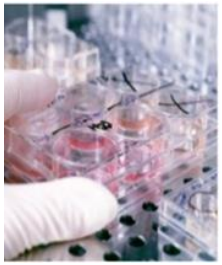
NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service



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


Erika Britz

South African Field Epidemiology Training Programme (SA FETP) resident
Centre for Opportunistic Tropical and Hospital Infections
National Institute for Communicable Diseases

Co-authors: O. Perovic, C. von Mollendorf, A. von Gottberg, S. Iyaloo, V. Quan, V. Chetty, C. Sriruttan, N. Ismail, A. Nanoo, A. Musekiwa, C. Reddy, K. Viljoen, C. Cohen and N.P. Govender


SAFETP FIELD EPIDEMIOLOGY TRAINING PROGRAMME

PEPFAR

DEPARTMENT OF HEALTH & HUMAN SERVICES USA

CDC CENTERS FOR DISEASE CONTROL AND PREVENTION

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA
Faculty of Health Sciences

# 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

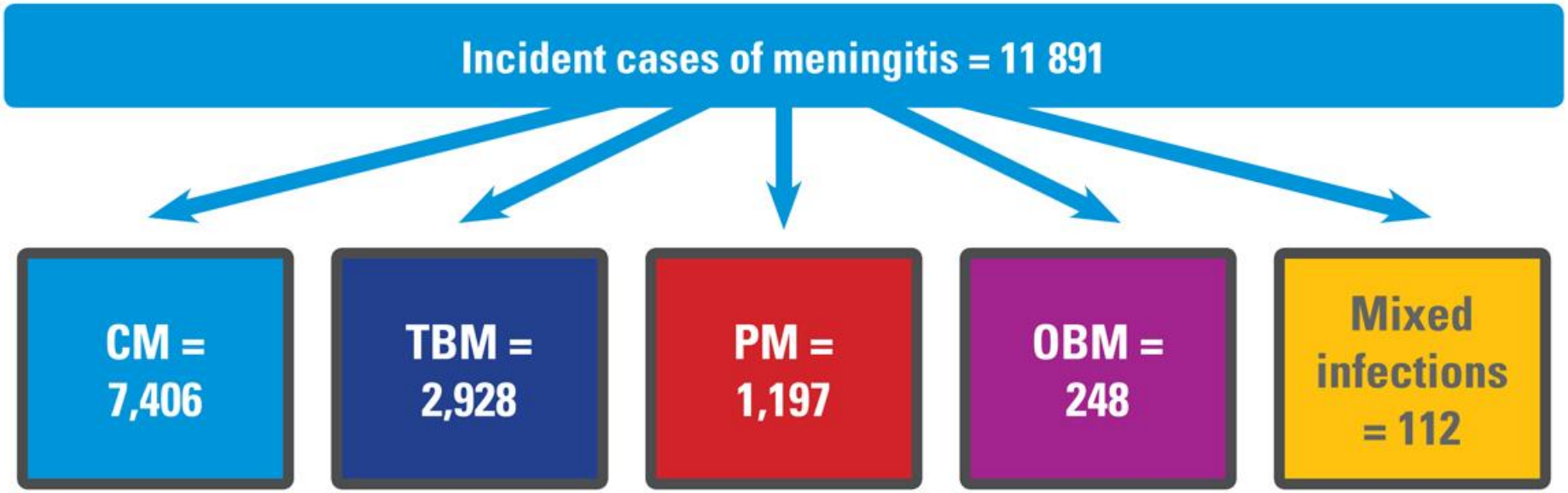
# Statistical analysis

- 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)

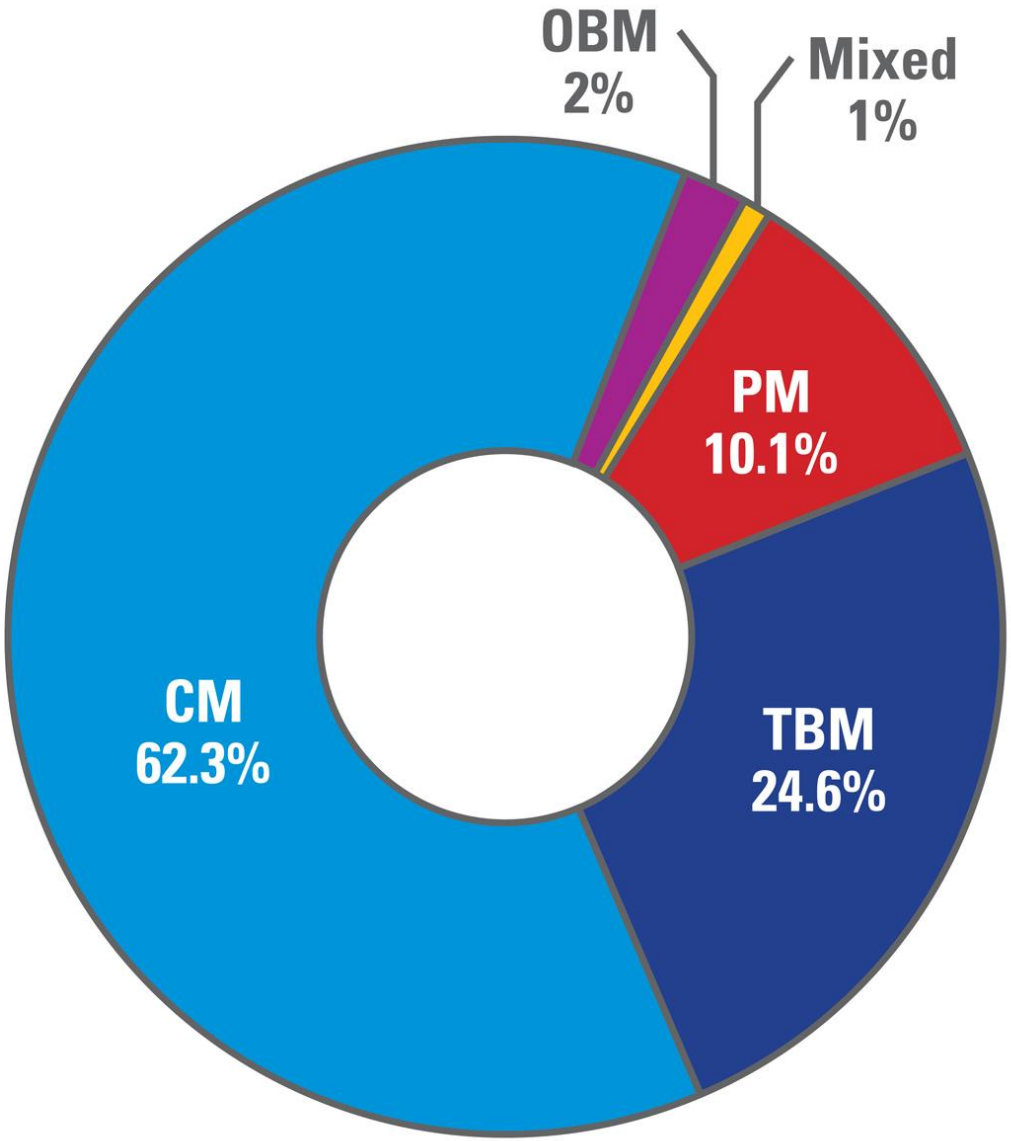
- CM predominantly male (53%) vs. other aetiologies female predominance (46.8% combined TBM, PM and OBM) ($p<0.001$)

- Males >35 years had the highest incidence of CM

**Table 1. Number and proportions of major pathogenic organisms isolated from all CSF specimens tested, as recorded in the NHLS CDW, per year - 2009 through 2012. (n=11,891)**

| | 2009 | 2010 | 2011 | 2012 | Total |
|---|---|---|---|---|---|
| **Organism** | n (%) | n (%) | n (%) | n (%) | |
| ***Cryptococcus neoformans*** | 2010 (59.1) | 1961 (62.7) | 1776 (63.2) | 1659 (65.0) | **7406 (62.3)** |
| ***Mycobacterium tuberculosis* complex** | 935 (27.5) | 718 (23.0) | 666 (23.7) | 609 (23.9) | **2928 (24.6)** |
| ***Streptococcus pneumoniae*** | 344 (10.1) | 341 (10.9) | 294 (10.5) | 218 (8.5) | **1197 (10.1)** |
| ***Neisseria meningitidis*** | 32 (0.9) | 35 (1.1) | 18 (0.6) | 8 (0.3) | **93 (0.8)** |
| ***Escherichia coli*** | 18 (0.5) | 23 (0.7) | 12 (0.4) | 19 (0.7) | **72 (0.6)** |
| ***Haemophilus influenzae*** | 8 (0.2) | 4 (0.1) | 3 (0.1) | 5 (0.2) | **20 (0.2)** |
| ***Listeria monocytogenes*** | 5 (0.2) | 4 (0.1) | 3 (0.1) | 4 (0.2) | **16 (0.1)** |
| ***Salmonella non typhi*** | 5 (0.2) | 6 (0.2) | 0 (0) | 4(0.2) | **15 (0.1)** |
| **Group-B *Streptococcus*** | 6 (0.2) | 4 (0.1) | 5 (0.2) | 2 (0.1) | **17 (0.1)** |
| ***Streptococcus pyogenes*** | 3 (0.1) | 3 (0.1) | 3 (0.1) | 0 (0) | **9 (0.1)** |
| **Other *Streptococci*** | 1 (0.03) | 1 (0.03) | 3 (0.1) | 1 (0.04) | **6 (0.1)** |
| **Mixed infections** | 33 (1.0) | 29 (0.9) | 26 (0.9) | 24 (0.9) | **112 (0.9)** |
| **Total** | **3400** | **3129** | **2809** | **2553** | **11891** |

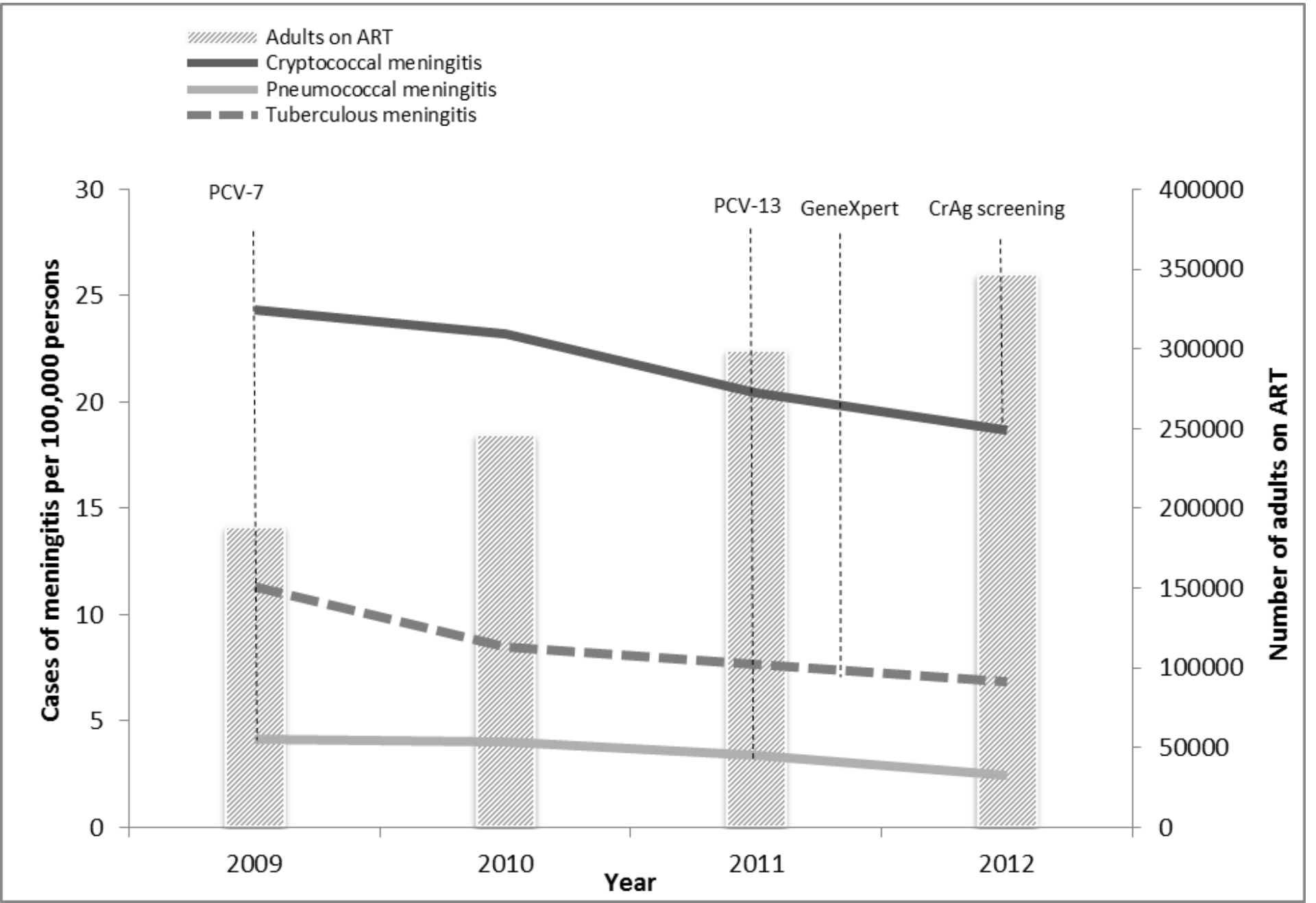
# Overall proportions (2009-2012)



# 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 - under-estimate 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

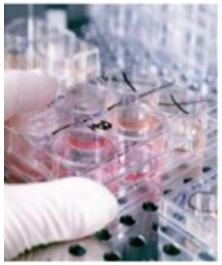
- This study confirms that CM was the most common cause of laboratory-confirmed meningitis among adults in Gauteng

- 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

# Acknowledgements


- Centre for Opportunistic, Tropical and Hospital Infections, National Institute for Communicable Diseases (NICD)
- South African Field Epidemiology Training Programme (SA-FETP)
  - Dorothy L. Southern
- University of Pretoria, School of Health Systems and Public Health
- US Centers for Disease Control and Prevention
- National Health Laboratory Service (NHLS)
  - Sue Candy and Thomas Papo from the NHLS Corporate Data Warehouse
  - Heleen Vrede at Groote Schuur Hospital NHLS
  - Staff at Charlotte Maxeke Johannesburg Academic Hospital and Helen Joseph Hospital NHLS

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service



# THANK YOU

SAFETP
FIELD EPIDEMIOLOGY TRAINING PROGRAMME

SOUTH AFRICANS AND AMERICANS IN PARTNERSHIP TO FIGHT HIV/AIDS
PEPFAR

DEPARTMENT OF HEALTH & HUMAN SERVICES-USA

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA
Faculty of Health Sciences