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<THE TOPIC OF THIS MONTH>
Mosquito-borne viral infections: Zika virus infection, Chikungunya fever and Dengue fever, 2011 to June 2016, Japan

Table 1. Mosquito-borne viral infectious disease under the category IV notifiable diseases of the Infectious Diseases Control Law, Japan

Disease	Agent[1)]	Incubation period	Life cycle	Vector species in Japan[2)]	Geographical distribution in Japan	No. reported cases[3)]	
						Imported	Domestic
Zika virus infection	Zika virus	2-12 days (mostly 2-7 days)	Human-Mosquito-Human	*Aedes albopictus*	Areas south of Aomori (as of 2015)	7	–
Chikungunya fever	Chikungunya virus	3-12 days (mostly 3-7 days)	Human-Mosquito-Human			10-20/year	–
Dengue fever	Dengue virus	2-15 days (mostly 3-7 days)	Human-Mosquito-Human			200-250/year in recent years	162 in 2014
Yellow fever	Yellow fever virus	3-6 days	Human-Mosquito-Human			–	–
West Nile fever	West Nile virus	2-14 days	Bird-Mosquito-Human	*Culex* mosquito species	Nationwide	1 in 2005	–
Japanese encephalitis	Japanese encephalitis virus	1-2 weeks	Pig-Mosquito-Human	*Culex tritaeniorhynchus*	Nationwide excluding Hokkaido	1 in 2011	1-10/year

1) Zika viurs, dengue virus and chikungunya virus belong to the genus *Flavivirus*, family *Flaviviridae*. Chikungunya virus belongs to the genus *Alphavirus*, family *Togaviridae*.
2) *Aedes aegypti*, a common mosquito vector for yellow fever, dengue fever and chikungunya fever, is not present in Japan.
3) National Epidemiological Surveillance of Infectious Diseases

All mosquito-borne infectious diseases are classified as category IV infectious diseases under the Infectious Diseases Control Law (Table 1). This article focuses on Zika virus infection, Chikungunya fever and Dengue fever. As these are associated with acute febrile illness and clinically similar in manifesting syndromes such as fever, rash, and arthralgia, and as there are many asymptomatic cases, differential diagnosis solely based on clinical information is difficult (see notification criteria for each disease described below). In Japan, majority of the reported cases for these three diseases have been acquired abroad (i.e. imported cases), but an autochthonous dengue fever outbreak was confirmed in Japan in 2014 for the first time in nearly 70 years (IASR 36: 33-35, 2015).

Epidemiologic situation

Zika virus infection: Zika virus infection in humans was reported from Africa in the 1950s and from Asia in the 1970s. In 2007, Zika virus was confirmed for the first time in the Federated States of Micronesia, causing an outbreak on Yap Island; during 2013-2014, French Polynesia reported that approximately 30,000 people were infected (see p. 121 of this issue). In 2013-2014, three cases, all infected abroad, were also reported in Japan (IASR 35: 45-46; 243-244, 2014). In 2015, circulation of Zika virus in Brazil and other areas in Central and South America was confirmed, and has since been spreading. In Brazil alone, approximately 40,000 people have been infected with Zika virus so far, including 12 deaths (WHO, Zika situation report, 16 June 2016). Since 2015, it has spread to 38 countries or areas in Central and South America and the Caribbean, 12 countries or areas in Asia and the Western Pacific region, the Republic of Maldives in the Indian Ocean and the Republic of Cabo Verde in North Africa (WHO Zika situation report, 16 June 2016).

Following 2-12 days of the incubation period, about 20% of Zika virus-infected persons become symptomatic and develop symptoms such as maculopapular rash, fever (majority <38.5˚C), arthralgia, myalgia, conjunctivitis, and malaise. In the 2013 epidemic in French Polynesia, association between Zika virus infection and Guillain-Barré syndrome was suspected. In the 2015 epidemic in Brazil, link between Zika virus infection and Guillain-Barré syndrome among adults and microcephaly among newborns was suspected. On 1 February 2016, WHO declared a "public health emergency of international concern (PHEIC)"

Table 2. Reported cases of Zika virus infection, week 7 to week 23 of 2016, Japan

	Age group (years)	Gender	Month of onset	Suspected place of infection	Clinical signs and symptoms
1	10-19	Male	February	Brazil	Fever, rash
2	30-39	Female	March	Brazil	Fever, rash, arthralgia
3	Unknown	Female	March	Brazil	Rash, arthralgia
4	40-49	Female	March	Central & South America*	Fever, rash, arthralgia, conjunctivitis, etc.
5	10-19	Male	April	Oceania/Pacific Islands	Fever, rash
6	20-29	Female	May	Central & South America*	Fever, rash
7	30-39	Male	June	Central & South America*	Rash

*Central & South America excluding Brazil

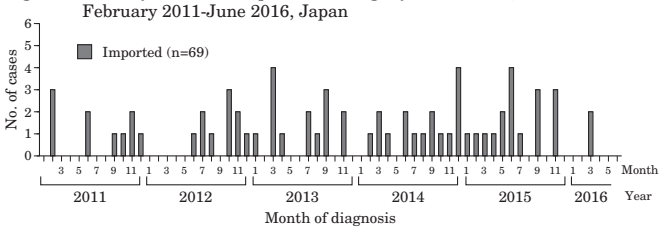
(National Epidemiological Surveillance of Infectious Diseases: as of June 22, 2016)

(Continued on page 120′)

regarding clusters of microcephaly and Guillain-Barré syndrome associated with Zika virus infection. On 15 February 2016, the Japanese government classified Zika virus infection (includes Zika virus disease and congenital Zika virus infection) as a category IV infectious disease that requires all cases to be notified by clinicians (notification criteria: http://www.nih.go.jp/niid/images/iasr/37/437/de4371.pdf). Since then till week 23 of 2016, a total of 7 cases infected in Central & South America and Oceania were reported (as of 15 June 2016) (Table 2).

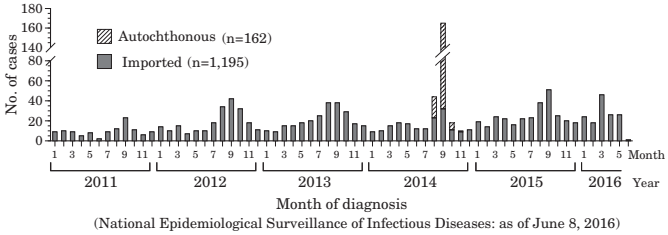
Chikungunya fever: Since 1 February 2011, chikungunya fever has been a category IV infectious disease (notification criteria: http://www.nih.go.jp/niid/images/iasr/37/437/de4372.pdf). Since then till week 22 of 2016, a total of 69 cases (average 13 cases per year) were reported (as of 8 June 2016); all were infected abroad (Table 3 in p. 121 of this issue). Forty (58%) cases were male and 29 (42%) were female; 23 (33%), 19 (28%), and 14 (20%) cases were in their 20's, 40's and 30's, respectively (median: 34 years; range 11-71 years). No clear seasonality was found (Fig. 1). Suspected place of infection are shown in Table 3 in p.121 of this issue and have been reported in IASR 36: 47-48, 2015.

Figure 1. Monthly number of reported chikungunya fever cases, February 2011-June 2016, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of June 8, 2016)

Figure 2. Monthly number of reported dengue fever and dengue hemorrhagic fever cases, January 2011-June 2016, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of June 8, 2016)

Dengue fever and dengue hemorrhagic fever: From 2011 to week 22 of 2016, a total of 1,357 dengue cases (1,310 dengue fever, 46 dengue hemorrhagic fever and 1 asymptomatic) were reported (notification criteria: http://www.nih.go.jp/niid/images/iasr/36/421/de4211.pdf). Among them, 162 were autochthonous cases from the 2014 outbreak, and the remaining 1,195 were infected abroad. Among the cases, 833 (61%) were male and 524 (39%) were female; 386 (28%), 328 (24%), and 239 (18%) cases were in their 20's, 30's and 40's, respectively (median: 32 years; range 0-82 years). Notifications of infection abroad were highest during August-September (Fig. 2), and this reflects an increase in the number of persons who travel abroad and dengue activity levels in their destinations (see p. 131 of this issue). Suspected place of infection are shown in Table 4 in p.121 of this issue and have been reported in IASR (36: 33-35, 2015, Table 3).

Mosquito vectors in Japan (Table 1)

Aedes albopictus mosquito capable of transmitting the causative viruses of the three diseases inhabits Japan. They are active during the day in outdoor settings, and feed on persons who enter environments with vegetative cover, such as parks (see p. 126 of this issue).

Laboratory diagnosis

On account of the similar symptoms and geographical distributions of the three diseases, laboratory tests are indispensable for diagnosis (see pp. 124 & 132 of this issue). Prefectural and municipal public health institutes (PHIs) and quarantine stations are ready to provide the service of PCR-based tests. Some PHIs may also provide antibody tests. Currently, laboratory tests available in clinical setting are the dengue virus non-structural protein NS1 antigen detection ELISA and immuno-chromatography for detection of both anti-dengue virus IgM antibody and NS1 antigen.

Treatment and prevention

A physician who examines a patient suspected of any of the three infections should, as appropriate, obtain advice from specialized medical facilities or refer the patient to such facilities (Clinical Examination Guidelines on the Mosquito-Borne Infections, 3rd Ed.) (see p. 123 of this issue). As no specific therapy is available, patients are treated symptomatically, including fluid therapy.

To prevent infection in endemic areas, appropriate use of repellents (see p. 128 of this issue) and minimizing skin exposure during outdoor activities is important. In order to reduce the potential for outbreaks in Japan, it is important to reduce containers and other artifacts that accumulate water which may serve as habitats for mosquito larvae (see p. 126 of this issue) ("Guidance for the local government on the prevention/control of mosquito-borne infections such as dengue fever and chikungunya fever" revised on 12 February 2016). On account of the risk of mother-to-child (see p. 124 of this issue) and sexual transmission of Zika virus, pregnant women or women expecting pregnancy should refrain from travel to Zika virus endemic regions. Furthermore, men who return from such regions should use a condom when they have sex with a partner for at least 8 weeks following return (or for the entire gestation period if the partner is pregnant), or abstain from sex.

Concluding remarks

It should be reminded that mosquito-borne infections can be introduced into Japan as had occurred in 2014 with dengue fever. Rio de Janeiro in Brazil, where the Olympic and the Paralympic games are to be held this year, is in the subtropical zone and the average temperature in August to September exceeds 20°C (http://www.data.jma.go.jp/gmd/cpd/monitor/nrmlist/NrmMonth.php?stn=83743). Those who are going to the Olympic games are advised to take appropriate measures described above against these viruses by minimizing the risk of mosquito bites.

To prevent the spread of mosquito-borne infectious diseases such as dengue fever and chikungunya fever, the Ministry of Health, Labour, and Welfare issued the "Special Guidelines on Prevention of Mosquito-borne Infections" in April 2015, to which guidance on Zika virus infection was added in March 2016. The guidelines recommend routine implementation of mosquito control measures, early detection of mosquito-borne infections, and emergency response including provision of appropriate medical care (see p. 129 of this issue). Updated information on Zika virus risk assessment is available from the National Institute of Infectious Diseases home page.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, and quarantine stations, have provided the above data.

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＜特集関連情報＞

ジカウイルス感染症の疫学

2014年から蚊媒介性ウイルス感染症の一つであるジカウイルス感染症が，これまで流行地でなかったアメリカ大陸で流行し始めた。

ジカウイルスは1947年にウガンダのジカ森林公園のサル（黄熱に関する研究のためのおとりサル）から初めて分離されたウイルスである[1)]。日本脳炎ウイルスやデングウイルス，西ナイルウイルスと同様にフラビウイルス科フラビウイルス属に分類される。ウイルスが分離されてから約70年が経過しており，ジカウイルス感染症は，アフリカやアジアの熱帯・亜熱帯地域では以前から継続的に流行している感染症であると考えられる。2015〜2016年のブラジル等の中南米における大規模流行が発生するまでは，ほとんど注目されることのなかった感染症である。そのためジカウイルス感染症に関する情報は限られているが，アフリカ・アジア等におけるジカウイルス感染症の疫学的情報をまとめる。

1）アフリカ

当初はヒトへは感染しないと考えられていたが，1953年にナイジェリアで初めてヒトへの感染が認識された[2)]。1970年代にアフリカのナイジェリアで実施されたジカウイルス感染症に関する研究成績が発表されている[3)]。発熱のある患者からジカウイルスが分離され，約40%の住民がジカウイルスに対する中和抗体を有していた。少なくともアフリカの一部では多くの人々がジカウイルスに感染している。上記ナイジェリアで実施された研究以外でも，ウガンダ，セネガル，シエラレオネ，ガボン，コートジボワール，中央アフリカ，エジプトにおいてもジカウイルス感染症が分布している事実が報告された[4–11)]。ただし，その詳細は調べられたことはなかった。

2）アジア

1969年にはマレーシアでネッタイシマカからジカウイルスが分離され[12)]，1977〜1978年にかけてインドネシアで行われた臨床研究により1名のジカウイルス感染症患者が報告されている[13)]。2010年にカンボジアで発症したジカウイルス感染症小児例が報告された[14)]。2012年にフィリピンで発症したジカウイルス感染症患者が報告された[15)]。両患者とも発熱，咽頭痛，結膜炎症状，頭痛，発疹等の症状を呈した。2012〜2014年にはタイへの渡航歴のあるジカウイルス病の症例が，日本を含む複数の国で報告されており[16)]，タイ国内での感染例も散発的に報告されている[17)]。

血清疫学的研究でも，アジア地域の熱帯・亜熱帯地域（インド，タイ，ベトナム，マレーシア，フィリピン，インドネシア）にジカウイルス感染症が存在することが示されている[18–23)]。

3）ジカウイルス感染症のアメリカ大陸への流行の拡大：ジカウイルスの遺伝子型

ジカウイルスの血清型は一つで，遺伝子型は大きく分けてアフリカ型とアジア型に分類される[24)]。アジア

(特集つづき)（THE TOPIC OF THIS MONTH-Continued）

表3. チクングニア熱症例の推定感染地，2015年1月〜2016年4月
Table 3. Suspected place of infection of chikungunya fever cases, January 2015-April 2016

推定感染地	Suspected place of infection	報告数 No. cases
アジア	Asia	
インド	India	4
インドネシア	Indonesia	1
フィリピン	Philippines	1
オセアニア	Oceania	
ニュージーランド	New Zealand	2
ソロモン諸島	Solomon Islands	1
ミクロネシア	Micronesia	1
仏領ポリネシア	French Polynesia	1
中南米・カリブ	Central & South America・Caribbean	
ニカラグア	Nicaragua	2
キューバ	Cuba	1
グアテマラ	Guatemala	1
コロンビア	Colombia	1
ボリビア	Bolivia	1
ホンジュラス	Honduras	1
メキシコ	Mexico	1
総　数	Total	19

（感染症発生動向調査：2016年5月10日現在報告数）
（National Epidemiological Surveillance of Infectious Diseases: as of May 10, 2016）

表4. デング熱・デング出血熱症例の推定感染地，2015年1月〜2016年4月
Table 4. Suspected place of infection of dengue fever and dengue hemorrhagic fever cases, January 2015-April 2016

推定感染地	Suspected place of infection	報告数 No. cases
アジア	Asia	
インドネシア	Indonesia	116
フィリピン	Philippines	87
タイ	Thailand	36
マレーシア	Malaysia	33
ベトナム	Vietnam	18
インド	India	17
ミャンマー	Myanmar	17
カンボジア	Cambodia	8
スリランカ	Sri Lanka	8
シンガポール	Singapore	6
バングラデシュ	Bangladesh	6
モルディブ	Maldives	4
台湾	Taiwan	4
東ティモール	East Timor	2
ラオス	Laos	1
オセアニア	Oceania	
仏領ポリネシア	French Polynesia	5
ハワイ	Hawaii	2
サモア	Samoa	1
中南米・カリブ	Central & South America・Caribbean	
ブラジル	Brazil	10
グアテマラ	Guatemala	1
パラグアイ	Paraguay	1
中東・アフリカ	Middle East・Africa	
コンゴ民主共和国	Democratic Republic of the Congo	1
パキスタン	Pakistan	1
その他（2カ国以上訪問）	Others (2 or more locations visited)	21
総　数	Total	406

（感染症発生動向調査:2016年5月10日現在報告数）
（National Epidemiological Surveillance of Infectious Diseases: as of May 10, 2016）