Prevalence of hepatitis B anti-core antibody in the Republic of Ireland

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SUMMARY
The aim of this study was to estimate the prevalence of hepatitis B exposure in the population of the Republic of Ireland, by measuring the prevalence of hepatitis B anti-core antibody in oral fluid collected by postal survey.

A random multi-stage stratified sample of Irish households was obtained, using the Irish electoral register as the sampling frame. A total of 962 households were selected, and a household response rate of 60.4% was achieved. Oral fluid specimens totalling 1714 were tested for antibody to hepatitis B core antigen (anti-HBc), using an Immune Capture Enzyme Immuno- Assay. Five specimens (0.29%) were found to contain anti-HBc. Adjusting for study design, the estimated anti-HBc prevalence in the Republic of Ireland is 0.51%.

This study demonstrates that self-collection of oral fluid samples is acceptable to the public, and based upon the data generated, that the Republic of Ireland has a low prevalence of hepatitis B infection.

INTRODUCTION
Hepatitis B virus (HBV) is one of the world’s most common and serious infectious diseases. It is estimated that about two billion people who are alive today have at some time been infected with HBV. About 350 million people are chronic carriers of HBV [1]. This represents a very large reservoir of virus.

Approximately 160000 cases of acute HBV infection are reported each year in the WHO European region [2]. Owing to under-reporting and the fact that at least 50% of HBV infections are asymptomatic, the World Health Organisation has extrapolated from these figures and estimates that one million people are infected in the WHO
European region annually. Of these, approximately 90000 will become chronically infected and about 22000 will die from cirrhosis and liver cancer [2]:

In 1991, the World Health Organisation (WHO) called on all countries to introduce universal hepatitis B immunization by 1997 [3]. In Western Europe, a number of countries have instituted national policies to immunize infants or adolescents against HBV. These include Belgium, France, Germany, Italy and Spain. However, Ireland, the United Kingdom, The Netherlands and the Scandinavian countries have not yet instituted national immunization programmes [4], having policies of targeting ‘at risk’ populations for immunization.

The prevalence of HBV infection in the general population of the Republic of Ireland is not known. HBV is a notifiable disease, and the number of notifications per annum between 1989 and 1997 ranged from 10 to 30, but increased sharply in 1998 to 155 [5], in a national population of 3.66 million. However, the extent of under-reporting or duplication of notifications of HBV infection is unknown. Testing of new blood donors has shown HBsAg positive rates of approximately 0.026% between 1993 and 1997 [5], whilst testing among the antenatal population in two Irish hospitals has show HBsAg positive rates of approximately 0.03-0.22% between 1995 and 1998 [5].

The aim of this study was to estimate the prevalence of HBV infection in the population of the Republic of Ireland. This was to be achieved by measuring the prevalence of anti-core antibody (anti-HBc), a marker of current or past HBV infection [6], in a representative sample of the Irish population using self-collected oral fluid samples.

METHODS
In the absence of a population register, the sampling frame used was the Register of Electors for Irish parliamentary elections. This register consists of 3444 local listings of the names and addresses of adults over the age of 18 who are registered to vote. These local divisions of electors are known as District Electoral Divisions (DEDs). The electoral register was last updated in April 1998.

The objective was to choose a representative sample from the 3444 DEDs that would reflect the Irish population. The 3444 DEDs were first stratified into urban and rural strata. These were then sub-stratified into three different socio-economic strata (high, middle and low socio-economic categories), using a classification system developed by the Small Area Health Research Unit [7]. Thus, there were six different strata of DED type. Three DEDs were chosen at random from each of the six strata, giving a total of 18 DEDs nationally.

Sample size calculations were performed using the Epi-Info software package [8]. Our experimental hypothesis was that the prevalence of anti-HBc in the Irish population was 1±0.5%. This was based on extrapolating from published data on hepatitis B positivity in blood donors and antenatal women [5]. A net household response rate of 50% was expected and a design effect of two was assumed. It was assumed that approximately 10% of persons listed at a given address would have died or moved elsewhere, based on the results of a national health promotion study that also used the electoral register [9]. Since the average Irish household size is 3.2

persons [8], a sample of 900 households was required from 18 DEDs. Households were selected at random from the 18 DED listings. However, in some DEDs, a larger than expected number of persons listed had either moved elsewhere or died. A small additional top-up sample was required in 10 of the 18 DEDs, where in 5 or more households, the individual contacted had died or moved. Thus the final number of households sampled was 962.

Sample collection took place between November 1998 and January 1999. Targeted households received an initial letter outlining the aims of the study. They then received a package containing a letter with easy-to-follow instructions, six foam swabs to collect the oral fluid and a reply postcard. The household member to whom the letter was addressed was asked to collect an individual sample from each household member, and to mark the age and sex of the individual on the outside of the transport tube using specially supplied labels.

Samples were returned to a free postal address in University College Dublin. Respondents were asked to return the postcard with their name and address to a separate free postal address in the North Eastern Health Board, where the study was co-ordinated. This postcard was to identify those individuals who had returned specimens so that they would not be contacted again. Respondents were asked to detail on this postcard whether all family members took part, or whether some individuals were missed.

Non-respondents received two reminder letters, and if possible, were also telephoned. A telephone helpline number was included in all mailshots. A press release describing the study was circulated to the national and local press.

The age, sex and area post code (DED) of origin of the oral swabs received were recorded in a database. The contents of the foam swab were eluted in Phosphate-Buffered Solution Tween (PBST) and stored at -20 °C in a Starstedt tube until testing. To determine the validity of a sample prior to anti-HBc investigation, an ‘in-house’ IgG quantification assay was used. Those with IgG concentrations in excess of 0.313 mg/l, a level established to provide an accurate result, were then tested for anti-HBc antibodies.

Two different anti-HBc assays were used, both of which were based on the immune capture technique. The first assay was a commercially available anti-HBc combined IgG/IgM test employing a peroxidase conjugated HBc antigen (Murex ICT™HBc, Murex Biotech Limited, Dartford, Kent, England). The second assay was an IgG-specific test, employing an alkaline phosphatase conjugated HBc antigen, which was developed and validated in the Virus Reference Laboratory, University College Dublin.

RESULTS

A total of 962 households were asked to participate. In 135 households, the person to whom the letter was written had changed address, whilst in 15 households the person had died. Sixty per cent (491/812) returned 1738 samples, an average of 3.6 samples per household. The response rate varied across the six DED strata, with the lowest response rate seen in the urban low socio-economic category (48%), and the highest response rate seen in the urban high socio-economic category (65%). The age and sex
profile of the respondent population closely matched the age and sex profile of the Irish population (Table 1).

Of the 491 households that returned samples, 447 (93%) also returned the, reply postcard. Of these, 84% indicated that everyone in their household supplied specimens and 16% indicated that one or more persons in their household had not participated. This incomplete household response rate of 16% was fairly uniform across the six different DED strata (range 13-19%).

A total of 1714 (98.6%) of the 1738 swab eluates were suitable for testing. Eleven (0.64%) were repeat reactive on the ICE™HBc assay, and of these, five were confirmed anti-HBc positive using the confirmatory assays. The remaining six were unconfirmed screen reactives, and classified as negative. Also 1703 (99.36%) tested negative for anti-HBc. Thus, the crude prevalence of anti-HBc in the study population was 0.29% (95% CI: 0.04-0.55%).

The age, sex and DED strata of these five confirmed positives are shown in Table 2. The crude prevalence of anti-HBc in the study population (0.29%) was adjusted to calculate an estimated Irish population prevalence for HBV exposure, taking account of the multistage stratified cluster design used. This was achieved using the svy package from Stata Corporation (Stata Corporation, 1997).

The adjustment for stratification and clustering had little effect on the estimated prevalence figure. However, the adjustment for sample weighting had a larger effect, with the estimated mean prevalence almost doubling to 0.51% (95% CI: 0.18-1.18%).

**Table 1.** Comparison of study population and Irish population by age and sex

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>% in study population</th>
<th>% in Irish population</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>6.3</td>
<td>6.9</td>
</tr>
<tr>
<td>5-14</td>
<td>15.3</td>
<td>16.8</td>
</tr>
<tr>
<td>15-24</td>
<td>16.9</td>
<td>17.5</td>
</tr>
<tr>
<td>25-44</td>
<td>29.7</td>
<td>28.0</td>
</tr>
<tr>
<td>45-64</td>
<td>22.3</td>
<td>19.4</td>
</tr>
<tr>
<td>65+</td>
<td>9.5</td>
<td>11.4</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>% in study population</th>
<th>% in Irish population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>48.6</td>
<td>49.6</td>
</tr>
<tr>
<td>Female</td>
<td>51.4</td>
<td>50.4</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 2.** Stratum type/age/sex of confirmed HBV positives

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Age</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rural middle socio-economic</td>
<td>40</td>
<td>Male</td>
</tr>
<tr>
<td>Rural middle socio-economic</td>
<td>52</td>
<td>Male</td>
</tr>
<tr>
<td>Urban middle socio-economic</td>
<td>58</td>
<td>Female</td>
</tr>
<tr>
<td>Urban low socio-economic</td>
<td>34</td>
<td>Male</td>
</tr>
<tr>
<td>Urban low socio-economic</td>
<td>70</td>
<td>Female</td>
</tr>
</tbody>
</table>
DISCUSSION
From a 30-year review of the Medline database, this is the first time that a national epidemiological study using oral fluid collection by postal survey has been published. A high response rate (60.4%) was achieved. Virtually all of the specimens (98.6%) provided were suitable for anti-HBc testing, indicating that this method of sample collection is feasible.

This study estimated that the prevalence of HBV exposure in the population of the Republic of Ireland was 0.51%. Thus, Ireland is classified as a low prevalence country for HBV infection [6].

The estimated anti-HBc prevalence in the Irish population of 0.51% had nominal 95% confidence intervals. This was because the study population prevalence of anti-HBc found in this study (0.29%) was lower than the estimated study population prevalence anticipated in the sample size calculations (0.5-1.5%).

There is no information on non-responding households. It was considered that contacting non-respondents after four mail shots and a telephone call would be excessive. No information on the presence of hepatitis B risk factors or past history of jaundice was collected, as we considered that asking for this additional information would adversely effect response rates. Thus, it is possible that high-risk individuals were not included in the study, either because they were not on the electoral register in the first place, or because they did not take part in the study.

The estimated Irish population anti-HBc prevalence of 0.51% was almost twice the crude study prevalence of 0.29%, due to the effect of sample weighting. This was because in 2 of the 6 strata, the DEDs selected had a smaller than expected population. Critically, 4 out of the 5 positives occurred in these 2 strata (urban low socio-economic stratum, rural middle socio-economic stratum). This under-representation was due to random sampling bias and not non-response bias.

In 1991, the WHO called for all countries to add hepatitis B vaccine to their national immunization programmes [3]. By 1999, most countries in Western Europe had introduced universal infant and/or adolescent vaccination programmes [4]. Some authors have argued that in the low endemicity countries of North Western Europe, this global strategy for hepatitis B is inappropriate [10]. Ireland, the United Kingdom, The Netherlands and the Scandinavian countries have not implemented universal vaccination programmes [4]. The National Immunisation Committee in Ireland has recommended a policy of selective rather than universal immunization [5].

A variety of arguments are advanced by those who advocate selective rather than universal immunization in low endemicity countries. The introduction of an additional infant vaccination may affect the uptake of other childhood vaccinations [11]. Universal infant immunization does not prevent perinatal transmission [11]. The introduction of adolescent immunization may be hampered by asking parents to accept an immunization against an infection that is spread sexually and through intravenous drug use [11]. No convincing economic case has been made to justify the cost of HBV immunization in low endemicity countries [12]. Thus, within Europe, the debate on universal versus selective immunization remains ongoing.
Based upon this study, the Republic of Ireland currently has a very low rate of HBV infection in the general population. This study has also found that oral fluid collection by postal survey is a useful tool for epidemiological surveys. The public are willing to provide self-collected oral fluid samples for virological investigations, provided the anonymous and unlinked nature of the study is emphasized.

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REFERENCES