Additional file S2: Characteristics of included studies

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **S. No** | **Study ID**  | **Study design** | **Study setting and period** | **Transmission**  | **Follow up** | **Subjects** | **Patient important outcome**  | **DHA-PQ** | **AL** |
| **Number of participants** | **Inclusion age** |
| **DHA-PQ** | **AL** |  |  |  |  |
| 1 | **Kamya-2007-UGA [97]** | Single-blind, RCT | Rural health center, March,2006-July, 2006 | High transmission | 42 days | 253 | 256 | 6 months-10 years | Vomiting  | 65 | 65 |
|  | Diarrhea | 25 | 19 |
|  Anorexia | 90 | 91 |
| Abdominal pain | 19 | 20 |
| weakness/malaise | 85 | 103 |
| Cough | 136 | 133 |
| Coryza | 127 | 121 |
| Pruritus | 14 | 22 |
|  SAE | 4 | 2 |
| 2 | **Zongo-2007-BNF** [98] | Single blind RCT | Government health dispensaries, August 2006- January 2007 | High transmission | 42 days | 196 | 197 | 6 months-10 years | Early vomiting | 7 | 3 |
|  | Vomiting | 20 | 27 |
| Diarrhea | 14 | 13 |
| Anorexia | 8 | 6 |
| Abdominal pain | 10 | 21 |
| Cough | 49 | 52 |
| Weakness/Malaise | 5 | 3 |
| Pruritus  | 5 | 11 |
| Headache | 11 | 22 |
| 3 | **Mens-2008-KEN** [111] | Open label RCT | Health center, Apr 2007 to Jul 2007 | High transmission | 28 days | 73 | 73 | 6 months-12 years | Headache  | 43 | 39 |
|  | Abdominal pain  | 25 | 26 |
| Weakness  | 19 | 30 |
| Anorexia  | 8 | 10 |
| Diarrhea  | 9 | 7 |
| Cough  | 16 | 17 |
| Vomiting  | 11 | 9 |
| Pruritus  | 4 | 3 |
| SAE | 1 | 0 |
| 4 | **Yeka-2008-UGA [99]** | Single-blind, RCT | Health center, August 2006- April 2007 | N/A | 42 days | 234 | 227 | 6 months-10 years | Vomiting  | 35 | 35 |
|  | Diarrhea | 26 | 23 |
| Anorexia | 47 | 49 |
| Abdominal pain | 17 | 24 |
| Weakness/malaise | 28 | 27 |
| Cough | 164 | 150 |
| Coryza | 159 | 150 |
| Pruritus | 8 | 3 |
| SAE | 5 | 2 |
| 5 | **Bassat-2009-AFR** [101] | Open-label, RCT  | Four rural sites and one peri-urban site,August 2005 and July 2006. | Mesoendemic | 1038 | 510 | 6–59 months  | Early vomiting  | 22 | 4 |
|  | Vomiting  | 71 | 35 |
| Splenomegaly | 41 | 19 |
| Hepatomegaly | 6 | 3 |
| 5 Prolonged QTc interval (Fridericia’s correction) | 2 | 1 |
| Electrocardiogram QT prolonged | 26 | 13 |
| Urticarial | 1 | 2 |
| Hypersensitivity  | 2 | 1 |
| Neutropenia | 18 | 12 |
| Alanine aminotransferase increased  | 20 | 19 |
| Electrocardiogram QT prolonged  | 26 | 13 |
| SAE | 18 | 5 |
| 6 | **Arinaitwe-2009-UGA** [100] | Open-label RCT | Local antenatal clinics in Tororo, August 2007-July 2008 | High transmission  | 63 days | 119 | 111 | 6 weeks- 12 months | Vomiting  | 23 | 20 |
|  | Diarrhea | 79 | 86 |
| Anorexia | 3 | 0 |
| Weakness | 1 | 0 |
| Cough | 177 | 153 |
| Pruritus | 0 | 0 |
|  SAE | 3 | 1 |
| 7 | **Borrmann-2011 –KEN [109]** | Not described, RCT | Pingilikani study site,September 2005 to April 2008 | Perennial transmission | 84 days | 233 | 241 | 6–59 months | Early vomiting  | 7 | 4 |
| 8 | **Nambozi-2011- ZAM** [37] | Open-label, RCT | Peri-urban health centers,September 2005 and May 2006  | Mesoendemic | 42 days | 203 | 101 | 6-59 months | Anorexia | 14 | 8 |
|  | Cough  | 42 | 15 |
| Diarrhea  | 14 | 4 |
| Fever  | 24 | 14 |
| Respiratory tract Infection  | 22 | 9 |
| Vomiting  | 5 | 4 |
| SAE | 4 | 3 |
| 9 | **4ABC-2011-AFR** [80] | Open label, RCT | Rural, urban or health facilities, 9 July 2007 and 19 June 2009 | Mesoendemic, perennial and high transmission | 63 days | 1475 | 1226 | 6 to 59 months | Death up to day 63 | 1 | 3 |
|  | Hepatomegaly  | 5 | 8 |
| Splenomegaly  | 88 | 80 |
| Anemia  | 141 | 38 |
| Diarrhea  | 166 | 142 |
| Vomiting  | 123 | 102 |
| Pyrexia  | 371 | 339 |
| Hgb decrease  | 103 | 83 |
| Anorexia  | 130 | 121 |
| Cough  | 470 | 387 |
| ALAT above normal range at day 0  | 10 | 16 |
| ALAT above normal range at day 7 | 3 | 4 |
| ALAT above normal range at day 28 | 4 | 1 |
| Creatinine above normal range at day 0 | 2 | 0 |
| Creatinine above normal range at day 7 | 0 | 0 |
| Creatinine above normal range at day 28 | 0 | 2 |
| SAE | 10 | 6 |
| 10 | **Agarwal -2013-KEN [35]** | An open label RCT | District hospital, October 2010 to August 2011 | High transmission | 42 days | 137 | 137 | 6 to 59 months | Early vomiting  | 7 | 5 |
|  | SAE | 1 | 2 |
| 11 | **Ogutu-2014-KEN** [42] | Open-label, RCT | Nyando District hospital, March, 2010- 30 November, 2011 | Not described | 42 days | 227 | 227 | 6 to 59 months | Cough  | 40 | 37 |
|  | Anemia  | 8 | 10 |
| Fever  | 14 | 7 |
| Tinea capitis  | 12 | 10 |
| Rhinitis  | 13 | 4 |
| Gastroenteritis | 5 | 9 |
| Loss of appetite  | 6 | 3 |
| Otitis media  | 5 | 7 |
| 12 | **Onyamboko-2014-DRC** [103] | Open label, RCT | Urban district of Kinshasa (DRC) (Hospitals), September 2011 and November 2012 | Intense and perennial | 42 days | 228 | 228 | 3 to 59 months | Early vomiting | 21 | 5 |
|  | Vomiting  | 17 | 2 |
| 173 | **Kakuru-2014-UGA** [110] | Not described, RCT | District Hospital, August 2007 and April 2008 | High transmission  | 28 days | 21 | 22 | 6 weeks -12 months | Vomiting  | 8 | 18 |
|  | Diarrhea | 27 | 23 |
| Anorexia | 6 | 4 |
| weakness/malaise | 2 | 2 |
| Cough | 64 | 74 |
| 14 | **Nji-2015-CAM** [106] | Open-label, RCT | Two distinct ecological regions,2009 to April 2013 | Low to moderate transmission | 42 days | 288 | 144 | 6 months-10 years | Abdominal pain  | 13 | 5 |
|  |  |  |  |
| Anorexia | 12 | 1 |
| Diarrhea  | 9 | 4 |
| Vomiting  | 27 | 8 |
| Fatigue | 4 | 3 |
| Fever | 3 | 2 |
| Cough  | 18 | 9 |
| Joint pain  | 2 | 2 |
| Rash | 16 | 4 |
| SAE | 0 | 1 |
| 15 | **Ursing-2016-GUB** [107] | Open-label, RCT | Bandimand Belem Health Centers, November 2012 and July 2015 | Low to high transmission  | 42 days  | 157 | 155 | 6 months-15 years | Early vomiting  | 7 | 4 |
|  |  |  |
| 16 | **Grandesso-2018-NIG** [104] | Open label, RCT | Health center,7 June 2013 and 22 September 2014 | Not reported | 42 days | 221 | 221 | 6–59 months |  |  |  |
| Early vomiting  | 1 | 0 |
|  | Fever  | 94 | 94 |
| Cough | 36 | 22 |
| Rhinorrhea | 27 | 17 |
| Diarrhea  | 14 | 15 |
| Conjunctivitis  | 7 | 15 |
| Pyoderma  | 6 | 6 |
| Vomiting  | 6 | 5 |
| Anorexia  | 4 | 1 |
| Abdominal pain  | 0 | 1 |
| Hepatomegaly  | 1 | 0 |
| Splenomegaly  | 2 | 1 |
| Another AE | 40 | 45 |
| SAE | 2 | 1 |
| Early vomiting  | 1 | 2 |
| 17 | **Yeka-2019-UGA** [105] | Single-blind RCT | Health center and Hospital, October 2015-December, 2016 | High transmission  | 42 days | 299 | 300 | 6-59 months | Vomiting  | 56 | 61 |
| Diarrhea | 155 | 114 |
| Anorexia | 12 | 3 |
|  | Abdominal pain | 41 | 45 |  |  |  |  |  | Cough | 233 | 203 |
| Headaches | 18 | 24 |  |  |  |  |  | Pallor | 22 | 13 |
| weakness/malaise | 42 | 33 |  |  |  |  |  | Skin rash | 56 | 42 |
| Cough | 233 | 203 |  |  |  |  |  | Pruritus | 24 | 16 |
| Pallor | 22 | 13 |  |  |  |  |  |  SAE | 6 | 6 |
| Skin rash | 56 | 42 |
| Pruritus | 24 | 16 |
|  SAE | 6 | 6 |
| 18 | **Gansane-2021-BNF** [73] | Open label, RCT | Primary health facility and district hospital, November 2017 to September 2018 | Moderate to high transmission  | 42 days | 360 | 360 | 6-59 months | Itchiness  | 0 | 1 |
| Otitis media  | 0 | 1 |
| Cough  | 17 | 21 |
|  | Abdominal pain  | 13 | 4 |  |  |  |  |  | Vomiting  | 33 | 54 |
| Skin rash  | 3 | 2 |  |  |  |  |  | SAE | 0 | 1 |
| Furunculosis  | 1 | 0 |
| Vomiting  | 33 | 54 |
| SAE | 0 | 1 |