Impact of hepatitis E virus testing on the safety of blood components in Germany – results of a simulation study

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Hepatitis E virus (HEV) infections may be acquired through transfusion of blood components. As transfusion-transmitted infections mostly affect vulnerable individuals, measures to ensure the supply of safe blood components are under discussion. On the basis of the epidemiological situation in Germany, different testing strategy scenarios were investigated through simulation studies. Testing for HEV RNA by nucleic acid amplification technique (NAT) assays with a pool size of 96, and a 95% LoD of 20 IU/ml will result in an 80% reduction in expected HEV transmissions as well as of consequent chronic infections with subsequent severe complications.

Key words: blood donation testing, blood safety, epidemiology, hemovigilance, residual risk estimation, transfusion transmissible, infections.

Introduction

The risk of transfusion-transmitted hepatitis E virus (HEV) infections has been extensively discussed during the last decade. Reported cases from several European countries were usually asymptomatic or self-limiting and caused by HEV genotype 3. However, HEV genotype 3 can cause serious liver damage and even liver failure in patients with chronic liver disease or immunosuppression [1–4], and consequently, HEV donor screening has been implemented in some European countries [5, 6]. From 2012 to 2015, seven confirmed cases of transfusion-transmitted HEV infections were reported by German blood establishments. Two patients had temporally limited symptoms, and one patient experienced a fatal exacerbation of his underlying disease [1, 7].

To support an informed decision on donor screening in Germany, the processing of blood components was simulated under different testing strategies which allowed an estimation of expected HEV infections including subsequent severe outcomes.

Methods

The frequency of transfusion-transmitted HEV infections has been calculated on the basis of a stochastic model of HEV transmissions through blood components in the Netherlands [8, 9]. The model follows the route of each viraemic donation during processing into blood components under different NAT testing strategies (technical details are provided in the Supporting Information). Probability estimates of a donation being viraemic in Germany vary between 0.0005 and 0.002 [10, 11]. We estimated the number of blood components transfused annually in Germany based on those released in 2016. Transmission probabilities of components were calculated from their viral load, that is viral concentration and the respective plasma volume. The number of blood components transfused to immunocompromised patients was based on the numbers of irradiated blood components produced in 2016 (Table S1 and Figure S1). We excluded the unlikely possibility of recipients being transfused with multiple viraemic components. In the model, only immunocompromised recipients develop a chronic infection with a probability in the range of 0.2–0.8 (cf. alternative implementation in Figure S2) [12]. Chronic infections can be treated successfully by reduction in...
immunosuppression with a probability between 0.2 and 0.4 [12], whereas antiviral treatment (e.g. ribavirin) is assumed to clear HEV with a probability from 0.75 to 0.95 [13]. These parameters were sampled uniformly within the given ranges in 10 000 simulations of the model.

Results

The overall risk of transfusion-transmitted HEV infection can be assessed by the transmission probabilities of different blood components which range from $10^{-4}$ to $10^{-3}$ as shown in Table S2 with large uncertainties due to unknowns in epidemiological parameters (cf. Methods). Each panel further shows the expected number of cases with the standard deviation of cases derived from the presented distribution.

Table 1: Expected number of transfusion-transmitted HEV infections and subsequent chronic and incurable cases per year in Germany (GER, based on 5 185 194 components in total, cf. Table S1) and the Netherlands (NL, based on 544 831 components in total, data reproduced from [8]) depending on testing scenario.

| Pool size | Expected HEV transmissions/ year [in %] | Expected chronic HEV cases/year [in %] | Expected incurable cases/year [in %] |
|-----------|----------------------------------------|----------------------------------------|-------------------------------------|
| No testing | NL: 187; GER: 1488 | NL: 5; GER: 93 | NL: 0.5; GER: 10 |
|           | 100% | 100% | 100% | 100% |
| 96        | NL: 27; GER: 279 | NL: 0.8; GER: 19 | NL: 0.08; GER: 2.0 |
|           | 14% | 19% | 16% | 20% |
| 48        | NL: 18; GER: 186 | NL: 0.6; GER: 13 | NL: 0.06; GER: 1.4 |
|           | 9.6% | 13% | 12% | 14% |
| 24        | NL: 13; GER: 139 | NL: 0.4; GER: 10 | NL: 0.04; GER: 1.0 |
|           | 7.0% | 9.3% | 8% | 11% |
| 1         | NL: 1; GER: 14 | NL: 0.04; GER: 1 | NL: <0.005; GER: 0.1 |
|           | 0.7% | 0.9% | 0.8% | 1.1% |

Discussion

HEV NAT screening of blood donors will reduce HEV transmissions as well as cases with chronic disease.
Depending on test sensitivity and NAT pool size (pool of 96 to single donor testing), a reduction of 80% down to 99% can be achieved in transmissions and subsequent chronic cases. An analogous study from the Netherlands shows comparable reductions in case numbers as shown in Table 1. It should be noted that risk estimates from other countries have only been based on the number of donations tested positive for HEV RNA as an approximation for the expected number of transmissions [5].

Transfusions from donations with low viral load result less frequently in HEV transmission than from those with high viral load [8, 14]. This causes a non-proportional relationship between increasing test sensitivity (reduction in test pool size) and reduction in HEV risk.

The simulation study shows that the implementation of any test strategy leads to a risk reduction but not to complete risk removal. Modelling can help to find an appropriate strategy for the implementation of proportionate risk minimization measures.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Numbers of blood components transfused to immunocompromised patients and estimated numbers of blood components transfused to transplant recipients in 2016 in Germany.

Figure S2 Distribution in the number of HEV infections (all cases, top row), those becoming chronic (chronic cases, middle row) and those not being amenable to therapeutic options (incurable cases, bottom row) seen in 10,000 simulation runs of an alternative implementation of the model.

Table S1 Product details of blood components in Germany.

Table S2 Expected infection probability (± one standard deviation) per blood component without screening in units of 10⁻⁴.