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REVIEW

Dengue Hemorrhagic Fever Virus in Saudi Arabia: A Review

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Abstract

Dengue fever is a global disease with a spectrum of clinical manifestation ranging from mild febrile disease to a severe disease in the form of dengue hemorrhagic fever and dengue shock syndrome. Dengue virus is one viral hemorrhagic fever that exists in the Kingdom of Saudi Arabia in addition to Alkhurma (Alkhurma) Hemorrhagic Fever, Chikungunya virus, Crimean–Congo Hemorrhagic Fever, and Rift Valley Fever. The disease is limited to the Western and South-western regions of Saudi Arabia, where *Aedes aegypti* exists. The majority of the cases in Saudi Arabia had mild disease and is related to serotypes 1–3 but not 4. The prospect for Dengue virus control relies on vector control, health education, and possibly vaccine use. Despite extensive collaborative efforts between multiple governmental sectors, including Ministry of Health, Ministry of Municipalities and Rural Affairs, and Ministry of Water, dengue remains a major public health concern in the regions affected.

Keywords: Dengue hemorrhagic fever, Dengue virus, DHFV

Introduction

DENGUE FEVER (DF) is a global disease with a spectrum of clinical manifestation ranging from mild febrile disease to a severe disease in the form of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). According to the World Health Organization (2012), severe dengue disease in suspected dengue patients is defined as the presence of any of severe plasma leakage that leads to shock (dengue shock) and/or fluid accumulation with respiratory distress; severe bleeding; or severe organ impairment.

Dengue infection occurs in an endemic form in 128 countries worldwide (Khetarpal and Khanna 2016). DF is one of several viral hemorrhagic fevers that exist in the Kingdom of Saudi Arabia (Alhaeli et al. 2016) in addition to Alkhurma (Alkhurma) Hemorrhagic Fever (AHF) (Zaki 1997, Al-Tawfiq and Memish 2017), Chikungunya Hemorrhagic Fever (Hussain et al. 2013), Crimean–Congo Hemorrhagic Fever (CCHF) (El-Azazy and Scrimgeour 1997, Hassanein et al. 1997, Leblebicioglu et al. 2015), and Rift Valley Fever (Balkhy and Memish 2003, Al-Afaleq and Hussein 2011). Of the four serotypes of Dengue virus, serotypes 1–3 but not 4 were reported in Saudi Arabia (Ashshi 2017). The first description of DF in Saudi Arabia dates back to 1994 when Dengue virus serotype 2 (DEN-2) was isolated from a fatal and a nonfatal case in Jeddah, Saudi Arabia (Fakeeh and Zaki 2001).

Search Strategy

The search included MEDLINE and Scopus databases for articles published in English as follows:

1. ''Dengue'' OR ''Dengue Virus'' OR ''Dengue Hemorrhagic Fever'' OR ''Dengue Fever''
2. ''Saudi Arabia'' OR ''Kingdom of Saudi Arabia'';
3. #1 AND #2.

In addition, we searched the Saudi Epidemiology Bulletin (available from the Saudi Ministry of Health 2007–2016 at: http://www.fetp.edu.sa/Bulletin.html).

The Virus

DF, DHF, and DSS are caused by the dengue viruses (DENV). Dengue virus is a member of the genus *Flavivirus*, a member of the family Flaviviridae. The genus *Flavivirus* is classified into two broad categories based on the vector of transmission: tick-borne viruses and mosquito-borne viruses (Fig. 1). The Dengue virus is a mosquito-borne virus. Four

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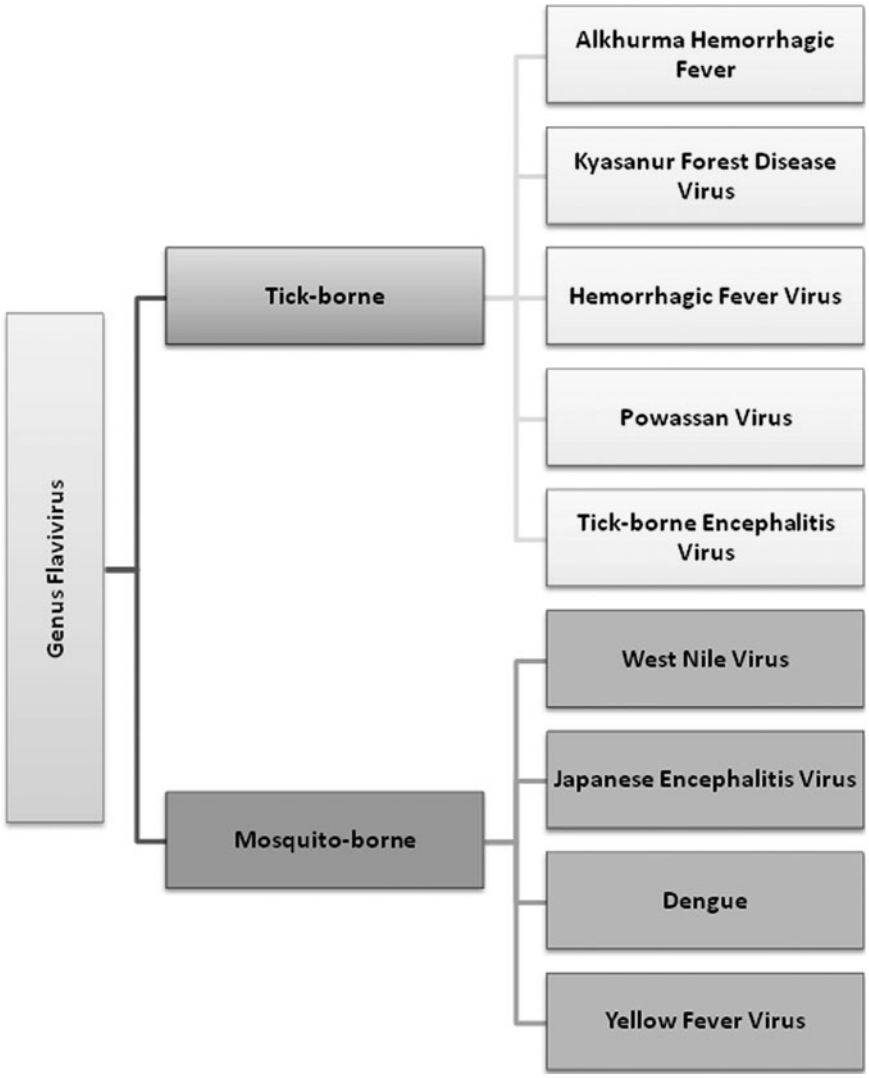

FIG. 1. Genus flavivirus and the Dengue virus.

antigenically related but distinct dengue virus serotypes exist and are: dengue virus types 1–4 (DENV-1, DENV-2, DENV-3, and DENV-4) (Khetarpal and Khanna 2016).

Virus Transmission

The Dengue viruses are transmitted to humans by the females of the mosquito *Aedes.* The most important vector is *Aedes aegypti* and other species such as *Aedes albopictus*, *Aedes polynesiensis*, and *Aedes niveus* are secondary vectors (Malavige et al. 2004). The virus is limited to the Western and South-western regions of Saudi Arabia (Fakeeh and Zaki 2001, Ayyub et al. 2006, Khan et al. 2008, Al-Azraqi et al. 2013, Alhaeli et al. 2016, El-Kafrawy et al. 2016). Four different *Aedes species* were identified in the Western part of Saudi Arabia (Abdullah and Merdan 1995, Jupp et al. 2002, Alahmed et al. 2009, Kheir et al. 2010, Al Ahmad et al. 2011, Aziz et al. 2012, Alikhan et al. 2014) and only *A. caspius* was identified in the Eastern region of Saudi Arabia (Wills et al. 1985) (Table 1). In a case–control study, the following factors were associated with the risk of Dengue virus infection: presence of stagnant water (OR = 4.9), indoor larvae (OR = 2.2), construction sites (OR = 2.2), and older age (OR = 1.2) (Kholedi et al. 2012). It is known that rainfall in Jeddah is low. The occurrence of *A. aegypti* with DF in Jeddah is in paradox with the low level of rain; however, water containers play a role as breeding sites for *A. aegypti* (Ghaznawi et al. 1997, El-Gilany et al. 2010). In addition, the occurrence of huge constructions between 2008 and 2012 in Makkah, Saudi Arabia may have resulted in increased number of cases due to the formation of stagnant water (alwafi et al. 2013). Moreover, Jeddah is the Hajj entry point and is the largest commercial port and airport welcoming many Pilgrims coming from Dengue High Disease Burden countries. Thus, in this context, the role of International Travel as the source of Dengue is a possibility. A recent study highlighted the role of visitors from dengue endemic countries in the importation of the virus into Saudi Arabia (Al-Saeed et al. 2017). The study showed that all dengue viruses in 2010–2015 were from the circulating Indian subcontinent lineage of the Cosmopolitan genotype (Al-Saeed et al. 2017).

Incidence

In Saudi Arabia, DF electronic registry was initiated by the MoH in 2008 after dengue was added to the notifiable

Table 1. *Aedes* Species According to the Region in Saudi Arabia

Species	*Region*	*Year*	*Reference*
Aedes aegypti, Aedes arabiensis, and *Aedes caspius.*	Western	1956	Alikhan et al. (2014)
A. caspius	Eastern	1985	Wills et al. (1985)
A. caspius	South western	1995	Abdullah and Merdan (1995)
Aedes vittatus	Southern	2001	Alikhan et al. (2014)
Aedes vexans arabiensis, Aedes vittatus, A. caspius, and *Aedes caballus*	Jizan	2002	Jupp et al. (2002)
A. caspius and *A. aegypti*	Jeddah	2011	Al Ahmad et al. (2011)
A. aegypti, *A. (Ochlerotatus) caspius*, *Aedes (Ochlerotatus) vexans* var. *arabiensis*	Jeddah	2014	Alikhan et al. (2014)
A. caspius, *A. aegypti*, and others	Makkah	2004–2006	Alahmed et al. (2009)
A. caspius, *A. aegypti*, and others	Madinah	2010	Kheir et al. (2010)
Cobreeding of Aedes, Culex, and Anopheles	Makkah	2008–2009	Aziz et al. (2012)

diseases list. The incidence of DENV infection among tested patients varies based on the location, year of the study, and the method of testing (Table 2) (Fakeeh and Zaki 2001, 2003, Ayyub et al. 2006, Khan et al. 2008, Shahin et al. 2009, El-Gilany et al. 2010, Memish et al. 2011, Al-Azraqi et al. 2013, alwafi et al. 2013, Gamil et al. 2014, Ashshi 2017, Ashshi et al. 2017, Organji et al. 2017). The number of DENV infection was 6512 cases in 2013; 2081 cases in 2014; and 4312 cases in 2015. The number of cases varies between 425 and 4312 per year (Alshamrani et al. 2015; Organji et al. 2017). The annual number of cases of Dengue virus in and *n* Saudi Arabia shown in Figure 2 and the highest number of cases was in 2013, 2015, and 2016. However, the overall prevalence of DENV is 40–48.7% among clinically suspected patients (Ayyub et al. 2006, Khan et al. 2008) and 31.7% among random sample of patients attending the outpatients' clinics (Al-Azraqi et al. 2013). In a study from 2008 to 2012, the incidence rate doubled to 110 per 100,000 population in 2009, indicating the occurrence of an outbreak (alwafi et al. 2013). The majority of affected patients are adults and infected children constituted 24% (Shahin et al. 2009) in one study and 6% in another study (Ayyub et al. 2006). In a recent study, the age-standardized incidence rates of dengue was 10–99 per 100,000 person-years in 2013 (Stanaway et al. 2016).

Seasonality

In a study of 159 cases in Makkah, 77% of the cases were during the spring and early summer (Shahin et al. 2009). Another study showed increased cases in the summer months and during the months of December and January (Kholedi et al. 2012). In a study of 4187 cases, the peak cases occurred in April–May (alwafi et al. 2013) and a similar finding was in a report of 264 cases from Jazan (Gamil et al. 2014) and a study of cases in 2013–2014 (Aziz et al. 2014a). Thus, the majority of cases occurred in April–May.

Clinical Presentations

DF is characterized by constitutional symptoms of fever, severe headache, backache, joint pains, nausea and vomiting, eye pain, and rash. The disease affects all age groups but tends to cause milder disease in young children. Dengue virus may cause one of four syndromes/diseases: undifferentiated fever, classic DF, DHF, or DSS. The first 207 patients had mild DF and only one patient had DSS and one had DHF (Fakeeh and Zaki 2001). The affected patients in Saudi Arabia were more likely to be males and of young age group (summarized in Table 3). The signs of symptoms of Saudi patients with dengue infections are summarized in Table 4 (Ayyub et al. 2006, Khan et al. 2008, Shahin et al. 2009, Ahmed 2010, El-Gilany et al. 2010, Badreddine et al. 2017). The majority of patients (60–93%) who presented with DF, 5–39.4% had DHF, and about 1% had DSS. The reported mortality was also low. Dengue infection accounts for a total of 0.15–0.29 mortality per million person-years in Saudi Arabia in 2013 (Stanaway et al. 2016). Men are more affected than women in the various studies included. This is mainly related to the fact that men work outdoors and that women in Saudi wear clothing covering head to toes (Alwafi et al. 2013).

Geographic Distribution

Dengue virus was mainly reported from the Western and South-western regions of Saudi Arabia (Fakeeh and Zaki 2001, Ayyub et al. 2006, Khan et al. 2008, Al-Azraqi et al. 2013, Alhaeli et al. 2016, El-Kafrawy et al. 2016). This geographic restriction is directly related to the presence of *A. aegypti* in the affected regions (Jupp et al. 2002, Alahmed et al. 2009, Kheir et al. 2010, Al Ahmad et al. 2011, Aziz et al. 2012, Alikhan et al. 2014) and not in other parts of the Kingdom of Saudi Arabia (Wills et al. 1985, Abdullah and Merdan 1995). Mathematical modeling showed that central Jeddah districts were the hotspots and the pattern changes greatly with time (Khormi et al. 2011). Using modeling techniques, a total of 111 districts in Jeddah were investigated for the risk of DF (Khormi and Kumar 2012). Of those districts, 15% were high risk, 22% were medium risk, 16% were low risk, and 46% were very low risk (Khormi and Kumar 2012). In analysis of 2288 cases of DF from Jeddah, the disease was found to be concentrated in the south and central-north regions of Jeddah, Saudi Arabia (Alzahrani et al. 2013).

Table 2. A Summary of the Incidence of Dengue Virus Infection Among Tested Patients Based on the Location, Year of the Study, and the Method of Testing

Study type	*Study population*	*Method of detection*	*Number included*	*% positive*	*Reference*
Cross sectional	Male blood donors	ELISA	910	39 IgG; 5.5 IgM	Ashshi (2017) and Ashshi et al. (2017)
Longitudinal	Suspected cases	Viral culture	985	21	Fakeeh and Zaki (2001)
Longitudinal	Suspected cases	ELISA	985	11	Fakeeh and Zaki (2001)
Cross sectional	Random sample of patients attending the outpatients' clinics in Jizan and Aseer region	ELISA	965	31.7 IgG	Al-Azraqi et al. (2013)
Longitudinal April to July 2004	Clinically suspected patients, Makkah	ELISA and RT-PCR	160	40 ($n=64$) IgM ELISA, 8.7 ($n=14$) by RT-PCR and 8.1 ($n=13$) by both	Khan et al. (2008)
Longitudinal May 2004–April 2005	Clinically suspected patients, Jeddah	ELISA	80	48.7	Ayyub et al. (2006)
NA	Clinically suspected patients, Makkah	RT-PCR	25	24	Organji et al. (2017)
Longitudinal 2006 to 2008	Clinically suspected patients, Makkah	ELISA or RT-PCR	159	100	Shahin et al. (2009)
Longitudinal 1994 to 2002	Clinically suspected patients, Jeddah	Virus isolation or ELISA	1020	31.3 (of those 65.5% by virus isolation and the rest were based on serology)	Fakeeh and Zaki (2003)
September to mid December in 2006	Admitted patients, Makkah	Virus isolation or ELISA	71	100	El-Gilany et al. (2010)
Longitudinal study 2008–2012, Makkah	Confirmed cases	NA	4187	100	alwafi et al. (2013)
Cross sectional April 2010–March 2011, Jazan	Suspected cases	ELISA	553	47.7	Gamil et al. (2014)
Cross-sectional, 2009, Saudi military forces, Jazan	Seroprevalence	ELISA	1024	0.1	Memish et al. (2011)

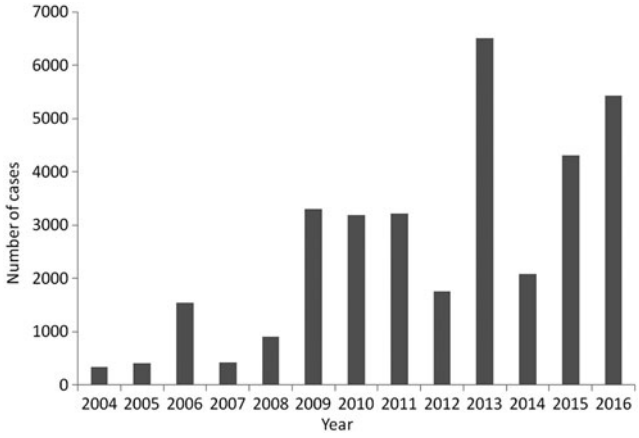

FIG. 2. Annual number of dengue fever cases in Saudi Arabia, data from (Alshamrani et al. 2015; Organji et al. 2017; Saudi Ministry of Health 2007–2016)

Virus Serotypes

Dengue virus serotype is associated with the risk of DHF with highest risks with DENV-2, DENV-3, DENV-4, and DENV-1, as well as the pre-existence of antidengue antibodies. In the initial study of 985 suspected cases, DEN-2 accounted for 138 (66.7%) of 207 isolates, DEN-1 for 56 (27%), and DEN-3 for 13 (6.3%) (Fakeeh and Zaki 2001). The contribution of each serotype to Dengue in Saudi Arabia is shown in Table 3. However, DENV-4 was not reported in any of the studies based on serology and molecular testing (Fakeeh and Zaki 2001, 2003, Ayyub et al. 2006, Khan et al. 2008, Organji et al. 2017). Phylogenetic analysis of 19 isolates showed that DENV-1 and DENV-2 caused the 1994 outbreaks and it was an America–Africa genotype (lineage India-2) (Zaki et al. 2008). DENV-3 was isolated in 1997 and the outbreak in 2005–2006 was caused by a strain from genotype Asia (lineage Asia-2) (Zaki et al. 2008). Sequencing of the Dengue virus DENV-1-Jeddah-1-2011 strain showed high similarity with the Asian genotype (D1/H/IMTSSA/98/606 isolate) reported from Djibouti in 1998 (Azhar et al. 2015).

Table 3. Summary of Characteristics of Confirmed Dengue Fever Cases in Saudi Arabia

Number	*Study population*	*Method of detection*	*Serotype*	*Age*	*Male to female ratio*	*Reference*
91	Clinically suspected patients, Makkah	ELISA and RT-PCR	DENV-2: 19 (20.8%) DENV-3: 4 (4.3%)	Median age: 26 (range 6–94)	1.5:1	Khan et al. (2008)
39	Clinically suspected patients, Jeddah	ELISA		Range: 2–60; mean 27.6 ± 11.2	3.3:1	Ayyub et al. (2006)
25	Clinically suspected patients, Makkah	RT-PCR	DENV-1 50% DENV-2 33.3%; DENV-3: 16.6%			Organji et al. (2017)
159	Clinically suspected patients, Makkah	ELISA or RT-PCR		25.6 ± 16.1 years (range 4–81 years)	2:1	Shahin et al. (2009)
319	Clinically suspected patients, Jeddah	Virus culture or serology	DENV-1: 27% DENV-2: 66% DENV-2: 6%	Adults between 15 and 40 years	2.6:1	Fakeeh and Zaki (2003)
71	Admitted to hospitals in Holly Makkah City, 2006 (during the Hajj)	Virus culture or serology		Adults 16–44 years	1.7:1	El-Gilany et al. (2010)
4187	Confirmed cases reported to the Ministry of Health	NA	NA	47% between 25 and 44 years	2.6:1	alwafi et al. (2013)
264	Confirmed cases, Jazan	ELISA	NA	52% between 15 and 44 years		Gamil et al. (2014)
19	Isolates in Jeddah	RT-PCR	DENV-1, DENV-2 and DENV-3			Zaki et al. (2008)
567	Cross-sectional of confirmed cases	RT-PCR in 29%	Not reported	85% were adults	2:1	Badreddine et al. (2017)

DENV, Dengue viruses.

Table 4. Signs and Symptoms of Patients with Dengue Fever, Numbers are Percentage Unless Indicated Otherwise

	Khan et al. (2008)	*Ayyub et al. (2006)*	*Shahin et al. (2009)*	*El-Gilany et al. (2010)*
Total number of patients	91	39	159	71
Fever	100	100	100	100
Malaise	83	66.7		67
Musculoskeletal	81		100	59
Headache	75	48.7	100	74
Nausea	69	25.6	27	42.3
Vomiting	65		27	39.4
Abdominal pain	48		24.5	39.4
Dengue fever	93		90	60.5
DHF	7	5	10	39.4
DSS	1		0.6	
Mortality		0	0.6	1.4

DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome.

Seroprevalence Among Asymptomatic Individuals

The seroprevalence of Dengue virus antibodies among asymptomatic individuals was found to be 47.8% (927/1939) and among blood donors was 37% (68/184) (Jamjoom et al. 2016). The seroprevalence of antidengue IgG was 31.7% among asymptomatic persons attending outpatient clinics (Al-Azraqi et al. 2013). In one study, male gender, older age, and communal and multistory housing were significant factors for positive ELISA tests (Jamjoom et al. 2016). In a seroprevalence study of 1024 soldiers, only 0.1% tested positive for DENV by ELISA (Memish et al. 2011). Thus, there is variable seroprevalence of dengue among the different populations studied and is higher among patients attending outpatient clinics (31.7%) than the general population (0.1%). The general population may also represent the different regions of the country, which are not affected by DF.

Prospect for Control

Strategies to control Dengue virus requires the control of the vector, *A. aegypti*, through elimination of breeding sites and the elimination of the vector itself. It is important to intensify the use of insecticides to control mosquito due to the quick and efficient knockdown activity (Aziz, et al. 2014b). In one study in Jazan, Saudi Arabia, *A. aegypti* mosquitoes were susceptible to Cyfluthrin and had variable resistances to other insecticides, such as lambda-cyhalothrin, Deltamethrin, Permethrin, Fenitrothion, Bendiocarb, and dichlorodiphenyltrichloroethane (DDT) (Alsheikh et al. 2016). Health education and awareness of the disease and its vector play a major role in the control of Dengue in Saudi Arabia (Aziz et al. 2014b). In one study from Saudi Arabia, high-school students' knowledge score was associated with family history of DF, having literate mothers, and age ≥17 years (Ibrahim et al. 2009). *Gambusia holbrooki* fish was effective in domestic water containers to control *A. aegypti* (Gamal 2012). In addition, the World Health Organization provides 36 boxes for the control of DF and includes *Aedes* control methods, Global Strategy for prevention and control of DF/DHF, and lessons learned from sustained efforts in countries

combating dengue virus (Parks and Lloyd 2004). One dengue virus vaccine was licensed in Latin America and Southeast Asia. Two large phase III randomized controlled trials of this vaccine showed about 60% efficacy against virologically confirmed dengue in the first 13 months postvaccine (Capeding et al. 2014, Villar et al. 2015). In a meta-analysis of nine studies, the vaccine efficacy was 54% with reduced efficacy of 34% for DENV2 (Malisheni et al. 2017). However, the vaccine was associated with higher relative risk of dengue infection during the third year postvaccination (Hadinegoro et al. 2015). The World Health Organization does not recommend the use of the vaccine for widespread vaccination nor for the use in areas with less than 50% seroprevalence (Anon 2016, World Health Organization 2017).

Conclusion

DF in Saudi Arabia is limited to the Western and Southwestern regions of the country and is linked to *A. aegypti*. The majority of the patients had mild disease and was caused by serotypes 1–3. Despite extensive collaborative efforts between multiple governmental sectors, including Ministry of Health, Ministry of Municipalities and Rural Affairs, and Ministry of Water, dengue remains a major public health concern in the regions affected. The prospect for Dengue virus control relies on vector control, health education, and possibly vaccine use.

Author Disclosure Statement

No competing financial interests exist.

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