Estimating the impact of HBV vaccination policies

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Project overview

- Prevalence review
  - Efficacy review
    - Statistical model (prevalence)
    - Static model
    - Dynamic model
HBsAg prevalence

- Impact of HBV vaccination on liver cancer and cirrhosis takes many years to become apparent
- HBsAg carriage is necessary pre-condition for HBV-associated chronic disease
- Impact on carriage can be more rapidly assessed
  - Serological surveys in vaccinated age cohorts (and others)


<table>
<thead>
<tr>
<th>Indicator C.9.a</th>
<th>Cumulated incidence of HBV infection in children 5 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicator category</td>
<td>Core</td>
</tr>
<tr>
<td>Measurement method, sources of data</td>
<td>HBsAg biomarker prevalence survey in children 5 years of age (immunization coverage surveys and administrative vaccination coverage data) (35)</td>
</tr>
</tbody>
</table>
Systematic review of HBsAg prevalence studies

Schweitzer et al. Lancet 2015

• Systematic review of studies on HBsAg published 1965-2013
• 1800 reports on HBsAg from 161 countries.
• Seroprevalence was 3·61% (95% CI 3·61-3·61)

But

• Potentially relevant background data were not extracted, e.g.
  – Age group
  – Sex
  – Exact geographical location
  – Vaccine status of surveyed group
• Missing data
  – particularly recent studies in vaccinated cohorts
Additional data extraction and search

• Papers in Schweitzer et al. study were retrieved and further data extracted on
  – Demographics of sample (age, sex, population group etc)
  – Geographical location (lat-long of centroid of study area)
• GDP per capita was assigned for each country using UN database.
• Vaccinated cohorts were identified for each database by linking with WHO/UNICEF data on HBV vaccine introduction (HBV3 & BD)

Additional search

• Targeted at countries with high/intermediate prevalence (>=2%) that had introduced vaccination
• Studies reporting local, regional or national data on HBsAg prevalence published in English, French Spanish, Portuguese between 2000 and 2016
• Similar inclusion and exclusion criteria to Schweitzer et al.
Total number of studies across countries

- 166 Countries
- 1377 Studies
- 5200 Data points
Studies with U5 data

- 75 Countries
- 207 Studies
- 371 Data points
Pre-vaccination

- 157 Countries
- 1214 Studies
- 4691 Datapoints
Post vaccination studies

- 73 Countries
- 263 Studies
- 509 datapoints
Estimating the HBsAg prevalence

- Logistical regression with geospatial random effects
  - Included geographic and GDP difference in a distance matrix as part of the correlated autoregressive function.
- Variables
  - sex, age, bias (e.g. indigenous peoples), vaccinated cohorts, birth dose
- \( Y_i \sim \text{Binomial} \left( \pi_i, N_i \right) \), \( \log \frac{\pi_i}{1-\pi_i} = \beta_0 + \sum_{j=1}^{p} \beta_j x_{ij} + u_i \)
- Bayesian statistical package WinBUGS
- Validation on random sample of studies (10%)
Country-level random effects: measures of distance

- Geographical distance (space)
  - Define neighbourhood around point of interest
  - Data points within neighbourhood contribute to estimate
  - Can either weight the points according to their distance or not

- Socio-economic distance (GDP per capita)

- Both “distance” measures used in the model
  - Weighted 2:1 in favour of GDP distance
Model validation

Validation
• Final model run using 90% of data
• Verified against remaining 10%
• Final model predictions incorporate all data

Log scale

Linear scale
Model selection and results

Selection
- Sensitivity analysis performed on assumptions
  - Incorporation of birth dose
  - Different methods for incorporating gender
  - “Bias”
  - GDP vs geographical distance
- Best fitting model selected based on deviance

Key result
- Vaccination significantly reduces prevalence
- Incorporation of birth dose significantly improves model fit & further reduces prevalence
Adult prevalence estimate pre-vaccination

HBsAg
U5 prevalence estimate post & pre vaccination
Global estimate carriage without vaccination

<table>
<thead>
<tr>
<th>Region</th>
<th>Total number</th>
<th>Overall HBsAg</th>
<th>Under 5 HBsAg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>15,453,613</td>
<td>1.8%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Americas</td>
<td>10,714,549</td>
<td>1.1%</td>
<td>0.7%</td>
</tr>
<tr>
<td>W. Pacific</td>
<td>137,947,933</td>
<td>7.9%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Africa</td>
<td>71,671,384</td>
<td>8.6%</td>
<td>4.3%</td>
</tr>
<tr>
<td>SE Asia</td>
<td>38,135,460</td>
<td>2.1%</td>
<td>1.0%</td>
</tr>
<tr>
<td>East Med</td>
<td>21,219,990</td>
<td>3.7%</td>
<td>2.0%</td>
</tr>
</tbody>
</table>
# Predicted current under 5 carriage

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence (%)</th>
<th>Pre-vac</th>
<th>Post-vac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>1.1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Americas</td>
<td>0.7</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>W. Pacific</td>
<td>4.0</td>
<td>0.2</td>
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</tr>
<tr>
<td>Africa</td>
<td>4.3</td>
<td>1.6</td>
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</tr>
<tr>
<td>SE Asia</td>
<td>1.0</td>
<td>0.2</td>
<td></td>
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<td>2.0</td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region</th>
<th>Pre-vac</th>
<th>Post-vac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>633,217</td>
<td>72,286</td>
</tr>
<tr>
<td>Americas</td>
<td>500,323</td>
<td>81,530</td>
</tr>
<tr>
<td>W. Pacific</td>
<td>4,765,849</td>
<td>258,441</td>
</tr>
<tr>
<td>Africa</td>
<td>6,786,242</td>
<td>605,557</td>
</tr>
<tr>
<td>SE Asia</td>
<td>1,852,959</td>
<td>370,431</td>
</tr>
<tr>
<td>East Med</td>
<td>1,569,459</td>
<td>473,973</td>
</tr>
</tbody>
</table>

14.2m under 5 carriers prevented
Predicting the impact on HBsAg carriage-related deaths

- Static model for 169 countries
- Markov-Model including perinatal infections
- Inputs
  - Country-level estimates of HBsAg prevalence
  - Demographic trends (UN)
  - Vaccine coverage (WHO/UNICEF)
    - Timing (Sanderson)
  - Vaccine efficacy (lit review)
- Outputs (country level)
  - Estimate of burden of HBV
  - Estimates of HCC cases and HBV-related deaths
  - Conservative estimates of vaccination effect
Predicted impact on carriage-related deaths

HCC cases by age group every 10 years in Wpr

Age Group
- Children (0-15)
- Young Adults (15-35)
- Adults (35-65)
- Seniors (65+)

Vaccination
- No Vaccination
- Birth + 3 E.P.I.
Summary

- Constructed an updated global database on HBsAg prevalence
  - Enhanced data for each point
    - Age group, vaccine status, GDP per capita
- Database very large, but has gaps (e.g. U5 post-vaccination)
- Used this database to construct and validate a statistical model to
  - Examine factors influencing prevalence (e.g. HBV3 and HBVBD coverage)
  - Predict the prevalence in areas where data are lacking
- Data and model demonstrate dramatic reduction in prevalence in children under 5 years of age post vaccination
- Prevalence estimates inform static model to predict the impact of vaccination on deaths associated with chronic HBsAg carriage
  - Large reductions in deaths expected in the long run
  - Meanwhile HBV-associated deaths expected to increase
    - Due to past population growth and increasing life-expectancy