SLIDE 1 Technical Seminar – Acute Respiratory Infections

Welcome. During this technical seminar on acute respiratory infections I will explain why certain signs and symptoms have been selected for the assessment of a child with a cough and difficult breathing. I'll then discuss the rationale for choosing different antibiotics for the treatment of pneumonia and very severe pneumonia or very severe disease. Finally, we'll look at the advantages, disadvantages and practicalities of including wheezing in a country's adaptation of the IMCI guidelines.

SLIDE 2 Pneumonia - Recognition

In first-level health facilities, we recognize pneumonia based on two simple clinical end points: **fast breathing**, and **lower chest wall indrawing (1)**. We first rely on the mother or caregiver to recognize cough or difficult breathing in their child — that's the entry point into our assessment of the child for cough and cold. About 95 percent of children with pneumonia will have a cough while a small proportion will have no cough but will have difficult breathing. Therefore, when assessing for pneumonia, you use **"cough OR difficult breathing," not "cough AND difficult breathing."**

Few children with cough — less than 25 percent — will also have difficult breathing. There are many causes of difficult breathing that are not related to cough. Some examples — acidosis in children with diarrhoea, chronic difficulty in breathing in children with congenital heart disease, rickets or congenital malformations. Thus, if you include difficult breathing, it may cause some false positive classifications. However, since the first priority is the accurate recognition and treatment of pneumonia, and because there are few false positives that have only difficult breathing but no cough, it was decided to leave the entry into assessment as **cough or difficult breathing**. In these circumstances, fast breathing or lower chest wall indrawing have sensitivities and specificities sufficiently high to predict pneumonia or very severe pneumonia reasonably accurately.

SLIDE 3 Sensitivity and Specificity - Definitions

It is important to understand the concept of sensitivity and specificity in order to understand the rationale for choosing different respiratory rate cut-offs for detecting pneumonia.

When using fast breathing to measure true disease, **sensitivity** is defined as the proportion of true cases of pneumonia that are classified as cases depending on a respiratory cut-off. **Specificity**, on the other hand, is the proportion of normal cases that are classified as non pneumonia cases using the respiratory rate cut-offs. A low sensitivity is associated with a reduction in the measured incidence of disease. However, a low specificity results in the disease incidence being higher than it actually is.

In general, a **low sensitivity of diagnosis is a more serious problem than low specificity**. This is especially true in the management of conditions being studied in IMCI. Thus, a low sensitivity would result in children not being treated, while a low specificity would result in children being over treated. The optimum situation is one where both sensitivity and specificity are high. However, there are very few tests in clinical practice that have extremely high sensitivities and specificities.

The decision regarding respiratory cut-off and the choice of exams to identify severe disease are based on optimizing the sensitivity, and finding the highest specificity for that cut-off point. In practice, this has been achieved by plotting the sensitivity and reciprocal of the specificity on a curve — the receiver operating characteristic, or **ROC curve**. The uppermost outermost point on this curve determines the cut-off.

SLIDE 4 Pneumonia — Fast Breathing

In a child with cough or difficult breathing, we define fast breathing based on **age-specific thresholds**. Since the assessment of pneumonia and very severe disease is different in the young infant aged 7 to 59 days, the age specific thresholds are not discussed in this section but will be discussed later in the section on the young infant.

Respiratory rates **greater than or equal to 50 per minute** in infants up to 12 months of age, and **greater than or equal to 40 per minute** in children aged 12 months up to five years, indicate the presence of pneumonia. If the respiratory rate is below these cut-offs and there are no danger signs and no chest wall indrawing, the classification is **no pneumonia, cough and cold**.

These children have upper respiratory tract infections and do not need antibiotics. These respiratory rate cut-offs are based on numerous studies that have been done around the world, which we summarize in the next slide.

The optimal method of obtaining a respiratory rate is the use of a **timing device**, either a wall clock or a hand held watch or timer. Since the respiratory rates can vary in some children, it is important to count the respiratory rate for **one full minute**. This may not be possible in busy clinics. Sometimes you must count for 30 seconds and multiply by two. This compromise, while being more efficient, can cause problems for younger children. They tend to breathe faster, and errors in counting are doubled.

Let me emphasize that the **best time to count the respiratory rate is when the child is in a quiet and alert state**. If a child is crying, the respiratory rate could be high. If the child is sleeping, the rate will be lower. However, in a child with pneumonia, the fast breathing persists in the awake or sleeping state. Hence, it is acceptable to count respiratory rates when a child is sleeping.

You should note that the respiratory rate is also **influenced by temperature**. Fever can increase the respiratory rate by 3 to 4 respirations per minute for every degree centigrade above normal. This is one of the reasons for a lower than 100 percent specificity of the respiratory rate cut-offs. However, it is not practical to wait for a child's temperature to come down before a respiratory rate is recounted. While these limitations do occur, we recommend that the cut-off rates be used without adjustment.

SLIDE 5 Pneumonia — Fast Breathing (continued)

Initially, WHO used a respiratory cut-off rate of 50 per minute to classify any child aged 2 months to 5 years with pneumonia. This was based on studies performed in **Goroka, Papua New Guinea (2)**.

In these initial studies, the sensitivity and specificity was 72 percent and 81 percent respectively. However, studies performed in India (3) and later in Gambia (4) and Philippines (5) demonstrated that this cut-off rate was **not specific enough for children 1 to 4 years of age**. Indeed, in that age group, the sensitivity of the respiratory rate of greater than or equal to 40 per minute was almost 15 percent higher with very little loss of specificity. In children aged 2 to 11 months, the best sensitivity and specificity was obtained using a respiratory rate of greater than or equal to 50 per minute. Hence, the higher respiratory rate was not sensitive enough and almost half of the children with pneumonia in 1-4 age group were being missed.

Based on these studies, **the threshold for the older children was lowered to greater than or equal to 40 per minute**. Studies from around the world since the early 80s have proven these respiratory rate cut-offs to be very robust. We acknowledge that two different cut-offs may cause some confusion and add to the complexity of decision making. However, the **added advantage of increased sensitivity** — i.e. not missing children who have pneumonia — has led to the current recommendations.

SLIDE 6 Severe Pneumonia - Lower Chest Wall Indrawing

While respiratory rate cut-offs have simplified the recognition of pneumonia, it has been **more problematic to recognize the sick child who requires urgent referral** to a hospital for further assessment and possible admission.

Based on studies in Papua New Guinea (2), the presence of "**retractions**" was suggested as an indicator of severe disease. There were retractions in most children in that study who were admitted to the hospital with severe pneumonia. In most

children with non-severe pneumonia, there were no retractions and children were sent home with oral antibiotics. Hence, it was suggested that retractions be used as an index of severity.

At that time, however, there were **multiple definitions of "retractions"** including suprasternal retractions, intercostal retractions (3), xiphoid retractions and subcostal retractions (4). From several studies, it was clear that the **frequency of suprasternal and xiphoid retractions was very low** and occurred in only the most severely ill children. In fact, suprasternal and xiphoid retractions occur in children with major obstruction to the airway or severe respiratory compromise. Conversely **intercostal retractions are very subtle and occur in many children**, even with blocked noses and upper respiratory tract infection. Intercostal retractions are those that occur between the lower intercostal spaces when a child breathes in. Clearing a blocked nose will often clear intercostal retractions. Finally, subcostal retractions are retractions that occur below the costal margin and indicate diaphragmatic and abdominal muscle use in a distressed child. The definition of subcostal indrawing also includes indrawing of the lower chest wall and has been variously interpreted in the literature.

These multiple definitions of "retractions" led to studies in the Philippines and Swaziland (5) to identify which type of "retractions" best identified children who required assessment or admission. These and other studies proved that "**lower chest wall indrawing**" best identifies these children with sensitivities and specificities ranging around 70 percent each. However, lower chest wall indrawing must be definite and present all the time.

SLIDE 7 Severe Pneumonia and Very Severe Disease — Recognition

There are several signs which help us determine which children should be urgently referred.

Children with cough or difficult breathing and general danger signs — such as history of convulsions, inability to feed, incessant vomiting and lethargy or unconsciousness — indicate severe disease such as sepsis, meningitis or hypoxia co-existing with the respiratory tract infection. These children should be urgently referred to hospital for assessment and further management.

Children with **stridor when calm** may or may not have fast breathing or lower chest wall indrawing. However, stridor implies obstruction to the upper airway and, as such, could be life threatening. The most common cause of stridor in children in developing countries is viral croup, and in the younger infant**,** congenital laryngeal stridor. Epiglottitis is very rare in developing countries. It is difficult if not impossible to differentiate between the various causes of airway obstruction at a first-level health facility. Clearly, these children need to be referred for assessment as well as management, if acute.

Also, a child with **one of these danger signs** noted earlier may have multiple complications of pneumonia, and hypoxia, sepsis and meningitis may all co-exist. In children with meningitis, the respiratory rate may be depressed and fast breathing and/or lower chest wall indrawing may not be present. It is for these reasons that **a danger sign alone** is sufficient to classify a child who is having severe pneumonia or very severe disease in the presence of cough or difficult breathing.

SLIDE 8 Severe Pneumonia or Very Severe Disease — Clinical Signs

This slide illustrates that lower chest wall indrawing, stridor when calm and general danger signs — either singly or in combination — identify most children with severe disease or diseases mimicking severe diseases that need assessment and or management at a hospital.

Lower chest wall indrawing identifies a child with **severe pneumonia**. While it can also indicate severe disease, it cannot be used to identify the complications of pneumonia that cause it. For example, a child with lobar pneumonia and a

pyothorax or a pyopneumothorax may have lower chest wall indrawing.

Conversely, an infant with **severe bronchiolitis** or an older child with asthma may also present with lower chest well indrawing alone. In the latter two conditions, audible wheezing may be heard in only about 30 percent of cases. It is impossible to differentiate between these three conditions without doing a complete physical examination and/or chest radiograph.

While conditions such as **severe pyopneumothorax or bronchiolitis with hypoxia** may need urgent hospital admission, other conditions such as asthma could be managed at a first-level health facility. However, since making this distinction is impossible at the first-level health facility, the use of lower chest wall indrawing has been used to indicate conditions that need either assessment or management in a hospital setting.

Children with epiglottitis or laryngotracheobronchitis are identified using stridor. They may not have all of the danger signs and may not have chest wall indrawing. However, as obstruction increases, lower chest wall indrawing almost inevitably occurs. Indeed, if obstruction is more proximal and obstructs the airway more completely, suprasternal and xiphoid retractions would also occur. In these conditions, hypoxia may lead to inability to feed, altered sensorium and even convulsions.

Infants and children with severe anaemia may have chest wall indrawing and/or have altered sensorium and/or convulsions from hypoxia if acute and very severe. In these children, if there is congestive cardiac failure or hypovolemic shock from acute blood loss, there will be lower chest wall indrawing and/or alteration of sensorium respectively.

Children with meningitis or septicemia will also often have an alteration of sensorium and lethargy or unconsciousness. Those with meningitis may also have convulsions. Clearly, a child that is abnormally sleepy may have one of many severe diseases — sepsis, meningitis, encephalitis, encephalopathy,

metabolic disturbances, cerebral malaria or a variety of other conditions. Differentiating these conditions at first-level health facilities is impossible without diagnostic procedures — these children need to be referred to a higher level health facility where assessments can be made.

On the other hand, the presence of convulsions, either febrile or afebrile, is not inevitably due to serious disease. Clearly a child with a fever and a convulsion may have a febrile seizure, meningitis, septicemia, encephalitis, cerebral malaria a brain tumour or other CNS infections. Afebrile seizures could be caused by a variety of conditions as well, but most often would be due to a seizure disorder.

Confident decision making between potentially life threatening diseases and benign conditions must be made by a proper physical examination at a higher level facility, including neurologic examination and/or investigations such as a lumbar puncture. Other investigations may also be necessary. The potential to do severe damage is high enough that any child with a seizure should be referred for further assessment and management.

SLIDE 9 Pneumonia — Antibiotics

This slide explains the rationale for choosing antibiotics to be used in a national IMCI program. The treatment of non-severe pneumonia can utilize a five-day course of either **oral cotrimoxazole or amoxicillin**. These two oral antibiotics are both relatively inexpensive, widely available, and are on the essential drug list of most countries. A country's choice to use one or the other will depend on a variety of factors (6).

Cotrimoxazole is the **least expensive** oral antibiotic costing about 25 cents for a five-day course. Because it is used twice a day, it is affordable, and compliance is good — both are advantages. Studies have shown compliance levels in excess of 75 percent with twice-daily dosing.

Cotrimoxazole has also been in use for many decades and the side effects are well known. **Adverse effects are few**, the most serious ones being related to drug rashes and drug eruptions

that can be life threatening. However, these are infrequent and are reversible once drug use is stopped. Bone marrow suppression may occur with higher doses but is uncommon with the doses and duration recommended for the treatment of pneumonia. It occurs more frequently with the high-dose treatment of Pneumocystis Carinii Pneumonia or PCP, in HIV patients.

The major disadvantage of cotrimoxazole, however, is **the increasing rates of resistance** of the two major pathogens that cause bacterial pneumonia — *S. Pneumoniae* and *H. Influenzae*. Recent studies from Asia (7) and Africa (8) have shown resistance rates between 30 to 60 percent. These *in vivo* rates are significant because they are associated with the treatment failures of up to 30 percent of children with non-severe pneumonia in Pakistan (7).

The alternative antibiotic, **amoxicillin**, is about **twice as expensive** as cotrimoxazole, which deters its use by national ARI or IMCI programmes. Furthermore, the standard dosage recommendation is three times a day. The **compliance** with three times a day dosing drops to 60 percent or less. Both these factors are disadvantages of amoxicillin.

Drug reactions with amoxicillin are less common, the most common of which is diarrhoea. Drug rashes are less common than with cotrimoxazole. The major advantage of amoxicillin, however, is that in higher doses, it is **effective clinically even against relatively penicillin-resistant *S. Pneumoniae***. Recent studies using two doses of amoxicillin in twice the usual dose have been shown to be as effective as the normal dose given three times a day in otitis media (9). Studies are currently underway to examine its efficiency against bacterial pneumonia. Of course, the higher dose would effectively increase the cost as well. One disadvantage of amoxicillin against *H. Influenzae* is that β- lactamase producing *H. Influenzae* completely inactivate the amoxicillin and it is not useful against this organism.

However *H. Influenzae* that are resistant to amoxicillin are still infrequent, with half or a quarter of the levels of resistance to cotrimoxazole.

While neither drug is a perfect solution, the costs and resistance patterns of the two major causes of non-severe pneumonia need to be used in making a decision about choice of antibiotics.

SLIDE 10 Severe Pneumonia or Very Severe Disease — Antibiotics

Children with severe pneumonia or very severe disease most likely have **invasive bacterial organisms** and diseases that may be life threatening. This warrants the **use of injectable antibiotics (6)**.

Parenteral use ensures that the drug is **delivered to the blood and/or meninges**, which may not occur with an oral antibiotic. Orally administered antibiotics such as chloramphenicol may be possible since blood levels after oral administration may be similar to those obtained after IV/IM administration.

However, in children in shock or those who are **vomiting incessantly or are unconscious**, administration of an oral antibiotic may be impossible or may result in low levels in the blood because of poor absorption. In these cases, parenteral antibiotics are essential.

While there are many antibiotics available, there are few that are inexpensive, routinely available at the first-level health facility, and can be safely administered intramuscularly or intravenously. The two recommended choices are **penicillin or chloramphenicol**.

Penicillin, the most widely used antibiotic over the past 50 years, is **inexpensive and widely available**. However, while it treats *S Pneumoniae*, and some *H Influenzae*, β-lactamase-producing bacteria inactivate penicillin completely. Most causes of severe pneumonia that have been treated with amoxicillin or cotrimoxazole and have failed treatment may be bacteria such as *Staphylococcus aureus*, or *Klebsiella pneumoniae* that are **resistant to penicillin (10).**

Another disadvantage is that penicillin is not optimal for the management of meningitis. **Penicillin does not penetrate the CSF very well** and is not the most effective drug in this regard.

It does get into the CSF with inflamed meninges sufficiently to inactivate bacteria.

SLIDE 11 Severe Pneumonia or Very Severe Disease — Antibiotics (continued)

An alternative — **chloramphenicol** — can be administered intramuscularly (11). While studies have shown that absorption of intramuscularly administered chloramphenicol was not as good as intravenous administration in adults (12), intramuscular and intravenous administration have equivalent absorption in children, who have more accessible muscle mass and less body fat (11).

An advantage of chloramphenicol is that it **works on a much broader range of organisms**, *S Pneumoniae, H Influenzae*, *S. aureus* and *Klebsiella pneumoniae* among others. Resistance rates to chloramphenicol are lower than penicillin but are increasing in some countries.

Another advantage — chloramphenicol **penetrates both the intact and inflamed meninges** very well. Hence, chloramphenicol is the drug of choice for use in the child with very severe disease.

The major disadvantage of chloramphenicol is its legacy. The **idiosyncratic aplastic anaemia that occurs in 1 in 80,000 to 1 in100,000 children or adults** who receive chloramphenicol has been a major argument against its use (13). The second reason for its non-use in other countries is the reluctance to use it at a first-level health facility. Please remember that, in the context of IMCI guidelines, this drug is only used as a **single dose as a pre-referral antibiotic**. Thus, while more expensive than penicillin, its other characteristics make it perhaps the best choice as a pre-referral antibiotic.

SLIDE 12 Wheezing — Causes

In infants and young children under the age of 2 years, the first attack of wheezing often occurs during the RSV season and **bronchiolitis is the usually the cause**.

In the older child and children with recurrent attacks of wheeze, **bronchial asthma or reactive airways disease are the most important causes** of wheezing.

The classification of this disease and its causes are still in a state of flux. What is clear, however, it that bronchiolitis almost always is the cause of the first attack of wheezing for the majority of children in RSV season. Some of these children — the younger ones with small lungs — tend to have wheezing for a few years which then disappears by age 5 or 6. These children are know as **transient wheezers.** They do not have atopy or immunoglobulin E (IgE) mediated responses to allergens. On the other hand, a small group of children with a family history of atopy and IgE mediated allergen responses tend to become **persistent wheezers**. This wheezing usually persists beyond age 5 or 6, but stops later in childhood. Clinically, it is difficult or impossible to distinguish between these groups of children (14).

Other causes of wheezing are less common but may still cause significant morbidity. For example, other **respiratory infections** such as viral pneumonia or mycoplasma may be associated with wheezing. **A foreign body** that is inhaled into the lower respiratory tract may get lodged in one or the other bronchus and acting as a ball valve causing a high pitched wheeze. Or an enlarged lymph node in the carina or paratracheal areas may compress the main stem bronchus and cause wheezing as well. The usual cause is **tuberculous lymph nodes** that compress the bronchus. Rarer causes include lymphomas and other tumours of the lymph nodes.

SLIDE 13 Wheezing — Drug Management

The management of wheezing can be broadly divided into two categories: young infants and children with bronchiolitis and those with asthma — either a first episode or recurrent episodes.

It is well known that only about a third of patients with bronchiolitis show some response to bronchodilators (15). Bronchodilators may make a difference in clinical scores but

not in reducing hypoxia or the duration of hospital stays, or for stemming the progression of bronchiolitis per se. Hence, they **have limited value for the management of bronchiolitis**.

On the other hand, children with **asthma or recurrent airways disease benefit greatly from bronchodilators**. Nebulizers, for the most part, are unavailable at first-level health facilities in most developing countries where IMCI is being implemented. An alternative is the use of a **metered dose inhaler, or MDI, with a spacer device**. Salbutamol inhalers are now **relatively inexpensive** at $1.50 per 200 doses at **0.1 mg per dose**.

When using an MDI, correct use of a spacer is most important. Spacers should be at least 750 ml or more in size which allows larger non-respirable particles to deposit on the surface of the inhaler while small respirable particles enter the airway. The MDI can be used in the outpatient department. Two - three doses, 15 - 20 minutes apart, can be used to determine responsiveness (16). If there is a decrease in respiratory rate and/or disappearance of audible wheeze, and the child is symptomatically better, **bronchodilator therapy can be continued at home**.

Depending on the availability of **inhaled steroids** — an expensive option — and the severity of recurrent wheeze, inhaled steroids can be added to the regimen of bronchodilator inhalation usually with significant improvement. Inhaled steroids are reserved for children with recurrent asthma.

SLIDE 14 Wheezing — Disadvantages of Adding to IMCI Guidelines

While wheezing is a very common symptom in infants and young children, it has not been included in the IMCI guidelines for a number of reasons.

The main reason is that wheezing and its causes are **not a major cause of mortality**. Rather, wheezing is a cause of significant morbidity and, when recurrent, can account for a significant number of clinic visits.

The major disadvantages of adding wheezing to a country's IMCI programme relate to assessment and management of these conditions. Some studies of children with bronchiolitis have shown that audible wheeze is present in only about a third of all children who wheeze. Furthermore, the **recognition of audible wheeze is poor with low specificity**. This means that most children classified by a health worker with wheeze probably don't have a wheezing condition but may have a blocked nose or respiratory secretions that cause other sounds mimicking wheezing . These children could then be incorrectly classified as having wheezing disease, and that may stigmatize a child as having asthma. An incorrect diagnosis could have serious implications, not on mortality but on **multiple clinic visits and expensive drug use**.

The second major disadvantage of including wheezing is the **provision of drugs to first-level health facilities**. While wheezing is an important cause of morbidity, the treatment of asthma requires bronchodilators supplied either as nebulizers or as a metered dose inhaler — or MDI — with spacers.

Most first-level health facilities have neither. The former are **expensive to buy and to maintain**, and require expensive supplies. While MDIs are less expensive, because they are multiple dose vehicles, the unit cost may be high. There are also problems associated with ineffective delivery of drugs with non-standard spacers.

A disadvantage of having expensive drugs available in first-level health facility, they are most often **diverted to adults** for their use since there is no difference in drug dosage for the MDI between children and adults.

SLIDE 15 Wheezing — Considerations for Adding to IMCI Guidelines

When should one consider adding wheezing to IMCI guidelines? While the earlier slide showed the disadvantages, it is not unreasonable to add wheezing in countries that **can afford bronchodilators and where mortality is less of a problem** than morbidity — in the former Soviet Union countries, for example, or some South American countries.

In situations where rapid acting **bronchodilators are available** at first-level health facilities, where **health workers are trained** to use them, and where **morbidity from asthma is significant**, wheezing can be added to the IMCI guidelines.

Slide 16 Wheezing — Considerations for Adding to IMCI Guidelines (continued)

The advantage of adding wheezing is that it **may decrease unnecessary referral to the hospital** — for lower chest wall indrawing caused by asthma, for example — or the use of unnecessary antibiotics — for fast breathing with wheeze — that disappears after bronchodilator use.

A **health worker must be trained to recognize audible wheeze** — excepting that this would only pick up about 30 percent of all actual wheeze (17). In a child with fast breathing or lower chest wall indrawing, with a wheeze, the administration of two doses of inhaled bronchodilator may result in the abolition of fast breathing and/or chest wall indrawing, if they were caused by asthma. Thus, a bronchodilator responsive wheeze in a child may diminish the use of antibiotics and over-referral of the child with lower chest wall indrawing.

Of course, symptomatic relief in the outpatient setting should be followed up by bronchodilators for use at home. This implies parental compliance, skill in administration and other skills that **caretakers must be taught.** It also implies making a proper clinical diagnosis before relegating the child to a diagnosis of asthma. Hence, a child who wheezes and responds should be referred to a hospital for assessment of wheezing disease at some stage.

A provision in these guidelines should also be made for the management of the child with recurrent wheeze when he or she comes back to the clinic. This requires a **health worker to recognize when a child with recurrent wheeze is not responsive in the first-level health facility** and should be referred to a hospital for urgent management.

Finally, it must be remembered that for children with wheezing, **underlying bacterial pneumonia** may occur concurrently which needs to be treated. The distinction between bronchiolitis and asthma with wheezing may be difficult in the young infant, but may be less difficult in the older child with recurrent wheeze. Provisions should be made in any adaptation to account for this problem.

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