

Meningitis – what's new?



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Conflicts of interests

- CB has been an investigator on investigator-initiated pneumonia research projects funded by Pfizer
- CB is co-chair of the Australian Technical Advisory Group of Immunisation, Australia's peak scientific advisory committee to the Australian Government.

All opinions expressed in this talk are his own opinions, not those of ATAGI.



Summary

- Aetiology
- Risk factors
- Signs and Symptoms
- Investigations
- Treatment
- Outcomes
- What's new
- Conclusions

Meningitis

- Bacterial meningitis
- Viral meningitis
- Fungal meningitis
- Parasitic meningitis
- Non-infective meningitis
 - Inflammatory
 - Chemical
 - Malignant

Meningitis

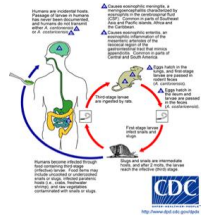
- Atypical bacterial meningitis
 - Mycobacteria tuberculosis
 - Leptospira
 - Treponema
 - Borellia
 - Nocardia
 - Bartonella
 - Brucella

Meningitis

- Fungal meningitis
 - Candida – especially neonates
 - Cryptococcus:
 - *neoformans* – especially HIV and SOT recipients
 - *gattii* – immunocompetent, rare in children
 - Histoplasmosis

Meningitis

- Parasitic meningitis
 - Toxoplasma
 - *Angiostrongylus cartonsensis*
- Non-infective
 - SLE
 - Behcets
 - Kawasaki disease
 - Sarcoidosis
 - Drugs and toxins including IVIg



Bacterial meningitis

- Presentation varies with age: pathogens

< 3 months	3 mo – 3 years	>3 years
<i>S. agalactiae</i>	<i>S. pneumoniae</i>	<i>S. pneumoniae</i>
<i>E. coli</i>	<i>N. meningitidis</i>	<i>N. meningitidis</i>
<i>Listeria monocytogenes</i>	<i>H. influenzae</i> (Hib)	<i>H. Influenzae</i>
<i>S pneumoniae</i>		<i>Listeria monocytogenes</i> (>50 years or immunocompromised)
<i>N. meningitidis</i>		
<i>H. influenzae</i> (Hib)		

Viral meningitis

- Presentation varies with age: pathogens

< 3 months	3 mo – 3 years	>3 years
<i>Herpes simplex</i>	<i>Enteroviruses</i>	<i>Enteroviruses</i>
<i>Enteroviruses</i>	<i>Influenza</i>	<i>Influenza</i>
<i>Parechoviruses</i>	<i>Measles</i>	<i>Measles</i>
<i>Others</i>	<i>Mumps</i>	<i>Mumps</i>
	<i>EBV</i>	<i>EBV</i>
	<i>Others</i>	<i>Others</i>

Risk factors for bacterial meningitis

- Young age
- Male gender
- Malnutrition or chronic illness
- Trauma or surgery
 - Head trauma
 - Neurosurgery / Shunt placement
 - Cochlear implant
- Anatomical defects

Risk factors for bacterial meningitis

- Tobacco exposure (NM)
- Contact with
 - Colonised individual (NM, SP, Hib)
 - Specific animals (*Salmonella* spp)
 - High risk foods (*Listeria* spp)
- Congenital or acquired immunosuppression
 - Complement deficiency (NM)
 - Asplenia (SP, NM and HiB)
 - HIV and chemotherapy (SP)

Risk factors for viral meningitis

- Young age
- Perinatal exposures
 - Maternal HSV disease
 - Older siblings
- Congenital or acquired immunosuppression

Clinical presentation

- Presentation varies with age: symptoms

< 3 months	3 mo – 3 years	>3 years
Poor feeding	Poor feeding	Headache
Vomiting	Vomiting	Vomiting
Irritability / high pitched cry	Irritability / high pitched cry	Photophobia
Drowsiness	Drowsiness	Delirium
Fever (maybe)	Fever	Fever
	Headache (rarely)	Neck stiffness

Clinical presentation

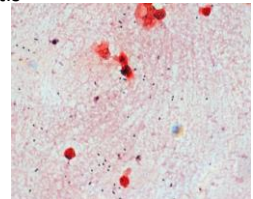
- Presentation varies with age: signs

< 3 months	3 mo – 3 years	>3 years
Fever (maybe)	Fever	Fever
Irritability	Irritability	Irritability
Drowsiness / Coma	Head holding	Drowsiness / Coma
Bulging fontanelle (late)	Drowsiness / Coma	Nuchal rigidity
Widening of sutures (late)	Nuchal rigidity	Kernig's and Brudzinski's sign
	Bulging fontanelle (late)	Photophobia

Investigation

- Examination of CSF remains the gold standard for diagnosis of meningitis

- Microscopy
- Gram stain
- Bacterial Culture
- Biochemistry
- Bacterial and viral nucleic acid detection



- CT or other imaging is not routinely required

Investigation

- Blood cultures should be performed in those suspected of having bacterial meningitis
- Other investigations are useful to explore other potential aetiologies:
 - Throat, rectal samples for enteroviruses
 - Upper respiratory samples for respiratory viruses
 - Skin, conjunctival, umbilical swabs for HSV (infants)
- Inability to perform investigations should not delay antibiotics therapy

Empiric treatment

- Australian Therapeutic Guidelines:
 - Empiric: 3rd Generation Cephalosporin
 - Add Vancomycin if gram positive cocci seen, known or suspected OM/sinusitis or recent beta-lactam treatment
 - Benzylpenicillin added in the very young and immunosuppressed
 - Modified in post surgical or post-traumatic meningitis

Targeted treatment

- Therapeutic Guidelines:
 - N. meningitidis*: penicillin or 3rdGC for 3-5 days
 - S. pneumoniae*: penicillin, cephalosporin or vancomycin depending on pneumococcal penicillin MIC for 10-14 days
 - H. influenzae*: cephalosporin for 7 days
 - Group B streptococcus: penicillin for 14-21 days
 - Gram negative meningitis: 3rdGC or carbapenem for 21 days

Corticosteroids

- Children
 - High quality evidence of reduction in hearing loss in Hib meningitis (in LMIC settings)
 - No evidence of impact on mortality and short-term neurological sequelae
 - Little evidence for dexamethasone in other bacteria
- Adults:
 - Evidence from randomised controlled trials of a reduction in short term neurological outcomes and mortality

Corticosteroids

- Recommended in all >3 months with suspected or confirmed bacterial meningitis
 - Dexamethasone 0.15mg/kg four times /day for 4d
 - Give early, preferably within 4 hours of antibiotics

Outcome

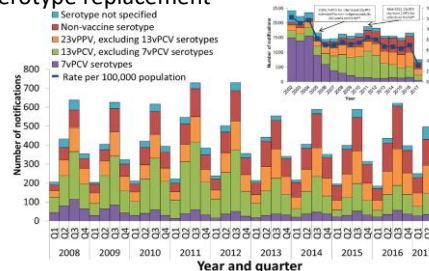
- Complications
 - Death: 2-5%
 - Intellectual disability, spasticity, seizures, hydrocephalus, deafness: 10-15%
 - Learning and behavioural disorders: 25-45%
 - Survivors have IQ approx. 5 points lower than controls
5.5 IQ points (95% CI: -7.19, -3.80, p = 0.02; Christie 2017 Plos One)
- Follow up should include audiology and developmental assessment

What's new:

- Streptococcus pneumoniae*
- Neisseria meningitides*
- Parechovirus
- Influenza

What's new: Pneumococcus

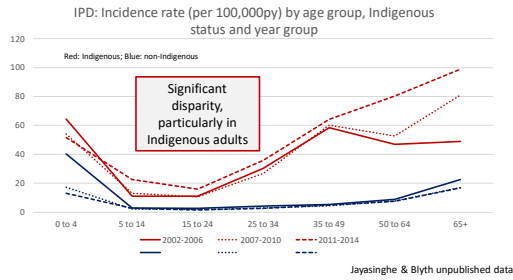
- Serotype replacement



<http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-survei-nndss-ipd-reports.htm>

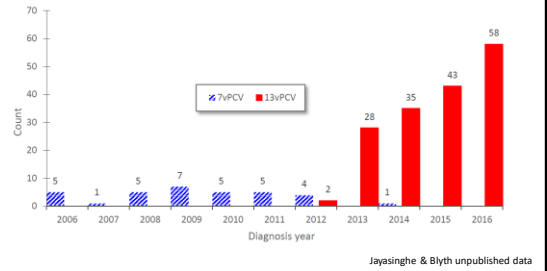
What's new: Pneumococcus

Ongoing disease in Aboriginal populations



What's new: Pneumococcus

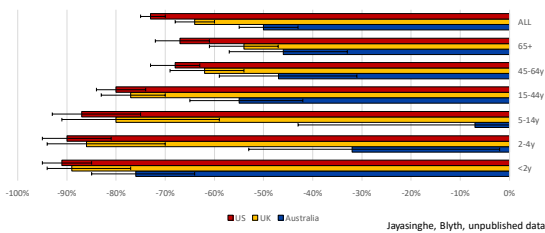
Increasing numbers of infant vaccine failures



What's new: Pneumococcus

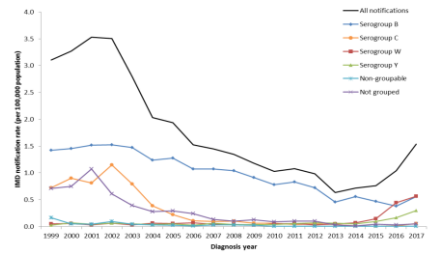
Lower than expected reductions in adult disease

Incidence rate reduction in 13valent (non 7 valent) serotype IPD by country and age group



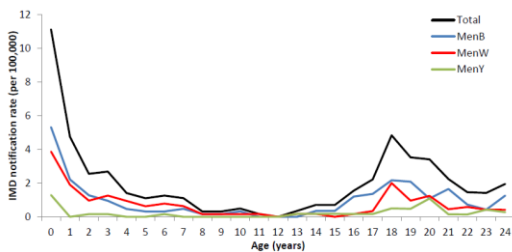
What's new: Meningococcus

Emerging serotypes



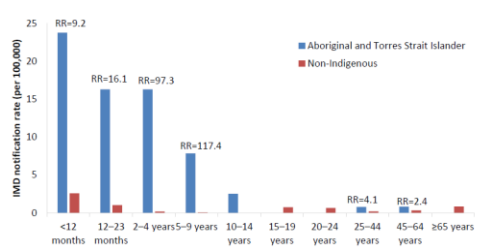
What's new: Meningococcus

Populations at risk

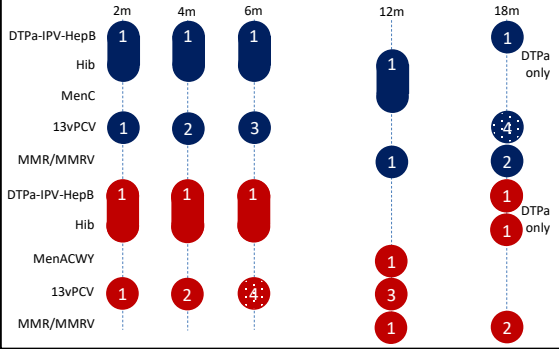


What's new: Meningococcus

Populations at risk

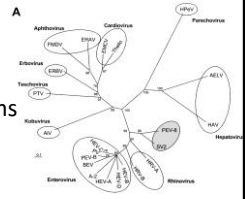


What's new: infant vaccine schedule



What's new: Parechovirus

- Recently described genus within the of the picornavirus family:
- Biennial epidemics have occurred in Australia since 2013
- Most HPeV infections are asymptomatic or present with mild flu-like symptoms or gastroenteritis



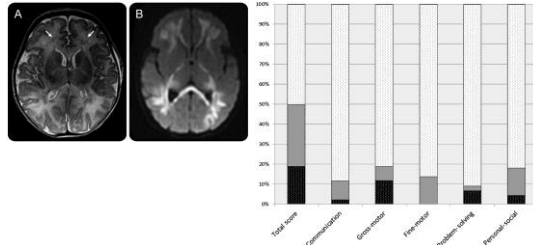
What's new: Parechovirus

- Red, hot and cranky
- Severe disease: meningoencephalitis, seizures or sepsis-like presentations
- Diagnosis: viral detection in CSF, blood, throat and stool
- No treatment: supportive only



What's new: Parechovirus

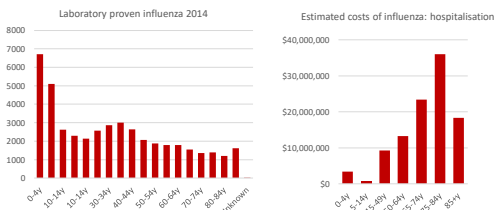
- Poor outcomes variably reported



Belcastro, Neurology 2014; Britton P et al JPMH 2018

What's new: Influenza

- Most common vaccine preventable disease
- Impact is greatest in the extremes of age



What's new: Influenza

- Increasingly recognised as a cause of severe meningoencephalitis
- 7.6% of paediatric flu hospitalisations



- >50% with significant ongoing morbidity

Britton & Blyth, CID 2017

What's new: Influenza

- Influenza vaccination is recommended for all 6 months and older:
- Influenza vaccine is funded under the NIP for:
 - ATSI children and adults
 - All adults aged ≥65 years
 - All persons aged ≥6 months with certain medical conditions which increase the risk of disease
 - Pregnant women (during any stage of pregnancy).
- Flu vaccine is funded by the state for young children
- Fluzone and Flud preferred for the elderly

Summary

- Suspected meningitis remains a medical emergency in all age groups
- Morbidity and mortality with bacterial meningitis remains significant
- Early recognition and prompt referral is critical
- Conjugate bacterial vaccines have had a significant impact on disease yet serotype/strain replacement has meant that the vaccine schedule needs regular revision

Summary

- Changes to the infant national immunisation program are expected to strengthen pneumococcal and meningococcal prevention strategies
- Influenza prevention strategies need to be strengthened (including in children)
- Not all viral meningitis is benign
- Any person with meningitis (bacterial and viral) requires post-discharge follow up