Hirschsprung’s Disease Prevalence in Europe: A Register Based Study

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Background: Hirschsprung’s disease is a congenital gut motility disorder, characterised by the absence of the enteric ganglion cells along the distal gut. The aim of this study was to describe the epidemiology of Hirschsprung’s disease, including additional congenital anomalies, total prevalence, trends, and association with maternal age. Methods: Cases of Hirschsprung’s disease delivered during 1980 to 2009 notified to 31 European Surveillance of Congenital Anomaly registers formed the population-based case-series. Prevalence rates and 95% confidence intervals were calculated as the number of cases per 10,000 births. Multilevel Poisson regression was performed to investigate trends in prevalence, geographical variation and the association with maternal age. Results: There were 1,322 cases of Hirschsprung’s disease among 12,146,210 births. The total prevalence was 1.09 (95% confidence interval, 1.03–1.15) per 10,000 births and there was a small but significant increase in prevalence over time (relative risk = 1.09; 95% credible interval, 1.01–1.18; p = 0.004). There was evidence of geographical heterogeneity in prevalence (p < 0.001). Excluding 146 (11.0%) cases with chromosomal anomalies or genetic syndromes, there were 1,176 cases (prevalence = 0.97; 95% confidence interval, 0.91–1.03 per 10,000 births), of which 137 (11.6%) had major structural anomalies. There was no evidence of a significant increased risk of Hirschsprung’s disease in cases born to women aged ≥35 years compared with those aged 25 to 29 (relative risk = 1.09; 95% credible interval, 0.91–1.31; p = 0.355). Conclusion: This large population-based study found evidence of a small increasing trend in Hirschsprung’s disease and differences in prevalence by geographic location. There was also no evidence of an association with maternal age.

Birth Defects Research (Part A) 0(0):000–000, 2014. © 2014 Wiley Periodicals, Inc.

Key words: Hirschsprung’s disease; congenital aganglionic megacolon; gut motility disorder; prevalence; trends

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Published online 0 Month 2014 in Wiley Online Library (wileyonlinelibrary.com), doi: 10.1002/bdra.23269
Introduction

Hirschsprung’s disease (or congenital aganglionic megacolon) is the most common congenital gut motility disorder, characterized by the absence of the enteric ganglion cells (aganglionosis) along the distal gut, which causes functional intestinal obstruction (Puri and Shinkai, 2004).

Previous estimates of the live birth prevalence of Hirschsprung’s disease have ranged between 1.63 to 2.26 per 10,000 live births in the United Kingdom, United States, and Columbia (Goldberg, 1984; Spouge and Baird, 1985; Best et al., 2012). While a recent study found evidence of a small increasing trend of Hirschsprung’s disease prevalence in the North of England, two older studies in the United States and Columbia, did not (Goldberg, 1984; Spouge and Baird, 1985; Best et al., 2012).

Hirschsprung’s disease is of neural crest origin (Martucciello, 1997) and has known associations with a variety of chromosomal anomalies and genetic syndromes, including Down syndrome and Waardenburg syndrome (Goldberg, 1984; Spouge and Baird, 1985; Moore, 2006; Amiel et al., 2008). Therefore, it is considered to be of genetic origin (Badner et al., 1990; Martucciello, 1997; Puri and Shinkai, 2004; Amiel et al., 2008). But despite this possible genetic etiology, there is limited research around the association with advanced maternal age (Badner et al., 1990; Martucciello, 1997; Puri and Shinkai, 2004; Amiel et al., 2008). In several studies, maternal age has been examined as a potential risk factor, but these studies have only compared the proportion of older mothers in cases with the study population; producing conflicting results. Goldberg (1984) for example, found a higher proportion of mothers aged ≥30 years among cases compared with the general population of Baltimore, Maryland, USA, whereas both Ryan et al. (1992) and Best et al. (2012) found no significant differences in proportions in Boston, Massachusetts, USA, and the North of England (Goldberg, 1984; Ryan et al., 1992; Best et al., 2012). Few other risk factors have been identified although there is a suggestion of an association with ethnicity, with the offspring of white women possibly at increased risk (Goldberg, 1984). Additionally, a male preponderance has consistently been reported (Goldberg, 1984; Spouge and Baird, 1985; Ryan et al., 1992).

The aim of this study was to investigate the epidemiology of Hirschsprung’s disease in Europe during 1980 to 2009 using high quality population-based register data. We describe the presence of additional congenital anomalies, pregnancy outcomes, 1-week survival, diagnosis, association with maternal age, total prevalence, trends in total prevalence and variation in prevalence according to geographic location.

Materials and Methods

The European Surveillance of Congenital Anomalies (EUROCAT) (EUROCAT, 2012a) is a collaborative network of population-based congenital anomaly registers. Thirty-eight registers in 20 countries use multiple sources to collect data on anomalies occurring in spontaneous fetal losses ≥20 weeks gestation, terminations of pregnancy for fetal anomaly following prenatal diagnosis at any gestation, and live births. EUROCAT surveys approximately 1.7 million births per year in Europe, representing almost 31% of the European birth population (EUROCAT, 2012b). Each register has ethical approval to collect data without patient consent (Greenlees et al., 2011). Cases are coded using the WHO International Classification of Disease (ICD) version 9 or 10 and minor anomalies such as skin tags and tongue tie are excluded; further details are available in the EUROCAT guide 1.3 (EUROCAT, 2012c).

All cases of Hirschsprung’s disease (ICD 9 code: 751.3 and ICD 10 code: Q431) with a delivery date between January 1, 1980, and December 31, 2009, notified to 31 EUROCAT registers formed this population-based case series. Denominator and maternal age data were provided by EUROCAT (EUROCAT, 2012a).

Cases of Hirschsprung’s disease were classified into three distinct groups: isolated cases, cases with additional major structural anomalies or cases occurring with chromosomal anomalies or genetic syndromes. Cases associated with structural anomalies directly related to Hirschsprung’s disease (e.g., intestinal obstruction or hypoplasia of the large intestine), were classified as isolated.

Cases from multiple pregnancies were excluded from analysis due to potentially different etiologies (Glinianaia et al., 2008).

Statistical Analysis

Total prevalence rates for Hirschsprung’s disease in each register were calculated as the number of cases (whether ending in fetal loss with gestational age ≥20 weeks), termination of pregnancy for fetal anomaly, or live birth) per 10,000 live and stillbirths. 95% confidence intervals (CIs) were derived from the binomial distribution.

Descriptive statistics were produced for: additional major congenital anomalies (including chromosomal anomalies, genetic syndromes and structural anomalies), sex, pregnancy outcome (classed as late miscarriage, stillbirth, termination of pregnancy for fetal anomaly, or live birth), timing of diagnosis amongst cases of isolated Hirschsprung’s disease cases (classed as antenatal diagnosis of any congenital anomaly, postnatal diagnosis of Hirschsprung’s disease: at birth, within the first week, within the first month, within the first year or after 1 year) and survival beyond 1 week of age (classed as yes or no). Figures for survival beyond 1 week refer to live births only, of which 86% had known survival status.

Multilevel Poisson regression (with two levels) was performed to estimate the relative risk (RR) of Hirschsprung’s disease over time. The number of cases per year (level 1) were nested within register (level 2) and modeled with a
random intercept (to better account for variation between registers), an offset equal to the log of the total births, and year as a continuous predictor. Heterogeneity between registers was tested by analyzing the model’s change in deviance (using a chi square test on the estimated difference in parameters) between the null model and the model incorporating the random intercept. Similarly, the models were also refitted to include additional random effects to examine inter-regional differences in trends over time.

Random intercept multilevel models were refitted to include maternal age (in years, categorized as <20, 20–24, 25–29, 30–34, and ≥35) as well as year of delivery. The following registers had >5% of their maternal age denominator data uncategorized: South Portugal, Saxony Anhalt, Reunion, Thames Valley, Northern England, and Valencia Region and so these registers were excluded from this analysis on maternal age. Tuscany and Strasbourg did not have denominator data from 1995 and 2006 respectively, so these years were removed from this analysis for these two registers. There were a further 71 cases with missing maternal age data, which were also excluded.

Multilevel model parameters were estimated using a random walk (Metropolis-Hastings) Markov Chain Monte Carlo (MCMC) algorithm. Assuming diffuse uniform priors, the procedure was run for a burn-in sample of 5000 observations, and an analysis sample of 1,000,000 thinned by 10 (numbers guided by Raftery-Lewis calculations) (Raftery and Lewis, 1992). Bayesian 95% Credible Intervals (CrIs), analogous to frequentist 95% CIs, were obtained from the posterior distribution for each parameter. All models were checked for overdispersion (by comparing model fit after the addition of another variation term) and trajectories for parameters and variance were checked to ensure appropriate mixing.

Statistical analyses were performed using Stata version 12, including the runmlwin command. \( p < 0.05 \) was considered statistically significant.

**Results**

A total of 1,374 cases of Hirschsprung’s disease were notified to the 31 EUROCAT registers. Of these, 33 (2.4%) cases occurring in twin pregnancies and 19 (1.4%) occurring in pregnancies with unknown number of fetuses were excluded from further analysis (Fig. 1). Hence, there were 1322 singleton cases among a population of 12,146,210 singleton total births between 1980 and 2009.

**ADDITIONAL ANOMALIES**

Of the 1,322 singleton cases, 15 (1.1%) occurred with genetic syndromes (including microdeletions) and 131 (9.9%) occurred with chromosomal anomalies (Fig. 1). The most common genetic syndromes were Smith-Lemli-Opitz and Waardenburg syndrome and the majority (93.9%) of the cases associated with chromosomal anomalies were Down syndrome (Table 1).

Excluding cases with chromosomal anomalies or genetic syndromes, there were 1,176 cases remaining (Fig. 1). Of these, 137 (11.6%) were associated with additional major structural anomalies (Table 1) and 1039 (88.4%) were cases of isolated Hirschsprung’s disease.

**SEX DISTRIBUTION**

There was a male predominance among all cases of Hirschsprung’s disease (73.5% vs. 26.2%) giving a male to female ratio of 2.8:1, which remained the same after excluding cases associated with chromosomal anomalies or genetic syndromes. The sex ratio of males to females was slightly higher (2.9:1) in isolated cases.

**PREGNANCY OUTCOME**

In total, 1,313 (99.3%) of all 1,322 singleton cases resulted in a live birth, two (0.2%) occurred in late miscarriages and seven (0.5%) cases resulted in termination of pregnancy for fetal anomaly. Both miscarriages occurred in cases associated with other major structural anomalies. The terminations of pregnancy were associated with chromosomal anomalies or genetic syndromes in three cases, major structural anomalies in two cases and isolated cases in two cases.

**BIRTH WEIGHT AND GESTATIONAL AGE**

Of the 1,313 live born children, the median gestational age at delivery was 39 weeks (interquartile range, 38–40), with gestational age missing in 77 (5.9%) cases. Of the live born cases, the mean birth weight was 3,276.5 grams (SD = 565.7), with birth weight missing in 256 (19.5%). Of the term cases (gestational age ≥37 weeks, \( n = 1,103 \)), the mean birth weight was 3,389.3g (SD = 540.6 g) and of the preterm cases (gestational age <37 weeks, \( n = 125 \)) the mean birth weight was 2,278.3 g (SD = 688.9 g).

**TOTAL PREVALENCE**

Table 2 shows the number of cases and total prevalence of cases of Hirschsprung’s disease by register. Including all
1,322 singleton cases, the total prevalence was 1.09 (95% CI, 1.03–1.15) per 10,000 births for all registers combined. Total prevalence ranged from 2.78 (95% CI, 1.89–3.94) in Malta to 0.07 (95% CI, 0.01–0.24) per 10,000 total births in South Portugal (Fig. 2). There was a significant difference in prevalence between registers ($p < 0.001$).

Excluding cases associated with chromosomal anomalies or genetic syndromes, the total prevalence was 0.97 (95% CI, 0.91–1.03) per 10,000 births, and this varied significantly between registers ($p < 0.001$).

There was a small but significant increase in Hirschsprung’s disease prevalence over the study period ($RR = 1.01; 95\% CrI, 1.00–1.02; p = 0.004$), which ranged from a modeled 1.04 per 10,000 in 1980 to 1984 to 1.42 per 10,000 in 2005 to 2009. There was no evidence that trends over time varied by register ($p = 0.203$).

Excluding cases associated with chromosomal anomalies or genetic syndromes, there was still evidence of increasing total prevalence over the study period ($RR = 1.01; 95\% CrI, 1.00–1.02; p = 0.006$), which ranged from a modeled 0.93 per 10,000 in 1980 to 1984 to 1.26 per 10,000 in 2005 to 2009.

**TRENDS IN PREVALENCE**

There was a small but significant increase in Hirschsprung’s disease prevalence over the study period ($RR = 1.01; 95\% CrI, 1.00–1.02; p = 0.004$), which ranged from a modeled 1.04 per 10,000 in 1980 to 1984 to 1.42 per 10,000 in 2005 to 2009. There was no evidence that trends over time varied by register ($p = 0.203$).

Excluding cases associated with chromosomal anomalies or genetic syndromes, there was still evidence of increasing total prevalence over the study period ($RR = 1.01; 95\% CrI, 1.00–1.02; p = 0.006$), which ranged from a modeled 0.93 per 10,000 in 1980 to 1984 to 1.26 per 10,000 in 2005 to 2009.

**MATERNAL AGE DISTRIBUTION**

There were 1,098 (83.1%) cases with available maternal age and corresponding maternal age denominator data. The prevalence was greatest among mothers aged $\geq 35$ but there was no increased risk of Hirschsprung’s disease in this age group compared with mothers aged 25 to 29 ($RR = 1.09; 95\% CrI, 0.91–1.31; p = 0.355$) (Table 3). Compared with women aged 25 to 29, there was no evidence of an association with maternal age in any other age group (Table 3). Accounting for maternal age, there was still a significant difference in prevalence between registers.

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**TABLE 1. Frequencies of Congenital Anomalies That Occurred in Addition to Hirschsprung’s Disease**

<table>
<thead>
<tr>
<th>Chromosomal anomalies and genetic syndromes, group and subtype</th>
<th>N</th>
<th>% of all cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal anomalies</td>
<td>131</td>
<td>9.9</td>
</tr>
<tr>
<td>45 X (Turner syndrome)</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Trisomy 2, mosaicism</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Trisomy 7</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Trisomy 8 mosaicism</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Trisomy 21 (Down syndrome)</td>
<td>123</td>
<td>9.3</td>
</tr>
<tr>
<td>Deletion of long arm chromosome 13</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>0.2</td>
</tr>
<tr>
<td>Genetic syndromes and microdeletions</td>
<td>15</td>
<td>1.1</td>
</tr>
<tr>
<td>Di George syndrome</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>Microdeletion 13</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Adams Oliver syndrome</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Mowat Wilson syndrome</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Smith-Leni-Optiz-syndrome</td>
<td>4</td>
<td>0.3</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Waardenburg syndrome</td>
<td>5</td>
<td>0.4</td>
</tr>
<tr>
<td>Total</td>
<td>146</td>
<td>11.0</td>
</tr>
</tbody>
</table>

**TABLE 1. Continued**

<table>
<thead>
<tr>
<th>Chromosomal anomalies and genetic syndromes, group and subtype</th>
<th>N</th>
<th>% of all cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital</td>
<td>13</td>
<td>6.3</td>
</tr>
<tr>
<td>Hypospadias</td>
<td>8</td>
<td>3.9</td>
</tr>
<tr>
<td>Limb</td>
<td>17</td>
<td>8.3</td>
</tr>
<tr>
<td>Hip dislocation/ dysplasia</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>Syndactyly</td>
<td>4</td>
<td>1.9</td>
</tr>
<tr>
<td>Musculo-skeletal</td>
<td>8</td>
<td>3.9</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
<td>5.8</td>
</tr>
<tr>
<td>Total</td>
<td>206</td>
<td>100.0</td>
</tr>
</tbody>
</table>

*Cases occurring in multiple pregnancies were excluded.

**Cases occurring with chromosomal anomalies, genetic syndromes, or microdeletions are excluded. Structural anomalies with $n < 3$ not shown.**
and there was still a statistically significant trend over time (RR = 1.01; 95% CrI, 1.00–1.02; p = 0.012).

After excluding cases associated with chromosomal anomalies or genetic syndromes, there were 974 cases. There was no evidence of an association between prevalence and maternal age in any age group. There was still evidence of a significant difference in prevalence between registers and a small increase in prevalence over time (RR = 1.01; 95% CrI, 1.00–1.02; p = 0.012).
Time of diagnosis was known in 803 (77.3%) isolated cases. A congenital anomaly was antenatally suspected in 11 (1.4% of 803) isolated cases at a mean gestational age of 31 weeks (interquartile range, 22–33). Hirschsprung’s disease was diagnosed at birth in 161 (20.0%) cases, in the first week in 354 (44.1%) cases, between 1 and 4 weeks in 116 (14.4%) cases, between 1 and 12 months in 95 (11.8%) cases, after 12 months in 25 (3.1%) cases. The remaining 41 cases were postnatally diagnosed but at an unknown time.

ONE WEEK SURVIVAL
There were 1,135 (86.4%) live born cases with known 1 week survival and 8 (0.7%) cases died in the first week of life. Four of these were isolated cases, two had chromosomal anomalies (Down syndrome) and two had other structural anomalies (Prune Belly Sequence and hip dislocation and/or dysplasia).

Discussion
This study is the largest to examine the epidemiology of Hirschsprung’s disease. Using data from 31 European congenital anomaly registers over a period of 30 years, we found a total prevalence of 1.09 per 10,000 births and a small but significant increase in Hirschsprung’s disease prevalence over time. We also found a difference in prevalence by geographic location and no evidence of an association between prevalence and maternal age.

### TABLE 3. Prevalence According to Maternal Age Category

<table>
<thead>
<tr>
<th>Age</th>
<th>All cases</th>
<th>Excluding non-structural anomalies*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>Prevalence (95% CI) per 10,000</td>
</tr>
<tr>
<td>&lt;20</td>
<td>45 (4.1)</td>
<td>0.96 (0.7, 1.29)</td>
</tr>
<tr>
<td>20–24</td>
<td>200 (18.2)</td>
<td>1.05 (0.91, 1.21)</td>
</tr>
<tr>
<td>25–29</td>
<td>340 (31.0)</td>
<td>0.97 (0.87, 1.08)</td>
</tr>
<tr>
<td>30–34</td>
<td>317 (28.9)</td>
<td>0.99 (0.88, 1.11)</td>
</tr>
<tr>
<td>35+</td>
<td>196 (17.9)</td>
<td>1.17 (1.01, 1.35)</td>
</tr>
<tr>
<td>Year</td>
<td>–</td>
<td>1.01 (1.00, 1.02)</td>
</tr>
</tbody>
</table>

Cases occurring in multiple pregnancies were excluded. As stated in the Materials and Methods section, several registers/years were excluded from this analysis.

*Excluding cases occurring with chromosomal anomalies, genetic syndromes or microdeletions.
The primary strength of this study is that it is based on data derived from established, high quality, population-based congenital anomaly registers. Standard methods of identifying and classifying cases across all registers and the use of multiple sources of notifications ensure high case ascertainment. The health services in Europe are organized to deliver care to a defined population, which allows contributing registers to maximize case ascertainment.

Additionally, this is one of very few studies to investigate the prevalence of Hirschsprung’s disease according to maternal age and to determine the relative risk of Hirschsprung’s disease in young women and women of advanced maternal age.

We have used advanced methods of analysis to analyze the trends in Hirschsprung’s disease prevalence over time and the association with maternal age. The multilevel methods used provide more accurate standard error estimates for the nested data than classical approaches and limit the potential for confounding due to registers contributing data from different time points (Austin, 2001).

A further strength of the study is that we had detailed information on associated anomalies. Thus we could investigate the epidemiology of Hirschsprung’s disease both including and excluding cases with chromosomal anomalies or genetic syndromes which may have different etiologies.

However, this study also has some limitations. The increasing trend in prevalence could be caused by improved ascertainment due to the registers becoming more established over the study period or due to improvements in diagnosis and coding over time. Additionally heterogeneity in prevalence between registers may be related to differences in ascertainment, especially as some of the registers (such as Paris and Emilia Romagna) have been in existence for almost 30 years whilst others have only been collecting data for 5 to 10 years. While most registers include cases diagnosed by age one (and older in some registers, including registers in the North of England and Vaud), several only include cases diagnosed in the first month (e.g., South Portugal register) or first week (e.g., Emilia Romagna register) of life. This may be a source of heterogeneity because Hirschsprung’s disease is not always picked up in the neonatal period. However, trends and geographic variation in prevalence may reflect true differences, perhaps related to differing exposures between regions. Although we were able to adjust for maternal age, we did not have access to data on other variables such as ethnicity, which may be associated with Hirschsprung’s disease prevalence (Goldberg, 1984).

With few cases occurring in terminations of pregnancy, late miscarriage or stillbirth, it is not too surprising that our total prevalence was not greater than the live birth prevalences of 1.63, 1.76, and 2.26 per 10,000 live births, reported by other studies (Goldberg, 1984; Spouge and Baird, 1985; Best et al., 2012). With Goldberg (1984) reporting a higher prevalence in non-whites compared with whites, other factors such as ethnicity may account for some of the variation between these studies.

This study found a small but significant increasing trend in the total birth prevalence of Hirschsprung’s disease, which was similar to that reported in our previous study, set in the North of England over a similar time period (1990–2008) (Best et al., 2012). However, this trend should be interpreted with caution; although our large sample size enabled us to detect a very small, statistically significant increase in prevalence, this increase may not be of clinical significance. Goldberg (1984) and Spouge and Baird (1985) found no evidence of trends over time between the 1960s to 1980s in Baltimore and British Columbia, respectively. However, these are smaller studies which may not have had the power to detect a small increase in prevalence. Moreover, these are older studies performed outside of Europe and so the population and environments may not be easily comparable to our study.

We found no evidence of an increased risk of Hirschsprung’s disease in cases born to women aged over 35 when chromosomal anomalies and genetic syndromes were included or excluded. This corresponds with the findings of Best et al. (2012), where the proportion of mothers aged over 35 was not significantly greater in cases compared with the general population. Goldberg (1984) found a significantly greater proportion of cases born to mothers aged over 30 compared with the general population but examined only 33 cases, and Ryan et al. (1992) found no difference in proportions at all. Therefore, there is little evidence that increased maternal age is a risk factor for Hirschsprung’s disease despite the anomaly having a known genetic element. However, there is some evidence of an interaction with ethnicity, with Goldberg identifying some association with increased maternal age in white women but not in non-white women (Goldberg, 1984). This interaction may need to be further investigated before maternal age is ruled out completely as a risk factor.

Acknowledgments
We thank the many people throughout Europe involved in providing and processing information, including affected families, clinicians, health professionals, medical record clerks, and registry staff. The EUROCAT Joint Action is co-funded by the EC, under the framework of the EU Health Programme 2008 to 2013, Grant Agreement 2010 22 04 (Executive Agency for Health & Consumers). EUROCAT registries are funded as fully described in Paper 6 of Report 9 - EUROCAT Member Registries: Organization and Activities (Birth Defects Research (Part A), 91, S51-S100). The responsibility for the interpretation of data and/or information supplied is the authors’ alone. This study reports on an independent study which is part-funded by the Policy Research Programme in the Department of Health, UK. The views expressed are not necessarily those of the Department.
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