Changing Trend of Infectious Diseases in Nepal

Shiba Kumar Rai

Abstract

Many infectious/communicable diseases (IDs) are endemic in Nepal. Until a decade and half ago, IDs were the major cause of both morbidity and mortality accounting 70% for both. However, as a result of various preventive measures implemented by both the state and non-state actors, the overall IDs have shown a changing (declining) trend. The most impressive decline has been seen in the intestinal helminth infection. Though the overall burden of IDs is decreasing, several newer infectious diseases (emerging infections) namely, dengue fever, scrub typhus, influenza (H5N1 and H1N1), and others are posing a great public health problem. On the other hand, though sporadic, outbreaks of endemic diseases together with HIV-TB coinfection and infection with drug resistance microbes during recent years have constituted a serious public health as well as medical problem. On the contrary, with the decline of IDs, noninfectious diseases (noncommunicable disease, NCD) namely, diabetes, cancer (and cancer therapy), and others are on the rise particularly in urban areas. Hence, currently Nepal is trapped in "double burden" of diseases. Risk of opportunistic infection has increased in immunocompromised person with NCD. To address the present situation, the multi-sectoral plan and strategies developed must be implemented effectively.

Keywords

Infectious diseases · Communicable diseases Nepal

Introduction

Federal Democratic Republic of Nepal is a brick-shaped small land-linked country situated in South Asia between China in the north and India in the south, east, and west. Nepal is located at 26° 26′ north to 30° 26′ north latitude and 80° 03′ east to 88° 15′ west longitude. The total area is 147,181 km^2 with a length of about 800 km (east to west) and width of 90 to 230 km (north to south). It lies in high seismic zone; just along the "fault line" of two tectonic plates; the Indian plate

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and Eurasian plate and therefore, earthquake occurs frequently. A devastating earthquake of magnitude M7.8 struck in Gorkha District (80 km north-west of Kathmandu—28.250°N latitude and 84.116°E longitude) on April 25, 2015 causing severe impact (both direct and indirect) on human health and economy [1, 2].

Administratively, Nepal is divided into seven provinces, 75 Districts, and 744 local levels (*Sthaniya Taha*) (Metropolitan cities = 4; Sub-metropolitan cities = 13; Municipalities = 246 and Village Councils = 481). Ecologically, it is divided into three broad regions; Mountain (subalpine and alpine region) (>3,000 m to as high as 8,848 m), Hill (subtropical and temperate region) (1,000–3,000 m), and *Terai* (plain and tropical area) (1,000 m). Hence, Nepal has highly diversified ecosystem with various kinds of flora and fauna including microbiota. However, the ecosystem in Nepal is threatened by multiple factors such as loss, degradation, and alteration of natural habitats, overexploitation, alien species invasion, pollution of water bodies, and others including natural disasters, climate change, demographic changes, poverty, and weak law enforcement [3].

According to census 2011, total population is approximately 27 million, out of which about one-fifth live in rural (village) setting. Life expectancy at birth is 69 years [4]. The population growth rate is 1.35% (decreased from 2.62% in 1981 to 1.35% in 2011). Literacy rate is 65.9% (increased from 23.3% in 1981 to 65.9% in 2011) though still there is a gap of 17.7% between males (75.1%) and females (57.4%).

Total fertility rate has been reduced by half during the last two decades (4.6 births per women in 1996 to 2.3 births per women in 2016) [5]. Maternal health care has improved significantly (antenatal care by skilled provider increased from 44% in 1996 to 84% in 2016; delivery at health facility increased from 18% in 1996 to 57% in 2016; and delivery attended by skill provider increased from 19% in 1996 to 58% in 2016). Vaccine (such as BCG, DPT, Polio, Measles) coverage has also increased significantly (43% in 1996 to over 78% in 2016). Nutritional status on children has also improved (stunting 57% 1996 has decreased to 36% in 2016; wasting 15% in 1996 to 10% in 2016; and underweight 42% in 1996 to 27% in 2016). Because of all these, neonatal, infant, and under-five mortality rates have also reduced significantly (neonatal mortality rate: 50 in 1996 to 21 in 2016; infant mortality rate: 78 in 1996 to 32 in 2016; and under-5 mortality rate: 118 in 1996 to 39 in 2016). Because of these achievements, Nepal has been awarded "Child Survival Award" (2009) by GAVI (global alliance for vaccines and immunizations) and "UN MDG-5 Award" (2010) by UN for its achievement in progress child health and maternal health, respectively.

Infectious Diseases in the Past

Planned development of health sector in Nepal began with the first planned development process that began in 1956 (2013 BS). The health system now has been widely expanded in the country. Until two decades ago, infectious diseases (mainly water and airborne diseases including rabies, tetanus, and others) were the common cause of morbidity and mortality in Nepal. About 70% of all health problems and cause of death was associated with infectious diseases [6, 7]. Many children were dying due to easily preventable communicable diseases primarily diarrhea and/or dysentery, typhoid fever, tuberculosis, and other respiratory infections. Until two decades ago, intestinal parasitic infection in some communities was very high (over 70%) and multi-parasitic infection was common [8–11]. Among the soil-transmitted helminth infection, *Ascaris lumbricoides* infection alone was over 75% in some communities with a mean annual prevalence of 35% among patients visiting a teaching hospital in capital city, Kathmandu [10–12]. Over one-third of soil samples tested revealed helminth parasites eggs [13].

High prevalence of soil-transmitted helminth (STH) infection in Nepal was associated with open defecation and in some places, use of feces as fertilizer [10–12]. Until the year 2000, infectious (communicable) diseases were in the top of "top-10 diseases" in Nepal [6, 7, 14]. Many

endemic infectious (communicable) diseases in Nepal, however, have shown a declining trend particularly during the last 10–15 years. Vaccine-preventable diseases such as diphtheria, pertussis (whooping cough), tetanus, polio, measles, and mumps have shown sharp decline. In addition, waterborne and food-borne infectious diseases such as diarrhea, dysentery, typhoid (enteric) fever, hepatitis (A and E), and intestinal parasitic infections particularly the soil-transmitted helminth (STH) infections are also decreasing [10, 15].

High morbidity and mortality rates due to infectious diseases in the past were associated mainly with poor sanitary and hygienic condition of people [6, 7, 11]. Infectious diseases as the cause of death among Nepalese, however, have come down to 49.7% in 2007 from 70% in the year 2000 [6, 7, 16]. However, epidemic-prone diseases, such as cholera and acute gastroenteritis, are endemic in all regions of the country with a constant threat to the public health system [17].

Water and Food-Borne Infection

Diarrheal Diseases

Until a decade ago, diarrheal disease (including cholera and dysentery) was in second position in the list of "top-10 diseases" [18]. However, now the position (rank) has gone down below of the disease list. Nevertheless, diarrhea still constitutes one of the most common causes of morbidity and mortality among children especially among under-five children. Approximately four percent of deaths are associated with diarrheal disease. Enteropathogens have been detected in over two-third of diarrheal feces [19]. Among the travelers, diarrhea is usually caused by *Campylobacter*, enterotoxigenic *Escherichia coli* (ETEC), *Shigella* sp., *Vibrio cholerae*, *Giardia lamblia*, *Entamoeba histolytica*, *Cyclospora cayetanensis*, and *Cryptosporidium parvum* including *Rotavirus* and other viruses [20].

Parasitic diarrhea and dysentery: Different intestinal protozoa causing diarrheal disease include *G. lamblia*, *E. histolytica, C. cayetanensis*, and *C. parvum* are commonly implicated. *E. histolytica* is implicated also in dysentery. Though intestinal helminth parasite has been declined significantly, prevalence of protozoan parasites (*E. histolytica* and *G. lamblia*), remained stable over the time, with higher prevalence of *G. lamblia* in urban areas [15]. Up to 43% of water samples tested in Kathmandu Valley have shown *Giardia* cysts suggesting that most of the infection occurs due to drinking of contaminated water [21]. To address this issue, "ODF (open defecation free) Campaign" has been launched under the "Sanitation and Hygienic Master Plan-2011" of Government of Nepal [22].

Bacterial diarrhea and dysentery: Diarrheal disease-causing bacteria include enterotoxigenic *Esherichia coli* (ETEC), *Shigella* sp., *Campylobacter* sp., *Vibrio cholerae*, and others. This is mainly attributed to bacterial contamination of drinking water, which is very common in Nepal [23].

Cholera has remained endemic since long time to till date with several big epidemics in the past even in Kathmandu Valley and elsewhere in the country. Largest cholera outbreak occurred in Jajarkot District and neighboring Districts in 2009; affecting thirty thousand and causing more than 500 deaths [24]. Up to 26.3% diarrheal cases have been found associated with *V. cholerae*. Most of the *V. cholerae* as well as other bacterial isolates are multidrug resistant. Cholera outbreak due to drug-resistant *V. cholerae* serogroup O1 biotype El Tor serotype Ogawa in Nepal has also occurred (2012). Among the *Vibrio* species, *V. cholerae* has been isolated in 43.5% of sewerage/river system in Kathmandu Valley [25]. All *V. cholerae* isolates we isolated in 2016 rainy summer had O1*rfb* gene and were positive for virulence gene such as *ctxA*, *ctxB*, *tcpA*, *tcpI, hlyA, rtxA, rtxC, rstR, zot,* and *ace*.

Viral diarrhea: It is mainly caused by *Rotavirus*. However, in few cases, *Norovirus* and Adenovirus are also detected [26]. Up to 32.3% of diarrheal cases are found associated with Rotavirus of genotypes: G12P [6] (32.9%) and G1P [8] (19.5%) [27, 28]. Of the *Norovirus*, genotypes: GII.4 Sydney (34.6%) and GII.7 (19.2%) are common.

Typhoid Fever

Typhoid fever caused by *Salmonella enterica* serovars Typhi and Paratyphi A (*S.* Typhi and *S.* Paratyphi A) is endemic in Nepal with peak during pre-monsoon and monsoon season. It is common mainly in communities with poor environmental sanitation leading to the contamination of drinking water and poor hygienic condition [23]. Enteric fever is seen to affect young population. However, year to year numbers of enteric fever cases have been seen slightly decreasing as recorded at one of the tertiary level hospitals in Kathmandu Valley but yet causing a considerable burden (*S. enterica* serovars Typhi: 68.5% and *S. enterica* serovars Paratyphi A 31.5%) [29]. The decrease in the number of enteric fever cases during recent years appears to be attributed to the improvement of sanitary and hygienic condition even in the rural areas primarily because of open defecation free campaign [22]. Outbreaks occur occasionally and some of times due to multidrug-resistant organism spread from a single point source [30] (Fig. 1).

Interestingly, enteric fever due to *S. enterica* serovars Paratyphi A is increasing in Nepal (from 25.0% in years 1993–1997 to 41.0% in years 2008–2011 [31]. Though drug resistance in the organisms was a great problem in the past, meta-analysis has shown to significantly decrease in the odds of multidrug resistance (MDR) over time for both *S. enterica* serovars Typhi and *S. enterica* serovars Paratyphi A ($P < 0.01$); however, prevalence of MDR *S. enterica* serovars Paratyphi A was lower at each time block compared with *S. enterica* serovars Typhi [31].

Viral Hepatitis (A and E)

Waterborne viral hepatitis caused by *Hepatitis A* virus (HAV) and *Hepatitis E virus* (HEV) is common in Nepal with occasional epidemic. Anti-HAV antibody has been reported in 99.1% of study population indicating almost everyone in the community is exposed to HAV [32]. However, the Kathmandu Valley is considered to be hyperendemic of HEV and is responsible for acute hepatitis [33]. Recently, in 2014, big outbreak of hepatitis due to HEV occurred in Biratnagar (second largest city in the country) [34]. This is mainly associated with fecal contamination of drinking water everywhere in the country [23].

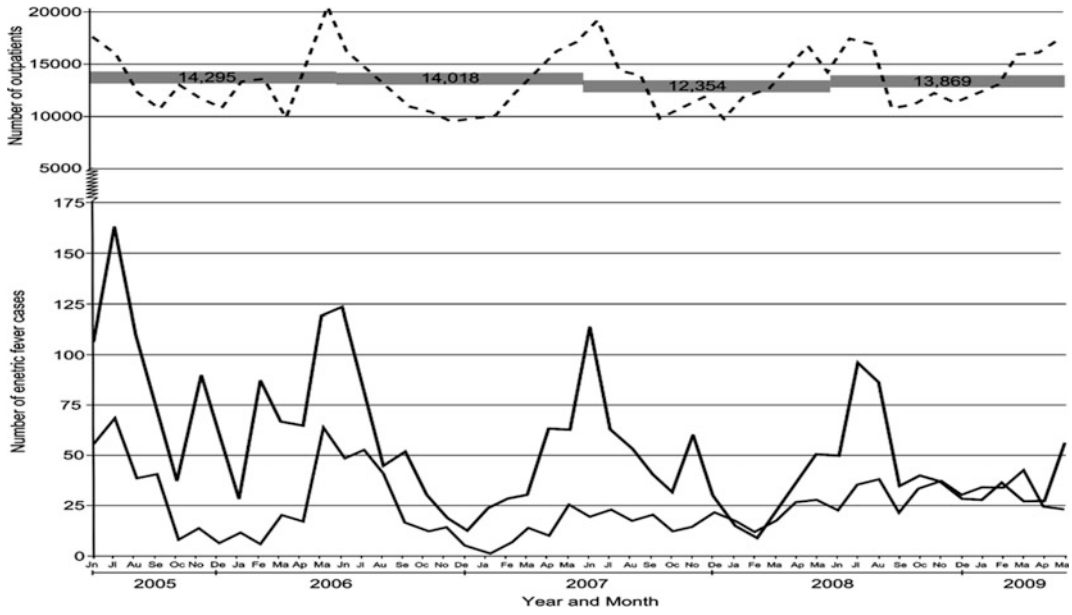

Fig. 1 Enteric fever case burden in patients attending a tertiary level hospital in Kathmandu Valley (2005–2009) [29]

Air Borne Infections

Acute Respiratory Infection

ARI caused by various kinds of pathogens is an important public health problem in Nepal particularly among under-five children. Many people suffer several episodes of ARI, many of them are self-resolved while others develop severe and complicated ARI and some even with fatal outcome. Recently, many "flu outbreaks" caused by various strains. Influenza A viruses have occurred across the country (*details are given in "emerging infection" section*). Both community and hospital-acquired (nosocomial) lower respiratory tract infections caused by MDR pathogens are on the rise. However, ARI has shown a declining trend (both in new cases: 33.37% in 2004/2005 to 31.0% in 2006/2007 and new severe cases: 2.1% in 2004/2005 to 1.2% in 2006/2007) [35]. Currently, ARI cases in under-five children are believed to be about 7.0% [36] with higher case in winter season and are associated mainly with both indoor and outdoor pollution, low socioeconomic status and nutritional condition.

Tuberculosis

Tuberculosis (TB) was one of the most important causes of public health problems in Nepal since a long time. Till one and half decade ago, TB estimated to cause 8,000–11,000 deaths per year. In the year 2000/01, over 31,000 TB patients were registered and treated under the National Tuberculosis Program (NTP), of which 13,000 were new smear positive [37]. The TB control program has achieved its goal in controlling TB significantly primarily due to effective case detection and treatment by DOTS (introduced in 1996) (with success rates of 85% or greater). However, TB remains as one of the major public health problems in Nepal and considered to be disease of poverty (malnutrition). According to Annual Report 2014, a total of 37,025 cases of TB were registered in 2014 out of which 51.0% were pulmonary TB mostly in people aged 15–24 years [38]. According to report, TB-HIV co-infection rate in Nepal is 2.4% (HIV among TB) and 11.6% (TB among HIV) based on the sentinel survey, 2011/12 and the TB program has saved 31,187 lives in 2014 nationally, but still 1049 deaths were reported among general TB cases [38]. However, there is big challenge of multidrug-resistant TB. Currently, 45% of total population is infected with TB, 40,000 people are infected with TB every year; 20,000 new sputum positive cases every year and 5000–7000 people die each year from TB [39].

STH and Other Infections

The decreasing trend of STH infection seen in the past (1986–1992) has been speeded up during the last one and half decade specially after the introduction of deworming program at school, improvement in environmental sanitation and freely available antihelminthic drugs at the healthcare facilities [10]. As a result, according to a systematic review, a sharp decrease in prevalence of STHs among school-aged children in Nepal in last decade with prevalence dropping below 5% for each of STHs with no variation in prevalence in rural and urban areas has been achieved (Fig. 2) [15]. Intestinal parasites particularly STH are known to cause malnutrition and its associated manifestations. Previous studies from Nepal have established that STH cause anemia, vitamin A deficiency, and other micronutrient deficiency among Nepalese [40, 41]. This might have contributed in the decreasing proportion of malnourished children during recent years [5].

Rabies

Though epidemiology and impact of rabies in Nepal are not known well, rabies is endemic in Nepal since long time. As more than 75% of the total anti-rabies vaccine used in Nepal was being used to treat the victims of dog bite cases in Kathmandu Valley, government launched rabies control program with killing of stray dogs in the valley and with the production of rabies vaccine

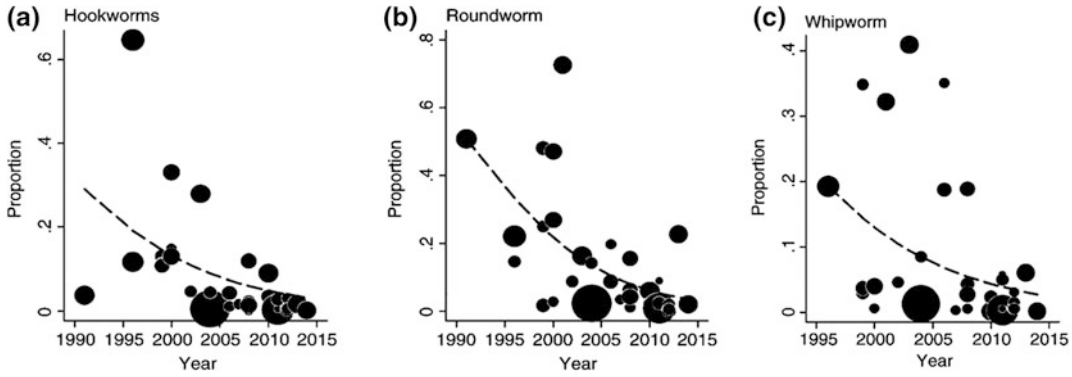

Fig. 2 Sharp decrease in the prevalence of STH in Nepal past decades [15]

within the country. Also, different non-state actors have been conducting rabies control activities over the years [42, 43]. During the period of 1992–1996, a total of 181 human rabid cases were reported (diagnosed clinically; among them one which was diagnosed by mouse inoculation) and were from 37 different Districts with the history of dog bite [44]. Per year, rabies is reported to kill about 100 livestock and 10–100 humans, while about 1,000 livestock and 35,000 humans are reported to receive rabies postexposure prophylaxis, however, these estimates are very likely to be serious underestimations of the true rabies burden [45] (Fig. 3).

Ocular Infections

Ocular infections (conjunctivitis, retinitis, blepharitis and others) caused by bacteria and fungi are common in Nepal. Few cases of ocular cysticercosis, toxoplasmosis, and toxocariasis have also been reported [11]. Recently, Herpes virus associated eye disease is reported to be 10.3% [46]. Epidemic of acute hemorrhagic conjunctivitis occurs on every 2 to 3 years and is found

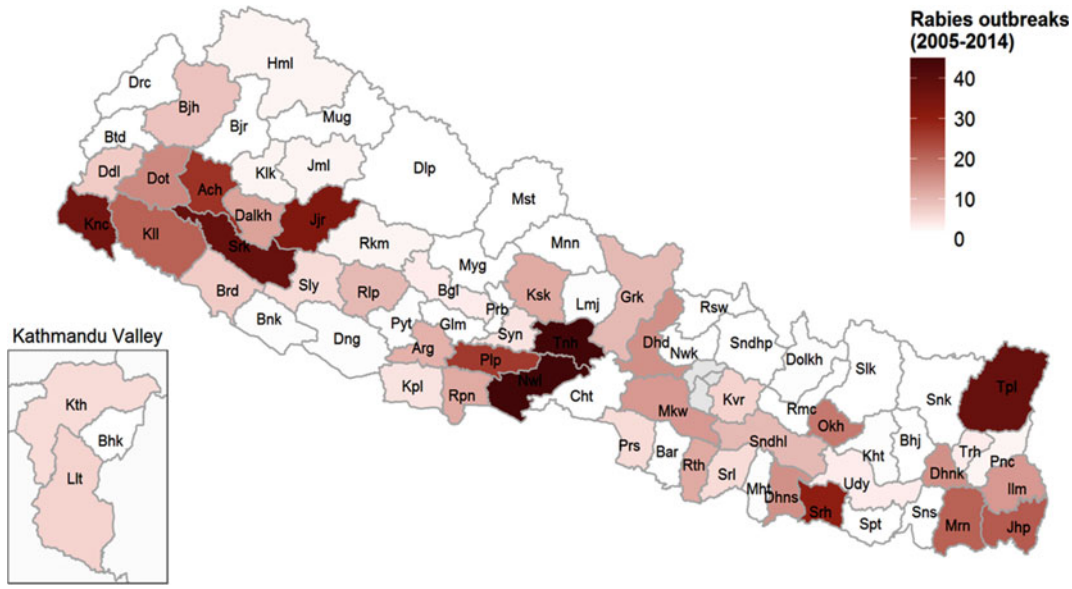

Fig. 3 Map of rabies outbreak in Nepal (2005–2014) [45]

to be associated with viruses such as *Adenovirus* and *Coxsackie virus* [47]. Interestingly, a mysterious ocular manifestation known as SHAPU (seasonal hyperacute panuveitis) predominantly affecting the children is reported only from Nepal [48]. It is presumed to be associated with a white *Tussock* moth however; bacteria (*Streptococcus pneumoniae* and *Acinetobacter* sp.) have also been isolated from SHAPU patients with granulomatous inflammation [48, 49].

Helicobacter Pylori Infection

Helicobacter pylori infection is common in Nepal. The reported prevalence in gastroduodenal diseases (as studied by rapid urease and serological tests, reportedly ranged from 39.0 to 86.6% [50]. In a study, 29.5% endoscopied biopsy materials taken from patients with gastroduodenal complaints were positive *H. pylori* [50]. Histological study has shown prevalence of *H. pylori* in 50.5% [51]. *H. pylori* antibody has been found 16.7% of children (5–16 years) with recurrent abdominal pain indicating that exposure to bacteria begins from small age [52]. Drug resistance in *H. pylori* isolates has been a challenge.

Sexually Transmitted Infections (STI)

STI is common in Nepal but the data are scarce as most of the studies are carried out in high risk groups. Among the patients visiting the tertiary care center for sexually transmitted diseases, majority were of 15–24 years with male to female ratio of 3.19:1 and 52.3% were married [53]. The common STI included genital wart, syphilis, gonorrhea, nongonococcal urethritis, *Herpes simplex virus* infection, HIV/AIDS, and moluscum contagiosum were more common, and according to occupation, students were most common followed by security personnel, housewives, businessmen, unemployed, transport staffs, and others.

HIV infection first reported in 1985 reached its peak in 2005–2009 and then has shown a slow declining trend every year. Currently, over 60,000 people are estimated to be infected and common among sexually active age group particularly among male migrant workers. Overall HIV prevalence in Nepal is estimated at 0.30% in the adult population and it is categorized as a concentrated epidemic [54]. The TB-HIV co-infection rate (the prevalence of HIV infection among TB patients) in Nepal is 2.4% [55].

Two-third of patients had polygamous relationship and married person living singly had more frequent extramarital sexual contact; most common type of partner for sex debut was wife/husband followed by friends and others including commercial sex workers, and patients aged 15–24 years had multiple (2–4) sex partners [53]. Of the patients studied, only 7.7% used condoms consistently [53]. One study showed high STI prevalence among drivers/conductors and migrant workers of sexually active age group [54]. Hence, STI is more common in Districts with highways running through. When, these sexual behaviors and relationships are considered, STI in the community appears to be spreading fast but go unrecorded as many patients get treated confidentially at private clinics. Therefore, the burden of STIs appears to be huge in Nepal [54].

Endemic Vector-Borne Infections

Japanese Encephalitis (JE)

JE in Nepal is endemic in *Terai* (plain) region and constitutes a big public health problem since its entry in 1978 during which similar big outbreak occurred in Indian State of Uttar Pradesh [56]. Cases start to appear in the month of April–May and reach its peak (in thousands) during August–September and declines from October with an average annual mortality rate of 150–300. In 2005, a total of 26,667 cumulative JE cases and total of 5,381 cumulative deaths with average case fatality rate of 20.2% since 1978 was reported [57]. More than 50% of morbidity and 60% of mortality occurred in children (aged below 15 years). JE initially confined in *Terai* with hyperendemicity in western *Terai* Districts has now spread to hilly and even in mountain regions as emerging infectious disease [56, 58–60] (Fig. 4).

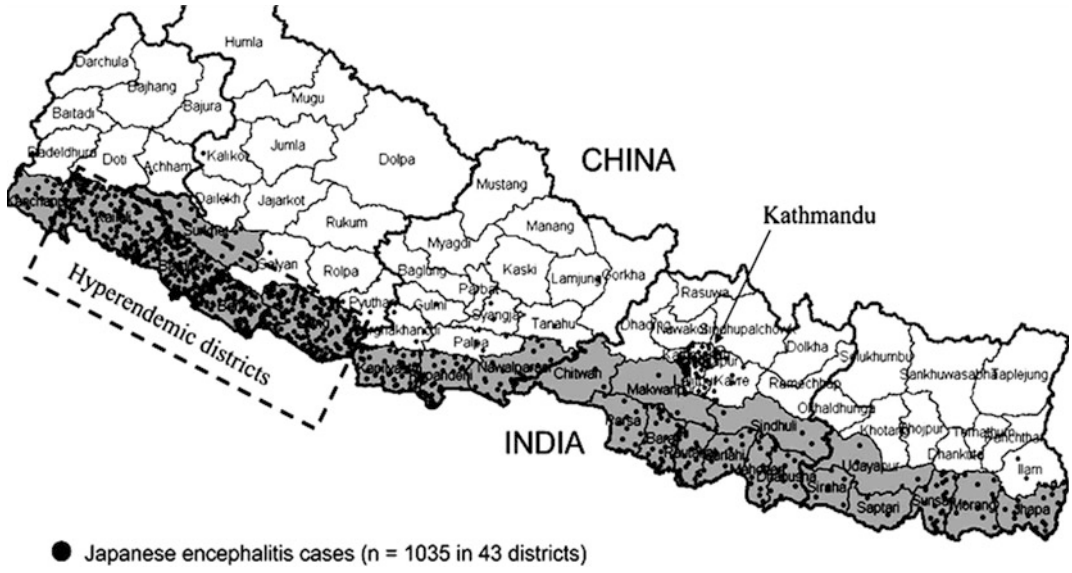

Fig. 4 Distribution of IgM-positive JE cases, May 2004 through April 2006, Nepal. (gray areas in JE endemic areas showing hyperendemicity in western part) [60]

Considering the JE burden and a devastating JE outbreak in 2005 (with 2,000 deaths in poor and rural communities in *Terai* area), mass JE vaccination campaign in JE affected areas was launched in 2006. JE vaccination has shown significant reduction if JE cases in Nepal. A recent impact analysis of immunization showed that vaccination prevented thousands of cases of JE and cut the JE rates in Nepal by at least 78% [61].

Malaria

Despite efforts made to control malaria since 1954, malaria still constitutes one of the major public health problems in Nepal. About 84% of populations were estimated to be at risk of malaria in 2012 with 4% at high risk [62]. About one million people live in areas with a reported incidence of more than one case per thousand populations per year [63]. The recorded confirmed malaria cases from 1963 to 2012 showed highest peak in 1985, after which, as a result of various malaria control efforts made, a significant decline in malaria cases (12,750 in 2002 vs. 2,092 in 2012; decline by 84%) has been observed with some outbreaks in between [62].

Though incidence of malaria has declined sharply during last two decades, malaria is spreading to hilly and even mountainous regions (mainly in river valley/belt and foot hills) as well (Fig. 5 Left) [64]. This appears primarily due to vector adaptation and north–south roads linking endemic *Terai* area and hilly/mountain region and climate change [3]. It is noteworthy that the incidence of indigenous malaria in Nepal is decreasing during last one decade, however, on the contrary, the incidence of imported malaria cases is on the rise (Fig. 5, Right) [64]. All most all imported cases are coming from India and are caused by *Plasmodium falciparum* most of which are drug resistant.

Considering the gravity of malaria burden, Nepal Malaria Strategic Plan 2011–2016 has a vision of malaria-free Nepal by 2026 and is based on the "Long Term National Strategy of Malaria Elimination" [65]. However, there are challenges of increasing entry of malaria cases through open border between Nepal and India, limited access to diagnostic facilities to clinically confirm suspected cases and their treatment, the development of resistance in parasites and vectors, climate change, and shifts of malaria

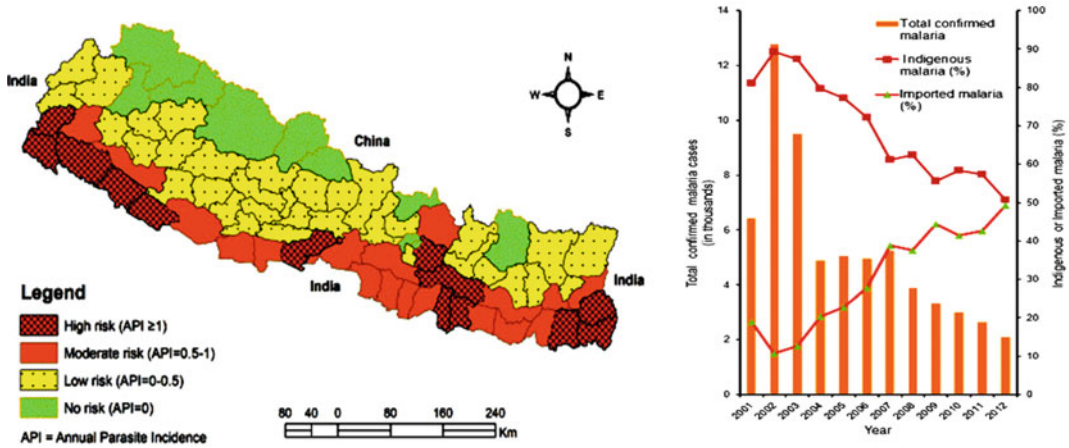

Fig. 5 Classification of malaria risk Districts in Nepal with annual parasite incidence (left) and malaria cases by origin (right) [62]

hotspots to new areas and stable persistence of malaria hotspots in specific areas despite more than 6 years of continuous vector control intervention [3, 62, 64].

Visceral Leishmaniasis (Kala Azar)

Visceral leishmaniasis commonly known as *Kala Azar* (KA) is one of the major public health problems in Nepal and is primarily confined to 12 low altitude tropical climate Districts in eastern *Terai* belt bordering the state of Bihar (India). The annual incidence of KA from 1980 to 2006 is shown in Fig. 6. The average incidence for the years 2004–2006 was about 2.43 per 10,000 populations in the 12 KA endemic Districts of Nepal. It is associated with low socioeconomic status, low literacy rate, and lack of good governance. To address the problems associated with poverty, government has implemented a plan to eliminate the KA from Nepal by 2015 with the reduction of poverty incidence from existing poverty 27% (2010) to at least 16% in KA endemic areas [66, 67]. Because of the implementation of comprehensive KA elimination plan and program, total KA cases and deaths have shown a significant decrease during last 13 years (Fig. 6). However, KA has shown changing epidemiology recently (cases endemic only in eastern *Terai* region have now spread to western *Terai* as well as some hilly Districts) [67].

Lymphatic Filariasis

Lymphatic filariasis (LF) caused by nematode *Wuchereria bancrofti* is endemic in Nepal with great public health impact. Mapping has shown 13% average prevalence in the country (ranging from <1% to as high as 39%) [68]. Keeping in view of the findings, Epidemiology and Disease Control Division is now implementing the National Plan of Action (2003–2020) aimed to eliminate the LF from Nepal. For this, "mass drug administration" (MDA) (Diethylcarbamazine and Albendazole) initiated in Parsa District in 2003, now scaled up to other endemic Districts as well (56 Districts out of 75 have been included). As a result, LF has shown a declining trend during recent years. However, five rounds of MDA were not sufficient to disrupt the transmission cycle in all Districts, probably because high baseline prevalence has posed as a challenge [69].

Opportunistic Infections

Opportunistic infections are increasing in Nepal during recent years. It is associated mainly with the spread of HIV/AIDS and increase of noncommunicable diseases (NCD) like diabetes, malignancies (cancer), chemotherapy/radiotherapy for malignancies, and organ transplantation that augment

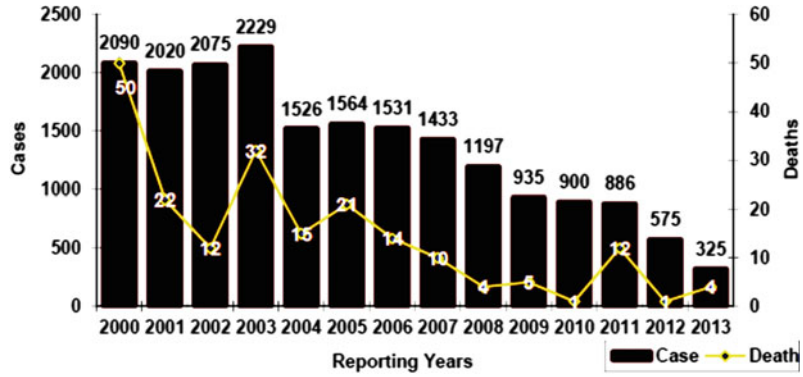

Fig. 6 Trend of *Kala Azar* cases and deaths in Nepal (2000–2013) [67]

immunodeficiency. TB and HIV co-infection is an important example; although TB was common pre-HIV/AIDS era also and was primarily associated with poverty and undernutrition/malnutrition that contribute to immunocompromization and with unavailability of diagnostic and treatment facilities [7, 55].

Opportunistic parasitic infection: Of the various opportunistic parasitosis, cryptosporidiosis is prominent. The prevalence in patients with diarrhea ranges from 0.4 to 17.0% [19, 70–72]. It is more common among young children compared to older people. Among the school going children, it is reported to be 29.4% [73]. Most of *Cryptosporidium* infections are associated with other intestinal protozoan and helminth parasites [72]. Infection is more common during rainy summer season. Nearly half (48.6%) of the young calves of cattle (cow and buffalo) are positive for *Cryptosporidium* oocysts suggesting that calves' feces are the major source of infection in Nepal [74].

Enteric parasites are reported to cause diarrhea (31.13%) of the HIV-seropositive patients. The majority of infections were among patients with CD4 count <200 cells/μl associated with opportunistic parasites (*Cryptosporidium*, *Cyclospora* and *Isospora*) [75]. Seven percent of HIV positive individuals were found infected with opportunistic coccidian protozoa [76]. One study of parasites in HIV/AIDS patients showed *Cryptosporidium* (10.7%), *Giardia* (6.7%), *Entamoeba histolytica* (5.33%), *Cyclospora* (2.67%), *Strongyloides stercoralis* (2.7%), and *Trichuris* (2.67%) [77]. Infection rate was higher in AIDS patients (61.5%) compared with 25.8% HIV-seropositive patients. *Cyclospora* has been detected in nearly 15% of diarrheal fecal samples and in vegetables samples collected in Kathmandu [25, 70, 78].

Toxoplasma gondii (coccidian protozoa) infection rate among apparently healthy population living in different geographical areas ranged from 24 to 76.1% with an average of 45.6% [79, 80]. Overall prevalence is significantly higher in females than in males, similarly higher prevalence is seen among *Tibeto-Burman* compared with *Indo-Aryans* [80]. Region wise higher prevalence is in western region followed by eastern and central regions, respectively. High prevalence is associated with the raw meat eating habits of locals [81]. There is high prevalence in common meat animals (pigs, goats, buffalos and chickens) in Nepal [82]. Prevalence is higher (55.4%) in pregnant women and women with bad obstetric history. Patients with malignancy (cancer) had highest prevalence (68.7%) and must be due to an opportunistic infection [83]. However, till now only one case of congenital toxoplasmosis has been reported [84] (Fig. 7).

Opportunistic fungal infection: According to a recent review, 2% of total populations are estimated to suffer from serious fungal infections (namely, keratitis is (approx. 73 per 100,000), chronic obstructive pulmonary disease allergic bronchopulmonary aspergillosis and severe asthma due to fungal sensitization, chronic pulmonary aspergillosis) in Nepal annually [85]. According to review, of the 22,994 HIV patients with CD4 counts <350, but not on antiretrovirals,

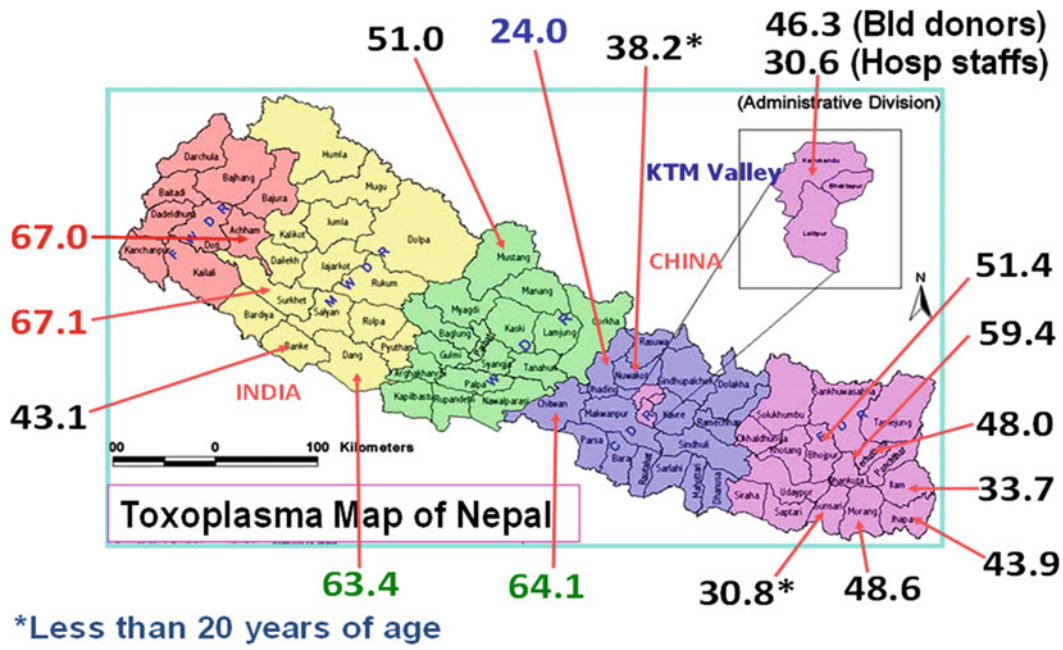

Fig. 7 Scenario of *Toxoplasma* infection in Nepal

Pneumocystis pneumonia infections are estimated at 990 annually. Cases of oral and oesophageal candidiasis in HIV/AIDS patients were estimated at 10,347 and 2950, respectively. Sporadic cases of opportunistic fungal infections have been reported in patients with diabetes, malignancies, and patients undergoing treatment of malignancies. Findings of review of published papers together with mycology expert indicate that there is significant burden of serious fungal infections in Nepal [85, 86].

Hospital Acquired Infection (HAI)

HAI also known as nosocomial infection is a great concern in Nepal though it is said to be improving with time (between 2003 and 2011) at some hospitals [87]. However, infection control committee (ICC) was established in 41.2% (7/17) of the hospitals and of them regular ICC meeting was held in only two hospitals; ICC's operational activities were far from adequate [87]. Accordingly, none of the hospitals studied had an infection control team (ICT). Common HAI causing bacteria in Nepal includes *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter* sp., *Escherichia coli, Klebsiella* sp., *Enterobacter* sp., *Citrobacter* sp., *Proteus* sp., and others. Most of these HAI bacterial isolates are MDR. These bacteria are mainly associated with urinary tract infection, ventilator-associated pneumonia, surgical site and implant-associated infection, catheter site infection, and soft tissue infections. This is primarily due to high microbial (bacteria and fungi) burden in hospital environment and high pathogen career rate among staffs (hands: 59.2% and nose: 73.7%) mainly *S. aureus* and most of them were highly drug resistant) [88].

Zoonotic Helminthes Infections

Hydatid disease (Echinococcosis) and Cysticercosis: Echinococcosis (hydatid cyst) in different organs has been reported from Nepal but the prevalence in the community is largely unknown [89]. An unusual and interesting case of uncomplicated hydatid cyst in lung (single cyst

of 8 cm) and in liver (two cysts of 7.5 cm each) in a 6-year-old girl has also been reported [90]. As in the case of hydatid cyst, prevalence of cysticercosis is also not known. However, it is suggested that the prevalence ranges from 0.002 to 0.1% in general population in Nepal [91]. Of the total 23,402 biopsied cases recorded at a hospital in Kathmandu Valley, 62 (0.3%) were diagnosed as cases of cysticercosis [89]. The cases of ocular and/or neurocysticercosis are on the rise and thought to be due to the availability of diagnostic facilities (particularly the CT and MRI) during recent years. As reviewed by Rai, there are sporadic reports on other zoonotic parasites [89]. The reported seroprevalence of *Toxocara* antibody is very high (81.0%) though the clinical cases of toxocariasis (visceral and/or ocular larva migraines) are not very common [92]. *Toxocara* eggs rank second (accounting 22.8%) among the helminth eggs contaminating the environment (soil) in Nepal1 [13]. Very rarely, cases of trichinosis, fascioliasis, paragonimiasis, and sparganosis have also been reported [89].

Emerging Infections

Though the overall rate of infectious diseases in South Asia is decreasing, the challenges of existing infectious diseases such as tuberculosis, HIV/AIDS, malaria, and others have been augmented by emerging and growing threats of dengue, chikungunya, healthcare-associated infections, and antimicrobial resistance [93]. Nepal is facing also the challenges of new vector-borne infectious diseases. *Culex* mosquito borne JE first appeared in Nepal in 1978 and limited in western *Terai* area has shown a changing epidemiological pattern (now has spread even in hilly areas) [56–60]. JE still constitute a public health problem despite the immunization against Japanese B encephalitis virus.

Dengue fever (*DF*): First case of *Aedes* mosquito-borne *Dengue virus*, was reported in 2004 from Chitawan District [94]. Since then, *Dengue virus* infection has spread in big way with a series of DF outbreaks in several Districts of Nepal [95–97]. Dengue IgM antibody among feverish patients has been seen in 27.8% to 29.1% with highest prevalence among children (<15 years) [98]. The disease is common during monsoon and post-monsoon season and affects mainly young adults (aged 21–40 years). A shift in *Dengue virus* serotype, serotype 1 in 2010 outbreak to serotype 2 in 2013 outbreak has also been observed [96] (Fig. 8).

The spatiotemporal analysis (2010–2014) has shown that Chitawan District (home for first case of DF) is the hotspot of DF followed by Jhapa and Parsa Districts [99]. Now, *Dengue virus* is spread even in hilly areas including Kathmandu Valley [99]. This has been thought to be associated with change in climate and biodiversity [3, 100–102]. DF and dengue hemorrhagic fever (DHF) might have been underestimated as many cases might have been misdiagnosed and/or undiagnosed. Among the various emerging infections in Nepal, DF has been a great health public problem, however, precise burden of DF and DHF in Nepal remains unknown, since most reports are confined to economically affluent city and/or town areas and do not account for regions of relative social deprivation where disease is more likely to occur [97].

Other emerging viral infections: Very recently, in 2014, first case of chikungunya (transmitted by *Aedes* mosquito) has also been found in Nepal [103, 104]. Serological study among patients presenting with fever has shown seropositive rate of 3.6% [105]. A case of chikungunya has been found even in Kathmandu Valley. West Nile virus infections (usually transmitted by *Culex* mosquito) and *Chandipura virus* (transmitted by *Phlebotomus* sand fly and earlier limited in Chandipura Village of Maharashtra, India) have also been reported from Nepal [106].

Influenza virus: Influenza A virus (H5N1) (avian influenza or bird flu) appeared in Nepal in 2009 with first confirmed outbreak in far-eastern Nepal (called Kakarbhitta) close to Indian border and subsequently, outbreaks occurred in Kathmandu and Bhaktapur Districts in Kathmandu Valley as well as other parts outside of valley causing millions of poultry were died/destroyed

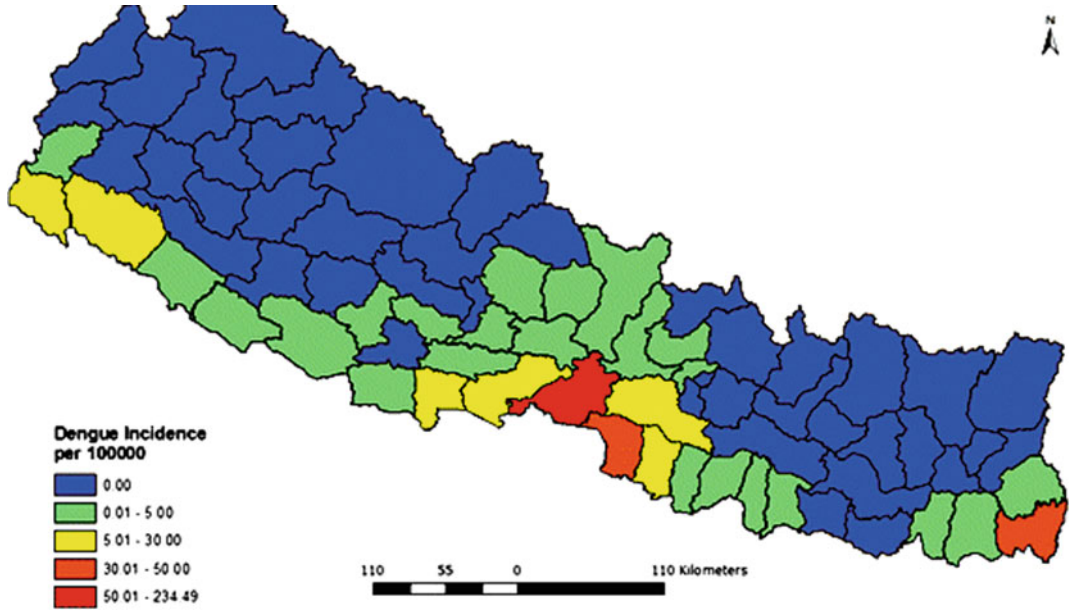

Fig. 8 Annualized average incidence of dengue fever in Nepal (2010–2014) [99]

[107]. Many outbreaks occurred in the year 2013. This resulted into great loss in economy particularly to poultry farmers and farm associated business (egg, meat, and feed business). As a result, government provided compensation to the poultry farmers and businesses concerned for the loss of chicks, eggs, bird feed, and chicken due to the spread of bird flu at six different places. To control H5N1, special plan, program and activities were launched and Nepal has been declared free of H5N1 highly pathogenic avian influenza (HPAI) in May 2014 [108]. However, another variant of avian influenza (H5N8) has been reported this year in eastern Nepal [109].

An outbreak of *Influenza A* (H3N2) was detected at three Bhutanese refugee camps in southeastern Nepal in July 2004 [110]. Outbreak of Pandemic *Influenza A*/H1N1 occurred in Nepal in 2009. Universal *Influenza A virus* was positive in 49.6%, more than half in young people. Among them 28.3% were H1N1 and 21.3% were seasonal influenza A. Case fatality of H1N1 was 1.74% [111]. After 2009 H1N1 is appearing every year with significant number of fatality. This year (Sept. 2017) alone, H1N1 has appeared as epidemic forcing the closure of school in Syanja District in western Nepal and dozens of deaths occurred across the country [112].

Other emerging viruses: Seroprevalence of *Hantavirus* infection is 8.7% with higher prevalence in *Tamang/Sherpa* ethnics (16.0%) who live mainly in hilly/mountain areas [113]. Though no cases of human *Hantavirus* infection have been reported till date (might have gone undiagnosed) it may emerge as a cause of health problem in future. Other viral infections existing in Asia, namely, *Nipah virus* (discovered in Peninsular Malaysia), Middle East respiratory syndrome coronavirus (MERS-CoV), and Crimean-Congo hemorrhagic fever are not evidenced yet. However, there is high possibility of entering of these infections into Nepal anytime in future considering the fact of climate change, vector and agent adaptation, and biodiversity modification during recent years [3].

Scrub typhus: Though, serological evidence of existence of scrub typhus in eastern Nepal was reported long back in 1981 clinical cases reported in 2015 with high numbers from Chitawan District where in 2004, also the first case of

dengue fever was recorded [94, 114, 115]. In the year 2016, over 800 cases were detected from all over the country out of which 14 (1.7%) died. This year (2017), as many as 37 cases have been reported in Chitawan District alone [115]. Scrub typhus, therefore, has constituted one of the newest and important health problems in Nepal, which demands active surveillance and public health awareness about the disease transmission and prevention.

Leptospira infection: First report on leptospirosis in Nepal appeared in 1981 [116]. In 2000, Rai et al. reported *Leptospira* seroprevalence rate of 32.0% among apparently healthy people with equal positive rate among males and females, and *Tibeto-Burman* and *Indo-Aryan* ethnic groups [117]. Seropositive rate among the suspected cases of leptospirosis in central *Terai* and in Kathmandu has been reported at 4.8% and 28.6% [118, 119], respectively. However, in western *Terai*, among the 144 febrile cases, 21% have been reported to be positive for leptospiral antibodies (IgM) indicating the acute leptospirosis [120]. Among the undiagnosed cases of acute encephalitis cases, 51.6% were positive and was higher in the age group of 6–15 years [121]. Most of the positive cases are occurring during rainy summer and autumn season and are associated with rain and flooding, and mostly adults are infected.

Emerging protozoan infection: *Cryptosporidium parvum* is reported in 0.4–17% in loose stool in Kathmandu [19, 70]. Up to 25% of water samples tested in Kathmandu Valley have shown *C. parvum* oocyst. The reported *Cyclospora* infection rate is as high as 30% in loose stool in Kathmandu [122]. Two percent of water samples tested in Kathmandu have shown *Cyclospora* oocysts.

Emerging fungal infection: Documented emerging fungal diseases in Nepal are scanty. Supram et al from Manipal Teaching Hospital; Pokhara in Western Nepal recently reported invasive infections in a group of hospitalized patients caused by *Magnusiomyces capitatus*, an emerging yeast [123]. Considering the increasing number of cases of immunocompromising conditions such as diabetes, malignancies, chemo- and radiotherapy for malignancies and HIV/AIDS, the opportunistic fungal infection must be existed but are not reported.

Issues of Bacterial Drug Resistance

Until 1990s, bacterial drug resistance was not common in Nepal. Drug-resistant *Escherichia coli* was reported in 1978 [124]. For the first time, methicillin-resistant coagulase-negative *Staphylococcus* and methicillin-resistant *S. aureus* (MRSA) reported in 1987 and 1990, respectively [125, 126]. In recent studies, over half of *E. coli*, *Klebsiella pneumoniae* and *Streptococcus pneumoniae* isolates were tested, and over 30% of some *Shigella* sp. and *Vibrio cholerae* isolates were resistant to first-line antibiotics and many other important bacterial pathogens are highly resistant to most first-line and some second-line antibiotics [127]. This resulted primarily due to misuse (overuse, underuse due to lack of awareness and lack of purchasing capacity, inappropriate use/prescribing, excessive use of antibiotic in agriculture/animal husbandry) of antibiotics and other drugs in the society.

Though antibiotic use in agriculture/animal husbandry especially animal food is poorly documented in Nepal, it is believed that antibiotics in animal feeds particularly of meat animals (chickens, pigs and others) are being used massively and are contributing to the overall antibiotic resistance. According to Global Antibiotic Resistance Partnership-Nepal (GARP-Nepal), the volume of veterinary antibiotic sales in Nepal rose over 50% from 2008 to 2012, most through retailers without veterinarian prescription [127]. Due to the indiscriminate and prolonged use of antibiotics in meat animals, high level of antibiotic residues has been found in the marketed meat and consumable broiler chicken liver, in particular, showed very high percentage of antibiotic residue [128]. As a result, some organisms have developed not only multi-drug resistance but pan-resistance and have become an alarming public health concern.

Double-Triple Burden of Disease

Though the prevalence/incidence of infectious (communicable) diseases is decreasing in Nepal, noninfectious (noncommunicable) diseases are on the rise. Hence, Nepal is now facing a double burden of diseases. The decrease in infectious diseases is attributed primarily to the health (curative, preventive and promotive) related activities (immunization, increased access in health service, free primary healthcare services including free essential drugs to poor and marginalized people as stipulated health as "fundamental right" in the constitution-2007, production of different levels of human resources on health including specialized specialist within the country and various efforts made by the state and non-state actors). Moreover, more than 52% of the diarrheal cases are being treated by Female Community Health Volunteers (FCHVs), the interface between healthcare facility and community. This may be the reason that spread and outbreak of various infectious diseases predicted after the earthquake 2015 did not occur. Infectious diseases are common in villages, but town and cities are not completely free of infectious diseases. Interestingly, some of the outbreaks of infectious diseases are occurring only in the town and cities. However, the overall prevalence of infectious diseases has come down. However, unusually heavy rainfall, floods, and landslide are creating good environment for the spread of infectious diseases.

Although infectious (communicable) diseases are decreasing, noncommunicable diseases (NCD) together with emerging/reemerging infectious diseases are on the rise in cities. Hence, there is double-triple burden of disease. The diabetes and associated conditions (nephropathy, retinopathy and others), cardiovascular diseases, cancer, and chronic obstructive pulmonary diseases are the major NCDs which are driven by various forces including aging, rapid but unplanned urbanization and unhealthy lifestyles.

Conclusions

Overall burden of infectious (communicable) diseases is decreasing during recent years. However, there is big challenge of tackling the emerging and reemerging infections. At the same time, there is rapid increase of various noninfectious (noncommunicable) diseases that enhances opportunistic infections. To combat the infections of different kinds, WHO recommended five interventions (innovative and intensified disease management; preventive chemotherapy; studies on vector ecology and management; veterinary public health services; and provision of safe water, sanitation and hygiene) which must be implemented together with the global action plan adopted by World Health Assembly-2915 to address the problem of drug resistance (improve awareness and understanding about antimicrobial resistance; strengthen the knowledge and evidence through surveillance and research; reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures; optimize the use of antimicrobial medicines in human and animal health; develop the economic case for sustainable investment that takes account of the needs of all countries and increase investment in new medicines, diagnostic tools, vaccines, and other interventions) [129].

In this regard, Nepal has developed several plans of action. These includes: "ODF Campaign" that has been launched under the "Sanitation and Hygienic Master Plan-2011", "Nepal water supply, sanitation and hygiene sector development plan: 2016–2030" and "Multisectoral Action Plan for the Prevention and Control of Non-communicable Diseases 2014–2020" (developed in accordance to the Global Action Plan for the Prevention and Control of NCDs 2013–2020 and Infectious Disease Control Guideline [22, 130–133]. Habitat destruction and infectious disease are dual threats to nature and people (as emerging infections), biodiversity and nature conservation [102, 103]. To address this,

"National Biodiversity Strategy and Action Plan 2014–2020" has been developed [3]. To facilitate and coordinate all these and others, "High Level Multi-sectoral Health Services Facilitation and Coordination Committee" has also been formed at National Planning Commission in 2012.

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