Ceftolozane/tazobactam:
Approved for:cUTI, cIAI, acute pyelonephritis and HAP/VAP. A 5th generation cephalosporin and act against multi-drug resistant *Pseudomonas aeruginosa* and coliforms but somewhat poor activity is observed for *Klebsiella* and *Enterobacter* species with extended spectrum beta lactamase expression.

Ceftazidime+Avibactam: Approved for: cUTI, cIAI, acute pyelonephritis and HAP/VAP. Avibactam is a novel non-β-lactam β-lactamase inhibitor that inhibits KPCs, AmpC, and some Class D beta lactamases, but not metallo beta lactamases and NDM-1. In cIAI, it is used in combination with metronidazole. The activity against the *P. aeruginosa* is variable, due to the potential presence of other resistance mechanisms in addition to beta lactamase production. Regarding *Haemophilus*, *Moraxella*, *Neisseria* and *Acinectobacter baumannii*, it offers little or no advantage over ceftazidime monotherapy, due to the widespread expression of resistance mechanisms other than beta-lactamase production.

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WHAT IS THE POTENTIAL RISK OF ACQUIRING THE FIFTH MALARIA SPECIES, *PLASMODIUM KNOWLESI* IN SRI LANKA?

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Abstract

Plasmodium knowlesi is the fifth species causing malaria in humans. Macaque is the natural host of the parasite. Infection is transmitted from monkey to humans by the bite of mosquitoes of *Anopheles leucosphyrus* group. Symptoms are similar to other malarial infections and also cause fatalities. *P.knowlesi* is frequently misdiagnosed as *Plasmodium malariae* during microscopy and molecular biological tests are useful in establishing the diagnosis. The vector and the reservoir hosts are present in Sri Lanka but fortunately neither category nor human is infected with *P.knowlesi.* Potential risk of introduction of *P.knowlesi* malaria to Sri Lanka is low.

Introduction

Prevalence of many parasitological diseases is low at present in Sri Lanka for variety of reasons such as upgrading in quality of life, improvement in health related knowledge, better health system and effective control programmes etc. However certain parasitic infections emerge or re-emerge from time to time. Considering the facts such as global warming, change of lifestyle, urban development, deforestation and increase of immune suppressed individuals, certain parasites have tendency to thrive.

Autochthonous cases of malaria in Sri Lanka have been successfully brought to zero since October 2012 and thus Sri Lanka is currently in the elimination and the prevention of re-introduction phase (1). Meanwhile efforts are also being taken to detect and treat imported cases of malaria. Certification of malaria elimination by World Health Organization (WHO) pertains only to four species of human malaria (2). Experience of other countries such as Brunei and Singapore indicates that elimination of human malaria and prevention of re-introductions not necessarily keeps the 'knowlesi malaria' away. Singapore received the malaria certification in November 1982 (3). Later, after two decades of stillness, Singapore started

reporting both autochthonous and imported cases of *P.knowlesi* since 2007. Brunei which was declared as 'malaria-free' by WHO in 1987 reported the first case of *P.knowlesi* malaria in 2013. Thus one needs to be vigilant about knowlesi malaria while on guard against human Plasmodium species. Is Sri Lanka at risk of acquiring the fifth malaria species, *P.knowlesi?* Do we have the reservoir hosts and vectors of *P.knowlesi* in Sri Lanka?

A recent case history of *Plasmodium knowlesi* quoted from ProMed (4).

"Two cases of *P.knowlesi* malaria that occurred after a camping trip involving 24 teenagers and 3 adults in Temburong National Park, Brunei. The trip occurred between 2nd and 9th November 2015 and the onset of illness was on 20th November 2015 for both individuals. Diagnosis of *P.knowlesi* was made by PCR speciation. None of the participants of the trip received malaria prophylaxis."

What is *Plasmodium knowlesi?*

P.knowlesi is considered the fifth *Plasmodium* species causing malaria in humans (5). The natural host of the parasite is the long tailed and pig-tailed Macaque (*Macaca fasicularis* and *Macaca nemestrina* respectively) monkeys. Infection is transmitted from monkey to humans through forest dwelling mosquitoes of *Anopheles leucosphyrus* (6) group. Several vector species (*A. balabacensis, A. latens, A. cracens, A.dirus* etc) have been implicated as having the ability to transmit *P.knowlesi* to humans (6). Biological characteristics such as peak biting time, host preference, survivorship and sporozoite rate etc differ widely in vectors implicated in transmission (7). Human to human transmission of *P.knowlesi* has still not been demonstrated but suspected in a region of Vietnam (6).

In the early days, *P.knowlesi* was misdiagnosed as *Plasmodium malariae by* microscopy until molecular biological tests established the correct diagnosis (8-9). Morphology of early trophozoites of *P.knowlesi* resembles that of *Plasmodium falciparum)* while rest of the stages look alike *P.malariae* causing this confusion (6). Careful examination may detect the minor differences of certain stages such as having 16 merozoites in *P.knowlesi* compared to 6-12 in *P.malariae.* However such differences are easily overlooked in a busy diagnostic laboratory and hard to detect with limited knowledge and experience in malaria diagnosis. As a result WHO has recommended to report *P.malariae* cases as *P.malariae /P.knowlesi* (10).

P.knowlesi has been considered for malariotherapy to treat neurosyphilis patients (6) as the researchers thought it only causes a mild infection. Later they found that it can cause a spectrum of clinical manifestations from mild infection to fatal disease. Overall case fatality rate of *P.knowlesi* malaria is 3.08 deaths/1000 cases in Malaysia (compared to 4.83 and 0.87 deaths per 1000 cases for *P.falciparum* and *P.vivax* respectively). All fatalities have been in over 15 years age category (11). Most cases are mild to moderate not requiring any treatment (12).

P.knowlesi parasite has a short (24 hours) erythrocytic phase compared to *P.malariae* which has a 3 day cycle. Thus parasitaemia increases rapidly causing a fast tract malaria infection by *P.knowlesi* in humans. Initial symptoms are similar to other malarial infections with fever, chills, rigors, headache, myalgia, arthralgia, malaise, poor appetite etc. Cough, abdominal pain and diarrhoea are the other manifestations. Clinical examination may find hepatomegaly and splenomegaly. Severe cases have had feature of respiratory distress, hypotension and jaundice. However cerebral malaria like syndrome has not been reported among knowlesi malaria patients (6). Thrombocytopenia has been the most commonly noted laboratory finding and this may complicate the decision making of the attending physician due to existence of dengue in these *P.knowlesi* endemic areas. Severe anaemia is not seen as in *P.falciparum.* Yet liver and renal functions can get affected. Since *P.knowlesi* is difficult to distinguish from *P. falciparum* and *P. malariae* by microscopy molecular biological techniques are essential to confirm the diagnosis. Treatment of *P.knowlesi* differ from country to country and Malaysia uses chloroquine or ACT (artemether lumifantrine combination) for treatment (13).

Which countries are burdened with *P.knowlesi* malaria?

P.knowlesi was first detected in macaque brought to India from Singapore in 1931. First case of *P.knowlesi* in humans was reported in Malaysia in 1965. Knowlesi malaria is prevalent in several countries in the Asian region namely Malaysia, Thailand, The Philippines, Myanmar, Singapore, Vietnam, Indonesia, Brunei and Cambodia (6). Since the report of first case of *P.knowlesi* from Malaysia in 1965, it accounts for the highest reported (38% of all) among all cases of malaria (13).

What is the potential risk of acquiring *Plasmodium knowlesi* in Sri Lanka?

There are over 20 species of *Plasmodium* infecting monkeys (14). Out of them certain species have the ability to cause human infections (12). Thirteen species of *Plasmodium* infecting non-human primates are present in Southeast Asia (7). Of those some species (*P. fragile, P.simiovale, P. cynomolgi* and *P. inui*) are present in Sri Lanka (7). However to date *P.knowlesi* has not been detected in macaques, mosquitoes or humans in Sri Lanka.

The countries reporting human knowlesi malaria cases have natural distribution of long tailed and pig-tailed macaques, infected macaques with the *P.knowlesi* parasite and natural distribution of mosquitoes of the *Anopheles leucosphyrus* group (6). Luckily even though present, long tailed and pig-tailed macaques in Sri Lanka are not known to be infected with *P.knowlesi* (6).

Transmission of vector borne diseases is dependent on the bionomics and the distribution of the vectors (6). Sri Lanka has natural distribution of mosquitoes of the *Anopheles leucosphyrus* group (*A.mirans*) (6),(15). The other important aspect of transmission of vector borne diseases is contact of vector (mosquitoes in this case) and humans. Overlapping of animal and human habitats caused by invasion of forest areas by humans for agricultural purposes, development activities, jungle trekking for leisure, wild game can increase the risk of acquiring *Plasmodia* of simian origin (5,14). Farmers, log cutters, wild game hunters, travellers to jungles are at risk (6). In Malaysia 78% of patients are males indicating the link to exposure (16). Duration, frequency, timing of occupation exposure is not known (16). Changes in land usage practices have been highlighted as key drivers to acquire *P.knowlesi* (16). Overlapping of animal and human habitats and encroachment into forest is not uncommon in many areas in Sri Lanka.

Frequent travelling occurs between Sri Lanka and *P.knowlesi* endemic countries. Naturally occurring knowlesi malaria cases have been reported in travellers from New Zealand, USA, Finland, Sweden, Spain, France, Germany, Australia and Netherland (17). Suspicion and consideration of malaria left alone knowlesi malaria, in a patient even with suggestive features in the differential diagnosis by the Sri Lankan physicians is low. Travel history may be missed out during history taking. Even when it is suspected and a sample is sent to the diagnostic laboratory, the limited experience in malaria blood smear examination of the microscopists and technicians in Sri Lanka may prevent arriving at the correct diagnosis. Even in areas where malaria is common in rest of the world, misdiagnosis is common for all malaria species when compared with molecular techniques (9). Molecular biology faculties are not readily available for most parasitic diseases currently existing in Sri Lanka.

Plasmodium malariae is the species which share similar morphologies to *P.knowlesi*. Since 1969 *Plasmodium malariae* cases has not been present (18) in Sri Lanka except one for two cases; one sporadic case in 1984 and another imported case of mixed infection with *P.falciparum* in 2008. The second case of *Plasmodium malariae* had been confirmed using Polymerase Chain Reaction (PCR) (19).

A series of maps have been developed by combining data on the occurrence of *P. knowlesi* parasite in humans, known and presumed macaques hosts and vector species and human malaria cases in the region. It illustrates the potential geographical range of the *P.knowlesi* parasite pertaining to each country. As for Sri Lanka, it shows that western and Sabaragamuwa provinces have the higher risk compared to rest of the country (20). This risk is due to the presence of macaque host and mosquito vectors. However these potential risks for those two provinces are at a point which is below the level of weak evidence range.

Conclusion

Frequent travelling occurs between Sri Lanka and countries endemic for *P. knowlesi*. These countries have natural distribution of long tailed and pig-tailed macaques, infected macaques with the *P. knowlesi* parasite and natural distribution of mosquitoes of the *Anopheles leucosphyrus* group (6). Fortunately except for having *Anopheles leucosphyrus* group (6) mosquitoes Sri Lanka do not have any of the other favourable factors similar to South East Asian countries burden with knowlesi malaria. Meanwhile Sri Lanka has been placed below the level of weak evidence range for potential geographical range of *P.knowlesi* parasite. Nevertheless we need to be watchful about knowlesi malaria not only because *P.knowlesi* is able to cause severe and fatal malaria in humans but due to the fact that Sri Lanka do not need any further vector borne diseases than what we currently struggle to control.

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