1 Current Knowledge about the Pathogen

1.1 Characteristics of Hepatitis E

First indications of hepatitis E as a distinct disease, which differs from hepatitis A, were found in 1980 when sensitive and specific detection systems for hepatitis A virus (HAV) first became available and hepatitis epidemics were examined in India. Epidemiologic studies up to that point pointed to the fact that these hepatitis infections with clinically very similar course were caused by HAV pathogens transmitted by the faecal-oral route. The experimental proof that a second virus transmitted by the faecal-oral route, which was later called hepatitis E virus (HEV), was provided in 1983 by the transmission studies of Balayan et al. [1]. In these experiments, HAV-immune voluntary individuals were infected with stool suspensions from patients with a hepatitis A-like disease which occurred in Tashkent, Uzbekistan. Spherical virus-like particles, 27–30 nm in diameter, could be isolated from the stools of the experimentally infected persons, which formed a band in the CsCl gradient at a density of 1.35 g/cm³. These particles could be detected by immuno-electron microscopy (IEM) both in the pre-clinical (as from the 27th day post infection (dpi)) and in the post-clinical phase (45 dpi, onset of the disease approximately 36 dpi) (fig. 1).

Up to 1990, IEM and the inoculation of monkeys were the only diagnostic methods for the detection of HEV infections and their differentiation from HAV. In 1991, Reyes et al. [2] succeeded in cloning the genome. This opened new paths for the development of diagnostic methods for serological and molecular detection of HEV infections. HEV was first categorised as part of the Caliciviridae family, based on its morphological properties. Sequence analysis, however, revealed that the genome structure of HEV is significantly distinct from this virus family. Therefore, HEV is today classified as the so far only representative of the hepevirus genus in the new family of Hepeviridae.

HEV is a small non-enveloped, single-stranded icosahedral virus with a diameter of approximately 32–34 nm. The capsid of the virus probably consists of one single protein. The genome is single-stranded positive-sense with a size of 7.2 kbp. It is flanked by non-encoding regions, polyadenylated at the 3' end, and bears a m7G-cap at the 5' end. The genome itself encodes for three overlapping open reading frames (ORF 1–3). Hepeviruses have the feature that the ORF 2 with a length of 2 kbp located at the 3' end encodes for the capsid protein. It is especially this characteristic that makes the HEV virus distinct from the calcivirus, in which the sequence encoding for the capsid is located at the 5' end. ORF 1 with a length of approximately 5 kbp is located at the 5' end and encodes for the non-structural proteins involved in RNA replication: RNA-dependent RNA polymerase, guanylyl and methyl transferases, helicase and a papain-like protease. ORF 3 with a length of 372 bp overlaps at the 3' end with the first 331 bp from ORF 2 and at the 5' end with ORF 1. ORF 3 encodes for a small immunogenic phosphoprotein with a size of not more than 123 amino acids.

Based on phylogenetic analyses, the isolates examined up to now are classified into four different genotypes which have different world-wide distributions [3]. For genotype 1 the Burma isolate represents the prototype, for genotype 2 the Mexican isolate, for genotype 3 the USA isolate, and for genotype 4 the Chinese isolate. The different genotypes are then further grouped into different genetic subtypes. Serologically, HEV seems to behave in a uniform manner, as neutralisation studies in the cell culture and protection studies with different genotypes in infection studies have shown [4].

Various studies provide evidence that HEV replicates in hepatocyte culture of humans and macaques. For this purpose, cell cultures were infected with HEV from stool suspensions. In such in vitro studies, Emerson et al. [5] were able to show that approximately half the HEV infectiveness was inactivated after heat treatment at 45–50 °C for 1 h and almost the entire HEV infectiveness at 56 °C. In addition, the authors were able
to show that, although different HEV isolates showed different degrees of heat stability, all isolates studied were sensitive to treatment at 60 °C for 1 h. In contrast to this, only half of the HAV could be inactivated when treated at 60 °C for 1 h and lost its infectiveness only after heat treatment at 66 °C. These findings thus revealed that HEV was more sensitive to heat than HAV [5]. Tanaka et al. [6] completed the thermostability studies of HEV with cell culture-adapted HEV. Heat treatment of HEV at 90 °C for 1 min or at 70 °C for 10 min inactivated HEV entirely. Incubation of HEV suspensions at 56 °C for 30 min reduced the titre in comparison to treatment at 25 °C.

1.2 Infection and Infectious Diseases

The course of HEV infections is similar to that of HAV infections. As a rule, acute HEV infection is self-limiting with a low death rate, which is, however, higher (0.5–4%) than that of the HAV infection (approximately 0.2%) [7]. HEV is usually transmitted by the faecal-oral route and is excreted in the stool for 3–4 weeks. In some patients, an excretion period of up to 120 days could be observed using PCR [8]. It is assumed that HEV first replicates in the intestinal duct and then reaches the liver via the blood vessels. There, replication of the virus takes place in the cytoplasm of hepatocytes. The virus is then excreted into the stool and the blood via the gall. The incubation period measured by the increase in transaminases can be between 3 and 8 weeks. In the acute incubation phase up to the late phase, the virus is excreted via the stool in high quantities [1]. Experimental oral infections of humans showed that viraemia was first detectable between the 22nd and the 28th dpi, approximately 1 week before the occurrence of symptoms [1, 9]. Symptoms of the disease then occurred between the 30th and the 36th dpi. The peak of the transaminases was observed at approximately the same time as the appearance of the first antibodies. Histologically, focal necroses and apoptosis of cells are found in the liver. Whether the observed alterations are caused by the virus itself or by the immune response is unclear, since only minor signs of inflammation could be detected [10]. Comparable courses of infection were also observed in experimental transmissions of HEV to primates [11, 12]. Similarly to hepatitis A, an IgM and an IgG response can be measured at approximately the time of the occurrence of symptoms in the acute HEV infection. HEV infections during pregnancy have a high percentage of serious outcomes, accompanied by a high mortality rate of approximately 20%. The mortality rate in men and non-pregnant women is 0.5–4% [7, 10, 13, 14]. In addition to the serious liver failure which is observed in particular in pregnant women in their third trimester, encephalopathies and disseminated intravascular consumptive coagulation disorders can occur. In the past few years, there have been an increasing number of reports about HEV infections with sub-clinical course [15, 16]. Increased levels of transaminases may act as infection markers. In this phase, HEV genome is detectable in the blood in a high percentage of the infected individuals. More or less simultaneously, an increase in the HEV-specific IgM and IgG antibody responses are observed. Transmissions of HEV by non-inactivated blood products from such donors have been reported from various countries [17–21].

1.3 Epidemiology

Acute hepatitis E is a very frequent cause of hepatitis acquired by the faecal-oral route world-wide. For a long time, HEV, the causative agent of this disease, was considered as a human-specific pathogen. As far as geographic distribution is concerned, one distinguishes between those regions, where HEV occurs endemically, and those where it is sporadic [22]. In this context, Southeast and Central Asia, the Middle East, Africa and Central America are considered as endemic areas. In these regions, pronounced epidemics have been observed in the past few decades, which were frequently caused by contaminated drinking water, but isolated sporadic cases of HEV infection have also been reported.
In the industrialised countries of Europe and America, HEV infections as a rule only occurred in travellers who had previously stayed in endemic areas. In the past few years, however, more and more reports have been published stating that sporadic hepatitis E also occurs in non-endemic areas, i.e. industrialised countries, without any connection with travelling to classic endemic areas [23, 24].

Most of the serious HEV infections in Asia and Africa are caused by genotype 1 while genotype 2 predominates in Mexico, Egypt, Nigeria, and Namibia. Genotype 3 has been observed in Asia, America and Europe as well as in New Zealand. The recently newly described genotype 4 has up to now been observed mainly in Asia [3, 25]. According to findings established, genotypes 1 and 2 have mainly been found with disease in humans in the respective endemic areas. Genotypes 3 and 4, however, have been found both in humans and in animals, especially domestic and wild pigs [25].

Animals, especially pigs, are regarded as the source of the infectious pathogens for humans in industrialised countries. Hepatitis E is therefore to an increasing extent considered to be a zoonosis. HEV was first detected successfully in a pig in the USA in 1997 [26]. A high HEV prevalence rate is shown in pigs in nearly all regions of the world [22]. Evidence for this could be provided by serological, virological and molecular detection methods. In addition, the close relationship of isolates from humans and pigs in the respective regions could be shown by phylogenetic analyses of the virus genomes.

Experimental infections in primates and pigs with HEV, and in pigs with human isolates, support the hypothesis that hepatitis E is a zoonosis [27]. Apart from pigs, HEV was detected in various other species such as rats, dogs and birds. It has so far been unclear which role these species play in the transmission to humans.

Sporadic outbreaks of HEV infection in Japan were attributed to the consumption of insufficiently cooked or raw pork, venison or boar meat [28]. This assumption has been supported by studies performed by Feagins et al. [29] who were able to isolate infectious HEV from commercial pork liver in the USA. Studies on the prevalence of HEV infections both in humans and in pigs were performed in various European countries. Studies in Spain have shown that HEV is very widespread in pig populations and that an age-dependent increase in the seroprevalence can be observed [30]. Furthermore, HEV could be detected in the faeces of the animals by NAT/PCR in the age group of 8–12 weeks. Comparable results were also obtained when studying pig populations in the Netherlands, where HEV genome could be detected in the faeces in a high percentage of the fattening farms [31]. A close relationship between human and porcine HEV was reported from the UK [32, 33].

Altogether, only few studies are available on the prevalence of HEV infections in humans. High antibody prevalence with approximately 13% has been reported from Sweden and lower antibody prevalence from France and Spain (approximately 3%) [34, 35]. In various studies, persons with close contact to pigs such as pig breeders and animal traders showed a higher seroprevalence compared with the general population [36, 37]. This indicates that pigs can be regarded as one of the transmitters of HEV to humans.

Tests of urban sewage water in various industrialised countries showed that for example in Barcelona (Spain), Nancy (France), and Washington, DC (USA) HEV genome could be detected, pointing to the fact that HEV infections in these countries may frequently take a subclinical course and remain undetected, since no simultaneous clinical HEV infection were observed [38]. The extent to which HEV is transmitted by insufficiently purified sewage water in industrialised countries remains unclear.

Only little information is available on the prevalence and incidence of HEV infections in Germany. It has been discussed for a long time whether acute hepatitis E only occurs in travellers returning from endemic areas [29]. More recent studies have revealed that HEV infections can also be acquired in Germany, and can lead to acute courses of disease [40, 41].

Data obtained on the basis of the requirement to notify hepatitis infections in compliance with the IfSG (Infektionsschutzgesetz; Infection Protection Act) show that approximately half of the German hepatitis E cases notified were acquired in Germany, and that there was no connection with travels to endemic areas (table 1). The few HEV cases which have so far been phylogenetically analysed in Germany confirm the close relationship to pig isolates found in various other European countries [41].

### 1.4 Detection Methods and Their Significance

Up to now it has not been possible to grow HEV routinely in cell culture for diagnostic purposes. Before molecular detection methods were established, virus detection was performed in the faeces by means of electron microscopy or IEM.

Today, HEV can be reliably detected using PCR in the acute phase from faeces or blood. The nucleic acid detection method and sequence analyses of the amplificates, however, have shown that there is a great number of genetic HEV variants. The sensitivity of the PCR therefore depends on the homology of the primer with the isolate to be examined. The extent to

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<th>Year</th>
<th>Cases of HEV reported in Germany total</th>
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<tr>
<td>2001</td>
<td>31</td>
<td>11</td>
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<td>2002</td>
<td>17</td>
<td>7</td>
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which real-time PCR and nested PCR systems are suitable for the detection of all 4 genotypes known up to now requires further examination [42–44]. Detection of viral RNA confirms the presence of active HEV. The extent to which antigen detection systems are suitable for the detection of viraemia can only be clarified by further development of experimental antigen detection systems [45]. Serological detection systems for diagnosing an HEV infection still represent the method of choice. Commercial antibody detection systems (ELISA) are available for the detection of IgG and/or IgM antibodies. These systems are based on recombinant ORF 2 and ORF 3 proteins expressed or synthetic peptides. Immunoblots based on recombinant proteins can be used for confirming the reactive sera. At the time of first detection of HEV antibodies and the presence of clear clinical symptoms of hepatitis, an HEV infection is likely, if hepatitis A, B and C can be excluded. To confirm, a second sample should be drawn 8–10 days later, in order to provide evidence for the increase in antibodies. In approximately 90% of the acute HEV infections, IgM antibodies can be detected 1–4 weeks after occurrence of the clinical symptoms. As a rule, these IgM antibodies can no longer be detected 3 months after the onset of the disease. More recent findings show, however, that anti-HEV IgA antibodies may provide a reliable way of detecting an acute HEV infection [24, 46]. The postulation that a stay in an endemic area of HEV should be one of the criteria for a suspected hepatitis E diagnosis can no longer be maintained based on the current state of knowledge. Studies on the spread of HEV in non-epidemic areas give rise to the assumption that HEV infections may take on an asymptomatic or subclinical course in industrialised countries.

2 Blood and Plasma Donors

2.1 Prevalence and Incidence in Donor Populations

Data on the prevalence of HEV infections in blood and plasma donors and/or in the general population are not available in Germany. In Japan, a country in which only sporadic cases of HEV have been reported, studies have been performed in 6,700 blood donors with elevated transaminases [16]. HEV-specific antibodies could be determined in 7.1% of the individuals studied. In 9 (0.13% of the samples studied) of these blood donors, HEV RNA could be detected, with 6 of these donors also showing anti-HEV IgM and/or IgA antibodies. Three donors were only HEV genome-positive. The authors rule out that in Japan, a country with a comparatively low number of reported acute HEV infections, more subclinical cases occur than expected. It must, however, be assumed that the prevalence in the donor cohort is comparable with that of the overall population. These results confirm previous reports from Japan that HEV was detected in blood donors by means of PCR [47]. To what extent antigen detection systems are suitable for detecting viraemia can only be clarified by the further development of experimental antigen detection systems [45]. Studies of blood donors in HEV-endemic areas such as India give rise to the assumption that in such countries there is an increased risk of transfusion-transmitted HEV [48]. Investigations performed on small random samples of blood donors in the Netherlands showed that 0.4% of the donations were HEV antibody-positive [49], while the number in Spain was 2.8% of the donations tested [34]. In France, a prevalence of 3.2% was determined in blood donors, with only 20–30 autochthonous cases reported annually in that country [35]. In a multi-centre study in 1993, data were collected on the prevalence of HEV infections in Germany [50]. In this study the prevalence of 0.5% HEV antibody-positive donors determined is possibly too low, since the sensitivity of the tests has meanwhile been improved. The number of autochthonous hepatitis E cases reported for Germany is comparable with that of France so that it cannot be ruled out that HEV seroprevalence in Germany is similar to that in France.

2.2 Definition of Exclusion Criteria

The guidelines of the Bundesärztekammer (German Medical Association) and the Paul-Ehrlich-Institut (PEI) [51, 52] form the basis for the exclusion criteria for blood donors. Individuals who are or have been diseased with infectious hepatitis of unclear aetiology should be permanently deferred from donating blood. These guidelines, however, do not deal explicitly with HEV infection. In the event of confirmed or suspected hepatitis E, the donors must be deferred from the donation. This also applies to suspected acute infection of persons who are in a close contact with the donor. Status after overcoming hepatitis E, or determination of anti-HEV IgG antibody confirming recovery from hepatitis E, is not an exclusion criterion. This recommendation is equivalent to the procedure for individuals who recovered from HAV infection [53].

2.3 Donor Testing and Significance

Donor testing for HEV genome by means of PCR or antibody detection (IgM and/or IgA as early infection markers) is possible in principle. Based on the findings available up to now on the epidemiology of HEV infections in Germany, donor testing for virus genome of HEV or HEV-specific antibodies is not considered necessary.

2.4 Donor Interviews

The volunteer who intends to donate blood is asked whether he/she has had a history of hepatitis before each donation, in
accordance with the guidelines of the Bundesärztekammer and the PEI. Recovery from a hepatitis E infection in the history is not a criterion for a general donor deferral.

2.5 Donor Information and Counselling

Since no special examination for HEV markers is performed, no HEV-specific donor information is necessary. If there are signs of hepatitis infection of unclear origin, HEV can be detected by using serological or molecular methods.

3 Recipients

3.1 Prevalence and Incidence of Blood-Associated Infections and Infectious Diseases in Recipient Populations

Neither donor- nor recipient-specific information is available on the prevalence and incidence of HEV infections in Germany. It can, however, be assumed that there is a prevalence for antibodies against HEV in these collectives which corresponds to that of the general population, as also described for other European countries.

Studies, in particular in Japan, give rise to the assumption that transmissions of HEV by blood transfusion can be observed. Retrospective data collections, particularly in transfusion recipients displaying increased transaminase values or a serious hepatitis infection, showed that part of these patients had acquired an HEV infection due to this transfusion [19, 34, 48]. Recently, HEV transmissions by transfusion have also been reported from Europe [20, 21]. Haemodialysis patients seem to have an increased infection risk [54]. To what extent this is due to the administration of blood products or has a different cause is unclear. Only few studies on haemophiliacs have been described in the literature [49, 55, 56]; none of these studies pointed to a recognisable transmission risk for HEV by coagulation factors.

3.2 Immune Status (Resistance, Existing Immunity, Immune Response, Age, Exogenous Factors)

No results are available on the prevalence rate among the recipients of blood and blood products in Germany.

3.3 Severity and Course of the Disease

Reports on HEV infections by contaminated blood products give rise to the assumption that the course of infection is comparable to that of a natural HEV infection [19]. Persisting infection following transfusion was reported in a T-lymphoma patient who was also receiving chemotherapy [57].

3.4 Therapy and Prophylaxis

Studies on possible passive immunisation have been reported [58], and the administration of anti-HEV immunoglobulin products as post-exposure prevention, especially for pregnant women, has been discussed.

The development of a vaccine has so far been hampered because HEV has been difficult to replicate in cell culture and because vaccines on the basis of inactivated viruses or non-pathogenic isolates have therefore not been available. The focus of vaccine development was therefore on DNA technology or recombinant proteins [59–63]. One candidate for a DNA vaccine is currently undergoing phase II of a clinical study [63].

3.5 Transmissibility

Retrospective studies by Arankalle and Chobe [17, 48] give reason to presume that HEV can be transmitted by blood transfusions in regions where it is endemic. Transfusion-associated HEV transmissions were reported from Saudi-Arabia, a country where HEV occurs endemically [18]. First reports on transfusion-associated HEV infections from Japan, which has not been rated as an endemic region, were published almost simultaneously [19, 54]. In one case, it could be demonstrated that transmission occurred by transfusion of FFP but not by the corresponding red blood cell concentrate from the same donor [19]. A case of transfusion-associated HEV transmission has recently been reported also in Europe in a region in which acute hepatitis E occurs only sporadically. In the UK, a patient was infected by a red blood cell concentrate. This concentrate only contained small amounts of plasma from the donor. Another patient who had received a platelet concentrate from the same donation was not infected [20]. A child in France was also infected by a red blood cell concentrate [21]. Both the donor in the UK and the donor in France had acquired their HEV infection in their own countries. Both blood donors were HEV RNA-positive at the time of the donation but did not show elevated transaminases.

As can be concluded from the few more exactly scrutinised HEV transmission cases, HEV can be transmitted by non-inactivated blood components. It can be assumed that this is the case especially during the viraemia phase (approximately 20–50 days following infection) by cell-free virus in the plasma.

3.6 Frequency of Administration, Type and Amount of Blood Products

No conclusions can be drawn from the few reported cases of transmission as to an increased risk of an HEV infection by frequent treatment with non-inactivated blood components,
even though several of the patients affected received transfusions from multiple sources.

4 Blood Products

4.1 Infectious Load of the Starting Material and Test Methods

Up to now, no tests have been performed on the viral HEV burden of the starting material. In principle, such a test on these materials for HEV genome would be possible by means of NAT.

4.2 Methods for Removal and Inactivation of the Infectious Agent

There are no investigations on the removal and inactivation of HEV in blood products. In the past few years, animal caliciviruses such as the feline calicivirus (FeCV) were used as model viruses for the validation of inactivation methods. To what extent these model systems reflect the stability of HEV is unclear.

4.3 Feasibility and Validation of Procedures for Removal/Inactivation of the Infectious Agent

In general, procedures of inactivation and/or removal of non-enveloped viruses during the preparation of plasma products are more limited than those for enveloped viruses. The assessment of the capacity of methods of inactivating and/or removing HEV is currently based on the experience with non-enveloped model viruses from other virus groups, especially from FeCV. Studies with HEV itself are available only to a very limited extent, since culturing adapted HEV isolates is difficult, and the cell culture systems are available to only a limited extent. Whether these systems are suitable for validating production steps during the manufacture of blood products remains to be examined.

In the past few years, studies on the thermostability of HEV were carried out. Compared with HAV, HEV proved to be less thermostable [5]. However, in these studies, no exact kinetics of inactivation was displayed, and no stabilisers applied in the production of coagulation factors were investigated. Preliminary studies show an effective inactivation of FeCV at 60 °C in liquid phase in the presence of such stabilisers (Blümel et al., unpublished; Gröner et al., unpublished). However, to what extent FeCV reflects the heat stability of HEV is unknown. The stability of FeCV and HEV during dry heat application is also unknown. Stability at low pH values (pH 3.7–4.2) as it is used in the production of antibody preparations is also unknown. Extrapolation from the inactivation data from other non-enveloped viruses is difficult. HAV and animal parvoviruses are usually stable under these conditions.

It can be assumed that filtration methods (virus filter, nanofilter) remove HEV effectively from the product if filters were used which remove smaller viruses such as HAV or parvoviruses. Such filters are often used in the production of factor IX or partly in the production of immunoglobulin preparations. For the filtration of complex coagulation factors, however, only filters with medium diameters of 35–50 nm are often used. In this case the retention of HEV or calicivirus is limited and may strongly depend on specific filters or production conditions. This should be evaluated on a case-to-case basis.

The risk of an HEV transmission by plasma products is currently estimated to be low since steps have been introduced for most of the products (except for SD-treated plasma) which are considered to be at least partly effective in activating or removing HEV. A more accurate assessment of the risk, however, is currently not possible since important data on the epidemiology, the HEV burden in the plasma pool, the prevalence of antibodies in plasma donations and/or plasma pools, and on the inactivation/removal of HEV during the manufacturing process is not available. A product-specific examination of the manufacturing procedures for inactivation/removal of HEV is required in those cases in which the data available on non-enveloped model viruses cannot clearly be transferred to HEV.

The effectiveness of the inactivation methods developed for plasma and cellular blood products (treatment with amotosalen, riboflavin, or methylene blue) is currently unknown. A risk of HEV transmission by blood components can therefore currently not be ruled out in general.

5 Assessment

For a long time, hepatitis E was considered as travel-associated disease. Today, however, evidence has been found that HEV infections not only occur in classical endemic areas with a low standard of hygiene but also in industrialised countries. In the classical endemic areas, particularly the HEV genotypes 1 and 2 have been found. The pathogen is transmitted by the faecal-oral route via contaminated water and food. In non-endemic areas, mainly sporadic HEV infections of the genotypes 3 and 4 are observed. Animals, mainly pigs, provide the reservoir for these two genotypes. Based on the current state of knowledge, pig populations worldwide show a very high HEV infection rate. Phylogenetically closely related viruses are found in industrialised countries in humans with HEV infections and in pigs. Although only low numbers of autochthonous human HEV infections have been reported in industrialised countries, the seroprevalence is relatively high, reaching approximately 13%, e.g. in Sweden.

These findings give rise to the assumption that a considerable number of HEV infections in industrialised countries shows a
References


This paper was completed on June 22, 2007, and approved by the German Advisory Committee Blood (Arbeitskreis Blut) on October 1, 2007. It was compiled by the members of the subgroup ‘Assessment of Pathogens Transmissible by Blood’ of the German Advisory Committee Blood (Ar-beitskreis Blut):

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subclinical course, and that these infections can only be detected by the identification of the HEV genome and/or seroconversion. It has been shown that not only individuals during the incubation and the clinical phase of hepatitis E, but also subclinically infected individuals display HEV viraemia, and that the virus can also be transmitted by blood donations from such donors.

The risk of HEV transmission by blood products has not been sufficiently examined in Germany. Data are missing on the prevalence of HEV infections in the population, in the blood donor collective, and in individuals with a higher risk of exposure for HEV such as veterinarians, pig breeders, pig fatten-ers, and the staff of abattoirs and butcher businesses. More-over, there is no information on the prevalence and incidence of HEV in the animal reservoir for Germany, particularly in pig populations. The current state of knowledge is not sufficient to judge the necessity of blood donor testing for HEV genome or HEV antibodies. Based on clinical experience, these tests do not seem to be necessary considering the cur-rent epidemiological situation. However, there is a major need for research, especially for collecting epidemiological data, and with regard to targeted look-back tests for transfusion-associated HEV infection in transfusion recipients and the corresponding donors.
Hepatitis E Virus


