

CKD and Infectious Diseases in the Asia Pacific Region: Challenges and Opportunities

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Abstract

The exact number of patients with chronic kidney disease in Asia-Pacific region is uncertain. In numeric terms, the region is home to the largest population of patients with untreated end-stage kidney disease. The climatic, geographic, social, cultural, economical, and environmental diversity within this region is higher than any other part of the world. Large parts of region face a climate-related burden of infectious diseases. Infections contribute to the development and progression of CKD and complicate the course of patients with pre-existing CKD (especially those on dialysis or who are immunosuppressed), increase the cost of CKD care and contribute to mortality and morbidity. Renal involvement is a feature of several infectious diseases prevalent in Asia-Pacific region, examples include malaria, leptospirosis, scrub typhus, tuberculosis, hepatitis B and C, dengue haemorrhagic fever and Hantaviruses infections. The contribution of infection-associated AKI to the overall burden of CKD has not been evaluated systematically. Research is needed to quantify the impact of infections on kidney health by undertaking prospective studies. Nephrologists need to work with infectious disease research groups and government infection surveillance and control programs.

Key words: Asia-Pacific, chronic kidney disease, infections, acute kidney injury, epidemiology

Introduction

The Asian Pacific Region is that part of the world in or near the Western Pacific Ocean (see map). It has a population of 4.46 billion (61.2% of the world's population), is expanding ¹, and has the largest population density in the world. The social, cultural, economical, environmental and religious diversity within the Asia-Pacific region are higher than any other part of the world. Particularly striking is the disparity in economic development – seven out of 44 countries (Japan, South Korea, Singapore, Taiwan, Brunei, Australia and New Zealand) are classified as developed countries. Others are in various stages of development and are considered “emerging economies”. Most have agrarian economies, with large number of people living in remote rural locations. Poorly managed economies, lack of skilled human resources and technology, weak infrastructure and an inappropriate health policy framework obstruct the promotion of healthcare delivery, as exemplified by failure to reach the health-related Millennium Development Goals ².

The disease spectrum in most parts of America and Europe has changed from infections to non-communicable diseases. This contrasts with large parts of Asia-Pacific which face climate-related burden of infectious diseases. Poverty increases the likelihood of exposure to infection-related health risks. The 2010 Global Burden of Disease (GBD) report ³ shows that infections are responsible for 40-60% of deaths and Disability Adjusted Life Years (DALYs) in the low income parts of Asia-Pacific region. Many of these infections are complicated by kidney injury. However, the GBD data do not allow estimating the contributions of kidney involvement on death and DALYs. Several individual studies, however, have shown that kidney involvement is an independent and major contributor to mortality and morbidity in these infections ⁴⁻⁷. East Asia and Pacific regions have the highest annual rate of death due to diseases of the genitourinary system ⁸. According to the data collected by the *International Society of Nephrology* as part of its *Oby25* initiative ⁹, the mortality rate of infection associated AKI in Asia was about 52%. Importantly, 7-16% patients went on to develop ESRD and 11 to 19% were left with residual kidney dysfunction despite being cured of the infection⁹.

Asia-Pacific region also exhibits an enormous variation of climate and topography, from tropical to arctic, and from the Himalayas to coral reefs. Most countries fall either completely or partially in the tropical zone. Tropical climate is characterized by high

ambient temperatures and humidity, and is conducive to growth of various life forms, making it a large reservoir of vectors responsible for disease transmission. Some of these climate-sensitive conditions include diarrheal diseases and vector borne infections, major preventable causes of kidney diseases ¹⁰.

The relationship with infection and CKD is bidirectional. Infections contribute to the development and progression of CKD but do not receive adequate recognition, and complicate the course of patients with pre-existing CKD – they are more severe, detected late, are harder to manage, increase the cost of CKD care and contribute to mortality and morbidity ¹¹⁻¹³.

We will describe the burden of CKD in the Asia-Pacific region with the possible links to infection, and the impact of infections on patients with pre-existing CKD.

CKD in Asia Pacific region

The incidence and prevalence of end stage renal disease (ESRD) and the consequent requirement for renal replacement therapies (RRT) are rapidly growing in the Asia-Pacific region. Except Japan, Taiwan, South Korea, Australia and New Zealand, where RRT is widely available, access to this life-changing but expensive therapy is limited in the other countries of the region. According to a recent report ¹⁴, out of about 2.89 million people who needed RRT in Asia and Oceania in 2010, only 0.993 million received the therapy. This number is likely to grow to about 2.21 million by 2030, making it imperative to develop CKD detection and prevention programs.

Accurate incidence and prevalence of earlier stages of CKD is uncertain, primarily because of lack of large-scale epidemiological studies. The published studies show figures ranging from 9% to 17% ¹⁵. The variations are also confounded by the definition of CKD. Studies that have included hematuria (which might be a surrogate for infection-related proliferative glomerulonephritis) to define CKD generally show higher CKD prevalence ¹⁶⁻

¹⁸.

The etiologic spectrum of CKD is also not uniform in the countries within the region. Despite the incessant increase in the proportion of patients due to CKD caused by diabetes, chronic glomerulonephritis (CGN) and chronic interstitial nephritis remain the leading

causes of CKD in several countries. CGN remains dominant in China, Indonesia and Malaysia ¹⁹⁻²¹, whereas a high frequency of chronic interstitial nephritis (CIN) has been described from parts of South Asia ²²⁻²⁴. Infections play an important etiological role in both these conditions. A high prevalence of CKD of unknown etiology has been reported from some parts of region ^{22, 24, 25}. Though not formally evaluated, the role of locally prevalent infections also needs consideration in light of poor sanitation, unsafe water, overcrowding and high concentrations of disease-transmitting vectors in the region.

Infection and CKD in Asia Pacific region

Several infectious diseases prevalent in Asia-Pacific region, such as malaria, leptospirosis, tuberculosis and HIV/AIDS, dengue haemorrhagic fever and Hantaviruses infections affect the kidneys (Box). The primary presentation is in form of AKI, either *de novo* or on the background of CKD. As many as 28% of the patients with no pre-existing kidney disease who recover from AKI develop *de novo* CKD ^{9, 26-29}. In those with pre-existing CKD, infections often accelerate the rate of progression ¹¹. Many of these patients have multiple comorbidities, making it complex to dissect the role of renal involvement on the overall outcome.

Pathogenesis of kidney injury in infections

Kidney injury in infections prevalent in Asia-Pacific may occur as a result of several mechanisms. These include direct invasion by the offending micro-organism leading to cytopathic injury, as in pyogenic infections, tuberculosis, leptospirosis and nematode infestations; through immune mechanisms involving microbial antigens that might lead to generation of circulating or *in situ* immune-complexes, or cause perturbations in innate and cellular immunity as in infection-related glomerulonephritis; and via systemic inflammatory response syndrome, hemodynamic disturbance, multiorgan failure, hemolysis, rhabdomyolysis, hepatorenal syndrome and nephrotoxicity of antimicrobial therapy.

The following section describes specific infections that lead to kidney disease in Asia-Pacific region.

Viruses

Hepatitis B: About 75% of the 350 million people affected with HBV worldwide are from Asia ^{30, 31}. The reported prevalence of kidney disease related to HBV infection closely parallels the geographic patterns of prevalence of HBV in the region, which range from 2.8% in South Korea to 20% in Taiwan and Vietnam ³²⁻³⁴. In a retrospective analysis of 11,618 kidney biopsies performed from 1987 to 2012 at a single centre in Beijing, China, 3% were reported to have HBV-associated nephritis ³⁵. Of the three main forms of glomerulonephritis associated with HBV infection, viz. membranous glomerulonephritis (GN), membranoproliferative GN and IgA nephropathy, membranous GN is most frequently reported in Asian populations, particularly amongst children. ^{36, 37}. In some areas, HBV-related disease accounts for up to 15% of all membranous nephropathy cases ³⁸. By contrast, mesangial proliferative forms with IgA deposits seem to be more common in adults. An association of HBV infection has also been described with mixed cryoglobulinemia, polyarteritis nodosa and FSGS ³⁹. the introduction of nationwide HBV vaccination in China in 1992 led to significant decreases in childhood glomerular disease

⁴⁰.

Hepatitis C: The Asia-Pacific region is home to 100 out of approximately 170 million people infected with hepatitis C virus (HCV) worldwide ⁴¹. The majority are in the Western Pacific (62.2 million) and Southeast Asia (32.3 million). The estimated prevalence of antibodies to HCV range from 0.3% in New Zealand to 5.6% in Thailand. HCV hyper-endemic parts of Japan, Vietnam and Taiwan have prevalence rates of 12-58% ⁴². In contrast to HBV infection, HCV is marked by silent onset and chronic course. The virus behaviour and response to treatment varies according to its genotype, and host characteristics. Genotype 1, the most virulent form, is the most frequent form encountered in Australia and North Asia, genotype 6 in Southeast Asia, and the less virulent genotype 3 in India and Pakistan ^{43, 44}. There is a strong – and likely causal – association between chronic HCV infection and several chronic glomerular diseases ^{45, 46}. An autopsy study revealed glomerular lesions in 55% of HCV-infected individuals, including mesangial proliferative GN (17.6%), MPGN (11.2%), and MN (2.7%) ⁴⁷. Recent population-based studies have shown a link between HCV infection and proteinuria ⁴⁸. Kidney disease is often clinically silent, and the presence of infection detected only during work up. Management of these patients is particularly

difficult when detected late. The recent discovery of orally active antiviral agents has the potential to revolutionize the treatment of HCV-related kidney diseases. The high cost of treatment, however, is likely to delay the introduction of these agents ⁴⁹.

Human immunodeficiency virus infection: UNAIDS 2013 report estimated that there were about 350,000 new cases of HIV infection in Asia-Pacific region in 2012, which represents a decline of about 26% since 2001 ⁵⁰. The increased risk of both AKI and CKD in HIV-infected patients is well-known. However, in contrast to the black population from sub-Saharan Africa, Asians infected with HIV seem to be at a lower risk of developing HIV-associated nephropathy. In most series of patients with HIV infection and kidney disease from the region, kidney disease seems to have been etiologically unrelated to the HIV infection ⁵¹⁻⁵³. At the same time, these patients do remain at increased risk of kidney disease as a result of predilection to other infections, or drug nephrotoxicity ⁵³.

Dengue: Dengue, transmitted by the bite of an *Aedes aegypti* mosquito, is endemic in several Asia-Pacific countries. More than 70% of the 2.5 million people affected globally reside in the region, 35% in southeast Asia alone ⁵⁴. The nature of kidney involvement ranges from asymptomatic urinary abnormality to AKI. AKI develops in about 1-5% of all patients, increasing to 33% in fatal cases ⁵⁵⁻⁵⁷. Histology usually shows proliferative immune complex glomerulonephritis. Long term outcome of patients with dengue and kidney involvement has not been studied. Some studies have reported high prevalence of persistent proteinuria and hematuria ^{58, 59}.

Hantaan viruses: Infection with this zoonotic rodent-borne virus causes hemorrhagic fever with renal and lung injury. Renal disease is the dominant manifestation in the Asia-Pacific region, presenting as AKI, proteinuria, and hematuria ⁶⁰. Renal replacement therapy is needed in 30-40% patients, and is associated with high mortality ⁶¹. Large number of deaths have been reported from China and South Korea ^{55, 62, 63}. Of those who recover from the acute phase, a significant proportion are left with residual decreased GFR, and may develop hypertension ⁶⁴⁻⁶⁶.

Bacterial infections

Bacterial infection continues to be a major health problem in many countries of the Asia-Pacific. Kidneys are particularly vulnerable to certain types of bacterial infections. Worth mentioning is the persisting high frequency AKI in the setting of puerperal and post-abortal sepsis *secondary to poor obstetric care* in the underdeveloped rural areas of the Asia-Pacific region (___). In many hospitals, about one-third of all AKI cases are following obstetric complications. Of those who survive the infection, as many 20% develop irreversible renal failure due to acute renal cortical necrosis, and another one-third show incomplete renal recovery ⁶⁷⁻⁶⁹.

Mycobacterial infections:

Tuberculosis (TB) and leprosy are the two common infections caused by mycobacteria. Both are endemic in South and South East Asia and involve the kidneys

Tuberculosis: In 2013, the largest number of new Tuberculosis (TB) cases in the world occurred in the South-East Asia and Western Pacific Regions, accounting for 56% of new cases globally with particularly high incidence in India, China and Indonesia ⁷⁰. Involvement of the genitourinary tract is seen in 6-8% of all cases with TB ⁷¹. Males are twice as likely to have GU involvement as females. The infection reaches the kidneys through the bloodstream but it is involvement of the collecting system – urinary bladder and the ureters that leads to obstructive nephropathy. When unrecognised destructive caseous lesions involve the renal parenchyma causing permanent loss manifesting as “putty kidney” (Fig 1) ⁷². Renal TB can also present with progressive kidney injury due to granulomatous interstitial nephritis that may be difficult to distinguish from sarcoidosis ⁷³. TB is the commonest cause of secondary amyloidosis in the Indian subcontinent ⁷⁴. Renal amyloid can develop several years after diagnosis and treatment of TB. The diagnosis of TB is difficult due to unsatisfactory culture techniques and lack of the newer nucleic acid based tests ^{13, 75}. Smear positivity in urine is unreliable for the diagnosis of genitourinary TB, as the urinary tract can be colonized by environmental mycobacteria.

Leprosy: Despite a large reduction in prevalence, this disease remains endemic in several parts of South when the bacillary load is high. In a report of 122 cases from India, reduced creatinine clearance and proteinuria were common ⁷⁶. Autopsy studies revealed a wide spectrum of renal lesions, including renal amyloidosis, glomerulonephritis,

tubulointerstitial nephritis and granulomatous disease (in decreasing order of frequency)

⁷⁷.

Protozoal infections:

Malaria: More than 2.2 billion people in the Asia-Pacific region live in malaria endemic zones, representing about two-thirds of the world's at risk population. These include 6 of the top 10 countries worldwide with the largest at risk populations – India, China, Indonesia, Bangladesh, Vietnam and the Philippines ⁷⁸. Of the five human malarial parasites – *Plasmodium falciparum*, *P. vivax*, *P. knowlesi*, *P. malariae* and *P. ovale*, the first 3 are prevalent in the region and cause kidney disease.

Renal involvement is mostly a feature of *P. falciparum* infection. The usual presentation is with AKI. A small but significant proportion exhibit glomerular involvement – either acute nephritic syndrome or nephrotic syndrome ⁷. The prevalence of kidney involvement varies from <1% in uncomplicated infections to over 50% in severe malaria ⁷⁹. Blackwater fever, seen in the setting of glucose-6-phosphate dehydrogenase deficiency, is encountered amongst children infected with falciparum malaria from Southeast Asia and parts of north-eastern India ⁸⁰⁻⁸². Ingestion of quinine precipitates intravascular hemolysis, leading to AKI. AKI substantially increases the mortality risk. Provision of RRT to these patients presents a challenge in resource-constrained environments. Modern RRT methods such as continuous renal replacement therapies are often not available. In such situations, peritoneal dialysis, is often life-saving ⁸³.

Previously considered benign, renal involvement in *P. vivax* infection is now being reported from South Asia, sometimes with severe and irreversible injury, especially in children ⁸⁴⁻⁸⁸. Renal involvement in *P. knowlesi* has been described from Thailand and Malaysia where it has become the predominant cause of malarial kidney injury ^{89, 90}. This phenomenon likely represents a change in the virulence characteristics of these two organisms and needs further studies.

The pathogenesis of kidney injury in malaria is multifactorial, with the main abnormality being haemodynamic alterations produced by unique properties of this parasite which produces hemorheologic changes leading to renal ischemia. Other factors include volume

depletion, intravascular hemolysis, rhabdomyolysis and altered levels of vasoactive cytokines⁷. Histology usually shows acute tubular necrosis, with occasional pigment casts.

Leishmaniasis: The disease (kala-azar) mostly seen in rural areas of the Indian subcontinent⁹¹. is caused by *Leishmania donovani*, transmitted to humans by the bite of infected female sandflies. is The organism predominantly involves the reticuloendothelial system, explaining the presentation with prolonged fever and hepatosplenomegaly. About 60% of patients exhibit proteinuria and urinary sediment abnormalities, implying the presence of proliferative glomerulonephritis, often associated with chronic tubulointerstitial damage^{92, 93}. Antimonials used to treat the disease can worsen proteinuria and CKD.

Fungal infections:

Candida, Aspergillus and Zygomycetes are the main fungal infections that involve the kidney and urinary tract in Asia-Pacific region. The first two are usually ascending infections in patients on long-term antibiotics and indwelling catheters, whereas the third is an angioinvasive infection that causes devastating renal damage. Renal zygomycosis has been described mainly from India, and presents as a febrile illness with invasion of renal vessels leading to tissue infarction^{12, 94, 95}. When bilateral (Fig 3), it causes irreversible kidney failure and carries a high mortality despite antifungal therapy and tissue debridement.

Other infections

Lymphatic filariasis: this is caused by the nematodes *Wuchereria bancrofti*, *Brugia malayi* or *B. timori* and transmitted by *Culex* mosquitoes. It is endemic to several countries in the region. India alone accounts for 40% of global prevalence⁹⁶. Kidney involvement occurs most often in form of chyluria (passage of “milky” urine) and hematuria, which occur because of obstruction of central lymphatic by filarial worms leading to dilatation and rupture of lacteals into the collecting system^{97, 98}. Chylous urine tests positive for protein, and may lead to a mistaken diagnosis of nephrotic syndrome.

A variety of glomerular lesions, independent of chyluria, have also been described in association with filariasis⁹⁹. A role for bacterial co-infection has been suggested. Once

established, both chyluria and glomerulonephritis persist despite successful therapy of filariasis. Fig 2 shows a spectrum of renal abnormalities in filariasis.

Scrub typhus: This has been identified by the WHO as a re-emerging disease in South Asia, South-East Asia and the South-Western Pacific region, scrub typhus (caused by the spirochete *Orientia tsutsugamushi* and transmitted by the bite of an infected trombiculid mite) accounts for about 23-50% of all acute febrile episodes in endemic regions in Asia ⁴, and has a case fatality rate of up to 50% if untreated ^{6, 100}. Renal involvement is seen in about 80% cases, with AKI in 53% ^{6, 101}. As this complication has come to light recently, the long term renal outcome in these patients is unknown.

Leptospirosis: Leptospirosis, the commonest zoonosis worldwide, is prevalent in India, Southeast Asia and Oceania ^{102, 103}. Caused by the spirochete *Leptospira interrogans*, the disease is transmitted when the organism present in animal urine comes in contact with abraded human skin or mucosal surfaces and gains entry to circulation. Seroprevalence varies from 20-53% in endemic areas ¹⁰⁴. Disease outbreaks are encountered during flooding in low lying areas. Presentation is with an acute febrile illness with AKI and jaundice, myositis and tissue hemorrhages ²⁸. The spectrum of renal injury include mild proteinuria, urinary sediment abnormalities, tubular dysfunctions, and AKI primarily due to interstitial nephritis ¹⁰⁵⁻¹⁰⁷. A proportion of survivors show persistent defect in tubular function and reduced GFR ^{108, 109}.

Infections in patients with CKD

Infections remain common causes of morbidity, mortality, and hospitalization in patients with CKD, especially amongst those on dialysis and after kidney transplantation. The pattern and outcome of infections is dependent upon local epidemiology and evolution of healthcare systems. Patients on hemodialysis (HD) in resource-poor parts of the region with immature healthcare systems and lax regulatory standards are particularly vulnerable. The predisposing factors include late referral, reliance on central vein dialysis catheters especially the uncuffed, frequent movement of patients between dialysis units and poor adherence to infection control measures ^{12, 110-113}.

Hepatitis B and C infections: Despite increasing use of low cost generic ESAs and decrease in blood transfusion, infections with the two hepatitis viruses is a major problem in the dialysis population in many countries of the region. CKD patients are often referred late and therefore not immunized for HBV, putting them at risk of contracting the disease in HD units ¹¹⁴. Moreover, serological assays rather than sensitive molecular nucleic acid techniques including PCR are still used for screening. This leads to underdiagnosis of infection in the window period, increasing the risk of horizontal transmission.

In a recent study ¹¹⁵ of dialysis registries of 10 countries in the Asia-Pacific region which included 201,590 patients, the HBsAg positivity rate ranged between 1.3% and 14.6%, and the HCV seroprevalence varied between 0.7% and 18.1%. A significant proportion of HCV RNA positive patients were seronegative. HBV prevalence was similar between PD and HD populations in China, Malaysia, Hong Kong and Thailand, but higher in PD patients in Japan and Taiwan and lower in PD patients in South Korea. For HCV, the prevalence was higher in HD than PD patients across the region (7.9 vs 3%). The seroconversion rate was greater in HD patients (0.1 vs 0.03 per 100 patient-years at risk).

In recent years, HCV infection has become a significant health threat in parts of the Asia-Pacific. A multicentric study from Vietnam of 8654 patients found an HCV prevalence of 11-43%. Single center studies from India have described prevalence of ~50%, leading to calls for isolation of HCV infected patients on HD similar to that practiced for those with HBV infection ^{116, 117}.

In addition to increasing the risk of chronic liver disease, the hepatotropic viruses predispose to hepatocellular carcinoma and death ^{118, 119}. HCV positivity has been shown to be a risk factor for premature death in Japanese HD population as well as in Australia and New Zealand ^{118, 120}. The availability of effective antiviral agents for HBV and more recently HCV are expected to change the management and outcomes in these patients.

Tuberculosis: The incidence of TB in patients with CKD is 10-15 times higher than that in the general population ^{12, 111}, increasing to >50-fold amongst those on dialysis and after kidney transplantation ^{121, 122}. About 7–10% of patients on maintenance dialysis and 10-13% of transplant recipients develop overt TB. In some of the historic reports from the

region, the overall mortality rate among organ transplant recipients with TB was 20–30%^{121, 122}.

There are a number of issues of management of TB in the region.. These include the difficulties in making a timely diagnosis of both active and occult TB; optimal method of detection and management of a potential transplant recipient with latent TB¹²³; minimizing the risk of donor-derived TB transmission to transplant tourists¹²⁴; dealing with the increasing prevalence of multi-drug resistance TB¹²⁵; and managing the interaction between anti-tuberculosis agents and post-transplant immunosuppression. Mortality from TB can be almost eliminated by keeping a high index of suspicion, insisting on invasive investigations to establish the diagnosis and instituting therapy promptly¹²⁶. Neither Mantoux testing nor the newer IFN- γ release assays have been found to be useful for identifying latent TB before transplantation in endemic regions¹²⁷. New anti-tuberculosis drug regimens which exclude rifampicin have simplified the problem drug interactions altering the concentration of CNIs in transplant recipients.¹²⁸

Fungal infections: The hot and humid climate, poor hygiene, and frequent use of broad-spectrum antibiotics increase the risk of colonization of CKD subjects with fungi prevalent in the tropical countries. A significant proportion develop clinical disease. The disease pattern, organ involvement and presentation is influenced by the stage of CKD, the type of renal replacement therapy (HD, PD or kidney transplant) and the local mycological flora^{12, 111}. The most common endemic mycoses in the Oceania are histoplasmosis, penicilliosis, and sporotrichosis, whereas the dominant infections in the tropical countries are by saprophytic and opportunistic fungi such as *Candida*, *Aspergillus* and *Zygomycetes*^{129, 130}.

There is a high (10-14%) prevalence of candida peritonitis reported in India^{131, 132}. Similarly, mucocutaneous fungal infections are quite frequent in kidney transplant recipients, seen in 60-72%. The causative organisms include *Tinea corporis*, *T. cutis* and *T. versicolor* (55–65%), followed by *Candida* (7–9%) and *Cryptococcus* (0–1%) (224). The incidence of tissue invasive fungal infections among renal transplant recipients is 4–7%^{133, 134}. Overall, aspergillosis remains the most frequently reported invasive mold infection in CKD and post-transplant patients within the Asia-Pacific region^{129, 135, 136}. A high prevalence of zygomycosis has been reported from India¹³⁷. Delayed diagnosis because of

lack of specialized laboratories and failure to employ invasive diagnostic tests increase the morbidity and mortality.

Challenges and future directions:

Because of the link between diabetes, hypertension and cardiovascular disease, CKD has been categorised under the broad heading of non-communicable diseases ¹³⁸. This paradigm might, however, be inappropriate in large parts of the world, including the Asia-Pacific region. We argue that the direct and indirect contribution of infection has a major impact on the onset and course of CKD in the region and deserves the attention of the research community and public health policymakers. The WHO has described several of the infections highlighted in this review as “neglected diseases” meaning they receive less attention from the scientific community and pharmaceutical industry. ¹³⁹,

Infection control in large parts of the Asia-Pacific region is limited by poverty, high population density, inadequate sanitary facilities, low uptake of vaccines, indiscriminate antimicrobial use leading to multidrug resistant organisms, isolation from healthcare access and periodic disasters and wars ¹⁴⁰. In large parts of the Asia-Pacific region with growing economies, land clearance and deforestation in the name of development have led to large-scale disruptions and loss of biodiversity, leading to emergence of new strains of Hantaan viruses, dengue viruses, multidrug resistant *E. coli* and artesinin resistant Plasmodium, all of which have implications for kidney disease ^{141, 142}. Increased population mobility reduces the likelihood of geographic containment. Global warming and climate change are expected to adversely affect the ecosystem, impacting on the availability of clean air, safe drinking water, sanitation facilities, sufficient food and secure shelter. There has as a consequence been a sharp increase in the number of infection disease causing outbreaks in the Asia-Pacific region ¹⁴³ (Fig 5)..

The paucity of good quality data limits an accurate assessment of impact of infections on CKD in the region. Most developing countries in the region do not have a systematic process for collecting data on CKD or ESRD subjects. Proper evaluation of the impact of renal involvement on the infection cycle is needed. It is possible that early recognition and aggressive management of kidney complications might improve short and long term patient outcomes in patients with infections. This knowledge gap can only be bridged by

prospective studies with particular attention to infections. Nephrologists need to establish linkages with infectious disease research groups and government infection surveillance and control programs. Infectious disease databases should collect data on the pattern and severity of kidney disease, and its impact on the short and long term outcomes, in particular the risk of CKD and its complications.

Development of strategies to combat infection in the Asia-Pacific region need to factor in the local geography and climate. A co-operative approach between different countries of the region is also needed. For example the failure of malaria eradication programs in India, is in part explained by the re-introduction of the vector and organisms from the neighbouring countries where similar eradication programmes were not implemented simultaneously ¹⁴⁴.

Lack of safe drinking water and adequate sanitation facilities remain major threats to kidney health. The important contribution of repeated clinical or subclinical episodes of kidney injury related to recurrent diarrheal illnesses, especially in children and in agricultural workers who work all day in hot and humid environment has not been adequately studied. Lessons must be learned from the descriptions of “Mesoamerican nephropathy” from Central America ¹⁴⁵, where some local governments have provided shaded “rest areas” and instituted mandatory “water-breaks” for these workers ¹⁴⁶. Cheap technology is needed for purifying water in rural areas to make it potable. Health education will help people change their drinking habits and encourage hand washing and cleaning raw fruits and vegetables gathered from potentially contaminated fields. The solutions require changes in all aspects of health systems. Close collaboration is needed between physicians, public health professionals, policy makers, social activists and the media. The successful eradication of smallpox from the globe and near eradication of polio are encouraging examples that suggest that despite huge obstacles these goals can be achieved.

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Box: Infections in Asia Pacific region that affect the kidneys

Viral infections:

Hepatitis B
Hepatitis C
Human immunodeficiency virus
Hantaanvirus
Dengue

Parasitic infections

Plasmodium falciparum, *P. vivax* and *P. knowlesi*
Wuchereria bancrofti
Brugia malayi, *B. timori*
Leishmania donovani (Kala-azar)

Bacterial infections

Leptospira interrogans
Orientia tsugatsugamushi (Scrub typhus)
Mycobacterium tuberculosis
Mycobacterium leprae
Streptococci and staphylococci
 Infection-associated glomerulonephritis
 Infection-associated interstitial nephritis
 Visceral and puerperal sepsis
Escherichia coli, *Proteus mirabilis*, *Klebsiella pneumoniae* and other bacteria (often multidrug resistant)
 Urinary tract infection

Fungal infections

Candida spp
Aspergillus spp
Zygomycetes

Figure legends

Fig 1: Putty kidney in a patient with genitourinary tuberculosis. Plain abdominal radiograph and CT scan show totally calcified left kidney and mural calcification of left ureter.

Fig 2: Renal disease in filariasis a. Milky white urine in a patient with chyluria due to filariasis. b. retrograde pyelogram in a patient with chyluria showing retrograde filling of lacteals (arrows), c. microfilariae in glomerular capillary lumen (arrows) in a patient with nephrotic syndrome. The urinary abnormalities resolved following diethylcarbamazine therapy.

Fig 3: Contrast enhanced CT scan showing lack of enhancement of renal parenchyma secondary to infarction due to renal zygomycosis. A thin rim of enhancement is seen in the posterior aspect of left kidney (arrow)

Fig 4: Increase in total outbreaks and total number of infectious diseases causing outbreaks since 1950 in Asia-Pacific countries. Reproduced with permission¹⁴⁰