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1 **Horizontal hepatitis B virus transmission through non-sexual close contact in**  
2 **Turkish chronic hepatitis B patients living outside of Turkey.**

3 Koc ÖM<sup>1-4,\*</sup>, Robaey G<sup>3-5</sup>, Yildirim B<sup>6</sup>, Posthouwer D<sup>1</sup>, Hens N<sup>7,8</sup>, Koek GH<sup>2,9,10</sup>

4 1. Department of Internal Medicine, Infectious Diseases and Medical Microbiology,  
5 Maastricht University Medical Centre, Maastricht, the Netherlands.

6 2. School of Nutrition and Translational Research in Metabolism (NUTRIM), University  
7 Maastricht, Maastricht, the Netherlands.

8 3. Department of Gastroenterology and Hepatology, Ziekenhuis Oost-Limburg, Genk,  
9 Belgium.

10 4. Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium.

11 5. Department of Hepatology, UZ Leuven, Leuven, Belgium.

12 6. Department of Gastroenterology, Ondokuz Mayıs University, School of Medicine, Samsun,  
13 Turkey.

14 7. Interuniversity Institute for Biostatistics and statistical Bioinformatics (I-Biostat), Hasselt  
15 University, Martelarenlaan 42, 3500 Hasselt, Belgium

16 8. Centre for Health Economic Research and Modelling Infectious Diseases, Vaxinfectio,  
17 University of Antwerp, Universiteitsplein 1, 2610 Antwerpen, Belgium

18 9. Department of Internal Medicine, Division of Gastroenterology and Hepatology, Maastricht  
19 University Medical Centre, Maastricht, the Netherlands.

20 10. Department of Surgery, University Hospital of the RWTH, Aachen, Germany.

21

22 Email: [ozgur.m.koc@gmail.com](mailto:ozgur.m.koc@gmail.com), [geert.robbaeys@uhasselt.be](mailto:geert.robbaeys@uhasselt.be), [beytullahy@yahoo.com](mailto:beytullahy@yahoo.com),  
23 [d.posthouwer@mumc.nl](mailto:d.posthouwer@mumc.nl), [niel.hens@uhasselt.be](mailto:niel.hens@uhasselt.be), [gh.koek@mumc.nl](mailto:gh.koek@mumc.nl)

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25 **Running title:** Horizontal HBV transmission in Turkish migrants.

26

27 **\*Corresponding author:**

28 Koc ÖM

29 Department of Internal Medicine, Infectious Diseases and Medical Microbiology,  
30 Maastricht University Medical Centre, Maastricht, the Netherlands.

31 P.O. Box 5800, 6202 AZ, Maastricht, the Netherlands

32 Tel: +31 43 3876644, Fax: +31 43 3876643

33 Email: [ozgurmkoc@gmail.com](mailto:ozgurmkoc@gmail.com)

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36 None declared.

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## 50 **Abstract**

### 51 **Background & Aims**

52 Hepatitis B virus (HBV) infection is a global threat and with the growing cultural diversity in  
53 Western Europe, knowledge on routes of infection in order to decrease HBV spreading is  
54 essential. This study assessed the risk of horizontal transmission through non-sexual close  
55 contact in the chronic hepatitis B (CHB) population in Maastricht (the Netherlands) and Genk  
56 (Belgium), with a main focus on the differences between ethnic groups.

57

### 58 **Methods**

59 In this multicenter retrospective study, 166 CHB patients, who were still under follow-up  
60 between December 2009 to December 2014, were recruited from the Hepatology Outpatient  
61 Departments of two hospitals, one in Maastricht and one in Genk. Ethnicity (defined as  
62 country of origin (COO)) and routes of transmission were collected from all patients.

63

### 64 **Results**

65 The CHB population in Maastricht and Genk consisted of 98 and 68 patients, respectively. In  
66 Maastricht, 31% were of Dutch and 16% of Chinese origin. In Genk, mainly Belgian (15%)  
67 and Turkish (50%) patients were included. The percentage of horizontal transmission in the  
68 total study cohort was 9%. Moreover, the COO groups Dutch/Belgian (n=40), Turkish (n=38)  
69 and Chinese (n=18) differed in the number of cases infected by horizontal transmission (4%,  
70 30% and 6%, p=0.030).

71

### 72 **Conclusions**

73 Although the prevalence of horizontal transmission in the total study cohort is low, non-

74 sexual close contact may play a role in the migrant population, particularly the Turkish. This  
75 should be an important public health target with respect to the prevention of HBV spreading.

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77 **Key words:**

78 Ethnicity; Hepatitis B; Horizontal transmission; Turkish; Migrant

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## 100 **Introduction**

101 Hepatitis B virus (HBV) infection is one of the most common infectious diseases globally. It  
102 has been estimated that two billion people have been infected, and more than 240 million are  
103 chronically affected with HBV worldwide in the year 2016 (1, 2). In the 2013 Global Burden  
104 of Disease Study, viral hepatitis was the seventh leading cause of death worldwide (3). Unlike  
105 most communicable diseases, between 1990 and 2013 global viral hepatitis deaths increased  
106 from 0.89 million to 1.45 million, a toll higher than that from HIV/AIDS, tuberculosis or  
107 malaria (3).

108  
109 The overall worldwide prevalence of hepatitis B surface antigen (HBsAg) is reported to be  
110 3.6%. However, it varies depending upon the geographic area. The prevalence of chronic  
111 HBV ranges from <2% in low-prevalence areas (e.g. Western Europe) to 2-7% in  
112 intermediate-prevalence areas (e.g. Turkey) and  $\geq 8\%$  in high-prevalence areas (e.g. Western  
113 Africa) (4-6).

114  
115 In areas of low prevalence, transmission of HBV predominantly occurs via injection drug use  
116 and high-risk sexual behaviors (7-9). In comparison, mother-to-child transmission is the most  
117 common route of transmission in high-prevalence areas, while horizontal transmission  
118 through non-sexual close contact accounts for most cases of chronic HBV infection in  
119 intermediate-prevalence areas (10-14).

120  
121 The precise mechanisms of horizontal transmission through non-sexual close contact are  
122 unknown. It may occur via frequent or long-term contact of non-intact skin or mucous  
123 membranes with tears, saliva, or blood-containing secretions (15, 16). Transmission from  
124 sharing personal care items such as toothbrushes may also occur (17, 18).

125  
126 As there is a growing cultural diversity in Western Europe due to migration for economic and  
127 political reasons, we are becoming gradually more aware of the importance of horizontal  
128 transmission through non-sexual close contact in low-prevalence areas. Therefore, this study  
129 aimed to assess the prevalence of horizontal transmission through non-sexual close contact in  
130 the chronic hepatitis B (CHB) population in two hospitals: one in Maastricht, the Netherlands  
131 and one in Genk, Belgium, with a main focus on the differences between ethnic groups.

### 132 **Patients and methods**

133 All consecutive CHB patients, defined as more than six months HBsAg positivity, who were  
134 still under follow-up between December 2009 to December 2014 at the Hepatology  
135 Outpatient Department of Maastricht University Medical Centre (MUMC+) in Maastricht, the  
136 Netherlands and Ziekenhuis Oost-Limburg (ZOL) in Genk, Belgium, were identified. Patients  
137 were identified by a list of the hospital's HBsAg positive patients to guarantee complete data  
138 capture.

139  
140 The following variables of each identified patient were collected from the digital hospital  
141 records program: age, sex, ethnicity, defined as mother's country of birth, socioeconomic  
142 status (SES), co-infection (hepatitis C virus; HIV; hepatitis delta virus) and routes of  
143 transmission (vertical; sexual; parenteral; horizontal through non-sexual close contact). Risk  
144 factors for vertical transmission were proven or possible HBsAg positive mother. Sexual  
145 transmission was defined as the presence of one of the following risk factors: sex worker, men  
146 who have sex with men (MSM), proven or possible HBsAg positive partner, co-infection with  
147 HIV. Risk factors for parenteral transmission were: haemophilia, intravenous drug use (IDU),  
148 blood transfusion before 1975 and 1974 in the Netherlands and Belgium, respectively (19),

149 dialysis patient, transplant patient, healthcare worker and co-infection with hepatitis C virus.  
150 For this study, we defined horizontal transmission through non-sexual close contact as no  
151 vertical, parenteral or sexual transmission and  $\geq 2$  proven or possible HBsAg positive family  
152 members.

153

154 SES was based on income and education as follows: Low/Middle/High (L/M/H):

155 L: net income beneath poverty line based on EU-SILC 2012 (20) without a degree of higher  
156 education

157 M: net income beneath poverty line with a degree of higher education or a net income above  
158 poverty line without a degree of higher education

159 H: net income above poverty line with a degree of higher education

160

161 In case of missing data regarding SES, routes of transmission and risk factors for HBV  
162 infection, patients were contacted by phone in Maastricht. In Genk, patients were asked to fill  
163 in a survey regarding ethnicity, SES, IDU, alcohol abuse, routes of transmission and risk  
164 factors for HBV infection at their next visit at the Hepatology Outpatient Department.

165

166 Subsequently, ethnicity was defined as country of origin (COO), i.e. mother's country of  
167 birth. The COO groups have been compared according to baseline characteristics (e.g. mean  
168 age, SES) and routes of transmission (e.g. horizontal through non-sexual close contact,  
169 vertical).

170

171 The study was approved by the Medical Ethical Committee of MUMC+ and Ethical  
172 Committee of ZOL and was conducted in accordance with the provisions of the Declaration  
173 of Helsinki and its amendments.

## 174 **Statistical analysis**

175 Our primary objective was to estimate the prevalence of horizontal transmission through non-  
176 sexual close contact in the total CHB population of two hospitals: one in Maastricht, the  
177 Netherlands and one in Genk, Belgium. For the secondary objective, the CHB patients were  
178 divided as Dutch/Belgian (NL/BE) (n=40), Turkish (TR) (n=38) and Chinese (CN) (n=18)  
179 since other COO groups were too small to compare statistically (Fig. 1). In the sub-analysis,  
180 we assessed whether there was a significant difference in the prevalence of horizontal  
181 transmission through non-sexual close contact between NL/BE, TR and CN patients. Chi-  
182 squared test or Fisher's exact test (in case  $\geq 20\%$  of expected frequencies were  $< 5$ ) was used to  
183 assess the secondary objective. Differences in two and several continuous outcomes were  
184 assessed by the independent t-test and one way-ANOVA test, respectively. In case the  
185 assumptions for parametric tests were violated, the Mann-Whitney test and Kruskal-Wallis  
186 were used instead for comparing two and several independent conditions, respectively. The  
187 level of statistical significance was set at p-value  $< 0.05$ . Results are presented as either  
188 frequencies (%) or mean (standard error of the mean, SEM). Data analyses were performed  
189 using SPSS (Release 21, Armonk, NY).

## 190 **Results**

### 191 **Ethnicity and routes of transmission of the total CHB population**

192 The CHB population in Maastricht, the Netherlands consisted of 98 patients of whom 31%  
193 were from Dutch, 4% from Turkish and 16% from Chinese descent. The other 49% patients  
194 came from other countries: 19% Europe, 44% of Asia, 35% of Africa and 2% of America.  
195 The Belgian CHB population consisted of 68 patients with 15% of Belgian, 50% of Turkish  
196 and 3% of Chinese descent. The other 32% came from other countries: 71% Europe, 10%  
197 Asia and 19% Africa (Fig. 2).



198 Out of the 38 patients from Turkish descent, 26 (68%) patients were born in Turkey, i.e. first-  
199 generation migrants, and 12 (32%) patients were born in the Netherlands or Belgium, i.e.  
200 second-generation migrants. All 18 patients of Chinese descent were born in China.

201

202 The overall percentage of horizontal transmission through non-sexual close contact in the  
203 total CHB population was 9%. Moreover, there was a significant difference in the prevalence  
204 of horizontal transmission through non-sexual close contact between Maastricht, the  
205 Netherlands and Genk, Belgium (1% versus 22%,  $p=0.004$ ). An overview of the routes of  
206 transmission for all CHB patients in Maastricht and Genk is depicted in table 1.

207

#### 208 **Baseline characteristics and routes of transmission by ethnicity**

209 Table 2 illustrates the baseline characteristics for the NL/BE, TR and CN group. In the TR  
210 group, the SES ( $p=0.071$ ), number of IDU ( $p=0.109$ ), MSM ( $p=0.012$ ), anti-HCV positivity  
211 ( $p=0.056$ ) and anti-HIV positivity ( $p=0.014$ ) was lower compared to the NL/BE group.  
212 However, in comparison to the NL/BE group, there was a higher percentage of infected  
213 family member as a risk factor in the TR group,  $p<0.001$ .

214

215 The routes of transmission for the COO groups NL/BE, TR and CN are presented in table 3.  
216 Horizontal transmission through non-sexual close contact was more common in the TR group  
217 compared to the NL/BE group and CN group ( $p=0.047$  and  $p=0.109$ , respectively). Sexual  
218 and parenteral transmission was confined to the NL/BE group in comparison to the TR  
219 ( $p=0.063$  and  $p=0.047$ , respectively) and CN group ( $p=0.001$  and  $p=0.029$ , respectively). In  
220 addition, vertical transmission was mainly seen in the CN group compared to NL/BE and TR  
221 group ( $p<0.001$  and  $p=0.002$ , respectively).

222 Regarding the Turkish population, the route of transmission was unknown in 14/26 (54%)  
223 patients born in Turkey, i.e. first-generation migrant, and in 1/12 (8%) patients born in the  
224 Netherlands or Belgium, i.e. second-generation migrant. Analysis in the Turkish population  
225 showed no difference in the percentage of horizontal transmission through non-sexual close  
226 contact between those born in Turkey (2/11, 18%) and those born in the Netherlands or  
227 Belgium (5/11, 46%) ( $p=0.361$ ).

228

## 229 **Discussion**

230 In Maastricht, the Netherlands, the CHB population consisted mainly of Dutch and Chinese  
231 patients, whereas in Genk, Belgium, the patients were from Belgian and Turkish descent.  
232 Nine percent of patients were most probably infected via horizontal transmission through non-  
233 sexual close contact and is rather low in this particular Western study cohort. A lower number  
234 of horizontal HBV transmission through non-sexual close contact was seen in Maastricht  
235 compared to Genk. However, higher prevalence of HBV horizontal transmission through non-  
236 sexual close contact was found in patients from Turkish descent (30%) in comparison to  
237 Dutch and Belgian (4%) and Chinese (6%) patients. In both Maastricht and Genk, vertical  
238 transmission, 58% and 39%, respectively, was the most common route of transmission in the  
239 total CHB population.

240 Toy et al (21) included CHB patients from Rotterdam, a city in the Netherlands with a large  
241 group of patients of which 84% are born abroad. They reported that vertical and horizontal  
242 non-sexual close contact transmission was higher in the foreign-born than in the Dutch-born  
243 group with a Dutch mother. Vertical and horizontal non-sexual close contact transmission  
244 was the most common route of transmission in their study cohort.

245 In the current study, we divided vertical and horizontal transmission through non-sexual close  
246 contact. In line with the study conducted in Rotterdam (21), vertical transmission was the  
247 most common route of transmission in both outpatient clinics. We also found significant  
248 differences in the routes of transmission between the different ethnic groups. Horizontal  
249 transmission through non-sexual close contact was confined to the Turkish population, sexual  
250 and parenteral transmission to the Dutch and Belgian population and vertical transmission to  
251 the Chinese population. Additionally, we report that horizontal transmission through non-  
252 sexual close contact was not confined to patients born in Turkey but was also present in  
253 patients born in the Netherlands or Belgium with a Turkish mother.

254 In countries with intermediate prevalence for hepatitis B, such as Turkey, horizontal  
255 transmission by non-sexual close contact besides vertical, sexual and parenteral transmission  
256 is quite common (12, 13, 22-24). The majority of HBVs are acquired during childhood and in  
257 early adulthood. In addition, it has been accepted that transmission between family members  
258 may occur in communities with poor socioeconomic and hygienic conditions (12, 25).  
259 Subsequently, we found lower SES in the Turkish study population compared to the Dutch,  
260 Belgian and Chinese patients.

261 Strengths of the present study are (1) separation of horizontal non-sexual close contact and  
262 vertical transmission based on well-characterized risk factors of exposure to HBV, (2) the  
263 robust digital hospital records program allowing to include relevant patient's data and (3)  
264 collection of missing data by phone or at the next visit at the Hepatology Outpatient  
265 Department. This study has also limitations. This study describes the population of specific  
266 regions in the Netherlands and Belgium. One should therefore realise that the major ethnic  
267 groups could differ regarding the studied region. In addition, a selection bias towards the  
268 CHB population exists; those cured and deceased have not been included in this study, and  
269 there is also a possibility that there are CHB patients that have not yet visited the OPD.

270 Furthermore, the amount of horizontal transmission through non-sexual close contact could be  
271 under- and overestimated. Underestimation is possible due to the exclusion of possible or  
272 proven HBsAg positive but hepatitis B e antigen negative mother. Owing to the retrospective  
273 design of the study and the use of questionnaires, there is also the possibility of  
274 overestimating the horizontal transmission through non-sexual close contact. Lastly, the  
275 results should be interpreted with caution as there was a high number of unknown  
276 transmission in the study cohort.

277 In conclusion, despite a low prevalence of horizontal transmission in the total study cohort,  
278 these results underline the importance of horizontal transmission through non-sexual close  
279 contact among the migrant population, particularly the Turkish. Transmission patterns are  
280 important features for targeting mass vaccination campaigns. Evidence of decreasing burden  
281 of HBV infection after the implementation of universal HBV vaccination is available for  
282 country-specific populations. However, some European countries have not yet introduced  
283 universal immunization against hepatitis B, thereby maintaining reservoirs of infection and  
284 continued HBV transmission. In addition to universal HBV vaccination, we think that health  
285 education, which aims at interrupting horizontal transmission through non-sexual close  
286 contact in particular migrant groups, may be useful.

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296 None.

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394 **Figure legends**

395 **Fig. 1 Included study patients and study objectives.**

396 **Abbreviations:** CHB: chronic hepatitis B; OPD: outpatient department; MUMC+: Maastricht  
397 University Medical Centre+; ZOL: Ziekenhuis Oost-Limburg; COO: country of origin, i.e. mother's  
398 country of birth.

399  
400 **Fig. 2 Ethnicity according to mother's country of birth in Maastricht, the Netherlands, and**  
401 **Genk, Belgium.**

402 **Abbreviations:** NL: Dutch origin; BE: Belgian origin; TR: Turkish origin; CN: Chinese origin.

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