Regional Analysis of Delays in Starting Tuberculosis Treatment: A Descriptive Statistical Analysis of the Bristol, North Somerset and South Gloucestershire Enhanced Tuberculosis Surveillance Data

Dr Charlotte Bigland, Dr Charles Beck, Mike Wade, Public Health England

Aim

- To identify the local distribution of delays between TB symptom onset and treatment start across selected socio-demographic and clinical characteristics through a descriptive statistical overview of the 2011-2015 BNSSG ETS dataset
- Use the study findings to inform recommendations to reduce local delays in starting TB treatment

Findings

1) Differences in national vs local profile of cases
   - The local profile of cases does not align well with the national profile, and thus is not well matched with national awareness campaigns
     - Non-UK Born ~75% nationally, 48% locally
     - Higher rate of social risk factor cases locally (15% vs 9%)

2) Variation in sub group time to presentation
   - Longer median times to presentation in those with social risk factors
   - UK born cases with social risk factors have median time to presentation twice that of other groups

3) Variation in sub group time to diagnosis
   - Median times to diagnosis appear to be longer for those who are “non-nationally typical” cases of TB
     - eg UK born, no social risk factors, women

Discussion

Clinicians are used to following national messaging around disease risk factors. The local profile of TB cases does not match the national profile, and this may be why there are long delays to clinician diagnosis for “non-typical cases” - those who are UK born, lack social risk factors or are female.

Recommendations

1) Focus on interventions to shorten the time to presentation for those with social risk factors, focusing on UK born cases
2) Focus on interventions to increase clinician understanding of the local profile of TB cases to reduce time to diagnosis for UK born cases
3) Consider further data analysis for other sub regions; consider a multiple linear regression analysis on top of the descriptive and stratified analysis

Background

What is time to treatment start?
- Time to presentation
- Time to diagnosis
- Time to treatment start

Why is it important?
- Delayed treatment start can lead to more complex disease, greater morbidity, mortality and cost, and higher rates of transmission

Why focus on this locally?
- South West trails other regions in terms of time to treatment start indicators; local and national priority indicator

Methodology

- Statistical description of BNSSG ETS dataset 2011 and 2015;
  - Excluded exclusively extra pulmonary cases, post mortem diagnosis, statistical review missing data
- Median times to presentation, diagnosis and treatments start for 8 socio-demographic and clinical variables
  - Age, sex, ethnicity, UK-Born, >=1 social risk factor, socioeconomic status, smoking status, sputum smear status
- Stratified analysis using UK-born and >=1 social risk factor


Acknowledgements: We would like to acknowledge the help and expertise provided by Dr Sarah Mungall and Simon Packer
Tuberculosis active case-finding among homeless and substance-misusing populations in Bristol: a process evaluation

Kwiatkowska RM, Trudgeon H, Packer R, Wade M, Beck CR, Hickman M
Public Health England South West; Health Protection Research Unit in Evaluation of Interventions

Proof of principle
TB active case-finding is an effective control measure in the context of low background incidence and no focal point for transmission.

• Did we screen all the right people?
• Did we reduce TB transmission?
• Did we improve health outcomes?

Conclusions
• Successful engagement with target population, mainly through services
• No active TB diagnosed, but liver disease identified & treated
• Stakeholders promoting TB awareness

Public health relevance
Findings can guide future interventions for control of communicable diseases among vulnerable populations.

Correspondence
rachel.kwiatkowska@phe.gov.uk

Context & Rationale
• High rates of Social Risk Factors (SRF) among local TB cases
• Transmission among homeless and substance-misusing populations

Active case-finding justified, however:
• Low background incidence in Bristol
• No geographical focal point for transmission

Intervention
• Stakeholder engagement
• Patient Public Involvement
• TB training/ awareness session
• ‘Find and Treat’ mobile chest x-ray unit
• Opportunistic screening (Hepatitis C, HIV, fibroscan) & vaccination (Influenza, Hepatitis B)
• Stakeholder debrief

Logic model

Results
• 213 attendees (>100% of screening target)
• 52% attendees reported ≥ 1 Social Risk Factor
• 42% used homeless/ drugs & alcohol services
• 67% had heard about the event through services
• No active TB identified
• Vaccine uptake: influenza 29%, Hep B 5%
• 8 cases advanced liver disease identified on fibroscan
• Engagement & positive feedback from stakeholders

References
ASSOCIATION BETWEEN RESPIRATORY VIRAL INFECTIONS AND MENINGOCOCCAL CARRIAGE IN BRISTOL SCHOOL STUDENTS IN 2014 - 2015

E. Oliver¹, H. Chappell¹, B. Morales-Aza¹, P. Sikora-Liszka¹, J. Oliver³, H. Christensen², I. Vipond³, J. Stuart², P. Muir³ and A. Finn¹

¹BCVC, Schools of Clinical Sciences & Cellular and Molecular Medicine, University of Bristol, Bristol, UK ²School of Social & Community Medicine, University of Bristol, Bristol, UK ³Public Health Laboratory Bristol, Public Health England, Bristol, UK.

INTRODUCTION AND STUDY DESIGN

- *N. meningitidis* causes meningococcal disease.
- If transmission of the meningococcus bacteria can be prevented, the incidence of disease could be reduced.
- Our aim is to investigate the relationship between respiratory viruses and meningococcal carriage.
- 5,456 pharyngeal swabs were collected from Bristol school students (15–19yrs), between September 2014 and May 2015. Longitudinal swabs were collected monthly for 6 months from 918 students.
- Bacterial and viral nucleic acids were extracted from samples.
- Quantitative real-time polymerase chain reaction (qPCR) was used to identify the presence of *N. meningitidis* and the presence of viruses: adenovirus (AdV), influenza A viruses (H1N1/09, seasonal H1N1 and H3N2) (FluA), influenza B (FluB), respiratory syncytial virus (RSV), human metapneumovirus (HMV), rhinovirus (RhV), parainfluenza virus types 1-3 (PF1-3) and enterovirus (EV).
- Analysed the first 230 samples from each visit to date.

RESULTS

**A)**

<table>
<thead>
<tr>
<th></th>
<th><em>N. meningitidis+</em></th>
<th><em>N. meningitidis-</em></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus+</td>
<td>11.8%</td>
<td>88.2%</td>
<td>100%</td>
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<tr>
<td>Virus-</td>
<td>7.0%</td>
<td>93.0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**B)**

<table>
<thead>
<tr>
<th></th>
<th><em>N. meningitidis+</em></th>
<th><em>N. meningitidis-</em></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>RhV+</td>
<td>12.9%</td>
<td>87.1%</td>
<td>100%</td>
</tr>
<tr>
<td>RhV-</td>
<td>7.0%</td>
<td>93.0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Results 2 – Association in the same sample between the presence of *N. meningitidis* and A) the presence of a virus and B) the presence of Rhinovirus.

CONCLUSIONS

- The overall viral detection rate is low, Rhinovirus is the most frequently detected virus, 6.7%.
- Evidence of an association between the detection of any respiratory virus and of Rhinovirus and *N. meningitidis*.
- In January the highest rate of carriage of *N. meningitidis* was observed, and the only month in which evidence of a relationship between the presence of a virus and *N. meningitidis* was found.
- No association was found between the *N. meningitidis* density level and the detection of a virus.
- We will have greater power to explore these relationships further as more analysis is done.
- The results of this study will help to inform us whether current flu control strategies may impact upon meningococcal carriage, transmission and so disease rates.

Funding from Meningitis Research Foundation, Wellcome Trust and NIHR HPRU in Evaluation of Interventions at the University of Bristol, in partnership with Public Health England (PHE). The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR, the Department of Health or Public.
• To measure carriage rates of different genogroups of Neisseria meningitidis (Nm) in 1,813 16-18 year olds by analysing oropharyngeal swabs using PCR assays.
• To assess whether density of carriage varies between genogroups.
• To compare the sensitivity of a generic Nm PCR (sodC) when performed directly on swabs in medium and following plate culture (“lawn PCR”).
• 1,813 oropharyngeal swabs were taken and stored in STGG broth.
• 100μL of STGG was plated onto a selective agar and incubated for 72 hours. All bacterial growth (the “lawn”) was harvested.
• qPCR assays to determine generic Nm sodC, B, C, W, X and Y genogroups were performed.
• sodC results were compared with direct and culture samples.

RESULTS

• Lawn culture yielded 277 Nm sodC positives, direct OPS 153, and culture 133.
• Overall Nm carriage rate was 17.7% by any three methods. There were 320 total positives, with single positives of 1, 42, and 121 for culture, direct and lawn culture respectively (Figure 1).
• Nm genogrouping detection rates by lawn culture qPCR were: nongenogroupable 9.3%, B 3.3%, C 0.2%, W 0.6%, X 0.3% and Y 1.7% (Figure 2).
• 5 samples showed multiple genogrouping (Table 1).
• Density by lawn culture varied across 3-4 orders of magnitude and 20 orders of magnitude (Figure 3).

CONCLUSIONS

• Nm lawn culture detection has increased sensitivity in comparison to direct and culture.
• Lawn culture allows multiple genogrouping detection in one sample.
• Given that lawn culture is cost effective and quicker, it should be considered the preferred approach for epidemiological studies.
Direct multiplexed digital detection of Neisseria meningitidis gene transcripts from culture and in vivo pharyngeal samples

Yenesh K Tekletsion¹, Hannah Christensen¹, Adam Finn¹

School of Cellular and Molecular Medicine, University of Bristol², Population Health Sciences (Bristol Medical School)²

Background

Pharyngeal carriage of Neisseria meningitidis (Nm) in healthy young adults varies in density. Detection of Nm transcripts from in vivo mucosal samples, as for all bacteria at relatively low densities in such complex samples, is especially challenging. In this study we evaluated gene expression for a panel of 47 genes, including genes encoding for Nm serogroup B vaccine proteins, from Nm cultures using the NanoString nCounter system. Gene expression was also assessed from selected pharyngeal swab samples with high density of Nm carriage.

Methods

• Nm ATCC BAA-335 strains were grown on Colombia blood agar at 37°C for 16 hours in 5% CO₂ suspended in PBS-B and inoculated into 10ml brain heart infusion broth (1:100 dilution). The bacterial suspension was collected at mid-log phase (OD600nm=0.5). Isolates were exposed for 3 hours to different temperatures (26°C, 37°C, 40°C).
• Pharyngeal swab samples were collected from healthy individuals. Nm density was measured by qPCR.
• RNA was extracted using RNeasy mini kit (Qiagen).
• NanoString assays were performed for Nm culture samples containing 1-100ng total RNA to assess technical reproducibility and detection limit, and 100ng RNA samples to measure fold change in gene expression. In a pilot study, gene expression was measured in swab samples with high density Nm carriage.

Probe design and NanoString assay

• 100 base non-redundant sequence probe pairs (the codeset) were custom designed for 47 genes.
• After overnight hybridisation of the target sequence with the codeset at 65°C, the mixture was purified, detected and genes counted using the digital analysers.
• Image quality control was checked using nSolver software. Data were analysed using Stata 14 software.

Results

• Nm mRNA was detectable from very low quantities of RNA (1ng/ul total RNA).
• The technic was highly reproducible (R²=0.99) (Fig 1).
• Variation in gene expression, including vaccine genes, was successfully shown for samples grown at different temperatures (Fig 2).
• In a pilot study, Nm gene expression was detected from pharyngeal samples (Fig 3).

Conclusion

• These are the first data on meningococcal transcriptomics obtained using the NanoString nCounter technology for gene analysis.
• They demonstrate the feasibility of accurate gene expression profiling using this platform.
• Initial experiments show the potential of this method to measure Nm gene expression from pharyngeal carriage samples and improve understanding of the role of vaccine protein antigens in carriage and transmission.

Acknowledgment

The research was supported by the NIHR Health Protection Research Unit in Evaluation of Interventions at University of Bristol. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the Department of Health or Public Health England.