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Epidemiology of dengue in Pakistan, present prevalence and guidelines for future control

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Abstract
Dengue is crucial vector-borne viral human disease across the tropical and subtropical region of world. Dengue is transmitted from one person to another person by biting of female *Aedes aegypti* and *Aedes albopictus*. Dengue is present in every corner of the world (WHO), almost 128 countries are known to dengue outbreak, about 100 billion dengue cases are reported worldwide and more than 390 million humans with chance of infection annually. Pakistan is subtropical country and main hotspot for vector-borne diseases such as dengue haemorrhagic fever, malaria, leishmaniasis, Crimean-cango and West Nile virus diseases. Four dengue serotypes are present in Pakistan and circulating whole year with peak outbreak between (September-November) during post monsoon periods. In Pakistan dengue epidemic is a major public threat since 2005, following millions of people at risk, till 2016 almost 71649 dengue cases are reported with 757 deaths. There are several factors such as climatic change, urbanization, travel, socioeconomic activity, miscommunication and shortage of surveillance. Worst dengue outbreak occurred in Pakistan during 2011 with 21685 dengue reported cases (350 deaths). Current literature was reviewed, stressing on epidemiology, vector distribution (different region) of country, pathogenesis and future strategies for control. The paper review assesses the epidemiology of *Aedes* vector capacity linked dengue threats and outbreaks public health burden and losses in different geographical settings in Pakistan.

Keywords: Dengue, epidemic, Infection, vector-borne diseases

Introduction
Dengue is vector borne viral disease of 21st Century and is regarded as a threat to public health results in heavy socio-economic encumbrance on a large number of tropical, subtropical and temperate region of world [1, 2]. Currently it is estimated 50 % of world population is living in dengue prone areas where they are in danger of dengue arboviral disease and 50% of world population live in dengue indigenous countries [2, 3]. Approximately 100 million dengue cases are reported and more than 390 million people with chance of infection worldwide each year [4]. The causal agent of dengue virus (DENV) belong to family Flaviviridae and genus Flavivirus, four anti genetically distinct serotype are (DENV 1, DENV 2, DENV 3, DENV 4) and five recognized serotype (DENV 5) characterized by neutralization assays [5, 6]. These virus are transferred by female *Aedes* mosquito (Diptera: Culicidae) especially *Aedes aegypti* (Linnaeus) and lesser extend *Aedes albopictus* (Skuse) that feed on human blood both indoors and outdoors during dawn to dusk and can be found in tropical and subtropical region particularly dominant in urban environment and spreading out to rural areas. These mosquitoes can also transfer chikungunya, Zika infection and yellow fever [7, 8]. Dengue is complex disease with clinical illness is traditional classified ranging from mild to severe form including undifferentiated fever, dengue fever (DF), dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS) and extended dengue syndrome. DF is a terrible, flu-like disease that distresses babies, young children, adults and causes rarely death. Dengue should be doubted with high fever (40 °C) followed by these signs: severe headache, joint and muscle discomfort, swollen glands nausea, pain behind the eyes and vomiting. After 4–10 days bite from an infected mosquito symptoms generally appeared and last for 2–7 days. However DHF and DSS are more severe and possibly lethal forms with symptoms like plasma leaking, respiratory distress, severe abdominal pain, fluid accumulation, severe bleeding, or organ injury.

Aedes mosquitoes flourish in areas with standing water, including water containers, puddles, water tanks, Plant vessels, tree hole, old tires and absence of proper sanitation [9]. The importance of this review paper to elaborate current epidemiology of dengue and also particular additional steps will need to complete understanding of dengue epidemiology in different region of Pakistan. Furthermore, different policies will make to manage dengue outbreak in future.

Worldwide distribution of dengue

The recorded history of dengue has been present since many centuries. Dengue like symptom recorded firstly in China Medical Encyclopedia mention over 992 AD ago [10]. This disease was known as 'water poison' and it is linked with flying insects, nevertheless no uniform agreement is available about geographically distribution of DENV [11, 12]. Outbreak of disease corresponded to dengue occurred in West India and Central America in 1635 and 1699 respectively [13]. Therefore some evidence which indicated that mosquitoes viruses were present in Asia and Africa forest with major outbreak in people living in Asia, Africa, Philadelphia and North America during 1780, epidemic happened in New Orleans during 1945 [11, 13]. Only 9 countries witness dengue epidemics previously 1970. The transmission of dengue viruses by mosquitoes 1st determined in 20th century. The fast dispersed of dengue throughout the world due to spread of its principle vector and origin of main vector *Aedes* mosquito is considered to be from Asia or Africa. Dengue has spread across the urban costal region of the world due to shipping watercraft with marketable expansion in 1800.The shipping watercraft support transformation of breeding sites for vector along with humans to complete the diffusion cycle and permit to distribution of virus and mosquito across the coastal region of world. Outbreak of dengue were separated within 10-40 year due to shipping way of transportation [14, 15]. The expansion of dengue across the world due migration, travelling to intra and inter countries and resulting of two desolation world wars, shipping and rapid development lead to enhance transmission of dengue in almost South East Asian countries with consequent beginning of the severe form of dengue, which results in more than 30 fold increased in dengue rate all across the world during 1960 to 2010 [11, 15]. There are some important factors which are responsible for endemic threat of dengue which includes deforestation, increasing population growth, accidental urbanization, traveling by air, inadequate public health care facilities, insufficient people knowledge, poor disease surveillance, difficult to vector control and global warming [16]. Currently more than 3.9 billion people of 128 countries live in tropical and subtropical areas where dengue viruses consider being transmitted [17]. Dengue is worldwide concern, about 75 % population disclosed to dengue belongs to Asia –Pacific region.1.3 billion of individual reported at risk belong to ten epidemic countries in the Southeast Asia region. In Southeast Asia region 187333 dengue cases were reported by WHO in 2010 and rate is 18 times higher as compared to America [3, 14]. In Australia dengue epidemic occurred in Northern Queensland due to the presence of *Aedes aegypti* and 1000 dengue were cases reported during 2009 to 2010 [18]. Dengue emerges in 22 African countries during 1960 to 2010.In Europe and Greece dengue was reported 1926 and 1928 respectively [3]. Above 2 000 cases was reported on the Madeira Islands of Portugal and 10 other countries of Europe in 2012 [3, 19]. In Eastern Mediterranean region of the world dengue is assorted as 'emerging disease' WHO reported for last 2 decade that dengue is epidemic in Saudi Arabia, Pakistan and Yemen and frequently outbreak of dengue is reported in Sudan, Djibouti and Somalia. Reported cases rise from 2.2 million during 2010 to 3.2 million in 2015 [19]. Dengue cases are increasing all around the world in 2016. The dengue cases reported in American region and Brazil was 2.38 million (1181 deaths) and 1.5 million (1032 deaths) respectively which are 3 times greater than 2014. 375000 suspected dengue cases reported in Western Pacific region due to prevalent of serotype DENV-1 and DENV-2. Currently dengue cases were reported from Malaysia, Cambodia, Philippines, Vietnam, The Lao People's Democratic Republic and Singapore and 91% cases reported from New Caledonia, Australia, French Polynesia and Vanuatu. 176411 and 100028 dengue cases recorded in Philippines and Malaysia while 7000 and 1061 dengue cases reported in the Solomon Islands and Africa region (Burkina Faso) respectively [18, 19]. It is expected that 0.5 million persons with severe dengue need hospitalization annually in which about 2.5% of those affected lead to death [3].

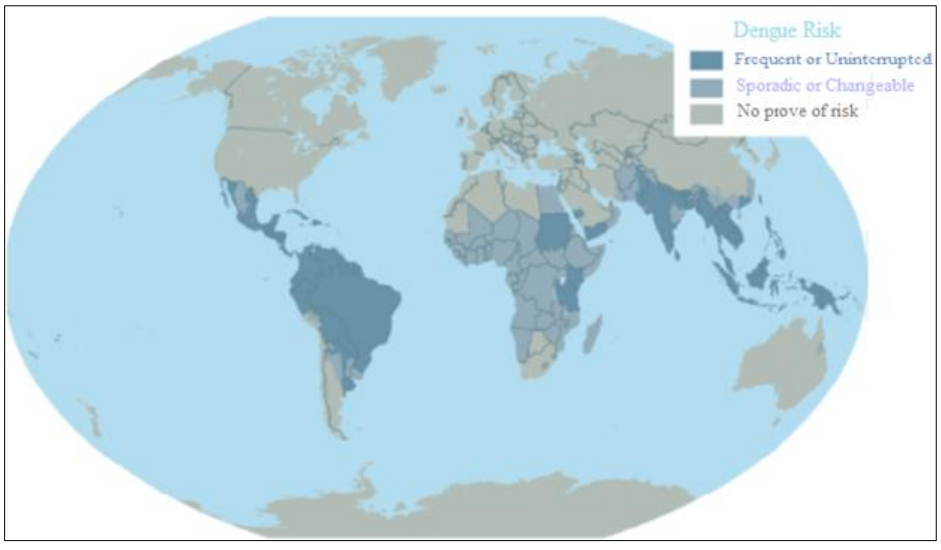

Fig 1: Different parts of the world with confirmation for threat of dengue virus infection [20, 21].

Epidemiology of dengue in Pakistan

The Pakistan is one of most prominent countries of south-east Asia. Pakistan has three main geographic areas, Indus plain, Balochistan Plateau and northern highlands. Pakistan shares its land border with India to east, China to northeast, Afghanistan to west and Iran to southwest. Pakistan also contributes its marine border 650-mile along Arabian Sea and Gulf of Oman in south [22]. Climate of Pakistan are particularly diverse, four seasons: a cool winter season, dry winter from December through February; a hot, dry spring from March to May; monsoon season, from June through September; and the retreating monsoon period of October and November. The beginning and interval of these seasons vary fairly according to locality [23]. Pakistan is a subtropical country and main spot for many vector-borne diseases such as dengue, dengue haemorrhagic fever, malaria, leishmaniasis, and West Nile virus disease, Crimean-Congo. Dengue fever is a new and fast emergent infectious disease in this region. In Pakistan four dengue serotypes are present circulating whole year with peak outbreak between (September-November) during post monsoon periods [24].

Table 1: Prevalent of serotype in reported dengue cases during different year in Pakistan [25, 26, 27].

Year	Prevalent Serotype	Year	Prevalent Serotype
1994	DENV-1,DENV-2	2009	DENV-2,DENV-3
1995	DENV-1,DENV-2,	2010	DENV-1,DENV-2
2003	DENV-2	2011	DENV-2,DENV-3,DENV-4
2004	N/A	2012	N/A
2005	DENV-2, DENV-3	2013	DENV-1,DENV-2,DENV-3,DENV-4
2006	DENV-2,DENV-3	2014	DENV-1,DENV-2,DENV-3
2007	DENV-2,DENV-3	2015	DENV-1,DENV-2,DENV-3,DENV-4
2008	DENV-2,DENV-3,DENV-4	2016	DENV-1,DENV-2,DENV-3,DENV-4

Though *Ae. aegypti* has been described sporadically from different parts of the country since 1934 [28]. The first dengue fever case reported in the late 1980s which shows either the DENV is somewhat new to this area or the virus may have been predominant in Pakistan, but due to miscommunication and shortage of surveillance, epidemic were not informed until 1994 [29]. Multiple dengue virus occurrences have been happened in Pakistan during last three decades. Dengue outbreak in Pakistan is main public health concern since 2005; allowing millions of people at danger, till 2016, 71649 cases were reported with 797 deaths [20, 28, 30].

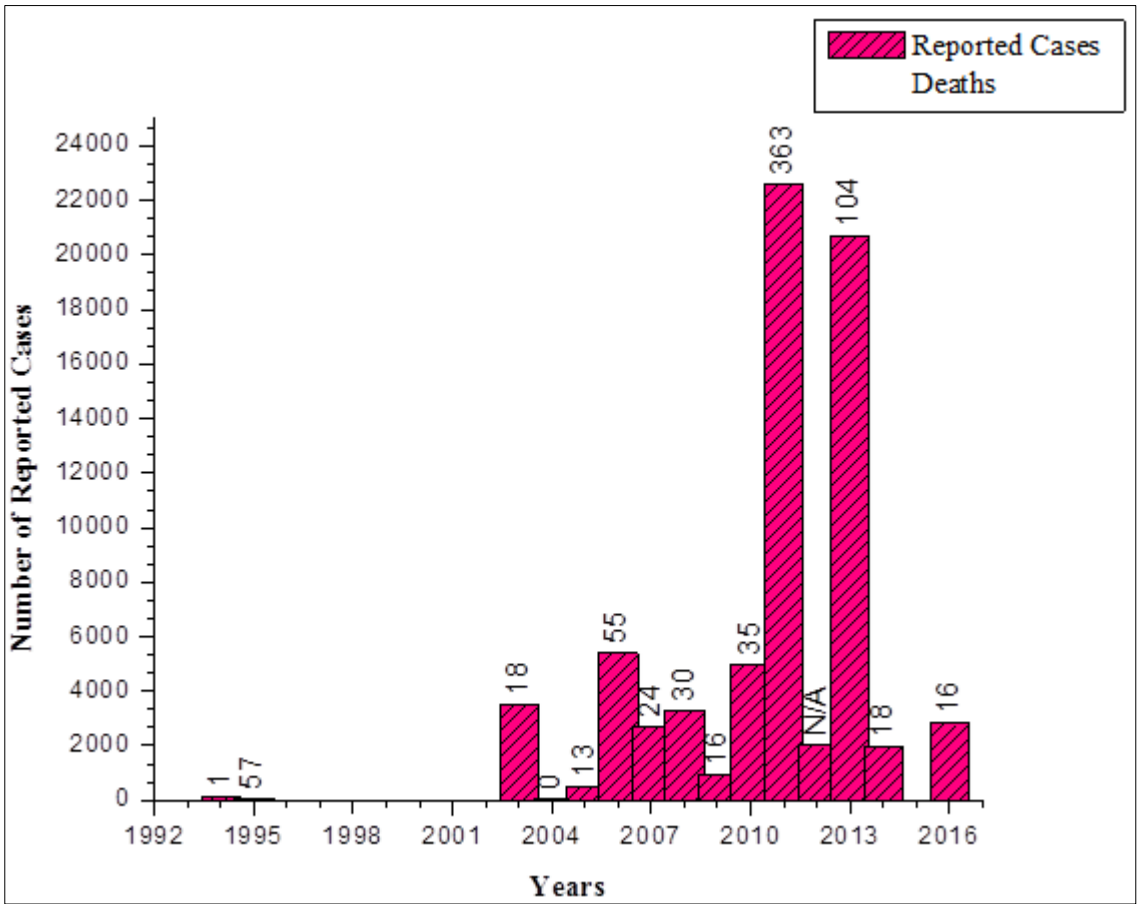

Fig 2: Reported dengue cases with deaths in different region of Pakistan during 1994 to 2016 [20, 26, 30, 31].

First dengue hemorrhagic case was reported in Karachi (southern part of Pakistan) in 1994 [32, 33]. In 1995 severe outbreak of dengue (type 1, 2, 3) was reported in Hubb, Baluchistan [29]. DENV-2 outbreak with 3500 dengue cases (18 deaths) was exposed in Haripur, Nowshera and Khushab district during 2003. Less dengue cases reported during 2004, 500 dengue cases with 13 deaths due DENV-2, DENV-3 in Islamabad and Karachi in 2005 [34]. Khana *et al.,* (2006) [35] first time reported largest outbreak of dengue hemorrhagic fever (DHF) in Karachi with 172 IgM-confirmed cases. Humayoun *et al*., (2008) [36] reported 110 dengue infested patients from September to December, 70 male and 40 female in two tertiary care hospitals in Lahore. The patients had symptoms comprised fever (100%), muscle pain (68.2%), headache (55.5%), nausea (39.1%), cutaneous (53.6%), mucocutaneous hemorrhagic manifestations (58.2%), and visual pain (20%). 41.8% of the patients had dengue fever (DF) while 56.4% had dengue hemorrhagic fever (DHF), and only 1.8% patient had dengue shock syndrome. 9900 dengue cases (79 deaths) due to serotype 1,2,3 was reported in different district of Pakistan in 2006-08. During 2010, 11024 dengue cases with 40 deaths due to DENV-1 and DENV-2 reported in Punjab, Khyber Pakhtunkhwa and Azad Kashmir [36]. In 2011, Dengue epidemic was stated in Lahore (eastern part of Pakistan) with 21685 dengue cases (350 deaths) while 6000 dengue cases (48 deaths) were reported in district Swat (western part of Pakistan) during 2012 [33, 37]. During 2011-12, dengue epidemic took place in different regions of Pakistan including Sheikhupura, Lahore, Faisalabad, Rawalpindi, Gujranwala and Attock. During 2011 to May 2012, 11283 dengue cases recorded in different hospital from nine town of Lahore. The most affected cases reported from Data GunjBaksh municipality with 18.3 % frequency while least case was recorded from Wahga town with 1.5 % prevalence. The most dengue cases was reported with respect to sex in male 89 % and female 35 in Samanabad and Shalimar town respectively. The highest dengue cases reported with respect to age group was 21 to 30 years [38]. Overcrowding and urbanization are mainly factors for outbreak of dengue in this region [38]. Four dengue serotypes was present in Punjab while DENV-1 and DENV-2 was firstly hosted in Swat, Khyber Pakhtunkhwa during 2013 [15]. Dengue epidemic occurred in Sawat and Mansehra during 2013-14 due presence of serotype 1,2,3 and causing 57 deaths [29, 39]. Major source of dengue transmission in Pakistan is *Aedes aegypti* and it came from India through tyres transaction [40]. Jahangir *et al*., (2013) [41] studied the outbreak of dengue in Swat and detected 7 larval and 34 adults mosquito pools were positive in which 30 and 4 pools of aduts *Ae. aegypti* and *Ae. albopictus* while 5 and 2 pools of *Ae. aegypti* and *Ae. albopictus* were positive respectively. They found DENV-2 Serotype (35% in 14 mosquito pools and 39 % in serum) while DENV-3 (65% in 27 mosquito and 61 % serum). Higher cases were reported in month of July and August due encouraging condition of vector development. Suidu was recorded more affected area with 26 % dengue cases while Kanju and Landikas were 20 % and 12 % dengue cases respectively.40 % dengue reported having age less than 15 years followed by 15-45 (35 %) and > 45(25%) years. The percentage of male and female dengue cases were recorded 55.3% and 44.7%, respectively. Muhammad *et al.* (2013) [42] conducted a study to determine breed habitat of *Ae. aegypti* and *Ae. albopictus* in three Punjab district, namely Lahore (217 m), Sheikhupura (214 m) and Faisalabad (184 m) during pre and post-monsoon seasons. Results showed that house index range from 12 to 18 % and 14 to 29 % for pre and post-monsoon seasons respectively while container index range was 11.40 to 13.71 for pre-monsoon and 11.22 to 30.39 % for post-monsoon. Breteau index was 11 and 69 % and premises index varied from 24.40 to 44.32 respectively for both season. The most prominent breeding potency was reported in Lahore followed by Sheikhupura followed by Faisalabad. In 2015 dengue outbreak occurred in Malakand district of Khyber Pakhtunkhwa due prevalent of serotype DENV-3. 9899 confirmed dengue cases was reported from three province of Pakistan including Punjab, Khyber Pakhtunkhwa and Sindh in 2015 [43]. Severity of dengue outbreak was higher in Punjab followed by Khyber Pakhtunkhwa and Sindh whereas more dengue cases were reported in Sindh followed by Punjab and Khyber Pakhtunkhwa during 2016 [43, 44]. Currently dengue cases has recorded from following province in Pakistan, Punjab (Faisalabad, Lahore, Sheikhupura, Rawalpindi, Islamabad), Khyber Pakhtunkhwa (Mansehra, Swabi, Malakand, Batkhela), Sindh(Karachi, Sukkar, Thar) and district Gwadar in Balochistan Province.

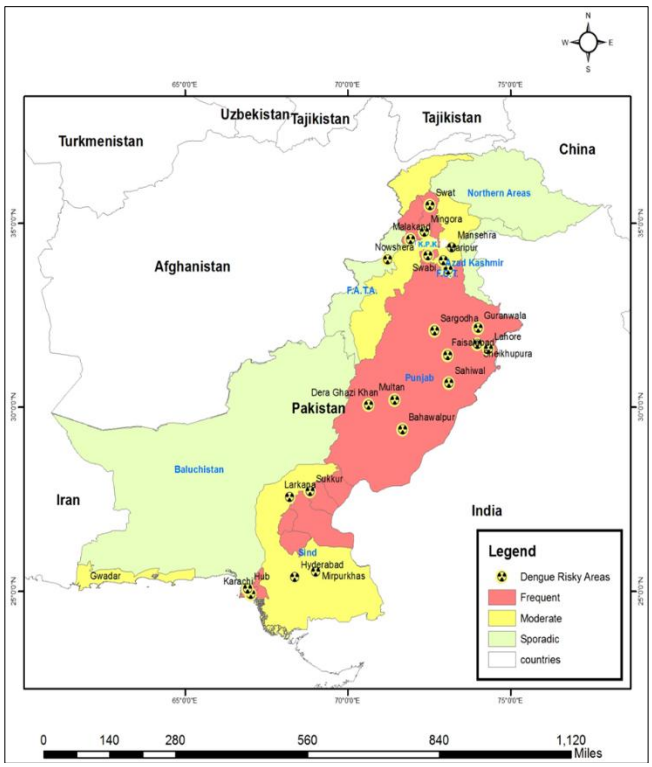

Fig 3: Dengue epidemic occurred in different region of Pakistan during 1994-2016 [20, 26, 30, 31].

Pakistan dengue species distribution

About 104 species of mosquitoes had reported in Pakistan and Bangladesh, while both of dengue causing mosquito species *Aedes aegypti* and *Aedes albopictus* was present in Pakistan but little data is available about their diversity and relative population dispersal in Pakistan [45, 46].

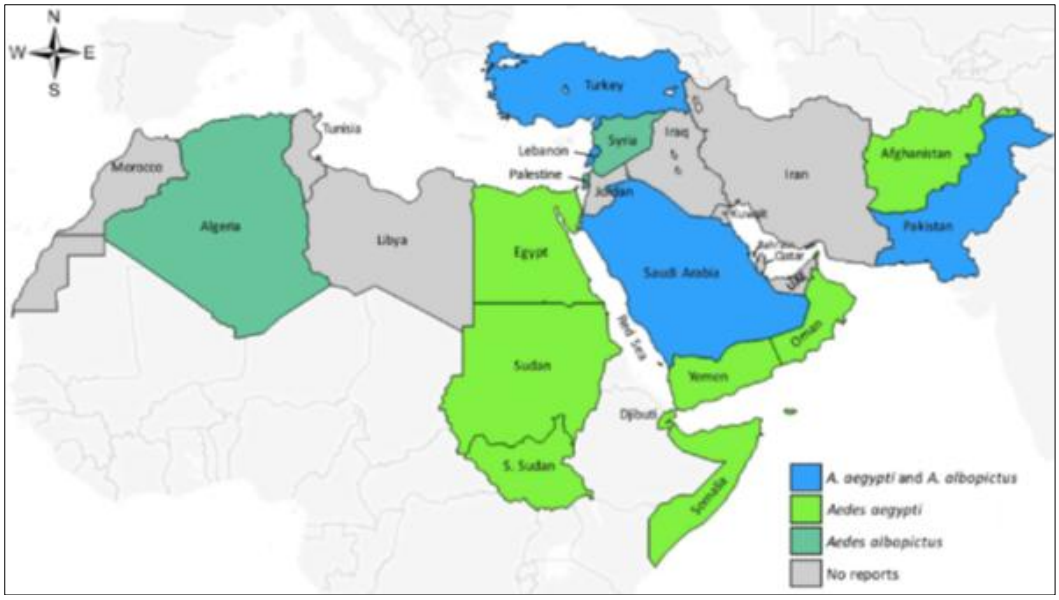

Fig 4: Information about distribution of *Ae. aegypti* and *Ae. albopictus* in Middle East and North African countries [47].

Both *Aedes aegypti* and *Aedes albopictus* has reported from all dengue affected district of Punjab, Pakistan, while *Aedes albopictus* was identified from more region. Both species were identified from urbanized setting of Central Punjab most squeezed with dengue. *Ae. aegypti* was collected at point ranging in height 112-1004 m and *Ae. albopictus* has altitude range from 110-672 m. Though *Ae. albopictus* was prominent species in Punjab but not identified at height site (1100 m) in Swat [48, 49]. *Ae. aegypti* and *Ae. albopictus* originally from Southeast Asia, but *Ae. albopictus* has prolong its range arousing alarm regarding polices of disease management [50, 51]. *Ae. aegypti* is the most widespread vector urban parts of Pakistan including Karachi, Lahore, Rawalpindi, Attock, haripur district such as hilly areas Abbottabad, Mansehra, Swat, Azad Jammu and Kashmir while *Ae. albopictus* had been also reported during the dengue outbreak [52].

Ae. aegypti and *Ae. albopictus* had widespread significant in Pakistan and *Ae. albopictus* was less diversity than *Ae. aegypti*. *Ae. albopictus* was wide distributed in different region of Punjab than *Ae. aegypti. Ae. aegypti* larvae was dominant (65 %) during the collections of sample from indoor water pots site in Lahore during 2011. *Ae. albopictus* spread in Pakistan and other part of world in current situation but *Ae. aegypti* decline many global regions [53, 54, 55]. Benedict *et al.*, (2007) [56] determined that *Ae. aegypti* and *Ae. albopictus* had different ecological priority, explore these species most found in urban area while latter these have common widespread in rural area. Outbreak of dengue in Pakistan during 2011 was very severe in different region and eliciting questions about possible part of its vector distribution and its cause. Imtiaz *et al.*, (2014) [57] observed that *Ae. albopictus* was present in Dir Upper district of Khyber Pakhtunkhwa-Pakistan. Ali *et al*., (2016) [58] observed that the existence of *Ae. aegypti* and *Ae. albopictus* population and their eggs in Rawalpindi. Both species had resistance to DDT, malathion, bendicarb and permethrin.

Strategies for future Control

Dengue outbreak is common problem in the world. *Ae. aegypti* is primary vector for dengue and preferentially bite on human in dawn and dusk period. *Ae. aegypti* mate, feed and live nearly residential area and lay its eggs in artificial water container in or around the houses. *Ae. albopictus* is secondary vector in Asia and extend to Europe and North America due to international business deal of tyre and other commodities [59]. The world scheme encourages sorting and collaboration between multi sectorial stakeholder, confirmed control measure of all stage, integrated vector management techniques and research and funding organization. Its leading rule is to accord prevention, surveillance (entomological and epidemiological) and reported case management with present heath care system with maintainable and effective sound [60]. Although cognizance for dengue prevention has various challenges like less funding, inadequate resources, insufficient knowledge and bad policies, unplanned speedy urbanization, migration of people to epidemic area, sanitation problem results in epidemic of dengue increasing in different geological areas. The death rate from dengue can be minimized lead to nearly zero by timely proper clinical management, Laboratory diagnosis, endogenous rehydration, trained staff availability and early reaction to serious disease. Training is very important factor in dengue for concern medical and non-medical staff in dengue affected area. People should be aware through workshops training program, when outbreak of dengue occur people should destruct the larvae habitat by environmental management or novel insecticides. Awareness should be delivered to epidemic area through electronic media and Workshop to management of this nationwide disaster. Adult mosquito population should be managing by using different insecticides to avoid resistance [61]. Surveillance system should be a component of national health information system in order to dengue prevention and control program [62]. Sustainable vector control: Efficient vector control programmed should be implementing to reduce the death rate due to dengue outbreak. Welfare organization and NGOs will be guiding the people in their working area to ensure cleanness in vicinity, use mosquito repellent mesh, mosquito quills, mosquito repellents, water container are free of mosquito propagation and decrease the chance of infection by disruption of vector. Randomly check all water container

and possible breeding dwelling shall be destructed in last week of July [63]. The main approach to control the dengue is to reduce the dengue vector resources: destruction of containers that are important site for egg laying and development of larvae stages by using insecticides. Sterile insect technique and Release of insects carrying Dominant Lethal System (RIDL) should be used for mass rearing of adults male mosquito. Another advance technique a lethal gene subsequently put into eggs of *Ae. aegypti* results production of toxic substance and cause death [64, 65]. Jeffery *et al.* (2009) investigated that dengue vector should be control by use of enosymbiotic bacterium Wolbachia and its intervention replication of dengue virus in *Ae. aegypti* mosquitoes [66]. *Wolbachia poporn* (wMelPop) is agent used to interfering dengue transmission and reduced the life of dengue vector [67]. Monitoring resistance of insecticide that is used for effective dengue control and should change insecticide policy to avoid resistance [68]. Countries should follow the integrated vector management technique to dengue vector control as determined by world health organization. The aim of integrated vector management should be to enhance efficiency, cost potency, bionomical wisdom and sustainability of vector control intercessions [69, 70]. Integrated vector surveillance should be observed on starting of vector density. The data record will be composed with daily temperature (mini and maxi) related with relative humidity along with rainfall. The public campaign organized affording to seasonal necessities by a committee at present informed by Health department [63]. The main principle of integrated vector management that assure wise application of insecticides combining with other treatment [69, 70].

Conclusion

There are many dengue cases which were reported from private and government hospital in different region of country including interior Punjab, interior Sindh and Khyber Pakhtunhkwa. Migration of most working people from rural to urban area, where dengue vector is present commonly and most of people are at risk of dengue infection. Several factors such as unawareness of people, climatic change, inadequate funding and poor surveillance are the major causes of dengue outbreak. Therefore scientific research should be enhanced in Punjab, interior Sindh and Khyber Pakhtunkhwa province of country, where dengue outbreak have been occurred for last decade and dengue is also actual risk of non-epidemic area. Moreover, research should be begun to discover the reasons behind this extension of dengue virus into before non-endemic areas for this purpose preventive and control measures may be taken, furthermore assure the collaboration between agencies involved in dengue control and researcher should share the available information on dengue and mosquito vector in Pakistan.

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