

# **Generic protocol to examine the incidence of lower respiratory infection due to respiratory syncytial virus in children less than five years of age**

## **Field test version**

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## **DEPARTMENT OF VACCINES AND BIOLOGICALS**



*World Health Organization*  
*Geneva*  
*2000*

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**The Department of Vaccines and Biologicals  
thanks the donors whose unspecified financial support  
has made the production of this document possible.**

This document was produced by the  
**Vaccine Assessment and Monitoring Team**  
of the Department of Vaccines and Biologicals

*Ordering code: WHO/N&B/00.08*  
*Printed : **March 2000***

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# Preface

The WHO Department of Vaccines and Biologicals has an increasing interest in vaccines against respiratory syncytial virus (RSV). Such vaccines are still in the early phases of development, but research is being pursued within a number of pharmaceutical companies and academic centres. The promise of having a vaccine available in the relatively near future emphasizes the need to understand the clinical impact of RSV in developing countries. It can be anticipated that the mortality from acute lower respiratory tract disease will be higher in developing countries than in industrialized countries, if only because of the general lack of respiratory support such as mechanical ventilation and supplemental oxygen. Viral pneumonias may predispose to the increased frequency and severity of bacterial pneumonias which are seen in developing countries (*WHO 1991*). Although the epidemiology of RSV disease is clearly defined in temperate climates, it is incomplete in developing countries.

The Steering Committee on Epidemiology and Field Research and the Steering Committee on Measles, Acute Respiratory Viruses and Poliomyelitis jointly identified the need to develop a practical method for immunization programme managers and clinical epidemiologists to assess the local burden of severe disease due to RSV. At the request of these Steering Committees, this generic protocol was prepared by staff at Vanderbilt University and the London School of Tropical Medicine and Hygiene.

This protocol provides a general outline for a study and describes the main procedures involved. It will need to be adapted to the local setting, and details of field work and operational procedures should be added by local investigators with experience of conducting field studies in the specific area. During 1998-2001, WHO is sponsoring studies based on this protocol in Indonesia, Mozambique, Nigeria and South Africa.

WHO provides this generic protocol free-of-charge. In return, the programme would appreciate being informed about studies conducted using this protocol. The generic protocol may be freely adapted, but this WHO document should be referenced in any publication resulting from its use. Comments or suggestions for improving this protocol are welcome and should be sent to: *Dr S. Robertson, Department of Vaccines and Biologicals, World Health Organization, 1211 Geneva 27, Switzerland.*

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# 1. Introduction

Severe respiratory syncytial virus (RSV) pulmonary disease, manifested as bronchiolitis and pneumonia, continues to play a major role in childhood morbidity and mortality that is best documented in industrialized countries. Estimates of impact in the USA are that 18 000 to 75 000 hospitalizations and 90 to 1900 deaths occur annually (*Anderson et al. 1990*). Vigorous initiatives are now under way for the prevention of RSV disease in industrialized countries. These include the development of live, attenuated RSV vaccines; subunit RSV vaccines for maternal or infant immunization; and passive antibody in the form of RSV immune globulin or monoclonal antibodies. The RSV immune globulin given prophylactically has been shown to be helpful in prevention of lower respiratory tract disease in those with underlying cardiopulmonary disease, particularly small, premature infants (*Groothuis et al. 1995*). It is anticipated that vaccines will be available for immunization against RSV within a decade (*Murphy et al. 1994*). Nonetheless, because the pathogenesis of RSV infection appears to be at least in part immunologically mediated and because of past experience of disease enhancement after killed vaccines, the introduction of RSV vaccines will have to be undertaken with particular care.

The purpose of this generic protocol is to describe a surveillance system which will allow estimation of the local burden of RSV disease. This will assist government health officials and immunization programme managers in the future, when they consider the introduction of an RSV vaccine to their immunization programme. This protocol may also be adapted later to demonstrate the impact of immunization.

Other bacteria and viruses cause severe lower respiratory tract illness (LRI) in young children, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, adenovirus, influenza virus, and parainfluenza virus. However, RSV represents a substantial amount of the burden of acute respiratory tract illness, particularly in the first year of life. It is the closest of the viral pathogens to having a vaccine available, although research is also being conducted to develop live attenuated influenza and parainfluenza type 3 vaccines. There have been previous attempts to define the totality of microbial pathogens causative in acute respiratory illness, notably the BOSTID<sup>1</sup> studies in the late 1980s. In retrospect, the BOSTID studies seem to have suffered from being overly ambitious in attempting to define all respiratory illness. Investigators using this WHO generic protocol are encouraged to focus on RSV, which can now be identified by rapid viral techniques on adequately collected samples of nasopharyngeal aspirations (see section 3.6).

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<sup>1</sup> A series of studies sponsored by the United States National Academy of Sciences Board on Science and Technology for International Development (BOSTID). These studies were reported in a 1991 supplement to *Reviews of Infectious Diseases*, entitled "Etiology and Epidemiology of Acute Respiratory Tract Infection in Children in Developing Countries" (*Bale 1990*).

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Although RSV causes considerable upper respiratory tract disease, some of which is associated with otitis media, RSV causes proportionately more LRI than other viruses. RSV vaccines are more likely to protect against severe disease than to give sterilizing immunity that protects against recurrent upper respiratory infection. Furthermore, as the main costs to the health service of RSV disease relate to LRI, the burden of RSV-associated LRI is of most interest to policy makers. For all of these reasons, this WHO generic protocol focuses on identification of RSV-associated LRI.

### 1.1 Types of severe RSV disease

Severe RSV disease has been traditionally divided into bronchiolitis and pneumonia, with RSV thought to account for approximately 85% of cases of bronchiolitis and approximately 20% of cases of childhood pneumonia. The clinical distinction between bronchiolitis and pneumonia is often not clear. In addition to hyperinflation, radiographs in bronchiolitis frequently show what is interpreted either as atelectasis or infiltrates, although the rarer lobar consolidation is likely to indicate pneumonia (*Forgie et al. 1991*). Wheezing, considered to be the hallmark of bronchiolitis, can be elicited in almost every infant when sequential observations are made. Thus, although there are suggestions that the pathogenesis of these two RSV-associated diseases is different, that is often not clear from clinical or radiographic examinations. However, one would still like to try to differentiate between these two illnesses, by documentation of wheezing and the findings of clinical chest auscultation, as well as radiographs where available.

### 1.2 Specificity of RSV diagnosis

Unlike some other respiratory viruses (e.g. adenovirus), it is uncommon to isolate or identify RSV from healthy children without evidence of respiratory illness. Some studies of RSV-related illness have included a control series of well children and found that less than 5% of controls have been positive for RSV (*Chanock et al. 1961, Forgie et al. 1991, Phillips et al. 1990*). RSV infection may be detected in appropriately collected specimens (nasal aspirates, nasal washes) by virus isolation or by rapid diagnostic methods (see section 3.6). Serology is not recommended for diagnosis of RSV infection, as up to 50% of young infants hospitalized with culture-proven RSV infection show no serological rise (*unpublished data, Vanderbilt University, 1996*). The detection of RSV in nasal secretions of a patient with respiratory infection is therefore taken as evidence that the illness is caused by RSV. This is likely to be an over-simplification, as there may be superimposed bacterial infections that contribute to the severity of disease. Although secondary bacterial infection is documented with RSV, it is not known whether this occurs more frequently in developing than in developed countries, though one study in the Gambia suggested that this is the case (*Forgie et al. 1991*). More recent data from the Gambia show that approximately 5% of children with documented RSV disease also had a positive blood culture for a bacterial agent (*Weber and Greenwood, personal communication, 1996*). The rate of mixed infections is difficult to estimate accurately, because of the difficulty in identifying a bacterial agent in lower respiratory tract infections (*Shann 1986*). In the Gambia, mixed viral-bacterial infections were identified in 13 (15%) pneumonia cases in infants less than one year of age, four of which involved RSV infection (*Forgie et al. 1991*).

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Children with mixed infections had higher mean temperatures and higher white blood cell counts than those with RSV infection alone, but other clinical parameters were similar in the two groups. In Uruguay, mixed infections were documented in 10 (5%) of 204 hospitalized children with pneumonia; seven of these involved RSV (*Hortal et al. 1990*). Although the potential for RSV to lead to increased susceptibility to bacterial infection is important in estimating the potential impact of a future RSV vaccine, the study of this possible interaction is likely to be impractical in many centres. It might be studied more readily by evaluating the reduction in overall LRI in an intervention trial, when RSV vaccines reach the stage of phase III clinical trials.

### 1.3 RSV serotypes

Two serotypes of RSV exist : A and B. There is some evidence of heterotypic immunity between the two. The analogy has been made that the two RSV serotypes are as closely related as sequential influenza strains of the same serotype. All current vaccine efforts are directed towards the development of a vaccine that will incorporate both strains or will be directed against the F protein, which is quite homologous between the two strains. The clinical impact of the strains appears to be relatively similar, although RSV A may cause slightly more severe disease than RSV B (*Hall et al. 1990*). It may not be possible to differentiate between types A and B easily in field studies, as this requires isolation of RSV virus followed by typing. Polymerase chain reaction (PCR) technology at a central laboratory may, however, provide the opportunity to serotype strains on specimens that do not contain viable virus.

### 1.4 Epidemiology of RSV disease in industrialized countries

RSV is now well documented as a cause of yearly winter epidemics of acute lower respiratory tract disease, including bronchiolitis and pneumonia. Studies have provided accurate estimates of invasive RSV disease burden in several industrialized countries. Data from Vanderbilt University, Nashville, Tennessee, USA, as an example, shows the rate of culture-proven RSV-associated LRI in otherwise healthy children to be 37 per 1000 child-years in the first two years of life and the risk of hospitalization 6 per 1000 child-years (*Fisher et al. 1997*). These rates are higher in the first six months of life: 45 per 1000 child-years for LRI and 11 per 1000 child-years for hospitalization. Incidence will be higher for children with cardio-pulmonary disease and those with prematurity. Patients with these risk factors constitute almost half of RSV-related hospital admissions in the USA (**Table 1**).

**Table 1: Risk factors for hospitalization with RSV-related illness among 95 hospitalized children, Vanderbilt University, Nashville, Tennessee, USA**

Risk factor	Number (%) of children	
Cardiac disease	15	(16)
Prematurity	27	(28)
Pulmonary disease	29	(31)
One or more of above risk factors	44	(46)

In eight European countries, 19% of LRI occurring in hospitalized patients under five years of age was attributed to RSV by virus isolation at the time of illness (Orstavik *et al.* 1984). This represented approximately 80% of the virally-proven LRI. Apnea is another presenting sign of RSV disease in 10-20% of hospitalized patients (Church *et al.* 1984). These studies serve as a basis for anticipating widespread use of RSV vaccines and other interventions in industrialized countries, where the costs of caring for patients with severe lower respiratory tract disease and their sequelae are substantial.

There is increasing recognition of the importance of RSV as a cause of substantial morbidity from influenza-like illness in the elderly in industrialized countries (Fleming & Cross 1993). We found no published data on the burden of RSV in the elderly in developing countries. While potentially an important question, a study of this age group is beyond the scope of this generic protocol.

## 1.5 Epidemiology of RSV in developing countries

### 1.5.1 Incidence of RSV-LRI

In developing countries there are few population-based estimates of the incidence of RSV disease. Table 2 shows the incidence of RSV-associated LRI in selected studies that were denominator based. Early population-based studies in India, that relied on throat swabs for virus isolation and appeared to have a low rate of RSV recovery (Ota *et al.* 1972) have not been included.

Other estimates have been derived from the incidence of LRI of all causes, and the proportion of LRI that is RSV-related. From community-based studies, the median incidence of pneumonia in under-five-year-olds in developing countries has been estimated as 0.4 episodes per child per year. This rate is as high as 0.7 per child-year in infants less than one year of age (Schwartz *et al.* *in press*). Pneumonia represents a median of 74% (range, 50-86%) of lower respiratory tract infections among hospitalized children, and 40% (range, 28-59%) of outpatient cases of LRI. Thus, the overall incidence of LRI in under-five-year-old children will lie between 0.54 ( $0.4 \times 100/74$ ) episode and one ( $0.4 \times 100/40$ ) episode per child per year, i.e. 540 to 1000 LRI episodes per 1000 child-years.

Viruses have been found to cause a median of 37% of LRI (range, 15-76%). This proportion is higher among infants, and is higher for bronchiolitis than pneumonia (Cherian *et al.* 1990). Among viral aetiologies, RSV is by far the most frequent, causing a median of 18% of LRI (range, 7-33%) (Schwartz *et al.* *in press*), and representing 62% of viral LRIs. This is similar to the proportion found in European countries. Applying this proportion to the incidence of all-cause LRI, the estimated incidence of RSV-associated LRI is 97 to 180 episodes per 1000 child-years. Although these are crude estimates, this developing country rate is 2.6 to 4.8 times the rate of RSV-associated LRI seen in the USA.

**Table 2: Incidence of RSV-associated LRI in selected studies from developing countries**

Reference	Site	Case ascertainment, dates	Age, sample size	Specimens for virology	Incidence of all LRI	Incidence of RSV-LRI
Berman <i>et al.</i> 1983	Cali, Colombia (urban, low SES <sup>a</sup> )	5 PHC clinics 2/77 - 10/78	<5 yr (n=4958), 5-15 yr (n=3790)	Throat swab (1977) NPA <sup>b</sup> , IFA <sup>c</sup> , & culture (1978)	70/1000 child-years (age 0-15 yr) 400/1000 child-years (age 0-2 yr)	36/1000 child-years <sup>d</sup> (age 0-15 yr)
Borrero <i>et al.</i> 1990	Cali, Colombia (urban, low SES)	Weekly home visits, 10/86 - 4/88	Birth cohort (n=340)	NPA, IFA, & culture	1700/1000 child-years (age 0-1.5 yr)	198/1000 child-years <sup>e</sup> 0-5 mo: 192/1000 6-11 mo: 255/1000 12-17 mo: 125/1000
Sutmoller <i>et al.</i> 1995	Rio de Janeiro, Brazil (urban, low SES)	Weekly community surveillance, 1/87 - 12/89	<5 yr (n=262)	NPA, IFA, & culture	64/1000 child-years (age 0-4 yr)	14/1000 child-years <sup>f</sup> (age 0-4 yr)
<p><sup>a</sup> SES, socioeconomic status.  <sup>b</sup> NPA, nasopharyngeal aspirate.  <sup>c</sup> IFA, immunofluorescent antibody.  <sup>d</sup> Total, 106 RSV isolates (9% of all LRI).  <sup>e</sup> Total, 67 RSV isolates.  <sup>f</sup> Total, 11 RSV isolates.</p>						

Among factors which may influence the incidence and severity of RSV-associated disease in developing countries are exposure to passive smoke (Holberg *et al.* 1991), malnutrition (Tupasi *et al.* 1990a), HIV infection (King *et al.* 1993), and crowding (Holberg *et al.* 1991). Breast feeding and vitamin A supplementation (Dowell *et al.* 1996) have not been shown to alter the frequency or severity of RSV-associated LRI. An attempt should be made to identify such potential risk factors in the children studied as part of this WHO generic protocol.

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### **1.5.2 Age distribution of RSV-LRI**

In industrialized countries, RSV-associated hospitalization rates fall dramatically after six months of age, and are negligible after 24 months of age (only 5 of 95 hospitalizations for RSV were in children over 24 months of age in a typical year at Vanderbilt University Medical Center, Nashville, Tennessee, USA).

In developing countries, the highest incidence of RSV-LRI is also in infants less than six months of age, and around two-thirds of RSV-LRI (80% of inpatient cases and 60-70% of outpatient cases) occurs in children under two years of age (*Vathanophas et al. 1990*). Nonetheless, several studies suggest that the burden of RSV-LRI in developing countries is not negligible in older children. A WHO collaborative study in 10 developing countries in the early 1960s identified RSV in 19% of children < 6 years of age hospitalized with severe respiratory illness. This proportion was highest in under-6-month-olds (37%) but remained at 12-16% of cases in one, two, three, and four year old children, falling to 8% in over-five-year-olds (*Chanock et al. 1967*). Similarly, studies in Colombia (*Berman et al. 1983*), Brazil (*Sutmoller et al. 1995*), and Bangkok (*Suwanjutha et al. 1990*) show that RSV caused 20-30% of LRI cases in children from one to four years of age. In the Gambia, the peak age has varied in different areas and different years, depending on the density of the population and the frequency of outbreaks.

### **1.5.3 Limitations of previous studies**

Although several hospital-based studies in developing countries have documented the relative importance of RSV as a cause of LRI, there have been few studies with a defined population denominator that allowed the calculation of incidence rates<sup>2</sup>. There has also been little information on the severity of the disease in different age groups.

Few studies have included adequate numbers of young infants to obtain detailed information on the median age at first infection. This information is important for vaccination programme planners, when considering the optimal schedule for vaccination. Maternal immunization against RSV may protect the infant in the first months of life. Documentation of disease in this age group is particularly relevant to vaccine strategy.

All of the community-based studies were conducted in urban populations, among lower socio-economic classes. It is not clear how generalizable these data are to rural areas, where exposure to environmental smoke, for example, may increase the

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<sup>2</sup> Several papers published after the development of this generic protocol provide additional information that may be helpful to groups planning a study of RSV infection. These include:

Weber MW, Mulholland EK, Greenwood BM. Respiratory syncytial virus infection in tropical and developing countries. *Tropical Medicine and International Health* 1998;3(4):268-280.

Weber MW, Dackour R, Usen S, et al. The clinical spectrum of respiratory syncytial virus disease in The Gambia. *Pediatric Infectious Disease Journal* 1997; 17(3):224-230.

Weber MW, Milligan P, Giadom B, et al. Respiratory illness after severe respiratory syncytial virus disease in infancy in The Gambia. *Journal of Pediatrics* 1999 (December): 683-688.

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risk of wheezing-associated illness. In rural areas, outbreaks of RSV may not occur every year, whereas they are annual in urban areas, and the average age at infection may tend to be later in rural than urban areas (*Weber and Greenwood, personal communication 1996*).

Studies in countries with temperate climates, such as Argentina and Pakistan, have shown marked seasonal variation similar to that in industrialized countries (*Ghafoor et al. 1990, Weissenbacher et al. 1990*). Some studies in tropical countries have reported an increase in RSV in the rainy season (*John et al. 1991, Nwanko et al. 1988, Phillips et al. 1990, Sung et al. 1987*), but this has not been a constant finding (*Berman et al. 1983, Forgie et al. 1991, Sutmoller et al. 1995, Nascimento et al. 1991, Tupasi et al. 1990b*). Some studies were only conducted for one year or less, and thus information on seasonality of infection over a number of years was not obtained. Although RSV has consistently appeared in epidemic form during some months of each year in urban areas, the timing of the epidemic has often varied from year to year (*Forgie et al. 1991, Vathanophas et al. 1990, Suwanjutha et al. 1990*). Thus, studies for more than one year are recommended.

The methods used for viral detection were standardized in the studies conducted under BOSTID funding, but laboratory assays in other studies were not standardized.

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## 2. Study objectives

The objectives of this WHO generic protocol are to enable a developing-country site to:

- 1) Document the incidence of RSV-LRI in children less than five years of age.
- 2) Determine the degree and consistency of seasonal variation of RSV.
- 3) Determine the age-specific incidence of RSV-LRI in the following age categories: 0-2, 3-5, 6-8, 9-11, 12-23, and 24-59 months.
- 4) Describe the clinical presentation, course, and severity of RSV-LRI.
- 5) Determine if sufficient disease occurs in the first three months of life to warrant further investigation of maternal immunization in the prevention of RSV.

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## 3. Methodology

### 3.1 Reference population

A well-defined area should be selected for the study, in which an adequate number of children under five years of age are identified (see section 3.2). The proposed population for surveillance should be defined geographically and age-specific population data should be available, broken down in the following age categories: 0-2, 3-5, 6-8, 9-11, 12-23, and 24-59 months. This may necessitate a baseline census at the start of the study.

A cohort study would be the ideal study, with regular follow-up of children for active surveillance of LRI and identification of births, deaths, and migrations, with modification of the denominator accordingly, as was conducted in some previous studies of LRI (*Borrero et al. 1990*). Such studies are expensive, and relatively complex to conduct and analyze. However, in order to estimate incidence rates of RSV-LRI, a cohort approach is ideal.

The alternative is to select a stable population in which the average demography of the population will not change greatly over a two-year period of study, and the age-specific profile of RSV-LRI cases can be compared to the age distribution of the population at the start of the study to obtain an approximation of the incidence rates.

If a cohort study is not feasible, it is important that the population is stable, and that episodes of RSV-LRI will be detected by the surveillance system. Thus, a population in which people commonly leave the area for several days or weeks, e.g. for seasonal work outside the area, would not be suitable. A community with one well-utilized primary source of medical care, for example a hospital or a well-equipped clinic, and with few other sources of medical treatment, would be ideal. Evidence of good access to and utilization of the clinic(s) or hospital selected for the study should be documented. For example, in planning the study, a retrospective record review of paediatric cases of LRI in the health facility (including outpatient cases, if registers are available) would be useful to compare the number of cases with that expected for that size of population (see section 1.5). This would also provide some insight into the seasonality of LRI, which will determine the seasonal variation in workload for the study. In communities with a variety of different sources of medical care, especially those with extensive use of private practitioners, case ascertainment would be much more difficult, and such sites are not recommended.

The existing population of children aged 0 up to five years should be enrolled at the beginning of the study by informing parents about the study and requesting them to bring the child to a designated clinic or hospital during episodes of respiratory illness.

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Because RSV is most severe in early life, provisions must be made to continue to include children born after the start of the study, so that young infants are well represented at the time of an outbreak of RSV. This will most accurately be accomplished by establishing a birth registration system in the area, and explaining, or reinforcing, the objectives and importance of the study to mothers who deliver during the study period. At the same time, once children reach their fifth birthday they should no longer be included in the study, as this would increase the effort and cost of the study.

Multiple episodes of RSV are common in children. This is because of incomplete cross-protection between strains, and also because there is not long-lasting immunity against the same strain. Therefore, a system is needed whereby each child has a unique identification number which is used for each consultation. This system will ideally be established at the beginning of the study, e.g. by giving each child a family record in a baseline census. An alternative would be to issue a card at the time of the first presentation of the child with suspect LRI. If home-based child or family health records are already in wide use in the area, then the child's study number and information about each episode can be recorded in the existing record. Copies of the family records should be held at the clinics in the area in case of loss of the home-based record. Each episode of LRI should be documented on the family record as well as on the case report forms used for the study.

Focusing on a community-based, defined population, should allow estimation of the incidence of lower respiratory tract illness with a reasonably sized population (see section 3.2). This would not be possible for hospitalization as the incidence is lower e.g. 2 to 10 per 1000 infants in the first year of life in the USA and Europe (*Glezen et al. 1981, Orstavik et al. 1980*), and it would certainly not be possible with mortality.

### **3.2 Size of population under surveillance**

The estimated population size needed for surveillance is based on the number of episodes of RSV-associated LRI required to obtain an estimate of incidence with a given precision in the 0-2 month age group. This group is selected because it is the narrowest age band of interest, and a population large enough to give rise to the desired number of episodes in this age group will also give adequate numbers in the other, larger age bands.

The expected rate of RSV-associated LRI in infants, detected by clinic-based surveillance, is in the order of 36 per 1000 child-years (**Table 2**, and data from Vanderbilt University, Nashville, Tennessee, USA). More intensive surveillance such as that in the study by Borrero et al. (*1990*) would produce higher incidence rates, but for the purposes of sample size estimation we have used the conservative figure of 36 per 1000 child-years. This is close to the experience of clinic-based surveillance in Vanderbilt University, USA (see section 1.4).

To measure an incidence rate of 36 per 1000 child-years, with a precision of +/- 20 per 1000 child-years, 346 child-years of follow-up would be required (*Kirkwood 1988*). Since the age band of 0-2 months represents only a one quarter-year period, 1384 child-quarters (346 x 4) are needed. Conceptually, this would be obtained in a cohort study by recruiting children at birth and following

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each child until they reach the age of three months, so that a total of 1384 child-months of observation of children less than three months old is obtained. Since the study will run for two years, we need a population large enough to generate 58 births each month (1384/24).

In areas with high neonatal mortality, this figure should be increased proportionally. For example, if the neonatal mortality rate is 60 per 1000 live births (e.g. 6 per 100 live births), the number of births required each month would be  $(58 \times 106/100) = 61$  births. Although some other deaths will occur between ages 1-three months, the contribution of this mortality is relatively small and has been omitted from the sample size calculations.

The total population required will depend on the crude birth rate (CBR) in the area of study. For example, if the CBR is 40 per 1000 population per year, then a total population of 18 500 people would have 740 births per year, or 61 births per month.

### 3.3 Case ascertainment

Cases of suspect LRI will be identified throughout the study at health facilities (and using outreach workers such as village health workers, if they are active in the area), and will be examined using standard methods (see below). Residents of the surveillance population should have good access to, and a high level of utilization of, health facilities for severe disease such as lower respiratory tract illness. The rapidity with which RSV occurs and can compromise a young infant suggests that access to the health facility be within an hour of the onset of serious illness to avoid deaths that may occur before children reach the facility.

Community participation in the study should be sought to increase the likelihood of case ascertainment and the ability to obtain the appropriate samples from children with LRI.

Since the incidence of RSV varies greatly at different times of the year, the number of positive RSV isolates from children with LRI each week should be monitored closely. When the RSV-detection rate begins to increase, more active surveillance for, and investigation of, LRI is encouraged. The methods used to institute active surveillance will vary depending on the local circumstances.

All health workers at health facilities and outreach workers who will be involved in the study should be trained in recognition of signs of LRI, preferably using the WHO methodologies (*WHO 1991*). The WHO methods have been validated and are readily taught to health care workers (*Simoes 1994*). Nevertheless, an experienced paediatrician should supervise the health workers regularly and monitor case ascertainment and diagnosis.

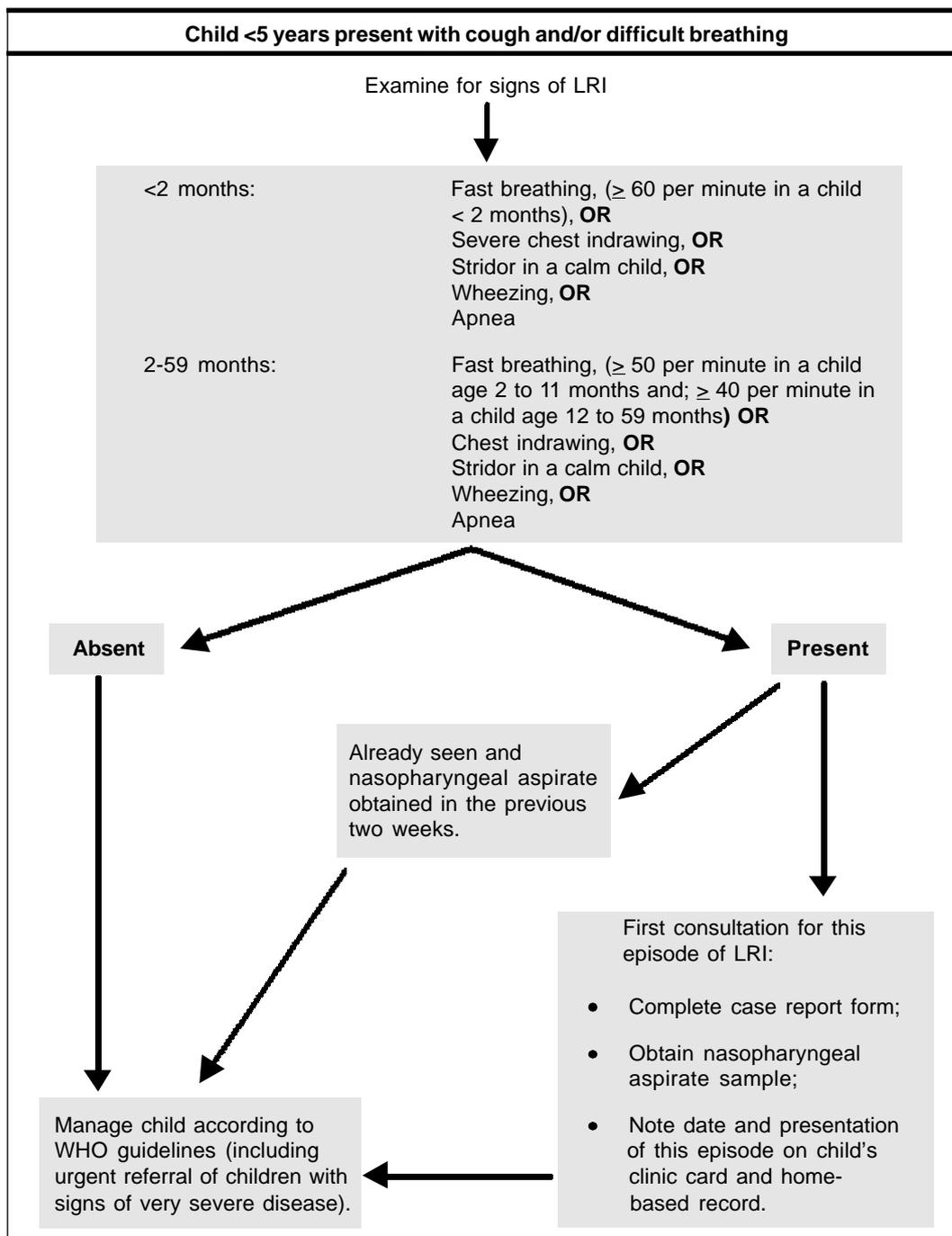
All children recognized with LRI who fit the WHO criteria for empiric antibiotic treatment because of age or severity of disease should be treated (regardless of the result of their screening test for RSV) because of the possibility of mixed bacterial-viral infections. Such treatment will not influence the result of the RSV screening test.

### 3.4 Case definition

#### 3.4.1 LRI

For the purposes of this study, the definitions developed by WHO will be adapted (*WHO 1991*). The general signs of LRI are age-dependent. The management of children should follow the WHO guidelines (**Annex 1**). The WHO algorithms were developed to facilitate choice of treatment strategy, and include signs of severe disease that may not be related to pneumonia (*Mulholland et al. 1992*).

Figure 1: RSV-LRI surveillance flow chart



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For the purposes of deciding from which children to take a sample for RSV detection, the signs of severe disease that are unrelated to LRI will not be included: see **Figure 1**. In addition, we have included apnea (history of or observation of cessation of respiratory effort for 20 seconds or greater) as an indication for taking a specimen for RSV detection.

### ***3.4.2 Definition of an episode of LRI***

Because children may present to a health facility more than once during the same episode of LRI, in this protocol we propose that a repeat visit within two weeks of onset of illness be considered part of the same episode. A visit more than two weeks after onset may be considered a new episode, and a further nasopharyngeal aspirate and new case report form would be completed in that instance.

## **3.5 Case report form**

A standard case report form should be developed and suitably pretested for the study. A list of the type of information to include is provided here, but suitable questions will need to be formulated in order to obtain that information. Previous studies in the area might help to identify suitable formats and phrases for use in questions, especially with regard to the kind of information to use to define socio-economic status. Careful attention will need to be given to standardize the recording of clinical signs. The case report form should be completed on all cases meeting the criteria for RSV-detection sample collection (**Figure 1**). The case report form should have the child's unique identification number clearly marked. The episode should be indicated, i.e. whether this is the first, second, third, or subsequent episode of LRI in the same child. The case report form should document the above signs (especially by measuring the respiratory rate, and noting presence of lower chest indrawing), which are needed to classify the disease.

The following additional information would be helpful to investigate the feasibility of developing a clinical case definition for RSV-LRI, to assess the costs to the health services of RSV-LRI, and to describe the socio-demographic features of children with RSV-LRI.

- **Clinical signs:**
  - Presence of rhinitis
  - Presence of wheeze
  - Occurrence of apnea
  - Auscultatory findings
  - Hypoxaemia (if oxymeter available)
  - Central cyanosis
  - Temperature
  - Nutritional status (weight for age, or weight for height)
- **Hospitalization:**
  - Duration of hospitalization
  - Special care required

- 
- **Therapy given:**
    - Bronchodilators
    - Oxygen
    - Mechanical ventilation
    - Other?
  
  - **Outcome:**
    - If died, apparent cause of death
    - (Document the circumstances of any death as carefully as possible.)

Radiographic and clinical laboratory analyses are not required for this study, but if they are conducted, the results should be recorded.

- **Socio-demographical data:**
  - Child's age
  - Child's sex
  - Mother's age
  - Child's birth order
  - Breast feeding
  - Exposure to passive cigarette smoking
  - Exposure to environmental smoke
  - Attendance at day care

In addition to documenting the above information on the locally-developed case report form, background data should be sought on **meteorological conditions**:

- Recordings on maximum and minimum temperature, rainfall, barometric pressure, and relative humidity on a regular basis in the study area during the entire study period. Altitude of the population served should be recorded, since RSV induced hypoxia may be worse at high altitudes.

### ***3.6 Specimen collection and processing***

RSV is an extremely unstable and heat labile virus. This makes virus isolation problematic except in well established laboratories immediately adjacent to the site of clinical care. For this reason, virus isolation is not required for this WHO generic protocol, even though it remains the gold standard for documentation of illness due to RSV. Study groups which already have good experience in RSV isolation should be encouraged to include this in their study.

The technique used for specimen collection influences the likelihood of recovery of virus either by culture or by rapid diagnostic techniques. Nasal and throat swabs should not be used. The optimal techniques are nasopharyngeal aspiration or nasal wash. Nasal wash yields three logs more virus than a nasal swab (*Hall et al. 1975*):

- ***Nasopharyngeal aspiration*** was used in all sites in the BOSTID trial. This involves deep nasopharyngeal suctioning of each nares into a sterile trap with flushing of the feeding tube with one cc of Hank's solution.
- For the ***nasal wash***, ten cc of phosphate buffered saline are placed in a 30 cc rubber bulb. With the patient held in a sitting position, the material is squirted into the nose and aspirated using the same bulb. A 30 cc plastic cup is used to retrieve fluid which comes out of the other nostril.
- Material collected from nasopharyngeal aspiration or nasal wash must be placed immediately on ice and transported to the laboratory as rapidly as possible.

### 3.7 Laboratory assays

A number of rapid diagnostic techniques are presently available for RSV. Table 3 provides a comparison of four of these tests and Annex 2 includes addresses of the companies that produce RSV rapid diagnostic products. When ordering diagnostic tests, their shelf life and storage requirements should be considered. The number of tests required should be estimated based on the number of LRI cases expected, not the number of cases of RSV-LRI. The laboratory workload will vary by season, and it may be possible to anticipate seasonality by a hospital record review at the start of the study.

These rapid diagnostic tests listed in Table 3 appear to be comparable in sensitivity and specificity and have the advantage that virus viability is not critical to their performance. According to the manufacturers, the sensitivity and specificity of the ELISA kits are 94% and 95% respectively for the Abbott product, and 97% and 97% respectively for the Becton-Dickinson product. The sensitivity and specificity may vary, however. Data from Vanderbilt University, Nashville, Tennessee, USA, on the performance of each ELISA assay in comparison to culture is shown in Table 4.

**Table 3: Comparison of four rapid diagnostic tests for RSV**

Test	Manufacturer	Equipment needed	Technical expertise	Reference
IFA monoclonal	Chemicon	IFA microscope	Moderate	WHO 1992
IFA monoclonal	Dako	IFA microscope	Moderate	Domingues et al. 1993
ELISA	Abbott	None	Minimal	Sweirkosz et al. 1989
ELISA	Becton-Dickinson	None	Minimal	Waner et al. 1989

**Table 4: Data from Vanderbilt University, Nashville, Tennessee, USA, on the performance of each ELISA assay in comparison to culture**

<b>4a) ELISA (Abbott) versus culture: sensitivity 89%, specificity 94%</b>		
	<b>Culture +</b>	<b>Culture -</b>
ELISA, Abbott +	8	3
ELISA, Abbott -	1	49

<b>4b) ELISA (Becton-Dickinson, B-D) versus culture: sensitivity 67%, specificity 97%</b>		
	<b>Culture +</b>	<b>Culture -</b>
ELISA, B-D +	12	1
ELISA, B-D -	6	36

Use of the IFA monoclonal (*WHO 1992*) is encouraged as this is a sustainable test in the developing country setting, but it requires a fully functional fluorescent microscope, greater technical skill, and more time than an ELISA-based assay. One or more of these tests, or comparable assays, are suggested for this study. Assays should be performed according to the manufacturer's instructions. WHO may consider making a discount purchase for this study of one or two tests that could be used by all study groups.

The remaining nasopharyngeal aspirate or nasal wash should be frozen at  $-20^{\circ}\text{C}$ . It is hoped that material can be submitted for PCR analysis to a central laboratory that will confirm the antigen positive samples and differentiate between A and B strains of RSV (*Cubie et al. 1992*). PCR does not require live virus. (Further instructions on preservation of material for PCR will be supplied when the central laboratory is identified).

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### 3.8 Laboratory log book

It is recommended that a log book be kept of the samples assayed and results of each assay. An example of an RSV-specimen logbook is shown in Table 5.

Table 5: Sample laboratory log book for RSV specimens

Specimen ID number	Date specimen received	Name of patient	Age of patient	Result of test (1)	Result of test (2) if done

### 3.9 Field work

Substantial preparatory time (e.g. three months) will be needed for this study, to obtain the baseline information on the demography of the community (ideally including baseline census and establishment of the birth registry system), to develop, pretest, modify and produce final versions of the case report forms, and to train personnel and establish quality control systems. A system to motivate parents to bring children with symptoms of LRI to the attention of health workers will be needed. All personnel involved in the study should be trained using WHO guidelines on classification of a child with respiratory illness. Particular attention should be paid to counting respiratory rates (ideally using the respiratory rate timers available from UNICEF, Annex 3) and identification of chest indrawing.

A supervisory system will need to be established to monitor the performance of health workers during the study, to maintain standard practices, and to ensure smooth and continuous collaboration with the community. Regular meetings of personnel involved in the study should be instituted, so that any problems that may arise can be discussed and solutions identified. Supervision of laboratory procedures and laboratory log book data will also be needed.

### 3.10 Data handling

The field work coordinator should review the questionnaires daily for completeness and discuss any potential problems with data collectors. Questionnaires should be double-entered onto microcomputer using suitable range and consistency data entry checks. Data from laboratory results will usually be entered onto a separate file, using the same unique identifier for the child as that on the questionnaire, so that files can be merged subsequently for analysis.

WHO may consider sponsoring a workshop for all participating study groups where a standard format for data analysis of all studies is jointly agreed.

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# Annex 1:

## Management of the child with cough or difficult breathing

(adapted from WHO document WHO/ARI/94.31)

<b>Ask:</b>	
<ul style="list-style-type: none"> <li>• How old is the child?</li> <li>• Is the child coughing? For how long?</li> <li>• Age 2 months up to 5 years: Is the child able to drink? Age less than 2 months: Has the young infant stopped feeding well?</li> <li>• Has the child had fever? For how long?</li> <li>• Has the child had convulsions?</li> </ul>	
<b>Look, listen: (Child must be calm)</b>	
<ul style="list-style-type: none"> <li>• Count the breaths in one minute.</li> <li>• Look for chest indrawing.</li> <li>• Look and listen for stridor.</li> <li>• Look and listen for wheeze. Is it recurrent?</li> </ul>	<ul style="list-style-type: none"> <li>• See if child is abnormally sleepy, or difficult to wake.</li> <li>• Feel for fever or low body temperature (or measure temperature).</li> <li>• Look for severe malnutrition.</li> </ul>
<b>Fast breathing</b>	
<ul style="list-style-type: none"> <li>• Young infant aged less than 2 months: 60 breaths per minute or more.</li> <li>• Child aged 2 months up to 12 months: 50 breaths per minute or more.</li> <li>• Child aged 1 up to 5 years: 40 breaths per minute or more.</li> </ul>	
<b>A child has chest indrawing if:</b>	
<ul style="list-style-type: none"> <li>• The lower chest wall goes in when the child breathes in.</li> <li>• Chest indrawing is a sign of severe pneumonia in children aged 2 months up to 5 years.</li> <li>• Only <b>severe</b> chest indrawing is a sign of severe pneumonia in young infants.</li> </ul>	

**CLASSIFY THE ILLNESS**  
**Does the child have danger signs?**

**The child (age 2 months up to 5 years)**

**Signs:**

- Not able to drink,
- Convulsions,
- Abnormally sleepy or difficult to wake,
- Stridor in calm child, or
- Severe malnutrition.

**Classify as  
very severe disease**

**Treatment:**

- Refer **urgently** to hospital.
- Give first dose of an antibiotic.
- Treat fever if present.
- Treat wheezing, if present.
- If cerebral malaria is possible, give an antimalarial.

**The young infant (age less than 2 months)**

**Signs:**

- Stopped feeding well,
- Convulsions,
- Abnormally sleepy or difficult to wake,
- Stridor in calm child,
- Wheezing, or
- Fever or low body temperature.

**Classify as  
very severe disease**

**Treatment:**

- Refer **urgently** to hospital.
- Keep young infant warm.
- Give first dose of an antibiotic.

**DOES THE CHILD HAVE PNEUMONIA?**

<b>The child (age 2 months up to 5 years)</b>		
<b>Signs:</b>		
<ul style="list-style-type: none"> <li>• Chest indrawing. (If also recurrent wheezing, go directly to</li> <li>• Treat wheezing, page 28.</li> </ul>	<ul style="list-style-type: none"> <li>• No chest indrawing, and</li> <li>• Fast breathing (50 per minute or more if child 2 months up to 12 months; 40 per minute or more if child 12 months up to 5 years.)</li> </ul>	<ul style="list-style-type: none"> <li>• No chest indrawing, and</li> <li>• No fast breathing (Less than 50 per minute if child 2 months up to 12 months; Less than 40 per minute if child 12 months up to 5 years.)</li> </ul>
<b>Classify as:</b>		
<b>Severe pneumonia</b>	<b>Pneumonia</b>	<b>No pneumonia: cough or cold</b>
<ul style="list-style-type: none"> <li>➔ Refer <b>urgently</b> to hospital.</li> <li>➔ Give first dose of an antibiotic.</li> <li>➔ Treat fever if present.</li> <li>➔ Treat wheezing, if present (If referral is not feasible, treat with an antibiotic and follow closely.)</li> </ul>	<ul style="list-style-type: none"> <li>➔ Advise mother to give home care.</li> <li>➔ Give an antibiotic.</li> <li>➔ Treat fever if present.</li> <li>➔ Treat wheezing, if present.</li> <li>➔ Advise mother to return with child in 2 days for reassessment, or earlier if the child is getting worse.</li> </ul>	<ul style="list-style-type: none"> <li>➔ If coughing more than 30 days, refer for assessment.</li> <li>➔ Assess and treat ear problem or sore throat, if present.</li> <li>➔ Assess and treat other problems.</li> <li>➔ Advise mother to give home care.</li> <li>➔ Treat fever, if present.</li> <li>➔ Treat wheezing, if present.</li> </ul>
<b>Reassess in 2 days a child who is taking an antibiotic for pneumonia</b>		
<b>Signs:</b>		
<b>Worse</b>	<b>The same</b>	<b>Improving</b>
<ul style="list-style-type: none"> <li>• Not able to drink.</li> <li>• Has chest indrawing.</li> <li>• Has other danger signs.</li> </ul>	<ul style="list-style-type: none"> <li>• No change.</li> </ul>	<ul style="list-style-type: none"> <li>• Breathing slower.</li> <li>• Less fever.</li> <li>• Eating better.</li> </ul>
<b>Treatment:</b>		
<ul style="list-style-type: none"> <li>➔ Refer <b>urgently</b> to hospital.</li> </ul>	<ul style="list-style-type: none"> <li>➔ Change antibiotic or refer.</li> </ul>	<ul style="list-style-type: none"> <li>➔ Finish 5 days of antibiotic.</li> </ul>

**DOES THE CHILD HAVE PNEUMONIA? (continued)**

**The young infant (age less than 2 months)**

**Signs:**

- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>• Severe chest indrawing, or</li> <li>• Fast breathing (60 per minute or <i>more</i>).</li> </ul> | <ul style="list-style-type: none"> <li>• No severe chest indrawing, and</li> <li>• No fast breathing (<i>Less than 60 per minute</i>).</li> </ul> |
|--|---|

**Classify as:**

<b>Severe pneumonia</b>	<b>No pneumonia: cough or cold</b>
<ul style="list-style-type: none"> <li>➔ Refer <b>urgently</b> to hospital.</li> <li>➔ Keep young infant warm.</li> <li>➔ Give first dose of an antibiotic.</li> </ul> <p>(If referral is not feasible, treat with an antibiotic and follow closely.)</p>	<ul style="list-style-type: none"> <li>➔ Advise mother to give following home care:                             <ul style="list-style-type: none"> <li>- keep young infant warm;</li> <li>- breastfeed frequently;</li> <li>- clear nose if it interferes with feeding.</li> </ul> </li> <li>➔ Return quickly if:                             <ul style="list-style-type: none"> <li>- breathing becomes difficult;</li> <li>- breathing becomes fast;</li> <li>- feeding becomes a problem;</li> <li>- the young infant becomes sicker.</li> </ul> </li> </ul>

TREATMENT INSTRUCTIONS								
<ul style="list-style-type: none"> <li>● <b>Give an antibiotic</b> <span style="float: right; border: 1px solid black; padding: 2px;">Antibiotics should not be used for coughs or colds</span></li> <li>➔ Give first dose of antibiotic in clinic.</li> <li>➔ Instruct mother on how to give the antibiotic for five days at home (or return to clinic for daily procaine penicillin injection).</li> </ul>								
Age or weight	COTRIMOXAZOLE trimethoprim + sulphamethoxazole ➔ Two times daily for 5 days			AMOXYCILLIN ➔ Three times daily for 5 days.		AMPICILLIN ➔ Four times daily for 5 days.		PROCAINE PENICILLIN ➔ Once daily for 5 days.
	Adult tablet single strength (80mg trimethoprim + 400mg sulphamethoxazole)	Pediatric tablet (20mg trimethoprim + 100mg sulphamethoxazole)	Syrup (40mg trimethoprim +200mg sulphamethoxazole per 5ml)	Tablet 250mg	Syrup 125mg in 5ml	Tablet 250mg	Syrup 250mg in 5 ml	Intramuscular injection
Less than 2 months (<5kg)*	1/4**	1**	2.5ml**	1/4	2.5ml	1/2	2.5ml	200 000 units
2 months up to 12 months (6 -9kg)	1/2	2	5.0ml	1/2	5.0ml	1	5.0ml	400 000 units
12 months up to 5 years (10 - 19kg)	1	3	7.5ml	1	10.0ml	1	5.0ml	800 000 units
<p>* Give oral antibiotic for 5 days at home only if referral is not feasible.</p> <p>** If the child is less than 1 month old, give ½ pediatric tablet or 1.25ml syrup twice daily. Avoid cotrimoxazole in infants less than one month of age who are premature or jaundiced.</p>								

## TREATMENT INSTRUCTIONS *(continued)*

### Advise mother to give home care *(For the child age 2 months up to 5 years)\**

- Feed the child
  - Feed the child during illness.
  - Increase feeding after illness.
  - Clear the nose if it interfered with feeding.
- Increase fluids
  - Offer the child extra to drink.
  - Increase breast-feeding.
- Soothe the throat and relieve the cough with a safe remedy.
- Most important: In the child classified as having **No Pneumonia: Cough or Cold**, watch for the following signs and return quickly if they occur:
  - Breathing becomes difficult.
  - Breathing becomes fast.
  - Child is not able to drink.
  - Child becomes sicker.

**This child may have pneumonia.**

\* See section on young infant in **Classify the illness** (page 23) for home care instructions for that age group

### TREAT FEVER

39° Centigrade or more means a HIGH FEVER

38° to 39° Centigrade means FEVER, NOT HIGH

35.5° Centigrade or less means LOW BODY TEMPERATURE

<ul style="list-style-type: none"> <li>• Fever is high (≥ 39° C).</li> </ul>	<ul style="list-style-type: none"> <li>• Fever is not high (38° – 39° C)</li> </ul>	In a falciparum malarious area: <ul style="list-style-type: none"> <li>• Any fever, or</li> <li>• History of fever.</li> </ul>	<ul style="list-style-type: none"> <li>• Fever for more than five days.</li> </ul>
→ Give paracetamol. ↓	→ Advise mother to give more fluids.	→ Give an antimalarial (or treat according to your malaria programme recommendations).	→ Refer for assessment.



#### Paracetamol doses: every six hours

Age or weight	100mg tablet	500mg tablet
2 months up to 3 years 6 – 14kgs	1	¼
3 years up to 5 years 15 – 19kgs	1 ½	½

Fever alone is not a reason to give an antibiotic except in a young infant aged less than 2 months.

Treat a young infant with fever or low body temperature as very severe disease.

**TREATMENT INSTRUCTIONS (continued)**

**TREAT WHEEZING**

Children with first episode of wheezing

If in respiratory distress → Give a rapid acting bronchodilator and refer  
 If not in respiratory distress → Give oral salbutamol

**Children with recurrent wheezing (asthma)**

- Give a rapid acting bronchodilator
  - Assess the child's condition 30 minutes later;
- If:
- |   |   |
|---|---|
| Respiratory distress or any danger sign | → Then:<br>Treat for severe pneumonia or very severe disease (refer). |
| No respiratory distress and:            |   |
| Fast breathing                          | → Treat for pneumonia<br>Give oral salbutamol.                        |
| No fast breathing                       | → Treat for no pneumonia: cough or cold. Give oral salbutamol.        |

Rapid acting bronchodilator		Oral salbutamol three time daily for five days		
Nebulized Salbutamol (5mg/ml)	0.5ml Salbutamol plus 2.0ml sterile water	Age or weight	2mg tablet	4mg tablet
Subcutaneous Epinephrine (adrenaline) (1:1000 = 0.1%)	0.01ml per kg body weight	2 months up to 12 months (<10kgs)	½	¼
		12 months up to 5 years (10 – 19kg)	1	½

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# Annex 2:

## List of manufacturers of rapid diagnostic tests for RSV

- Abbott Diagnostics:** Postfach 1303, 85003 Wiesbaden, Germany  
*Fax:* (06122) 5 81244  
**Test name:** TESTPACK RSV (list no. 2027), enzyme immunoassay for rapid detection of respiratory syncytial virus
- Baxter-Bartels Diagnostics:** PO Box 3093, Bellevue, Washington 98009, USA  
*Tel:* (1) 206-392-2992;  
*Fax:* (1) 206-392-0409  
**Test name:** RSV EIA kit, PRIMA product line
- Becton Dickinson:** PO Box 243, Cockeysville, Maryland 21030, USA  
*Tel:* (1) 800-638-8663  
**Test name:** Directigen RSV
- Chemicon Laboratories:** Temecula, California 92509, USA  
*Tel:* (1) 909-676-8080  
**Test name:** Respiratory Syncytial Virus (Antigen Test) - DFA Kit, labeled monoclonal antibodies and control slide.
- Dako:** USA  
*Tel:* (1) 800-23505763  
*Fax:* (1) 800-566-DAKO  
**Test name:** IMAGEN Respiratory Syncytial Virus (RSV) (no. K6102 IVD)
- Sanofi Diagnostics Pasteur:** Marnes la Coquette, France  
*Tel:* (33) 01 4795-6000  
*Fax:* (33) 01 474-9133  
**Test name:** PathFinder RSV ELISA (no. 79674)

# Annex 3:

## Respiratory rate timer



**CODE** PIS A2/01

**Respiratory rate timer (ARI Timer)**

**COMPANY NAME AND ADDRESS**

UNICEF (Denmark)  
 UNICEF Plads  
 Freeport, DK 2100 Copenhagen  
 Denmark  
*Telephone: 45 35 27 35 27*  
*Fax: 45 35 26 94 21*  
*Telex: 19813 unicef dk*

**SPECIFICATIONS**

<b>Operating temperature</b>	0 to +50°C
<b>Storage temperature</b>	-10 to +50°C
<b>Timing duration</b>	60 seconds
<b>Timing accuracy</b>	Within 0.1 second
<b>Timing source</b>	Crystal oscillator of 32768 Hz
<b>Packaged</b>	40 per box
<b>Neck cord</b>	Approximately 1 metre long

**COMMENTS**

The Respiratory Rate Timer has been carefully made to provide a life span of 8 000 counting cycles of 60 seconds under normal usage.

**How to use the timer:**

- Push the Start/Stop button once. A short “beep” sound will be heard to show that the timer is starting. Actual counting of the respiratory rate must begin as soon this initial beep is heard. Audible clicks will sound every second so that you can be sure that timing is in progress while you continue to observe the patient.
- The timer will give another short beep at the 30 second point of the timing cycle, and two short beeps at the end of 60 seconds when it will automatically shut off. The timer can be stopped at any time during the counting cycle, if needed, by pushing the Start/Stop button once.

**Notes on handling:**

- Always store the timer in a cool, dry place after use. If the timer is exposed to excessive temperature and moisture, its life span will be shortened.
- If it is necessary to clean the timer, use a moist, clean cloth. Do not use chemicals or detergents as they may damage the unit.

**2000 PRICES (FCA)**

<i>Shipping weight / volume:</i>	<i>box of 40</i>	<i>2 kg / 0.008 m<sup>3</sup></i>
	<i>carton of 5 boxes</i>	<i>10 kg / 0.04 m<sup>3</sup></i>
<i>Manufacturer's minimum order:</i>	<i>1 timer</i>	

Item	Quantity	UNICEF stock number	Price	
Respiratory rate timer	1 timer	08 450 10	US\$	3.66
	box of 40 timers	08 450 10	US\$	144.00
	carton of 200 timers	08 450 10	US\$	720.00