CONTINUING MEDICAL EDUCATION

Viruses Acquired Abroad

What Does the Primary Care Physician Need to Know?

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SUMMARY

Background: Viral infections are imported by travelers and immigrants from tropical or subtropical regions. The primary care physician should be able to include these diseases in the differential diagnosis of various clinical conditions.

Methods: This review is based on pertinent articles retrieved by a selective search of the literature, including guidelines from Germany and abroad.

Results: The available data on imported viral infections in Germany constitute low-level evidence, because most such infections are not reportable in this country. Useful data have, however, been collected by international surveillance networks. Imported viral infections usually present with fever, often also with a rash and elevated transaminases. An average of 230 cases occur in Germany each year; the most common diagnosis among them is dengue fever. An imported viral infection should also be included in the differential diagnosis of fever with arthralgia, as chikungunya virus causes an average of 38 such cases per year. On the other hand, in the past two years, there have been only five cases of imported viral infections causing encephalitis (West Nile virus and Japanese encephalitis virus).

Conclusion: The primary care physician should take a thorough history so that specifically targeted laboratory tests can be ordered as soon as possible. If the suspicion of an imported viral infection is confirmed, the patient should be transferred to a specialized treatment center.

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Data on the epidemiology of diseases imported by travelers and immigrants are available from worldwide surveillance networks. The most important one is the GeoSentinel network, sponsored by the International Association of Travel Medicine and the Centers for Disease Control and Prevention (CDC), Atlanta, USA (1), which has collected data on more than 180 000 travelers as of September 2012. Imported infections usually present with fever, diarrhea, or a rash; other symptoms, such as arthralgia, are rarer. Studies of imported viral diseases have shown that dengue fever is becoming more common in Germany (2–4).

Learning objectives

This article will help readers to

- gain an overview of the clinical features of viral diseases in tropical and subtropical regions, and
- learn the symptoms and signs that should arouse suspicion of these diseases in travelers and immigrants.

Viruses: general characteristics

Viruses are obligate intracellular parasites that need a host cell to reproduce themselves (replicate). They have no metabolic apparatus of their own and contain only one kind of nucleic acid, either DNA or RNA.

In tropical regions, many viruses are transmitted to man by arthropods (mosquitoes in particular) and are thus called arthropod-borne viruses, or arboviruses for short (2). The arboviruses and mosquito vectors that were once found only in the tropics are now increasingly seen in Europe (including Germany) as a result of international passenger travel and trade. They can now cause local outbreaks of disease here as well (4).

The primary care physician should know that arboviral disease is usually diagnosed by the indirect

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Imported viral infections

Dengue fever is becoming increasingly common in Germany.

BOX 1

The evaluation of fever after travel to tropical or subtropical regions (31)

- Always:
 - physical examination
 - examination of the blood for Plasmodia (the only areas known to be free of malaria are: the Caribbean, except Haiti and the Dominican Republic; Tunisia and a few other countries in the Middle East; and the Pacific islands to the south and east of Vanuatu)
 - Complete blood count, platelet count, erythrocyte sedimentation rate, C-reactive protein
 - Transaminases, γ -GT, creatinine, glucose
 - Urinalysis
- When tests for malaria are negative:
 - Cultures of blood, stool and urine (especially for abdominal typhus)
 - Chest x-ray
 - ECG
 - Ultrasonography (especially for amebic liver abscess)
- Further evaluation, depending on accompanying symptoms and signs:
 - fever and rash: dengue fever, chikungunya fever, cytomegalovirus infection, Epstein-Barr virus infection, HIV, rickettsioses
 - fever and elevated transaminases: testing for hepatitis, dengue fever, Rift Valley fever, lymphotropic virus infection, rickettsioses, Q fever, leptospirosis, brucellosis, visceral leishmaniasis (in the presence of splenomegaly and pancytopenia), syphilis (typical: high alkaline phosphatase); also consider viral hemorrhagic fever
 - fever and splenomegaly: dengue fever, lymphotropic viruses, tuberculosis (persistent fever), abdominal typhus (spleen usually palpable from the second week onward), sleeping sickness (acquired in Africa), Q fever, brucellosis, visceral leishmaniasis (in the presence of pancytopenia)
 - fever and eosinophilia: akute schistosomiasis = Katayama syndrome
 - fever and thrombocytopenia: viral infections, also leptospirosis, rickettsioses, visceral leishmaniasis (in the presence of pancytopenia)

demonstration of the pathogen. An infection can be proved beyond any doubt by the detection of virus-specific IgG and IgM antibodies in the patient's serum (Table). The nucleic acids of most arboviruses can only be directly detected in the serum in the first week of the illness (Table).

The diagnosis of viral infection

An infection can be proved beyond any doubt by the detection of virus-specific IgG and IgM antibodies in the patient's serum.

The differential diagnosis of fever

Fever after travel in tropical regions

Fever must be evaluated immediately, as it may be a sign of an acutely life-threatening illness (Box 1). Heading the differential diagnosis is malaria, the most common imported illness, with an average of 638 cases in Germany per year. Further diagnoses that should always be considered in cases of monosymptomatic fever are typhus, paratyphus, and amoebic liver abscess (Box 1) (2). The most common imported viral disease is dengue fever, with an average of 230 cases in Germany per year. Dengue virus infection is the leading cause of fever in persons returning from Southeast Asia (3).

Dengue fever

Dengue fever (DF) is caused by dengue viruses (DENV), of which there are four serotypes. It is endemic in tropical and subtropical regions around the world. In 2010, the first indigenous cases of dengue fever were diagnosed in the south of France and in Croatia (4). DENV is mainly transmitted by the yellow fever mosquito (*Aedes aegypti*), but an increasing number of cases are now being transmitted by the Asian tiger mosquito (*Aedes albopictus*).

DF is among the illnesses that are often imported from tropical and subtropical regions (5, 6). Typical source countries are Thailand, India, Brazil, and the Caribbean islands. Recent years have seen a rising number of cases imported to Germany and reported to the Robert Koch Institute (RKI), the German analogue of the CDC (Figure 1).

After an incubation period of 4 to 7 days (maximum, 14 days), the disease usually begins abruptly with fever up to 40°C (Table). Often, shaking chills, severe retro-orbital headache, and conjunctivitis follow, and the fever persists for 48 to 96 hours (2). Skin erythema is common, mainly on the face and chest, often with white dermatographism (Figure 2). The fever is often, but not always, biphasic: after transient defervescence, the temperature rises again. At this time, about half of all patients develop a maculopapular rash (2). There is usually a mild elevation of transaminases, along with thrombocytopenia and lymphopenia. The characteristic triad consists of fever, rash, and pain in the head, muscles, and joints. Once the acute disease has subsided, there is long-lasting serotype-specific immunity, but only a brief period of cross-immunity. Thus, after a short time, the patient is no longer protected against infection with other DENV serotypes (2).

Dengue fever: symptoms

In dengue fever, skin erythema is common, mainly on the face and chest, often with white dermatographism.

TABLE

The main types of imported viral infection (2)

Main symptom	Family	Virus	Disease	Incubation time (days)	Diagnostic testing: week of illness, test, material to be tested	Vector or reservoir	Distribution	Person-to-person transmission
Fever	Flaviviridae	Yellow fever	Yellow fever	3–6	1st wk / RNA / serum, from 2nd wk / IgG and IgM / serum	Mosquito	Africa, tropical Americas	No
		Dengue	Dengue fever, Dengue hemorrhagic fever	(3) 4–7 (14)	from 1st wk / NS-1, IgG and IgM / serum	Mosquito	Eurasia, Africa, tropical Americas	No
	Bunyaviridae	Rift Valley	Rift Valley fever	2–6	from 1st wk / IgG and IgM / serum	Mosquito	Africa, Arabian Peninsula	No
		Crimean-Congo	Crimean-Congo hemorrhagic fever	2–13	1st wk / RNA / serum, from 2nd wk / IgG and IgM / serum	Tick	Africa, Eurasia	Yes
		Hantaan, Dobrava-Belgrad	Hemorrhagic fever with renal syndrome	(5) 12–21 (42)	from 1st wk / IgG and IgM / serum	Rodent	Eurasia	No
		Sin-Nombre, Andes	Hantavirus cardio-pulmonary syndrome	7–39	1st wk / RNA / serum, from 2nd wk / IgG and IgM / serum	Rodent	America	No (Sin Nombre) Yes (Andes)
		Tahyna	Valtice fever	5–15	from 1st wk / IgG and IgM / serum	Mosquito	Eurasia	No
	Arenaviridae	Lassa	Lassa fever	(3) 7–10 (21)	1st wk / RNA / serum, from 2nd wk / IgG and IgM / serum	Rodent	West Africa	Yes
		Junin	Argentine hemorrhagic fever	6–14	1st wk / RNA / serum, from 2nd wk / IgG and IgM / serum	Rodent	Argentina	?
		Machupo	Bolivian hemorrhagic fever	7–16	1st wk / RNA / serum, from 2nd wk / IgG and IgM / serum	Rodent	Bolivia	Yes
		Guanarito	Venezuelan hemorrhagic fever	7–14	1st wk / RNA / serum, from 2nd wk / IgG and IgM / serum	Rodent	Venezuela	?
	Filoviridae	Marburg	Marburg hemorrhagic fever	(3) 5–7 (10)	from 1st wk / RNA / serum, from 4th wk / IgG and IgM / serum	Fruit bat	Africa	Yes
		Ebola	Ebola hemorrhagic fever	2–25	from 1st wk / RNA / serum, from 4th wk / IgG and IgM / serum	Fruit bat	Africa	Yes
Arthritis / Arthralgias	Flaviviridae	Dengue	Dengue fever	(3) 4–7 (14)	from 1st wk / NS 1, IgG and IgM / serum	Mosquito	Eurasia, Africa, tropical America	No
	Togaviridae	Chikungunya	Chikungunya fever	(2) 3–7 (12)	from 2nd wk / IgG and IgM / serum	Mosquito	Eurasia, Africa	No
		Sindbis	Ockelbo disease, Pogosta disease, Karelian fever	2–18	from 2nd wk / IgG and IgM / serum	Mosquito	Eurasia, Africa, Australia	No
		O'nyong-nyong	O'nyong-nyong fever	8–14	from 2nd wk / IgG and IgM / serum	Mosquito	Africa	No
		Ross River	epidemic polyarthritis	3–14 (21)	from 2nd wk / IgG and IgM / serum	Mosquito	Australia and Oceania	No
		Barmah Forest	Barmah Forest disease	3–14 (21)	from 2nd wk / IgG and IgM / serum	Mosquito	Australia	No
		Mayaro	Mayaro fever	(3) 7–14	from 2nd wk / IgG and IgM / serum	Mosquito	South America	No

Main symptom	Family	Virus	Disease	Incubation time (days)	Diagnostic testing: week of illness, test, material to be tested	Vector or reservoir	Distribution	Person-to-person transmission
Meningo / Encephalitis	Flaviviridae	West Nile	West Nile fever	2–15	1st wk / RNA / serum, CSF from 2nd wk / IgG and IgM / serum	Mosquito	Eurasia, America, Africa, Australia	No
		Japanese encephalitis	Japanese encephalitis	5–15	1st wk / RNA / serum, CSF, from 2nd wk / IgG and IgM / serum	Mosquito	Asia, Australia	No
		St. Louis encephalitis	St. Louis encephalitis	5–15	1st wk / RNA / serum, CSF, from 2nd wk / IgG and IgM / serum	Mosquito	America	No
		Powassan	Powassan encephalitis	8–34	1st wk / RNA / serum, CSF, from 2nd wk / IgG and IgM / serum	Tick	North America	No
		Murray Valley	Murray Valley encephalitis	7–28	1st wk / RNA / serum, CSF, from 2nd wk / IgG and IgM / serum	Mosquito	Australia	No
		Usutu	Usutu fever	5–15	1st wk / RNA / serum, CSF, from 2nd wk / IgG and IgM / serum	Mosquito	Europe, Africa	No
	Bunyaviridae	Oropouche	Oropouche fever	3–8 (12)	from 1st wk / IgG and IgM / serum	Midge	South America	No
		La Crosse	La Crosse encephalitis	5–15	from 1st wk / IgG and IgM / serum	Mosquito	North America	No
	Paramyxoviridae	Nipah	Nipah fever	4–14 (60)	from 1st wk / RNA / serum, CSF	Fruit bat, Pig	Southeast Asia	Yes
		Hendra	Hendra fever	4–14 (60)	from 1st wk / RNA / serum, CSF	Fruit bat, Horse	Australia	No
	Picornaviridae	Polio	Poliomyelitis	(3) 7–14 (35)	from 1st wk / RNA / stool, throat washings, CSF	Man	Africa, Asia	Yes
	Togaviridae	Western equine encephalitis	Western equine encephalitis	5–10	1st wk / RNA / serum, CSF, from 2nd wk / IgG and IgM / serum	Mosquito	America	No
		Eastern equine encephalitis	Eastern equine encephalitis	4–10	1st wk / RNA / serum, CSF, from 2nd wk / IgG and IgM / serum	Mosquito	America	No
		Venezuelan equine encephalitis	Venezuelan equine encephalitis	1–6	1st wk / RNA / serum, CSF, from 2nd wk / IgG and IgM / serum	Mosquito	America	No
	Rhabdoviridae	Rabies	Rabies	(7) 28–84 (Years)	from 1st wk / RNA / saliva, CSF	Various mammalian hosts	Worldwide	Yes
	Arenaviridae	LCMV	Lymphocytic choriomeningitis	6–13	from 1st wk / IgG and IgM / serum	Rodent	Worldwide	No
	Reoviridae	Colorado tick fever	Colorado tick fever	(2) 3–6 (21)	from 1st wk / IgG and IgM / serum	Tick	North America	No

Dengue fever: incidence

Dengue fever is the most common imported viral disease, with an average of 230 cases in Germany per year.

Chikungunya fever: clinical presentation

Fever and arthralgia are the clinical hallmarks in patients infected with the chikungunya virus.

In severe cases, DF can cause hemorrhage; such cases, known as dengue hemorrhagic fever (DHF), are mainly seen among children in hyperendemic areas (2). DHF can also present as dengue shock syndrome (DSS), which is characterized by fewer hemorrhages, but also by a massive shifting of fluid from the intravascular compartment into the tissues. DENV secondary infections seem to be of the DHF type more commonly than primary infections are, owing to an intensification of infection by antibodies. Persons returning from endemic areas with DENV infections usually have an illness of the DF type (6); fewer than 1% have DHF. There has been only one death from DHF in Germany to date (7).

A newly arisen DENV infection can be diagnosed by the demonstration of DENV-RNA, DENV-NS-1 antigen, or DENV-specific IgG and IgM antibodies (*Table and Figure 3*). Serologic testing in the first three weeks after disease onset should always include simultaneous testing for NS-1, IgM and IgG, for maximal clinical sensitivity and specificity (7).

Patients with dengue fever should be observed until their laboratory values have renormalized. They may need to be hospitalized in case of severe thrombocytopenia, petechiae or other signs of hemorrhage, or elevated transaminases (8). There is no available treatment directed at the cause of the disease. Drugs with anticoagulant effects (e.g., acetylsalicylic acid) are contraindicated. If the hematocrit rises by more than 20%, intravenous fluids should be given early to prevent DSS. Vaccines against DENV infections are now being developed (phase 3), but the initial findings on their putative effectiveness are not promising (9) and no vaccine is expected to be approved in the next few years. Persons traveling to Southeast Asia or South America should observe 24-hour precautions against mosquito exposure.

Sandfly fever

Sandfly fever is transmitted by Sandfly fever Naples virus and Sandfly fever Sicilian virus (SFNV, SFSV) and the Toscana virus (TOSV) (2). These viruses usually cause fever without any other accompanying symptoms; they are found throughout the Mediterranean region, all the way to Asia Minor, corresponding to the geographical distribution of their vector, the sandfly *Phlebotomus spp.* (2). TOSV, however, can also cause aseptic meningitis. TOSV infections have been observed in Europe in recent years in Italy, Spain,

FIGURE 1

Transmitted cases of dengue fever in Germany 2001–2011, according to the reference definition of the Robert Koch Institute; up to date as of 4 April 2012 (see www3.rki.de/SurvStat/)

Portugal, France, and Cyprus; they usually arise in summer and are one of the most common causes of aseptic meningitis in Italy (2). Returning travelers are often among the affected persons (10). From the first week of infection onward, the diagnosis can be made serologically by the demonstration of anti-SFNV, -SFSV, or -TOSV antibodies (IgG and IgM) in the patient's serum (*Table*). There is no specific, causally directed treatment for sandfly fever. Antipyretic and analgesic drugs can be given symptomatically (2).

The differential diagnosis of viral hemorrhagic fever (VHF)

Viral hemorrhagic fever in general

Viral hemorrhagic fever (VHF) should be included in the differential diagnosis when a patient presents in a severely ill state with marked elevation of serum transaminases and signs of renal involvement or a hemorrhagic diathesis (*Box 1*). These diseases are very rarely imported (2), but they are life-threatening (11). Lassa virus infections have only been imported to Germany twice to date, and Ebola virus infections not at all (2). Some VHF viruses can be transmitted directly from person to person, possibly in respiratory droplets (Lassa, Ebola, Marburg, and Crimean-Congo hemorrhagic fever virus); this fact has major implications for clinical management because of the risk of nosocomial transmission (11). In contrast, imported yellow-fever-virus infections and dengue-virus

Sandfly fever

These viruses, which are found throughout the Mediterranean region all the way to Asia Minor, usually cause fever without any other symptoms. The Toscana virus, however, can cause aseptic meningitis.

Viral hemorrhagic fever

Viral hemorrhagic fever (VHF) should be considered when a patient presents in a severely ill state with marked elevation of serum transaminases and signs of renal involvement or a hemorrhagic diathesis.

Figure 2: Dermatographism in the rash of dengue fever

infections are not contagious, so these patients do not need to be isolated. In suspected cases of VHF, the patient should be isolated at the site of diagnosis if possible, and the responsible public-health authorities should be informed so that they can arrange transport of the patient, under strict isolation precautions, to a competence center for the appropriate treatment. The goal is to provide optimal medical treatment for the patient while minimizing the risk of spread to other persons, including the treating team (12). There are a number of high-security isolation wards of this type in Germany (Box 2).

The primary care physician should think of VHF when the patient has a fever above 38.5°C, has been in sub-Saharan Africa in the past three weeks, and may have had contact there with persons suffering from VHF, or is already suffering from a hemorrhagic diathesis or unexplained shock. Important elements of the differential diagnosis are malaria, fulminant viral hepatitis, leptospirosis, meningococcal sepsis, and intoxications of various kinds (13).

The diagnostic assessment, which must be carried out in a high-security laboratory (*see eBox*), relies mainly on the demonstration of the RNA of the viral pathogen using reverse transcriptase polymerase chain reaction (RT-PCR) in the first week of the illness (*Table*). Virus-specific IgG and IgM antibodies can be detected in the serum from the second to fourth week of disease onward (*Table*), but this test is often still negative (2).

The differential diagnosis of VHF

Important elements of the differential diagnosis are malaria, fulminant viral hepatitis, leptospirosis, meningococcal sepsis, and intoxications of various kinds.

Lassa fever

Lassa fever is named after the town in northeastern Nigeria where, in 1969, the disease was first described and the Lassa virus (LASV) was first isolated. It is endemic to Sierra Leone, Guinea and Liberia in the west and Nigeria in the east, and in a number of other West African countries. The virus's natural host is the African rodent *Mastomys natalensis*. Most LASV infections are mild or asymptomatic. An estimated 100 000 to 300 000 persons become infected with LASV each year, of whom 1% to 2% die (2). Only two cases are known to have been imported to Germany in recent years (2). The overt illness usually presents nonspecifically with fever, headache, sore throat, coughing, and gastrointestinal symptoms. Typically, there is progressively severe edema of the eyelids and face, along with conjunctivitis, severe myalgia, proteinuria, hypotension, ulcerating pharyngitis (sometimes with laryngeal edema), coughing, nausea, and vomiting. Thereafter, pneumonia, hepatitis, encephalitis, and hemorrhagic fever can develop, the latter potentially leading to multi-organ failure. High GOT values and marked viremia are unfavorable prognostic signs. The patients often do not appear seriously ill until shortly before they develop multi-organ failure. The disease is particularly serious in pregnant women. Post-exposure prophylaxis with ribavirin is recommended for persons who have had unprotected, direct contact with the blood or bodily fluids of patients with Lassa fever (14).

Ebola and Marburg hemorrhagic fever

The Ebola and Marburg viruses are among the more dangerous pathogens known to medical science. Types that can infect human beings are found only in sub-Saharan Africa (15). Marburg virus was discovered in Marburg, Germany, in 1967, when a number of laboratory workers there, and in what was then Yugoslavia, became acutely ill with a fever of unknown origin. This first epidemic of Marburg fever was caused by the transport of infected primates from Uganda to Europe for research purposes (2). Two further, highly lethal ones occurred, in 1998–2000 in the northern region of the Democratic Republic of the Congo (DRC) and in 2004–2005 in Angola (2). Ebola virus was first described in 1976, when it caused large epidemics in Zaire (now the Democratic Republic of the Congo) and in the Sudan (15). Further epidemics have occurred in Central Africa in recent years. 2300

Lassa fever: symptoms and signs at onset

The overt illness usually presents nonspecifically with fever, headache, sore throat, coughing, and gastrointestinal symptoms. Typical findings include progressively severe edema of the eyelids and face, conjunctivitis, and severe myalgia.

cases of Ebola fever and 450 of Marburg fever have been registered to date (2).

Travelers very rarely import these viruses into non-endemic regions. Two imported filovirus infections were treated in South Africa (15). In 2008, a woman imported a case of Marburg fever from Uganda to the Netherlands (16). The natural reservoir of this virus is in fruit bats; there have been a few cases of travelers who were infected on visits to fruit-bat caves, by direct contact with the animals or their infectious excreta (15). Contact with infected primates can also lead to infection (15).

The incubation time of Ebola virus is generally 2–25 days, while that of Marburg virus is generally 5–7 days, rarely as long as 10 days (Table). The affected patients suddenly develop fever, severe headache, arthralgia, myalgia, chest pain, abdominal pain, and loss of appetite. Fairly typical findings include pharyngitis, conjunctival infection, and a morbilliform, non-pruritic, non-hemorrhagic rash that is readily visible, particularly on white skin (15). Gastrointestinal symptoms are common, including bloody diarrhea in fatal cases. There is a generalized bleeding tendency, with epistaxis, hematuria, hemoptysis, hematemesis, metrorrhagia, and spontaneous abortion (days 5–7 of illness). Neurological and psychiatric manifestations (hemiparesis, psychosis) are also common, and anuria may develop. In fatal cases, death usually occurs from day 6 to day 16 of the illness. Survivors may suffer from myelitis, hepatitis, psychosis, or uveitis (15).

Crimean-Congo hemorrhagic fever

Crimean-Congo hemorrhagic fever (CCHF) is caused by the virus of the same name (CCHFV), which was first isolated and characterized in the Belgian Congo (now the DRC) and originally known as Congo virus (2). In the 1970's, this virus was shown to be identical to the pathogen causing hemorrhagic Crimean fever, a disease that had been known since 1944 (2). CCHFV is the most geographically widespread tick-borne virus. It is usually transmitted by ticks of the genus *Hyalomma* and is endemic to many countries of Africa, Asia, Southeastern Europe, and the Middle East. It can infect many different vertebrates (both wild and domestic), but animals, unlike humans, do not become ill when infected. Transmission to man is either through a tick bite or by contact with infected animals. The risk of transmission from a hospitalized patient with CCHF to

Crimean-Congo hemorrhagic fever

CCHFV is the most geographically widespread tick-borne virus. It is usually transmitted by ticks of the genus *Hyalomma*.

FIGURE 3

The course of serologic findings in dengue virus infection; NS1, NS1 antigen test

other persons is high: A number of highly lethal nosocomial outbreaks have been documented, most recently in Turkey and Kazakhstan. Only two imported cases have been registered in Germany in the last five years (17).

In man, cases of CCHF infection can range in severity all the way from an asymptomatic state, to a flu-like course, to a highly lethal hemorrhagic fever. Fever arises suddenly after a 2–13 day incubation period (Table). Further manifestations include malaise, weakness, irritability, headache, pain in the limbs, loss of appetite, and sometimes vomiting, diarrhea, and epigastric pain. Hemorrhage may occur after only a few days of illness and may be massive, with cutaneous hemorrhage, gastrointestinal bleeding, or hematemesis, often combined with liver dysfunction (2). 10% to 50% of the affected patients die, usually 5 to 14 days after the onset of the disease (2).

Viral infections characterized by persistent arthralgia

The causes of arthralgia after travel to tropical regions

Returning travelers often complain of arthralgia (18). The possible causes include post-infectious arthritis

The clinical features of CCHF

In man, cases of CCHF infection can range in severity all the way from an asymptomatic state, to a flu-like course, to a highly lethal hemorrhagic fever.

BOX 2

Special treatment centers for infections with highly virulent contagious pathogens in Germany

- Berlin, Universitätsklinikum Charité—Campus Virchow-Klinikum, Medizinische Klinik mit Schwerpunkt Infektiologie
- Düsseldorf, Universitätsklinikum, Leber- und Infektionszentrum
- Frankfurt am Main, Universitätsklinikum, Medizinische Klinik III, Zentrum für Innere Medizin
- Hamburg, Bernhard-Nocht-Klinik für Tropenmedizin, Universitätsklinikum Hamburg-Eppendorf
- Leipzig, Klinikum St. Georg, 2. Klinik für Innere Medizin
- München, Städtisches Krankenhaus München-Schwabing, 1. Medizinische Abteilung
- Saarbrücken, Klinikum Saarbrücken, Medizinische Klinik I
- Stuttgart, Robert-Bosch-Krankenhaus Stuttgart, Innere Medizin I
- Würzburg, Missionsärztliche Klinik, Abteilung für Tropenmedizin

and viral illness. In the tropics, certain arboviruses are particularly strongly associated with arthritis (*Table*).

Chikungunya fever

This disease is mainly found in eastern and southern Africa, on the Indian subcontinent, in Southeast Asia, and (in recent years) on islands in the Indian Ocean (2). Seasonal outbreaks are now occurring in southern Europe as well, e.g., in Italy in 2007 (19). The main explanation for the latter is the increase in international travel and trade, but the wide distribution of competent mosquito vectors in Southern Europe also increases the danger of indigenous infection. Chikungunya virus (CHIKV) is transmitted by various mosquito species (especially *Aedes albopictus*) from a reservoir of various warm-blooded animals (rodents, non-human primates, and others) to other warm-blooded animals.

Chikungunya fever is frequently imported by travelers (though less frequently than dengue fever). There are an average of 38 imported cases in Germany per year (20–22).

After a 2- to 12-day incubation period, patients develop sudden, rapidly rising fever, headache, con-

junctivitis, myalgia, and arthralgia. Arthralgia is a prominent symptom, usually bilateral and mainly affecting the limbs (2). The joints are swollen and tender. There may be a maculopapular rash or generalized redness of the skin. The fever may take a biphasic course. A small percentage of patients (5–10%) have arthralgia that persists for months or, rarely, years (2). CHIKV infection can be diagnosed in the first few days of the illness by the detection of viral RNA in the patient's serum with RT-PCR (*Table*) (2). IgM and IgG antibodies can only be detected from the second week of illness onward (*Table*).

There is no specific treatment for chikungunya fever. It is treated symptomatically with nonsteroidal anti-inflammatory agents and other drugs (2). The only means of prevention is round-the-clock protection against mosquitoes.

Ross River fever or epidemic polyarthritis

Ross River fever is the most common mosquito-borne viral infection in Australia (23). It is characterized by persistent arthralgia and thus causes considerable morbidity, with corresponding economic effects. There are an average of 4,800 cases in Australia each year (23). The disease is also endemic to Papua New Guinea, and there have been major outbreaks in Fiji, Samoa, the Cook Islands, and New Caledonia (23). Ross River fever should be included in the differential diagnosis of arthralgia in returning travelers with a suggestive history (23, 24).

The incubation period is usually 3–14 days, but can rarely be as long as 21 days (*Table*). Asymptomatic infection is apparently common. Further typical clinical features include fever, a maculopapular rash, and persistent arthralgia (epidemic polyarthritis). Fever and rash arise in 50% of patients (2). The rash usually lasts 5 to 10 days and is mainly on the limbs and trunk. Most patients acutely develop symmetrical arthritis, mainly in the peripheral joints (2). In about half of all patients, arthritis lasts more than a year.

From the second week of illness onward, Ross-River-virus-specific IgG and IgM antibodies can be detected in the patient's serum (*Table*). The treatment is symptomatic, with non-steroidal anti-inflammatory drugs (2).

Viral encephalitis

Meningoencephalitis acquired in tropical regions

Meningoencephalitis acquired in tropical regions has an extensive differential diagnosis. Cerebral malaria

Chikungunya fever: incidence

After dengue fever, chikungunya fever is the second most commonly imported viral disease, with an average of 38 imported cases in Germany each year.

Ross River fever

Ross River fever is the most common mosquito-borne viral infection in Australia.

is always a possibility after a trip to sub-Saharan Africa (2). The meningoencephalitic stage of sleeping sickness, though rare, should also be considered. Viral illnesses are listed in the *Table* according to the geographical regions where they can be acquired.

West Nile fever

West Nile Virus (WNV) is a mosquito-borne virus that was first isolated from the blood of a Ugandan woman in 1937. The first documented epidemic occurred in Israel in 1950. WNV is a classic example of an “emerging virus”: It appeared in North America in 1999, then spread to cause 1.8 million infections in North America by 2010, with at least 1308 fatalities (25). Clearly, even well-developed countries are not spared the danger of epidemic disease from imported, mosquitoes-borne viruses. WNV is now widespread on all five inhabited continents; there were major outbreaks in Europe in 2010 and 2011 (26). The last major outbreak was in Greece in 2010, with 197 cases, 33 of them fatal (26). A number of avian species serve as a reservoir for the virus by being a source of infection for blood-sucking mosquitoes. Aside from human beings, horses can also become ill with West Nile fever.

The importation of WNV to Germany is only to be expected, because the mosquito vector (the common house mosquito) is found throughout Germany and WNV is already circulating in neighboring countries (France, Austria, and the Czech Republic). In 2011, we documented the first imported WNV infection in Germany (from Canada) (27). In 2012, there were two further cases of imported WNV infection, this time from within Europe (Montenegro and Greece). The incubation time in man is 2 to 15 days (*Table*). Most infections are subclinical (80%) or have nonspecific symptoms (26). The fever curve may be biphasic. Half of all patients have a maculopapular rash (2). The disease can be complicated by inflammation of the central nervous system—meningitis, encephalitis, encephalomyelitis, or polyradiculitis. The risk of neurological complications is higher in the elderly and in persons with pre-existing cardiovascular disease (26). Among elderly patients, WNV meningoencephalitis carries a mortality of 5–10%.

WNV infection can be diagnosed in its early stages by the detection of viral RNA in the patient’s serum or cerebrospinal fluid with RT-PCR (*Table*). WNV-specific IgM and IgG antibodies are detectable only

FIGURE 4

The main area of distribution of Japanese encephalitis (2)

from the second week of illness onward (*Table*). In serological diagnosis, it must be borne in mind that cross-reactions with other flaviviruses can occur. There is no specific treatment for WNV infection (2).

Japanese encephalitis

Japanese encephalitis, caused by a virus of the same name (abbreviated JE virus), is the most common type of viral encephalitis in Asia, with 30 000 to 50 000 cases reported per year (2). Its area of distribution ranges from the west Pacific islands to the eastern border of Pakistan, and from Korea to northern Australia (*Figure 4*). Several species of water fowl and pigs that are kept in human habitations serve as viral reservoirs and amplifying hosts. The virus is transmitted by nocturnally active mosquitoes of the genus *Culex*, most frequently by the rice-paddy mosquito, *C. tritaeniorhynchus*. The disease is found mainly in rural areas with rice paddies and in areas abundant in water and swampland. Recently, cases have also been seen in cities in the endemic areas (2).

JE virus infection was hardly a concern for travelers from Germany until quite recently. In the last few years, however, two German vacationers have

Meningoencephalitis acquired in the tropics

Meningoencephalitis acquired in tropical regions has an extensive differential diagnosis. Cerebral malaria is always a possibility after a trip to sub-Saharan Africa.

West Nile fever

WNV-specific IgM and IgG antibodies are detectable only from the second week of illness onward.

developed the illness (28). A vaccine is available for travelers at risk (29). JE virus infection usually manifests itself as a mild, flu-like febrile illness. In about one in 250 cases, however, acute meningoencephalitis develops: Fever, headache, and vomiting are followed by impairment of consciousness, abnormal reflexes, confusion, altered behavior, tremor, or paresis (2). Neuro-imaging may reveal hemorrhagic lesions in the thalamus (30). Defervescence usually begins after the tenth day of illness. CNS involvement carries a 30% mortality, and permanent neurological and neuropsychological damage is common among survivors. Survivors have lifelong immunity. Dengue fever, another potential cause of encephalitis, should be considered in the differential diagnosis.

JE virus infection can be diagnosed in the first few days of illness by the detection of viral RNA in the patient's serum or CSF with RT-PCR (*Table*). JE-virus-specific IgM and IgG antibodies can be detected from the second week of illness onward (*Table*). In serological diagnosis, it must be borne in mind that cross-reactions with other flaviviruses can occur. There is no specific treatment for JE virus infection (2).

Conflict of interest statement

The authors declare that no conflict of interest exists.

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Japanese encephalitis

JE virus infection was hardly a concern for travelers from Germany until quite recently. In the last few years, however, two German vacationers have developed the illness. A vaccine is available for travelers at risk.

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Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

What serologic test(s) must be performed to diagnose an acute primary infection with dengue virus?

- a) Only anti-dengue virus IgM
- b) Only anti-dengue virus IgG
- c) Both anti-dengue virus IgM and anti-dengue virus IgG
- d) Dengue virus NS1 antigen and anti-dengue virus IgG
- e) Dengue virus NS1 antigen and both anti-dengue virus IgM and anti-dengue virus IgG

Question 2

What is the most common arboviral infection among travelers returning to Germany?

- a) Chikungunya virus infection
- b) West Nile virus infection
- c) Dengue virus infection
- d) Japanese encephalitis virus infection
- e) Ross River virus infection

Question 3

What laboratory test should be performed regularly in a person with dengue virus infection so that a potentially serious complication can be prevented in time?

- a) Dengue virus RNA
- b) Dengue virus NS1 antigen
- c) Hematocrit
- d) Leukocyte count
- e) Erythrocyte sedimentation rate

Question 4

A 22-year-old man who came back 8 weeks ago from a year's travels in Australia presents to you complaining of arthralgia, mainly in the interphalangeal joints and ankles. He also says he was briefly febrile two days after his return.

What viral test(s) should you order?

- a) Mayaro virus IgG and IgM
- b) West Nile virus RNA
- c) Chikungunya virus IgG
- d) Ross River virus IgM und IgG
- e) Barmah Forest virus RNA

Question 5

What pathogen is the most common cause of meningo-encephalitis in Southeast Asia?

- a) Nipah virus
- b) Dengue virus
- c) FSME virus
- d) West Nile virus
- e) Japanese encephalitis virus

Question 6

For which kind of imported viral disease is person-to-person transmission the usual pathway of infection?

- a) Ebola virus
- b) Dengue virus
- c) Ross River virus
- d) Mayaro virus
- e) Tahyna virus

Question 7

How long is the incubation time for Ebola hemorrhagic fever, in days?

- a) 0–3
- b) 1–8
- c) 2–25
- d) 6–10
- e) 8–14
- e) 10–12

Question 8

How many persons suffer from Japanese encephalitis in Asia each year?

- a) 10 000–20 000
- b) 20 000–40 000
- c) 30 000–50 000
- d) 40 000–60 000
- e) 60 000–80 000

Question 9

A 43-year-old woman who returned two days ago from two weeks of vacation in Thailand (Krabi) presents to you complaining of pain in the muscles and joints for the last three days. Her temperature is 39.4°C. Physical examination reveals a rash on the trunk with white dermatographism. The patient says that, while in Thailand, she was bitten several times by mosquitoes.

What viral infection is the probable diagnosis?

- a) Lassa virus
- b) Marburg virus
- c) Lymphocytic choriomeningitis virus
- d) Ross river virus
- e) Dengue virus

Question 10

To which continent is Ross River virus endemic, and how is it transmitted?

- a) South America, mosquitoes
- b) Africa, rodents
- c) Africa, ticks
- d) Australia, mosquitoes
- e) Asia, rodents

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