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Review

Child pneumonia – focus on the Western Pacific Region

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EDUCATIONAL AIMS

The reader will come to appreciate that in the Western Pacific region:

- Pneumonia is a major cause of death in young children
- The pneumonia pathogen profile is variable and changing with increased uptake of conjugated vaccines
- The rise of drug resistant infections is fostered by inappropriate antimicrobial use
- Clinical management protocols and primary pneumonia prevention strategies can be strengthened

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SUMMARY

Worldwide, pneumonia is the leading cause of death in infants and young children (aged <5 years). We provide an overview of the global pneumonia disease burden, as well as the aetiology and management practices in different parts of the world, with a specific focus on the WHO Western Pacific Region. In 2011, the Western Pacific region had an estimated 0.11 pneumonia episodes per child-year with 61,900 pneumonia-related deaths in children less than 5 years of age. The majority (>75%) of pneumonia deaths occurred in six countries; Cambodia, China, Laos, Papua New Guinea, the Philippines and Viet Nam. Historically *Streptococcus pneumoniae* and *Haemophilus influenzae* were the commonest causes of severe pneumonia and pneumonia-related deaths in young children, but this is changing with the introduction of highly effective conjugate vaccines and socio-economic development. The relative contribution of viruses and atypical bacteria appear to be increasing and traditional case management approaches may require revision to accommodate increased uptake of conjugated vaccines in the Western Pacific region. Careful consideration should be given to risk reduction strategies, enhanced vaccination coverage, improved management of hypoxaemia and antibiotic stewardship.

INTRODUCTION

Pneumonia is the biggest killer of young children; globally accounting for nearly one in five deaths among children less than 5 years of age in 2011 [1,2]. The epidemiology of child pneumonia, as well as the pathogen profile and management practices, is variable in different parts of the world [2]. The greater Asia-Pacific region, which includes the World Health Organization (WHO) defined regions of Southeast Asia and the Western Pacific, reports the greatest number of pneumonia cases in children every year (Figure 1) [1,3]. We review global pneumonia disease burden estimates, consider the importance of various respiratory pathogens and discuss standard management approaches in infants and children less than five years of age, with a focus on the WHO Western Pacific Region; Viet Nam in particular.

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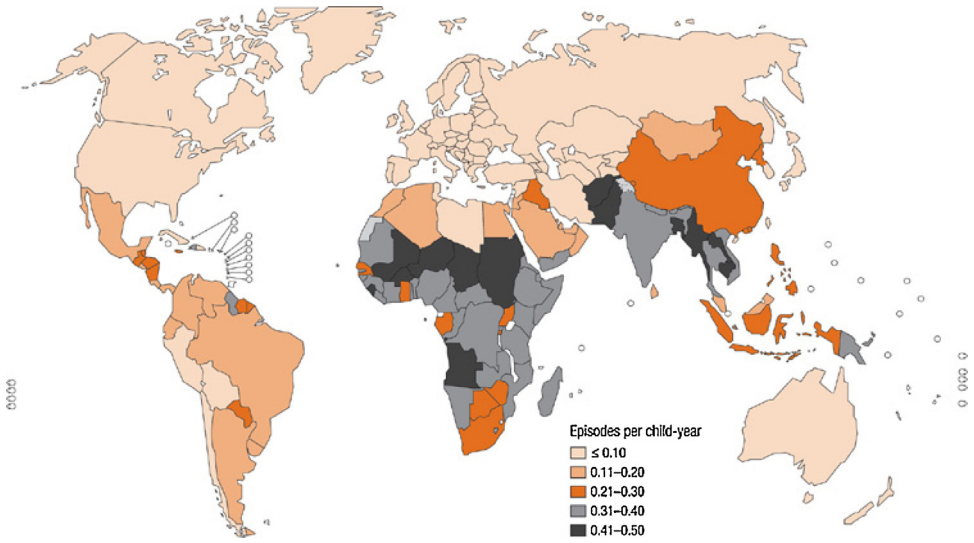

Figure 1. Estimated incidence of clinical pneumonia in children less than 5 years of age (2008).*
Small circles represent island populations.
*Adapted from World Health Organization 2008 [3].

BURDEN OF CHILD PNEUMONIA

In 2011, child pneumonia accounted for an estimated 1.3 million deaths, with more than 90% occurring in low and middle income countries [1,4]. Africa experienced the highest disease burden with an estimated 0.27 pneumonia episodes per child-year and 540,600 pneumonia-related deaths in children under 5 years of age, followed by South-East Asia (0.26 pneumonia episodes per child-year; 443,800 deaths) [1]. Estimates for the Western Pacific were 0.11 pneumonia episodes per child-year with 61,900 pneumonia-related deaths [1]. Table 1 summarizes the pneumonia disease burden and number of pneumonia-related deaths estimated to have occurred in the various WHO regions in 2011.

In the WHO Western Pacific Region, the pneumonia-related under-5 mortality rate decreased from 52.1 per 1000 live births in 1990 to 35.5 per 1000 live births in 2000 and 15.3 per 1000 live births in 2013. Data on pneumonia disease episodes are less complete, but declined from 850,000 in 2000 to 395,000 in 2013 [5]. Despite these impressive reductions, pneumonia remains one of the biggest killers of young children. In 2015, 14% of under-5 deaths in the WHO Western Pacific region were attributed to pneumonia [5]. Other causes of under-5 mortality were mostly concentrated in the neonatal period, including prematurity (16%), intra-partum complications (13%), congenital anomalies (13%) and neonatal sepsis (4%), with injuries (11%) and diarrhea (6%) making substantial contributions in the post-neonatal period [5]. The available data indicate that the majority (>75%) of pneumonia-related deaths occur in six countries; Cambodia, China, Laos, Papua New Guinea, the Philippines and Viet Nam [6]. Table 2 provides a country-specific breakdown of the pneumonia-related disease burden in the Western Pacific Region.

In 2008, the WHO included Viet Nam among 15 "high child pneumonia countries" with an estimated 2.9 million cases and 0.35 pneumonia episodes per child-year in children less than 5 years of age [3]. Despite recent progress, the pneumonia disease burden in Viet Nam remains nearly 10 times higher than in developed country settings like Australia and Europe. In 2015, WHO estimated that acute respiratory infection accounted for 11% of under-5 mortality in Viet Nam; while human immunodeficiency virus (HIV) infection and malaria combined, accounted for less than 2% [5]. To achieve further reductions in pneumonia incidence and pneumonia-related deaths, careful assessment of risk factors and local clinical practice is required to optimize prevention and care.

CAUSES OF CHILD PNEUMONIA

Knowledge of the most common causative pathogens informs strategies for case management and prevention [7]. Table 3

Table 1
Estimated pneumonia disease burden in children less than 5 years of age by WHO region.*

WHO Region	Population (<5yrs of age)	Estimated Disease Burden n (95% confidence interval)		
		Episodes per child- year	Total Episodes (x10^6)	Total Deaths (×10^3)
Africa	133,340,762	0.27 (0.14-0.63)	36.4 (18.2-84.4)	540.6 (43.8-627.3)
Americas	76,995,700	0.08 (0.04-0.18)	6.4 (3.3-14.5)	23.9 (22.6-35.6)
Eastern Mediterranean	72,151,965	0.23 (0.11-0.53)	16.4 (8.2-38.0)	168.4 (147.3-217.1)
Europe	54,605,243	0.03 (0.02-0.04)	1.6 (1.3-2.1)	18.1 (14.7-23.4)
South East Asia	179,956,087	0.26 (0.13-0.61)	47.4 (23.7-109.8)	443.8 (336.7-534.2)
Western Pacific	116,411,580	0.11 (0.05-0.24)	12.2 (6.2-28.2)	61.9 (50.7-78.0)
World	633,461,337	0.19 (0.10-0.44)	120.4 (60.8-277.0)	1256.8 (1053.2-1482.9)

WHO – World Health Organization; yrs - years.
* Estimates for 2011 [1].

Table 2
Country-specific estimated pneumonia disease burden in children less than 5 years of age in the Western Pacific Region.*

Country	Population (<5 yrs of age)	Pneumonia Disease Burden			
		Total episodes N	Episodes per child-year	Severe episodes n (%)	Deaths n (%)
Australia	1,457,527	32,776	0.02	8,374 (25.5)	38 (0.1)
Brunei	37,385	899	0.02	239 (26.6)	3 (0.3)
Japan	5,430,793	135,770	0.02	36,251(26.7)	231(0.2)
New Zealand	311,974	7,036	0.02	1,800 (25.6)	31(0.4)
Singapore	230,550	5,764	0.02	1,539 (26.7)	9 (0.2)
China	81,595,595	6,488,544	0.08	746,183 (11.5)	43,089 (0.7)
Malaysia	2,828,151	285,716	0.10	32,652 (11.4)	199 (0.1)
South Korea	2,371,820	249,811	0.10	28,728 (11.5)	56 (0.02)
Papua N.G	962,437	166,267	0.17	19,051 (11.4)	2,038 (1.2)
Pacific islands[a]	273,315	53,309	0.19	5,132 (0.09)	204 (0.4)
Mongolia	296,799	60,292	0.20	6,889 (11.4)	332 (0.6)
Philippines	11,254,421	2,428,448	0.22	279,254 (11.5)	8,974 (0.4)
Viet Nam	7,185,862	1,728,193	0.24	197,920 (11.4)	3,553 (0.2)
Cambodia	1,491,690	373,583	0.25	42,699 (11.4)	2,101(0.6)
Laos	682,861	212,441	0.31	24,312 (11.4)	1,076 (0.5)
All combined	116,411,180	12,228,849	0.11	1,431,023 (11.7)	61,934 (0.5)

yrs – years.
[a] Pacific islands reflect combined data for the following pacific island nations; Cook Islands, Fiji, Kiribati, Marshall Island, Micronesia, Nauru, Niue, Palau, Samoa, Solomon Island, Tonga, Tuvalu and Vanuatu.
* Adapted from [96]; reflects the estimated number of total episodes and severe episodes in the year 2010, but the estimated number of deaths in the year 2011. Episodes per child-year was calculated from estimated total episodes and population numbers for children <5 yrs; arranged in ascending order of pneumonia episodes per child-year.

provides an overview of pathogens implicated in child pneumonia. The prevalence of each of these pathogens will vary depending on a range of factors that include age, seasonality, geographic location, vaccine coverage, socioeconomic status and prevalence of co-morbidities such as HIV or malnutrition. It is difficult to determine the relative importance of individual pathogens in young children with pneumonia due to the low sensitivity and uncertain specificity of microbiological techniques used for pathogen detection [8]. In addition, specimen collection poses a major challenge since young children are unable to expectorate and contamination with upper airway flora is a problem with non-invasive specimen collection methods [9–12]. Table 4 summarizes respiratory and non-respiratory specimen collection methods used to identify pulmonary pathogens in children, with a brief assessment of special considerations and limitations.

Bacteria

Studies conducted in the 1980's identified *Streptococcus pneumoniae* and *Haemophilus influenzae* type B (Hib) as the most common bacteria causing lobar pneumonia in children [13,14]. These direct transthoracic needle lung biopsy studies together with autopsy findings, confirmed that most pneumonia deaths were caused by bacteria [15], which had a major influence on case-management and immunization strategies. Bacteria are also recognized as important co-infections that can be fatal in children with primary viral infections (e.g. influenza, measles) or tuberculosis [16–18].

Haemophilus influenzae

Six distinct *H. influenzae* serotypes (a through f) have been identified; type B has a particularly thick polysaccharide capsule that seems to be the main virulence factor [19]. Introduction of the highly effective Hib conjugate vaccine eliminated severe disease (pneumonia, meningitis and epiglottitis) in settings with good vaccination coverage [19–21]. Since Hib vaccination reduces carriage rates in young children, there is less transmission in the community and therefore unvaccinated individuals benefit as well [20]. By the end of 2014, Hib vaccination has been introduced to 192 countries with 56% of children being fully immunized; full vaccination coverage in the WHO Western Pacific Region was only 21% [22]. In Viet Nam, free Hib vaccination has been included in the National Expanded Program on Immunization since July 2010. At the end of 2013, 59% of Vietnamese infants had received all three doses [4]. In south-east Viet Nam radiological child pneumonia was reduced by 39% after Hib vaccine introduction [21]. Disease caused by non-type B *H. influenzae* may be increasing in prevalence [19,23]. A lung aspirate study from The Gambia reported that 20% of positive *H. influenzae* samples from young children with pneumonia were non-type B [24] and in a follow-on study, *H. influenza* (all non-type b) accounted for 5% of all bacteria isolated in young children with severe pneumonia [25].

Streptococcus pneumoniae

S. pneumoniae remains the single biggest cause of bacterial pneumonia in children [25–27]. There are more than ninety *S. pneumoniae* serotypes, but less than 20 serotypes are responsible for more than 70% of invasive disease [28]. The most common serotypes found in the USA were included in the initial 7-valent conjugated pneumococcal vaccine (PCV-7), which reduced pneumonia-related hospitalization by 39% [29]. In South Africa, a 9-valent PCV vaccine (PCV-9) reduced the incidence of invasive *S. pneumoniae* disease by 83% (65% in HIV-infected children) and all-cause X-ray diagnosed pneumonia by 20% among HIV uninfected children [30]. As observed with the roll-out of conjugated Hib vaccine, benefit also accrued to non-vaccinated children and older adults [31]. In 2007, the WHO recommended PCV in all childhood immunisation programs, but global implementation has been poor. By 2014, PCV was introduced in 117 countries with 31% global coverage [22]. In addition to cost, there were concerns about sub-optimal serotype composition for developing country settings. This has been partially addressed by the newer PCV-10 and 13 conjugate vaccines. PCV-10 also provides protection against non-type B *H. influenza* [28], but in cost-effectiveness trials conducted in Malaysia and Hong Kong, PCV-13 seemed to offer the best value [32]. In Viet Nam, PCV use is advised in national guidance documents, but it is not provided free of charge and coverage is low. Limited data on the etiology of child pneumonia in the WHO Western Pacific region makes it difficult to convince policy makers to fund vaccines for prevention. Given the limitations of etiological studies, indirect evidence should be collected by measuring the impact of programmatic

Table 3
Pathogens associated with pneumonia in children of different age groups.*

Age	Common pathogens	Less common pathogens
<2 months	Group B streptococci	Influenza virus (A and B)
	Listeria monocytogenes	Human metapneumovirus
	Chlamydia trachomatis	Rhinovirus
	Bordetella pertussis	Adenovirus
	Enteric (gram -) bacteria	Enterovirus
	RSV	CMV
2-23 months	*Streptococcus pneumoniae*	*Mycoplasma pneumoniae*
	Haemophilus influenzae	*Mycobacterium tuberculosis*[a]
	B. pertussis	*Chlamydophila pneumoniae*
	RSV	*Staphylococcus aureus*
	Influenza virus (A and B)	*Streptococcus pyogenes*
	Parainfluenza virus	*C. trachomatis*
	Human metapneumovirus	Human bocavirus
	Rhinovirus	Human corona virus
	Measles	CMV
		Adenovirus
		Enterovirus
2-4 years	*S. pneumoniae*	*M. pneumoniae*
	H. influenzae	*C. pneumoniae*
	Moraxella catarrhalis	*S. aureus*
	RSV	*Klebsiella pneumoniae*
	Influenza virus (A and B)	*S. pyogenes*
	Parainfluenza virus	*M. tuberculosis*[a]
	Rhinovirus	Human metapneumovirus
	Measles	Human bocavirus
		Human corona virus
		CMV
		Adenovirus
		Enterovirus
5-14 years	*S. pneumoniae*	*C. pneumoniae*
	M. pneumoniae	*H. influenzae*
	M. catarrhalis	*K. pneumoniae*
	S. aureus	*S. pyogenes*
	Influenza virus (A and B)	*M. tuberculosis*[a]
	Parainfluenza virus	*Legionella pneumophila*
	Rhinovirus	RSV
		CMV
		Adenovirus

RSV - Respiratory Syncytial Virus; CMV – Cytomegalovirus; *S. aureus* includes methicillin resistant strains (MRSA); *H. influenzae* includes type B and non-typable strains.

[a] The risk of tuberculosis is dependent on the likelihood of *M. tuberculosis* exposure/infection; it is a particular problem in settings with uncontrolled transmission.

* Adapted from [5,34].

implementation of bacterial conjugate vaccines on the burden of radiographic pneumonia and hospitalizations due to pneumonia in Western Pacific countries.

Other bacterial pathogens

Other respiratory pathogens include *Bordetella pertussis*, which causes whooping cough. An estimated 16 million disease episodes and 195,000 deaths are attributed to pertussis every year; 95% occurring in low and middle income countries [33,34]. In recent years the numbers of reported cases have increased even in countries with high vaccination coverage [33] with concern about the durability of protection provided by acellular pertussis vaccines [35]. Respiratory pathogens that are currently not vaccine-preventable include *S. aureus, Klebsiella pneumoniae* and atypical bacteria. An earlier study from Chile found *S. aureus* to be a common isolate in young children diagnosed with pneumonia (60.5%) [36], but recent studies found it mostly in children at the severe end of the pneumonia disease spectrum. A multi-centre trial conducted in Bangladesh, Ecuador, India, Mexico, Pakistan, Yemen and Zambia found *S. aureus* in 42% of 112 bacteria isolated from blood and lung aspirate samples in children with WHO-defined "very severe" pneumonia [37]. Methicillin resistant *S. aureus* (MRSA) is of increasing concern and often presents with empyema or necrotic pneumonia following influenza [34]. *S. aureus*, *S. pneumoniae*, *H. influenza*, *K. pneumonia* and *Escherichia coli* have been identified as the most common bacterial pathogens in severely malnourished children with pneumonia [38]. Non-typhoid *Salmonella* species have also been recognized as important pathogens causing invasive sepsis with clinical features of pneumonia in malaria and HIV-endemic parts of sub-Saharan Africa [39], but its relevance in other settings has not been confirmed [40,41]. Group B streptococci and the atypical bacterium *Chlamydia trachomatis* may infect babies during vaginal delivery and are mainly restricted to the perinatal period [34]; other atypical bacteria are common respiratory pathogens across the age range.

Atypical bacteria

Mycoplasma pneumoniae (M. pneumoniae), *Chlamydophila pneumoniae (C. pneumoniae)* and *Legionella pneumoniae* are usually associated with mild to moderate respiratory symptoms, but severe pneumonia can occur. Atypical pathogens have been identified in the majority of pneumonia cases in parts of China and Viet Nam [42,43], but their relative contribution to all-cause pneumonia is difficult to assess given select patient recruitment and un-certain methodology in some of these studies. *M. pneumoniae* IgM was detected in 57% of serum samples in children with acute respiratory symptoms in Hubei, China [43]. Similar findings from Suzhou identified *M. pneumoniae* and respiratory syncytial virus (RSV) as the most common respiratory pathogens in hospitalized children [44]. A study in Ha Noi, Viet Nam, found atypical pathogens in 45% (97/215) of pneumonia cases in whom a potential pathogen was identified. Among children with atypical pneumonia, *M. pneumoniae* was considered the likely pathogen in 87% (84/97) of "severe" cases [42]. More information is required to assess the contribution of atypical bacteria to pneumonia morbidity and mortality in the Western Pacific region.

Tuberculosis

Globally, *Mycobacterium tuberculosis* is the commonest cause of death due to an infectious disease and the majority of cases occur in the Asia-Pacific region [45,46]. Western Pacific countries with high caseloads include China, Viet Nam, The Philippines, Cambodia and Papua New Guinea. High incidence rates are indicative of poor epidemic control and since children develop disease in settings where adults spread the infection, Figure 2 indicates areas where *M. tuberculosis* is likely to be an important lung pathogen in children. The WHO estimated that one million children developed tuberculosis in 2014 [47], but case detection is a major challenge [48]. Tuberculosis is rarely considered in young children presenting with acute severe pneumonia, although its presence as a primary cause or co-infection is well documented in these cases [49,50]. Tuberculosis was diagnosed at autopsy in 11% of HIV-infected and 8% HIV-uninfected children who died from pneumonia in five African countries [51]. Among 270 severe pneumonia cases evaluated in Uganda, around 20% had clinical manifestations suggestive of tuberculosis and 10% were culture-confirmed for *M. tuberculosis* [52]. Unfortunately, service delivery channels for children with tuberculosis are poorly developed in most tuberculosis endemic areas [53]. In China and Viet Nam children (<15 years) represented less than 1% of all reported tuberculosis cases in 2014 [45]. This is well below the estimated global average of 10%. Of 103 children (<15 years) diagnosed with tuberculosis in Northern Viet Nam, most were in the 5-14 year age range [54], suggesting gross under-detection in young children who are known to be most vulnerable [55]. Following a successful proof-of-concept study in 4 provinces [48], the Viet Nam National Tuberculosis Control Program plans to expand community-based contact screening and provision of preventive therapy to all provinces by 2020.

Table 4
Specimen collection methods for lung pathogen detection.*

Method/Specimen	Considerations
Respiratory	
Sputum microscopy and culture	- Young children cannot expectorate - Contamination with upper airway flora
Induced sputum	- Equipment required[a]; health care workers unfamiliar - Contamination with upper airway flora
Nasopharyngeal aspiration	- Minimal equipment required[b] - Valuable for viral diagnostics (also used for *M. tuberculosis)* - Contamination with upper airway flora
Nasopharyngeal swab	- Used for *Bordetella pertussis* (use swab with flexible shaft and immediately place in transport medium; collection may provoke a coughing paroxysm) - Contamination with upper airway flora
String test	- Young children (<4yrs) cannot swallow the string - Value in *M. tuberculosis* isolation (resistant to stomach acid) - Contamination with upper airway flora (on retrieval)
Stool	- DNA of respiratory pathogens (eg. *M. tuberculosis*) can be retrieved from stool in children unable to expectorate - Difficult specimen to work with
Transthoracic needle lung biopsy	- Invasive; risk of pneumothorax - Few experienced practitioners
Bronchoalveolar lavage	- Invasive; anaesthetic risk - Equipment/expertise required; resource intensive
Open lung biopsy	- Highly invasive; anaesthetic risk - Equipment/expertise required; resource intensive
Autopsy	- Most accurate diagnosis (culture and histology) - Strong selection bias; fatal cases only - Cultural barriers; resource intensive
Non-respiratory	
Blood culture	- To consider in all children hospitalized for IV antibiotics - Low yield; select subgroup
Urinary antigen testing	- Quick and simple - Poor diagnostic accuracy
Serum antibodies	- Detect immune response to bacteria and viruses that are difficult to grow or detect by PCR (*M. pneumoniae*, measles) - Best accuracy with both IgM and 4-fold rise in IgG titres - Difficult to collect antibody levels during convalescence

M. tuberculosis - Mycobacterium tuberculosis; M. pneumoniae – Mycoplasma pneumoniae; IV – intravenous; PCR – polymerase chain reaction.
[a] Bronchodilator, nebulizer, saturation monitor, hypertonic-saline, respiratory suction.
[b] Can use a simple syringe and catheter.

Viruses

The role of viruses in child pneumonia is increasing following socioeconomic development and the introduction of bacterial conjugate vaccines [56]. However, studies that detect viruses in children with pneumonia are difficult to interpret given the uncertain clinical relevance of highly sensitive tests that detect a wide range of viruses, frequent co-infection and asymptomatic infection, seasonal influences etc. A study in the USA detected respiratory viruses in 83% and 42% of children

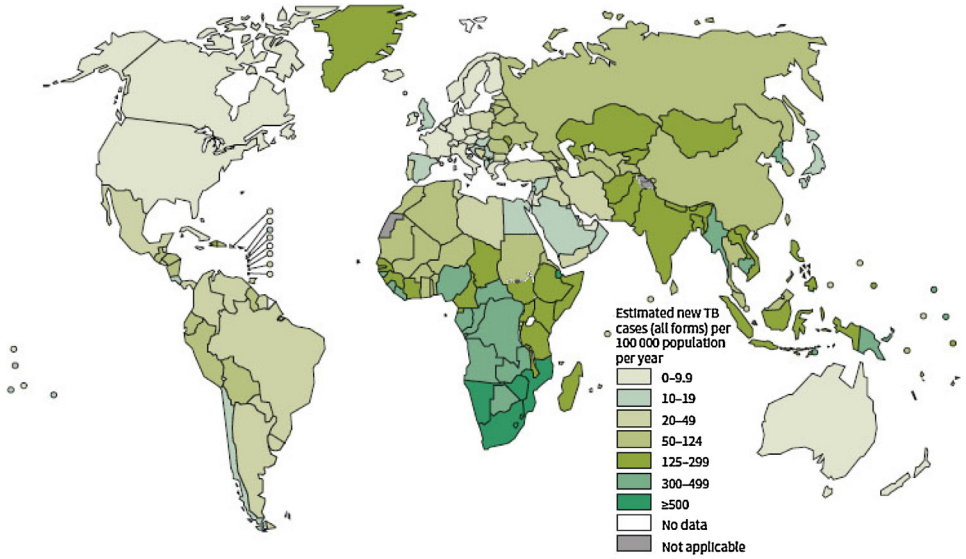

Figure 2. Global tuberculosis incidence estimates (2014).*
Small circles represent island populations.
*Adapted from World Health Organization 2015 [45].

with and without respiratory symptoms [57]. In Papua New Guinea, respiratory viruses were identified in 86% (69/80) of child pneumonia cases and in 73% (198/273) of children without symptoms [58].

Respiratory syncytial virus

RSV is the most common virus detected in the upper respiratory tract. The estimated annual burden of respiratory tract infections caused by RSV is 38.8 million episodes in children less than 5 years of age; 10% presenting as severe pneumonia [59]. Mortality resulting from RSV is estimated at 66,000-199,000 child deaths-year; mostly in young children from middle and low-income countries [60]. RSV is considered to be responsible for one third of pneumonia deaths among infants [59]. In Thailand, RSV was found to be the most common viral pathogen in children with severe pneumonia (49% of positive nasopharyngeal samples) [61], but it was detected in only 5.6% of 1,292 pneumonia cases with an identified pathogen in Suzhou, China [62]. In Viet Nam, RSV was identified in 73/222 (24%) children hospitalized with acute respiratory infections in whom a virus was detected (222/309; 72% of all cases); influenza viruses were found in 17% [63]. In addition to being a contributor to severe pneumonia, RSV is commonly associated with wheezing that results in hospitalization and unnecessary antibiotic use [60]. No effective vaccine is available, but more than 50 vaccine candidates are in development [59].

Influenza

Seasonal influenza epidemics are mostly caused by influenza A, but influenza B strains have shown increased prevalence in recent years [64]. A study from Bangladesh found influenza virus in 10% of pediatric pneumonia cases, but only 28% of all children in whom influenza virus was detected developed pneumonia [65]. In Suzhou, China, influenza viruses were found in 17% of positive nasopharyngeal swabs in children with pneumonia [62]. The most effective way to prevent influenza is seasonal vaccination [66], but this is rarely used in Viet Nam; not even among health care workers who are at high risk of contracting and spreading the infection within health care facilities [67]. Maternal influenza vaccination provides protection to newborn babies (49% in a study in South Africa) [68], but vaccine delivery in pregnancy remains controversial in many Western Pacific countries. Avian influenza strains found in wild and domestic bird populations have caused cases of severe pneumonia in China [69]. So far wide-scale epidemic outbreaks have not been recorded, but the risk that a new human-adapted influenza strain with pandemic potential may emerge, requires constant vigilance.

Measles

Measles can be a primary agent of pneumonia or lead to secondary bacterial infection due to respiratory tract inflammation and immune suppression [18]. Fortunately, the measles vaccine is highly efficacious and since humans are the only reservoir species measles eradication is considered feasible. By 2013, it was estimated that 84% of all children received at least one dose of measles vaccine before their second birthday; in Viet Nam the figure was 98% [4], but more than 100 children died of measles in 2014 [70]. Outbreaks still occur in settings where children remain unvaccinated; 667 cases were reported in the US in 2014 [71]. Vitamin A supplementation is given in many countries to reduce measles-related mortality, as well as the risk of pneumonia in a child with measles [72,73]. Widespread measles vaccination and vitamin A supplementation may explain reductions in severe *S. aureus* pneumonia, especially in settings where malnutrition and measles were common.

Other viruses

Other respiratory viruses include rhinovirus, para-influenza and adenoviruses as well as human metapneumo, boca or coronavirusses. A study in Japan that documented viral pathogens in 1,700 children with X-ray confirmed pneumonia found rhinovirus in 14.5%, with RSV, para-influenza, metapneumovirus and bocavirus in 9.4%, 7.2%, 7.4% and 2.9% respectively [74]. A study in Papua New Guinea found rhinovirus in 63% of 80 children with acute respiratory infection [58], but it was found in only 4% of children hospitalized with acute respiratory infection in Ho Chi Minh city, Viet Nam; 20% of patients (62/309) had co-infections with multiple viruses [63]. Non-respiratory viruses can also cause respiratory symptoms. Rota and enterovirus infections frequently cause mild respiratory symptoms and cases of severe rotavirus pneumonia have been documented [75].

Parasites and fungi

Fungal pneumonia is mostly seen as opportunistic infections. *Pneumocystis jirovecii*, is a significant pathogen in immune-compromised children, commonly causing severe pneumonia associated with high mortality in HIV-infected infants [1,50,76,77]. Pneumocystis pneumonia can be prevented by cotrimoxazole preventive therapy and early anti-retroviral therapy initiation in HIV-infected infants. Intestinal parasites can cause cough and wheezing as larvae migrate through the lung, so-called Loeffler syndrome, but this rarely cause severe symptoms and is uncommon in settings with adequate sanitation [78]. The lung fluke *Paragonimus westermani* is found in the Western Pacific Region (including China, the Philippines, Japan, Viet Nam, South Korea), but it is limited to specific geographic areas and has not been implicated in acute childhood pneumonia [79]. In general, parasites and fungi are uncommon lung pathogens and not considered in routine management protocols.

STANDARDIZED CASE MANAGEMENT

Since the bulk of the global pneumonia disease burden occurs in countries with limited resources and weak healthcare systems, a primary-care focused clinical case management approach was developed [80]. The WHO acute respiratory infection case management strategy aimed to reduce child mortality by providing antibiotics to pneumonia cases and reducing inappropriate antibiotic use in children with upper respiratory tract infections [7]. All children with respiratory symptoms and fast breathing were classified as ''pneumonia'' with specific features distinguishing ''severe'' and ''very severe'' cases (Table 5). A systematic review demonstrated that adoption of a standardized case management approach reduced under-5 pneumonia deaths by 70% in developing country settings [81]. Subsequent studies showed no benefit if children with ''severe pneumonia'' received intravenous compared to oral antibiotics [82,83] and in 2013 WHO published a technical update in which pneumonia was classified in only 2 categories, ''pneumonia'' and ''severe pneumonia''. Table 5 summarizes previous and current WHO case management guidelines [84]. The WHO also published a guidance for effective hypoxaemia management [85], using clinical signs in settings without pulse oximetry [86]. Hypoxaemia management was shown to be cost-effective in countries like the Philippines and Viet Nam [87]. A multi-hospital study in Papua New Guinea with more than 11,000 cases achieved a 35% reduction in deaths in children hospitalized with severe childhood pneumonia, using oxygen supplementation in hypoxaemic cases [88].

Table 5
Revised WHO child pneumonia classification and case management.*

Clinical signs *Cough or runny nose with*	**Original classification**	**Revised classification**	**Treatment guidance**
No fast breathing	No pneumonia	No pneumonia	No antibiotics
Fast breathing Chest in-drawing	Pneumonia Severe pneumonia[a]	Pneumonia	Oral antibiotic at home - if no response refer to hospital[b]
Any danger sign[c]	Very severe pneumonia	Severe pneumonia	Stat dose of oral antibiotic - urgent referral to hospital

WHO – World Health Organization.
[a] Hospitalisation for intravenous antibiotics previously advised.
[b] Hospitalisation for appropriate supportive care and intravenous antibiotics.
[c] Danger signs: Not able to drink (cyanotic), persistent vomiting, convulsions, lethargic or unconscious, stridor in a calm child or severe malnutrition.
* Adapted from [84].

Integrated Management of Childhood Illness (IMCI)

The United Nations Millennium Development Goal (MDG) 4 aimed to reduce under-5 mortality by two-thirds within 15 years, compared to 1990 figures. The IMCI approach was developed by the WHO and the United Nations Children's Fund. IMCI adopted the standardized pneumonia case management approach and was first implemented in Africa in 1998. IMCI uptake in the Western Pacific Region was slow and by 2013 only fourteen countries had implemented IMCI; Cambodia, China, the Federated States of Micronesia, Fiji, Kiribati, the Lao People's Democratic Republic, Malaysia, Mongolia, Papua New Guinea, the Philippines, Solomon Islands, Tuvalu, Vanuatu and Viet Nam [5].

Challenges to IMCI implementation in the Western Pacific Region include a well-developed private sector that is commercially incentivized; unregulated access to antibiotics and a strong expectation to provide patient centered care equivalent to high-income countries. Unfortunately, patient centered care is hampered by poorly defined disease aetiology and limited microbiology services. IMCI also had difficulty in identifying high profile champions to lead integration within local health systems and adoption by training institutions in the Western Pacific Region [86,89].

Rational antibiotic use

Before the availability of effective conjugated vaccines, improved antibiotic access reduced pneumonia-related mortality [13,16,90]. However, the profile of causative pathogens has changed in settings with adequate Hib and PCV vaccination coverage, while increased antimicrobial resistance is now recognized as a major global public health challenge [91]. According to the World Economic Forum, the emergence of new infectious diseases and the rise of drug-resistant infections are now ranked as second only to water crises in terms of potential global impact [92]. Antimicrobial resistance is predominantly driven by excessive antibiotic use, which is a particular problem in Asia given unrestricted access to antibiotics, strong commercial incentives and uncertain disease aetiology with uncharacterized drug resistance profiles. Studies have demonstrated that many children with non-severe pneumonia do not require any antibiotics at all [93]. Asian countries are more likely to follow developed country guidelines than those developed for low income settings [94]. In Indonesia, as in Viet Nam, children with mild respiratory symptoms are often hospitalized and treated with prolonged courses of broad spectrum antibiotics [95].

CONCLUSION

Child pneumonia remains a major cause of disease and death globally and in the WHO Western Pacific Region. With the widespread use of conjugated vaccines, we require a better understanding of the changing disease etiology and underlying risk factors associated with childhood pneumonia. This is particularly relevant in the Western Pacific region where standardized case management approaches may require revision, primary prevention strategies should be enhanced and careful consideration should be given to the rise of drug-resistant infections fueled by inappropriate antimicrobial use.

FUTURE DIRECTIONS

For improved pneumonia management in the Western Pacific region, there is an urgent need to:

- Better describe the etiology of severe pneumonia, as well as the drug resistance profile of common bacterial pathogens
- Understand and improve local clinical practice
- Reduce the irrational use of antibiotics and limit unnecessary hospitalization
- Explore risk factors for severe pneumonia and enhance primary prevention strategies

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