

# Global Invasive Bacterial Vaccine Preventable Diseases (IB VPD) Information and Surveillance Bulletin

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The World Health Organization (WHO) produces this twice-yearly global IB VPD Information and Surveillance Bulletin to share activities and data with partners at the national, regional and global levels.

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## Spotlight on Efforts to Improve Data Quality

### Challenges

IB VPD surveillance is needed to provide information related to the introduction and use of vaccines that prevent severe illness and death among children (i.e. Hib and PCV) to Ministries of Health and other decision makers. However, launching a global high quality IB VPD surveillance network is challenging for many reasons, including:

- **Weak health infrastructure:** Capacity for IB VPD surveillance is weak in many developing countries. When it exists, it is mainly limited to academic institutions engaged in research, rather than public health facilities and laboratories that provide data to national Ministries of Health. Initiating surveillance in sentinel hospitals and linking them with laboratories often require providing infrastructure (e.g. microscopes, and laboratory reagents), providing training to clinicians and laboratory personnel, and establishing internal and external quality assurance programmes. In countries with the weakest health systems, at least 2 to 3 years may be required to build the required capacity and generate surveillance data of sufficient quality to meet public health needs. In many instances, the data from such surveillance may not by themselves provide a comprehensive picture of disease epidemiology, but may need to be bridged to data from more intensive surveillance in the region to inform local policy.

- **Fragile organisms:** There are inherent diagnostic difficulties in isolating and identifying the bacteria causing IB VPD, particularly *Haemophilus influenzae* and *Streptococcus pneumoniae*. These organisms are fastidious and fail to grow in media containing human blood, which is often used instead of the recommended sheep or horse blood in many developing country laboratories. In addition, prior antibiotic use, improper specimen handling, and delays in processing samples affect the ability to isolate the bacteria in culture.
- **Forming a new surveillance network:** Before WHO assumed full coordination of the IB VPD surveillance network in 2009, countries in the network were conducting surveillance using different protocols and standard operation procedures. In order to align countries under a global network, time will be required to implement standardized surveillance practices (e.g. by developing a WHO global IB VPD standard operating procedure), establish quality assurance systems, monitor compliance with standards using pre-defined indicators and periodic audits, and to clearly define roles and responsibilities within the network.

## Update on Actions Implemented to Improve Quality

To improve the quality of the WHO-coordinated surveillance network for IB VPD, WHO works with Ministries of Health to:

### 1. Strengthen the IB VPD Laboratory Network

- **By conducting trainings**

Ongoing training of laboratory professionals ensures adherence to standard procedures. The Global Reference Laboratories (GRL) provide support and training to Regional Reference Laboratories (RRL), who in turn train sentinel site laboratorians (photo).

- **By utilizing RRL Diagnostic Capacity**

RRL support to sentinel sites can include provision of advanced diagnostic testing methods, such as polymerase chain reaction (PCR). For example, the WHO African Region coordinates a process in West Africa whereby cerebrospinal fluid (CSF) samples tested negative at sentinel hospital laboratories are sent to the Gambia RRL for additional testing. During 2010, 450 of 1509 (30%) CSF samples tested negative by Gram stain and culture at the sentinel hospital laboratories were found to contain a bacterial organism by PCR (table and photo, pg 3). The information not only highlights the importance of RRL support to sentinel sites, but also illustrates the weakness of conducting surveillance that depends only on Gram stain and conventional bacterial culture to detect bacterial pathogens of meningitis. These results are also provided to sentinel sites and used during training (table and photo, pg 3).

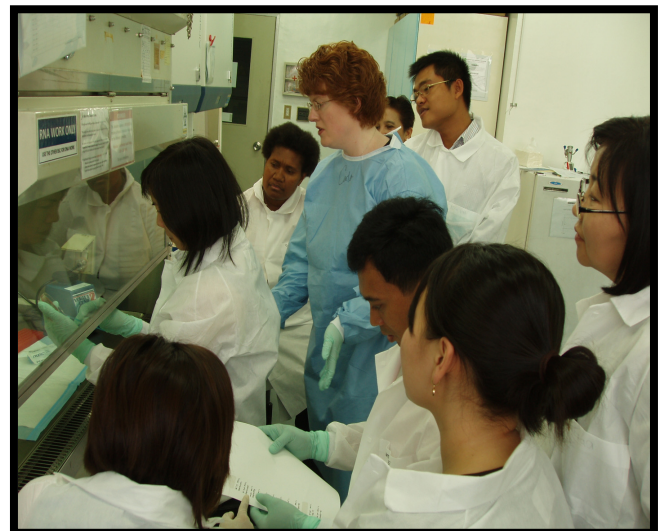


Photo: WHO-coordinated IB VPD training in the Western Pacific Region in March 2011. Here, the U.S. CDC GRL provides training to RRL colleagues from Australia and South Korea, and NL colleagues from Vietnam, Papua New Guinea, Mongolia, Philippines and Laos.

Vaccine preventable bacterial pathogens detected by polymerase chain reaction at the Gambia Regional Reference Laboratory (RRL) from meningitis cases with culture-negative cerebrospinal fluid (CSF) at the hospital sentinel site laboratory, January to December 2010

Country	<i>Hib</i>		<i>S. Pneumoniae</i>		<i>Neisseria meningitidis</i>		Total No. (%) of CSF samples received by RRL	
	No.	%	No.	%	No.	%	No.	%
Nigeria	7	12	53	18	15	14	306	20
Senegal	13	23	107	37	19	18	332	22
Ghana	19	33	94	33	32	30	696	46
Togo	1	2	7	2	0	0	20	1
Benin	17	30	27	9	39	37	127	8
Niger	0	0	0	0	0	0	18	1
Gambia	0	0	0	0	0	0	10	1
<b>Total</b>	<b>57</b>	<b>100</b>	<b>288</b>	<b>100</b>	<b>105</b>	<b>100</b>	<b>1509</b>	<b>100</b>

- **By purchasing laboratory supplies**

WHO purchased basic laboratory supplies, such as tubes, pipettes, reagents of assured quality, and microscopes, for needy sentinel hospital laboratories. While countries in all WHO Regions were supported, most countries were in the WHO African Region and included: Benin, Burundi, Burkina Faso, Cameroon, Cote D'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Gambia, Ghana, Kenya, Lesotho, Madagascar, Malawi, Mali, Mozambique, Namibia, Niger, Nigeria, Rwanda, Senegal, Swaziland, Tanzania, Togo, Uganda, Zambia, and Zimbabwe.



Photo: Practical training on various laboratory techniques for diagnosis and characterization of bacterial pathogens, MRC The Gambia; 22-27th February 2010.

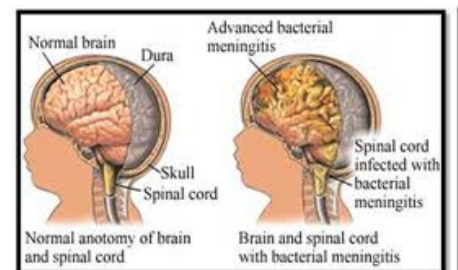
**2. Ensure adherence to standardized meningitis case definitions at sentinel hospital sites:**

Sentinel hospitals participating in the WHO-coordinated IB VPD surveillance network should use the following case definitions:

**Suspected Meningitis Case:** Any child aged 0-59 months admitted to a sentinel hospital conducting surveillance with sudden onset of fever (> 38.5 °C rectal or 38.0 °C axillary) plus a history of one of the following signs: neck stiffness, altered consciousness with no other alternative CNS diagnosis, or other meningeal sign.

**Probable Bacterial Meningitis Case:** A suspected meningitis case (as defined above) with CSF examination showing at least one of the following:

- Turbid appearance;
- Leukocytosis (> 100 cells/mm<sup>3</sup>);



Source: Meningitissymptomsuide.com

- Leukocytosis (10-100 cells/ mm<sup>3</sup>) AND either an elevated protein (>100 mg/dl) or decreased glucose (< 40 mg/dl)

Note: if protein and glucose results are not available, diagnose using the first two conditions (i.e. turbid appearance or leukocytosis > 100 cells/mm<sup>3</sup>)

**Confirmed IB VPD Meningitis Case:** A suspected meningitis case that is laboratory-confirmed by growing (i.e. culturing) or identifying (i.e. by Gram stain<sup>1</sup>, antigen detection, PCR or other methods) a bacterial pathogen (Hib, pneumococcus or meningococcus) in the CSF or from the blood in a child with a clinical syndrome consistent with bacterial meningitis

### **Summary of January through June 2010 IB VPD Surveillance Data**

The global IB VPD surveillance network collects data related to the detection of 3 vaccine-preventable organisms: *Haemophilus influenzae* (Hi), *Streptococcus pneumoniae* (Spn) and *Neisseria meningitidis* (Nm). Furthermore, the global IB VPD sentinel surveillance utilizes a 3-tiered approach:

- Tier 1 surveillance targets children under-five with suspected meningitis;
- Tier 2 surveillance also targets children under-five with pneumonia and/or sepsis;
- Tier 3 surveillance seeks to determine incidence rates of IB VPD

The current network, consisting mainly of tier 1 sentinel sites, provides information that will be useful to monitor trends in disease occurrence and to estimate vaccine effectiveness using a case-control approach, once high-quality data are obtained. However, information from tier 1 sites should be bridged with data from tier 2 and tier 3 surveillance sites as well as from special studies in order to provide a comprehensive understanding of disease epidemiology.

This Bulletin presents IB VPD surveillance data for January through June 2010. Summarized below are the main findings:

- 44 Member States reported IB VPD surveillance data to WHO
  - 34 of 44 (77%) reporting countries were GAVI Phase II eligible countries
- Among children with probable bacterial meningitis:
  - Spn, Hi and Nm were not detected in 14 of 43 (32%) reporting countries (11 were from the African Region), pointing to the need to strengthen surveillance practices in these countries
  - Deaths were reported in 23 of 42 (55%) participating countries

*As previously discussed, data in this bulletin come from a nascent IB VPD surveillance network where quality assurance systems are only now being established. Thus, care needs to be taken in interpreting the data and drawing conclusions. The wide variation in data from different countries reported in this bulletin may represent variation in surveillance quality, rather than true epidemiological differences.*

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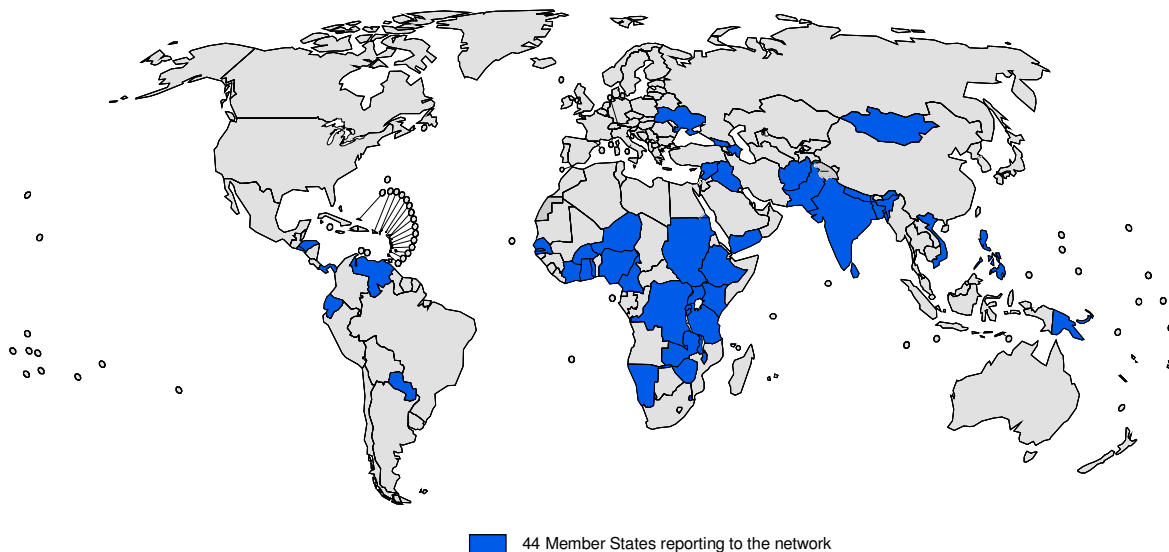
<sup>1</sup> The use of Gram stain in culture negative specimens as an indicator of confirmed meningitis will be further validated using newer diagnostic tests such as PCR

## Annex: January through June 2010 IB VPD Surveillance Data

### The Global IB VPD Surveillance Network

In the first semester of 2010, 44 WHO Member States participated in the global surveillance network for IB VPD and reported data to WHO (Figure 1). Twenty-one (48%) of these countries were based in the African Region. Overall, 34 of 44 (77%) participating countries were eligible for GAVI funding (Table 1).

Figure 1: WHO Member States reporting to the global surveillance network for IB VPD – Jan-June 2010.



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.  
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Source: Data collected from WHO Regions and partners. Date of slide: 29 March 2011

WHO Region*	Total number of countries reporting	Number of GAVI-eligible countries reporting	% of all countries reporting who are GAVI-eligible	Total number of sentinel sites reporting
AFR	21	19	90%	25
AMR	6	1	17%	20
EMR	6	4	67%	27
EUR	3	3	100%	5
SEAR	4	4	100%	8
WPR	4	3	75%	20
Total	44	34	77%	105

\*The following countries participated in the global surveillance network for IB VPD from January through June 2010: Burkina Faso, Burundi, Cameroon, Côte d'Ivoire, Democratic Republic of the Congo (the), Ethiopia, Gambia (the), Ghana, Kenya, Malawi, Namibia, Niger (the), Nigeria, Rwanda, Senegal, Swaziland, Togo, Uganda, United Republic of Tanzania (the), Zambia and Zimbabwe in the African Region (AFR); Ecuador, El Salvador, Honduras, Panama, Paraguay and Venezuela (Bolivarian Republic of) in the Region of the Americas (AMR); Afghanistan, Iraq, Pakistan, Sudan (the), Syrian Arab Republic (the) and Yemen in the Eastern Mediterranean Region (EMR); Azerbaijan, Georgia and Ukraine in the European Region (EUR); Bangladesh, India, Nepal and Sri Lanka in the South-East Asian Region (SEAR); Mongolia, Papua New Guinea, Philippines (the) and Viet Nam in the Western Pacific Region (WPR).

Out of 44 countries that reported Tier 1 meningitis surveillance data, 15 countries also reported Tier 2 pneumonia and/or sepsis surveillance data from January through June 2010. Furthermore, 1 country in the Western Pacific Region reported Tier 3 surveillance data (Table 2).

WHO Region	Type of IB VPD surveillance		
	Tier 1	Tier 2	Tier 3
	Meningitis	+Pneumonia and/or Sepsis	+Population-based
AFR	21	0	0
AMR	6	6	0
EMR	6	4	0
EUR	3	0	0
SEAR	4	4	0
WPR	4	1	1
Total	44	15	1

### Tier 1 - Meningitis Surveillance

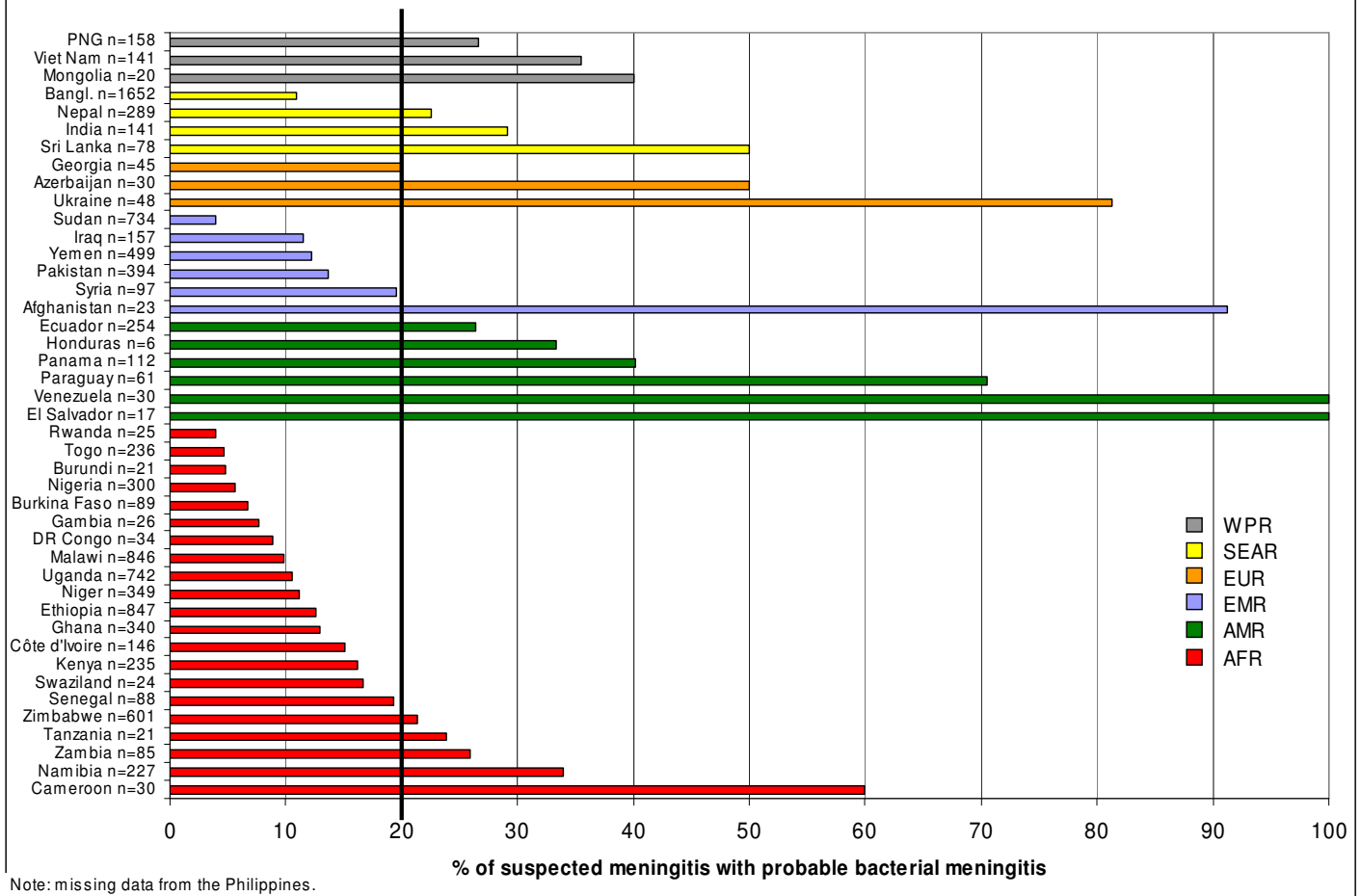
From January through June 2010, 10,350 children <5 years of age with suspected meningitis were reported to the global IB VPD surveillance network; 51% were from the African Region (Table 3).

WHO Region	Suspected meningitis		
	No.	% of Total	Range (by country)
AFR	5,312	51	21-847
AMR	480	5	6-254
EMR	1,904	18	23-734
EUR	123	1	30-48
SEAR	2,160	21	28-1,652
WPR	371	4	20-158
TOTAL	10,350	100	6-1,652

Among children with suspected meningitis, the percent with probable bacterial meningitis varied greatly between countries (range: 4 - 100%). All countries in the Region of the Americas, the European Region and the Western Pacific Region met or exceeded the network target of 20%. In the African Region, 16 of 21 (76%) countries reported less than 20% of suspected meningitis cases as probable bacterial meningitis. (Figure 2).

Low detection may be due to problems with case ascertainment, adherence to case definitions, specimen collection, transportation and laboratory practices; issues with data management procedures may also contribute. WHO Regional Offices are working with countries and sites to improve data management practices and to provide technical support to identify and rectify problems.

Figure 2: Percent of suspected meningitis cases with probable bacterial meningitis, by country and WHO region - Jan-June 2010. The number of suspected meningitis cases (n= ) stated next to the country.

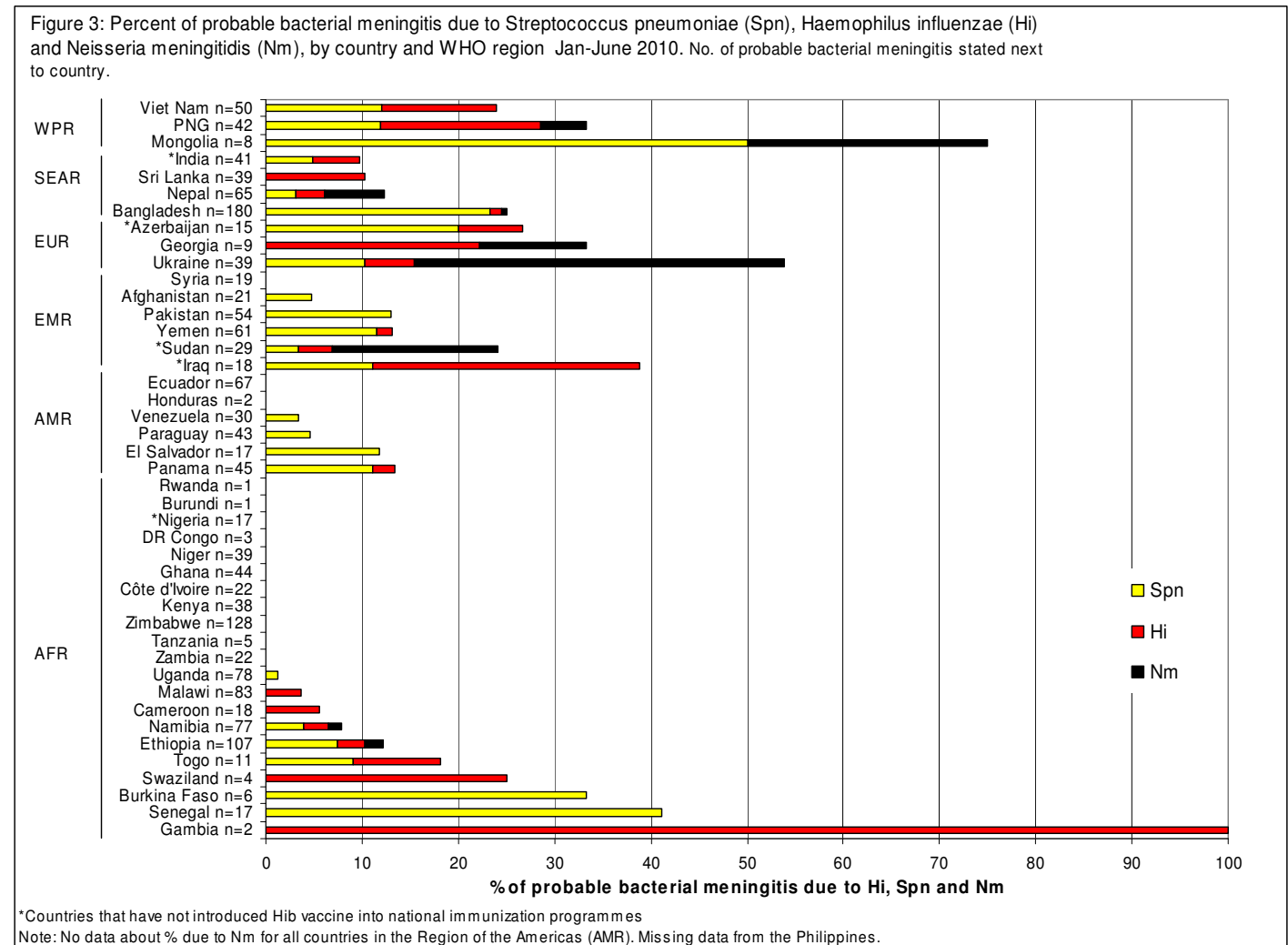


From January through June 2010, Spn was detected in 23 of 43 (53%) reporting countries, Hi in 20 of 43 (46%) countries, and Nm in 9 of 37 (24%) countries (Figure 3). Furthermore, the percent of probable bacterial meningitis due to Spn, Hi and Nm varied greatly between countries, which likely reflects differences in specimen handling processes, laboratory capacity and choice of detection methods.

Among children with probable bacterial meningitis, 14 of 43 (32%) reporting countries (11 from the African Region) did not detect any of the 3 organisms (Figure 3). The IB VPD surveillance network is working to include information on the number of samples with bacterial contaminants, but there is currently no information on the percent of probable bacterial meningitis due to other pathogens.

Inability to identify the 3 organisms of interest may be attributable to several factors including prior use of antibiotics, poor specimen storage and transportation conditions, weak laboratory capacity, and low sensitivity of detection methods used. In most countries in the African Region, only conventional culture techniques are used to detect bacteria pathogens, the sensitivity of which is affected by the above factors. WHO is working to improve access to antigen detection and PCR diagnostics either at the sentinel site or at the supporting RRL. Furthermore, the global EQA programme

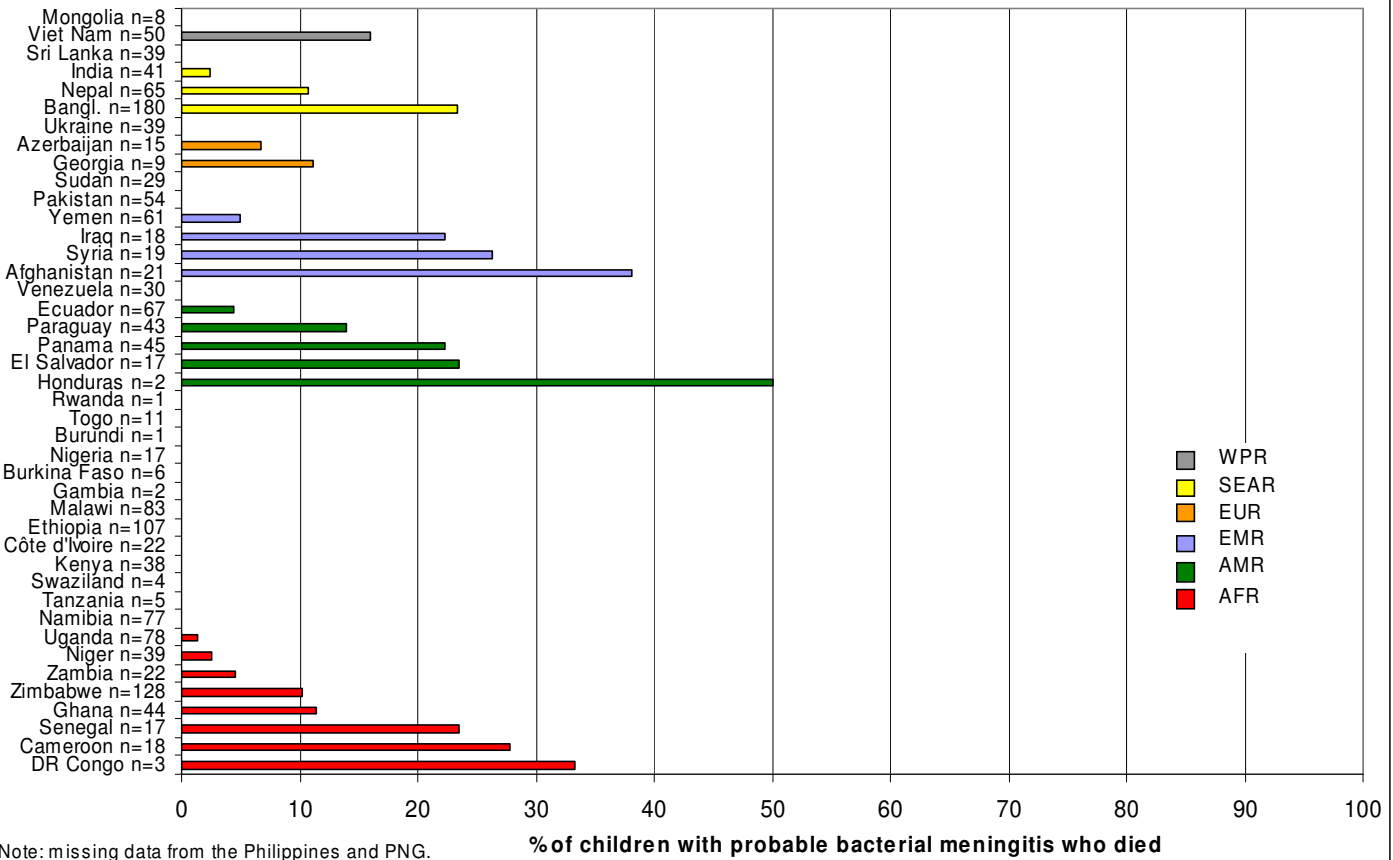
launched in the first quarter of 2011 will provide valuable information to help better target WHO's support.



## Mortality

From January through June 2010, deaths among children with probable bacterial meningitis were reported from 23 of 42 countries (55%) that provided data to the global IB VPD surveillance network. The percent of children with probable bacterial meningitis who died varied between countries; however, it is important to note that some countries reported very few cases of probable bacterial meningitis (Figure 4).

Figure 4: Percent of children with probable bacterial meningitis who died, by country and WHO region - Jan-June 2010. The number of probable bacterial meningitis cases (n= ) stated next to the country.



## Tier 2 - Pneumonia and/or Sepsis Surveillance

From January through June 2010, 4 of 6 WHO Regions reported Tier 2 surveillance data<sup>2</sup>. A total of 14,933 children <5 years of age with pneumonia were captured in the IB VPD surveillance network; 84% of these children came from the Region of the Americas and the South-East Asia Region. The Eastern Mediterranean Region and Western-Pacific Region reported a total of 118 children <5 years of age with sepsis (Table 4).

Table 4: Number (No.) of children <5 years of age with pneumonia and sepsis, by WHO region - Jan-June 2010

WHO Region	No. of countries reporting	Pneumonia			Sepsis		
		No. of children	% of Total	Range (by country)	No. of children	% of Total	Range (by country)
AMR	6	5,921	40	90-2,164	NS	NS	NS
EMR	4	833	6	2-711	76	64	2-48
SEAR	4	6,599	44	96-5,645	ND	ND	ND
WPR	1	1,580	11	---	42	36	---
TOTAL	15	14,933	100	0-5,645	118	100	2-48

NS: No Surveillance  
ND: No Data

<sup>2</sup> Tier 2 surveillance data from the African Region are not reported in this Bulletin. However, pneumonia surveillance is currently under-way in the Region and data is expected to be presented in future issues of the Bulletin.

In 11 countries reporting from January through June 2010, Hi was isolated from the blood of less than 2% of children with pneumonia who had blood cultures performed, and the isolation of Spn ranged from 0-6.7% (Figure 5).

Difficulties in detecting the etiological agents of pneumonia may be partly due to limitations with current diagnostic tools and the low predictive value of the clinical case definitions used for pneumonia. The clinical case definitions for pneumonia were formulated for case management, where specificity was sacrificed to get optimal sensitivity. Hence, the positive predictive value of the case definitions of pneumonia for identifying radiologically confirmed pneumonia among children with cough would range from 7 to 26%.<sup>3</sup>

Among children with radiologically confirmed pneumonia, clinical trials have shown that the proportion of radiological pneumonia prevented by Hib and pneumococcal vaccines far exceeds the proportion with a positive blood culture.<sup>4 5 6</sup> In addition, studies looking at the occurrence of pneumococcal bacteraemic pneumonia by blood culture have reported results as low as 1.6 - 3.8%.<sup>7,8</sup> Although our surveillance data is in keeping with expected numbers, such low isolations rates may suggest a need to review the Tier 2 surveillance strategy.

In 5 countries reporting from January through June 2010, Hi was not detected in the blood of any children with sepsis who had blood cultures performed, and Spn was detected in <2.5% of these children (Figure 6). These data should be interpreted cautiously as information on the vaccination status of these children is unavailable. Thus, it is not possible to determine whether the low detection of Hi is due to Hib vaccine receipt.

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<sup>3</sup> Cherian T, John TJ, Simoes E, Steinhoff MC, John M. Evaluation of simple clinical signs for the diagnosis of acute lower respiratory tract infection. *Lancet* 1988;2(8603):125-8

<sup>4</sup> Klugman K.P., Madhi S.A., Huebner R.E., Kohberger R., Mbelle N., Pierce N. et al. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *New England Journal of Medicine*. 2003;349(14):1341-8.

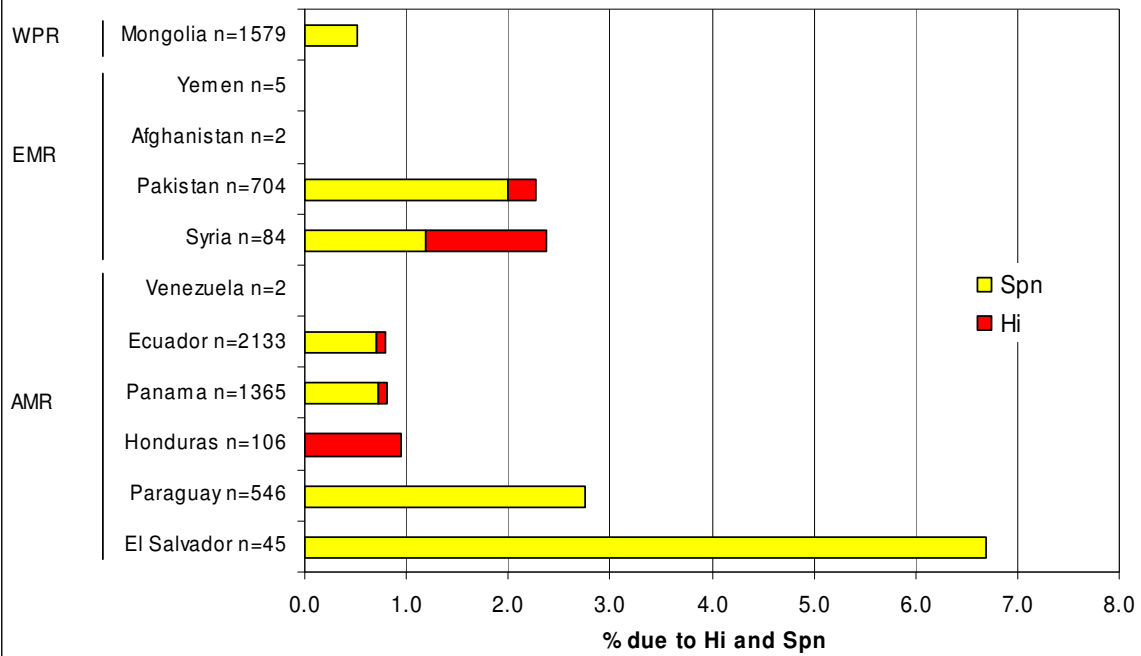
<sup>5</sup> Mulholland K, Hilton S, Adegbola R. Randomised trial of *Haemophilus influenzae* type b-tetanus protein conjugate for prevention of pneumonia and meningitis in Gambian infants. *Lancet* 1997;349:1191-7

<sup>6</sup> Cutts FT, Zaman SMA, Enwere G, Jaffar S, Levine OS, Okoko JB et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet* 2005;365:1139-46

<sup>7</sup> Resti M, Moriondo M, Cortimiglia M, Indolfi G, Canessa C, Becciolini L, et al. Community-acquired bacteremic pneumococcal pneumonia in children: diagnosis and serotyping by real-time polymerase chain reaction using blood samples. *Clin Infect Dis* 2010 Nov 1;51(9):1042-1049.

<sup>8</sup> Shah SS, Alpern ER, Zwerling L, McGowan KL, Bell LM. Risk of bacteremia in young children with pneumonia treated as outpatients. *Arch Pediatr Adolesc Med* 2003 Apr;157(4):389-392.

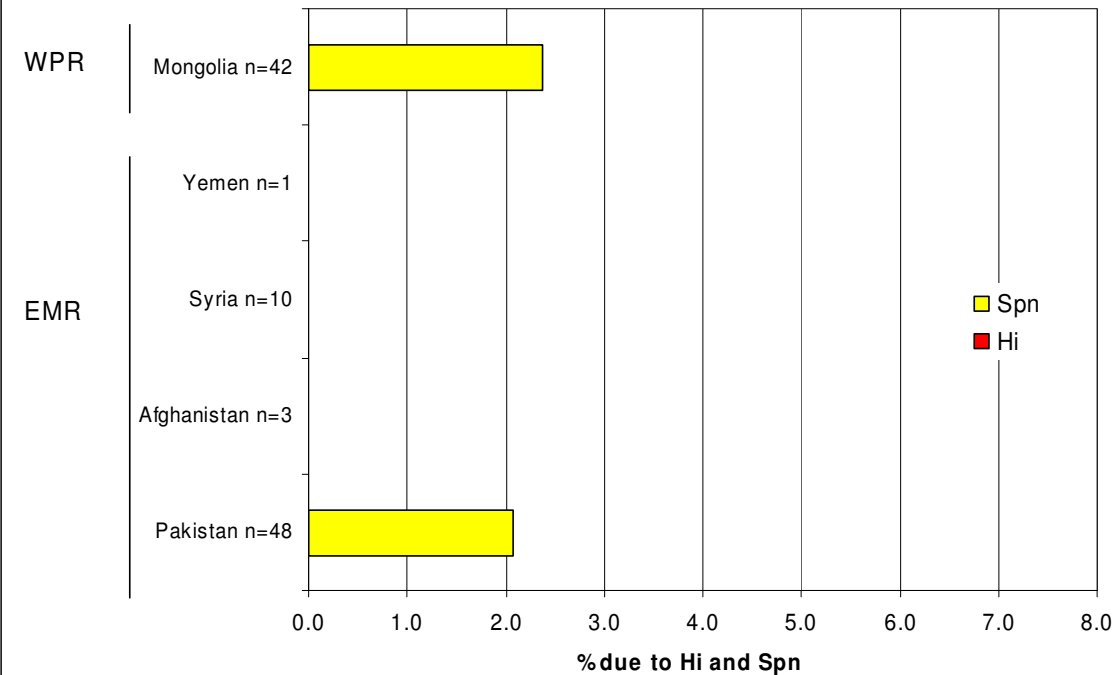
Figure 5: Percent of pneumonia cases due to Streptococcus pneumoniae (Spn) and Haemophilus influenzae (Hi),\* by country and WHO region - Jan-June 2010. Number of pneumonia cases with blood culture performed (n= ) stated next to country.



\*Among pneumonia cases with blood culture performed

Note: Countries in the South-East Asia Region not show n because data not differentiated between pneumonia and sepsis cases.

Figure 6: Percent of sepsis cases due to Streptococcus pneumoniae (Spn) and Haemophilus influenzae (Hi),\* by country and WHO region - Jan-June 2010. Number of sepsis cases with blood culture performed (n= ) stated next to country.



\*Among sepsis cases with blood culture performed

Note: Countries in the South-East Asia Region not show n because data not differentiated between pneumonia and sepsis cases. Countries in the Region of the Americas do not conduct Tier 2 surveillance for sepsis.

### Tier 3 - Population-based Surveillance (Mongolia)

From January through June 2010, Mongolia reported population-based surveillance data for IB VPD. This is the first time the global surveillance network for IB VPD has received population-based surveillance data, and more countries (particularly in the African Region) are expected to report similar data in the future.

A total of 99,264 children under 5 years of age were enumerated in the catchment area of the sentinel hospital sites; in order to accommodate surveillance data collected from January through June 2010, 49,632 child-years of observation were used to calculate incidence rates for meningitis, pneumonia and sepsis, as well as Hi, Spn and Nm (Table 5).

Rates generated from sentinel site surveillance may be large under-estimates as they only reflect children under-five with access to the sentinel hospitals, and among those, children who are hospitalized with a syndrome under surveillance and tested for the pathogens of interest. Furthermore, pneumonia is the most common syndrome captured at sentinel sites in Mongolia, but the incidence rates reflected here only include cases of bacteraemic Hi and Spn pneumonia cases. Challenges in isolating these organisms (as previously discussed) must also be taken into consideration when interpreting these incidence rates.

Hib vaccine was introduced into the country during 2005-2008, which may account for the absence of Hi detected.

Table 5: Incidence rates of IB VPD and aetiologic agents - Mongolia.

		Incidence rate from 2009 IB VPD sentinel site surveillance (per 100,000 child-years)
Syndrome (all-cause)	Suspected meningitis	36
	Pneumonia	3180
	Sepsis	85
Pathogen (all-syndrome)	Hi	0
	Spn	28
	Nm	4

### **Acknowledgements**

WHO gratefully acknowledges the dedicated efforts of the numerous individuals and organizations involved with compiling this surveillance information, including Ministries of Health, sentinel hospitals, as well as the network of global, regional and national reference laboratories.

### **WHO IB VPD Surveillance Websites**

[http://www.who.int/immunization\\_monitoring/diseases/meningitis\\_surveillance/en/index.html](http://www.who.int/immunization_monitoring/diseases/meningitis_surveillance/en/index.html)  
<http://www.who.int/nuvi/surveillance/en/>