-value = 0.005). Sputum bacterial densities, inflammatory markers, exercise tolerance, and subjective well-being did not change. There were no noticeable side-effects. Azithromycin 4 to 6 month trial is justified in children with cystic fibrosis who do not respond to conventional treatment. Azithromycin long-term administration in children with cystic fibrosis has improved outcomes. A randomized controlled trial was conducted to compare the effect of two oral azithromycin doses (5 mg/kg once-daily or 15 mg/kg once-daily) on forced expiratory volume 1 (FEV1) and pulmonary exacerbations in children with cystic fibrosis [22]. A total of 56 children (28 in high dose group and 28 in low dose group) were enrolled. A total of 47 children (24 and 23 children in low and high dose groups, respectively) completed 12-months of follow-up. In this randomized, controlled trial no difference was observed in the effect of 2 azithromycin doses, on change in percentage predicted FEV1, and clinical scores, Pseudomonas colonization rates, pulmonary exacerbations, and the need for antibiotics. There was increase in exacerbations after stopping azithromycin in both groups. The present results suggest that, the decrease in the incidence of LRTI persists only till 6-months after azithromycin discontinuing.

Indigenous children, in high-income countries, have a heavy burden of bronchiectasis unrelated to cystic fibrosis. Valery *et al*. [23] established whether long-term azithromycin reduced pulmonary exacerbations in Indigenous children with neither cystic fibrosis nor bronchiectasis or chronic suppurative lung diseases. A total of 89 Indigenous Australian, Maori, and Pacific Islands, aged 1 to 8 years, were enrolled. Children were randomized (1:1 ratio, by computer-generated sequence with

permuted block design, stratified by site and exacerbation frequency [1 to 2] versus ≥ 3 episodes in the preceding 12 months]) to receive either oral azithromycin (N = 45, 30 mg/kg) or placebo (N = 44) once a week for up to 24 months. Compared to placebo, children receiving azithromycin had significantly lower exacerbation rates (P-value < 0.0001). However, children in the azithromycin group developed significantly higher carriage of azithromycin-resistant bacteria (19 of 44, 43.2%) than those receiving placebo (4 of 37, 2.7%, P-value = 0.002). The most common adverse-events were non-pulmonary infections. In azithromycin group, 71 of 112 had adverse-events (63.4%) compared to 132 of 209 had adverse-events (63.1%) in the placebo group) and bronchiectasis-related adverse-events (episodes, 22 of 112 adverse-events (19.6%) in the azithromycin group versus 48 of 209 adverse-events (23.0%) in the placebo group); azithromycin and placebo were well tolerated with no serious adverse-events attributed to the intervention. Azithromycin administered once-weekly for up 24 months (long-term) decreased pulmonary exacerbations in these children. This strategy was accompanied by increased carriage of azithromycin-resistant bacteria. Azithromycin has modest efficacy against malaria. Oldenburg *et al*. [24] evaluated the effect of annual versus biannual mass azithromycin distribution over a 3-year period (long-term) on malaria prevalence during the peak transmission season in a region with seasonal malaria transmission in Niger. Twenty-four communities in Matameye, Niger, were randomized to annual, or biannual-targeted, mass azithromycin distribution (3 distributions to the entire community during the malaria peak transmission season) or biannual-targeted azithromycin distribution (6 distributions to children aged <12 years, including 3 in the peak malaria transmission season and 3 in the low malaria transmission season). Malaria indices were evaluated at 36 months during the high transmission season. Parasitemia prevalence was 42.6% in the biannual distribution arm, compared to 50.6% in the annual distribution arm (P-value = 0.29). There was no difference in parasite density or haemoglobin concentration in the 2 arms.

Kauss *et al*. [25] identified a candidate formulation for further development of at home or near-home administrable paediatric rectal form of azithromycin. Azithromycin is used orally or intravenously for the treatment of respiratory diseases. Various pharmaceutical forms, i.e. rectal suspension, two different rectal gels, polyethylene glycol suppository, and hard gelatine capsule were assessed for in-vitro dissolution and in vivo bioavailability in the rabbit. Azithromycin suppository appears to be a promising candidate. Drugs that are rectally administered are generally considered to enter the circulation system without passing through the liver first. Maeda *et al*. [26] prepared an azithromycin suppository and investigated the pharmaceutical proprieties of the rectal administration route in humans. The bioavailability of azithromycin suppository through rectal administration was 23% higher compared to oral administration. Azithromycin absorption by the rectum, and the ensured safety, in children, makes azithromycin suppository an effective preparation in case where oral administration is not tolerated.

Azithromycin effects in infants and children

Nuclear factor-kappaB plays a central role in regulating key pro-inflammatory mediators. The activation of nuclear factor-kappaB is increased in tracheal aspirate cells from premature infants developing bronchopulmonary dysplasia. Aghai *et al*. [27] studied azithromycin effect of on the suppression of nuclear factor-kappaB activation and the synthesis of pro-inflammatory cytokines IL-6 and IL-8 in tracheal aspirate cells obtained from premature infants. Tracheal aspirate cells were stimulated with tumour necrosis factor-α and incubated with azithromycin. Stimulation of tracheal cells, by nuclear factor-α, increased the activation of nuclear factor-kappaB, which was suppressed by azithromycin addition. Increased activation of nuclear factor-kappaB was also associated with increased levels of pro-inflammatory cytokines (IL-6 and IL-8). Azithromycin significantly reduced IL-6 and IL-8 production to the levels similar to control. Tumour necrosis factor-α also stimulated increased degradation of inhibition kappaB-α which was restored by azithromycin addition. The present results suggest that azithromycin therapy may be an effective alternative to steroids in reducing lung inflammation and preventing bronchopulmonary dysplasia in ventilated premature infants.

Oral poliovirus vaccine is less immunogenic and effective in low-income than in high-income countries, similarly to other oral vaccines. Grassly *et al*. [28] did a double-blind, randomized, placebo-controlled trial of azithromycin effect of on immunogenicity of serotype-3 monovalent oral poliovirus vaccine given to healthy infants, aged 6 to 11 months, living in 14 blocks of Vellore district, India. Infants were randomly assigned (1:1) at enrolment to receive azithromycin orally at a dose of 10 mg/kg or placebo, once-daily for 3 days, followed by serotype-3 monovalent oral poliovirus vaccine on day 14. A total of 754 infants were randomly assigned: 376 infants (49.9%) received azithromycin and 378 infants (50.1%) received placebo. In the azithromycin group, 175 infants (46.3%) seroconverted to serotype-3 poliovirus compared to 192 infants (50.8%) in the placebo group (P-value = 0.366). Azithromycin reduced faecal biomarkers of environmental enteropathy (calprotectin, myeloperoxidase, and α1-antitrytripsin) and the prevalence of bacterial but not viral or eukaryotic pathogens. Viral pathogens were associated with lower seroconversion. Three serious adverse-events were reported (2 in azithromycin group and 1 in the placebo group), but none was considered related to the study intervention. Azithromycin did not improve the immunogenicity of oral poliovirus despite reducing biomarkers of environmental enteropathy and the prevalence of pathogenic intestinal bacteria. Viral interference and innate antiviral immune mechanisms might be more important determinants of the immunogenicity of live-virus oral vaccine.

Parker *et al* [29] characterized the intestinal microbiota in 60 Indian infants, aged 6 to 11 months, who received a 3-day course of azithromycin or placebo during a randomized trial of oral poliovirus vaccine immunogenicity. These authors sequenced the V4 region of the bacterial 16S rRNA gene in stool samples collected before and 12 days after finishing treatment. The presence of common bacterial, viral, and eukaryotic enteropathogens in the same samples were used by real-time PCR in a Tapman array card format. Azithromycin induced a modest decline in microbiota richness and a shift in taxonomic composition driven by a reduction in the relative abundance of Proteobacteria and Verrucomicrobia (especially Akkermansia muciniphila). The former phylum induces pathogenic strains of Escherichia coli and Campylobacter species that declined in prevalence based on the Tapman array card assay. These findings differ from previous observations

among older children and adults in Europe and North America, suggesting that azithromycin effects on the bacterial microbiota may be specific to the age and geographic setting of its recipients.

Coles *et al*. [30] evaluated azithromycin mass distribution effect for trachoma on the risk of acute respiratory infection during a 6-month period among young children living in 8 communities in rural Tanzania. A cohort of randomly selected children (N = 1,036) was followed for incidence of acute lower respiratory infection episodes. Azithromycin single-oral-dose treatment for trachoma was provided in 4 of the 8 communities, where trachoma prevalence was 10%. Incidence of acute respiratory infection episodes was calculated for 0 to 1 month, 1 to 3 months, and 3 to 6 months post-treatment and in comparable time points in the non-treated villages. In multivariate analysis, children's living in a village was associated with a 38% decreased risk of acute respiratory infection in the 0- to 1-month of follow-up period as compared to those in the untreated communities after adjusting for covariates and clustering. There were no significant differences in acute respiratory infection incidence by exposure status in the 1- to 3-month and in the 3- to 6-month follow-up periods. Azithromycin single oral dose for trachoma is associated with significant short-term reduction in acute respiratory infection morbidity among young children. Wang and Yang [31] analyzed azithromycin clinical effect of sequential therapy with in 160 children with Mycoplasma pneumoniae pneumonia infection. Children were randomly divided into two groups: study-group and reference-group and each group consisted of 80 cases. Children in study-group were carried for out sequential therapy of erythromycin, and azithromycin sequential therapy in the reference-group. The overall treatment efficiency, the incidence of adverse reactions, the time of symptom recovery, and the length of hospitalization stay were compared between the two groups. The study-group had more significant advantages than the reference-group (P-value < 0.05). The study-group had significantly less time of symptoms recovery and hospitalization than the reference-group (P-value < 0.05). The adverse-reactions were not different in two groups. Azithromycin therapy in children, with Mycoplasma pneumoniae pneumonia infection, achieved good therapeutic effect and had no serious adverse-reactions.

Hart *et al*. [32] assessed azithromycin mass administration effect of regimens on spleen size in 3,646 children aged 0 to 5 years. Clinical assessment of spleen size was carried out during cluster-randomized trial of azithromycin mass treatment for trachoma elimination. Twenty-four communities received treatment at baseline only. At 30-months of follow-up, children had spleen examination and measurement. Palpable splenomegaly was significantly lower in annual treated versus baseline-only treatment communities and in treated versus untreated children at 24 months in the annual treatment arm. The present results suggest that azithromycin effect on spleen size at the individual level, and the most plausibly due to azithromycin, due to the antimalarial effects of azithromycin. Lee *et al*. [33] examined the relationship between ocular Chlamydia trachomatis infection and follicular trachoma in 3,200 children, aged 5 years or younger, prior to and following multiple rounds of annual azithromycin mass administration. Thirty-two communities, with endemic trachoma, were offered annual azithromycin mass administration as part of a district-wide trachoma control program. Chlamydia trachomatis

infection was detected using the Amplicor CT/NG assay and follicular trachoma was identified by clinical examination using the WHO simplified grading system. The association between chlamydial infection and follicular trachoma in children was evaluated at baseline, prior to any treatment, and 12 months, after each of three annual rounds of azithromycin mass treatment. Factors associated with infection were examined using generalized estimating equation models. At baseline, the overall prevalence of chlamydial infection and follicular trachoma was 22% and 31%, respectively. Among children with clinical signs of follicular trachoma, the proportion of those with infection was 49% prior treatment, and declined to 30%, after three azithromycin mass administrations. Infection positivity among children with clinical signs of follicular trachoma decreased by 26% (P-value < 0.01) with each azithromycin mass administration, after adjusting for age. For children, aged < 1 year, who did not receive treatment, the relationship was unchanged. The association between ocular Chlamydia trachomatis infection and follicular trachoma weakened in children with each azithromycin mass administration, and both infection and clinical disease prevalence declined. However, three azithromycin mass administration courses were still a significant proportion of follicular trachoma cases with infection.

Childhood asthma is a type 2 helper T cell-driven inflammatory airway disease characterized by recurrent episodes of airway obstruction. Azithromycin may prove beneficial effect for asthmatic children. Lin *et al*. [34] determined the effect of azithromycin on type 2 helper T cells from atopic asthmatic children and non-atopic controls. CD4+ cells were isolated from peripheral mononuclear cells in 9 children with asthma and 9 non-atopic children. Cells were evaluated with respective as Th0 and differentiated into type 2 helper cells. Azithromycin effect on activated CD4+ cells was evaluated with respective cell proliferation and cytokine production. Th0 and type 2 helper T CD4+ T cells from atopic asthmatic children produced greater interleukin (IL)-5 (type 2 helper T cytokine) but lower interferon (IFN)-y (Th1 cytokine) compared to the non-atopic controls, respectively. Azithromycin inhibited IL-5 production of Th0 and Th2 cells from atopic asthmatics in a dose-depended fashion, without significantly affecting their IL-13 and IFN-y production of their Th0 cells. Azithromycin at a higher dose decreased cell viability by inhibiting CD4+ T cell proliferation and enhanced their apoptosis, an effect similarly observed in Th0 and type 2 helper T cells, and did not differ between asthmatic children and controls. The present findings show that azithromycin preferentially down-regulates IL-5 production and suggest its therapeutic potentials in controlling childhood asthma. The WHO has recently targeted the elimination of trachoma as a public health problem by the year 2020. Whitty *et al*. [35] compared azithromycin effects with those of topical tetracycline given as treatment for children with trachoma in eight rural Gambian villages. The entire population of children in four villages received oral azithromycin suspension in doses of 20 mg/kg on days 1, 8, and 15; the children of four other villages received topical tetracycline eye ointment for 42 days. Morbidity surveys of children, aged 3 months to 14 years, were conducted on days 0, 7, 14, 21, and 28. Of 804 children recruited completed follow-up data were available on 791 children (98.4%) (412 children received azithromycin, and 379 children (92.0%) were treated with tetracycline). Fever and headache were the most common complaints. Apart from

cough, other symptoms, were equally prevalent in both groups at baseline. Azithromycin group had 20% fewer illness, fever and headache episodes and 40% fewer diarrhoea and vomiting episodes at follow-up than did the tetracycline group. Azithromycin treatment for trachoma had favourable short-term on childhood morbidity in rural Gambian villages, particularly in the high malaria transmission season, and adverse-effects were not a problem.

Azithromycin adverse-effects in children

Half of prescription drugs commonly given to children lack product labelling on paediatric safety, efficacy, and dosing. Oshikoya *et al*. [36] determined the risk of serious paediatric adverse-events when oral azithromycin is used off-label compared to on-label in paediatric intensive care units. Six paediatric hospitals participated in a retrospective chart review of 241 children who received oral azithromycin. Outcomes were azithromycin serious adverse-events by and labelling status off-label compared to on-label by FDA-approved age and/or indication. Twenty-one children receiving azithromycin experienced serious adverse events. Off-label use of azithromycin was not associated with a high risk of serious adverse events. Azithromycin off-label use in paediatric intensive care units not appears to be associated with an increased risk of serious adverse events. Azithromycin mass distributions for trachoma have been associated with secondary benefits, including reduction in child mortality [37]. In the partnership for the rapid trachoma elimination, cluster-randomized trial in Niger, 24 communities were randomized to annual treatment of everyone and other 24 communities were randomized to biannual treatment in children, aged < 12 years, for 3 years. Azithromycin single-oral-dose of 20 mg/kg was administered to children. Among children, aged 6 months to < 5 years, 404 deaths occurred during the study period. Mortality rate was 35.6 deaths per 1,000 person-years, (231 deaths) in the annual arm and 29.0 deaths per 1,000 person-years (173 deaths) in the biannual arm. The mortality rate ratio comparing children in the biannual arm to the annual arm was 0.81. The mortality rate ratio comparing children who died from infectious causes in the biannual arm to the annual arm was 0.73. This secondary analysis, of a cluster-randomized trial, found a non-significant 19% decreased in mortality rate among children, aged 6 months to < 5 years, who received biannual azithromycin compared to children who received annual azithromycin. This study was conducted in a high mortality, trachoma-endemic area; thus, results may be specific to this environment only. In addition, the trial was neither designed, nor powered, to detect a mortality effect, and these results cannot rule out the possibility that mortality differences resulted from bias.

Azithromycin reduces the mortality in children

Oro *et al*. [38] examined whether baseline mortality risk, as a function of child age and site, modified azithromycin mortality-reduction effect in the Macrolide Oraux pour réduire les Décès avec un Oeil sur la Résistance (MORDOR) clinical trial. These authors used the Cox proportional hazards model with an interaction term. Three models were examined representing three sources for the baseline-risk covariate: two using sources external to MORDOR. All three models provided moderate evidence for the effect becoming stronger with increasing baseline mortality (P-values = 0.02, 0.02, and 0.07, respectively) at the rate of approximately 6% to 12%

additional mortality rate reduction per doubling of baseline mortality. MORDOR I trial showed that in Niger, azithromycin mass administration twice per year, for 2 years, resulted in 18% lower postnatal childhood mortality rate, than administration of placebo Keenan *et al*. [39] randomly assigned 594 communities to four twice-yearly distributions of either azithromycin or placebo to children aged 1 to 59 months. In MORDOR II, all these communities received two azithromycin distributions additional open-label. All-cause mortality was assessed twice yearly by census workers who were unaware of participants' original assignment. In the MORDOR II, the mean+SD azithromycin coverage was 91.3+7.2% in the communities that received twice-yearly azithromycin for the first time (i.e., had received placebo for 2 years in MORDOR I), and 92.0+6.6% in communities that received azithromycin for the third year (i.e. had received azithromycin for 2 years in MORDOR I). In MORDOR II, mortality was 24.0 per 1,000 person-years in communities that had originally received placebo in the fist and 22.1 to 26.3 per 1,000 person-years in those that had originally received azithromycin in the first year, with no significant difference between groups. In communities that had originally received placebo, mortality decreased by 13.3% when the communities that had originally received azithromycin and continued receiving it for an additional year, the difference in mortality rate between the third year and the first 2 years, was not significant. There was no evidence that the effect of azithromycin mass administration on child mortality in Niger waned in the third year of treatment. Childhood mortality rate decreased when communities, that had originally received placebo, received azithromycin.

Keenan *et al*. [40] hypothesized that azithromycin mass distribution, or a broad-spectrum antibiotic to preschool Children would reduce mortality rate in areas of sub-Saharan Africa that are currently far from meeting the Sustainable Development Goals of the United Nations. In this cluster-randomized trial, these authors assigned communities in Malawi, Niger, and Tanzania to four twice-yearly of either azithromycin mass distribution (approximately 20 mg/kg) or placebo. Children, aged 1 to 59 months, were identified in twice-yearly censuses and offered participation in the trial. Vital status was determined at subsequent censuses. The primary outcome was aggregate all-cause mortality; country-specific rates were assessed in prespecified subgroup analyses. A total of 1,533 communities underwent randomization, 190,238 children were identified in the census at baseline, and 323,302 person-years were monitored. The overall annual mortality rate was 14.6 deaths per 1,000 person-years in communities that received azithromycin (9.1 in Malawi, 22.5 in Niger, and 5.4 in Tanzania) and 16.5 deaths per 1,000 person-years in communities that received placebo (9.6 in Malawi, 27.5 in Niger, and 5.5 in Tanzania). Mortality was 13.5% lower in communities that received azithromycin than in communities that received placebo (P-value < 0.001); the mortality rate was lower 5.7% lower in Malawi, 18.1% lower in Nigeria, and 3.4% lower in Tanzania. Children, aged 1 to 5 months, had the greatest effect from azithromycin (24.9% lower mortality than with placebo). Serious adverse-events, occurring within a week after administration of azithromycin, or placebo were uncommon, and the rate did not differ significantly between groups. Evaluation of selection for azithromycin is ongoing. Among post-neonatal, preschool children, childhood mortality rate was lower in communities randomly assigned to receive azithromycin mass distribution

than in those assigned to placebo, with the largest effect seen in Niger. The odds ratio for childhood mortality rate in the intervention communities was 0.51 (P-value = 0.02; clustered logistic regression) compared with the control-group. In the treated communities, the estimated overall mortality rate during this period for children, aged 1 to 9 years, in the untreated group was 8.3 per 1000 person-year, while among the treated communities; the estimated overall mortality rate was 4.1 per 1000 person-years for children aged 1 to 9 years. A cluster-randomized trial demonstrated that azithromycin oral mass distribution reduced childhood mortality rate by 49.6% [41].

The relative risk of childhood mortality rate was then estimated using two approaches: an expert survey and a Bayesian analysis. The survey asked public health experts to estimate the true effect of mass azithromycin distribution on childhood mortality rate. The Bayesian estimation used the Trachoma Amelioration in Northern Amhara study's results and prior estimates of the efficacy of other effective population-level innervations. The experts believed that mass azithromycin reduces" childhood mortality. The Bayesian analysis estimated a relative risk of 0.71. Both estimates suggested that azithromycin may have a true mortality benefit, though of a smaller magnitude than found in the single available trial. Mass azithromycin distribution affected communities are a cornerstone of the WHO trachoma elimination program. Porco *et al*. [42] compared mortality rate of children, aged 1 to 9 years, in treated communities with those in untreated communities. These authors conducted a cluster-randomized mass azithromycin administration clinical trial for trachoma control. Forty-eight communities (known as subkebeles) were randomized into 1 of 3 treatment schedules (annual of all residents [15,902 children], biannual treatment of all residents [17,288 children], or quarterly treatment of children only [14.716 children]) or into 1 group for which treatment was delayed by 1 year (control, 18,498 children). Twelve subkebeles were randomized to each of 4 schedules with all children in each of 3 communities being eligible for treatment. Trial was conducted in a field setting in rural Ethiopia. Azithromycin single oral dose (adults, 1 gram; children, 20 mg/kg) was administered for ocular Chlamydia trachomatis infection. Azithromycin coverage levels for children, aged 1 to 9 years, exceeded 80% at all visits. The mean outcome was the community-specific mortality risk for children, aged 1 to 9 years, over 1 year course. Mortality rate was measured by enumerative census at baseline and again after 1 year. Comparison of the risk of mortality rate was a prespecified outcome for the clinical trial.

Azithromycin penetration into tonsils, adenoids, and middle ear effusion of children: Azithromycin concentrations were measured in tonsils of 56 children, treated with azithromycin 10 or 20 mg/kg, for 3 days [43]. Azithromycin levels in plasma and tonsil samples were determined up to 8.5 days after azithromycin last dose. Azithromycin 20 mg/kg regimen resulted in an improved azithromycin tonsillar distribution, suggesting the achiement of enhanced therapeutic concentrations at infective sites of the upper respiratory tract. Baschiera *et al*. [44] compared azithromycin concentrations in tonsils of children. Sixty-four children were treated with azithromycin oral dose of 10 or 20 mg/kg, and underwent surgical removal of tonsils. After azithromycin dose of 20 mg/kg, azithromycin tonsillar concentrations were higher than those obtained with azithromycin dose of 10 mg/kg up to 6.5

days after administration. Azithromycin highest concentration in tonsils was obtained on days 0.5 and 2.5 hours after administration. The present results suggest that increments of azithromycin dose might ensure enhanced therapeutic levels at infective sites of the upper respiratory tract. Vaudaux *et al*. [45] measured azithromycin concentrations in tonsillar and adenoid tissues of children aged, 1.6 to 7.5 years, who underwent surgical removal of tonsils and adenoids. Azithromycin 10 mg/kg oral suspension was administered to children for 3 days. The mean tissue to serum concentration ratios were 227+54, 547+184, and 956+355 after 1, 2, and 4 days of treatment, respectively. The present results show that azithromycin concentrations were consistently higher in tissue than in serum, and remained elevated up to 8 days, after the end of azithromycin dosing, supporting that azithromycin short-course (3-days, once-daily) is appropriate to combat infections of the upper respiratory tract. Azithromycin concentrations in middle ear effusion and plasma were measured in 29 children, aged 1 to 8 years, who were treated with azithromycin dose of 10 mg/kg [46]. Azitrhomycin penetrated middle ear effusions, and azithromycin concentration was approximately two orders of magnitude higher in tissue than in plasma, at 12, 24, and 48 hours after azithromycin dosing.

Azithromycin migration into breast-milk

In literature, there is only one study on azithromycin migration into breast-milk and it was reported by Salman *et al*. [47]. These authors characterized azithromycin infant intake and the associated potential benefits and risk. Azithromycin was administered at a dose of 2 gram to 20 women during labor. The median estimated absolute and relative cumulative azithromycin infant doses were 4.5 mg/kg and 15.7% of the maternal dose, respectively. Although some infants with bacterial infections may benefit from in azithromycin breast-milk, there is a risk of hypertrophic pyloric stenosis.

Azithromycin prevents illness in infants and children
Ureaplasma respiratory tract colonization is associated with bronchopulmonary dysplasia in preterm infants. Viscardi *et al*. [48] performed a nonrandomized, single-arm, open-label study of azithromycin pharmacokinetics and safety after azithromycin intravenous single-dose of 20 mg/kg in 13 mechanically ventilated infants, with a mean gestational age of 24 weeks, and postnatal ages of 0 to 6 days. Azithromycin AUC, over 24 hours at steady-state, divided by Ureaplasma MIC_{90} was 7.5 hours. Simulations suggest that, azithromycin 20 mg/kg for 3 days, maintains azithromycin concentrations > MIC_{50} of 1 µg/ml for Ureaplasma isolates for $\geq$ 96 hours. Azithromycin was well tolerated, drug-related adverse events were 1 of 6 (14.3%) in Ureaplasma-positive infants and 3 of 6 (50.0%) in Ureaplasma-negative infants who developed bronchopulmonary dysplasia. Azithromycin eradicated Ureaplasma in all treated infants. Simulations suggest that an azithromycin multiple-dose regimen may be efficacious for Ureaplasma clearance. Macrolides have been used for the treatment of Ureaplasma specie infection. Nair *et al*. [49] performed a meta-analysis to evaluate the use of macrolides in the prevention of bronchopulmonary dysplasia. Six studies, involving 469 preterm infants, were eligible for the analysis. Macrolides, when used prophylactically (4 studies) did not show significant reduction in bronchopulmonary dysplasia or death. Similarly, there was no statistically significant difference in bronchopulmonary dysplasia or death, when

macrolides were used in Ureaplasma-positive infants. However, azithromycin prophylactic therapy (3 studies) was associated with significant reduction of bronchopulmonary dysplasia, and death. This meta-analysis demonstrated that azithromycin prophylactic therapy was associated with statistically significant reduction of bronchopulmonary dysplasia and death in preterm infants. Many preschool children developed recurrent severe episodes of lower respiratory tract illness. Bacharier *et al*. [50] performed a randomized, double-blind, placebo-controlled, parallel-group trial conducted across 9 academic US medical centers. Children were randomly assigned to receive azithromycin (12 mg/kg once-daily for 5 days, N = 307) or matching placebo (N = 300) during 12- through 18-month period. A total of 92 children (azithromycin group, N = 35; placebo group, N = 57), experienced lower respiratory tract illness when children were treated with azithromycin. Azithromycin significantly reduced the progression risk of severe lover respiratory tract illness compared to placebo; absolute risk for lover respiratory tract illness: 0.05 for azithromycin, 0.08 for placebo; risk difference was 0.03. Induction of azithromycin-resistant organisms and severe adverse-events were infrequently observed. Among young children with histories of recurrent severe lover respiratory tract illness, azithromycin use reduced the likelihood of severe lover respiratory tract illness compared to placebo. Recurrent acute rhinosinusitis is characterized by acute rhinosinusitis multiple episodes between which symptom and signs resolved completely. Veskitkul *et al*. [51] evaluated azithromycin effect to prevent recurrent acute rhinosinusitis in children with nonallergic rhinitis. A randomized, double-blind, placebo-controlled study was conducted in nonallergic rhinitis children, aged 5 to 15 years, with recurrent acute rhinosinusitis. Azithromycin (5 mg/kg once-daily) for 3 days per week for 12 months or placebo was assigned to the study-group and the control-group, respectively.

Forty children were enrolled, 20 children were assigned randomly to receive azithromycin or placebo. IgG subclass and specific antibody deficiencies, were found in 83% and 2.5% (P-value = 0.0001), respectively. After 12 months, the number of rhinosinusitis episodes in the azithromycin group reduced significantly from 5 to 0.5 (P-value = 0.001) compared to placebo. The average visual analog scale score, and the average adjunctive medication score, in the azithromycin group (but not in placebo group), reduced significantly compared to baseline (2.2 ± 1.4 versus 5.4 ± 1.8) and (3.9 ± 1.7 versus 5.4 ± 1.1), respectively (P-value < 0.001). Azithromycin prophylaxis can reduce the number of rhinosinusitis episodes and medication score and improves nasal symptoms in nonallergic rhinitis children with recurrent acute rhinosinusitis.

Azithromycin pharmacokinetics in infants and children

Merchan *et al*. [52] refined azithromycin population pharmacokinetics in 15 preterm infants with a gestational age of 24 to 28 weeks and a postnatal age < 72 hours. Seven infants (46.7%) were culture and PCR positive for Ureaplasma specie infection, and 4 infants (26.7%) developed bronchopulmonary dysplasia. Infants were treated with 20 mg/kg azithromycin intravenously, once-daily, for 3 consecutive days. Blood samples (0.25 ml) were collected at 1, 2, 4, 6, 8, 25, 48, 96, 120, and 168 hours after azithromycin first dose. Plasma was separated from blood and used for azithromycin concentration determination. Azithromycin plasma concentration versus time data were compiled and analyzed using the nonlinear mixed-effects modeling software NONMEN 7.2. Table 1 summarizes azithromycin pharmacokinetic parameters. Jacobs *et al*. [53] characterized azithromycin pharmacokinetics and tolerance after azithromycin single intravenous dose of 10 mg/kg (maximum 500 mg), infused via syringe pump, in children aged 0.5 to 2

Table 1. Azithromycin parameter estimates of the population model in 15 infants with a gestational age of 24 to 28 weeks and a postnatal age < 72 hours, by Merchan et al. [52]

Parameter	Estimate (% relative SE)	% Intersubjet variability
Clearance (L/h/kg$^{0.75}$)	0.15 (10)	58.1 (25)
Central distribution volume (L/kg)	1.88 (11)	78.2 (41)
Intercompamental clearance (L/h.kg$^{0.75}$)	1.79 (10)	64.3 (37)
Peripheral distribution volume (L/kg)	13.00 (12)	78.1 (30)
Residual error (%)	28 (24)	---

Table 2. Azithromycin pharmacokinetic parameters were measured in infants and children*. The figures are the mean$\pm$SD, by Jacobs et al. [53]

Age (years)	N	Dose mg	mg/kg	AUC$_{0-72}$ (μg.h/ml)	AUC$_{0-infinite}$ (μg.h/ml)	Cmax (μg/ml)	Clearance (ml/min/kg)	Distribution volume (L/kg)	Half-life (hours)
0.5 – 2	8	101	10	9.5 ± 1.9 (3)§	9.5 ± 1.9 (3)	2.2 ± 0.9	16.4 ± 4.9 (5)	29.2 ± 18.3 (5)	83.0 ± 61.0 (2)
>2 - < 6	8	158	10	7.7 ± 1.5 (7)	7.7 ± 1.5 (7)	2.3 ± 0.7	17.7 ± 4.9 (7)	45.5 ± 15.9 (7)	62.6 ± 14.4 (7)
6 - < 12	8	380	9.8	8.4 ± 2.3	8.4 ± 2.3	2.6 ± 0.6	16.0 ± 7.0	52.2 ± 22.9	75.6 ± 43.4
12 - <16	8	488	8.0	8.0 ± 1.2	8.0 ± 1.2	2.6 ± 0.9	11.9 ± 3.8	44.2 ± 14.3	65.2 ± 31.9
P-value	---	---	---	0.504	0.0752	0.6519	0.1837	0.1963	0.4292

*For comparisons of each parameters by one-way analysis of variance (ANOVA). §Numbers in parenthesis = number of children with evaluable data. Clearance and distribution volume were corrected by the body weight

Table 3. Azithromycin pharmacokinetic parameters were measured in 48 children aged 6 months to 16 years. Azitrhromycin once-daily oral dose was 12 mg/kg. The figures are the mean$\pm$SD, by Stevens et al. [54]

	Cmax (μg/L)	C$_{24-hours}$ (μg/L)	Tmax (hours)	Clearance* (L/h/kg)	Half-life (hours)
Single dose (N = 14)	364 ± 166	38 ± 28	2.4 ± 1.2	4.46 ± 3.66	49.0 ± 32.6
Multiple dose (N = 9)	4.27 ± 273	56 ± 25	2.4 ± 1.1	5.41 ± 3.62	64.1 ± 42.9
P-value	0.0293	0.1322	0.9999	0.5206	0.5484
Children with cancer (N =11)	235 ± 110	25 ± 18	2.6 ± 1.1	4.57 ± 2.53	53.0 ± 41.0
Children without Cancer (N = 12)	360 ± 198	39 ± 29	2.3 ± 1.1	5.07 ± 4.45	55.8 ± 34.0
P-value	0.0693	0.1836	0.5206	0.7469	0.8597

C$_{24 hours}$ = azithromycin serum concentration at the end of 24-hours dosing interval.*Azithromycin oral clearance was corrected for body weight. Statistical analysis was performed by unpaired t test.

Table 4. Comparison of azithromycin pharmacokinetic parameters in HIV-infected and not-HIV-infected children aged 4 to 13 years. The figures are the mean±SD and (range), by NGO et al. [55]

Group and infection (regimen)	Number of children	Cmax (ng/ml)	Css (ng/ml)	Tmax (hours)	AUC_{0-24} (ng.h/ml)	Clearance/F (L/h/kg)
		Azithromycin pharmacokinetic parameters are the mean±SD and (range)				
HIV-infected children (5 mg/kg once-daily)	7	230±130 (48 - 447)	91±66 (28 - 222)	2.0±1.0	2,632±1,632 (699 - 5,561)	3.04±1.96 (0.93 - 6.95)
*Not-HIV-infected children	13	224±120 (65 - 496)	77±27 (40 - 110)	1.8±04	1,841±651 (651 - 2,634)	3.03±1.28 (1.82 - 6.10)
P-value	---	0.9186	0.5062	0.5282	0.3487	0.9891

*children, suffering from acute otitis media, received azithromycin 10 mg/kg, on day 1, and 5 mg/kg on days 2 to 5. Css = azithromicin concentration at steady-state. Clearance was corrected for bioavailability and body weight. Statistical analysis was performed by unpaired t test.

years N = 8), > 2 to > 6 years (N =8), 6 to < 12 years (N = 8), and 12 to < 16 years (N = 8). Blood samples (0.75 ml) were collected at 0 hour (predose): and 1, 2, 6, 24, 48, 72, 96, 120, and between 144 and 168 hours after azithromycin dosing. Serum was separated from blood and used for azithromycin concentration determination. Pharmacokinetic analysis was conducted with WinNonlin (version 3.2). Table 2 summarizes azithromycin kinetic parameters. Stevens *et al.* [54] characterized azithromycin disposition in 46 children aged 6 months to 16 years. Azithromycin was administered orally at a dose of 12 mg/kg once-daily for 5 consecutive days. Blood specimens were collected at time 0 (predose), and 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours after azithromycin dosing in both the single- and multiple-dose groups. Additional samples were scheduled in the multiple-dose group at 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours after the azithromycin final dose on day 5. Serum was separated from blood and used for azithromycin concentration determination. Azithromycin two-compartment absorption model was fit using weighted nonlinear least squares regression (ADAPT II modeling software). Table 3 shows azithromycin pharmacokinetic parameters. Cmax is significantly (P-value = 0.0293) higher after multiple-dose than single-dose. The other parameters are not significantly different after single-dose and multiple-doses. Children infected with HIV have an increased risk of serious and recurrent infection, among which the most common is Pneumocystis carinii pneumonia. Azithromycin co-administered with atovaquone is used in the prophylaxis of multiple opportunistic infections. NGO *et al.* [55] evaluated azithromycin pharmacokinetics in HIV-infected and not-HIV-infected children aged 4 to 13 years. HIV-infected children (N = 7) were treated with oral mass azithromycin administration 5 mg/kg, once-daily orally, for 15 consecutive days, and not-HIV-infected children (N = 13), suffering from acute otitis media, received 10 mg/kg azithromycin, orally, on day 1, and 5 mg/kg, on days 2 to 5. Table 4 summarizes azithromycin pharmacokinetic parameters in HIV-infected and not-HIV-infected children.

Azithromycin trials in infants and children

McCallum *et al.* [56] performed an international, double-blind, randomized, placebo-controlled trial to determine if azithromycin 3 weeks treatment improved clinical outcomes in Indigenous infants with bronchiolitis. Two hundred and nineteen infants, aged ≤ 24 months, were enrolled from three centers and received either azithromycin 30 mg/kg once-weekly for 3 weeks (N = 106), or placebo (N = 113). No significant between-group differences were found for hospital length of stay, time receiving oxygen, day-21 symptoms, or rehospitalisation within 6 months. Azithromycin reduced nasopharyngeal bacterial carriage (P-value < 0.001), but had

no significant effect upon virus detection rates. Despite reducing nasopharyngeal bacterial carriage, azithromycin three large once-weekly doses did not confer any benefit over placebo during bronchiolitis illness or 6 months post hospitalization. Azithromycin should not be used routinely to treat infants hospitalized with bronchiolitis.

Pinto *et al.* [57] tested the hypothesis that azithromycin reduces the length of hospitalization and oxygen requirement in infants with acute bronchiolitis. These authors performed a randomized, double-blind, placebo-controlled trial in 184 hospitalized infants, aged < 12 months, with acute bronchiolitis and were recruited in 2 hospitals. Infants were randomized to receive either oral azithromycin (N = 88) or placebo (N = 96), for 7 consecutive days. Baseline clinical characteristics and viral identification were not different in two groups. Virus was detected in 112 infants (60.9%), and 92% infants were positive for respiratory syncytial virus. Azithromycin did not reduce the hospitalization length or oxygen requirement. Azithromycin therapy should not be given for acute bronchiolitis because it provides no benefit and overuse increases overall antibiotic resistance. Globally, bronchiolitis is the most common form of acute lower respiratory infection during infancy. Compared to non-Indigenous, Indigenous Australian infants, have greater bacterial density in their upper airways and more severe bronchiolitis episodes. Chang *et al.* [58] tested the hypothesis that anti-microbial and anti-inflammatory properties of azithromycin improve the clinical outcomes of Indigenous Australian infants hospitalized with bronchiolitis. These authors conducted a dual centre, randomized, double-blind, placebo-controlled, parallel-group trial in northern Australia. Two hundred Indigenous infants, aged ≤ 24 months, with a clinical diagnosis of bronchiolitis received either 30 mg/kg per dose azithromycin or placebo once-weekly for three doses. Nasopharyngeal swabs were collected twice once-daily. Azithromycin, in Indigenous infants with bronchiolitis, is efficacious in reducing the morbidity of bronchiolitis. The intervention would lead to improve short-term (and possibly long-term) health benefits.

Bacteria and viruses are equally associated with the risk of acute episodes of asthma-like symptoms in young children, suggesting that antibiotics are potential treatment for such episodes. A randomized, double-blind, placebo-controlled trial was conducted in 158 children, aged 1 to 3 years, with recurred asthma-like symptoms. Stokholm *et al.* [59] assessed azithromycin effect on the duration of respiratory episodes in these children, hypothesizing that it reduces the duration of the symptomatic period. The mean duration of the episode after treatment was 3.4 days for children (N = 79) receiving azithromycin compared to 7.7 days for children (N = 79), (P-value < 0.0001). The size effect increased with early initiation

of treatment, showing a reduction of 83% if treatment was initiated before day 6 of the episode compared to 36% if initiated on, or after, day 6 (P-value < 0.0001). Azithromycin reduced the duration of episodes of asthma-like symptoms in young children, suggesting that azithromycin could have a role in acute management of exacerbations. Early target attainment is the key factor influencing the outcome of antimicrobial therapy. Liu *et al*. [60] evaluated azithromycin concentration relationship, during the first 24 to 48 hours of therapy, and the clinical outcome in order to optimize antimicrobial therapy. Forty-four children, aged 5.25 ± 3.72 years, with lower respiratory tract infections, received azithromycin monotherapy. Azithromycin concentration > 0.25 mg/l had a more significant improvement in antibacterial efficacy, compared to trough concentration $\leq$ 0.25 mg/l (N = 36). No azithromycin-related adverse-events were observed. The present findings show azithromycin clinical benefits at early treatment. A target trough azithromycin concentration of 0.25 mg/l, in the first 24 to 48 hours of hospitalization, was required to ensure better antibacterial efficacy.

Valery *et al* [61] conducted a multicentre, randomized, double-blind, placebo-controlled clinical trial in children, aged 1 to 8 years, diagnosed with bronchiectasis (or probable bronchiectasis) having at least one episode of pulmonary exacerbation in the last 12 months. Children received either 30 mg/kg once-weekly azithromycin or placebo for 12 to 24 months from study entry. This trial demonstrated that azithromycin is efficacious in reducing the number of pulmonary exacerbations in children. Antibiotics are frequently used to treat wheezing children. Macrolides may be effective in treating bronchiolitis and asthma. Mandhane *et al*. [62] completed an azithromycin prospective, double-blind, randomized, placebo-control trial among 300 wheezing preschool children aged 12 to 60 months. Children were randomized to receive either azithromycin or placebo for 5 consecutive days. Of 300 children, 222 (74.0%) were analyzed for resolution of respiratory symptoms after treatment initiation, and 169 children (56.3%) received short-acting β-Agonists, during 21 consecutive days at follow-up, for the following 6 months. Children who received azithromycin had a 0.91 hazard ratio for time to six-month exacerbation compared to placebo (P-value = 0.65). A pre-determined subgroup analysis showed no differences in outcomes for children with their first or repeat episodes of wheezing. There was no significant difference in the proportion of children experiencing an adverse event. Azithromycin neither reduced duration of respiratory symptoms, nor time to respiratory exacerbations, in the following 6 months after treatment among wheezing preschool children. There were no statistically significant different effects among children with either first-time or prior wheezing.

Azithromycin repeated oral administration targeted only to children who have proven affectivity in reducing the ocular Chlamydia that causes trachoma. Oldenburg *et al*. [63] assessed whether an enhanced coverage target of at least 90% children is superior to the WHO recommendation of at least 80% of children. Twenty-four trachoma-endemic communities in Matamèye, Niger, were randomized to once-daily azithromycin administration, for at least 80% coverage, or up to 4 consecutive days of treatment and > 90% coverage of children, aged > 15 years, were monitored for ocular Chlamydia infection by PCR every 6 months for 36 months in children, at baseline, and 36 months in adults. Ocular

Chlamydia prevalence in children decreased from 24.9% to 4.4% (P-value < 0.001) in the enhanced coverage arm. Enhanced coverage reduced ocular Chlamydia prevalence in children more quickly over time compared to standard (P-value = 0.04). There was no difference between arms at 36 months and no infection was detected in adults at this time. Increasing azithromycin coverage among children from 80% to 90% may yield only short term improvements for trachoma control programs. Targeting treatment to children alone may be sufficient for trachoma control in this setting. McCarty [64] performed a multicenter, open-label trial to evaluate oral azithromycin efficacy and safety once-daily for 5 consecutive days for treatment of clinically and bacteriologically established acute otitis media. Two hundred children with acute otitis media from 10 US centers, received oral 10 mg/kg azithromycin and were treated on day 1, followed by 5 mg/kg once-daily for the next 4 days. Tympanocentesis and subsequent culture of middle ear effusion were performed at baseline. Analysis of clinical efficacy in children 11 days after the initiation of therapy showed that the rate of satisfactory responses (cured of improved) ranged from 79.6% to 82.4% in children infected with Haemophilus influenzae, or Moraxella catarrhalis. Satisfactory clinical response at day 30 was reported in 70% of children, and eradication of Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis was presumed in 64% to 73%. Relapses occurred in 14% of children. Among the treated children 8.5% reported mild side effects. Azithromycin is an effective, safe, and well tolerated treatment for children with acute otitis media.

Sawires *et al*. [65] compared azithromycin immunomodulatory effects combined with steroid therapy, with that of steroid alone, in children with steroid-dependent nephrotic syndrome. Fifty-seven children with steroid-depended nephrotic syndrome were enrolled in a multicenter, randomized placebo-control trial. Children were classified into two groups: group A (intervention-group, N = 29) and group B (control-group, N = 28). After achievement of remission with full-dose once-daily steroids, children in group A received azithromycin in conjunction with steroids which was tapered gradually, while children in group B received steroids alone. Urine protein creatinine ratio and TNF-α were measured at different points of follow-up throughout the study period (5 months after achieving remission). After achievement of remission by full-dose steroids, there were significant differences of TNF-α between two groups after 1-, 3-, and 5-months of follow-up (P-values 0.001, 0.003, and 0.001, respectively). Also, there was significant difference of TNF-α in both intervention and control-groups after exclusion of the relapsed cases at 3-, and 5-months of follow-up (P-values = 0.031, and = 0.03, respectively). There was significant difference between both groups after 5-months of follow-up as regards the number of relapsed children (group A = 4, group B = 11, P-value = 0.015). Azithromycin was capable of reducing serum TNF-α which is one of the inflammatory cytokines implicated in the pathogenesis of nephrotic syndrome. Children with primary nephrotic syndrome were treated with azithromycin combined with prednisone (intervention group, N = 106) and with prednisone alone (control-group, N= 105) for 6 months. Azithromycin, 10 mg/kg once-daily, was administered for 3 consecutive days [66]. The median duration before remission was 6 days in the intervention group, and 9 day in the control-group (P-value < 0.0001) at the end of treatment. Relapse rate differed among the groups at 3 months (11.6% versus 21.4%, P-value = 0.049). No difference in relapse rate was observed

between the two groups within 4 to 6 months and at 6 months. After 4 weeks of treatment, steroid resistance occurred in 1 out 95 (1.05%) children in the intervention group, and in 10 out 98 (10.2%) children in the control-group (P-value =0.006). After 8 weeks of treatment, no difference was found in steroid resistance between two groups. During follow-up at 6 months, no difference was exhibited by two groups on frequent relapse rate.

Bacterial resistance to azithromycin in children

In literature, there is only one study about bacterial resistance to azithromycin in children and was reported by Coles *et al.* [67], and no study is available in infants. Emerging evidence suggests that azithromycin mass distribution for trachoma treatment may increase circulation of macrolide resistance in bacteria associated with severe paediatric infections in treated communities. Coles *et al.* [67] examined the effect of azithromycin on nasopharyngeal carriage of antibiotic-resistant Streptococcus pneumoniae, among 1,015 young children, living in rural Tanzania. Azithromycin single-oral-dose was administered to 4 of 8 communities where trachoma prevalence was ≥ 10%. Isolates were tested for azithromycin and commonly used antibiotics. Susceptibility to azithromycin was tested using disk diffusion and E-test. The proportion of antibiotic-resistant Streptococcus pneumoniae was tested at baseline, and again at 1, 3, and 6 months, after treatment. Azithromycin-resistant proportion in isolates was similar between groups at baseline; however, this proportion was greater in azithromycin group (81.9% versus 46.9%, P-value < 0.001). Odds of azithromycin-resistant carriage were 5-folds greater in the azithromycin group. The proportion clinically-resistant isolates to azithromycin (MIC ≥ 16 µg/ml) was also significantly greater in azithromycin group at 6 months. Azithromycin single oral dose for trachoma treatment was associated with increased circulation of macrolide-resistant Streptococcus pneumoniae, among young children at 6 months following treatment. It is crucial that changes in antibiotic resistance patterns, and their clinical significance, in the treatment of severe paediatric infections be assessed in azithromycin trials in future.

DISCUSSION

Azithromycin is the most active macrolide antibiotic. It is an azalide antibiotic. This antibiotic inhibits protein synthesis by binding reversibly to 50S ribosomal subunity [3]. Azithromycin is bacteriastatic, but may be bactericidal at high concentrations. This drug is used for the treatment of respiratory tract infections caused by common pathogens of community-acquired pneumoniae. Azithromycin is active against streptococci, gram-positive bacilli, Clostridium perfringens, Corynebacterium diphtheria, Listeria monocytogenes, Haemophilus influenzae, Neisseria meningitis, Neisseria gonorrhoea, Bordetella pertussis, Campylobacter jejuni, Mycoplasma pneumoniae, Legionella pneumophila, and Vibrio cholera [3]. Azithromycin is efficacy in infants and children [4-13]. For treatment of bacteria conjunctivitis or trachoma, azithromycin 1.5% eye drops is given for 2 to 5 consecutive days [10-12]. The rationale for single and high dose treatment regimen with azithromycin was suggested by Gordon and Blumer [14]. Different authors suggested giving azithromycin oral daily dose of 10 to 30 mg/kg for 2 to 5 consecutive days to children [15-23]. The azithromycin effects were investigated by different authors

[27-35]. This drug changes the intestinal microbiota, reduces IL-6 and IL-8 production, the risk of acute lower respiratory infection, infection symptoms and hospitalization stay, ocular Chlamydia trachomatis infection, and it is used to treat trachoma. Azithromycin has limited side-effects in children [36, 37]. This antibiotic reduces the mortality rate [38-42]. Azithromycin reaches therapeutic concentrations in tonsils and adenoids, and in these tissues, azithromycin concentrations are several times higher than in plasma [43-46]. Azithromycin migration into the breast-milk is poor, and little dose is transferred to breast feeding newborn [47]. This drug prevents illness in infants and children [48-51]. Azithromycin pharmacokinetics have been extensively investigated in infants and children [52-55]. In infants, azithromycin mean clearance and distribution volume are 0.15 L/h/kg and 13 L/kg, respectively [52]. After oral administration to children, Tmax is 2 hours, and the mean Cmax, $AUC_{0-24 \text{ hours}}$, and clearance are 230 ng/ml, 1,841 ng.h/ml, and 30.3 L/h/kg, respectively [55]. Azithromycin trials have been extensively studied in infants and children [56-66]. Only one study of bacteria-resistant to azithromycin has been reported by Coles *et al.* [67] and no data are available in infants. Nakajima [68] described the resistance mechanisms of macrolides: (1) drug efflux by an active pump mechanism, (2) ribosomal protection by inducible or constitutive production of methylase enzymes, which modify the ribosomal target and decrease drug binding, (3) macrolide hydrolysis, by esterase produced by Enterobacteriacae, and (4) chromosomal mutation that alter a 50S ribosomal protein (in Bacillus subtilis, Campylobacter species, mycobacteria, and gram-positive cocci). In conclusion, azithromycin is the most active macrolide antibiotic and is used to treat infection respiratory diseases. This antibiotic inhibits protein synthesis by binding reversibly to 50S ribosomal subunity. Azithromycin is bacteriastatic, but may be bactericidal, at high concentrations. Azithromycin is active against streptococci, gram-positive bacilli, Clostridium perfringens, Corynebacterium diphtheria, Listeria monocytogenes, Haemophilus influenzae, Neisseria meningitis, Neisseria gonorrhoea, Bordetella pertussis, Campylobacter jejuni, Mycoplasma pneumoniae, Legionella pneumophila, and Vibrio cholera. Much of azithromycin undergoes biliary excretion, and the rest is inactivated in the liver. In infants, azithromycin dose is 10 mg/kg for treating and preventing diseases. In children, azithromycin doses are 10 to 30 mg/kg. Azithromycin has a long half-life, of approximately 80 hours, and thus it is administered once-daily. Azithromycin 1.15% eye drops is given for 2 to 5 consecutive days treat bacterial conjunctivitis or trachoma. This antibiotic is efficacy and safety in infants and children. Azithromycin reduces the mortality rate, and prevents illness in infants and children. Azithromycin trials have been extensively investigated in infants and children. Azithromycin pharmacokinetics has been extensively performed in infants and children. In infants, the clearance and the distribution volume are 0.15 L/h/kg, and 13 L/kg, respectively. In children, Tmax is 2 hours, and the mean Cmax, $AUC_{0-24 \text{ hours}}$ and, clearance, are 230 ng/ml, 1,841 ng.h/ml, and 3.03 L/h/kg, respectively. Little is known about bacteria-resistance in children and no data are available in infants.

Acknowledgments

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