DEFEATING MENINGITIS BY 2030:

baseline situation analysis

20 February 2019

The 2010 MenAfriVac® vaccine launch in Burkina Faso PATH/Gabe Bienczycki

Contents

1. Overview

1.1 Purpose

The baseline situation analysis (BSA) is intended to inform the development of the global roadmap Defeating meningitis by 2030 and to provide a sound basis to inform its key priorities.

1.2 Scope

Meningitis, a devastating disease with many deaths and significant long-term sequelae in survivors, remains a major global public-health challenge *(1)*. Cases and outbreaks are a threat in all countries of the world. The illness, an inflammation of the membranes that surround the brain and spinal cord, is predominantly caused by infection with bacteria and viruses. Infection with fungi and parasites can also cause meningitis, with cryptococcal meningitis having an increasing importance among adults living with HIV *(2)*. Meningitis can also develop as a result of non-infectious factors, including certain medications, cancer and autoimmune diseases.

Bacterial infection is a major cause of meningitis, carrying a high case fatality and substantial after-effects *(3,4*). The roadmap focuses on the main infectious pathogens responsible for acute bacterial meningitis (as shown in Table 1 below), for which vaccines are either available, or likely to become available, in the next few years, namely, *Neisseria meningitidis (*Nm, the meningococcus*), Streptococcus pneumoniae (*Spn, the pneumococcus*), Haemophilus influenzae* (Hi) and *Streptococcus agalactiae (*group B streptococcus (GBS)). Other bacteria, such as non-typhoidal salmonella, *Listeria monocytogenes*, *Streptococcus suis* and, in health-care settings, pathogens such as *Staphylococcus aureus* or *S*. *epidermidis* also cause meningitis, even if less frequently. The scope of pathogens to be specifically addressed by the roadmap was defined by the Technical Taskforce on defeating meningitis by 2030, based on the worldwide burden of the resulting disease, as well as on the impact that this global strategy could have to diminish the burden by 2030. In this sense, other important causes of meningitis, such as tuberculosis (TB) or cryptococcus, are not a focus of this roadmap, as they are already included in other preventive strategies. However, it should be highlighted that several goals directed at reducing the burden of disease are equally applicable to other causes of meningitis, particularly in support, after-care, advocacy and information. The meningitis roadmap will thus reinforce and complement these other existing global prevention and control strategies, such as the End TB Strategy *(5)*, the global health sector strategy on HIV *(6)*, the integrated Global Action Plan for Pneumonia and Diarrhoea *(7)* and the Global Action Plan on Antimicrobial Resistance *(8)*.

1.3 Content

- Summary of global and regional burden of meningitis.
- Main elements of current public-health policies and practice, as well as research and development (R&D) landscape for meningitis and its sequelae, covering prevention and epidemic control, diagnosis and treatment, surveillance, support and after-care, advocacy and information.
- Barriers to implementation of public-health policies or to R&D.
- Main gaps in policy implementation, knowledge and R&D, in terms of where we are and where we want to be (where we want to be may well be a desired situation beyond current recommended practice).

2. Global and regional burden of meningitis

2.1. Epidemiology

The Global Burden of Disease (GBD) Study 2016 estimated that the number of global meningitis cases increased from 2.50 million (95% UI 2.19–2.91) in 1990 to 2.82 million (2.46–3.31) in 2016 *(1)*. While global meningitis deaths decreased by 21.0% from 1990 to 2016, the overall burden of meningitis remains high. Progress in reducing mortality and morbidity from this group of infections has substantially lagged behind that for other vaccine-preventable diseases (VPDs) such as measles, tetanus and diarrhoeal disease.

Table 1. Characteristics of main four pathogens covered by the roadmap *(4,9–13)*

Pathogen	*Neisseria meningitidis* (Nm)	*Streptococcus pneumoniae* (Spn)	*Haemophilus influenzae* (Hi)	*Streptococcus agalactiae* (group B streptococcus, GBS)
Classification	12 serogroups: A, B, C, W, X, Y cause most Nm meningitis	At least 97 serotypes: predominant disease-causing serotypes vary by region	6 serotypes: type b causes most Hi meningitis (Hib), with occasional cases from type a	10 serotypes: Ia, Ib, II, III, IV, V cause most disease
Main carriage site	Human pharynx	Human pharynx	Human pharynx	Human gastrointestinal and genitourinary tract
Main transmission	Person-to-person via respiratory droplets	Person-to-person via respiratory droplets	Person-to-person via respiratory droplets	From mother to child around birth. Person-to-person contact, or nosocomial
Main clinical disease	Meningitis, sepsis	Pneumonia, sepsis, meningitis	Meningitis, pneumonia, sepsis, epiglottitis	Sepsis, pneumonia, meningitis
Main age groups affected by meningitis	Young children, adolescents, adults (especially in African meningitis belt)	Young children, adults especially HIV-infected and the elderly	Children <5 years	Babies <3 months including stillbirths, immunocompromised adults, the elderly
Case-fatality ratio estimates*	5–20%	20–90% (children 1–59 months)	7–30% (children 1–59 months)	5–20% (babies 0–89 days)
Epidemic potential	High	Moderate	Low	Very low

* Substantial variations in case fatality exist by country depending on access to and quality of care

<u>Nm meningitis</u>

Incidence of meningococcal meningitis and septicaemia characteristically peaks in infants and teenagers. Nm is transmitted from person-to-person through droplets of respiratory or throat secretions from carriers. Smoking, close and prolonged contact including kissing or coughing, or living in close quarters, facilitate the spread of disease. Clusters and outbreaks of meningococcal meningitis occur in all parts of the world, most

significantly in the so-called meningitis belt, an area of sub-Saharan Africa with a population of > 400 million extending from Senegal to Ethiopia *(14)*.

The meningitis belt is characterized by seasonal epidemics during the dry season from December to June (annual incidence rates are often 10–100 cases per 100 000 population) and explosive epidemics occur in 8–12-year cycles when incidence rates can exceed 1000 cases per 100 000 population. The risk of epidemics is linked to climate (low absolute humidity, dust, high temperatures); indeed, climate change may be increasing the geographical range of the countries at risk *(15)*. Historically, epidemics in the meningitis belt were mainly due to serogroup A meningococci. Since the introduction of a serogroup A conjugate vaccine in 2010, epidemics due to this serogroup have disappeared, although those due to other meningococcal serogroups continue *(16)*.

Incidence of Nm meningitis in other regions is variable over time and by serogroup *(17)*. Several countries outside the belt have had periods with incidence rates above 4/100 000 persisting for several years, but most normally record rates of 2/100 000 or less *(18,19).* The lowest rates are recorded in Asia *(20)*.

Risk factors include household crowding, active smoking, exposure to smoke and close contact with a case, or immune deficiencies, such as HIV infection, asplenia or complement deficiency *(21,22).* Epidemics linked to attendance at the Hajj are well recognised. Influenza and respiratory syncytial virus (RSV) infection may predispose to invasive meningococcal disease *(23,24)* and a high incidence of upper respiratory tract infections have been linked with epidemics in the meningitis belt *(25)*.

Spn meningitis

Although the burden of Spn meningitis in children <5 years is falling in countries that have introduced pneumococcal conjugate vaccines (PCVs) (12), half of the global infant population is not yet covered by PCV vaccination. Also, while there have been reductions in the overall burden of pneumococcal disease, with falling incidence of vaccine-type disease, an increase in disease due to non-vaccine types has been observed *(26)*. In 2015, Spn meningitis incidence in 1–59 month children was estimated as 13/100 000 globally, highest in Africa (21/100 000) (12), with the highest burden in the meningitis belt seen in young children before the introduction of PCVs *(27).* Outbreaks affecting older children and adults occur in this region, even after introduction of PCVs, but less frequently than outbreaks of meningococcal meningitis *(28,29,30)*. Risk factors for Spn meningitis include HIV infection, immunosuppression, malignancy, asplenia, chronic disease, active or passive smoking, household crowding, day-care attendance *(21)* and preceding viral infection, such as influenza or RSV *(23)*.

Hi meningitis

The burden of Hi meningitis (often referred to as Hib since type b is the predominant disease-causing serotype) in children <5 years around the world is falling following introduction of Hib vaccines *(12)*. In the pre-vaccination era, Hib was the leading cause of bacterial meningitis in those under the age of five years. Hib incidence has decreased by nearly 50% from 1990–2016 *(1)* and is now the least common cause of bacterial meningitis. In 2015, incidence was estimated as highest in Asia and the Western Pacific (8 and 11/100 000 respectively) *(12)*, probably because some countries in these regions had not introduced Hib vaccination programmes. Risk factors for Hib meningitis include immune deficiencies such as HIV infection or immunosuppression, exposure to smoke, household crowding and day-care attendance, with outbreaks of Hib meningitis occurring in day-care centres before the era of conjugate vaccines *(21)*.

GBS meningitis

GBS is recognised as an important pathogen causing sepsis and meningitis in neonates *(31,32,33)*. According to recent estimates, in 2015, there were 319 000 infant cases of invasive GBS globally, with the highest burden

in Africa and Asia *(34)*. Maternal colonization by GBS is also a recognised cause of stillbirth and is the primary risk factor for GBS infection in neonates *(34,35,36)*. Although rates are highest in the newborn and peripartum periods, GBS is an important cause of meningitis and sepsis in older adults and immunosuppressed subjects *(37)*. Risk factors for GBS disease in babies include delivery at less than 37 weeks of gestation and premature rupture of membranes at any gestation.

2.2. Modelling the burden of meningitis

The following models provide estimates on the global burden of meningitis and/or neonatal sepsis to show the disease burden at both a global and regional level: 1) Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease (GBD) study; 2) World Health Organization (WHO) Global Health Estimates (GHE); 3) Maternal Child Epidemiology Estimation (MCEE) syndromic mortality estimates, at Johns Hopkins University (JHU) where disease-specific models have also been developed on Hib and pneumococcal disease (referred to here as MCEE for syndromic estimates and JHU models for disease estimates); 4) London School of Hygiene and Tropical Medicine (LSHTM) estimates of the burden of GBS disease. Estimates from the different models were used in this analysis and differences between the figures are presented. Estimates for the year 2015 (as published by IHME, MCEE and WHO in 2017, and JHU models from their 2018 paper) were used for current burden, as 2015 was the most recent year for which estimates were available from all models *(12,38,39,40)*.

The models used different methodologies to calculate the estimates. MCEE and JHU models restrict analysis to less than five years of age. WHO and IHME models provide age-specific estimates for 0–59 months and five years and older, but WHO draws on IHME analyses for the over five-year-olds when vital registration data for a particular country is unreliable (most high burden countries). IHME models are the only source for all cause meningitis disease incidence data. WHO uses IHME incidence/prevalence estimates to calculate the years lived with disability (YLD) component of the disability-adjusted life year (DALY). IHME and MCEE, but not WHO, include viral meningitis in all cause meningitis estimates and MCEE, but not WHO or IHME, include encephalitis in meningitis deaths. JHU models provide estimates by organism (Spn and Hib) and potentially soon for Nm; IHME provides estimates for Nm, Spn, and Hib and other causes, and LSHTM has estimated the burden for GBS *(34).* It is important to note that relatively few countries have reliable data from registration of deaths, such that estimates from most countries rely on verbal autopsy data or extrapolation from these data to countries without data on cause of death. For example, over 90% of deaths classified by MCEE/JHU use modelling that rely on verbal autopsy as the underlying data source. In addition, in countries for which cause of death estimates are based on vital registration, the range of international classification of diseases, tenth edition (ICD-10) codes on cause of death in the different categories vary by model.

2.3. Global mortality and incidence

In 2015, WHO estimated deaths in all ages from meningitis at around 290 000 (see Table 2) in the same range as IHME estimates of around 320 000. The estimated numbers of deaths from neonatal sepsis and meningitis combined (including GBS) differed substantially between WHO and IHME (402 000 versus 248 000 respectively). One reason may be the difficulty in distinguishing between neonatal sepsis and meningitis using verbal autopsy, and also clinically in the absence of lumbar puncture (LP) and cerebrospinal fluid (CSF) culture results.

Table 2. Estimates of global mortality for bacterial meningitis1 and neonatal sepsis by age group, 2015

Bacterial meningitis[1]		
All ages	Deaths (*n*) (UI)[2]	288 649 (235 464–333 101)
	Mortality rate	3.9 per 100 000
1–59 months	Deaths (*n*) (UI)	94 883 (UI not available)
	Mortality rate	14.3 per 100 000
Neonatal sepsis and meningitis		
0–28 days	Deaths (*n*) (UI)	402 414 (UI not available)
	Neonatal mortality rate	2.87/1000 live births
Source: WHO Global Health Estimates (in collaboration with MCEE and IHME) *(39)* [*(40)* for live births].		

WHO estimates suggest that deaths from all cause bacterial meningitis, (excluding TB), decreased from 7.0/100 000 in 2000 to 3.9/100 000 in 2015. Incidence and mortality, according to IHME, also fell in this period (40.7/100 000 to 37.8/100 000 and 6.1/100 000 to 4.4/100 000 respectively). The IHME-estimated number of cases of meningitis due to Nm, Spn and Hib (all ages) was 1 607 200 in 2015. A systematic review (search interval 1980 to 2010) estimated median case fatality for bacterial meningitis globally as 14.4% (31.3% in the African Region)(41).

[1] Deaths from TB meningitis not included. Viral meningitis deaths also included in 0–59 month olds but not in older age groups.
[2] Uncertainty interval.

Incidence and mortality from pneumococcal and Hib meningitis in those aged 1–59 months have decreased since 2000 according to the JHU model, a trend supported by vaccine impact studies. Estimates showing the continuing burden, especially from Spn meningitis in young children in 2015, are illustrated in Table 3 below. Estimates on burden of meningococcal meningitis were not available from WHO or the JHU models, but should be finalised, for 1–59-month-olds, by JHU in 2019. IHME also estimated a declining incidence of pneumococcal and Hib meningitis over time, with a relatively stable incidence of meningococcal meningitis and an increasing incidence of meningitis due to other causes. IHME estimated just over 300 000 cases of Nm meningitis in 1–59-month-olds in 2015 (17.5% case-fatality ratio) with similar numbers for Spn meningitis and for Hib meningitis, and 270 000 meningitis cases due to other bacteria and viruses. It should be noted that although IHME estimated numbers of cases and deaths independently, their case-fatality ratios currently deviate widely from those documented in the published literature. JHU models estimated numbers of Spn and Hib meningitis cases by applying literature-derived case-fatality ratios to their modelled estimates of deaths due to those organisms.

Table 3. Meningitis burden due to Spn and Hib in 1–59 month olds, 2015

		Pneumococcal meningitis	Hib meningitis
1–59 months	Cases (*n*) (UI)	83 900 (36 100–169 000)	31 400 (13 400–50 800)
	Incidence rate/ (UI)	13/100 000 (5–26)	5/100 000 (2–8)
	Deaths (*n*) (UI)	37 900 (15 400–79 700)	7200 (2700–11 300)
	Mortality rate (UI)	5/100 000 (2–11)	1/100 000 (0–2)
	Case-fatality ratio (UI)	44% (18–93)	19% (7–29)
Source: JHU/MCEE *(12)*.			

Over 300 000 cases of invasive disease in babies under three months of age, including around 70 000 cases of meningitis, were estimated to be caused by GBS in 2015 *(34)* (see Table 4). Up to 3.5 million pre-term births may be attributable to GBS, recognising that GBS, meningitis and sepsis in young babies are under-reported *(42,43)*.

Table 4. Estimated burden of GBS disease in babies and mothers in 2015

Estimate	*n* (UI)
Early onset GBS cases in babies 0–6 days	205 000 (101 000–327 000)
Late onset GBS cases in babies 7–89 days	114 000 (44 000–32 600)
Total cases of invasive disease in babies 0–89 days	319 000 (119 000–417 000)
Cases of invasive disease presenting as meningitis[3] in babies 0–89 days	72 480
Total infant deaths (0–89 days)	90 000 (36 000–169 000)
Foetal infections/stillbirths	57 000 (12 000–104 000)
Neurodevelopment impairment (NDI) in children after GBS invasive disease	10 000 (3000–20 000)
Invasive GBS disease in pregnant or postpartum women	33 000 (13 000–52 000)
Source: LSHTM *(34)*.	

[3] This estimate was not published in the paper by Seale at al. However, the authors state that cases of neurodevelopmental impairment were estimated by calculating cases of meningitis survivors and assuming that a proportion of these were left with neurodevelopment impairment. An assumption was made that 12% of early onset survivors would present as meningitis and 42% of late onset survivors would present as meningitis. Therefore, to calculate cases of meningitis we applied the above proportions to early and late onset GBS cases.

2.4. Regional mortality and incidence

Table 5. Bacterial meningitis and neonatal sepsis deaths by WHO Region, 2015 (see map (44))

WHO Region		Africa (AFRO)	Americas (AMRO)	Europe (EURO)	Eastern Mediterranean (EMRO)	South-East Asia (SEARO)	Western Pacific (WPRO)
All cause bacterial meningitis[4]							
All ages*	Deaths (*n*)	193 871	6546	4658	25 683	46 543	11 179
	Mortality rate	19.5 per 100 000	0.7 per 100 000	0.5 per 100 000	3.9 per 100 000	2.4 per 100 000	0.6 per 100 000
1–59 months*	Deaths (*n*)	61 965	1906	737	11 910	15 545	2790
	Mortality rate	39.2 per 100 000	2.6 per 100 000	1.3 per 100 000	15.0 per 100 000	9.0 per 100 000	2.3 per 100 000
Pneumococcal meningitis							
1–59 months**	Deaths (*n*) (UI)	20 400 (8000–43 700)	600 (200–1600)	600 (200–1100)	4200 (1600–8900)	10 200 (4300–20 800)	1900 (1000–3500)
	Mortality rate	13 (5–28) per 100 000	1 (0–2) per 100 000	1 (0–2) per 100 000	5 (2–11) per 100 000	6 (2–12) per 100 000	2 (1–3) per 100 000
Hib meningitis							
1–59 months**	Deaths (*n*)	2000 (600–3100)	<100	<100	300 (100–400)	4200 (1600–6500)	700 (300–1100)
	Mortality rate	1 (0–2) per 100 000	0 (0–0)	0 (0–0)	0 (0–1)	2 (1–4) per 100 000	1 (0–1) per 100 000
All cause neonatal sepsis							
0–28 days*	Deaths (*n*) (UI)	172 965 (135 476–214 465)	14 780 (12 662–17 523)	5264 (4016–6909)	78 700 (55 909–96 268)	119 061 (85 151–142 540)	11 230 (8878–13 796)
	Mortality per 1000 live births	4.80	0.98	0.47	4.58	3.28	0.46

Source: *WHO Global Health Estimates (in collaboration with MCEE and IHME) **JHU models *(12).* NB. Meningococcal meningitis to be added when data available.

The WHO African Region was estimated to have more than 60% of the deaths for all cause meningitis (see Table 5 above). A similar geographical distribution was seen in IHME global estimates *(1)*. The African, Eastern Mediterranean and South-East Asian Regions had the highest mortality from neonatal sepsis. South-East Asia was estimated to have the highest mortality from Hib meningitis and the second highest mortality from pneumococcal meningitis in the 1–59 month age group (Table 5). For meningococcal meningitis, the highest burden was seen in the meningitis belt, with lower incidence across Europe and North America, but surveillance across much of South America, South-East Asia and the Western Pacific is patchy such that the true burden is uncertain *(18,20)*. LSHTM estimates of GBS burden also varied by region with over 90% of global deaths from stillbirths and from early/late onset GBS disease occurring in babies in Africa and Asia *(13)*.

2.5. Complications and sequelae

A high degree of disabling sequelae occurs among survivors of meningitis (see Table 6 below). The clinical course of bacterial meningitis is frequently complicated by neurologic and systemic complications including strokes, seizures and focal neurologic deficits such as hearing loss, limb weakness, difficulties with sight, speech, language and communication. Long-term disability from focal deficits is frequent. Neonates are a particularly high-risk population, with acute complications such as ventriculitis, hydrocephalus and brain abscess. There are likely to be many more sequelae, such as behavioural changes, that are not picked up in studies in low- and middle-income countries (LMICs) where detailed assessment may be limited. Studies in children have shown that measures of intelligence, learning and neuropsychologic skills are lower than age- and grade-matched controls. Additional sequelae from co-existing sepsis, especially meningococcal septicemia, include amputations (fingers, toes, limbs), skin scarring and bone growth problems. Even in the absence of meningitis, bacterial sepsis can cause learning delays, poor concentration and memory, and psychological problems.

Table 6. Risk of sequelae by pathogen and data source

Source			All cause meningitis Median (IQR)[5] risk	Nm Median (IQR) risk	Spn Median (IQR) risk	Hib Median (IQR) risk	GBS Mean (95% CI)[6] risk
Risk of disability	Edmond *(45)*[7]	All ages (>=1 major sequelae) Median risk	12.8% (7.1–21.1%)	7.2% (4.1–11%)	24.7% (16.2–35.4%)	9.5% (7.1–15.2%)	-
	Kohli-Lynch *(46)*	Moderate to severe neurodevelopmental impairment 18 months after GBS meningitis	-	-	-	-	32% (25–38%)

[4] Deaths from TB and fungal meningitis not included. Viral meningitis deaths included in 0–59-month-olds but not in the older age groups.
5 Interquartile range.
6 Confidence interval.
7 Risks of long-term disabling sequelae highest in LIC, where burden of bacterial meningitis is greatest, and most reported sequelae potentially averted by vaccination with Hib, pneumococcal and meningococcal vaccines.

A systematic review of the global and regional risk of disabling sequelae from bacterial meningitis performed in 2010 found that approximately 13% (Median, IQR 7–21%) of survivors experienced severe sequelae *(45)*. The proportion of survivors with severe after-effects varied by pathogen, with the highest for pneumococcal meningitis, and survivors in low-income countries (LIC) were worst affected. The risk of major sequelae was twice as high in Africa and South-East Asia as in Europe, and the risk of sequelae in children aged less than five years was higher than in those aged five years or more. The GBD Study 2016 also found that pneumococcal meningitis resulted in more years of life lived with disability (YLD) than meningitis due to Nm and/or Hib *(1)*. A systematic review concentrating on GBS disease among infants under three months of age in middle and high-income contexts *(46)* reported that 32% of survivors (95% CI 25%–38%) had neurodevelopmental impairment (NDI) at 18 months of follow-up, including 18% (95% CI, 13%–22%) with moderate to severe NDI. This proportion is likely to be higher in LIC.

Meningitis sequelae can have an enormous impact on families and communities, both financially and emotionally. In the United Kingdom, significant detriments were found to the quality of life of those who care for disabled meningitis survivors *(47)*. In low-income settings, the devastating costs of meningitis on households and communities has been described *(48,49)*, illustrating how meningitis prevention could contribute to poverty reduction goals. Although there is growing knowledge of the proportion of household expenditure spent on health in LMICs, there is only one study from Senegal on affordability of care and the loss of income due to meningitis, including the extent to which meningitis contributes to household impoverishment *(48)*.

2.6. Monitoring roadmap progress from 2015 to 2030

It is recognised that all global burden estimates have a high degree of uncertainty given that reliable data on incidence and cause of death from meningitis are not available for many countries, and that cause of death estimates rely heavily on data from verbal autopsy studies. Given this uncertainty, a meeting of global health modellers, in November 2018, concluded that monitoring progress towards a reduction in meningitis burden by 2030 should be based on trends rather than specific target numbers, and that multiple indicators and data sources could be used to achieve this (see Table 7 below).

It was also suggested that a reality check could be useful to compare trends and evaluate the accuracy and reliability of estimates from different modelling groups, for example, using high-quality surveillance data from selected sentinel sites.

As it is not possible to separate the two syndromes of meningitis and sepsis in the neonatal period based on verbal autopsy, indicators to monitor success of any future GBS vaccination programmes can only be taken from specific estimates for overall invasive GBS disease.

It is recognised that the baseline estimates for 2015 will be updated as global burden estimate methodology is refined over time. The best available estimates at any time point should be used for setting provisional baselines and assessing trends and progress.

Table 7. Potential indicators of trends in incidence and mortality from meningitis. (These indicators will be converted to rates per 100 000 population or per 1000 live births for analysis.)

	Proposed indicator	Source
Adults and children over five	Cases and deaths due to Spn meningitis	IHME
	Cases and deaths due to Hib meningitis	IHME
	Cases and deaths due to Nm meningitis	IHME
	Cases due to bacterial meningitis	IHME[8]
	Deaths due to bacterial meningitis	WHO GHE, IHME
Children aged 1–59 months	Cases and deaths due to Spn meningitis	IHME, JHU[9]
	Cases and deaths due to Hib meningitis	IHME, JHU
	Cases and deaths due to Nm meningitis[10]	IHME
	Cases due to bacterial meningitis	IHME
	Deaths due to bacterial meningitis	MCEE[11], WHO GHE, IHME
Neonates[12]	Cases due to neonatal meningitis	IHME
	Deaths due to neonatal meningitis	WHO GHE, IHME
	Deaths due to neonatal sepsis and meningitis	MCEE[13], IHME
Babies 0–89 days	Deaths due to GBS sepsis and meningitis	LSHTM
	Cases due to GBS sepsis and meningitis	LSHTM

8 IHME publish cases and deaths due to bacterial and viral meningitis combined, but estimate the two separately, so it should be possible to obtain data for bacterial meningitis only.
9 JHU apply an aetiological split to MCEE's all cause envelope (which includes encephalitis deaths) when calculating deaths due to Spn and Hib.
10 JHU are partway through collecting estimates for cases and deaths due to Nm meningitis from 2000 to 2015.
11 MCEE estimates for deaths from bacterial meningitis include encephalitis. IHME and WHO GHE estimates do not.
12 Neonatal GBS data may be available from IHME in future GBD studies.
13 MCEE do not separate neonatal sepsis and meningitis. Over 90% of deaths are assigned using modelling based on verbal autopsy and it is not possible to accurately distinguish meningitis from sepsis using this method.

3. Prevention and epidemic control

Preventing meningitis is the most important way to reduce burden and impact of the disease. Suitable, affordable, safe, effective vaccines are needed to deliver long-lasting protection. An integrated approach to routine and epidemic vaccination programmes can lead to sustainable reductions of the disease burden. Antibiotics are also used as prophylaxis to help prevent infection in those at high risk of invasive Nm and GBS disease, while controlling epidemics of Nm meningitis relies on both vaccination and antibiotic administration. This section will cover vaccines, vaccination programmes, chemoprophylaxis and epidemic control.

3.1 Prevention: licensed vaccines and vaccines in clinical development

Meningococcal vaccines

The first polysaccharide vaccines against meningococcal disease were developed in the 1940s *(50)* followed in the 1990s by the more effective conjugate vaccines. Conjugate vaccines are now used in high-income countries (HIC) as a component of the national immunization programmes in monovalent (A, C) or multivalent formulations (AC, ACY, ACW, ACYW). Conjugate vaccines are also used in support of travel/Hajj requirements.

Polysaccharide vaccines continue to be sourced for global vaccine stockpiles to support an outbreak response through the International Coordination Group (ICG). In addition, some countries use polysaccharide vaccines as part of their routine immunization programmes for at-risk populations. It should be noted that there are no WHO prequalified polysaccharide meningococcal vaccines available on the market.

Novel protein-based vaccines against meningococcal B disease are now being used at a public-health scale in some countries.

Some of the current concerns and/or gaps in the development of meningococcal vaccines to prevent meningitis include:

- lack of a vaccine against the group X meningococcus, in development;
- lack of quality-assured polysaccharide products;
- lack of affordable conjugate products (multivalent) and B protein vaccines for LIC; the demand is not clear globally from all market segments as many countries have chosen a high-risk, target population approach to meningococcal vaccine programmes, or rely on using vaccines only for outbreak response;
- further development of global policy for optimal use, including strategies for epidemic response and optimal vaccine schedules;
- further documentation of vaccine effects on meningococcal carriage and transmission patterns in different settings;
- further assessment of correlates of protection.

Summaries of the multivalent (quadrivalent and pentavalent) meningococcal conjugate vaccines licensed and in clinical development are presented in Tables 8a and 8b, while Table 9 presents the meningococcal B vaccines. Several formulations of mono-, bi- and trivalent meningococcal conjugate vaccines are also licensed or in clinical development, including a licensed and WHO prequalified monovalent A conjugate vaccine tailored for the needs of countries in the African meningitis belt.

Table 8a. Licensed quadrivalent/pentavalent meningococcal conjugate vaccines, as of July 2018

Manufacturer	Commercial name	Active constituents	Indication	WHO prequalified
Sanofi Pasteur	Menactra®	ACWY polysaccharide – conjugated to diptheria toxoid (DT)	2 doses age 9–23 months 1 dose age 2–55 years	Yes
GSK (ex Novartis) *Arabio	Menveo® *Aramen®	ACWY polysaccharide – conjugated to CRM197 (detoxified diphtheria toxin)	2 doses age 7–23 months 1 dose age 2–55 years	Yes
Pfizer (ex GSK)	Nimenrix®	ACWY polysaccharide – conjugated to tetanus toxoid (TT)	1 dose age ≥ 12 months	Yes

*Same product, different manufacturer and commercial name.

Table 8b. Quadrivalent/pentavalent meningococcal conjugate vaccines in clinical development, as of July 2018

Manufacturer	Phase	Active constituents
Sanofi Pasteur	3	ACWY polysaccharide – conjugated to TT
Serum Institute of India Pvt. Ltd.	2	ACWYX polysaccharide – conjugated to TT and cross-reacting material (CRM)
Beijing Minhai Biotechnology Co., Ltd.	3	ACWY polysaccharide – conjugate
CNBG (Lanzhou)	3	ACWY polysaccharide – conjugate
Tianjin CanSino Biotechnology Inc.	3	ACWY polysaccharide – conjugate
Chongqing Zhifei Biological Products Co. Ltd.	1	ACWY polysaccharide – conjugate

Table 9. Licensed meningococcal B vaccines, as of July 2018

Manufacturer	Commercial name	Active constituents	Indication	WHO prequalified
GSK	Bexsero®	Protein-based vaccine (B NHBA fusion protein, B NadA protein, B fHbp fusion protein and OMV B strain NZ98/254 PorA B:4:P1.7–2,4)	3 doses age 2–5 months 2 doses age six months to 50 years	No
Pfizer	Trumenba®	Protein-based vaccine (B fHbp subfamily A and B fHbp subfamily B)	2 or 3 doses age ≥ 10 years	No
Finlay Institute of Cuba	VA-MENGOC-BC®	Bivalent C polysaccharide and OMVs B strain CU385 B:4:P1.19,15:L3,7,9	2 doses age three months to 24 years	No

Pneumococcal vaccines

Pneumococcal conjugate vaccines (PCVs) are reducing the global burden of pneumococcal disease. However, there are still gaps existing with the current PCVs.

1. Serotype coverage and replacement: although current PCVs covered strains responsible for most of disease, serotype replacement means that there is a significant residual burden of disease.
2. Cost: at more than US$ 9 for the three doses currently required, PCVs consume a large portion of the Gavi budget. The high cost is driven primarily by PCV manufacturing complexity. This is already a challenge for non-Gavi eligible middle-income countries (MICs) and will be a major challenge for sustainability in Gavi-eligible countries as they move out of Gavi eligibility.

As a result of these gaps, more affordable and broader coverage pneumococcal vaccines are needed. Tables 10 and 11 respectively present multivalent pneumococcal conjugate vaccines licensed and in late-stage development, as of July 2018.

Table 10. Licensed pneumococcal conjugate vaccines, as of July 2018

Manufacturer	Commercial name	Active constituents	Indication	WHO pre-qualified
Pfizer	Prevenar 13®	13 valent: serotypes 1,3,4,5,6A,6B,7F,9V,14,18C,19A,19F,23F polysaccharides – conjugated to CRM197	Infants: 3 doses – either a 3+0 schedule (6,10,14 weeks) or 2+1 (6,14 weeks and booster at 9–12 months)	Yes
GSK	Synflorix®	10 valent: serotypes 1,4,5,6B,7F,9V,14,18C,19F,23F polysaccharides – conjugated to protein D from non-typable *Haemophilus influenzae* except 18C (TT) and 23F (DT)	Infants: 3 doses – either a 3+0 schedule (6,10,14 weeks) or 2+1 (6,14 weeks and booster at 9–12 months)	Yes

Table 11. Multivalent pneumococcal conjugate vaccines in late stage development, as of July 2018

Manufacturer	Commercial name	Active constituents	Phase
Merck		15 valent	3
Pfizer		20 valent	2
Serum Institute of India	Pneumosil®	10 valent	3
Walvax		13 valent	Licensure
SK Chemicals	SKYPneumo®	13 valent	Licensed in the Republic of Korea
SK Chemicals		12 valent	2
Biological E		14 valent	2
LG Chemicals		14 valent	2
CNBG (Lanzhou)		13 valent	2
Finlay		7 valent	3

Additionally, there are numerous pneumococcal protein vaccine candidates in development but, thus far, none have progressed beyond a Phase 2 trial. The future of the most advanced candidate (until recently being developed by GSK) is uncertain, given that recent results showed that efficacy against acute otitis media or carriage could not be demonstrated. A vaccine derived from whole bacteria was being evaluated in Kenya but is not being pursued further following findings of excess respiratory illness in immunized toddlers.

Group B streptococcal vaccines (GBS)

Currently, no vaccine exists for prevention of GBS disease. A WHO roadmap was published in 2017 that aims to develop and license safe, effective and affordable GBS vaccines for maternal immunization during pregnancy *(51)*. Prevention strategies in high- and middle-income countries have reduced the incidence of GBS disease in babies in the first week of life, but these strategies have not reduced GBS disease elsewhere. A GBS vaccine could significantly impact GBS-related stillbirth and invasive GBS disease in neonates and young infants, as well as GBS-related maternal infection and pre-term labour. It will be appropriate for use in high-, middle- and low-income countries. It may also be useful for preventing GBS disease in other adults, including the immunocompromised and the elderly.

Table 12. Group B Streptococcal vaccines in development, as of July 2018

Manufacturer	Active constituents	Phase
Pfizer	6 valent conjugate vaccine: serotypes Ia,Ib,II,III,IV,V. All conjugated to CRM197	1/2
GSK (ex Novartis)	3 valent conjugate vaccine : serotypes Ia,Ib,III. All conjugated to CRM197	2 – programme on hold.
Minervax	Protein vaccine (Alpha C and Rib)	1/2
Biovac	5–6 valent conjugate vaccine	Preclinical

As noted in the table above, the GSK (formerly Novartis) trivalent conjugate vaccine candidate is on hold due to competitive products in development with higher valency, and lower than expected immunogenicity in Phase 2 trials in pregnant women. Minervax is reformulating its protein vaccine candidate to provide better coverage against global strains. The 6-valent vaccine from Pfizer is therefore the most advanced candidate. The biggest challenges for GBS vaccines are the demonstration of effectiveness and regulatory pathways to licensure and WHO prequalification. Recent interactions with regulators suggest that there may be a pathway for initial licensure based on a correlate of protection and demonstration of effectiveness in post- licensure studies (to be defined).

Hib vaccines

All vaccines currently licensed for use against Hib disease are conjugates. Four conjugate Hib vaccines have been developed using different protein carriers, size of polysaccharide components and chemical conjugation linkages. Several formulations of monovalent or diphtheria-tetanus-pertussis (DTP)-Hib-and/or Hepatitis B and/or inactivated polio (IPV) combination vaccines have been developed and are extensively used to simplify and enhance compliance with childhood immunization schedules. A Hib-MenCY combination vaccine is also available. Current active areas of vaccine R&D focus mostly on developing more combination vaccines and

early stage development of vaccine candidates for non-typeable Hi, as well as Hia disease, considering limited reports of increased invasive disease rates.

Antimicrobial resistance (AMR)

Global widespread use of antibiotics has resulted in increased worldwide antimicrobial resistance in bacteria. The role that vaccines can play in AMR strategies is increasingly recognized, notably their potential to prevent bacterial infections avoiding the need for antibiotics and reducing opportunities for emergence and transmission of antibiotic-resistant strains. Objective 5 of the WHO Global Action Plan on Antimicrobial Resistance is formulated to highlight such a role, to "develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions. Accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines"*(8)*. The positive effect of conjugate vaccines in reducing antibiotic use and AMR has been well established for Hib as well as Spn. Although Nm and GBS are still susceptible to most antibiotics used for treatment and prophylaxis of invasive disease, their reduced susceptibility, and in some instances non-susceptibility to antibiotics, raises growing concern that strains with antibiotic resistance may emerge widely in the future. Global antibiotic resistance surveillance is recommended, and meningococcal and GBS vaccines could also play a major role in combatting AMR.

3.2 Prevention: vaccination programmes

3.2.1 Recommended vaccination programmes (EPI, outbreaks)

Meningococcal vaccines

Whenever feasible, conjugate vaccines are preferred over polysaccharide vaccines, due to their advantageous effects on direct and indirect protection.

WHO recommends, dependant on the disease burden, either:

(a) Large-scale vaccination in countries experiencing:

- high (>10 cases/100 000 population/year) or intermediate (2–10 cases/100 000 population/year) endemic rates of invasive meningococcal disease;
- countries with frequent epidemics.

This includes introduction of MenA conjugate vaccine in the African meningitis belt (campaigns targeting 1–29-year-olds and introduction into the routine immunization schedule);

or

(b) Targeted vaccination for defined risk groups.

Pneumococcal vaccines

WHO recommends that inclusion of PCVs be given priority in childhood immunization programmes worldwide, with one of the two following schedules:

- 3 primary doses (3p+0 schedule)
- 2 primary doses plus a booster (2p+1 schedule).

The WHO recommendation mentions that catch-up vaccination, as part of introduction, will accelerate development of herd protection and therefore the impact of PCVs on disease and carriage. The WHO Position Paper is being revised and an updated version should be published in 2019.

Hib vaccines

WHO recommends the inclusion of conjugate Hib vaccines in all infant immunization programmes following any one of the following schedules:

- 3 primary doses without a booster (3p)
- 2 primary doses plus a booster (2p+1)
- 3 primary doses with a booster (3p+1).

3.2.2 Implementation status: global/regional

Meningococcal vaccines

Vaccination policies vary significantly from country-to-country. Table 13 below represents the number of national programmes (nationally funded when applicable) using different types of vaccines, for different targets:

- infants and children
- adolescents
- special groups, including specific at-risk groups, for example, the military, defined parts of the country.

Table 13. Meningococcal vaccine policy by region: number of national programmes using each of the respective vaccines, as at 31.12.2017

Vaccine	AFRO	AMRO	EMRO	EURO	SEARO	WPRO	Total
Infant children systematic vaccination programmes	6	5	6	23		3	43
MenA cj	6		1				7
MenA Ps						1	1
MenC cj		2		14			16
MenAC cj			1				1
MenAC Ps						1	1
Hib-MenC cj				2		1	3
MenACWY cj		2	3	3			8
MenACWY Ps			1				1
MenB				4			4
MenBC		1					1
Adolescents systematic vaccination programmes		4	1	8		1	14
MenC cj		1		3		1	5
MenAC cj			1				1
MenACWY cj		3		5			8
Special groups vaccination programmes		1	12	9	2	4	28
MenA cj			2				2
MenACWY cj			7	6	2	3	18
MenACWY Ps			3	2			5
MenB				1		1	2
MenBC		1					1

Source: WHO/UNICEF Joint Reporting Form.

ps = polysaccharide, cj = conjugate

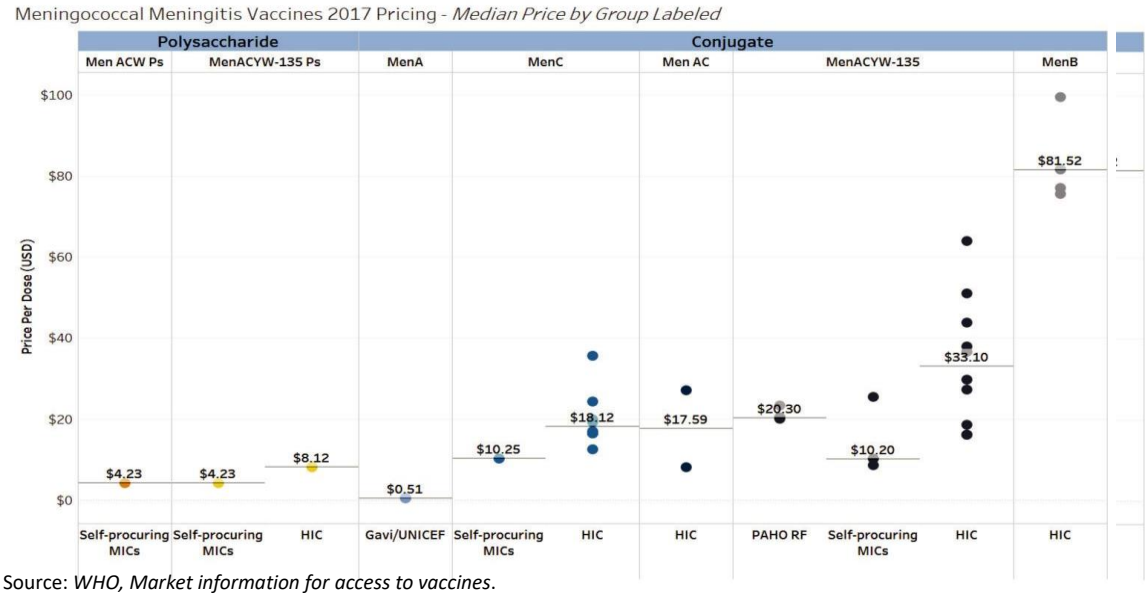
Countries that use multiple vaccines are counted more than once, for example, countries using MenB and MenC are counted twice.

Programmes for travellers are not included in the table.

Since December 2017, further vaccine programme introductions include: MenB vaccination in Lithuania and southern Australia; introduction of MenA conjugate in Côte d'Ivoire, and a switch from MenC to MenACWY conjugate for children 12 months of age in Australia.

Fig. 1 below shows indicative vaccine costs.

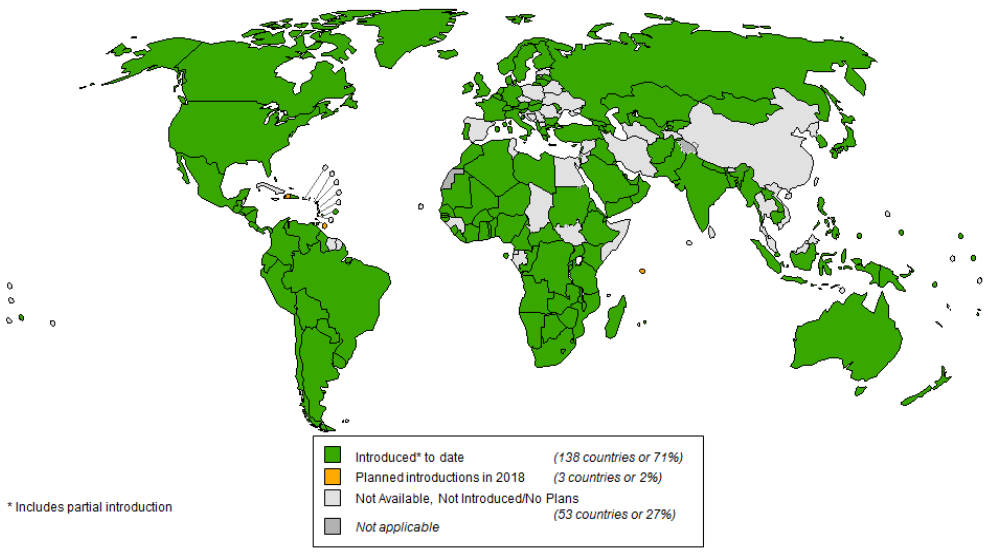
Fig 1. Indicative vaccine prices per dose



Source: *WHO, Market information for access to vaccines*.

Pneumococcal vaccines

Fig 2. Pneumococcal vaccination programmes by country (as of May 2018)



As of December 2017, pneumococcal vaccination programmes had been introduced in 140 out of 194 countries (72%) including five (India, Indonesia, Mongolia, Nigeria and the Philippines) that have introduced the vaccine only partially. Table 14 represents the number of countries having/not having introduced PCV in

routine programmes, per region and their Gavi-eligibility status. Around 50% of the global infant population is not covered by PCV vaccination. Overall, MICs, not eligible for Gavi support, lag behind Gavi-eligible countries regarding introduction of PCV. An overall 15% (8 of 52) of Gavi-eligible countries and 35% of non Gavi-eligible countries (46 of 142) have not introduced PCV into routine programmes.

Table 14. PCV routine immunization programme status by region and Gavi eligibility, as at 31.12.2017

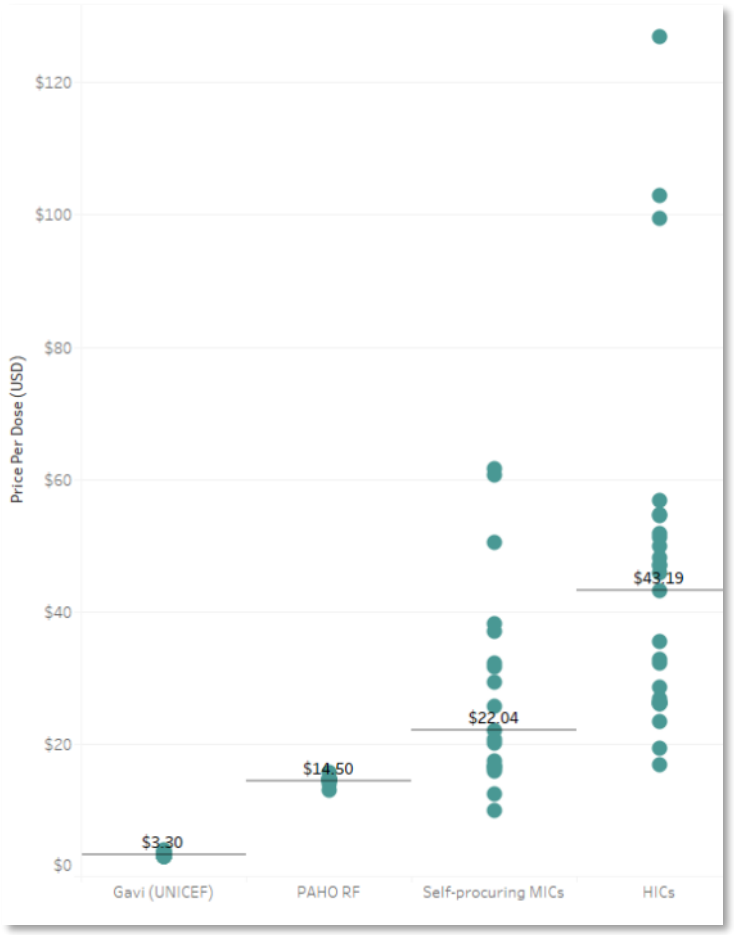
	AFRO	AMRO	EMRO	EURO	SEARO	WPRO	Total
Number of countries with PCV in routine immunization programmes	**39**	**24**	**15**	**40**	**5**	**17**	**140**
Among whom introduction is not nationwide but partial	1				2	2	5
Gavi-eligible countries	*31*	*0*	*5*	*1*	*4*	*3*	*44*
Non Gavi-eligible countries	*8*	*24*	*10*	*39*	*1*	*14*	*96*
Number of countries without PCV in routine immunization programmes	**8**	**11**	**6**	**13**	**6**	**10**	**54**
Among whom programmes for specific high-risk groups are implemented		3		4			7
Gavi-eligible countries	*4*	*1*	*1*	*1*	*1*		*8*
Non Gavi-eligible countries	*4*	*10*	*5*	*12*	*5*	*10*	*46*
Total countries	**47**	**35**	**21**	**53**	**11**	**27**	**194**

Table 15 represents the schedules implemented for the 140 countries that have introduced PCV, among which 86% (121 of 140) countries use a 3-dose and 13% (18 of 140) a 4-dose schedule; with a total of 56% (79 of 140) countries with schedules including a booster dose, a booster dose being defined as a last dose received at age nine months and above. WHO does not recommend use of 2+0 schedules. Ongoing trials are evaluating different infant/toddler schedules. In addition, many countries have programmes using polysaccharide vaccines for protection of elderly and at-risk groups. Fig. 3 below shows indicative vaccine costs.

Table 15. PCV vaccination schedule by region, as at 31.12.2017

	AFRO	AMRO	EMRO	EURO	SEARO	WPRO	Total
Number of countries without a booster in childho	**36**	**6**	**6**	**3**	**3**	**7**	**61**
3+0 doses	36	6	6	2	3	7	60
2+0 doses				1			1
Number of countries with a booster in childhood	**3**	**18**	**9**	**37**	**2**	**10**	**79**
2+1 doses	3	15	5	34	2	2	61
3+1 doses		3	4	3		8	18
Total countries with PCV in routine programmes	**39**	**24**	**15**	**40**	**5**	**17**	**140**

Fig 3. Indicative vaccine prices per dose (range of priced and median prices)



Data source: *WHO, Market information for access to vaccines.*

Hib vaccines

As of May 2018, Hib vaccine had been introduced in 191 countries (98%) (Fig. 4). It has not yet been introduced in China, the Russian Federation or Thailand.

Fig 4. Hib vaccination programmes by country (as of May 2018)

3.2.3 Barriers to implementation

Pathogen	Financial	Technical and programmatic	Others
Nm	-Scarcity (low supply) and high cost of multivalent conjugate meningococcal vaccines, although conjugate vaccines are the most effective vaccines to protect populations (herd protection through impact on carriage) - Affordability for s	-Lack of data as evidence to design and advocate for vaccination policies -Competition with other vaccines for introduction at country level	-Communication around "vaccination against meningitis", as immunization programmes target only a portion of causal pathogens -Political will to introduce MenAfriVac® into routine immunization programmes in lower incidence countries in the meningitis belt (after dramatic impact of mass campaigns) may not be as strong as in higher incidence countries
Spn	-Relatively expensive vaccine, often the most expensive vaccine in immunization programme -Sustainability for Gavi-transitioning countries -Affordability for MICs	-Limited country surveillance and laboratory capacity, especially for serotyping	
Hib	-	-Only China, Russia and Thailand yet to introduce; determinants for introduction in these countries need to be specified	
GBS	-Development and licensure of vaccines		

3.2.4 Gap analysis (programme implementation, R&D)

Where we are	Where we want to be
Nm	
Lack of data as evidence to design and advocate for vaccination policies (outside the African meningitis belt)	Higher completeness and quality of surveillance data
Variable use, limited availability and high price of multivalent conjugate vaccines, with some serogroups not included in current vaccines	Introduction into routine schedules of affordable ACYW conjugates (and when available in the meningitis belt ACYWX conjugates) to achieve herd protection Optimization of schedules as disease evolves
New MenB protein vaccines do not cover all strains and may not induce herd protection	Development of new improved MenB vaccines
Spn	
Incomplete introduction of PCV vaccines	Universal introduction into routine schedules
Current vaccines targeted against 10–13 of >97 serotypes	Development, availability and affordability of higher valence or universal pneumococcal vaccines that would prevent a higher proportion of pneumococcal disease
Concern and need for continued monitoring for possible serotype replacement	Improved surveillance of serotypes causing disease and carriage
Evidence gaps for wider protection, including protection of older children and adults	Optimization of schedules - Use of PCVs in older children and adults - Most efficient schedule to provide herd protection and prevent outbreaks
Hib	
Although most countries have introduced Hib infant vaccination, a large proportion of global birth cohort is not covered since China, Russia and Thailand have not yet introduced a Hib vaccine	Universal introduction into routine schedules
Some countries not using a booster dose	Consideration of the conditions under which a booster dose is needed, and implementation accordingly
GBS	
Lack of comprehensive evidence on burden of disease, econ impact and cost-effectiveness analysis of vaccination *(51)*	More and better evidence to inform the use of intrapartum prophylaxis and the use of a GBS vaccine when available. More evidence to inform acceptability of a GBS vaccine in LMICs
No vaccine available	At least one effective, safe, affordable vaccine developed and licensed. Global introduction of maternal vaccination. Safety communication and acceptance/coverage (lessons from TT vaccination of pregnant women) by proactive early engagement with maternal, neonatal and child-health programmes

3.3 Prevention: chemoprophylaxis

3.3.1 Recommended practice

(a) Chemoprophylaxis of contacts and communities (Nm, Hib)

The risk of meningococcal disease is increased 400 to 800-fold in individuals with close contact to a case (52). In meta-analysis, oral rifampicin, injectable ceftriaxone and oral ciprofloxacin were shown to be effective at clearing nasopharyngeal carriage of the meningococcus at one week, with rifampicin and ciprofloxacin also effective in a one-two week period (53). Meta-analysis has also shown that chemoprophylaxis significantly reduces the risk of invasive meningococcal disease in the following month (54). The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommends antibiotic prophylaxis with one of the three above agents for "close contacts" of patients with invasive meningococcal disease (55). Close contacts are defined as household members, child-care centre contacts and anyone directly exposed to oral secretions. US CDC recommends antibiotic prophylaxis for close contacts (not defined) of someone with meningococcal meningitis, and family members (especially those "at risk") of cases of Hib meningitis.

African meningitis belt (Nm)

Outside of epidemic periods, WHO recommends prophylaxis for close contacts with single-dose ciprofloxacin, or with single-dose ceftriaxone if ciprofloxacin is contraindicated. During epidemics, chemoprophylaxis is not currently recommended (56); however, a trial in Niger in 2017 showed a 60% reduction in attack rate in villages receiving village-wide single-dose ciprofloxacin within 72 hours of the notification of the first case in the village (57). A WHO panel suggested that more evidence was needed before changing current recommendations (58), and this issue needs revisiting (59,60).

(b) Maternal screening and prophylaxis (GBS)

Universal screening, using laboratory tests for maternal GBS carriage, is performed in nearly all high-income countries, though Nordic countries and the United Kingdom use a risk-based approach *(61)* to determine which women should be offered prophylactic antibiotics in labour against early-onset GBS infection. A positive test result during pregnancy or labour, a previous baby with GBS disease, or pre-term labour, are all widely accepted as prompting intravenous antibiotics in labour. Universal screening is costly and difficult to implement in LMICs. In MICs the risk-based approach is more common. Few LICs have a prevention strategy for early-onset GBS infection *(61)*.

Regardless of which screening strategy is used to select who to treat, the intrapartum prophylaxis recommended is intravenous penicillin with an initial loading dose (5 million units penicillin G or 3 grams benzylpenicillin) given as soon as possible after the start of labour, followed by repeat doses (2.5–3 million units penicillin G or 1.5 grams benzylpenicillin) every four hours until delivery *(62,63)*. Alternatives are recommended for women who are allergic to penicillin, which vary by region and the severity of the penicillin allergy *(62,63)*.

Although intrapartum antibiotics have reduced early-onset GBS infection, they are an important but imperfect means of reducing early-onset GBS disease and many women are given antibiotics unnecessarily. They do not impact pre-term births, stillbirths, or late-onset infections caused by GBS. A maternal vaccine would reduce all these additional GBS infections, as well as reducing unnecessary intrapartum antibiotic use.

3.3.2 Implementation status: global/regional

In HICs, recommendations for chemoprophylaxis of contacts of Nm meningitis cases are well-accepted and widely implemented. Programmes to prevent early-onset GBS disease are implemented with different tools and algorithms but are generally widespread in the wealthiest countries *(61)*. In LMICs, there is little information about uptake, but anecdotal evidence suggests that antibiotic prophylaxis for close contacts of meningococcal meningitis cases is generally not used, and that intrapartum prophylaxis against early-onset GBS disease is rarely implemented.

3.3.3 Barriers to implementation

In HICs, there are few barriers to implementation of recommended practices for chemoprophylaxis for Nm, Hib and GBS. In LMICs, particularly in the African meningitis belt, drug availability and lack of funding are important barriers, as are lack of resources, including laboratories, equipment and trained personnel. Rapid diagnostic tests for GBS testing in pregnancy could contribute towards reducing early-onset GBS infection, but cost and logistic barriers would need to be overcome *(64)*.

3.3.4 Gap analysis

Where we are	Where we want to be
A randomized trial showed success of community chemoprophylaxis during an outbreak of meningococcal meningitis in the meningitis belt	Further evaluation to provide additional evidence. Review of chemoprophylaxis policy for Nm meningitis in the meningitis belt.
Testing for maternal GBS carriage and the use of intrapartum antibiotic prophylaxis are standard in most HICs Testing for maternal GBS carriage or using risk-factors to identify which women to offer intrapartum antibiotic prophylaxis are both uncommon in many LMICs	An affordable and effective GBS vaccine available for all women of childbearing age in high-, medium- and low-income countries Prior to the introduction of such a vaccine, availability of an affordable and easy-to-use point-of-care test to identify maternal GBS carriage late in pregnancy in LMICs, and use of intrapartum antibiotic prophylaxis based on test results and/or recognized risk factors

3.4 Epidemic control

3.4.1 Recommended practice

Nm. The meningitis belt of sub-Saharan Africa, running across the continent from Senegal to Ethiopia, is prone to major epidemics of meningococcal meningitis. Control of these epidemics relies on efficient surveillance, prompt detection of weekly incidence rates in districts that cross an epidemic threshold and rapid mass reactive vaccination where indicated *(56)*. The use of polysaccharide vaccines for mass vaccination is recognised as an imperfect strategy as vaccination is often implemented late in the course of an outbreak and these vaccines do not result in long-term or herd protection. Affordable broad-based conjugate vaccines are urgently needed for Africa, and elsewhere, for epidemic control. Other regions of the world have varying outbreak definitions, but vaccination programmes for at-risk populations, accompanied by chemoprophylaxis to close contacts and sometimes to a wider population, are often recommended in the case of clusters (for example, in educational institutions) and community outbreaks (see 3.3.1)*(22)*.

Spn. Pneumococcal meningitis outbreaks are less common but are well documented in sub-Saharan Africa within and outside the traditional meningitis belt. Recommendations do not exist for use of pneumococcal vaccines to prevent or respond to pneumococcal meningitis outbreaks. Modelling and further analyses are needed to define best approaches to prevent and respond to such outbreaks. Some of the options to be investigated may include reactive vaccination campaigns, mass preventive or catch-up campaigns, or revision of immunization schedules.

Hib. Outbreaks of Hib meningitis are small and rarely recorded now that Hib vaccines are widely used.

GBS. GBS is not known to cause outbreaks.

3.4.2 Implementation status

Nm. The need for a public-health response to epidemics is well established across the world. Delays in detection of the causative organism and in vaccine deployment during outbreaks in the meningitis belt can limit the efficacy and effectiveness of such responses.

For outbreak response in the meningitis belt, preparation should be made for a possible vaccination campaign as soon as the alert threshold has been crossed, and vaccination should be conducted as soon as possible (provided confirmation of the Nm serogroup).

An international vaccine stockpile to respond to meningococcal meningitis epidemics is managed by the International Coordinating Group (ICG) on Vaccine Provision for Epidemic Meningitis Control. Members are MSF, IFRC, UNICEF and WHO, which also hosts the ICG Secretariat. Currently, the stockpile is mainly made up of polysaccharides vaccines, with a need to move towards conjugate vaccines exclusively. In recent years, the stockpile has not reached the planned level of 5 million doses due to limited production and the high cost of conjugate vaccines. Within the meningitis belt, countries have been encouraged to develop a national stockpile to initiate the response to outbreaks pending the completion of the ICG process to deliver vaccines to the country.

3.4.3 Barriers to implementation

Nm. Barriers in the meningitis belt include limited laboratory capacity, difficulties in accessing meningococcal vaccine stockpiles and insufficient stock of affordable vaccines**.** The unpredictability of epidemics and pathogens involved, combined with the long vaccine production cycle and limited shelf lives of vaccines, hampers the availability of appropriate vaccines for outbreak response, though a higher proportion of laboratory confirmation in cases during and between epidemics may help in assessing the spread of, and threat from, new clones.

3.4.4 Gap analysis

Where we are	Where we want to be
Limited capacity to predict, detect and respond rapidly to large-scale/major outbreaks of meningococcal meningitis	Increased laboratory capacity at all levels, reduced transit times for vaccines, guaranteed mechanisms for stockpile replenishment, full replacement of polysaccharide vaccines by conjugate vaccines in the ICG stockpile, good information on circulating strains and improved reliability of outbreak prediction
Continuing epidemics due to NmC, NmW, NmX in the meningitis belt	Elimination of epidemics in the meningitis belt through implementation of multivalent conjugate vaccines in routine immunization programmes.
Lack of clear approach to prevent and/or respond to an Spn meningitis outbreak	Policies for prevention and response to outbreaks of pneumococcal meningitis

4. Diagnosis and Treatment

4.1 Diagnosis

4.1.1 Laboratory tests

By identifying the causative organism of bacterial meningitis and determining its antimicrobial susceptibility, laboratory scientists (i) provide valuable information to clinicians for appropriate patient treatment, and (ii) provide data to guide public-health responses to epidemics, inform vaccination strategies and allow properly allocated resources for the targeted population. Thus, a well-trained laboratory scientist and a well-equipped diagnostic laboratory are critical to improve health care for individuals and populations.

Initial diagnosis of bacterial meningitis is conducted by clinical examination followed by a lumbar puncture (LP). The appearance, white blood cell count and levels of protein and glucose of a CSF specimen are assessed for initial diagnosis of bacterial meningitis. Gram stain and rapid diagnosis testing kits, such as latex agglutination tests, may presumptively identify a causative organism. The presumptive causative organism (for example, Nm, Spn or Hi), is confirmed by obtaining an isolate from clinical specimens collected from sterile sites, such as CSF and blood, or detecting the target DNA by polymerase chain reaction (PCR). Serogrouping/serotyping and antimicrobial susceptibility testing of the causative organism are important to inform public-health control and prevention measures and requires culture and PCR capacity *(65)*. However, PCR and culture are underutilized in some regions due to the lack of resources and proper laboratory infrastructure, so further evaluation is needed to identify the gaps. Isolating GBS as the causative pathogen can be difficult if insufficient blood specimens are taken from neonates and if there are delays in collection of blood or CSF, especially after giving intrapartum antibiotics. The proportion of undiagnosed early onset GBS infection could be significant *(42,43)*.

Several commercial multiplex PCR assays capable of simultaneously detecting an array of pathogens from a single specimen have become available. While these assays can rapidly identify species, they are relatively expensive, and most do not determine serogroup/type or provide information on antimicrobial sensitivity. Molecular typing, however, can provide useful information for determining whether a group of cases represent an outbreak. Multilocus sequence typing (MLST), pulse-field gel electrophoresis and whole genome sequencing (WGS) have been used for molecular typing of surveillance and outbreak strains. However, WGS provides highest resolution for assessing strain genetic similarity and identifying epidemic-prone strains. Molecular typing may not be needed for immediate decisions on case treatment or in deciding which vaccine to deploy but it (especially WGS), improves our understanding of the virulence and transmission of the circulating and emerging strains. Knowledge obtained from WGS may have great impact on public-health response and outbreak preparedness. Spread of hyper-invasive strains may require a more vigorous public-health response and an outbreak preparedness plan. While sequencing of an isolate provides more extensive and complete dataset, MLST and WGS may be performed directly on a clinical specimen (for example, CSF or blood) when an isolate is not available *(66,67)*. Table 16 presents laboratory tests widely available for diagnosis of meningitis.

Table 16. Widely available laboratory tests for diagnosis of meningitis

	Nm	Spn	Hib	GBS
Point of care/rapid diagnostic tests	Commercial multiplex PCR assays – simultaneously detect an array of pathogens at species level (Nm/Spn/Hi/GBS) from a single specimen; do not determine serotype or serogroup			
	Latex agglutination methods – detect bacterial meningitis pathogen species (Nm/Spn/Hib/GBS), Hi serotype b and selected meningococcal serogroups			
	Lateral flow-based method – detects meningococcal serogroups A, C, W, X and Y from CSF	Lateral flow-based method – detects Spn from CSF & urine (urine test non-specific in children)		
Bacterial culture	Direct culture from specimen, inoculated trans isolate (TI) medium (CSF), or blood culture bottle on blood agar plates (BAP) or chocolate agar plate (CAP)	Direct culture from specimen, inoculated TI medium (CSF), or blood culture bottle on BAP or CAP	Direct culture from specimen, inoculated TI medium (CSF), or blood culture bottle on CAP with hemin and nicotinamide-adenine-dinucleotide	CSF or blood: culture on chromogenic or Granada agar
PCR	Real-time PCR assays: species-specific (*ctrA*, *sodC*); genogrouping of ABCWXY	Conventional and real-time PCR assays: species- specific (*lytA, psaA, ply*); multiplexed serotyping assays based on geographic prevalence	Real-time PCR assays: species-specific (*hpd*); serotyping of a–f	Real-time PCR assays: species specific (*cfb*) when culture negative/not available; conventional/real-time PCR 10 serotypes (Ia/b, II-IX)
Whole genome sequencing (WGS)	WGS for species confirmation, capsular genotyping, molecular typing, MIC predictions	WGS for species confirmation, capsule serotype, molecular typing, and MIC predictions	WGS for species confirmation, capsular genotyping, and molecular typing	WGS for species confirmation, characterization of isolates, serotype, MIC predictions, MLST, penicillin binding protein type, various vaccine candidate surface proteins
Antimicrobial resistance	Kirby-Bauer disk diffusion screen for antimicrobial susceptibility testing Minimal inhibitory concentration (MIC) by antimicrobial gradient strips Molecular testing for genetic mutations associated with antibiotic resistance WGS MIC predictions, including PBP2x typing, to detect decreased beta-lactam susceptibility (restricted to pen R for Spn)			

* Culture remains the gold standard for diagnosis of meningitis. Gram stain and rapid diagnostic testing are useful in many places for quick clinical feedback and where laboratory capacity is poor.

4.1.2 Recommended practice

Persons with suspected meningitis should undergo specimen collection from a normally sterile body site as indicated by the presenting symptoms (for example, CSF, blood). In the meningitis belt, TI medium *(68)* is recommended for storage and transport of specimens to a microbiological laboratory with appropriate testing capacity *(69)*. Preliminary identification of the causative agent from CSF includes detection of bacteria by Gram stain and Nm, Spn, Hib or GBS antigen by latex agglutination, but culture and PCR are the only confirmatory

tests. Culture should always be attempted whenever a specimen is obtained, given its relatively low cost and the ability of public-health laboratories to subsequently characterize the isolate. PCR, as more sensitive and allowing for faster results, should be performed on all specimens from suspected meningitis patients when capacity allows. However, PCR testing of blood specimens cannot confirm Spn infections in children since carriers can be positive without invasive disease. Once a causal pathogen is confirmed, identification of the serogroup/type can be important to define control measures.

It is of public-health interest to know the serogroup/type to focus vaccination efforts and to monitor impact of vaccination programmes. Serogrouping/typing can be done on a bacterial isolate (if available from culture) or on clinical specimens positive for a pathogen. Specimens/isolates from confirmed or probable cases should be stored for further strain characterization, such as serogrouping/serotyping and antibiotic susceptibility testing. Laboratories that are unable to perform these tests should transfer the isolate or specimen to a reference laboratory that can perform the tests. Depending on capacity, strain characterization and/or WGS should be performed at national, regional or global reference laboratories (such as, a WHO Collaborating Centre for Meningitis), especially during outbreaks, for country interest, or for other reasons within the country *(11)*.

For identification of maternal colonization by GBS, screening may be performed at 35–37 weeks of gestation. Vaginal or rectal swabs should be inoculated into selective broth medium and sub-cultured onto an agar plate for bacterial isolation and further characterization by DNA probe, latex agglutination or direct PCR (direct or culture-based)*(70)*.

Antimicrobial susceptibility testing (AMST) of isolates is recommended, (for example, by the European Committee on Antimicrobial Susceptibility Testing), to be performed on isolates to monitor emerging resistance. Determination of antimicrobials used for AMST should be based upon those used in the treatment or chemoprophylaxis according to national or regional guidelines. If WGS is performed, resistance-related genes should be characterized. National and regional reference laboratories/WHO Collaborating Centres can be utilized for this when necessary *(11)*.

Quality management systems, such as external quality assessment (EQA) and confirmatory testing between laboratories, should be in place to monitor laboratory performance and ensure that data generated from laboratories are accurate, as laboratory confirmation of a case is essential to case classification in surveillance and treatment decisions in case management by clinicians. WHO, in collaboration with Public Health England, coordinates a global EQA programme consisting of proficient testing panels for Invasive Bacterial Vaccine Preventable Diseases (IV-VPD) that assesses laboratory performance on an annual basis.

4.1.3 Implementation status: global/regional

	Nm	*Spn*	*Hib*	GBS
Confirmation and characterization tests	Rapid diagnosis testing such as latex agglutination implemented at country level; culture and real-time PCR implemented in many countries with some LMIC lagging, particularly in some high incidence countries; Nm genogrouping by PCR widely implemented; Spn serotyping not fully implemented at country-level in LMICs			Common in HIC countries; many LMIC health facilities lack access to diagnostic tests, laboratory capacity or resources to screen for/ diagnose GBS infection
Whole genome sequencing	Common in HIC countries; uncommon in LICs unless through WHO Collaborating Centre Laboratories, regional/global reference laboratories or research institutions			

4.1.4 Barriers to implementation

CSF collection	**LP not allowed to be done by non-physicians in many LMICs because of lack of authorization, training and/or experience. LPs are also not always done by clinicians where indicated because of lack of sterile LP kits, tendency to treat empirically, limited laboratory capacity and case notification requirements not enforced**
Diagnostic R&D	Simple affordable point-of-care diagnostic tests unavailable commercially – limited market for outbreak detection in Africa, opportunities for global market not identified
Laboratory capacity	Challenges not specific to meningitis diagnosis: weak areas in LMICs include microbiology capacity, specimen transportation, laboratory supply procurement, equipment maintenance and laboratory workforce/trained laboratory staff

4.1.5 Gap analysis

	Where we are	Where we want to be
External quality assurance	IB-VPD network supports EQA proficiency test (PT)(Gavi funded); CDC and other international partners support EQA duplicate testing and PT in collaborator countries	Integrated and sustainable EQA in all countries
CSF collection	LPs often not done in suspect cases, especially in rural health facilities. When done, cultures are not undertaken CSF volumes from very young children might not always be enough to perform laboratory testing so laboratories have to prioritize the testing methods	Authorization and training of non-physicians to take LPs; CSF samples taken from majority of suspect cases and sent to microbiology laboratories in transport medium; policy strengthened with clear guidelines in LIC
Health-worker training	Health workers are not routinely trained or resourced to identify potential cases of meningitis	Health workers in village health centres, primary health facilities and hospitals are routinely trained and resourced to diagnose and treat meningitis, with integration into horizontal health systems, protocols and initiatives
Transport medium production	Limited TI production; only a few organizations have the capacity to produce the medium. WHO African facility has challenges in distribution to meet the regional needs; other organizations, such as NIPH Oslo and CDC, provide limited support	Local and sustained production at multiple sites

Whole genome sequencing/global genome library	Limited sequencing capacity at country level	Country-level recommendations developed; regional/global support for DNA extraction and sequencing for countries that do not have the facility Active sequencing and upload
Specific blood marker (or other specimen, for example, urine)	Not identified	Identified, enabling rapid diagnostic test (RDT) development (see below on confirmation capacity)
Capacity to identify Spn serotypes and Nm serogroups at country level	Limited	Availability in all countries
Confirmation capacity	Limited (PCR/culture) at national level; lack of affordable and reliable RDTs for point-of-care (POC) testing Three RDT use cases defined by WHO meeting *(71)*: (i) A POC test to identify the **causative organism including meningococcal serogroup** rapidly at the peripheral level (health centre/district hospital) for epidemic settings, especially in the meningitis belt, in order to determine vaccine response (ii) A RDT for individual case management **at peripheral level** (first contact with the patient) in order to identify bacterial infection and decide on the need for immediate antibiotic Blood test ideal (iii) RDT to identify **multiple meningitis pathogens** such as Nm, Spn, Hib, GBS, salmonella, listeria, echovirus, coxsackievirus, herpes simplex or cryptococcus. Ideally as POC test (on CSF or blood)	Confirmation capacity (culture and rt-PCR for the four main pathogens) available in all countries in at least one national laboratory Development and availability of affordable, quality assured RDTs as defined by WHO in use cases A separate RDT for GBS screening for rapid diagnostics during labour

4.2 Treatment

4.2.1 Recommended practice

(a) Antibiotic treatment regimens

Significant evidence from a variety of observational studies suggests that delayed antibiotics treatment leads to poorer outcomes (72–76), but while ESCMID recommends treatment to begin within the first hour (55) regardless of whether LP has been performed, the Infectious Disease Society of America (IDSA) recommends treatment as soon as the diagnosis is "considered likely"(77). Guidelines from major organizations for empiric antibiotic regimens are broadly convergent in HICs (see Table 17 below). The WHO has issued therapeutic guidelines for children but not for adults (78). In HICs, duration of empiric therapy is not based on evidence but on expert opinion and is typically recommended as 7–14 days (79, 80).

In LMICs, ceftriaxone (if available) is often used as a first line treatment. Evidence from a single multicentric trial has shown that, among children <12 years with meningitis and clinical improvement on day five of treatment, a 5-day empiric course of ceftriaxone is equivalent to a 10-day course for treating meningitis due to Spn, Hib or Nm (81). In the meningitis belt, during meningococcal meningitis epidemics prior to the introduction of MenAfriVac®, single-dose ceftriaxone was recommended as the empiric treatment (82). Since 2014, a 5-day course has been recommended because of concerns over a possible increase in the proportion of cases with a non-meningococcal aetiology necessitating longer treatment courses (56).

Table 17. Recommended antibiotic regimens for empiric treatment of bacterial meningitis

Organization ***Patient age***	**1st line**	**Alternatives**
HICs		
ESCMID **(2016)*(55)***		
<1 month	Amoxicillin/ampicillin/penicillin plus cefotaxime or amoxicillin/ampicillin plus aminoglycoside	
1 month—50 years	Cefotaxime or ceftriaxone plus vancomycin or rifampicin	Cefotaxime or ceftriaxone alone if pneumococcal resistance not a concern
>50y or at risk for Listeria	Cefotaxime or ceftriaxone plus vancomycin or rifampicin plus amoxicillin/ampicillin/penicillin G	Cefotaxime or ceftriaxone plus amoxicillin/ampicillin/penicillin G
IDSA **(2004)*(77)***		
<1 month	Ampicillin plus cefotaxime or ampicillin plus an aminoglycoside	
1 month—50 years	Vancomycin plus third-generation cephalosporin	
>50 years	Vancomycin plus ampicillin plus third-generation cephalosporin	
LMICs		
MSF **(2013)*(83)***		
<1 month	Ampicillin plus cefotaxime	Gentamicin instead of cefotaxime, or cloxacillin instead of ampicillin if associated skin infection
1—3 months	Ampicillin plus ceftriaxone	Gentamicin instead of cefotaxime, or cloxacillin instead of ampicillin if associated skin infection
>3 months	Ceftriaxone	Add cloxacillin if associated skin infection
WHO **(2013)*(78)*** **0—2 months** **>2 months (children)** WHO – **meningitis belt epidemics only (2014)*(56)***	Ampicillin plus gentamycin Ceftriaxone or cefotaxime	Ceftriaxone or cefotaxime, plus gentamycin Chloramphenicol plus ampicillin or plus benzylpenicillin
All ages	Ceftriaxone	

When causative pathogens are identified, antibiotic regimens should ideally be tailored to the sensitivity of the organism (see Table 18). However, recommendations are generally based on country- or region-wide antibiotic susceptibility patterns as individual-level patient susceptibility testing is rarely available, particularly for Nm. Pathogen-specific recommendations have not been developed for LMICs, where a 5-day course of ceftriaxone is recommended.

Of concern in all settings is the increasing rate of pneumococci resistant to third-generation cephalosporins (84). Resistance of meningococcus to third-generation cephalosporins is uncommon, as is resistance to ciprofloxacin and rifampicin. Nonetheless, given resistance patterns in other pathogenic Neisseria species, ongoing microbiologic and molecular surveillance remains important (85).

Table 18. Examples of recommended antibiotic regimens for specific pathogens

Organism Group	1st line	Alternative	Duration (days)
Nm			
ESCMID **PCN MIC<0.1 µg/ml** **PCN MIC≥0.1 µg/ml**	Penicillin or amoxicillin/ampicillin Ceftriaxone or cefotaxime	Ceftriaxone, cefotaxime, chloramphenicol Cefipime, meropenem, ciprofloxacin or chloramphenicol	7
IDSA **PCN MIC<0.1 µg/ml** **PCN MIC≥0.1 µg/ml**	Penicillin G or ampicillin Third-generation cephalosporin	Third-generation cephalosporin, chloramphenicol Chloramphenicol, fluoroquinolone, meropenem	7
Spn			
ESCMID **PCN MIC<0.1 µg/ml** **PCN MIC >0.1 µg/ml** **AND** **3GC MIC <2.0 µg/ml** **3GC MIC ≥2.0 µg/ml**	Penicillin or amoxicillin/ampicillin Ceftriaxone or cefotaxime Vancomycin plus rifampicin, or vancomycin plus ceftriaxone or cefotaxime, or rifampicin plus ceftriaxone or cefotaxime	Ceftriaxone, cefotaxime, chloramphenicol Cefepime, meropenem, moxifloxacin Vancomycin plus moxifloxacin, linezolid	10–14
IDSA **PCN MIC <0.1 µg/ml** **PCN MIC 0.1-1.0 µg/ml** **PCN MIC ≥2.0 µg/ml** **OR** **3GC MIC ≥1.0 µg/ml**	Penicillin G or ampicillin Third-generation cephalosporin Vancomycin plus a third-generation cephalosporin	Third-generation cephalosporin, chloramphenicol Cefepime, meropenem Fluoroquinolone	10–14
Hi			
ESCMID **β-lactamase negative** **β-lactamase positive** **β-lactamase negative-ampicillin resistant**	Amoxicillin or ampicillin Ceftriaxone or cefotaxime Ceftriaxone or cefotaxime plus meroepenem	Ceftriaxone, cefotaxime, chloramphenicol Cefepime, ciprofloxacin, chloramphenicol Ciprofloxacin	7–10
IDSA **β-lactamase negative** **β-lactamase positive**	Ampicillin Third-generation cephalosporin	Third-generation cephalosporin, cefepime chloramphenicol, fluoroquinolone Cefepime, chloramphenicol, fluoroquinolone	7–10
GBS			
IDSA	Ampicillin or penicillin G	Third-generation cephalosporin	14-21

(b) Steroids and other adjunctive therapies

There are few, if any, curative treatments for severe sequelae, so much focus has been on their prevention with adjunctive, non-antimicrobial therapies. A Cochrane review suggested that, among all cases of bacterial meningitis, dexamethasone decreased hearing loss and neurologic sequelae but did not reduce mortality except in pneumococcal meningitis (86). There was significant heterogeneity in the results; notably, there was no benefit from dexamethasone in preventing sequelae in Africa – late presentation was hypothesized to be one of the possible reasons. Few data are available regarding dexamethasone in neonatal meningitis, for which GBS is the main culprit, and current recommendations vary significantly. The IDSA recommends dexamethasone only prior to, or concurrent with, antibiotic administration in adults with pneumococcal meningitis (77). The more recent ESCMID guidelines recommend empiric treatment with dexamethasone for all non-neonatal cases of meningitis, in high-income settings, up to four hours after the initiation of antibiotic treatment (55). Heterogeneity of results and the antibiotic regimens used, as well as study settings, means that no recommendations have been made for LMICs (77). Data regarding other adjunctive therapies (osmotic agents, antiepileptics, etc.) are relatively scant and have not yet shown much promise at reducing case fatality or sequelae. There is a critical need to synthesize evidence on adjunctive therapies to enhance care, particularly in resource-limited regions.

(c) Screening for complications and sequelae

IDSA makes no recommendations. ESCMID recommends formal hearing testing for children and adults during hospital admission. ESCMID does not recommend routine neuropsychiatric evaluation, but instead that patients should be informed about the nature and frequency of cognitive disorders after bacterial meningitis (difficulty with concentration, cognitive slowness or memory deficits). If cognitive defects are suspected, neuropsychologic examination should be performed and referral to a (neuro)psychologist/rehabilitation physician may be indicated. Recommendations state that simple neuropsychologic tests may suffice, for example, the Montreal Cognitive Assessment test. Although severe sequelae are more common in LMICs *(45)*, no guidance has been issued for this setting, either for screening or treatment. Screening and seizure management should be performed according to the WHO mental health gap (mhGAP) guidelines *(87)*.

4.2.2 Implementation status

In HICs, recommendations for antibiotic treatment are well-accepted and widely implemented. In LMICs there is little information about implementation, but anecdotal evidence suggests that treatment guidelines are well-established in the African meningitis belt. Steroids are not used in LMICs and screening for sequelae is not a standard part of meningitis care in many LMICs.

4.2.3 Barriers to implementation

In HICs, there are few barriers to implementation of recommended practices for treatment for all four pathogens. In LMICs, LPs may not be done for several reasons (see 4.1.4) and, particularly in the African meningitis belt, ceftriaxone availability can be limited, which could lead to suboptimal treatment regimens. Limited access to care leads to delays in starting treatment which, in turn, leads to poor outcomes (more deaths and sequelae). Limited microbiological capacities and the lack of affordable and easy-to-use diagnostic tests lead to reliance on empiric treatments. If hospital-level microbiology capacities cannot be reinforced, surveillance should be put in place to ensure appropriate recommendations for empiric treatment. Health-care workers (HCW) in LMICs may not be aware of the importance of screening for acute complications, including seizures, and signs of increased intracranial pressure, as well as sequelae, particularly if no treatment options are available.

4.2.4 Gap analysis

Where we are	Where we want to be
Antibiotic treatment recommendations are established in both HICs and LMICs, although WHO does not currently have guidelines for treatment of adults **Recommended antibiotics are not always available in LMICs**	The shortest-length effective antibiotic regimens continue to be used as a matter of routine Supply of recommended antibiotics for treatment of meningitis is assured at all levels of the health system
Case fatality remains high; the rate of severe sequelae is very high	Outstanding questions are answered about the role of adjunctive therapies, particularly in LMICs. One or more effective, affordable and easy-to-administer adjunctive therapies are available
Screening for complications is not a standard part of meningitis care and management of sequelae is nearly non-existent in many LMICs	National and international guidelines emphasize the importance of screening for important meningitis sequelae, such as deafness Networks are developed for the treatment and support of meningitis survivors with sequelae in all settings Packages of care are developed for all stages of meningitis, from the acute illness to potential sequelae

5. Disease surveillance

5.1 Introduction

Data produced by surveillance are used to detect and respond rapidly to cases, clusters and outbreaks. Surveillance data allow evaluation of changes in the epidemiology of bacterial meningitis, over time, to guide public-health policy, development and implementation of prevention and control strategies (for example, vaccine introduction) and monitoring of their impact. Collection of invasive disease-causing isolates from a broad and representative population is an important contribution to inform vaccine policy and guide development of new vaccines, as well as to monitor the circulation/emergence of epidemic strains.

Surveillance for GBS needs particular attention as it is virtually nonexistent, or meagre, in most regions/countries. Quantifying the burden of neonatal GBS disease remains a challenge even in HICs; clinical characteristics are non-specific and often difficult to differentiate from non-infectious causes *(88)*. Invasive infections are most commonly diagnosed based on isolation of GBS from a normally sterile site (for example, blood, CSF) in microbiological culture; however, sensitivity of blood culture varies depending on the bacterial load, blood volume collected and culture method, and typically requires 36 to 48 hours for positive results to become available. Many GBS infections in newborn babies are not culture-proven; isolating pathogens in samples taken from babies whose mothers have received intrapartum antimicrobial prophylaxis is particularly problematic. Estimating GBS disease burden in LMIC is even more difficult: a portion of births may occur outside hospital settings; facility-born infants may be discharged quickly after birth; care seeking, particularly early in life, may be limited; access to care, particularly in rural areas, may pose challenges, and health facilities may lack access to diagnostic tests, laboratory capacity or resources to diagnose GBS infection. As a result, particularly for early-onset disease, most of which occurs within the first 24–48 hours of life, GBS disease is likely to be under-represented in studies from these settings.

5.2 Recommended surveillance practices

(a) Surveillance type

	Nm	*Spn*	*Hib*	GBS
Main surveillance objective	Detect cases and outbreaks Inform vaccine policies Monitor vaccine impact	Inform vaccine policies Monitor vaccine impact	Inform vaccine policies Monitor vaccine impact	Burden of disease (including early/late onset disease, stillbirths, pre-term birth, maternal infection) Support evaluation of the potential impact of a new vaccine
Recommended type	Meningitis embedded into invasive Nm disease: nationwide, case-based, among all ages; laboratory main point-of-entry	Meningitis: Sentinel hospital surveillance - case-based, paediatric. Embedded into invasive Spn disease. Should include children <5 years of age, but can be expanded to include older children and adults*	Meningitis: sentinel hospital surveillance; case-based, paediatric, for all Hi Embedded into invasive Hi disease; sentinel, laboratory point-of-entry, children <5	Laboratory population-based; babies <3 months of age Colonizing GBS and antibiotic administration in maternal infections Clinical surveillance in a population-defined region Sentinel sites – invasive disease (meningitis and septicaemia), stillbirths when possible
Multi-pathogen approach	Integrated bacterial meningitis surveillance (syndromic) For outbreak detection: aggregated data, laboratory information limited; integrated into IDSR (AFRO) For vaccine policies: case-based data; systematic laboratory information			Invasive bacterial pathogens (CDC)*(89)*

* Including older age groups is useful to assess herd protection and serotype replacement.

(b) Three main surveillance components

To meet the objectives, each country should design and implement a surveillance system integrating public and private health actors and covering major surveillance components: epidemiology (case detection, data analysis); laboratory (species confirmation, molecular characterization) and data management (tools to report, collate and present data). Several guidelines and standard operating procedures (SOPs) are available at a global and regional level describing standards and recommended tools *(65)*. Each country should adapt these guidelines as part of their enhancement of national surveillance practices *(90,91)*.

(c) Regional reporting and dissemination of information

To allow for the monitoring of the epidemiology in each WHO Region, country data should be reported and disseminated systematically (for example, for the African meningitis belt *(92)*). An innovative project monitoring child mortality is the CHAMPS Network that tracks the causes of under-five mortality and stillbirths at sites in sub-Saharan Africa and south Asia *(93)*. A good example has been developed for Europe *(94)*. International collaboration on molecular surveillance (global genome library and metagenomics) is key, with easy country access to reference centres.

5.3 Implementation status: global/regional

Neisseria meningitidis	***Streptococcus pneumoniae (SP)***	***Haemophilus influenzae type b***	**Group B streptococci (GBS)**
Invasive disease surveillance completeness: **Western Europe, Americas, Australia: high** **Rest of the world: low, challenged because of high burden, poor infrastructure or data management**	WHO IB-VPD network Implementation is high and assessing vaccine impact is challenging. Few countries: IPD notifiable nationally (USA, Europe)	WHO IB-VPD network Implementation is high	Limited in LIC, extremely variable in HICs and MICs; examples of strong surveillance in USA (HIC), South Africa (MIC), Mozambique (LIC).
***Integrated bacterial meningitis completeness*:** **African belt (26 countries): high (aggregated part of IDSR) – case based in sentinel districts in five countries (MenAfriNet)** **All regions: sentinel sites (IB-VPD network); conducted with international regional reference laboratories**			

5.4 Barriers to implementation

Policy	**Not considered as a high priority in many regions (WPRO, SEARO) -> no guidance for surveillance implementation in country (some countries have clear guidelines, the majority do not)**
Financing	Surveillance is still externally driven in the majority of LIC
Support functions	Laboratory: logistics for LP. Sample transport, laboratory supplies procurement, international shipment, maintenance of equipment, quality control Data management: decentralized access to online tools Dedicated human resources

5.5. Gap analysis

		Where we are	Where we want to be
Policies	National systems	Partial implementation	All countries have designed and implemented a national surveillance system
	Global VPD surveillance guidelines	IMD/IPD surveillance not implemented in three regions	Global implementation
	GBS Surveillance guidelines	No international reference, not a notifiable disease	International guidelines available Standardization of case definitions and ascertainment methodologies for GBS disease Strong platforms for invasive GBS surveillance in each Region
Epidemiology	Suspect case definition of meningitis	Clinical, very sensitive	Through research a more specific case definition has been adopted Etiology of non-confirmed suspected cases
Laboratory	National confirmation capacity	Partial (African example in Fig.1)	All countries have national reference confirmation capacity and serogrouping/typing
Global burden	Monitoring global burden	Models of global meningitis burden differ widely in their estimates Meningitis data on burden is stored, in many places, based on pathogen. There is no single place to see this information and help track baseline progress	Convergence and increased confidence in burden estimates from different models A single source of data (synthesizing existing sources) exists for Nm, Spn, Hib and GBS to enable tracking of progress against meningitis
	Molecular surveillance	Done through dedicated expert centres Need for bioinformatics support to interpret sequence-based information	Strain identification and tracking is coordinated globally Global genome library allowing sequence-based global surveillance for meningitis pathogens
Data management	Case-based data management tool	Various available (Epi-Info, Excel, etc.) Transmission of information too slow Laboratory and EpiData not linked	Various options available Data integration into recommended regional tool Online tools are used
	Country reporting to the international level	Good in the African belt (WHO) and western Europe (ECDC)	Country data sent to the regional level Regional databases gathering country data in all Regions All Regions report country data

6. Support and after-care for families and survivors

6.1 Introduction

Given the high case-fatality rate and severity of complications and sequelae, the burden of meningitis on people and families is high (see 2.4). Because bereavement and disability are common features of life after meningitis and sepsis, suitable services and resources for survivors and their families play a vital role in support and after-care (though bereavement often requires shorter-term support and disability support can be needed for a lifetime). Providing appropriate support and after-care for survivors of meningitis with these types of sequelae requires sensitivity to both medical and human rights issues. Disability is a recognized issue of human rights addressed in the WHO Global Disability Action Plan (95) in alignment with the Convention on the Rights of the Child and the Convention on the Rights of Persons with Disability (CRPD)(96). Acquired impairment, such as limb loss, can require medical support throughout a person's life, and disabled people often have health-care needs requiring long-term medical treatments. The ongoing psychosocial impacts of bereavement and disability can have both medical and rights-based dimensions. Both disability (the environmental limitations and barriers to a fulfilling life) and impairment (often a physical or neurological condition) are therefore relevant when considering how to provide suitable support and after-care to families and survivors.

Discrimination against people with disabilities has existed in every community throughout history and persists today, but it is not inevitable. Powerful and effective advocacy by disabled people's organizations (DPOs) over the past 30 years has led to emergent recognition of the need to move from an approach largely rooted in terms of medical and rehabilitative needs (the medical model), towards a reframing of disability in terms of human rights, focused on equity, non-discrimination and social inclusion (the social model). Equity represents the fundamental starting point. It demands that all children have an equal opportunity to survive, develop and reach their full potential without discrimination, bias or favouritism. Realizing that goal for children with disabilities requires an awareness of the barriers that impede the realization of their rights in order that they can achieve the same access as all other children to education, health care, sanitation, clean water, protection and other services necessary for their survival, growth and development. The same principles of equity apply to adults with disabilities. This requires a commitment to mainstreaming disability as an integral part of the strategies relevant for sustainable development.

6.2 Recommended practice: rehabilitation and psychosocial support

The type of support and after-care needed for an individual and/or their family is dependent on the consequence of the meningitis incidence (for instance, if someone died, or they survived with sequelae, or they survive without sequelae), age, severity of impairment, individual response, availability of services, available financial resources and cultural context. Therefore, no standard support model exists for all aspects of meningitis after-care and support, although WHO has extensive guidance on community-based rehabilitation (97) which has many relevant features (for example, for early year's rehabilitation and for assistive devices) and an overarching goal to see people with disabilities achieve their highest attainable standard of health.

In order to deliver an effective rehabilitation programme in the community and at home, an initial assessment should be performed to determine the person's concerns and priorities so that he or she understands why particular exercises and advice are given. Engaging people in planning their own treatment increases their motivation and is in line with the person-centred care approach. When family members are involved in planning treatment, the individual will have support for day-to-day activities at home. Specific interventions to improve mobility, functioning and daily activities, swallowing and speech, and to reduce pain and fatigue,

should be part of a tailored rehabilitation programme for each individual. Neuro-rehabilitation is critical for people suffering from functional sequelae of bacterial meningitis *(97)*.

The effects of interventions on functioning and overall recovery should be monitored regularly and adjustments made, as necessary.

However, key features of support and after-care can include (but are not limited to):

- suitable discharge information and service sign-posting (98);
- discharge follow-up assessments either at a health facility, in the community or at home;
- ongoing medical assessment and treatment;
- community-based rehabilitation services (cross-cutting);
- access to specific disability support (for example, hearing aids, wheelchairs, external fixators for limbs, prostheses);
- access to trained health workers with specific sequelae expertise or knowledge;
- rehabilitation and physiotherapy services;
- psychosocial support services (specialist and/or community based) especially for bereavement;
- health-care access support (for example, financial support and transportation to get to a health facility);
- proactive encouragement and involvement of patient groups;
- facilitated legal redress for substandard health care;
- suitable national and legal frameworks embedding the rights of disabled people.

Because of the high burden of meningitis for survivors and families, the Wilton Park meeting in May 2017 made two crucial recommendations:

- to ensure a step-change in support available to survivors and their families;
- to ensure that survivor care is seen as an intrinsic part of any meningitis response – a distinct strand but fully integrated in these responses.

6.3 Implementation status

There is no systematic global measurement of implementation for support and after-care for meningitis survivors or support for their families, but very few receive all the support and after-care they believe they need. Bereavement experience and practice also varies greatly by culture (7) making a standard model even more unlikely.

Certain features of the experience of bacterial meningitis – particularly its speed and severity of impact – might make tailored support necessary. However, the majority of support required has more in common with a wide range of disability causes and, rather than creating or strengthening vertical support mechanisms, working with horizontal disability support services could be more beneficial and cost effective.

It is known that, in general, access to support services is often resource-dependent at both a national and

CASE EXAMPLE 1: GETTING HEARD IN PARLIAMENT

UNICEF Montenegro supports a children's session of the National Parliament, in partnership with a local NGO, Centre for Child Rights. They organize workshops with children to enable members of school parliaments from all municipalities to identify the most urgent issues that children are facing. The job is to propose possible solutions and to prepare questions for the key decision-makers. Heads of political parties of the parliament, all ministers, the Ombudsman and representatives of national institutions participate in this children's session of the National Parliament every year on 20 November.

It's About Ability campaign was initiated in September 2010 by UNICEF and the Government of Montenegro to address the social exclusion and discrimination of children with disabilities. In 2011 and 2012, a parliament session was dedicated to inclusion in society. The children especially emphasized the importance of creating conditions for inclusion of children with disabilities in Montenegrin society. Participants noted that Montenegro needed to reduce the number of children living in homes and to increase the number of children living with families, including foster care or other alternatives to placement in institutions. The children's session of the Montenegrin Parliament lasted for two and a half hours and was broadcast live on the public service television TVCG.

According to the latest findings on the attitudes of Montenegrin citizens towards inclusion of children with disabilities, from January 2015, Montenegro is consistently progressing on the road to becoming an inclusive society. The percentage of citizens who find it acceptable for a child with disability to attend the same class with their peers increased from 35% in 2010 before the campaign to 78% in January 2015. Similarly, the percentage of Montenegrin citizens who find it acceptable for a child with disability to be the best friend of their child increased from 22% in 2010 before the campaign to 60% in January 2015.

Source: *(99, 100)*.

individual level. In developed economic settings, and for wealthier individuals, more services are widely available than for those in low-resource settings or for those in poverty. Whilst clinicians and the medical profession can play an important role in support and after-care, it is often families and communities, alongside civil society and faith/community groups, who complete the network of services, and often provide the majority of care needed to provide good support and after-care. Getting a clearer picture of how support and after-care for survivors and families after meningitis relates to existing services, and what is already available, is a key piece of research required during the roadmap process.

6.4 Barriers to implementation

Despite knowing the importance of prevention and early detection for the support of children and adults with disabilities, little progress has been made. Obstacles are seen in the early detection of the disability, due to lack of knowledge of relatives and professionals, and a lack of appropriate diagnostic services. As a result, parents or family members may delay their request for specialized services resulting in permanent disability that could be preventable.

Because bacterial meningitis is usually seen as a vaccine-preventable condition that can be treated with antibiotics at the point of incidence, measures taken to defeat it have historically focused on a medical model of prevention (vaccines), diagnosis (developing bacterial cultures) and treatment (antibiotics). However, unlike the organisms that cause meningitis, support and after-care for sequelae such as deafness, neurological impairment or limb loss, are not meningitis-specific by nature. Meningitis and sepsis cause them, but they are also conditions resulting from congenital impairments or acquired through other life-changing events. It is therefore easy to lose sight of them in the overall picture.

A paradigm shift is needed in the way we think about meningitis, to recognize the functional and psychosocial sequelae of meningitis whilst at the same time taking action to integrate responses within existing initiatives in the disability and support field.

WHO and UNICEF recognize multiple barriers and problems for disabled people that are relevant to those affected by meningitis (Table 19).

Table 19. Examples of barriers for disabled people (adapted from WHO (101) and UNICEF (102))

Barrier	Example
Prohibitive costs	51–53% of people with disabilities are unable to afford health care compared to 32–33% of non-disabled people
Limited availability of services	In low-income settings, services frequently do not exist
Physical barriers	Uneven access to buildings (hospitals, health centres), inaccessible medical equipment, poor signage, narrow doorways, internal steps, inadequate bathroom facilities and inaccessible parking areas create barriers in and to health-care facilities
Inadequate skills and knowledge of health workers	People with disabilities were more than twice as likely to report finding health- care provider skills inadequate to meet their needs, four times more likely to report being treated badly and nearly three times more likely to report being denied care
Stigma, discrimination and violence	Stigmatizing attitudes or discriminatory behaviour from communities to accept a child as a member with equal rights with other children, or based on prejudice, such as "children with disabilities are more difficult".
Decision-making	The voices of children with disabilities are largely silent in critical decisions affecting their lives – decisions about their health and education, or where they live. Mostly due to prejudice and negative attitudes around the world, adults have low expectations for children with disabilities, doubting their capacity to develop or express a point of view

6.5 Gap analysis

The gap between what exists and what is needed is huge. Although most issues identified are not meningitis-specific, they are highly relevant to improving support and after-care for survivors and families after a meningitis diagnosis.

Issue	Where we are	Where we want to be
Cost	• High cost of health care reducing access to those in need	• Affordable health-care services
Policy and legislation	• Inconsistent or absent policies • Lack of connection between policies and CRPD • Lack of sanctions for failure to deliver • Lack of services • Voices of people with disabilities are largely silent in critical decisions affecting their lives	• Stronger policies • Available services • Planned improvements for access and inclusion • CRPD aligned legal frameworks. Health-care standards related to care of persons with disabilities with enforcement mechanisms • Participatory environment at the national, local and community level by involving children and adults with disabilities in decisions affecting their lives • Comprehensive regulatory framework with inclusion of specific objectives regarding the rights of children with disabilities in education, health and social services, and monitoring of the allocation of funds for their implementation
Financing	• Lack of affordable public or private health financing and insurance • Unequitable access to public-health programmes	• Where private health insurance dominates health-care financing, cover for people with disabilities and measures to make the premiums affordable

	• Lack of comprehensive assessment, treatment and follow-ups • High out-of-pocket expenses	• People with disabilities benefit equally from public health-care programmes • Financial incentives to encourage health-care providers to make services accessible and provision of comprehensive assessments, treatment and follow-ups. • Options for reducing or removing out-of-pocket payments for people with disabilities who do not have other means of financing health care services
Service delivery	• Limited modifications and adjustments made to facilitate health access • Variable information, training and peer support • Sporadic use of community-based rehabilitation • Lack of targeted interventions based on need	• Broad range of modifications and adjustments (reasonable accommodation) to facilitate access to health-care services • Empowerment of people with disabilities to maximize their health by providing information, training and peer support • Detailed responsibilities of all professionals in the health, education and social protection system developed on the identification and referral of children with disabilities • Community-based rehabilitation (CBR) to facilitate access for disabled people to existing services • Identification of groups that require alternative service-delivery models, for example, targeted services or care coordination to improve access to health care
Human resources	• Limited training on disability for health-care professionals • Low use of evidence-based guidelines	• Integration of disability education into undergraduate and continuing education for all health-care professionals • Evidence-based guidelines for assessment and treatment
Data and research	• Infrequent inclusion of people with disability in health-care surveillance • Some research exists on needs, barriers, and health outcomes for people with disabilities	• People with disabilities and also people/children with special needs or developmental retardation included in health care surveillance • More research on the needs, barriers and health outcomes for people with disabilities
Bereavement	• Lack of trained psychosocial support for bereavement	• Trained psychosocial support for bereavement more widely available
Sequelae-dependent services	• Lack of services • Lack of resources for services	• Suitable services for survivors and families, tailored to sequelae and context • Facilities for audiological assessment and management of patients after meningitis

7. Advocacy and information

7.1 Advocacy

7.1.1 Introduction

Advocacy can drive lasting change and makes the case for that change. Advocacy goals for meningitis include better protection against meningitis, better diagnosis and treatment, and better support and after-care for those who have experienced meningitis, and their families. Meningitis advocacy takes place at several levels. Advocacy targets decision-makers, opinion leaders/influencers and key stakeholders in governments and institutions, to support and implement actions. At a macro level, this means changing international or national policy to support objectives. At a meso level, advocacy can entail changing technical or local policy and practices. At a micro level, advocacy entails changing the practice of programme implementers and mobilizing community voices to support desired changes. Those who understand meningitis can be the strongest advocates for change, whether they are academic experts, health professionals or affected individuals (103). It is often citizen representative groups, non-governmental organizations (NGOs) or families/individuals who have been affected, who act as advocates towards defeating meningitis.

Prevention advocacy goals for meningitis include: meningitis being prioritized as a global-health issue; more accurate data on global burden of meningitis being available and easily accessible; new, effective, affordable vaccines being developed and manufactured; policies and funding being in place that support introduction and optimization of vaccine schedules; increasing awareness of vaccines and VPDs (104, 105), and encouraging vaccine uptake (106). In addition to reducing GBS disease, a safe and effective GBS vaccine would also reduce the amount of antibiotics against GBS disease being given to women in labour, and in HICs increase the choices women have over where they give birth.

Diagnosis and treatment advocacy goals for meningitis and its sequelae include: development of a new RDT for meningitis; better supply of affordable antibiotics; health professionals routinely providing evidence-based safety netting information; health-worker training, including management of meningitis, and materials/resources for routine health-worker education including meningitis. Facilities for audiological assessment and management of children recovering from meningitis are crucial for the detection of significant hearing impairment and the implementation of rehabilitation programmes.

After-care and support advocacy goals for meningitis include: ensuring health services for after-care and support; health services providing suitable signposting of after-care support, and a suitable legal framework in place that supports the rights of those with ongoing after-effects, impairments and disabilities.

CASE EXAMPLE 1: Increasing vaccine uptake

During the introduction of the MenAfriVac® vaccine into the African meningitis belt, there was a challenge convincing adolescents and young adults, particularly males between 15 and 29 years of age, to take part in the vaccination campaigns (107). Several new strategies were employed in social mobilization that contributed to success in increasing vaccination rates in this population, including peer education, vaccination lines for young boys only, targeted social mobilization messages, the participation of celebrities known to young people and the launch of vaccination campaigns in universities and schools. In other populations, community discussions with the aim of engaging tribal and administrative leaders, or the use of social mobilization through public criers and other techniques, before, after, and especially during the official ten days of the vaccination campaign, improved outreach to the desired targets. The same approaches and strategies, involving administrative, tribal and religious leaders, were applied in Nigeria, a country that introduced the vaccine over four years. This led to an increase in participation among young people and a demand for additional vaccine doses during the subsequent phase of introduction in 2013.

CASE EXAMPLE 2: Advocacy to change government policy

a) For two decades, the scientific community had been developing an innovative new MenB vaccine for the European market. In the United Kingdom, MenB had been the leading cause of death from meningitis since the introduction of the successful MenC programme in the 1990s. Despite new evidence of efficacy, the United Kingdom government at first rejected, and then accepted, MenB into the infant schedule in 2015. The introduction of the vaccine followed years of campaigning by a civil society organization (CSO) through a social media #wheresourvaccine campaign, petitions, press releases, cost evaluations, evidence to support more favourable parameters for cost-effectiveness evaluation, letters to the appropriate health authority (Minister of Health) from clinicians, scientists and professional medical bodies (such as, the Royal Colleges), events for members of parliament and collaborative working with sector partners.

b) Advocacy need not be limited to vaccines, however. A CSO campaigning in the United States of America in the 1990s, and supported by leading clinicians, led to a national recommendation from the CDC in 2002 for universal antenatal screening for GBS carriage. Similarly, again in the United Kingdom, a CSO focussed specifically on GBS has worked since 1996 to improve clinical and public knowledge and awareness of GBS, keep GBS prevention on the national agenda and advocate improvements to the national prevention programme. This campaigning has led to significant improvements to national prevention recommendations on GBS, and markedly increased public awareness and knowledge of GBS.

CASE EXAMPLE 3: A current gap? The need for advocacy with vaccine manufacturers

In July 2015, WHO sounded the alarm over insufficient stockpiles of vaccines, as the threat of epidemics caused by serogroups W and C appeared to be increasing in the African meningitis belt. Shortages were arising because of manufacturing issues, unpredictability of demand and economic reasons, leading to a limited supplier base. While there are currently three quadrivalent conjugate vaccines (A, C, W, Y) licensed and WHO prequalified, their current high costs and limited availability make them, for the time being, unaffordable for African countries. Despite efforts to smooth the transition from polysaccharide vaccines to conjugate, vaccine manufacturers have started phasing out production of affordable polysaccharide vaccine production in favour of conjugate vaccines, which confer longer-lasting protection and herd immunity. Advocacy is required with vaccine manufacturers to meet current and future vaccine demands, ideally from affordable conjugate vaccines.

7.1.2 Recommended practice

There is no single set of recommended advocacy approaches for meningitis, but the following model contains key elements taken from successful examples and experience of practitioners, for example, Save the Children's Advocacy and Campaigning Course.

- Set clear advocacy goals.
- Plan strategies and resources and allow for evolution based on dynamics and feedback from the campaign as it evolves.
- Take a culturally- and gender-sensitive approach to all aspects of the advocacy campaign.
- Identify and segment stakeholders, influencers and decision-makers and provide a clear communication/engagement plan for each audience or stakeholder group.
- Build a case for change using evidence and respected/trusted voices.
- Involve experts and credible influencers who can also act as spokespeople and sponsors.
- Create awareness that builds to a crescendo around intended point-of-action (policy decisions, vaccine decisions).
- Engage stakeholders and potential supporters in all aspects, including planning.
- Boost the skills of delivery teams in community dialogue and other interactive techniques, if necessary.
- One approach is not suitable for all *(108)*. Use subjects from the target recipient groups (for example, age group) in designing advocacy/information materials, to ensure materials are tailored appropriately, are effective and also understood.

7.1.3 Status

Advocacy is an output, not an outcome, and its success is measured on whether its intended goals are achieved. This varies by campaign and activity and makes a current status hard to assess.

However, the history of meningitis advocacy can be seen in three phases. The focus of early efforts of advocacy, brought on by rising population demand and technological advances, was to develop vaccines and get them introduced into countries that could afford them. The second phase, starting in the 1990s, identified sub-Saharan Africa as the area of the world with the highest burden and epidemic potential and, following the development of conjugate vaccines, major efforts were focused on the Meningitis Vaccine Project that went on to successfully vaccinate over 300 million people, for eight years, against NmA. The third phase started in 2015 with the new Sustainable Development Goals (SDGs) providing a framework for health and wellbeing around the world, including a vision for universal health care including ‘leaving no one behind’ as a key principle and access to affordable vaccines.

Today, many NGOs, companies, institutions and health organizations continue to make the case for new vaccines, stronger health systems and better after-care. WHO, UNICEF and NGOs such as MSF, Meningitis Research Foundation (MRF) and the Confederation of Meningitis Organisations (CoMO), are advocating for a new global plan for meningitis aligned to the SDGs, with the principle of good advocacy identified as a core feature of the roadmap. However, meningitis continues to be under-represented at the top table of global health, despite its burden remaining high and progress lagging substantially behind that of other VPDs (1). The next decade of advocacy will need to address this in full, demanding change from governments, institutions, funders, officials and populations alike.

The introduction of MenAfriVac® across the African meningitis belt has dramatically reduced the burden of MenA disease. However, this success, as well as its economic impact, will not be maintained without a long-term immunization strategy. The success of MenAfriVac® vaccine has attracted high-level political and popular interest, and forward-looking ministries of health can channel this high-level interest towards strengthening routine immunization to achieve maximum vaccination coverage and public-health benefits. MenA introduction provided an opportunity to address inequity issues, as well as to contribute to achieving regional immunization targets. Disease burdens tend to be disproportionately concentrated in more marginalized

populations, hence, reaching more people will not only achieve a greater degree of equity, but will also achieve a greater health impact and contribute to economic development.

7.1.4 Barriers to implementation

Barrier	Issues
Poor data and story	Paucity of data at national and international level means telling the story of meningitis in a coherent way to influence global-health policy and engage citizens is very difficult.
Funding	Meningitis is not seen as a global and regional health priority and funding for advocacy is therefore not prioritized and is spent on other diseases.
Prioritization	As meningitis is not seen as a global health priority, most large NGOs do not choose to advocate for meningitis, and smaller NGOs find it more difficult to source funds to do so. This continues the mismatch of priority with burden.
Bias	Because meningitis has been missed as a global health priority, highlighting that meningitis and sepsis results in a similar number of deaths to malaria in under 5-year-olds worldwide is met with disbelief. This bias is a major barrier to the success of global advocacy for meningitis.
Vaccine hesitancy	People are becoming more skeptical about vaccines due to misinformation and confusion about multiple vaccines. Advocating for vaccine uptake with clear and consistent messages, aimed at the specific audiences (not only the person who delivers the vaccine and the recipient, but also those who influence them) is therefore essential.
Horizontal/vertical programme thinking	Meningitis needs to be placed alongside other VPDs for training purposes and health programming, but struggles to get space, being dismissed as a single issue.
Monitoring and accountability	No one is tasked with monitoring global progress on advocacy and so there is no one who is responsible for building the skills and networks necessary to span different contexts and settings.

7.1.5 Gap analysis

Advocacy is needed to improve the recognition of meningitis as a global, regional and national priority. Examples of gap analyses where advocacy can play a key role are shown below.

	Goals	Where we are	Where we want to be
Advocacy	Better protection	Meningitis is not seen as a global health priority in proportion to its burden, especially after the success of MenAfriVac® introduction in the African meningitis belt Funding is not in place to roll out a new effective pentavalent meningococcal vaccine when available for Africa Many vaccines are available, but often not affordable or accessible for those who need them most Low population engagement resulting in low awareness; vaccine confusion; vaccine hesitancy and anti-vaccination movements; low engagement with community leaders, all resulting in sub-optimal vaccine uptake	Meningitis is seen as a global health priority in order to meet SDG3 and features WHO, Gavi the Vaccine Alliance and regional health priorities and plans Funding is secured for the roll out of the pentavalent vaccine Manufacturers produce affordable, effective vaccines that are available for use in outbreak and epidemic settings Populations have routine access to protective vaccines as part of universal health care provision High level of community engagement with widespread communication about safety of vaccines and addressing inaccurate information about adverse effects. High demand for vaccines and and high uptake
	Earlier diagnosis and better treatment	Low population recognition of symptoms and seriousness of meningitis, resulting in late consultation, diagnosis and treatment	Increased communication and community engagement resulting in population awareness of meningitis signs and the importance of early consultation
	Better after-care and support	Lack of services to manage sequelae and information on how to access them Inconsistent and frequently absent legal frameworks that support rights of disabled people Limited links between government health services and other service providers, for example, NGOs	Families and survivors of meningitis have access to affordable services and know how to access them Legal frameworks exist in every country that support rights of disabled people Partnerships between civil society, including NGOs and government

7.2 Information

7.2.1 Introduction

Suitable awareness information and resources for populations, at-risk groups and health workers, as well as specific information for people that have been directly affected by meningitis and sepsis, and their families and communities, can play an important role in defeating meningitis.

Meningitis poses specific communication challenges. The rapid onset leaves little time to act, increasing the need for good, targeted information. It is frequently confused with other fever-causing diseases, such as malaria, increasing the need for good quality health-worker resources and training. Disability is a common feature of life after meningitis, meaning good after-care information is essential.

Effective information can make people aware of the need to get vaccinations (104, 109) and increased demand from populations is known to increase vaccine uptake (106). Effective communication can increase acceptance and demand for vaccination and help caregivers and communities to know the signs and symptoms and make timely decisions to seek health care (87,89,93).

Information encourages people to seek help when they need to, based on an awareness of signs and symptoms, though knowledge alone is often insufficient to translate intent into behaviour (110). Awareness information needs to include the typical signs and symptoms and the potential outcomes, together with what action the patient and/or their carers should take if signs consistent with meningitis or sepsis arise, appropriate to their situation/location and available resources. Information, in the form of clinical guidelines, and simple summaries of these guidelines for relevant clinicians and health workers, can help to ensure health workers and clinicians are trained and resourced to respond. When it exists, information can also help to ensure patients are signposted to the services they need to support them.

CASE EXAMPLE 1: Spotting the sickest children in Malawi

An impact assessment study using Theatre for Development as a tool for raising awareness of symptoms of severe illness and improving primary level health-seeking behaviour in Malawi, found that there was evidence of a significant change in response times to seeking treatment and recognition after information-sharing through theatre. From July 2015 to July 2016, the African Centre of Communication for Development (ACCD) implemented a health campaign using Theatre for Development as a communication tool in two townships in Blantyre, namely: Mpemba and Ndirande. The project was supported by the Malawi Liverpool Wellcome Trust with funding from the Meningitis Research Foundation (MRF). Before the intervention, caregivers lacked the ability to recognize severe symptoms. After the intervention, caregivers recognized symptoms quickly and responded in line with the message of the theatre production.

CASE EXAMPLE 2: Getting adolescents vaccinated in the United Kingdom

Starting in 2009, the United Kingdom saw a rising incidence of deadly MenW meningitis in teenagers. Despite vaccine availability, uptake was low due to lack of information, misunderstanding and low awareness of the new MenACWY vaccine that offered protection. Targeted social media advertising was distributed to mothers of new students, and to new students. A direct postal mailing was delivered to all parents of first-year students. An online 'eligibility checker' also provided accurate information to avoid confusion over vaccine eligibility. Posters and fliers were distributed directly to students at universities. This resulted in ~70 000 additional vaccinations compared to the same period in previous years without the same level of information distribution.

7.2.2 Recommended practice

There is no single recommended global practice for meningitis information and communication. Academic literature on approaches to awareness and information tends to focus on specific conditions in specific locations. For example, studies in Malawi have suggested that, in resource-poor settings, radio is an effective tool for increasing the exposure of men to health information. However, radio was not compared to other means of communication, and responses to radio may vary in different regions (111).

This means that success in terms of delivering meningitis information will involve the need for assessment and insights development dependent on objectives and audiences and the testing of multiple approaches. It will require collaboration through a range of experts – experts in the condition, in government bodies, in the location and its infrastructure, in the local medical structures and in-patient involvement and in-patient groups, as well as in communications skills, both for medical and lay audiences.

Table 20 below shows the different functions communication can perform in the care pathway and can be used as a guide for recommended information types.

Table 20. Some useful roles for meningitis information resources

Prevention and capacity-building	Diagnosis	Treatment	After-care and support
Awareness of vaccines Access to health services and to vaccines Awareness of high-risk groups/activity Awareness of antibiotic prophylaxis When/how to seek help, including safety- netting information Health-worker training	Awareness of signs and symptoms Provision of diagnostics	Access to antibiotic prophylaxis Reassurance for local populations when there is a case Health-worker resources	What to expect Service signposting Legal redress

Table 21 shows the recommendations for improving practice arising from the Wilton Park meeting in May 2017. Across all areas there was a demand for improved practice and involving communities in need assessments.

Table 21. Wilton Park recommendations for improvement

Information
a. Make meningitis education a routine part of health information campaigns. b. Further develop a standardized rapid response/disaster recovery education strategy. c. Create a new template of resources for meningitis education materials. d. Establish national, regional and international networks of best practice to raise awareness. e. Provide data and analysis to governments on, for example, the economic and social costs of meningitis outbreaks. f. Ensure survivor support is included in all information about meningitis available to people and communities (112).

Additional GBS-specific recommendations would be to ensure that GBS education is a routine part of information provided to new and expectant parents by knowledgeable health-care providers, and to create a new template of resources for GBS information and education materials for new/expectant parents and their health-care providers.

7.2.3 Implementation status

Global implementation of effective information practice is variable or low across all areas set out in Table 22. This is partly dependent on relative economic development and also disease incidence.

Table 22. Implementation status variability by setting

	Low incidence	High incidence
High income	Example: The United Kingdom Good information widely available Good signposting and support services Legal redress available	N/A
Low income	Example: Malawi Little/no information Few support services Training for HCWs not routine Few meningitis HCW resources Few support services	Example: the African meningitis belt Information on other diseases (for example, malaria) may be more prevalent than meningitis and sepsis14 Episodic bursts of information around major campaigns/outbreaks (113) Training for HCWs not routine Few meningitis HCW resources Few support services

Organizations like CoMO and MRF and, for GBS, Group B Strep Support, supply information for the public and health professionals on prevention, diagnosis and treatment, and also support and after-care, but this is not available to, or adapted for, all countries affected by meningitis and sepsis.

Guidelines for health professionals are also produced on a country level by country experts (such as the United Kingdom's *Meningitis and meningococcal septicaemia in under 16s: recognition, diagnosis and management guideline* (114)) and, more broadly, by the WHO (56,78).

Research gauging awareness of meningitis is limited, although examples do exist in some countries.

14 Recent interviews by MRF into community awareness in Uganda concluded "…community awareness of the signs/symptoms, cause and fast-action of meningitis is very low. General symptoms were never recognized as meningitis and were almost always assumed to be malaria".

7.2.4. Gap analysis

		Where we are	Where we want to be
Information	Awareness of available vaccines	Low population awareness Multiple vaccines (types and doses) causes confusion Vaccine hesitancy/anti-vaccination movement (objections/concerns about safety) Lack of engagement with community leaders	High population awareness of available and different types of vaccines High population confidence in vaccines Engaged community
	Awareness of non-vaccine prevention strategies for GBS, meningitis and sepsis	Low population awareness Different strategies in different countries/regions Confusion over efficacy	High population awareness of available prevention High population confidence in prevention strategy Engaged community
	Awareness of signs and symptoms	Low awareness of signs and symptoms Confusion with malaria and/or other fever causing conditions	High awareness of signs and symptoms
	Seeking help	Reluctance to seek help Low availability and high cost of transport	Health-seeking behaviours based on signs and symptoms Affordable transport/financial support for transport
	Safety-netting information (advice on potential course of illness and what to do about it)	Lack of context/culturally appropriate information	Culturally appropriate/context suitable safety-netting information readily available
	Health-worker training	Meningitis not included in core training	Meningitis included in core training
	Health-worker materials/resources	Context/culturally appropriate and condition specific information not called for or provided	Culturally appropriate/context suitable and condition-specific materials and resources readily available
	Service signposting	Lack of services to signpost to Limited links between health service and providers, for example, NGOs	Signposting from health facilities to services available for people with sequelae and their families, and psychosocial services for bereavement
	Legal redress	Lack of legal framework Lack of knowledge about how/when to seek redress Financial barriers to legal engagement	Law allows for legal redress for poor standard health care Citizens can access financial support for legal redress

8. Acknowledgements

This document is the result of the collaborative efforts of the WHO Technical Task Force (TTF) for “Defeating Meningitis by 2030”.

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Expert reviewers

The TTF wish to thank the following colleagues for their vital contribution in reviewing the baseline situation analysis during its development, and especially to Natacha Blake, Rob Dawson, Xin Wang and Claire Wright for additional contributions to the drafting.

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This document has been produced with the financial assistance of the Bill & Melinda Gates Foundation. The views expressed herein are those of the authors and do not necessarily represent the decisions, policies, or views of their respective institutions, of donors or collaborators.

9. Abbreviations & acronyms

ACCD	African Centre of Communication for Development
AFRO	WHO Regional Office for Africa
AMR	antimicrobial resistance
AMRO	WHO Regional Office for the Americas
AMST	antimicrobial susceptibility testing
BAP	blood agar plates
BSA	baseline situation analysis
CAP	chocolate agar plates
CBR	community-based rehabilitation
CDC	Centers for Disease Control and Prevention (US)
CI	confidence interval
CoMO	Confederation of Meningitis Organisations
CRM	cross-reacting material
CRPD	Convention on the Rights of Persons with Disability
CSF	cerebrospinal fluid
CSO	civil society organization
DALY	disability adjusted life year
DPO	disabled people's organization
DT	diphtheria toxoid
DTP	diphtheria-tetanus-pertussis vaccine
ECDC	European Centre for Disease Prevention and Control
EMRO	WHO Regional Office for the Eastern Mediterranean
EPI	Expanded Programme on Immunization
EQA	external quality assessment
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
EURO	WHO Regional Office for Europe
GBD	Global Burden of Disease Study
GBS	group B streptococcus
GHE	Global Health Estimates (WHO)

HCW	health-care worker
Hi	*Haemophilus influenzae*
Hib	*Haemophilus influenza* type b
HIC	high-income country
ICG	International Coordination Group
IDSA	Infectious Disease Society of America
IDSR	Integrated Disease Surveillance and Response
IFRC	International Federation of Red Cross and Red Crescent Societies
IHME	Institute for Health Metrics and Evaluation
IMD	invasive meningococcal disease
IPD	invasive pneumococcal disease
IPV	inactivated polio vaccine
IQR	interquartile range
IV-VPD	Invasive Bacterial Vaccine Preventable Diseases
JHU	Johns Hopkins University
LIC	low-income country
LMIC	low- and middle-income countries
LP	lumbar puncture
LSHTM	London School of Hygiene and Tropical Medicine
MCEE	Maternal Child Epidemiology Estimation
MenA	meningitis A vaccine
MIC	middle-income country
MLST	multilocus sequence typing
mnGAP	WHO mental health gap
MRF	Meningitis Research Foundation
MSF	Médecins Sans Frontières
NDI	neurodevelopmental impairment
NGO	non-governmental organization
NIPH	Norwegian Institute of Public Health
Nm	*Neisseria meningitidis*
OMV	outer membrane vesicle
PCR	polymerase chain reaction

PCV	pneumococcal conjugate vaccine
PCV	pneumococcal conjugate vaccines
POC	point-of-care
PT	proficiency test
R&D	research and development
RDT	rapid diagnostic test
RSV	respiratory syncytial virus
SDG	Sustainable Development Goals
SEARO	WHO Regional Office for South-East Asia
SOP	standard operating procedure
Spn	*Streptococcus pneumoniae*
TB	tuberculosis
TI	trans isolate
TT	tetanus toxoid
TTF	Technical Task Force
UI	uncertainty interval
UNICEF	United Nations Children's Fund
VPD	vaccine-preventable disease
WGS	whole genome sequencing
WHO	World Health Organization
WPRO	WHO Regional Office for the Western Pacific
YLD	years lived with disability

10. References

1. Zunt JR, Kassebaum NJ, Blake N, Glennie L, Wright C, Nichols E et al. Global, regional, and national burden of meningitis, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018;17(12):1061–82.
2. Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis. 2017;17(8):873–81.
3. van de Beek D. Progress and challenges in bacterial meningitis. Lancet. 2012;380(9854):1623–4.
4. McIntyre PB, O'Brien KL, Greenwood B, van de Beek D. Effect of vaccines on bacterial meningitis worldwide. Lancet. 2012;380(9854):1703–11.
5. The End TB Strategy. Geneva: World Health Organization; 2014 (available from: http://www.who.int/tb/strategy/en/).
6. Global health sector strategy on HIV, 2016–2021. Geneva: World Health Organization; 2016 (available from: http://www.who.int/hiv/strategy2016-2021/ghss-hiv/en).
7. World Health Organization. Ending preventable child deaths from pneumonia and diarrhoea by 2025: the integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD) 2013 (available from: https://www.who.int/maternal_child_adolescent/documents/global_action_plan_pneumonia_diarrhoea/en/).
8. Global Action Plan on Antimicrobial Resistance. Geneva: World Health Organization; 2015 (available from: https://www.who.int/antimicrobial-resistance/publications/global-action-plan/en/).
9. Bacterial meningitis. Atlanta: Centers for Disease Control and Prevention; 2018 (available from: https://www.cdc.gov/meningitis/bacterial.html).
10. Chapter 2: Epidemiology of meningitis caused by Neisseria meningitidis, Streptococcus pneumoniae, and Haemophilus influenza. Atlanta: Centers for Disease Control and Prevention (available from: https://www.cdc.gov/meningitis/lab-manual/chpt02-epi.html).
11. Vaccine preventable disease surveillance standards. Geneva: World Health Organization; 2018 (available from: http://www.who.int/immunization/monitoring_surveillance/burden/vpd/standards/en/).
12. Wahl B, O'Brien KL, Greenbaum A, Majumder A, Liu L, Chu Y et al. Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000–15. Lancet Glob Health. 2018;6(7):e744–e57.
13. Madrid L, Seale AC, Kohli-Lynch M, Edmond KM, Lawn JE, Heath PT et al. Infant group B streptococcal disease incidence and serotypes worldwide: systematic review and meta-analyses. Clin Infect Dis. 2017;65(suppl 2):S160–s72.
14. Greenwood B. Manson Lecture. Meningococcal meningitis in Africa. Trans R Soc Trop Med Hyg. 1999;93(4):341–53.
15. Greenwood B. Editorial: 100 years of epidemic meningitis in West Africa – has anything changed? Trop Med Int Health. 2006;11(6):773–80.
16. Trotter CL, Lingani C, Fernandez K, Cooper LV, Bita A, Tevi-Benissan C et al. Impact of MenAfriVac in nine countries of the African meningitis belt, 2010–15: an analysis of surveillance data. Lancet Infect Dis. 2017;17(8):867–72.
17. Borrow R, Alarcon P, Carlos J, Caugant DA, Christensen H, Debbag R et al. The Global Meningococcal Initiative: global epidemiology, the impact of vaccines on meningococcal disease and the importance of herd protection. Expert Rev Vaccines. 2017;16(4):313–28.

18. Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. Vaccine. 2009;27(suppl 2):B51–63.
19. Sridhar S, Greenwood B, Head C, Plotkin SA, Safadi MA, Saha S et al. Global incidence of serogroup B invasive meningococcal disease: a systematic review. Lancet Infect Dis. 2015;15(11):1334–46.
20. Borrow R, Alarcon P, Carlos J, Caugant DA, Christensen H, Debbag R et al. The Global Meningococcal Initiative: global epidemiology, the impact of vaccines on meningococcal disease and the importance of herd protection. Expert Rev Vaccines. 2017;16(4):313–28.
21. Lundbo LF, Benfield T. Risk factors for community-acquired bacterial meningitis. Infect Dis (Lond). 2017;49(6):433–44.
22. Cohn AC, MacNeil JR, Clark TA, Ortega-Sanchez IR, Briere EZ, Meissner HC et al. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2013;62(Rr-2):1–28.
23. Jansen AG, Sanders EA, A VDE, AM VANL, Hoes AW, Hak E. Invasive pneumococcal and meningococcal disease: association with influenza virus and respiratory syncytial virus activity? Epidemiol Infect. 2008;136(11):1448–54.
24. Cohen AL, McMorrow M, Walaza S, Cohen C, Tempia S, Alexander-Scott M et al. Potential impact of co-infections and co-morbidities prevalent in Africa on influenza severity and frequency: a systematic review. PLoS One. 2015;10(6):e0128580.
25. Mueller JE, Woringer M, Porgho S, Madec Y, Tall H, Martiny N et al. The association between respiratory tract infection incidence and localised meningitis epidemics: an analysis of high-resolution surveillance data from Burkina Faso. Sci Rep. 2017;7(1):11570.
26. Izurieta P, Bahety P, Adegbola R, Clarke C, Hoet B. Public health impact of pneumococcal conjugate vaccine infant immunization programs: assessment of invasive pneumococcal disease burden and serotype distribution. Expert Rev Vaccines. 2018;17(6):479–93.
27. Kambire D, Soeters HM, Ouedraogo-Traore R, Medah I, Sangare L, Yameogo I et al. Nationwide trends in bacterial meningitis before the introduction of 13-valent pneumococcal conjugate vaccine-Burkina Faso, 2011–2013. PLoS One. 2016;11(11):e0166384.
28. Greenwood B. Pneumococcal meningitis epidemics in Africa. Clin Infect Dis. 2006;43(6):701–3.
29. Stuart JM. Can infant vaccination prevent pneumococcal meningitis outbreaks in sub-Saharan Africa? Trop Med Int Health. 2017;22(5):514–5.
30. Kwambana-Adams BA, Asiedu-Bekoe F, Sarkodie B, Afreh OK, Kuma GK, Owusu-Okyere G, et al. An outbreak of pneumococcal meningitis among older children (>/=5 years) and adults after the implementation of an infant vaccination programme with the 13-valent pneumococcal conjugate vaccine in Ghana. BMC Infect Dis. 2016;16(1):575.
31. Lin SM, Zhi Y, Ahn KB, Lim S, Seo HS. Status of group B streptococcal vaccine development. Clin Exp Vaccine Res. 2018;7(1):76–81.
32. Heath PT. Status of vaccine research and development of vaccines for GBS. Vaccine. 2016;34(26):2876–9.
33. Edmond KM, Kortsalioudaki C, Scott S, Schrag SJ, Zaidi AK, Cousens S et al. Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. Lancet. 2012;379(9815):547–56.
34. Seale AC, Bianchi-Jassir F, Russell NJ, Kohli-Lynch M, Tann CJ, Hall J et al. Estimates of the burden of group B streptococcal disease worldwide for pregnant women, stillbirths, and children. Clin Infect Dis. 2017;65(suppl_2):S200–s19.

35. Bianchi-Jassir F, Seale AC, Kohli-Lynch M, Lawn JE, Baker CJ, Bartlett L et al. Preterm birth associated with Group B streptococcus maternal colonization worldwide: systematic review and meta-analyses. Clin Infect Dis. 2017;65(suppl_2):S133–s42.
36. Hall J, Adams NH, Bartlett L, Seale AC, Lamagni T, Bianchi-Jassir F et al. Maternal disease with group B streptococcus and serotype distribution worldwide: systematic review and meta-analyses. Clin Infect Dis. 2017;65(suppl_2):S112–s24.
37. ABCs Report: group B streptococcus, 2016. Atlanta: Centers for Disease Control and Prevention; 2018 (available from: https://www.cdc.gov/abcs/reports-findings/survreports/gbs16.html).
38. Network GBoDC. Global Burden of Disease Study 2016 (GBD 2016) Results. Seattle: Institute for Health Metrics and Evaluation; 2017 (available from: http://ghdx.healthdata.org/gbd-results-tool).
39. Global health estimates 2016: deaths by cause, age, sex, by country and by region, 2000–2016. Geneva: World Health Organization; 2018 (available from: http://www.who.int/healthinfo/global_burden_disease/estimates/en/).
40. Global health estimates: child causes of death, 2000–2016. Geneva: World Health Organization; 2018 (available from: http://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html).
41. Luksic I, Mulic R, Falconer R, Orban M, Sidhu S, Rudan I. Estimating global and regional morbidity from acute bacterial meningitis in children: assessment of the evidence. Croat Med J. 2013;54(6):510–8.
42. Carbonell-Estrany X, Figueras-Aloy J, Salcedo-Abizanda S, de la Rosa-Fraile M. Probable early-onset group B streptococcal neonatal sepsis: a serious clinical condition related to intrauterine infection. Arch Dis Child Fetal Neonatal Ed. 2008;93(2):F85–9.
43. Luck S, Torny M, d'Agapeyeff K, Pitt A, Heath P, Breathnach A et al. Estimated early-onset group B streptococcal neonatal disease. Lancet. 2003;361(9373):1953–4.
44. WHO Regional Offices. Geneva: World Health Organization (available from: http://www.who.int/about/regions/en/).
45. Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. Lancet Infect Dis. 2010;10(5):317–28.
46. Kohli-Lynch M, Russell NJ, Seale AC, Dangor Z, Tann CJ, Baker CJ et al. Neurodevelopmental impairment in children after group B streptococcal disease worldwide: systematic review and meta-analyses. Clin Infect Dis. 2017;65(suppl_2):S190–s9.
47. Al-Janabi H, Van Exel J, Brouwer W, Trotter C, Glennie L, Hannigan L et al. Measuring health spillovers for economic evaluation: a case study in meningitis. Health Econ. 2016;25(12):1529–44.
48. Griffiths UK, Dieye Y, Fleming J, Hajjeh R, Edmond K. Costs of meningitis sequelae in children in Dakar, Senegal. Pediatr Infect Dis J. 2012;31(11):e189–95.
49. Colombini A, Bationo F, Zongo S, Ouattara F, Badolo O, Jaillard P et al. Costs for households and community perception of meningitis epidemics in Burkina Faso. Clin Infect Dis. 2009;49(10):1520–5.
50. Vipond C, Care R, Feavers IM. History of meningococcal vaccines and their serological correlates of protection. Vaccine. 2012;30 (suppl 2):B10–7.
51. Group B streptococcus vaccine development technology roadmap. Priority activities for development, testing, licensure and global availability of Group B streptococcus vaccines. Geneva: World Health Organization; 2017 (available from: https://www.who.int/immunization/documents/research/who_ivb_17.10/en/).
52. Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM. Meningococcal disease. N Engl J Med. 2001;344(18):1378–88.

53. Zalmanovici Trestioreanu A, Fraser A, Gafter-Gvili A, Paul M, Leibovici L. Antibiotics for preventing meningococcal infections. Cochrane Database Syst Rev. 2013(10):Cd004785.
54. Telisinghe L, Waite TD, Gobin M, Ronveaux O, Fernandez K, Stuart JM et al. Chemoprophylaxis and vaccination in preventing subsequent cases of meningococcal disease in household contacts of a case of meningococcal disease: a systematic review. Epidemiol Infect. 2015;143(11):2259–68.
55. van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek AT et al. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect. 2016;22 (suppl 3):S37–62.
56. Meningitis outbreak response in sub-Saharan Africa: WHO Guideline. Geneva: World Health Organization; 2014.
57. Coldiron ME, Assao B, Page AL, Hitchings MDT, Alcoba G, Ciglenecki I et al. Single-dose oral ciprofloxacin prophylaxis as a response to a meningococcal meningitis epidemic in the African meningitis belt: a 3-arm, open-label, cluster-randomized trial. PLoS Med. 2018;15(6):e1002593.
58. World Health Organization. Continuing risk of meningitis due to Neisseria meningitidis serogroup C in Africa: revised recommendations from a WHO expert consultation. Wkly Epidemiol Rec. 2017;92(41):612–7.
59. Klugman KP, Izadnegahdar R. Antibiotic prophylaxis. Preventing severe infections and saving lives in poor countries with very high mortality risk. PLoS Med. 2018;15(6):e1002594.
60. McNamara LA, MacNeil JR, Cohn AC, Stephens DS. Mass chemoprophylaxis for control of outbreaks of meningococcal disease. Lancet Infect Dis. 2018;18(9):e272–e81.
61. Le Doare K, O'Driscoll M, Turner K, Seedat F, Russell NJ, Seale AC et al. Intrapartum antibiotic chemoprophylaxis policies for the prevention of group B streptococcal disease worldwide: systematic review. Clin Infect Dis. 2017;65(suppl_2):S143–s51.
62. Prevention of early-onset neonatal group B streptococcal disease: Green-top Guideline No. 36. BJOG. 2017;124(12):e280–e305.
63. Verani JR, McGee L, Schrag SJ. Prevention of perinatal group B streptococcal disease–revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010;59(Rr-10):1–36.
64. Nishihara Y, Dangor Z, French N, Madhi S, Heyderman R. Challenges in reducing group B Streptococcus disease in African settings. Arch Dis Child. 2017;102(1):72–7.
65. Laboratory methods for the diagnosis of meningitis caused by Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenzae. Geneva: World Health Organization; 2011.
66. Birtles A, Hardy K, Gray SJ, Handford S, Kaczmarski EB, Edwards-Jones V et al. Multilocus sequence typing of Neisseria meningitidis directly from clinical samples and application of the method to the investigation of meningococcal disease case clusters. J Clin Microbiol. 2005;43(12):6007–14.
67. Bozio CH, Vuong J, Dokubo EK, Fallah MP, McNamara LA, Potts CC et al. Outbreak of Neisseria meningitidis serogroup C outside the meningitis belt-Liberia, 2017: an epidemiological and laboratory investigation. Lancet Infect Dis. 2018;18(12):1360–7.
68. Ajello GW, Feeley JC, Hayes PS, Reingold AL, Bolan G, Broome CV et al. Trans-isolate medium: a new medium for primary culturing and transport of Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenzae. J Clin Microbiol. 1984;20(1):55–8.
69. Managing meningitis epidemics in Africa: a quick reference guide for health authorities and health-care workers. Geneva: World Health Organization; 2015.
70. Kobayashi M, Vekemans J, Baker CJ, Ratner AJ, Le Doare K, Schrag SJ. Group B Streptococcus vaccine development: present status and future considerations, with emphasis on perspectives for low and middle income countries. F1000Research. 2016;5:2355.
71. Developing new generation RDTs for meningitis. Geneva: World Health Organization; 2018.

72. Short WR, Tunkel AR. Timing of administration of antimicrobial therapy in bacterial meningitis. Curr Infect Dis Rep. 2001;3(4):360–4.
73. Feldman WE, Ginsburg CM, McCracken GH Jr., Allen D, Ahmann P, Graham J et al. Relation of concentrations of Haemophilus influenzae type b in cerebrospinal fluid to late sequelae of patients with meningitis. J Pediatr. 1982;100(2):209–12.
74. Lebel MH, McCracken GH Jr. Delayed cerebrospinal fluid sterilization and adverse outcome of bacterial meningitis in infants and children. Pediatrics. 1989;83(2):161–7.
75. Aronin SI, Peduzzi P, Quagliarello VJ. Community-acquired bacterial meningitis: risk stratification for adverse clinical outcome and effect of antibiotic timing. Ann Intern Med. 1998;129(11):862–9.
76. Proulx N, Frechette D, Toye B, Chan J, Kravcik S. Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. QJM. 2005;98(4):291–8.
77. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. 2004;39(9):1267–84.
78. Pocket book of hospital care for children: guidelines for the management of common childhood illnesses. Geneva: World Health Organization; 2013.
79. O'Neill P. How long to treat bacterial meningitis. Lancet. 1993;341(8844):530.
80. Karageorgopoulos DE, Valkimadi PE, Kapaskelis A, Rafailidis PI, Falagas ME. Short versus long duration of antibiotic therapy for bacterial meningitis: a meta-analysis of randomized controlled trials in children. Arch Dis Child. 2009;94(8):607–14.
81. Molyneux E, Nizami SQ, Saha S, Huu KT, Azam M, Bhutta ZA et al. 5 versus 10 days of treatment with ceftriaxone for bacterial meningitis in children: a double-blind randomized equivalence study. Lancet. 2011;377(9780):1837–45.
82. Nathan N, Borel T, Djibo A, Evans D, Djibo S, Corty JF et al. Ceftriaxone as effective as long-acting chloramphenicol in short-course treatment of meningococcal meningitis during epidemics: a randomized non-inferiority study. Lancet. 2005;366(9482):308–13.
83. Clinical guidelines: diagnosis and treatment manual. Paris: Médecins Sans Frontières; 2013.
84. van de Beek D, Brouwer MC, Thwaites GE, Tunkel AR. Advances in treatment of bacterial meningitis. Lancet. 2012;380(9854):1693–702.
85. Acevedo R, Bai X, Borrow R, Caugant DA, Carlos J, Ceyhan M et al. The Global Meningococcal Initiative meeting on prevention of meningococcal disease worldwide: epidemiology, surveillance, hypervirulent strains, antibiotic resistance and high-risk populations. Expert Rev Vaccines. 2018.
86. Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev. 2015(9):Cd004405.
87. WHO Mental Health Gap Action Programme (mhGAP). Geneva: World Health Organization (available from: https://www.who.int/mental_health/mhgap/en/).
88. Bedford Russell AR, Kumar R. Early onset neonatal sepsis: diagnostic dilemmas and practical management. Arch Dis Child Fetal Neonatal Ed. 2015;100(4):F350–4.
89. Active bacterial core surveillance: laboratory characterization. Atlanta: Centers for Disease Control and Prevention (available from: https://www.cdc.gov/abcs/methodology/lab-characterization.html).
90. Guidance for the evaluation and public health management of suspected outbreaks of meningococcal disease. Atlanta: Centers for Disease Control and Prevention; 2017.
91. Quan V, Verani JR, Cohen C, von Gottberg A, Meiring S, Cutland CL et al. Invasive group B streptococcal disease in South Africa: importance of surveillance methodology. PLoS One. 2016;11(4):e0152524.

92. Meningococcal meningitis: weekly reports [3 February]. Geneva: World Health Organization (available from: https://www.who.int/emergencies/diseases/meningitis/epidemiological/en/).
93. CHAMPS. Child Health and Mortality Prevention Surveillance (available from: https://champshealth.org/).
94. Disease data from ECDC surveillance atlas for meningococcal disease. Stockholm: European Centre for Disease Prevention and Control (available from: https://ecdc.europa.eu/en/meningococcal-disease/surveillance-and-disease-data/atlas).
95. WHO Global disability action plan 2014–2021. Geneva: World Health Organization (available from: http://www.who.int/disabilities/about/action_plan/en/).
96. Convention on the Rights of Persons with Disabilities (CRPD) 2008. Geneva: United Nations (available from: https://www.un.org/development/desa/disabilities/convention-on-the-rights-of-persons-with-disabilities.html).
97. Community-based rehabilitation guidelines. Geneva: World Health Organization (available from: https://www.who.int/disabilities/cbr/guidelines/en/).
98. Your guide: recovering from bacterial meningitis and septicaemia in Ireland. Dublin: Meningitis Research Foundation; 2018.
99. It's about ability. Geneva: United Nations Children's Fund (available from: https://www.unicef.org/montenegro/en/its-about-ability-implemented-2010-2013).
100. The strategy for the protection of persons with disabilities from discrimination and promotion of equality 2017–2021 Podgorica: Ministry of Human and Minority Rights Montenegro; 2016.
101. Disability and health. Geneva: World Health Organization; 2018 (available from: http://www.who.int/news-room/fact-sheets/detail/disability-and-health).
102. Take us seriously! Engaging children with disabilities in decisions affecting their lives. Geneva: United Nations Children's Fund; 2013 (available from: https://www.unicef.org/disabilities/files/Take_Us_Seriously.pdf).
103. The change equation: key drivers and influencers of new vaccine implementation. Bristol: Confederation of Meningitis Organizations; 2016 (available from: http://www.comomeningitis.org/blog/2016/01/the-change-equation-key-drivers-and-influencers-of-new-vaccine-implementation/).
104. Owais A, Hanif B, Siddiqui AR, Agha A, Zaidi AK. Does improving maternal knowledge of vaccines impact infant immunization rates? A community-based randomized-controlled trial in Karachi, Pakistan. BMC Public Health. 2011;11:239.
105. Immunization advocacy library. Geneva: World Health Organization (available from: http://www.euro.who.int/en/health-topics/disease-prevention/vaccines-and-immunization/publications/communication-and-advocacy/immunization-advocacy-library).
106. Johri M, Perez MC, Arsenault C, Sharma JK, Pai NP, Pahwa S et al. Strategies to increase the demand for childhood vaccination in low- and middle-income countries: a systematic review and meta-analysis. Bull World Health Organ. 2015;93(5):339–46c.
107. Berlier M, Barry R, Shadid J, Sirica C, Brunier A, Hasan H et al. Communication challenges during the development and introduction of a new meningococcal vaccine in Africa. Clin Infect Dis. 2015;61(suppl 5):S451–8.
108. Slater MD. Theory and method in health audience segmentation. J Health Commun. 1996;1(3):267–83.

109. IVAC. Accelerating global access to life-saving vaccines. Baltimore: Johns Hopkins Bloomberg School of Public Health (available from: https://www.jhsph.edu/ivac/).
110. MacKian S. A review of health seeking behaviour: problems and prospects. Manchester: University of Manchester Health Systems Development Programme; 2003. Contract No.: HSD/WP/05/03.
111. Nyirenda D, Makawa TC, Chapita G, Mdalla C, Nkolokosa M, O'Byrne T et al. Public engagement in Malawi through a health-talk radio programme ' Umoyo nkukambirana': a mixed-methods evaluation. Public Underst Sci. 2018;27(2):229–42.
112. Borrow R, Lee JS, Vazquez JA, Enwere G, Taha MK, Kamiya H et al. Meningococcal disease in the Asia-Pacific region: findings and recommendations from the Global Meningococcal Initiative. Vaccine. 2016;34(48):5855–62.
113. David KV, Pricilla RA, Thomas B. Meningococcal meningitis C in Tamil Nadu, public health perspectives. J Family Med Prim Care. 2014;3(4):438–9.
114. Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management. London: National Institute for Health and Care Excellence; 2010.