The epidemiology of bacterial and fungal meningitis among adults in Gauteng province, 2009-2013

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Introduction

• Meningitis is a major cause of mortality and morbidity in sub-Saharan Africa
• Despite increasing access to antiretroviral treatment (ART) in sub-Saharan Africa, HIV-infected persons have increased mortality due to meningitis

“Overall, meningitis patients living with HIV had 2-10 times higher mortality rates than meningitis patients who were HIV negative.” (Veltman, 2014)
• Common organisms:
  – *Cryptococcus neoformans*
  – *Streptococcus pneumoniae*
  – *Neisseria meningitidis*
  – *Mycobacterium tuberculosis* complex

• A change in the aetiologies of meningitis among adults with HIV and TB infection from mostly bacterial meningitis to cryptococcal meningitis (CM) and tuberculous meningitis (TBM)

• CM causes an estimated 135,300 deaths (95%CI: 91,810 to 188,830) in sub-Saharan Africa annually (Rajasingham et al. CROI 2016 *submitted abstract*)
Meningitis is potentially preventable

• Several interventions introduced in SA since 2004
  – Expanded ART
    • From 2009 to 2012, number of people on ART almost doubled
  – Enhanced TB control
    • Improved diagnostics e.g. GeneXpert, intensified case finding, INH prophylaxis since 2011
  – Pneumococcal conjugate vaccines
    • PCV-7 and PCV-13 included in the EPI in 2009 and 2011
  – Cryptococcal disease screening and treatment
    • Started in Gauteng and WC provinces in late 2012
    • Included in national HIV guidelines in 2014
Study rationale

• Focus resources for prevention, early diagnosis and treatment, especially in a population with a high HIV prevalence

• Diagnostic decision-making
  – WHO still recommends third-generation cephalosporin for empiric treatment of meningitis
  – Diagnostic algorithms in sub-Saharan Africa should include point-of-care CSF or blood CrAg testing and measuring of CSF opening pressure
Objectives

1. To describe the aetiologies of laboratory-confirmed fungal and bacterial meningitis and frequencies among adults in Gauteng province, 2009-2012

2. To compare the trends in incidence and proportions of lab-confirmed cryptococcal, pneumococcal and TB meningitis
Methods

Study design

• Analysis of secondary laboratory data from NHLS Corporate Data Warehouse (CDW)

Study population

• Adults ≥ 18 years
• Gauteng province, public healthcare facilities
• CSF specimens submitted to NHLS labs
Data sources

• Data extracted on all CSF specimens submitted to public-sector laboratories in Gauteng, 2009 – 2012

• Additional separately-extracted data on TBM from the CDW were combined with a master dataset
  – 88% of these records matched by record-linking (using combinations of patient name, laboratory number and/or date of birth)
  – Non-linked records were included in the analysis
Definitions

Categorised cases into 4 groups:

1) **CM**: positive India-ink test, a positive CrAg test or a positive culture of *Cryptococcus* spp. on CSF
2) **PM**: *S. pneumoniae* cultured from CSF
3) **TBM**: *M. tuberculosis* complex observed on CSF microscopy (acid-fast bacilli) or CSF culture of *M. tuberculosis* or a positive TB-PCR (or Xpert MTB/Rif Assay) on CSF
4) Other bacterial meningitis (**OBM**): bacteria other than *S. pneumoniae*, assessed as potentially pathogenic by the study authors, cultured from CSF (latex antigen tests and bacterial PCR were not included)

Mixed infection was diagnosed when a combination of any of the 4 categories of meningitis was present
Statistical analysis

- Proportions = no of cases per aetiology/ total no of lab-confirmed cases
- Population incidence = total no of new cases/ Stats-SA mid-year population estimates
- Incidence in HIV-positive population: ASSA2008 model used for denominators
- Estimated HIV-specific incidences by applying HIV prevalence estimates, by meningitis category from GERMS-SA surveillance data, to cases of meningitis
  - CM ~99%
  - PM ~91%
  - TBM ~65% (WHO global TB report 2013)
- ASSA2008 model also used as the source of ART data
- Poisson regression used to determine if incidence trends were significant
- STATA (version 13)
Results

1. Aetiologies

- 11,891 incident cases of meningitis over 4-years
- 110,885 CSF specimens tested
2. Characteristics of study population

For incident cases of meningitis (n=11,891):

• Median age all aetiologies
  – 37 years (IQR: 30-46)

• CM predominantly male (53%) vs. other aetiologies female predominance (46.8% combined TBM, PM and OBM) (p<0.001)

• Males >35 years had the highest incidence of CM
<table>
<thead>
<tr>
<th>Organism</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cryptococcus neoformans</strong></td>
<td>2010 (59.1)</td>
<td>1961 (62.7)</td>
<td>1776 (63.2)</td>
<td>1659 (65.0)</td>
<td>7406 (62.3)</td>
</tr>
<tr>
<td><strong>Mycobacterium tuberculosis complex</strong></td>
<td>935 (27.5)</td>
<td>718 (23.0)</td>
<td>666 (23.7)</td>
<td>609 (23.9)</td>
<td>2928 (24.6)</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td>344 (10.1)</td>
<td>341 (10.9)</td>
<td>294 (10.5)</td>
<td>218 (8.5)</td>
<td>1197 (10.1)</td>
</tr>
<tr>
<td><strong>Neisseria meningitidis</strong></td>
<td>32 (0.9)</td>
<td>35 (1.1)</td>
<td>18 (0.6)</td>
<td>8 (0.3)</td>
<td>93 (0.8)</td>
</tr>
<tr>
<td><strong>Escherichia coli</strong></td>
<td>18 (0.5)</td>
<td>23 (0.7)</td>
<td>12 (0.4)</td>
<td>19 (0.7)</td>
<td>72 (0.6)</td>
</tr>
<tr>
<td><strong>Haemophilus influenzae</strong></td>
<td>8 (0.2)</td>
<td>4 (0.1)</td>
<td>3 (0.1)</td>
<td>5 (0.2)</td>
<td>20 (0.2)</td>
</tr>
<tr>
<td><strong>Listeria monocytogenes</strong></td>
<td>5 (0.2)</td>
<td>4 (0.1)</td>
<td>3 (0.1)</td>
<td>4 (0.2)</td>
<td>16 (0.1)</td>
</tr>
<tr>
<td><strong>Salmonella non typhi</strong></td>
<td>5 (0.2)</td>
<td>6 (0.2)</td>
<td>0 (0)</td>
<td>4 (0.2)</td>
<td>15 (0.1)</td>
</tr>
<tr>
<td><strong>Group-B Streptococcus</strong></td>
<td>6 (0.2)</td>
<td>4 (0.1)</td>
<td>5 (0.2)</td>
<td>2 (0.1)</td>
<td>17 (0.1)</td>
</tr>
<tr>
<td><strong>Streptococcus pyogenes</strong></td>
<td>3 (0.1)</td>
<td>3 (0.1)</td>
<td>3 (0.1)</td>
<td>0 (0)</td>
<td>9 (0.1)</td>
</tr>
<tr>
<td><strong>Other Streptococci</strong></td>
<td>1 (0.03)</td>
<td>1 (0.03)</td>
<td>3 (0.1)</td>
<td>1 (0.04)</td>
<td>6 (0.1)</td>
</tr>
<tr>
<td><strong>Mixed infections</strong></td>
<td>33 (1.0)</td>
<td>29 (0.9)</td>
<td>26 (0.9)</td>
<td>24 (0.9)</td>
<td>112 (0.9)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>3400</td>
<td>3129</td>
<td>2809</td>
<td>2553</td>
<td>11891</td>
</tr>
</tbody>
</table>
Overall proportions (2009-2012)
3. Incidence of meningitis among adults

• Significant reductions in incidence of the three major causes of meningitis over 4-year period

  – CM ↓ by 23.4% (from 24.4 cases per 100,000 persons in 2009 to 18.7/100,000 in 2012; p<0.001)
  – TBM ↓ by 39.6% (11.3/100,000 in 2009 to 6.8/100,000 in 2012; p<0.001)
  – PM ↓ by 41.2% (4.2/100,000 in 2009 to 2.5/100,000 in 2012; p<0.001)

• Similar reductions among HIV-positive persons
Population incidence of cryptococcal, tuberculous and pneumococcal meningitis among adults in Gauteng province, showing key treatment interventions, 2009-2012 (n=11,531)
Discussion and recommendations

- **CM** leading cause of meningitis among adults
  - Findings in keeping with previous studies in Cape Town, Uganda & GERMS-SA surveillance (Jarvis, 2010; Rajasingham, 2014)

- **ART programme expansion** likely contributed to overall decline in meningitis

- Large decline in PM likely due to **PCV vaccination**
  - Vaccine effectiveness among children and herd immunity among adults previously demonstrated (von Gottberg, 2015)

- **Recommend**
  - Screening for cryptococcal disease using CrAg
  - Improved TBM diagnostics
  - HIV diagnosis and early ART, with a special focus on older men
Limitations

• Ecologic nature of study limits causal inferences
• Only laboratory-confirmed meningitis - underestimate true disease burden
• Use of secondary data – selection bias (cases excluded due to missing age/DOB [~5%])
• Patient-level data on HIV status not available, population-data used to estimate incidences among HIV-positive persons
Conclusions

• This study confirms that CM was the most common cause of laboratory-confirmed meningitis among adults in Gauteng.

• The decrease in incidence of all three major causes of meningitis coincides with a period of ART programme expansion, enhanced tuberculosis control and conjugate pneumococcal vaccination.
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