Type: Invited Presentation

Final Abstract Number: 12.003
Session: Malaria - Hot Topics
Date: Thursday, March 3, 2016
Time: 15:45-17:45
Room: Hall 6

Malaria prevention strategies

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Abstract: Substantial gains have been made in the control of malaria; in many regions malaria has reached historically low prevalence. Still the global malaria burden remains unacceptably high and the spread of antimalarial and insecticide resistance threatens a resurgence.

A number of malaria prevention strategies have been evaluated since the turn of the century. Intermittent presumptive therapy (IPT) held initially great promise but has ultimately disappointed and has not been implemented. Seasonal malaria chemoprophylaxis has evolved from IPT and restricts presumptive therapy to the months with the highest malaria incidence. This strategy is finding increasing acceptance. Malaria vaccines have a long history but have yet to result in the roll-out of a safe, highly protective, long lasting product. The last candidate, RTS,S/AS01 held great hope but also has ultimately disappointed and the inclusion in the expanded program of immunisations has not been recommended at the end of last year. There are new vaccine candidates on the horizon but there is no reasonable hope that a vaccine can be used to prevent malaria on a population level in the near future.

The ultimate hope to prevent malaria has to be the elimination of malaria. While considered unrealistic until recently a range of novel strategies aim now at the elimination of malaria.

http://dx.doi.org/10.1016/j.ijid.2016.02.069

Type: Invited Presentation

Final Abstract Number: 12.004
Session: Malaria - Hot Topics
Date: Thursday, March 3, 2016
Time: 15:45-17:45
Room: Hall 6

Management of relapsing Plasmodium vivax malaria

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Abstract: *Plasmodium vivax (P.vivax)* endemicity covers large and diverse geographical regions. Transmission is lower than *Plasmodium falciparum*, however, relapses caused by hypnozoite forms increase the number of infections and sustain transmission. Resistance against chloroquine is increasing and assessment of efficacy is confounded because recrudescence, relapse and reinfection cannot be distinguished reliably. Background incidence of new *P.vivax* infections are needed for comparing efficacy of treatment regimens. Primaquine is the only currently widely available treatment effective against relapses (hypnozoite stage) of *P.vivax* and assessment of its radical curative efficacy using currently recommended dosing is required. Optimising primaquine regimens may be necessary to improve adherence in some populations. The assurance of primaquine safety in persons with glucose-6-phosphate-dehydrogenase (G6PD) deficiency is essential if deployed universally for malaria elimination.

Methods: Between March 2010 and July 2015 a series of studies were conducted in northwestern Thailand along the Myanmar border. In the first study, a rolling cohort of 200 healthy subjects with a history of *P.vivax* were given primaquine for radical cure and followed until a new *P.vivax* infection. The overall incidence of new *P.vivax* infection was 0.13 infections per person-year. In a parallel study 650 subjects with *P.vivax* malaria were randomized to artesunate, chloroquine or chloroquine+primaquine (only G6PD normal subjects) and followed for one year. At least one recurrence with *P.vivax* occurred in over 70% subjects in non-primaquine arms and in 18% subjects taking primaquine. The burden of relapse was calculated to be 78%. In a third study, 680 G6PD normal subjects were randomized to chloroquine+primaquine 7 days (1mg/kg/day), chloroquine+primaquine 14 days (0.5mg/kg/day), dihydroartemisinin-piperaquine+primaquine 7 days or dihydroartemisinin-piperaquine+primaquine 14 days. Recurrences within one year follow up with *P.vivax* were treated with a standard dose of chloroquine+primaquine 14 days (0.5mg/kg/day). Subjects with at least one recurrence were not significantly different between the 7 and 14-day primaquine regimens, although non-inferiority of the 7-day regimen was inconclusive.

Conclusion: Relapse contributes substantially to the burden of *P.vivax* malaria. High dose primaquine (7mg/kg) over 7 or 14-days are efficacious and universal deployment is likely necessary for *P.vivax* elimination. However, safety of these regimens in persons with G6PD deficiency requires confirmation.

http://dx.doi.org/10.1016/j.ijid.2016.02.070

Type: Invited Presentation

Final Abstract Number: 13.001
Session: New Insights on Rickettsial Infections
Date: Thursday, March 3, 2016
Time: 15:45-17:45
Room: G.01-03

Epidemiology and ecology of rickettsial infections

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Abstract: Rickettsiae are obligatory intracellular bacteria, transmitted to vertebrates by arthropod vectors, primarily by fleas and ticks. A rapid increase in the incidence of four endemic rickettsioses; Rocky Mountain spotted fever, Mediterranean spotted fever, North Asian tick typhus, and Queensland tick typhus was noted since 1970s and for Japanese spotted fever, since its discovery in mid-1980s. As a result, spotted fever group of rickettsiae (SFG) currently include over 25 formally recognized species. Elevated attention to rickettsial diseases, advent and adaptation of new molecular tools used for field and laboratory studies in the 1990s and increase in funding support have lead to this second pronounced increase in the discovery of novel species and the increase in incidence of tick-borne rickettsial diseases in the last 40 years. Change in ecological factors which determine the vector species

and their behaviour, particularly those driven by climate change or human activities such as deforestation, human behavioural changes such as recreative activities that involve close association with nature, human population increases and the improvements in surveillance methodologies may contribute to the change in rickettsial disease ecology and epidemiology. Since the use of molecular technologies, numerous rickettsiae from kown to unknown or variable degrees of pathogenicity for humans are being found to co-circulate in overlapping geographic regions and demonstrated in the same tick species. Furthermore, the discovery and description of novel nosological entities caused by previously unknown SFG rickettsiae, ability of most rickettsiae to circulate in diverse sylvatic or peridomestic reservoirs without having obvious impacts on their vertebrate hosts or affecting humans, occurance of rickettsiae in association with a wide range of hard and soft ticks which feed on very different species of large and small animals, their mmaintenance in these vector systems by both vertical and horizontal transmission has lead to a degree where the traditional views of tick-borne rickettsioses as endemic diseases with largely focal distributions, limited host and geographic ranges, predetermined seasonality and defined tick associations to become obsolete or at least very incomplete. Therefore, continuous vigilance, survailance, research and funding are warranted in order to understand the changing ecology and epidemiology of rickettsial diseases.

http://dx.doi.org/10.1016/j.ijid.2016.02.071

Type: Invited Presentation

Final Abstract Number: 13.002
Session: New Insights on Rickettsial Infections
Date: Thursday, March 3, 2016
Time: 15:45-17:45
Room: G.01-03

Challenges and opportunities in the diagnosis and management of rickettsial infections in Southeast Asia

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Abstract: Rickettsial infections are increasing in all regions of Southeast Asia where sought. Given the non-specific presenting symptoms resembling those of other endemic infections, diagnosis can be challenging, even to the most experienced clinician. Available tests have limitations, with no good gold standard diagnostic test. Serological tests are the mainstay of diagnosis with the IgM indirect immunofluorescence assay being the reference test. However, the enzyme-linked immuno-sorbent assay is used more commonly due to the ease of performance and a good sensitivity and specificity. Paired samples, obtained at least two weeks apart, demonstrating a minimum 4 fold titre rise, are needed for improved serologic specificity, limiting its clinical feasibility. Other methods of testing have become available, but at this time, these remain insufficient to provide the rapid point-of-care diagnostics that would be necessary to significantly change the management of this infection by providers in endemic areas. The mainstay of treatment is Doxycycline although the intravenous formulations are unavailable in several countries. Macrolides have proven efficacy in mild cases and intravenous Azithromycin is used along with oral Doxycycline in seriously ill with suboptimal gastrointestinal absorption and bioavailability. This presentation reviews the challenges in the laboratory diagnosis and management of rickettsial infections unique to Southeast Asia, and examines data on emerging resistance to antimicrobial drugs.

http://dx.doi.org/10.1016/j.ijid.2016.02.072

Type: Invited Presentation

Final Abstract Number: 13.003
Session: New Insights on Rickettsial Infections
Date: Thursday, March 3, 2016
Time: 15:45-17:45
Room: G.01-03

Current understanding of scrub typhus immunity and vaccine development: the way ahead

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Abstract: An effective vaccine against scrub typhus is needed because of the high incidence (1 million cases annually is likely an underestimate), large geographic distribution in Asia and islands of the Indian and Pacific oceans, difficulty of diagnosis at the time of presentation as undifferentiated febrile illness, lack of an effective low-cost point-of-care diagnostic method to be deployed in rural areas, case fatality rate of 7-10%, and natural resistance to many commonly used antibiotics.

Scientific obstacles to development of a vaccine include great antigenic diversity of the immunodominant 56 kDa surface protein antigen that has four major variable domains; weak, short-lived cross protection against the numerous heterologous strains; loss of protection against even the homologous strain after a few years; and poor knowledge of the mechanisms of immune protection, which are mostly based on studies in an invalid animal model.

Current knowledge indicates that the target cells of intracellular *Orientia tsutsugamushi* are dendritic cells and macrophages in the mite feeding inoculation lesion (eschar) and mainly endothelial cells, and secondarily, macrophages in the full-blown disseminated infection. Studies in a valid disseminated endothelial cell target model indicate that CD8 T lymphocytes play an important role. Earlier studies using the invalid peritoneal infection model suggest that antibodies to the 56 kDa protein provide protection against only the homologous strain, cross protection is T cell dependent, and gamma interferon likely plays an important role. The 47 kDa and ScaA proteins, which are conserved among strains, stimulate partial protection.

The critical gaps in knowledge include determining the basis for insufficient immunological memory triggered by natural infection, defining the contributions of T lymphocyte subsets, NK cells, dendritic cells, and various cytokines and chemokines to vaccine-induced immunity, the orientiacidal mechanisms particularly in infected endothelial cells, and the prevalence, mechanisms, and consequences of persistent *Orientia* infection.

The approach toward vaccine development should utilize the valid disseminated endothelial cell infection model, bioinformatics identification of potential conserved vaccine antigens, especially subdominant surface and secreted proteins, and determination of which novel adjuvants enhance long-lived protective memory T and B cells. The goal is to do better than nature by stimulating sterilizing, sustained cross-protection against all strains of *O. tsutsugamushi.*

http://dx.doi.org/10.1016/j.ijid.2016.02.073