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COMITE ASESOR EN INVESTIGACIONES MEDICAS

Caracas, Venezuela
29 y 30 de abril de 1982

REUNION DEL SUBCOMITE DE INFECCIONES RESPIRATORIAS AGUDAS

REUNION DEL SUBCOMITE DEL COMITE ASESOR DE LA OPS SOBRE INVESTIGACIONES MEDICAS

INFECCIONES RESPIRATORIAS AGUDAS

En su 20a Reunión, el Comité Asesor de Investigaciones Médicas (CAIM) de la Organización Panamericana de la Salud (OPS) pidió a uno de sus miembros, el Dr. F. Robbins, que convocara un grupo encargado de estudiar una importante iniciativa regional en el sector de enfermedades respiratorias agudas.

La reunión inicial se celebró en la Sede de la OPS (Washington, D.C.) el viernes, 16 de octubre de 1981. Se acompañan a la presente la lista de participantes y el programa.

A continuación figura un breve resumen de las deliberaciones.

El Dr. F. Robbins dio la bienvenida a los participantes y expuso en líneas generales el objeto de la reunión.

El Dr. George Alleyne describió la estructura del CAIM y la manera en que funcionan sus subcomités. Destacó que la OPS no era un organismo de financiamiento, sino que actuaba principalmente promoviendo actividades a nivel regional y nacional. Aludió brevemente a la estructura de los programas especiales de la OMS, cuyos resultados habían sido tan satisfactorios en la promoción de las investigaciones y la adopción de medidas en los sectores específicos de enfermedades tropicales, reproducción humana y enfermedades diarreicas.

El Dr. Fabio Luelmo se refirió a las actividades de la OPS/OMS en materia de enfermedades respiratorias, particularmente las de los niños, señalando que, en 1980, la OPS había incluido específicamente las

infecciones respiratorias agudas de los niños en su programa. Se han observado dificultades para el mantenimiento de una acción sostenida en ese sector, debido en parte a la falta de pediatras interesados. El orador aludió brevemente al cuadro regional de morbilidad y mortalidad, señalando que esta última es unas 20 veces mayor en América Latina que en América del Norte. Los esfuerzos de la OPS se han orientado principalmente hacia la investigación y el establecimiento de flujogramas de tratamiento y normas terapéuticas. El Dr. Luelmo hizo hincapié en la necesidad de aunar la labor de los programas ampliados de inmunización, el Programa de Control de las Enfermedades Diarreicas y el Programa de Control de las Enfermedades Respiratorias.

El Dr. Floyd Denny describió la base etiológica de las infecciones respiratorias agudas en Carolina del Norte, indicando los síndromes clínicos y su división anatómica. Los virus respiratorios son en potencia una causa de infección de las vías respiratorias superiores, pero a menudo es difícil distinguir los síndromes clínicos en lo que respecta a etiología. Otros agentes de diversa importancia son los estreptococos del grupo A., H. Influenzae y Mycoplasama pnemoniae. Las infecciones de las vías respiratorias inferiores son particularmente frecuentes en el segundo semestre del primer año de vida, pero ha de tenerse en cuenta que la distribución se basa en los casos de consulta externa y no en los hospitalizados. El grupo de agentes etiológicos más importantes de infecciones de las vías respiratorias inferiores está constituido por los virus sincitiales respiratorios, los de la parainfluenza, los adenovirus, los virus de la influenza y Mycoplasma pneumoniae. Sin embargo, en los primeros días o semanas de vida, revisten importancia destacada los estreptococos del grupo 3, los microorganismos entéricos gram negativos y Staphylococcus aureus.

Desde el punto de vista de la epidemiología y de los síndromes clínicos, las asociaciones de agentes etiológicos de infecciones de las vías respiratorias inferiores son en cierto modo pronosticables. Por ejemplo, entre los escolares, Mycoplasma pneumoniae es el agente causante del 50-60% de todos los casos. Entre niños de corta edad con trastornos respiratorios infecciosos, el agente patógeno más corriente es el virus sincitial.

El Dr. Mohs se refirió al problema en la medida en que afecta a América Latina y, más específicamente, a Costa Rica. En este país, el 45% de todos los casos de enfermedades de notificación obligatoria correspondieron en 1980 a la influenza, mientras que en Bolivia más del 10% de todas las consultas médicas externas fueron para infecciones respiratorias agudas. Según los estudios realizados por el Dr. Mata en Guatemala, la incidencia de las infecciones respiratorias es de alrededor de 5,5 episodios por niño al año durante los tres primeros años de vida. Las secuelas nutricionales de esas infecciones son fácilmente demostrables. La mortalidad por infecciones respiratorias agudas está disminuyendo constantemente en América Latina, y también se observa una baja regular de la prevalencia de las infecciones mastoideas crónicas consecutivas a la infección de las vías respiratorias superiores. Aunque no abundan los datos sobre la etiología de las infecciones respiratorias agudas en América Latina, se supone que el agente principal es vírico. Ello no obstante, según un estudio realizado en Costa Rica a base de punción pulmonar, el microorganismo Streptococcus pneumoniae es frecuente en niños afectados de pneumonía y pleuresía.

En Costa Rica es notable la constante disminución de la mortalidad por infecciones respiratorias agudas. Las causas de ello son el mejoramiento

de las condiciones socioeconómicas y de la cobertura de los servicios de salud, y el tratamiento específico de los niños afectados.

El Dr. Chanock describió los estudios básicos en curso para la preparación de una vacuna contra la neumonía vírica. La vacuna existente de adenovirus vivos se ha abandonado porque esos microorganismos causan tumores en los hamsters, aunque de momento no se ha observado el mismo efecto en el hombre.

Por lo que respecta a las vacunas contra el virus de la influenza hay indicios de que el individuo que la recibe adquiere inmunidad pero que ésta desaparece poco a poco, con lo que, a la postre, el sujeto es tan susceptible como los testigos no vacunados. Es interesante el hecho de que las personas que son inmunes en el momento de la vacunación siguen siéndolo durante más de cinco años. Hasta ahora, el problema que plantean todos los virus RNA es que producen mutantes satisfactorios. El Dr. Chanock describió seguidamente algunas técnicas recientes de manipulación genética que permiten mutaciones predeterminadas de una parte del genoma vírico y, en consecuencia, la aparición de mutantes de las características que se desean.

El Dr. John Robbins se refirió a la posible utilidad de las vacunas bacterianas. La tos ferina sigue constituyendo un problema importante en América Latina, siendo así que a menudo es dudosa la calidad de la vacuna empleada. Para algunos países latinoamericanos sería conveniente participar en los ensayos clínicos de nuevas vacunas antitosferínicas. También es probable que el estudio de vacunas neumocócicas conduzca a una reducción de los síndromes clínicos resultantes de la infección por esos microorganismos. La OPS debería estimular la vigilancia de las infecciones debidas a Haemophilus influenzae, posiblemente

por medios serológicos. Están preparándose conjugados covalentes de mayor potencia inmunógena, con la posibilidad de que puedan efectuarse ensayos clínicos.

Debate

Hubo un animado debate sobre las medidas que deberían adoptarse. El problema clínico existe, a no dudarlo, pero también hay grandes lagunas de los conocimientos sobre numerosos aspectos específicos. Se reconoció que el enfoque apropiado del problema era epidemiológico. Los estudios en hospitales deberían estar complementados por estudios sobre el terreno. Se manifestó la opinión de que el principal problema provenía de que en algunos países aumentaba la mortalidad asociada con infecciones que en otros países no eran mortales. Se estimó conveniente centrar la atención en medios sencillos de reducir la morbilidad y la mortalidad, basados en las técnicas ya existentes. Esas técnicas entrañan protocolos de tratamiento simplificados y empleo de medios de difusión que aseguren un uso eficaz de los materiales preparados. Se llegó al consenso de que la fase inicial de los programas fuera la identificación de unos pocos centros en condiciones de participar en estudios clínicos y prácticos bien concebidos sobre infecciones respiratorias agudas. No deben olvidarse los aspectos de adiestramiento y, por otra parte, convendría mejorar la capacidad y la aptitud de los países para el ensayo de vacunas y reactivos, y para otros tipos de estudios.

Recomendaciones

1. Convendría preparar un documento indicativo del estado actual de los conocimientos en la materia.

2. Debe establecerse un grupo técnico de planificación.
3. Habría que designar unos pocos centros latinoamericanos en que pudieran emprenderse estudios epidemiológicos y clínicos.
4. La OPS debería fomentar la formación de becarios en América Latina para mejorar los medios nacionales de investigación sobre enfermedades respiratorias agudas.
5. La OPS debería incorporar como objetivo a los programas regionales el establecimiento de instalaciones de laboratorio para preparación de reactivos y ensayo de vacunas.
6. En todos los programas regionales debería dedicarse atención especial al problema de la tos ferina.
7. Convendría que la Secretaría de la OPS preparara propuestas sobre esta iniciativa regional, teniendo en cuenta las útiles sugerencias formuladas en la reunión.

REUNION DEL SUBCOMITE DEL COMITE ASESOR DE LA OPS SOBRE INVESTIGACIONES MEDICAS

INFECCIONES RESPIRATORIAS AGUDAS

Lista de participantes

Dr. Robert Chanock	Jefe, Laboratorio de Enfermedades Infecciosas Institutos Nacionales de Salud Bethesda, MD
Dr. Floyd Denny	Profesor de Pediatría Universidad de Carolina del Norte Chapel Hill, N.C.
Dr. David Fraser	Subdirector de Ciencias Médicas Centro de Enfermedades Infecciosas Centro de Control de Enfermedades Washington, D.C.
Sra. Sharon King	Programa de Investigaciones sobre Enfermedades Tropicales Fundación Edna McConnell Clark Nueva York, N.Y.
Dr. Claude Lenfant	Director Centro Internacional Fogarty Institutos Nacionales de Salud Bethesda, MD
Dr. Edgar Mohs	Director Hospital Nacional de Niños "Dr. Carlos Saenz Herrera" San José, Costa Rica
Dr. Robert Parrott	Director Centro Médico del Niño Washington, D.C.
Dr. Frederick Robbins (Presidente)	Presidente Instituto de Medicina Academia Nacional de Ciencias Washington, D.C.
Dr. Frank Tyeryar	Institutos Nacionales de Salud Bethesda, MD

Secretaría de la OPS

Dr. George A.O. Alleyne	Jefe, Servicio de Promoción y Coordinación de Investigaciones División de Recursos Humanos e Investigaciones
Dr. Fabio Luelmo	Enfermedades Transmisibles División de Prevención y Control de Enfermedades
Dr. Gabriel Schmuñis	Servicio de Promoción y Coordinación de Investigaciones División de Recursos Humanos e Investigaciones
Dr. Francisco Pinheiro	Enfermedades Transmisibles División de Prevención y Control de Enfermedades

REUNION DEL SUBCOMITE DEL CAIM SOBRE INFECCIONES RESPIRATORIAS AGUDAS

Washington, D.C., 16 de octubre de 1981

Programa

9:30 Alocución de bienvenida - Dr. F. Robbins

9:40 Antecedentes de la reunión

Estructura y cometido del CAIM - Dr. G. Alleyne

9:50 Actividades de la OPS en el sector - Dr. F. Luelmo

10:00 Situación actual de las investigaciones - Dr. F. Denny

10:30 PAUSA

10:45 Importancia y naturaleza del problema clínico en los países en desarrollo - Dr. E. Mohs

11:00 Preparación de vacunas víricas - Dr. R. Chanock

11:15 Preparación de vacunas bacterianas - Dr. J. Robbins

11:30 Debate general

1. Labor que se puede realizar o promover
   - investigaciones básicas
   - investigaciones epidemiológicas
   - intervención a nivel de atención primaria
2. Manera en que debiera estructurarse una importante campaña regional
3. Financiamiento

13:30 Resumen - Dr. F. Robbins

DRAFT (4th revision)

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ACUTE RESPIRATORY INFECTIONS

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SUMMARY

This paper sets out the problem presented by acute respiratory infections (ARI), with special focus on the Region of the Americas. The available data show that they are a major cause of mortality and morbidity and must consume a considerable amount of the health resources. The risk of dying from ARI in Latin America is 30 times higher than in North America.

The factors which predispose to this mortality are presented and it is shown that especially in developing countries, the interaction between ARI and malnutriton are clear both in terms of cause and effect.

The aetiologic agents which are known to cause ARI are presented in some detail as a background to discussion on the possible development of vaccines -mainly antiviral.

The sequelae of ARI are of importance both for developed and developing countries and the evidence reviewed shows that there is a strong relationship between childhood respiratory infections and the possibility of developing persistent obstructive airways disease in adult life.

Some research issues have been developed. The most critical area is epidemiological research in order to determine the clinical syndromes which occur, their age specificity and periodicity. There is need for basic research on the organisms which cause ARI -particularly the viruses

and the development of vaccines against these agents. Especially in the developing countries applied research can be started immediately on establishing and evaluating treatment norms especially for use in primary care settings. Health services and behavioural research should be parts of any programme of research in ARI in order to assist in designing better systems of care for children with ARI and determining the relevant contributory social variables amenable to change in the short or medium term.

A training component should be built into a research programme. This strengthens national capability and will allow for research on peculiar local problems to be done on site.

The paper ends by advocating that any program of control of ARI on a national level should be integrated with other programmes focussed on child care.

We believe that the time is now opportune for a major effort at all levels directed against a group of diseases which now constitute a major, if not the most important, cause of morbidity and mortality in children.

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ACUTE RESPIRATORY INFECTIONS

ACUTE RESPIRATORY INFECTIONS

1. BACKGROUND

The significance of the problem

There is a growing body of information about the significance of acute respiratory infections as a cause of morbidity and mortality especially in the developing world. Riley[1] makes the point that it is only recently that any but the classical tropical parasitic diseases were regarded as important in the tropical developing world. Tropical disease was virtually synonymous with parasitic communicable disease - this was the perspective of the pioneers of classical tropical medicine and therefore, little or no attention was paid to other diseases which were perhaps equally important in terms of mortality and morbidity in the tropics. Walsh & Warren[2] argue that in assessing priorities for disease control in the developing world based on prevalence, mortality, morbidity and feasibility of control, more attention should be paid to diseases like measles and the diarrheal diseases which have a high prevalence, high mortality and morbidity and for which there is effective control. The respiratory diseases with high prevalence, morbidity, and mortality have no effective control and therefore would deserve less priority attention. This view is perhaps defeatist: the fact is that the morbidity and mortality from the diarrheal diseases have only been reduced as a result of the production of an appropriate technology

through research and similar efforts must be expended to solve the problem of acute respiratory disease.

The aim of this review is to point out the importance of respiratory diseases globally but especially in the children of the Americas, and indicate possible lines of approach in developing the appropriate technologies to be applied in preventing or controlling them.

The involvement of the World Health Organization and the Pan American Health Organization

For many years, the World Health Organization has been placing increasing emphasis on respiratory diseases in the context of its programme of technical cooperation. The focus has been mainly on the developing countries although the developed countries themselves have certainly not eliminated morbidity or mortality from acute respiratory diseases in the young. The 29th World Health Assembly in 1976 decided that the Sixth General Program of Work beginning in January 1978 should have a component dealing with the control of acute respiratory diseases.

In Resolution WHA32.33, 1979, the Assembly requested the Director-General:

(i) to stimulate and to intensify the involvement of Member States in the control of respiratory diseases, and to promote technical cooperation with them as well as among them, in respect of the formulation of national control programs, with particular reference to their integration into current and future development activities in health and other fields.

(ii) to accord high priority to research activities for the development of simple and effective methods for the prevention of acute and chronic respiratory diseases, their timely detection and diagnosis, and appropriate curative services, e.g., optimal package treatment.

In June 1981, at the 20th Meeting of the PAHO Advisory Committee on Medical Research, it was agreed that the topic of acute Respiratory diseases, especially in children, should be explored further as there was sufficient evidence to point to its significance as an importance cause of morbidity and mortality especially in the developing world. A small Subcommittee was established and the report of the meeting of that Committee is included in Annex 1. It was recommended that this background paper should be prepared, setting out the extent of the problem and indicating the areas in which further research was necessary and the steps to be taken in establishing a regional program in research in this field.

In the Americas, the Regional Strategies[3] for achieving the goal of HFA and the Plan of Action for implementing those Strategies also refer to the importance of acute respiratory diseases. The Plan of Action, PAHO Document No. 179, points out that the focus should be on the strengthening of primary health services for more effective etiological diagnosis and treatment of acute respiratory infections and on the development of surveillance and monitoring systems. The Plan of Action in pointing out action to be taken called for:

-Development of standard diagnostic criteria for acute respiratory infections for primary health care personnel.

-Development of simplified standard treatments and referral criteria for ARI.

-Establishment of ARI control activities integrated into the primary health care services with priority given to children and old age groups.

-Improvement of laboratory capability for identification of etiological agents through personnel training, provision of reagents, upgrading physical facilities and equipment.

-Conduct field trials of new vaccines as they are developed.

-Development of surveillance and monitoring systems.

-Implementation of new methods for surveillance of incidence, treatment and outcome of ARI in children.

-Training of health personnel and community health workers using materials and methods adapted to meet local health system needs.

The suggested indicators to be used as a measure of the efficacy of action on a regional basis were:

-Number of countries with diagnostic and treatment standards and guidelines for the control of ARI.

-Measurement of extent of implementation of standards for diagnosis and treatment.

-Number of laboratories capable of identification of etiological agents.

-Number of hospital discharges for ARI.

-Mortality trends in children under 5 years of age.

The approach by WHO and the Regional Strategies and Plan of Action direct attention to the primary level of care. It is believed that any intervention which makes a major impact on the problem of ARI must be in the form of technology which can be part of a primary health care strategy. The analogy of diarrheal diseases and oral rehydration is apt. It is now accepted that most acute diarrhea is secretory in origin and cholera as the classical model of secretory diarrhea acts by producing a toxin, a subunit of which activates intracellular adenylate cyclase, increases cyclic adenosine 3,5 monophosphate and triggers active chloride secretion.(4) The basic physiological mechanisms which have been discovered have directed research into anti-diarrheal agents towards either substances which stimulate the normal absorptive processes and counterbalance the secretion or substances which inhibit the secretion. The oral glucose-electrolyte solutions which were developed as an example of the first approach now constitute the mainstay of effective intervention therapy in the diarrheal diseases and represent the result of a considerable amount of sophisticated basic, clinical and laboratory research.(5)

Any program of control of acute respiratory disease will hopefully embrace the kind of research which will lead to vaccine production, research on the basic pathophysiology which accompanies or results from acute respiratory infection, research on the social correlates of the disease and research on the kind of appropriate technology which will lead to a reduction in morbidity and mortality from acute respiratory infections.

It is only in this way that respiratory diseases will take their place alongside diseases like diarrheas, measles, whooping cough, and tetanus - diseases which are of high prevalence, high mortality and morbidity, but in which there is a possibility of effective control.(4)

2. MORTALITY AND MORBIDITY FROM ACUTE RESPIRATORY INFECTIONS

Mortality Data - General

The most widely quoted data on the global importance of acute respiratory infections are those of Bulla and Hitze, who analyzed information from 88 Member States of WHO.(6)

Table 1 shows the mortality from respiratory diseases broken down according to various regions. The authors indicate that the data should be interpreted with caution because of such problems as differences in disease notification, hospital bias of some statistics, and the lack of good laboratory backup data in several countries. However, the aggregate information shows interesting inter-area differences. In Africa, for example, upper respiratory tract infections are the predominant cause of death in the ARI category whereas in the Americas, viral and bacterial pneumonias are overwhelmingly the predominant cause of death in this category. If Oceania is omitted, deaths from ARI account for half to two-thirds of the deaths from all respiratory diseases. The data are analyzed further in Table 2 and in Middle America, mortality from ARI as a percentage of all causes of death is 13.6 percent, apparently higher than in any other part of the world. The total (Table 2) shows deaths

TABLE 1. Mortality from respiratory diseases in the world: latest available reference years, 1970-1973 (all ages).

Continent and number of reporting countries	Population in thousands	Acute respiratory infection (ARI)				Deaths from ARI as a percentage of deaths from all respiratory diseases
		Acute upper respiratory tract infections	Influenza	Viral and bacterial Pneumonia	Total	
Africa (9)	77,420	51,095[a] (64.0)	332 (0.4)	28,460 (35.6)	79,887 (100.0)	64.7
America (29)	401,573	17,775 (7.3)	29,624 (12.1)	197,527 (80.6)	244,926 (100.0)	71.2
Asia	227,310	23,097 (18.1)	5,117 (4.0)	99,633 (77.9)	127,847 (100.0)	62.5
Europe (28)	462,936	12,062 (5.8)	24,074 (11.5)	173,518 (82.7)	209,654 (100.0)	51.6
Oceania (8)	16,895	272 (6.1)	232 (5.3)	3,908 (88.6)	4,412 (100.0)	31.5
TOTAL (88)	1,186,134	104,301 (15.6)	59,379 (8.9)	503,046 (75.5)	666,726 (100.0)	61.0

[a]Percentage are in parenthesis.
Data taken from Bulla & Hitze (Ref. 6).

TABLE 2. Mortality due to acute respiratory infections in the world, 1970-1973 (all ages).

Continent	Number of Countries	Mortality	Mortality from ARI as a percentage of all causes of death	
		Rate per 100,000 population	Excluding Influenza	Including Influenza
Africa	9	103.2	12.9	12.9
America	29	61.0	5.9	6.7
North	3	30.5	3.0	3.3
Middle	18	115.5	11.7	13.6
South	8	87.5	8.3	9.5
Asia	14	56.2	8.5	8.9
1st group[a]	2	26.3	4.0	4.1
2nd group[b]	12	84.3	12.8	13.4
Europe	28	45.3	3.9	4.4
Oceania	8	26.1	3.0	3.2
1st group[c]	2	25.7	2.9	3.0
2nd group[b]	6	32.6	7.6	7.9
TOTAL	88	56.2	5.7	6.3

[a]Israel and Japan.
[b]Developing countries.
[c]Australia and New Zealand.
Data taken from Bulla & Hitze (Ref. 6).

from ARI constituting 6.3% of deaths from all causes. Deaths from ARI are of greatest concern in the very young and the very old. Table 3 gives the mortality due to ARI in children below the age of 14. This Table shows marked differences between the developed and developing countries.

In Middle America, the mortality rate is 10 to 15 times higher than in North America and similar patterns are seen when the developing countries of Asia and Oceania are compared with their developed counterparts. The age specific mortality rates decline with age in every case. The mortality rate in the young was also compared with that in the elderly and except in the case of Africa, the rates for the elderly were all higher. It would have been of interest to divide countries into developed and developing for this analysis to determine if the picture seen in Africa was a result of the predominance of developing countries. This must not obscure the importance of ARI in the developed countries. Cockburn analyzed data from 23 countries which had more reliable reporting[7]. These were all industrialized, but it was still possible to divide them into two groups - 14 more developed and 9 less developed. In neither group of countries was there any major change in the death rates over a 20-year span. However, the infectious diseases as a whole showed reductions of 72 percent in both developed and developing countries. When the infectious diseases were broken down further, acute respiratory infections were the leading cause and the striking feature is that there was little or no reduction in death rates from these diseases. The authors conclude that only by controlling the respiratory

TABLE 3. Mortality due to acute respiratory infections in the world, 1970-1973; infants and children

Continent	Number of Countries	Infants	Children 1-4 years	Children 5-14 years
		Rate Per 100,000 Population		
Africa	6	1,454.1	467.0	21.6
America	23	886.5	82.8	7.9
North	2	146.3	8.0	1.5
Middle	13	1,495.0	149.3	16.5
South	8	1,110.5	112.6	10.8
Asia	11	822.1	132.3	15.5
1st group[a]	2	130.5	9.7	1.9
2nd group[b]	9	1,242.4	204.1	23.4
Europe	28	390.3	15.3	2.1
Oceania	3	177.6	9.3	1.2
1st group[c]	2	159.8	8.2	1.1
2nd group[b]	1	566.1	33.6	2.7
TOTAL	71	762.2	101.3	8.4

[a]Israel and Japan.
[b]Developing countries.
[c]Australia and New Zealand.
Data taken from Bulla & Hitze (Ref. 6).

diseases can any further significant reduction in death rates be obtained in the developed world." The data from England and Wales show this pattern clearly[8](Table 4). This shows the expected high rate of mortality in children under one year, declining dramatically in older children. Mortality in all groups has declined sharply since the 1940s, but in children less than one year, the rate of decline has decreased and within the 12-year period prior to 1967, there has been no decrease in mortality from respiratory diseases. The decline in mortality from respiratory disease like other diseases may be related to medical or socioeconomic causes. It is remarkable that if socioeconomic factors influenced the decline in the other age groups, there has been no change in the children under one year. One explanation may be that there is a specific pathologic process which is the major contributor to death from respiratory diseases in this age group. It will be shown later that there is a predominance of specific etiologic agents in respiratory disease at this age.

Considerable attention has been given to this problem in the Western Pacific Region, and the situation may be compared in a developed country like Australia with that obtaining in a developing country like the Philippines.

In Australia ARI accounts for 2.8 percent of all deaths, whereas in the Philippines, the figure is 6 times higher. In children, ages 1 to 4, the death rate from ARI is 71 times higher in the Philippines than in Australia (Table 5).

TABLE 4. Death rates per million for all diseases of the respiratory system, by age and sex, in England and Wales, from 1940-1967.

	Age in Years							
	Under 1		1-4		5-9		10-14	
	Male	Female	Male	Female	Male	Female	Male	Female
1940-1944	12,860	9,844	1,019	904	128	109	74	69
1945-1949	8,632	5,869	438	393	64	55	42	42
1950-1954	4,501	3,634	265	238	55	51	38	37
1955-1959	3,143	2,490	224	194	51	47	36	46
1960-1963	3,347	2,590	223	186	49	41	33	25
1964-1967	3,123	2,363	169	141	35	34	28	24

Data taken from Ref. 8.

TABLE 5. Age specific mortality rates (per 100,000 population) from all causes and from pneumonia and influenza (ICD-8 Codes A90-92) for two countries in the Western Pacific Region, 1974.

Age Group (Years)	AUSTRALIA		PHILIPPINES	
	All Causes	Pneumonia & Influenza	All Causes	Pneumonia & Influenza
1	1,615.5	66.5	5,889.7	1,562.2
1-4	83.8	4.1	745.7	290.8
5-14	36.2	.7	151.2	36.3
15-24	111.7	1.6	174.1	17.6
25-34	107.0	2.6	242.2	18.0
35-44	226.9	5.9	449.2	28.8
45-54	634.2	13.2	760.4	48.2
55-64	1,593.6	28.0	1,375.1	91.6
65-74	3,771.9	76.9	5,829.8	449.3
75 and above	11,723.1	455.8		
All ages	868.4	24.7	685.0	117.8

Source: World Health Statistics Annual Volume 1, 1977, and Fiji Health Statistics Division, Taken from R. M. Douglas (Ref. 9).

Mortality Data - The Americas: recent data and comparison with data of 10 years previously

Table (6a,b) shows the latest data available in the countries of the Americas on mortality from all causes and from ARI in children under 5 years of age, and compares them with those reported approximately 10 years earlier.

These data should be interpreted with some caution, since their quality varies considerably from country to country. Vital statistics for infants at best tend to be unreliable, and the same holds for the certification of causes of death. This is illustrated by the high and sometimes increasing proportions of "symptoms and ill-defined conditions" reported by some countries. These problems, as well as those inherent in population estimates may partly explain the wide range of variation observed.

Thus, in the countries of Latin America and the Caribbean, the mortality rates from all causes varied between 61 and 454 deaths per 10,000 children under 5 years of age in 1968, and between 33 and 272 in 1978. For the same years, the mortality rates from ARI in that age group varied between 6 and 109, and between 5 and 56 per 10,000 respectively.

Undoubtedly the most striking aspect of the data is the North South differential observed for the ARI mortality rates at each of the two points in time. For every 10,000 children under 5, one died from ARI in North America, 6 in the Caribbean and 31 in Latin America in 1978, compared with 6, 21 and 57 respectively reported 10 years earlier.

Because of the possibility that the level of socioeconomic development has a major role to play in the incidence of many diseases, efforts were made to explore further the relationship between ARI

mortality and development level, estimated by various social and economic indicators and by composite development scores. However, no such direct relationship was found and it is possible that data more reliable than those now available will be required to unveil the relationship assumed to exist.

It is clear, however, that the "North-South" gap is far from closing. In the 10-year period studied, the risk of dying from ARI in Latin America relative to that same risk in North America, increased from 9.5 to 31 for children under 5 years of age.

Nevertheless, mortality from ARI seems to have decreased faster than mortality from all causes as reflected in the decreasing proportion of deaths from ARI over deaths from all causes. As can be seen in Table (7), this is more evident in the highly developed countries and in the countries of the Caribbean reporting for both years. In Latin America, and especially in the Latin-American Caribbean, ARI seems to follow more closely the pattern of all causes. This is consistent with the earlier statement regarding the increase in differentials regarding ARI between developed and developing nations. In the countries of the Latin American Caribbean, mortality rates from all causes and from ARI diminished at approximately the same rate of 50% in the years between 1968 and 1978. In that same time period, mortality from all causes in North America was reduced by 31%, while mortality from ARI achieved a 83% reduction. These data point out clearly the urgency for intervention in the countries of Latin America.

Table (6a)

MORTALITY FROM ACUTE RESPIRATORY INFECTIONS IN CHILDREN
UNDER FIVE YEARS OF AGE
Latin America

REGION / COUNTRY	YEARS		Mortality rates[a]				% over all causes			
			all causes		ARI[b]		ARI[b]		Ill defined	
	1	2	1	2	1	2	1	2	1	2
A. LATIN AMERICA[c]			20.8	13.1	5.7	3.1	27.3	23.5		
1. Andean Area			21.0	12.4	5.8	3.1	27.6	25.2		
BOLIVIA			...	...	...	...	...	...		
Colombia	1968	1977	21.7	11.7	5.8	2.7	26.6	23.3	7.8	8.9
Ecuador	1968	1978	31.8	17.6	7.8	5.0	24.4	28.2	15.7	13.4
Perú	1968	1978	20.3	13.2	7.9	4.4	38.9	33.1	11.0	6.5
Venezuela	1968	1978	14.0	9.5	2.0	1.2	14.5	13.0	28.4	15.0
2. Southern Cone			16.4	10.8	4.1	1.4	25.0	12.5		
Argentina	1969	1978	14.4	11.5	2.6	1.2	18.2	10.1	11.7	8.5
Chile	1968	1979	19.4	8.4	7.1	1.5	36.6	17.8	5.5	9.9
Paraguay[d]	1968	1978	25.6	16.1	5.6	3.2	21.7	19.6	17.3	17.9
Uruguay	1968	1978	12.7	10.0	1.5	.8	12.0	8.5	6.5	9.9
3. Brazil	----	----	...	...	...	...	...	...	...	...
4. Central America[c]			28.0	17.6	5.4	3.1	19.4	17.8		
Costa Rica	1968	1979	14.7	6.4	2.3	.8	15.8	12.1	8.0	8.2
El Salvador	1968	1974	22.0	16.8	2.8	2.3	12.7	13.7	37.5	33.3
Guatemala	1969	1978	45.4	27.2	10.9	5.6	23.9	20.7	11.9	12.6
Honduras	1968	1978	17.1	9.4	1.7	1.1	10.0	11.4	40.3	30.0
Nicaragua	1968	1978	20.0	...	2.1	...	10.3	...	22.5	...
Panamá	1968	1974	14.6	10.3	2.6	2.1	17.6	20.0	21.7	19.3
5. México	1968	1976	23.0	15.0	7.5	4.2	32.7	28.3	7.6	9.9
6. Latin Amer.Caribbean			11.9	5.8	1.4	.7	12.2	11.2		
Cuba	1968	1978	9.0	3.8	1.8	.6	20.3	15.1	1.0	.6
Dominican Republic	1968	1978	20.2	9.0	1.2	.8	6.1	9.3	43.9	24.5
Haiti	----	----	...	...	...	...	...	...	...	...
Puerto Rico	1969	1977	6.1	4.5	.6	.5	10.0	10.4	3.7	1.8

(a) per 1000 children 0-4 years; children under 1 year estimated by live births.
(b) ICDA-8, codes A-017, 078, 089-091, 093.
(c) Except Nicaragua
(d) Information area

Table (6b)

MORTALITY FROM ACUTE RESPIRATORY INFECTIONS IN CHILDREN
UNDER FIVE YEARS OF AGE
Caribbean and North America

REGION / COUNTRY	YEARS		Mortality rates[a]				% over all causes			
			all causes		ARI[b]		ARI[b]		Ill defined	
	1	2	1	2	1	2	1	2	1	2
B. CARIBBEAN[c]			11.1	5.6	2.1	.6	19.0	11.3		
Antigua	1969	1978	6.2	3.5	.7	.3	10.5	8.1	-	5.4
Bahamas	----	1979	...	11.5	...	1.2	...	10.1	-	8.5
Barbados	1968	1978	10.0	6.4	1.4	1.2	14.3	19.2	.7	1.3
Belize	1968	1979	14.3	...	3.4	...	23.8	10.0	27.7	17.0
Cayman Islands	----	1979	...	4.8	...	1.4	...	30.0	...	10.0
Dominica	1969	1979	20.2	3.3	4.1	.3	20.3	8.9	3.8	-
French Guyana	1968	1978	13.8	...	1.6	...	11.8	8.7	8.6	13.0
Grenada	----	----	...	...	...	...	...	...	...	...
Guadaloupe	1969	----	11.4	...	...	...	...	...	...	...
Guyana	----	1977	...	...	...	...	...	13.0	...	5.0
Jamaica	1968	1971	11.9	9.4	1.9	1.8	15.7	18.8	8.7	7.2
Martinique	1968	1975	7.1	4.2	.9	.4	13.1	9.7	22.3	21.4
Montserrat	----	1979	...	6.9	...	-	...	-	...	-
Netherl. Antilles	----	1971	...	6.2	...	...	...	...	...	...
St. Kitts, Nevis, Ang.	1969	1978	...	8.5	...	1.1	32.9	13.1	-	6.6
St. Lucia	1968	1978	15.8	6.4	4.0	.6	25.3	9.3	3.1	9.3
St. Vincent	----	1979	...	7.7	...	.9	...	11.8	...	3.7
Suriname	----	1978	...	8.9	...	1.0	...	11.1	...	5.1
Trinidad & Tobago	1969	1977	8.5	5.7	...	.8	...	13.8	...	.7
Turks & Caicos	----	1979	...	5.6	...	-	...	-	...	-
Virgin Islands (UK)	1968	1976	10.1	...	1.9	-	18.8	-	-	-
Virgin Islands (USA)	----	1973	...	8.0	...	...	...	...	...	...
C. NORTH AMERICA			4.9	3.4	.6	.1	11.8	4.2		
Canada	1969	1978	4.4	3.0	.5	.2	10.2	5.2	2.5	10.7
United States	1968	1978	4.9	3.5	.6	.1	11.9	4.1	3.7	11.0

(a) Per 1000 children 0-4 years; children under 1 year estimated by live births.
(b) ICDA-8, codes A-017, 078, 089-091, 093.
(c) Countries with data for both periods, except Jamaica.

Table (7)

DECREASE OF MORTALITY FROM ALL CAUSES
AND FROM ACUTE RESPIRATORY INFECTIONS IN CHILDREN UNDER 5 YEARS

1968 - 1978

REGION (*)	PER CENT REDUCTIONS OF RATES	
	ALL CAUSES	A R I
LATIN AMERICA	37.0	45.6
Andean Area	41.0	46.6
Southern Cone	34.1	65.9
Brazil	...	...
Central America	37.1	42.6
Mexico	34.8	44.0
Latin Caribbean	51.3	50.0
CARIBBEAN	49.5	71.4
NORTH AMERICA	30.6	83.3

(*) For countries included see table

Morbidity data

Figures for morbidity are even more difficult to acquire than for mortality. Respiratory illnesses vary very widely in severity and the level of socioeconomic development of the country, the adequacy of primary health care, as well as some basic cultural beliefs, all affect the reported patterns of morbidity from ARI. Miller has analyzed the collection of morbidity data and refers to the major sources of such data[10]. The first possible source is through primary medical care in health systems, which are well developed. The limitations of this system include adverse effects on the consultation rates because of organizational or cultural problems, unreliability of numerator data, lack of uniform or even wide coverage, and lack of standardized diagnostic criteria. Sickness benefit claims through the Social Security System provide another method of gaining access to morbidity data from ARI. The major disadvantages of this is that again there is usually no universal coverage, the variation in severity of illness influences the reporting patterns and also the diagnostic information available is often of the scantiest especially in cases in which the patients, interest is not well served by having the exact diagnosis revealed.

Hospital attendance is a traditional method of getting morbidity statistics, but these can only be significant if the hospital system covers the majority of the primary care. Perhaps the best way of obtaining good morbidity data is by special surveys which are specifically focussed on the illness patterns in groups of people. Special surveys almost certainly will include other characteristics of

TABLE 8. Frequency of acute respiratory diseases, 45 cohort children, birth to age three years, Santa Maria Cauque, 1964-1969.

Disease or Illness	Cases	Rate Per 100 Person/Year	Attacks Per Child/Per Year
Upper respiratory	493	372.1	3.72
Bronchitis	256	193.2	1.93
Pneumonia, bronchopneumonia	70	52.8	0.53
Tonsillo-pharyngitis	10	7.6	0.08
Acute laryngitis	7	5.3	0.05
Otitis media	6	4.5	0.04
Bronchiolitis	5	3.8	0.04
Laryngotracheobronchitis	4	3 0	0.03
Other	2	1.5	0.01
TOTAL	853	643.8	6.44

Based on 132.5 person-years of observation, taking into account attrition due deaths.
After Mata, 1978.

the persons under study, allowing for the identification of risk factors. There are few specific surveys on ARI which are genuinely intercountry and allow the derivation of the kinds of data which will provide global estimates of morbidity from ARI.

Laboratory reports are yet another method of gaining retrospective information on ARI. These data cannot give true incidence rates and since they are all or none, they do not allow for grading of severity and therefore, any true measure of morbidity.

The following section describes isolated surveys and studies which serve only to give the crudest of measures of morbidity. It must be observed that most of these data give attack rates and little information about true morbidity - the burden of illness to the individual, family, community, or nation.

Mata followed a cohort of 45 children in the Santa Maria Cauque Valley in Guatemala from birth to 3 years and gives figures for the incidence of respiratory tract infections[11]. Diarrheal disease accounted for 43 percent of total recognized cases, followed by acute respiratory disease with 35 percent. Over a three-year period, children had 853 episodes of respiratory infections with 6.44 attacks per child, per year (Table 8). The upper respiratory infections clearly predominate.

Severe bronchopneumonia and bronchitis were 17 percent of the cases. When the cases were analyzed by age, both diarrhea and bronchopneumonia had maximal attack rates at the end of the second year. It was an interesting finding that up to the age of six months the upper respiratory infections seemed to have higher rates of incidence in

children with higher birthweights. After the age of 6 months, birthweight had no influence on the incidence of infectious disease. Very little has been written about the duration of illness in children of the developing countries. Mata shows that the duration of symptoms in children with upper respiratory tract illness decreased significantly from 8.6 days in children 0-5 months to 6.9 days in children at the end of their third year. The duration of symptoms in children with bronchopneumonia did not vary with age, averaging approximately 7.5 days. If children have approximately 6 attacks per year and each episode lasts about 7-8 days, this gives some indication of the amount of time children are ill. This also gives some idea of the burden of illness to the community as a whole.

There have been similar studies in India[12] although not for as long or in as detailed a manner as the study in Guatemala. A longitudinal survey of morbidity patterns of 350 children up to 5 years was carried out in an urban area for approximately one year. The overall episodes of illness per year of follow-up were 4.4 per child in the age group 0-1 year with acute respiratory tract infections as the leader, contributing 20 percent of the illness. Diarrhea came next with 30 percent. The average child in the age group 0-1 had approximately 38 days of illness per year. In other urban settings in India, similar results have been found[13].

It is not only in the developing countries that respiratory infections represent a major clinical problem. In a study in a Day Care Center in Chapel Hill, North Carolina, records were kept of all

respiratory illnessess, irrespective of severity[14]. It is critical to note that mildly ill children were not specifically excluded. The frequency of respiratory illnesses ranged from 6.7 per child/year in children aged 5 to 9.6 per child/year in children less than one year with an overall average of 8.4 respiratory illnesses per child/year. In a similar study in Cleveland, USA[15] there was also a rate of about 7 respiratory illnesses per child, per year.

Some of these data are set out in Table 9: there is a remarkable similarity between the data from Guatemala and the USA, which show that in the first year of life, the average child will get about 7 attacks of ARI. The low figures for the Indian studies may be a reflection of the design of the study which was relatively short - a period of 12 months, and did not identify a cohort of children for follow-up, as was the case in the studies in Guatemala. The longer duration of the studies in the USA and Guatemala probably accounted for the fact that they produced similar data. If it were necessary to establish the frequency of acute respiratory disease again in any population it would be critical to ensure an adequate sample size and a long enough period of follow-up to accommodate the well-known seasonal variations in disease attack rates.

A committee on Child Health Services in Britain[16] examined the reasons for which children and young people consulted their general practioners (Table 8). Respiratory diseases was the most frequent (28%) cause of attendance at a GP for a child below 5. The next common were symptons and ill defined conditions (12,7%), infectious diseases (11.0%), skin disease (10.1%), preventive procedures (9.9%) and accidents (5.8).

TABLE 9. Longitudinal studies of acute respiratory infections.

Country	Number of Children	Age	ARI Rate	Reference
United States	30	0-1	9.6	(13)
United States			6.9	(14)
Guatemala	45	0-3	6.4	(10)
India	71	0-1	1.9	(11)

Table 10

CHILDREN AND YOUNG PEOPLE CONSULTING A GENERAL PRACTITIONER
ENGLAND & WALES

Rates per 1000 population by age and diagnosed condition

Cause	0 - 4	5 - 14	15 - 24
Inefective and parasitic disease	181.7	141.9	73.7
Diseases of the nervous system and sense organs	235.2	127.2	84.2
Diseases of the respiratory system	548.2	325.7	256.8
Diseases of skin and subcutaneous tissue	176.5	127.1	139.3
Symptoms and ill defined contidtions	264.7	139.3	121.7
Acute vomiting and/or diarrhoea	101.7	29.2	29.7
Accidents poisonings and violence	84.6	99.5	121.1
Lacerations and minor trauma	46.5	54.5	57.0
Prophylactic procedures and other medical exams	270.0	60.4	216.2
All diseases and conditions	896.8	639.0	686.7

Data taken from Fit for the Future. Report of the Committee on Child Health Services, London, HMSO, 1976. (Ref. 16)

The most common respiratory problems were due to infection, accounting for half of all illness in children under 5, resulting in some 2000 deaths per year. Even although the absolute numbers decrease, respiratory diseases still represented the commonest reason for consulting a GP in all persons below 24 years of age. In the same study it was found that respiratory disease was the commonest cause of admission to hospital for children and accounted for 21.1% of all pediatric admissions. Respiratory disease caused 34.7 per cent of all infant deaths.

All the studies mentioned above attempted to determine the true incidence of ARI in the community. Another approach to determining the significance of a disease is to measure the amount of health resources consumed.

In Venezuela, 26.2 percent of all consultations in rural medical care stations was for ARI. In Australia, respiratory infections accounted for 32.2 percent of all disease episodes presenting to general practitioners in 1974[17]. The morbidity from ARI may also be considered in terms of the extent to which it causes social disruptions in the children at risk. Acute respiratory illness was the principal cause of absenteeism accounting for more than 1/3 of total absence days in school age children attending kindergarten through twelfth grade[18]. The upper respiratory tract infections were commonest and the average duration of any single illness was 3.8 days.

We have dealt with ARI as a single group, but there have been studies in which the more serious lower respiratory tract infections were

examined specifically. In a group practice in North Carolina, when the illnesses presenting to the physician were counted, the attack rate for lower respiratory tract infections varied from approximately 16 illnesses per 100 children, per year, at age 5, to almost 50 during the first year of life[19]. The clinical categories included in this study were epiglottitis, croup, tracheobronchitis, bronchiolitis, and pneumonia, which formed 28 percent of the total.

In a subsequent study the same group analyzed their cases of pneumonia, defined as children having rales or signs of pulmonary consolidation. Pneumonia attack rates were relatively low in the children less than 6 months of age, and in those between 6 months and 5 years, the rate was 40/1000/ year[20].

In less affluent settings, pneumonia may be even more common. A survey was carried out among Navajo Indians over a 2-year period and pneumonia was diagnosed when there was an illness of less than 3 weeks duration associated with a temperature of greater than 100°F, a cough, and infiltrates on a chest X-ray[21]. In the age group less than one year, the pneumonia attack rate was 252 per 1000 children per year, and 50 in children between 1 and 5 years of age. Similar data have been shown for children in Papua, New Guinea, and the results from the three studies are shown in Table 11.

The agreement between the data on the Navajo Indians and the rural children in Papua, New Guinea, is striking and remarkably different from those seen in North Carolina. The incidence of ARI in general is similar in developed and developing countries, thus the question must be asked -

TABLE 11. Attack rates for pneumonia in children in three different clinical settings.

	Ages (Years)		
	0-1	1-5	Reference
Group 1	10	32	(20)
Group 2	252	50	(21)
Group 3	278	59	(1)

Attack rate - attacks of pneumonia/1,000 children/year.

Group 1 - Children studied in a group pediatric practice in Chapel Hill, North Carolina, USA. Predominantly middle class.

Group 2 - Navajo Indians in New Mexico and Arizona.

Group 3 - Children of the Huli people of the Tari Basin in Papua, New Guinea.

why is there such a marked difference in incidence of severe pneumonia? This problem will be discussed in relation to the etiology and predisposing factors for ARI as a whole.

3. RELEVANT ANATOMICAL AND PHYSIOLOGICAL FACTORS

The normal infant is more prone to respiratory infections than an adult because of a combination of anatomical and other host factors.

Anatomical factors.

It is known that considerable development takes place in the lung after birth. For example, the full complement of alveoli is not reached until about the time somatic growth stops[22]. Because of differences in the time relationships between alveolar multiplication and growth and immaturity of the perialveolar elastic fibers, the lung in children is much less compliant than in adults[23]. This poor compliance plus a relative reduction in thoracic gas volume leads to a tendency for closure of the airways. A second important factor is the relatively higher peripheral resistance in infants[24]. Finally, because of relatively easy fatiguability in the diaphragmatic musculature, the young child is less able to mount the cough effort which is necessary to clear the pulmonary tree of foreign particles. All of these factors predispose the normal infant to respiratory infection. They also set the stage for persistent damage as a result of apparently minor infections.

Pulmonary defence mechanisms (for review see 26, 27)

The lung and the skin are the organs most exposed to infectious agents and the ability of these organs to withstand overt infection depends on a combination of physical and immunological factors. Although some infectious agents reach the lung by the bloodstream or by direct spread from adjacent tissues, by far the majority of pulmonary infections result from inhalation of infectious agents. The mechanisms which keep the respiratory tract free of infection include physical factors as well as factors leading to "neutralization" of the infecting potential of the organisms. First it is the particle size which determines the fate of the inhaled material. Physical laws determine that the larger particles will become lodged in the nasal cavity, nasopharynx and the mainstem bronchi with only the smallest particles 0.5-2.0nm settling in the bronchioles and alveoli. The particles which are deposited on the bronchi are wafted upwards by mucociliary transport mechanisms. When organisms do reach the alveoli or bronchioles, they are dealt with by the alveolar macrophage or by an immunologic process.

Mucociliary transport is an important pulmonary phenomenon[27], but there are few specific experimental data on the importance of this mechanism in protecting against acute respiratory tract infection. Normal mucociliary function naturally depends on both functionally intact ciliated epithelium as well as adequate quantity and normal quality of respiratory mucus. Acute respiratory viral infections lead to impairment of mucous transport[27] and this will impair other pulmonary defences, possibly potentiating existing infection or predisposing to retention of secretions and further facilitation of infection.

There is a considerable amount of information on the irritant effect of cigarette smoke in impairing muco-ciliary transport[27,28]. Even short-term exposure to smoke in animal models and in vitro, causes depressed ciliary function and depressed particulate clearance. Long term exposure produces impairment of mucous transport which may precede other abnormalities in the lung. Exposure to atmospheric pollutants such as sulphur dioxide and nitrogen dioxide also depresses mucociliary function[27].

If particulate matter does reach the alveoli, the alveolar macrophage constitutes the major primary defence mechanism. It functions by ingesting the inhaled particle by phagocytosis, transporting the ingested particle out of the lung or by destroying it. The mechanism of phagocytosis has been well established as consisting of attachment of the particulate material, uptake and finally intracellular processing. Once the particle has been ingested by the macrophage it may migrate from the alveoli via the lymphaters or eventually by the mucociliary escalator. The intracellular mechanisms for detoxifying ingested material are either lysosomal proteolytic enzymes or oxygen dependent systems.

The immunologic mechanisms which form part of the defence mechanisms are both humoral and cellular. Secretory IgA is produced mainly in the upper respiratory tract and IgG in the alveoli, with a mixture of both being found in the bronchi. IgA antibodies from the bronchi neutralize a wide range of viruses, but there is little evidence of antibacterial activity. IgA also facilitates particle aggregation and thus may promote mucociliary clearance of infective particles. The role

of IgG in respiratory secretions is less clear. Cell mediated immune mechanisms may also be of importance in activating macrophages and thus enhancing the phagocytic and enzymatic digestive capabilities.

This brief review does not allow us to discuss the other factors such as the alveolar fluid composition and behaviour as well as the blood stream defenses which are probably also important to our understanding of the aetiology and predisposing factors for acute respiratory tract infections especially in children.

4. PREDISPOSING FACTORS IN THE CHILD

Nutrition

Nutrition is an important determinant of the occurrence of ARI in children and the interaction between nutrition and infection has been very well documented. The malnourished child is prone to many types of infection particularly diarrhea and respiratory infection and the basis for this is multifactorial[29]. There is good evidence for the presence of immunological abnormalities in malnutrition. In severe malnutrition in the very young, the serum immunoglobulin levels are depressed but when IgA, IgM and IgG were measured in classical kwashiorkor patients the levels were within normal limits[30]. Although the serum immunoglobulins are normal there may be impairment of antibody synthesis. In malnourished Mexican children the immune response to diphtheria toxoid was markedly impaired[31] and this finding of failure to elaborate specific antibody in response to innoculation has been seen in malnourished children in several pats of the world.

It is directly relevant to the occurrence of respiratory infections that Sirisinha et al[32] showed in an analysis of nasal washings from malnourished children that secretory IgA concentrations were significantly lower than normal and did not return to normal levels until some 70 days after treatment was started. The authors also showed that the concentration of IgG and albumin in the nasal washings were only slightly decreased, and they make the point that the decrease in secretory IgA was probably selective and not due to a general reduction in all proteins. Unfortunately the IgA levels could not be related to the presence or absence of clinical infection but it is well known that it may be very difficult to make a firm clinical diagnosis of infection in malnourished children.

The serum levels of complement proteins are also depressed in malnutrition[33] and appear to be lowest in children with the severest infections, but it is impossible to be certain of the causal relationship between the complement levels and infection.

Cell mediated immunity is also depressed in malnutrition[34]. This may be demonstrated by the in vivo response to skin test antigens and by the significantly impaired sensitivity after BCG vaccination[35]. In vitro tests show impairment of T cell rosette formation by lymphocytes from malnourished children[34]. Recent studies have shown that zinc deficiency may be a potent cause of this depression of cell mediated immunity[36].

The function of leucocytes is also depressed in malnutrition. There is a delay in macrophage migration in response to an inflammatory

stimulus[37] and intracellular killing of ingested bacteria is impaired,[38] perhaps as a result of iron deficiency. McFarlane et al have demonstrated decreased serum transferrin levels[39]. It is not known if this depression of leucocyte function is also seen in pulmonary alveolar macrophages, but if it were, it would obviously contribute to the increased risk of respiratory infections.

Malnutrition may also contribute to respiratory infections because of the muscle weakness which is present. Children with gross electrolyte disturbances such as potassium and magnesium deficiency[30] in addition to protein deficiency, are often too weak to cough - thus removing the physical response to infection. There are no data as yet on the possibility that infection may alter any aspects of the pulmonary functions described above. Finally malnutrition may be important because many of the clinical signs of infection do not appear in the malnourished child and severe infection may be present in the absence of any pyrexia.

Breastfeeding

Breastfeeding is associated with a decrease in many infections including those of the respiratory tract( ). However, failure to breastfeed is often associated with other factors e.g., mothers who smoke are less likely to breastfeed their infants, thus the effect of breastfeeding may have been expressed through smoking. However, a recent study in London has reexamined this association and it is clear that fewer episodes of acute bronchitis and pneumonia occur in children who were breastfed compared with those who were bottle fed[40]. The

anti-infectious and immune properties of breast milk are well accepted and it has been shown that significantly enhanced resistance to enteric infection is seen among breastfed babies not only when the environment is sanitary but even in the presence of poor environmental sanitation[41]. Similar data are needed for resistance to respiratory infections.

Environmental factors

The fall in death rates from ARI began to be apparent in the developed world long before the advent of antibiotics and it has been claimed that social and environmental factors have been in the main responsible. In Britain, diseases of both upper and lower respiratory tract are commonest in children of parents in the lower social classes. One factor related to social class is clearly the environment. Overcrowding in the home increases the risk of respiratory illness[16]. In Michigan, in a study across all ages it was found that reported respiratory illnesses decreased as the family got richer, but increased with the level of education of the head of the household[42]. These data have implications for prevalence studies based on reported illnesses. With increasing education, the family becomes more concerned with earlier symptoms and reports minor illnesses which less privileged families do not. Thus the true incidence of severe respiratory disease may indeed fall with the increasing wealth and education, but the perception of severity changes with education, leading to over reporting. It would be surprising if the answer did not lie in this

direction, since education and financial means are usually closely correlated in populations.

Another factor relating to respiratory disease in the child is air pollution. High levels of air pollution cause a rise in mortality from respiratory disease in infants[42] and air pollution may be a contributing factor to any differences which may occur between children in urban and rural areas. Douglas and Waller investigated a national sample of 3,866 children and found that lower respiratory tract infections were more severe and more frequent in children from more polluted areas[43]. These data all refer to lower respiratory tract infection, as the association between upper respiratory infection and air pollution is not as clearcut as for lower respiratory infection.

Passive inhaling of smoke may also contribute to respiratory infection in children. In a study based in London, it was found that in a group of 2,205 children studied over their first 5 years, parents' smoking habits were directly related to the presence of ARI in children under the age of 1 year. When both parents smoked the children had most ARIs: this was least when neither parent smoked and intermediate when one parent smoked[44]. The authors also showed in that study that social class and family size were unlikely to be related to the pattern of respiratory disease incidence. They adduced another possible explanation. Since birthweights of infants of smoking mothers are lower than those of infants from mothers who do not smoke, and since infants of lower birthweight are more prone to respiratory infections, then the relationship between smoking and respiratory infection is possibly caused

by the birthweight. There were no data on the influence of paternal smoking. This would have been of interest since it might have been possible then to separate the effect of inhalation of smoke by the infant and birthweight. There are other data relating parental smoking to respiratory infection in children[45] and it is clear now that parents do their infants a disservice by smoking. There are no data from the developing countries on the influence of parental smoking but it has been shown that exposure to domestic wood smoke had no effect on acute respiratory infection in school children in Papua, New Guinea[46]. Interpretation of these data must take into account the findings that parental smoking only had an effect on respiratory infections before the age of one year. In view of all the other data relating smoking and air pollution to respiratory infection, it would be of interest to reexamine the effect of domestic smoke in respiratory infection in children less than 1 year of age especially in countries of the developing world.

Smoke from cooking fires is not a problem in houses in developed countries, but even here it can be shown that the domestic environment is important. Fossil fuels release gases which can cause respiratory damage. Speizer et al surveyed some 8000 children ages 6-10 from 6 communities in the USA, comparing respiratory function in those living in homes in which gas stoves were used with those who lived in homes using electricity. There was an increased incidence of respiratory disease before the age of 2 in children from homes using gas. There was a small but significant reduction in respiratory function as shown by lower levels of $FEV_{1.0}$ and FVC. The differences could not be explained by

social class or parental smoking habits. The concern was expressed that those childhood abnormalities might lead to reduced lung size and function in the adult[47].

5. CLINICAL SYNDROMES OF ACUTE RESPIRATORY INFECTIONS

There are no anatomical barriers to specific pathogenic agents which cause respiratory tract infections in children, but in general, the clinical syndromes have been described on an anatomical basis. The following descriptions represent the most widely used terms which are most useful[48,49.50.51].

Acute nasopharyngitis

The common cold is the usual cause of acute nasopharyngitis, The main symptoms are sneezing, nasal discharge, and sometimes, a fever. There may be feeding difficulties in the very young child who has nasal obstruction so severe as to make mouth breathing mandatory. Postnasal discharge may produce coughing. These symptoms usually disappear in 3-4 days, but occasionally respiratory streptococcal infection may produce prolonged febrile nasopharyngitis.

The commonest serious complication here is acute otitis media and in some children acute sinusitis may also occur. Health workers should be taught to be aware of the unilateral nasal discharge indicating a foreign body.

Acute pharyngotonsillitis

The child is usually febrile and a convulsion may occur. The throat is red, often with petechial mottling of the soft palate and a faucial exudate. The clinical features often do not distinguish between viral and bacterial causes of pharyngotonsillitis, although it is said that with a viral illness there are two peaks on the temperature chart. This disorder is still of major importance in developing countries where rheumatic fever continues to occur. Acute glomerulonephritis may also follow acute streptococcal pharyngitis in children of the developing world, but the main site of infection in these cases is usually the skin.

Acute laryngitis

The main clinical feature of this disorder is respiratory obstruction and respiratory stridor and because of anatomical considerations, the infant gets a greater degree of obstruction. In addition, the infection may involve not only the larynx but other parts of the respiratory tract, producing acute laryngotracheobronchitis. Acute laryngitis is the commonest cause of croup and the commonest age affected is 6 months to 2 years. Acute laryngitis is usually a mild illness but when there is laryngotracheobronchitis, there may be more extensive clinical features with diminution of intensity of breath sounds, rhonchi, and scattered rales. The critical factor leading to fatal outcome is severe hypoxemia and it is this which makes it of such importance in the developing countries. The kind of appropriate technology is not available to deliver oxygen to remote parts of rural

areas. Acute epiglottitis is an uncommon but dramatic cause of upper airway obstruction in young children usually older than 3 years of age. The child may or may not have had an upper respiratory infection and develops a high fever and drooling with severe respiratory distress. The characteristic feature is the cherry red epiglottis. Since the management of this condition is immediate relief of the airway obstruction it is likely that most children with this condition in remote areas die because of lack of skilled attention.

Acute bronchitis

Acute bronchitis is characterized by a cough and often follows an episode of viral upper respiratory tract infection. There may or may not be a fever and initially the respiratory rate is normal. The chest is usually clear but if the disease persists there may be rhonchi and occasionally rales heard. Some young children have recurrent attacks of bronchitis in the first 4-5 years without progressing to chronic bronchitis. Some children with acute bronchitis wheeze and it has been suggested that this is commoner than expected and is missed because wheezing takes place mainly at night. In an ingenious study of children with "bronchitis", acoustic analysis of wheezing by audio frequency spectroscopy showed that a considerable number of these children had low pitched wheezing at night and early morning even when there were no such sounds audible and no abnormal findings on physical examination during the day[52].

Acute bronchiolitis

The term "bronchiolitis" is usually reserved for the clinical syndrome occurring in children under 1 year of age. There is an initial period of coughing which in a few days may proceed to a syndrome with raised respiratory rate, and all the signs of small airway obstruction and progressive hypoxemia. This disorder is said to be typically epidemic in winter.

Bronchiolitis can be a significant part of respiratory disease. Khatua[53] studied 205 cases in Calcutta and found that they constituted 2 percent of all admissions to hospitals and 8.5 percent of all respiratory disease. The cases were diagnosed mainly on clinical grounds and were severe enough to warrant admission to hospital. In keeping with many other studies, most of the admissions were in the winter months, 91 percent were below the age of 1 year and males predominated. The case mortality in this series was 8.3 percent.

Henderson, et al[54] have challenged this concept of wheezing acute respiratory infection being restricted to any particular age group. In their pediatric practice over an 11-year period, they found that only half of all children with an acute wheezing illness were less than 2 years and only 30 percent less than 6 months of age. They point out that the idea that the occurrence of bronchiolitis is limited to the first months of life should be modified. Bronchiolar obstruction could be found accompanying acute respiratory infection throughout childhood. The important point to be made is that conclusions about type of syndrome have to be related to the patient population under study and it is

probable that the data of Henderson et al[54] bear a closer relation to what occurs in the community than the other hospital-based studies which deal mainly with severe respiratory disease.

Pneumonia

By definition, this means parenchymal inflammation. In the typical case of bacterial pneumonia in children, the onset is sudden with high fever, toxicity and signs of lobar consolidation on clinical examination. This is more typical in the older child, but in the children less than 2 years, bacterial pneumonia may present a diagnostic challenge. The child may have a fever and be irritable with very few, if any, signs specific for the respiratory tract. It is only by blood and radiologic investigations that the diagnosis is sometimes made. Perhaps the most dreaded form of bacterial pneumonia in children is staphylococcal pneumonia, which often occurs in the compromised host and may have a fulminant course with numerous complications and a high fatality rate. Pneumonia may also be secondary to viral illnesses. In children ages 5-10 mycoplasma pneumonia occurs but is usually a mild illness. The patients are not usually toxic, have a marked cough with headaches and chills, and examination of the chest may reveal a few rales when an X-ray of the chest shows much more extensive disease.

Most of the studies on childhood pneumonia come from the developed countries and most clinicians are not familiar with the very severe pneumonia in children which occurs in developing countries and mimics the clinical picture which was seen in the developed countries decades ago.

Riley[1] carried out an intensive study of 91 infants and children with severe acute lower respiratory tract infections at the Tari Hospital in Papua, New Guinea. He used respiratory rate in relation to age as a major discriminating factor. It was the onset of fever or dyspnea rather than cough which brought the child to the hospital. Of the 91 caes with severe disease, 4 had bronchiolitis and pneumonia and 31 had pneumonia alone. It was almost impossible to separate the diagnostic categories on the basis of the clinical signs. The point is made that in these situations it is not useful to distinguish between the various types of syndromes, but to classify children on the basis of severity. The two most useful signs of this severity were cyanosis and flaring of the alae nasi.

Denny and Clyde (personal communication) have proposed a clinical classification of acute respiratory infection which is shown in Table 12. This encompasses all of the clinical syndromes described above, but makes the differentiation first on the basis of the anatomical localization. By far the greatest number of respiratory infections in children fall in the uncomplicated category.

6. GENERAL LABORATORY DIAGNOSIS OF ACUTE RESPIRATORY INFECTIONS

Although clinical features are sometimes so characteristic that diagnosis can be made with a certain amount of security, in other cases, the etiological agent needs to be identified. Epidemiological studies and sometimes management of individual cases requires the help of a

Table 12

CLASSIFICATION OF ARI

Upper Respiratory Infections (URI)

Uncomplicated		Complicated
Streptococcal	Non-strep	Otitis Media
		Sinusitis
		Peritonsillar Abcess
		Retropharyngial Abcess
		Mastoiditis

Lower Respiratory Infections (LRI)

Uncomplicated	Complicated
Epiglottitis	Mediastinitis
Croup	Empyema
Tracheo-bronchitis	Pneumothorax
Bronchiolitis	Lung Abcess
Pneumonia	Bronchiectasis
	Pericarditis

diagnostic laboratory. Identification of viruses is indispensible for epidemiological studies, but this is not easy, requiring special conditions for transport of the specimens, tissue culture facilities, and equipment for serology. On the other hand, bacteriological diagnosis, even a simple direct smear microscopy of nose or throat secretions or sputum, may provide limited but useful information. When at least 80% of the flora is the same organism this points to a bacterial bronchoneumonia; a rich polymorphic bacterial flora suggests a chronic supurative illness, while the presence of few bacteria and leukocytes may suggest a viral infection(reviewed in 55).

Culture is a more precise diagnostic method. However the isolated organisms should be of known pathogenicity, and the patient should not have been given antibiotics before the sample is obtained. Contamination of deep secretions by oropharyngeal flora as well as the time interval between collection and innoculation of the sample can also be the cause of dubious results(55,56).

Interpretation of results from cultures obtained from children with lower respiratory tract infections will depend on the source of the specimen and the type of organisms recovered. While some of them are always considered as pathogens (e.g. Mycoplasma pneumoniae or RSV) others are part of the normal flora of the upper respiratory tract (like pneumococci or Staphylococcus aureus). Therefore, interpretation of their possible pathogenic significance will largely depend on evidence of their origin in the lower respiratory tract.

The normal flora of the oropharynx contains several dozen bacterial species. Thus, specimens like expectorated sputum, cough swabs, nasopharyngeal aspirates and/or swabs and bronchoscopy aspirates will almost certainly be contaminated, yielding data that are difficult to interpret. Cultures free of oropharyngeal contamination such as those from blood, transtracheal aspirates, transthoracic lung aspirates, open tissue biopsy, pleural fluid, etc., are more easily interpreted. However, except in the case of hemoculture, these procedures should be performed by the physician. Moreover, hemoculture will only give valid information in cases of bacteriemic pneumonia. The choice in most cases is then made between transtracheal and transthoracic lung aspiration. Both procedures yield excellent samples but are associated with risk of complications[55,56]. Theoretically, specimens obtained by transtracheal aspiration are not contaminated with the flora of the upper airway[57,58]. However, this technique had not been shown to provide uncontaminated cultures[59-61] and specimens from patients without clinical evidence of pneumonia have contained potential pathogens[55].

Despite possible oropharyngeal contamination, expectorated sputum, cough swabs and nasopharyngeal aspirates/swabs are the specimens most commonly used. It has been shown that if a gram-stained sample is examined microscopically before being cultured there is a reasonable chance of arriving at a correct diagnosis. Based on the correlation observed between the results of sputum culture and those of transtracheal aspiration it has been concluded that specimens showing less than 25 squamous epithelial cells per field (x 100) are acceptable for culture

irrespective of the number of leucocytes. Specimens with more than 25 squamous epithelial cells are considered unacceptable for culture because of oropharyngeal contamination [55,62-64].

Further innoculation of the specimens in blood agar, Bordet Gengou media, chocolate agar and McKonkey agar for possible bacterial pathogens, mycoplasma broth, for mycoplasma and primary rhesus monkey kidney, Hep-2, Hela human diploid lung fibroblasts, and chicken embryo for viral pathogens, will give a reasonable chance of isolating and recovering most of the etiological agents responsible for ARI. However, diagnosis of etiological agents responsible for ARI are a delicate task that requires careful collection, handling, storage and transport of the specimens as well as the use of appropriate selection of culture media, cell types for virus growth, or the proper immunodiagnostic tests when available.

As culture takes time, thereby delaying the diagnosis, several methods have been developed that allow a diagnosis to be made within six hours of obtaining the specimen.

Rapid diagnosis

Bacterial infections

The last ten years have seen the development of interesting new techniques that can be applied in the diagnosis of the bacteria responsible for ARI. Although culture and recovery of the organisms from the sample are definitive as far as certifying the diagnosis, this usually takes at least two days. Therefore great effort has been made to develop and evaluate methods that will provide rapid and accurate diagnosis.

Early work using the quellung reaction for specimens possibly containing pneumococci were directed toward the same objective i.e. quick microscopical diagnosis by the binding of anti-pneumococcal antibodies to the organism capsular polysaccharide. If the organism were St. pneumoniae, a change in the refractive index would cause the capsule to appear swollen. All other methods are also based on an antigen-antibody reaction and their sensitivity and specificity will vary in relation to antibody preparation and the method of amplifying the reaction. In the coagglutination (COA) and latex agglutination (LA) tests the antibody binds specifically to protein A of staphylococci or by hydrophilic interaction to the latex particles surface, respectively. In both methods the antigen will be particulate. In the immunofluorescence (IFA), Enzyme labelled Immunoassay Test (ELISA) and Radioimmunoassay (RIA) a fluorescent dye, an enzyme or an isotope is coupled with the antibody. In the counter current immuno-electrophoresis (CIE) a precipitation line is formed under the influence of an electrical field. Some of these tests can be used to detect either bacteria or soluble antigens (e.g. COA, LA) while others only detect intact organisms (IFA).

The COA test is based on the binding of the F_c receptor of the immunoglobulins to the protein A present in the staphylococci aureus[65,66]. The bacteria acts then as an inert particle carrier when sensitized with specific antibody. The tests detect antigens and a positive reaction is characterized by the aggregation of the organisms. It can be used either for typing isolated bacteria such as pneumococci, streptococci or H. influenza or for detection of bacterial antigens in

specimens such as sputum, urine, serum and cerebrospinal fluid[67-74]. The test is simple, rapid, sensitive and specific when the antiserum used is of good quality. In these conditions, from 107 to 10^8 bacteria/ml from culture[75] and at least 10ng/ml of soluble antigen is required to give a positive test[68,72]. False positive reactions seen when testing body fluids usually result from the fact that IgA in the staphylococci is able to takeup additional IgG. Thus, the bacteria reacts with immunoglobulins present in the sample. Heating of the sample before testing[74], or absorbing the serum with protein A or staphylococci will prevent this problem[3,12].

Latex agglutination - This test in which the antibodies bind to latex particles was used for detecting St. pneumoniae and H. influenza antigens in body fluids[78-81]. It has been found to be similar or more sensitive than CIE for establishing antigens in body fluids such as serum, CSF or urine[77,81], but not enough experience has been gathered as yet with sputum. Moreover, false positive reactions may occur, which originate from antigen sharing by pathogenic and non pathogenic organisms[82,83] as well as nonspecific autoagglutinations induced by body fluids or normal sera(77,78).

ELISA - This assay can be used for detection of bacterial antigens by using antibodies conjugated with an enzyme[84-90]. In the direct assay, the specific antibodies directed against the bacterial antigen to be detected are labelled with the enzyme. In the indirect assay an

unlabelled specific antibody is used. The presence of the antigen-antibody complex is then quantified by means of an antibody labelled enzyme directed against the antibacterial globulin. The appropriate substrate is added for the enzymatic reaction and products originating in the enzymatic cleavage develop a specific color that can be measured. The indirect method is more sensitive and especially useful if the laboratory performs tests for antigen detection on several species of bacteria, as a single labelled antibody can be used for any ELISA provided that the antibacterial antibody is of the appropriate animal species[89,90]. In both cases the reactant must be bound to a solid phase. This assay was shown to be highly sensitive for detection of H. influenza type B capsular polysaccharide[91-93] as well as pneumococcal antigen[94,95].

The radio immunoassay (RIA) - In this test antibodies against the antigen to be tested are fixed to a solid phase. The specimen that presumably has the antigen and specific antibodies labelled with I^{125} or other isotope are then added in turn. If the antigen is present in the specimen, the labelled antibodies are not removed by washing and radioactivity is detected. This technique is very sensitive and has been used to detect antigens of St. pneumoniae and H. influenza[96,97]. However, there is not yet enough experience on the practical use of RIA for the laboratory diagnosis of ARI.

Counter-current immunoelectrophoresis (CIE) - This technique detects the combination between antigen and antibody that gives a line of precipitation. Movement of the reacting antigen-antibody in an agarose

gel is produced by an electrical field. This test can detect nanograms of antigen and has been successfully used for establishing antigens of pnuemococci, streptococci and H. influenza in secretions or body fluids[77,82,98,99].

Fluorescence antibody technique (FAT) - By this method it is possible to identify bacteria but not soluble antigens. Furthermore the organisms should have their characteristic morphology for proper identification. Basically, the identification of the bacteria is possible because of the interaction between the bacterial surface antigens and the fluorescent labelled antibody. This can be done either by the direct method in which the specific antibacterial antibody is labelled with fluorescein, or by the indirect method in which the unlabelled antibacterial antibody is allowed to bind to the antigen of the bacteria. This binding is then visualized by adding a fluorescein labelled antibody directed against the specific antibacterial globulin.

The indirect method is more sensitive and aliviates the necessity for having fluorescent labelled antiserum against different bacteria. FAT was very sensitive for detecting H. influenza, N. meningitidis, and St. pneumoniae in cerebrospinal fluid[68] and especially useful for diagnosis of B. pertussis on nasopharyngeal swabs[100]. Further studies comparing FAT with isolation by culture demonstrated the higher sensitivity of the FAT over culture either for detecting B. pertussis or parapertussis[101-103]. On the other hand, attempts to use FAT in smears of throat swabs for detection of streptococci had not been entirely satisfactory[104-107]. FAT can also be used for

identification of B. pertussis, B Hemolytic Streptococci, and other organisms in culture. With B streptococci, good results can be obtained in broth culture innoculated 2 to 24 hours previously[107].

Viral diseases

Isolation of the virus in culture and antibody detection are lengthy procedures. However, is now possible to demonstrate specific viral antigens a few hours after the specimen is collected. The FAT[108, Rev. in 109)] and ELISA[110] tests have been used for this purpose. Until know there is enough experience with the former, which was shown to be sensitive and specific. Reliable results depend upon the quality of the reagents and the manner in which the specimens are collected. Proper collection of nasopharyngeal secretions by suction with a catheter into a mucus trap, provides a convenient amount of virus infected cells. Nasal or throat washings, sputum, gargles or cough swabs can be also used although the sensitivity is lower because fewer infected cells are obtained. Throat swabs are not appropriate[111]. The cells recovered from the specimen by centrifugation are washed, smeared on slides and allowed to dry. The slides can be processed immediately or kept frozen at -40°C for the direct or indirest FAT test. The latter is the method of choice because of its greater sensitivity. Provided that antisera are available the following viral antigens can be identified: Influenza types A and B, RSV, measles, Adenovirus (group), and parainfluenza 1,2,3,4.[109]. As large numbers of specimens can be examined for several viral antigens in a relatively short time, the method is extremely suitable for epidemiological studies.

Identification of viral antigens in secretions of the respiratory tract point to a pathogenic role for the virus. On the other hand identification of the virus (eg adenovirus) in culture, with a negative FAT, strongly suggests that the presence of the virus is unrelated to the disease.

Although ELISA has been successful for detection of RSV antigen in nasal secretion and was also useful for detection of adenovirus in simulated clinical samples consisting of normal nasal wash specimens seeded with varying concentrations of adenovirus, it should be further evaluated for this purpose[111].

7. AETIOLOGICAL AGENTS, DIAGNOSIS AND VACCINATION

Either bacteria or viruses could be responsible for ARI in children. In developing countries, where most of the studies have been done, it is accepted that viruses play a more important role than bacteria as aetiological agent of ARI. However, the same may not be true in the developing world. studies in which attempts were made to isolate all posible etiological agents are lacking and in some cses the studies were directed to specific groups of patients in which only a few organisms were studied. Furthermore, previous antibiotic treatment or the selection of unappropriate control groups have biased the results obtained.

A brief description of the main characteristics of the most common organisms responsible for ARI are given below and are also described in

Tables 13, 14 and 15. The order in which these organisms are described is related with their relative importance as agents of ARI as suggested by most previous studies.

Viruses

Respiratory syncytial virus

Clinical and epidemiological features

Lesions and therefore clinical patterns produced by RSV infection are definitively related with age [113,114]. In older children and adults the initial infection results from viral multiplication in epithelial cells of the upper respiratory tract that does not progress. However in infants, the virus may spread to the lower respiratory tract. Primary infection in infants and small children is usually characterized by respiratory symptoms associated with fever [114]. One in 100 or 200 of these patients may be severely ill with symptoms of bronchiolitis or pneumonia. Both are more commonly seen during the first year of age, but pneumonia can also be observed in older children [113-115]. After primary infection during infancy or early childhood, reinfections in which virus can be isolated are frequent [116,117]. These infections may be asymptomatic or associated with common cold-like symptoms of less severity than primary infections [113,116,117]. Although they are not life threatening, they play an important role in spreading the disease.

After the acute episode, RSV is eliminated from the host. Serum neutralizing antibodies either passively transferred from the mother to the newborn or induced by the infection are not able to provide

Table 13

PREDOMINANT VIRUSES CAUSING UPPER AND LOWER ARI IN INFANTS AND CHILDREN

Characteristics of the Virus	Serotypes	Common serotypes producing illness	Common respiratory symptoms in target populations: Infants	Common respiratory symptoms in target populations: Children	Epidemiology: Source of infection	Epidemiology: Penetrability	Epidemiology: Usual manner of presentation
PARAMIXOVIRUSES							
The virions are roughly spherical enveloped particles with an average size of 125-250nm. A lipid containing outer envelope about 10nm thick is studded with short (8-10nm) spikes. Inside the envelope exists an inner helical nucleocapside with a diameter of 18 nm and periodic serrations. They have one large molecule of single-stranded RNA. The envelope has a non-glycosylated protein forming its inner layer (M protein) and two more glycoproteins form the projection that emerges from the envelope. One has neuraminidase and hemagglutinin activity (HN), while the other is hemolytic and also capable of lysing the membrane of host cells (F). These viruses are able to induce the fusion of neighboring cells leading to production of a syncitium.							
PARAINFLUENZA							
They have some characteristics of their own. They are lacking hemagglutination, hemadsorption, hemolytic and neuraminidase activity. Virions and nucleocapside are extremely fragile and f filamentous virions may be detected. Spherical virions are smaller; the nucleocapside has smaller diameters and the helix has larger regular periodicity than the other paramixovirus. Although isolated strains have a common nucleocapside antigen and also a specific surface antigen, a great cross-reactivity exists among strains.	1	1	Common cold with fever, bronchiolitis, Pneumonia	Common cold with or without fever, Pneumonia, asthma exacerbation	Children	High.	Epidemic, autumn, winter or spring, annually.
SRV							
They have specific antigens responsible for their type specificity, the hemagglutinin-neuraminidase (HN), the fusion-hemolysin (F) surface antigen and the internal nucleocapside antigen (NP). The appearance of heterotypic antibody responses to different types (and mumps too) in infected individuals, indicates the immunologic relationships among the members of the group. They are immunologically unrelated to the influenza viruses.		1	Common cold with or without fever, Croup, Tracheobronchitis, Bronchiolitis, Pneumonia			Moderate, High	Epidemic, autumn, every two years.
	4	2	Common cold with or without fever, Croup, Tracheobronchitis, Pneumonia		Children	Moderate	Epidemic, autumn, every two years.
		3	Same as 1.			High	Endemic
		4	Common cold-like illness with or without fever. Uncommonly detected.			Low	Endemic
ADENOVIRUSES							
Unenveloped DNA containing viruses that multiply in the cell nucleus. The virion is 60-90nm in diameter with a central core of one linear double-stranded DNA molecule associated with proteins. The outer capside is composed of 252 capsomers (240 hexons and 12 fiber-topped pentons responsible for the attachment of the virus to the cells). Hexon and penton proteins are responsible for the immunological reactivity. The exons have a cross-reacting antigen that characterizes the family as well as a type specific reactive site that is identified by neutralizing antibodies. The pentons provide minor antigens of the virion and also a family-reactive soluble antigen that is found in infected cells. The fibers have a major type-specific antigen and a minor subgroup antigen.		1,2,5,6*	Common cold with or without fever. Pharyngitis with or without exudate. Bronchitis, Pneumonia. *Less Common		Children	High	Endemic, nonseasonal
Intact pentons have a toxic effect on the cells as shown by the rounding, clumping and detachment of culture cells. On the other hand, Purified fibers may block DNA, RNA and protein synthesis and cell division, making the cells unable to support the growth of other viruses. An important property of some human serotypes is their ability to produce latent infections in tonsils and adenoid tissue. They are classified in four groups in relation to their ability to agglutinate rhesus monkey or red blood cells. Those producing ARI belong to groups I (Types 3, 7, 14, 21) and II (1, 2, 4, 5, 6). Some of them have been shown to be oncogenic in newborn hamsters.	15	3,7	Common cold with or without fever. Conjunctivitis, Pharyngitis with or without exudate. Bronchitis. Pneumonia.		Children or young adults	Moderate	Endemic, sometimes epidemic
		*4,14	Less common in this age group				
		21	Rare in this age group				
INFLUENZA							
These viruses are roughly spherical or ovoid with a diameter of 80-120nm. Filamentous forms from fresh isolates are somewhat larger. The viral particles are characterized by spikes that cover their entire surface and extend from a lipid bilayer membrane. This surrounds a protein matrix and a helical nucleocapside containing a single-stranded RNA. The viral projections consist of two subunits with different structure. The hemagglutinin, responsible for the attachment of the virus to the host tissues, and the neuraminidase, which favors the release of the virus from infected cells. Two antigens are detectable on the surface of the virion. One is a glycoprotein that biologically and immunologically corresponds with the hemagglutinin. It is detectable by inhibition of hemagglutination activity, neutralization of infectivity or complement fixation. The other glycoprotein antigen corresponds to neuraminidase (in A and B influenza viruses only) and can be measured by inhibition of the enzyme activity. Immunity against the hemagglutinin is probably the main factor responsible for resistance. However, antibodies directed against neuraminidase also play a role as they can reduce viral spread from infected cells, decreasing the impact of infection. Influenza C virus is lacking neuraminidase. The viral envelope has an antigenic matrix protein (M protein) that can be measured by complement fixation. M protein antibodies are unable either to neutralize the viral infectivity or the hemagglutinin and neuraminidase activity. The RNA protein core provides the nucleocapside antigen which is identical to the soluble antigen that appears in infected cells. Based on the M protein and nucleocapside antigens, which are unique and do not cross react, the influenza viruses can be grouped in three different genera: A, B, and C. Distinction between immunotypes A and B can be made by antigenic differences in their hemagglutinin and neuraminidase glycoproteins. The external antigens are unstable and may undergo variation. In influenza A virus an abrupt variation may occur in one or both surface antigens, (antigenic shift). This antigenic shift is usually associated with a pandemic. Through the years Influenza A viruses have undergone several antigenic shifts and subtypes with surface antigens barely related to the original strain have been identified. Surface antigens may also undergo gradual changes (antigenic drift). Influenza B virus only undergoes antigenic drift. In this case variations among the new B variants and the older ones are not so extreme as to allow their classification as new subtypes.		A	Common cold with fever. Croup, Bronchitis, Pneumonia		Children or young adults	High	Epidemic in winter every 1-2 years (new subtype.
	3	B				High	Epidemic in winter every 3-5 years.
		C	Uncommonly febrile illness		Children	-	Endemic

Table 14

PREDOMINANT VIRUSES CAUSING UPPER ARI IN INFANTS AND CHILDREN

Characteristics of the Virus		Serotypes	Common serotypes producing illness	Common respiratory symptoms in target populations: Infants	Common respiratory symptoms in target populations: Children	Epidemiology: Source of infection	Epidemiology: Penetrability	Epidemiology: Usual manner of presentation
PICORNAVIRUSES — They are small (23-30nm), single stranded RNA viruses that do not have lipids. There are apparently 32 capsomers per virion. They are relatively stable at room temperature and multiply in the cell cytoplasm. Some differences in physical, chemical and biologic characteristics allow them to be classified in two genera: the rhinoviruses and the enteroviruses. There are two species within the enteroviruses that sometimes may produce respiratory instead of intestinal or neurologic disease (Coxsackievirus and Echovirus). The Rhinovirus primarily produces acute respiratory infection.	RHINOVIRUSES — They can be distinguished from the other picoruaviruses because they are inactivated at low ph (3.0), maintain their infectivity at 50°C and show optimum growth at lower temperature (33°C). This last fact is what determines the nasal mucosa as the primary disease site. These viruses are unable to cause agglutination of red blood cells, but are capable of inhibiting the spontaneous hemagglutination observed when human red blood cells are treated with trypson. Each one of the 113 serotypes described until now has a type specific antigen. These genera of viruses do not have any group specific antigen, but some cross reactions are consistently found among some of the serotypes. This allows the establishment of groups of rhinoviruses that are more antigenically related than others. It is possible that in the future many of the different serotypes will be found within a few closely related groups.	113	1-113	Common cold with or without fever		Children	Moderate	Endemic with peaks in autumn and spring.
	ENTEROVIRUSES — ECHOVIRUSES — They are characterized by the specific antigen present in the viral capside, Although there is not a common group antigen among them, heterotypic cross reactions can be detected. Twelve of the 32 echoviruses are able to agglutinate human red blood cells. The hemagglutin is an integral part of the virion, varying the optimal temperature of the reaction with the echovirus type involvad. Maximum titers are needed at 4°C for types 3, 11, 13 and 19; types 6, 24, 29, and 30 are more effective at 37°C, while types 7, 12, 20 and 21 are temperature independent.	32	4,8,9,11 19,20,22 25	Common cold		Children	High - Moderate in close populations	Endemic with summer or early autumn peaks.
	COXSACKIEVIRUSES — They are characterized by their higher pathogenicity in suckling rather than adult mice. In view of the lesions produced in suckling mice, they are classified in Group A (23 serotypes) and B (6 serotypes). Each serotype has a specific antigen that can be measured by complement fixation and neutralization. All group B and one group A serotype share a common group antigen. Group A serotypes do not have a common group antigen, but cross-reactivity among them is common. A virion antigen found in types B1, B3, B5 and A20 and A21 is able to agglutinate human red blood cells.	29	Coxsackie A 2,4,5,6,8, 10	Pharynigits without exudate		Children	High in closed populations	Endemic with summer or early autumn peaks
			2,4,5,6,8, 9,10,16,21	Herpangina				
			Coxsackie B 2,3,5	Pharyngitis without exudate				
CORONAVIRUSES — These viruses are round or eliptical with a diameter of 80-160nm. They have a lipid outer membrane and an inner nucleocapside containing a mol cule of single stranded RNA. Their main morphologic characteristic is their club-shaped surface projections which give to the virions the aspect of a solar corona. Human coronaviruses can be categorized in three antigenic types, B814, 229E, and OC43, by neutralization assay.		3	229E OC43,B814	Common cold with or without fever Less common.	Common cold with or without fever	Older children, Young adults.	Moderate	Epidemic, winter, early spring.

Table 15

CLINICAL SYNDROMES MORE COMMONLY PRODUCED BY ETIOLOGICAL AGENTS OF ARI IN CHILDREN

Etiologic Agent	Characteristics	Clinical Syndrome
Bordetella pertussis	Small, capsulated (when virulent), gram negative bacillus. Their complete antigenic make up is found in recent isolates (phase I, capsulated organisms with pili). Prolonged transfers in the laboratory lead to intermediate (phase II and III) and phase IV organisms in which virulence, capsule and pili are lost. Several antigens are shown by agglutinating reactions. They are genus, species and even strain specific. The pili has a hemagglutinin and the cell wall has a heat-stable and a heat-labile toxin that are also antigenic. Supernatant fluid obtained from recent isolates has a lymphocyte promoting factor (LPF) that induces lymphocytosis, a histamine sensitizing factor (HS), and a factor that is mitogenic for T lymphocytes. Protection seems to be confered by the hemagglutinin and a lypoprotein found in the plasma membrane which except for low agglutinogenic activities is lacking the other activities mentioned above.	Common cold, cold-like illness; upper respiratory tract infection coriza; Rhinitis; Rhinopharyngitis; acute catharral tonsilopharyngitis.
Corinebacterium diphtheriae	Gram-positive, rodlike organisms with club-shaped swellings at their poles that are arranged in palisades. Strains producing toxin are lysogenic, if they lose their specific phage they become relatively avirulent.	Acute tonsilopharyngitis with exudate and membranes; Acute laryngitis
Hemophilus influenza	When obtained from tissues these organisms are gram negative, small encapsulated cocco-bacilli. Isolates from the upper respiratory tract obtained from the normal population usually are non-capsulated (up to 50% of the children may be carriers). Capsulated strains possess polysaccharides that allow their characterization in six serotypes (a through f) by agglutination, capsular swelling (quellung test) or precipitation. The b type is the one most commonly found in the infections. This type is also the capsulated strain usually recovered from carriers. A somatic protein that is common to all types and an endotoxin resembling that found in enterobacterias have also been described as antigenic. The virulence of this organism is related to the presence of the capsule.	Common cold; cold-like illness; upper respiratory tract infection coriza, rhinitis, rhinopharyngitis, acute catharral tonsilopharyngitis; acute laryngitis, Laryngotracheobronchitis (croup); acute epiglotitis (croup); bronchiolitis; pneumonia.
Klebsiella pneumoniae	Gram negative, Capsulated bacilli that could be found in the respiratory or intestinal tract of 5 to 10% of normal individuals. They possess 5 (O) and 72 capsular polysaccharide antigens (K). Their virulence depends probably on their capsule as avirulent strains are lacking the capsule.	Pneumonia
Mycoplasma pneumoniae	They are very pleomorphic. The spherical ones may be 300-800nm in diameter, while the filamentous varieties have a diameter of 100-300 nm with a length of 3nm to 150 nm. Their morphological variations are related to the lack of a cell wall. The majority of the nine species that could be found in the respiratory tract are commensals. However, M. pneumoniae is able to produce pneumonia. The major antigenic determinants of M. pneumoniae are membrane proteins and glycolipids. The latter are haptens that cross react with glycolipids in human brain. M. pneumonia can attach to the surface of the respiratory epithelium by binding its tip to neuraminic acid receptors. Neither penetrates the cells nor goes under the epithelial surface. Cell damage is probably produced by release of hydrogen peroxide by the organisms.	Common Cold, cold-like illness; upper respiratory tract infection; coriza; rhinitis; rhinopharyngitis; acute catharral tonsilopharyngitis; bronchiolitis; pneumonia

Table 15B

CLINICAL SYNDROMES MORE COMMONLY PRODUCED BY ETIOLOGICAL AGENTS OF ARI IN CHILDREN

Etiologic Agent	Characteristics	Clinical Syndrome
Streptococcus pneumoniae	They are encapsulated, gram positive, lancet shaped diplococci that are characterized by their antigenic structure. The capsule has an immunologically distinct polysaccharide for each of the 83 types described. The somatic portion of the bacteria contains a characteristic M protein for each type and an R protein antigen and C carbohydrate that are species specific. The presence of the capsule is related to the pathogenicity of the organisms as is shown by the strong protection against the homologous type conferred by active or passive immunization with the specific polysaccharide.	Pneumonia
Staphylococcus aureus	Gram-positive cocci whose name reflects the grouping of organisms in irregular clusters. They have high salt tolerance and are among the hardest of all non-spore-forming bacteria. A few strains are capsulated. Other main antigens are a surface component known as Protein A that binds unspecifically to the FC portion of immunoglobulins and the polysaccharide A that is species specific. Extracellular enzymes such as a coagulaze, staphylokinase, nuclease, lypase and hyaluronidase are produced by these organisms which also have toxins like 4 different types of hemolysins, a leukocidin, an epidermolytic toxin and an enterotoxin.	Pneumonia
Hemolytic streptococci Group A	They are gram positive cocci that have been classified in relation to their hemolytic properties on agar blood plates (a wide clear zone of complete hemolysis). Further characterization in groups A through O is based on the immunological properties of a carbohydrate (C antigen) linked to the mucopeptid matrix of the cell wall. (Some groups have strains that are non-hemolytic. Strains belonging to group N are non-hemolytic.) Most human infections are caused by hemolytic streptococci that belong to group A (streptococcus pyogenes). Many strains of this group produce a capsule containing hyaluronic acid that is not immunogenic. Furthermore, they have in the cell wall a specific protein (M antigen) attached to the fimbria that allows classification of the group in more than 80 types. This antigen (as well as the hyaluronate capsule) is involved in the virulence of these organisms as they interfere with their phagocytosis by phagocytic cells. Two more protein antigens (T and R) are also present in the cell wall while the cytoplasmic membrane has a lypoprotein antigen. Unlike the M antigen, none of these is involved in stimulating protective antibodies. The body of the cell has a nucleoprotein antigen (P antigen) that cross-reacts with antigens found in the pneumococci and staphylococci and is common to the hemolytic streptococci. The group A streptococci produce several extracellular products, some of which induce antibodies that can be detected in humans recovering from the infection. The better characterized are Hyaluronidase, Streptokinase, Streptodornase, DNAase, DPNase, Streptolysins (O and S) and the erythrogenic toxin.	Febrile nasopharyngitis, acute tonsilopharyngitis with exudate or membrane; pneumonia
Hemolytic streptococci other than group A		Pneumonia

protection against infection or disease[113,115]. The finding that inactivated RSV stimulates cell-mediated immunity but does not provide resistance to the infection is an indication that this type of immune response may not play a role in resistance[118]. On the other hand, studies in volunteers suggest that resistance to RSV is related to the presence of local respiratory tract secretory antibodies[119]. However, this protection is incomplete; it could only be demonstrated by reduction in the severity of the symptoms after several reinfections.

RSV is recognized as a major pathogen for infants and children[120-125]. It is also considered a leading cause of hospital admissions because of lower respiratory tract disease[113,114,125] as well as a major contributor to hospital acquired infections among newborns and young infants[126-128].

RSV is worldwide in distribution[129] and in contrast with other viruses may cause sizeable annual outbreaks with an attack rate of 30 to 60% in exposed infants of less than one year of age [113,114]. Reinfection rates ranged from 8 to 41% per epidemic [130]. However, the fact that it spreads through respiratory secretion by person to person contact, and its high penetrability favor its persistence in the population. Those who escape infection during the first year of life will usually be infected during the second year or shortly thereafter.

Laboratory diagnosis

A precise diagnosis of RSV requires isolation of the virus from nasal or pharyngeal secretions by innoculation in Hep-2, Hela or primary rhesus monkey kidney cells. Although this virus is labile and may be preserved in transport medium, the best isolates are obtained when the tissue cultures are directly inoculated with the sample obtained from the patient. From two days to two weeks later, the characteristic giant cells can be detected. While immunofluorescence can be used to confirm the presence of RSV in the tissue cultures identification of a new isolate is made by CF or neutralization test with standard antisera.

Serology with the complement fixation test or the neutralization test is used to detect a rise in antibodies. However, in young infants, the normal serological response is poor, so the diagnosis will depend mainly on the isolation of the virus.

Although tissue culture or serological techniques are useful tools for diagnosis of RSV infection, it may take up to two weeks until the identification of the etiological agent is completed. A great advance in diagnostic capacity is provided by the use of the immunofluorescence test that allows a rapid diagnosis of the infection. For this purpose the indirect or direct FAT has been used[109,131,132]. A recent report showed that 94% of the samples that were negative by the FAT test did not yield virus growth in Hep2, W138 or rhesus monkey kidney cells. On the other hand, in 93% of the samples in which RSV was isolated by tissue culture the FAT test was positive[111]. The fact that in 6% of the samples the FAT detected infected cells while tissue culture did

not[111] may be explained by the higher sensitivity of the former method. Providing that the sample is transported promptly to the laboratory, it has enough exfoliated cells and is processed immediately after arrival, the diagnosis can be made in 4 to 6 hours.

Vaccines

Early work using inactivated RSV has shown that although vaccinated children had antibodies, they were not protected and could develop bronchiolitis when they underwent natural infection[133,134]. It has been hypothesized that an immunological phenomenon, either by augmented delayed hypersensitivity, an Arthus type immune complex deposition on the bronchiolar wall or an IgE mediated allergic reaction, may be responsible for the deleterious effect of previous vaccination on RSV infection [114,115,135]. An immunological phenomenon has also been suggested as playing a role in the RSV bronchiolitits produced in small infants who still had antibodies passively transferred from the mother. Several possibilities should be considered. Viral antigen, coupled with the mother-specific IgG may produce antigen-antibody complexes; maternal antibodies may have an immune-suppresant effect on the child's immune response to the virus, or previous inapparent infection may also act as a sensitizing stimulus, inducing an augmented immune response to a subsequent infection[115,136]

Vaccination with attenuated RSV administered through the respiratory tract has not been very successful up to this time. The degree of attenuation is variable and they are not very stable[137,138].

However, more research is needed on temperature susceptible mutants with the expectation that their temperature sensitivity would restrict growth in the target organ, the lung[138]. Recently, it was reported that parental administration of wild-type RSV grown in human diploid fibroblasts developed neutralizing antibodies in young children without causing symptoms of disease[139]. However there is no evidence that RSV given by the parental route may reproduce, nor that immuno-suppressive activity of passively transferred maternal antibodies might be overcome by this route of vaccine administration. Both aspects are important. If the virus failed to replicate it may act as an inactivated antigen that could potentiate the disease when further natural infection occurs. Furthermore, the greatest need for an effective RSV vaccine is in the first few month of life when maternal antibodies are still in the infant.

Another problem that may hamper vaccine development is the recent finding indicating the existence of antigenic variation in a new strain of RSV[140]. A longitudinal study in which children were followed for several years after natural infection or reinfection with RSV indicate what would be expected from vaccination to prevent RSV infection[117]. Immunity elicited by the first infection has a negligible effect on the attack rate of subsequent infections or severity of illness caused by reinfection one year later. However the third infections were less severe. Therefore, although vaccines would not protect the host against reinfections, they may have a beneficial effect on reducing the severity of symptoms in further infections[117].

Parainfluenza viruses

Clinical and epidemiological features

Four types of parainfluenza viruses may infect man[141]. They penetrate through[142] the respiratory route and multiply and produce inflammation in the upper segments of the respiratory tract and in some circumstances in the lower respiratory tract. Even in children most of the cases appear to be clinically inapparent. In infants and young children, however, they may cause symptoms that vary from mild upper respiratory infections to croup, bronchiolitis or pneumonia. At this age, these viruses are the second most common agents of lower respiratory infections only surpassed by the RSV[120,121,141,142]. The type of illness induced by parainfluenza viruses is not only related with the age of the host but with the type of serotype producing the infection. Primary infections produced by type 1 induce febrile illness in about 50% of infected children. Twenty-five percent may show symptoms of bronchopneumonia or pneumonia. Type 2 is less apt to cause severe illness but produced fever in 60% of the infections. Both types might produce tracheobronchitis in a low percentage of the patients (more commonly type 1). Type 3 produced fever in 80% of primary infections. One third of them with symptoms of lower respiratory tract involvement that characterize bronchitis and/or pneumonia. Type 3 has been isolated also from cases of croup. Infections with type 4 seem to be generally asymptomatic, when associated with illness, the symptoms are usually mild. Type 3 infections usually occur during the first months of life while infection by types 1 and 2 occurs after the 4th month[141-143].

The obvious implication is that passively transferred maternal antibodies may be effective to prevent infection produced by type 1 and 2 but not those produced by type 3[141]. Another possibility that should be taken into account is that an immunological phenomenon triggered by the presence of maternal antibodies and type 3 virus could be the origin of the bronchiolitis or pneumonia produced by this type of virus before the 6th month of life.

Primary infection by types 1 and 2 occurs in most of the cases after the first year of age. Three to four years later, more that 60% of the children have positive serology against these two serotypes. On the other hand, 50 to 60% of children reaching 1 or 2 years of age have been already infected by type 3. When they reach 4 to 5 years of age, positive serology is as high as 80 to 90%. Regarding type 4, serology is positive in 80% of the samples obtained from ten year old children[Rev.in 143].

Despite the fact that primary infection gives rise to neutralizing antibodies in the sera and local secretions of the respiratory tract[144,145], reinfection by parainfluenza viruses is common[141-143]. In these cases symptoms occur less often and are of lesser severity. The main source of protection from these viruses is local secretory IgA antibodies, but it decreased 1 to 6 months after the infection.

Worldwide, serological surveys and viral isolations indicate that parainfluenza viruses infect and are able to cause illenss in children[124,141]. In this age group they are also a cause of hospital acquired infection[146].

The fact that these viruses are not able to persist long in the environment, the high rate of infection and frequency of reinfections indicate that they spread by person to person contact. The higher penetrability was shown to occur for type 3[142]. All individuals in a semiclosed population can be infected in short time. In this regard types 1 and 2 are less effective.

In temperate climates the epidemic outbreaks with 1 and 2 serotypes usually occur in cold weather (fall and early winter) of every other year. One year type 1 is present and the next year type 2 would be responsible[141,143]. Small epidemics in cool months or in the rainy season have also been detected in some tropical countries[147-150], but not in others in which a rather endemic pattern of prevalence is seen throughout the year[124,151].

Laboratory diagnosis

The virus responsible for the infection can be isolated by culture of respiratory tract secretions on primary monkey or embryonic human kidney. Type 4 is the most difficult to isolate. Usually between 5 to 10 days after innoculation of the sample, viral growth can be recognized by hemadsorption of guinea pig red blood cells and specific serotypes may be further identified by hemadsorption inhibition techniques. Immunofluorescence is even quicker as it allows a diagnosis to be made in 24 to 72 hours. Determination of cytopathic alterations in the culture is of no value because they appear very slowly or are not detectable (except with type 2).

Detection of a rise in serum antibodies by hemagglutination inhibition or complement fixation titration can also be used for detection of infection. However, while the serologic response to the primary infection is homotypic, repeated reinfections in humans with one or more viruses of the gourp gives rise to a heterotypic response. Therefore, serology is not a reliable tool for identifying the infecting virus type.

Although the FAT test has been succesfully applied for the rapid diagnosis of viral antigens on infected cells obtained from respiratory secretions, its use is not yet widely spread[109].

Vaccines

Studies on volunteers have shown that the presence of serum neutralizing antibodies against type 1 virus is not related to protection. On the other hand, antibodies in the nasal secretions were critical in establishing whether the volunteer would be reinfected or not after challenge with the homologous virus type[144]. Therefore it was not surprising that either monovalent or polyvalent vaccines of formalin-inactivated virus, although able to induce high titers of neutralizing antibodies after parental innoculation, do not induce any obvious protection. On the other hand, vaccinated individuals do not acquire a more severe illness when subsequently exposed to a wild type virus. Experimentally, encouraging results have been obtained using live attenuated vaccines administered intranasally, but results on human trials are not yet available. The usefulness of a parainfluenza vaccine,

either comprised of killed or inactivated virus, would be measured by its protective effect on children. Specifically a vaccine against type 3 serotype should be given in the 1st month of life, and against type 1 and 2 from the 4th month on[143]. Establishing the safety of such a vaccine will not be an easy task.

Adenoviruses

Clinical and epidemiological features

Primary infections with adenoviruses usually occur in early life, infection being inaparent in most of the cases[114,152].This virus is probably responsible for up to 7% of ARI found in children[153]. It was shown that in adenoviruses confirmed cases of ARI 63% had mild upper respiratory symptoms, 10% pharyngitis/bronchitis, 3.4% croup, 8.6% bronchiolitis and 14% pneumonia[153]. Pharyngitis in young and older children, pharyngo-conjunctival fever as well as febrile illnesses with upper respiratory tract symptoms have also been associated with these viruses[121,152-154]. Further proof of the disease potential of the adenoviruses has been demonstrated in case-control studies during epidemic outbreaks[155], longitudinal studies in defined closed population groups[156], virus watch type studies in open communities[157] and clinical practice[153].

When the infection is not asymptomatic it is a self-limiting illness followed by a complete recovery and persistent type specific immunity. It is not clear, however, whether the infection terminates or becomes permanently latent. Neutralizing, hemagglutination-inhibiting

and complement fixing antibodies usually appear 7 to 10 days after infection reaching a maximum titer after 2-3 weeks. IgA and IgG antibodies may be present in the nasal secretions at the same time or shortly thereafter. Complement fixing antibodies decline in the third month after infection but can still be detected one year later. Titers of neutralizing and hemagglutinin-inhibiting antibodies persist for a longer time and they are related to the homotypic high resistance to disease and relative resistance to infection induced by this family of viruses.

Adenoviruses are distributed worldwide and as they are relatively stable in the free state, transmission may involve not only person to person contact but also indirect mechanisms. These viruses can be eliminated through feces, pharyngeal and conjunctival secretions. In abortive primary infections the virus is eliminated briefly through the feces. In the invasive type of infection the virus is intermittently shed through the feces and respiratory secretions for a long time. Renewal of viral shedding may represent a reinfection or a recrudescence of a latent infection.

Throughout the world, the most common serotypes associated with illness are, in order of importance, 2, 1, 3, and 5 [158]. However, in specific areas and seasons the frequency in which the different serotypes are found may not follow this order[151,153,159]. Serologic surveys in children have shown that in a given area as many as 80% of them may have antibodies[143]. Infections by types 1, 2 and 3 are frequent in one-year-old children, types 1 and 2 are less common in the group aged 5

to 9 years while types 5 and 7 are found in older children[157]. On the other hand other studies have shown different prevalence related with age[160-162].

Laboratory diagnosis

This can be done by serology or by isolation of the virus using human embryonic kidney or HEp-2 cells. Although a cytopathogenic effect can be seen as early as 48 hours after innoculation it may also take a much longer time. Complement-fixing titration using animal or human convalescent sera will permit the identification of the virus as an adenovirus by detecting the cross-reacting hexon and penton family antigen[166]. Further identification of the isolated virus can be carried out by establishing hemaglutinating capacity in rat or rhesus monkey red blood cells. After the grouping is made, the specific type can be assessed through the hemaglutination-inhibition assay. Detection of the family common antigen by the immunofluorescence technique on cells obtained from respiratory or ocular secretions is also a useful and rapid tool for diagnosis despite the fact that specific serotypes can not be identified by this method[109].

As adenoviruses can be excreted intermittently for a prolonged period of time and produce latent infections (50 to 80% of surgically removed tonsils and adenoids yield an adenovirus when cultured in vitro), isolation of a virus can not establish whether the infection is a new or a long-standing one. Therefore, a positive isolation does not exclude the necessity of a serological examination for detecting antibodies in

order to certify the etiology of symptoms. Titration of neutralizing antibodies on paired serum samples obtained during the acute and convalescent period of the disease are especially helpful for determination of the virus type responsible for the infection. Moreover, the hemagglutination-inhibition technique can also be used for this purpose. The complement fixation test that detects the cross-reacting common family antigen is less useful, as individuals may have antibodies to this antigen because of previous infection.

Vaccines

Vaccines to prevent adenovirus infection were first made to prevent respiratory illness in military recruits. The long lasting type of specific immunity induced by natural infection would suggest that effective means of preventive immunization could be obtained against these viruses. Early attempts were made with formalin killed 3, 4 and 7 virus types grown in monkey kidney cells. Although this vaccine was highly protective, different batches showed very irregular antigenicity. It was therefore replaced with a live vaccine cultured in human diploid fibroblasts to eliminate from the vaccine SV40 virus present in the monkey kidney cells and known to be oncogenic. This vaccine, containing the different serotypes responsible for ARI in recruits, is given orally in enteric coated gelatin capsules. The viruses colonize the intestinal tract giving rise to a highly resistant state similar to that induced by the natural infection.

Influenza virus

Clinical and epidemiological features

Symptoms produced during the acute infection by influenza viruses are related to the infection and destruction of ciliated epithelial cells that cover the upper respiratory tract, trachea and bronchi. Virus containing droplet enter through the nasopharynx and attach by the hemagglutinin spikes to susceptible host cells which have mucoprotein receptors. Although mucoproteins of the respiratory secretions may bind to the virus, the virus neuraminidase hydrolyzes and blocks their activity. During the infection, epithelial cells decrease their ciliary function, thus decreasing tracheobronchial clearance. Infected cells die and desquamate and debris and fluid tend to accumulate in the bronchioles. Experimental data suggest that a cytotoxic reaction between T. lymphocytes and cells with viral antigen might be also partially responsible for cell damage.

Respiratory symptoms are followed by fever, chills, headache, prostration and myalgia. These symptoms are difficult to explain as viremia is not a frequent event in influenza. It is possible that they originate in toxic products coming from viral components or a breakdown of constituents of dead cells absorbed into the bloodstream.

Usually the disease is self limiting and the patient usually recovers 5-7 days after the onset of symptoms[114]. Virus shedding decreases after the fourth or fifth day of illness and a correlation has been found between the quantity of virus shed and the degree of clinical illness[167].

Influenza A and B virus may produce symptoms of upper tract illness, croup, tracheobronchitis or pneumonia in infants and children. A recent report emphasizes that the importance of influenza virus as cause of disease in children has been underestimated because of the failure to appreciate the full spectrum of disease associated with this etiology[168]. During a 1975-76 epidemic in USA influenza A was associated with ARI even more commonly than RSV. Furthermore during a 3 year period, influenza was the most important cause of illness in children in ambulatory care [168].

Death caused by influenza is not frequent. When it occurs it is usually the result of a secondary bacterial pneumonia produced by streptococcus pneumoniae, staphylococcus aureus, Hemophilus influenza or B-Hemolytic streptococcus[114]. The increased susceptibility to bacterial infection in influenza patients may be due to a decrease in the polymorphonuclear cell function induced by certain viral strains[119].

Immunity against viruses of the same antigenic composition seems to be of long duration and is raised by symptomatic or asymptomatic infections. However, reinfections can be caused by variants with minor differences in antigenic composition. Immunity is mainly induced by the hemagglutinin since it can be restimulated by innoculation of this glycoprotein. The neuraminidase antibodies does not prevent infection but decreases viral spread and ameliorates the disease. On the other hand antibodies against the nucleocapside, although present, do not confer resistance[170].

Immunity is type and usually sub type specific. The serum antibodies against the hemagglutinin and neuraminidase are present in the host for years. When reinfection with the same subtype occurs symptoms are usually mild. Local IgA specific antibodies also appear after infection but they decrease in titer after one or two months despite high titers of serum antibodies. Probably, antibodies in the nasal secretions are the main cause of resistance to reinfection[170].

The degree of immunity will depend on the intensity of the original immune response to infection, reinfections stimulating an ananmestic response and probably genetic and other unknown host factors.

Influenza occurs worldwide. In the tropics it can appear at any time; in temperate climates from autumn to early spring. Influenza A outbreaks may occur annually, major epidemics every 2-3 years and pandemics at 10-15 year intervals. Susceptible individuals are of all ages. Type B epidemics appear with longer intervals between them (3-7 years) and the most affected are the child population, although older groups are also infected[Rev.in 143,171].

In general the attack rate varies from 10 to 30% for symptomatic cases and a similar rate for the asymptomatic ones. In crowded conditions the attack rate may reach 50 to 60%.

It is still not clear how influenza viruses are maintained in the community. One possibility for an epidemic situation would be that the virus may become latent in the human host after the illness disappears as such, and unknown factors may trigger its reappearance. On the other hand it is possible to hypothesize that viral dissemination happens

continuously but with a level of infection and viral shedding that remains below the threshold of detection. In the case of a pandemic like that produced by influenza A, it was thought that it may have been an expression of viral cycling. Its reappearance could be related to the accumulation of a new generation of susceptibles. The fact that in 1977 appeared a subtype that was common in the early 1950's tends to support the above mentioned possibility. How this virus remained dormant for 25 years is not known. Both isolated had essentially similar genome, thus there is no evidence that the 1977 subtype originated as a genetic reassortant. The possibility that the 1977 subtype came from animals or birds in which it had been circulating for years without antigenic drift is improbable. Furthermore, antibodies against the 1977 subtype had not been found in the animal or bird populations[143,170].

Laboratory diagnosis

The clinical and epidemiological pattern that characterizes influenza virus infection may suggest that these viruses are responsible for the infection. Although laboratory diagnoses are not employed in individual or sporadic cases, they are essential for establishing the presence of virus, which type is involved in the infection of the community, and also for epidemiological studies that permit constant surveillance. Determination of the prevalent strain and its accurrate antigenic characterization is of obvious value for vaccine preparation

Virus isolations can be made by inoculation of nasopharyngeal secretions, sputum or nasal or throat washings into the amniotic sack of

chick embryos 11 to 13 days old. After 2-3 days incubation, A and B virus can be detected in the amniotic fluid using guinea pig or human red blood cells or chick red blood cells for type C virus. Theoretically, it should be possible to isolate and identify an influenza virus in 48 hours, but in practice it may take a week or more before an isolate is obtained and identified, as it is necessary to undertake a blind passage of the specimen before a negative result is accepted.

As most of the persons already have influenza antibodies at the time of infection, results of serology are reliable only when an increase in the antibody titers is demonstrated in paired samples obtained during the acute and convalescent periods. Even in this case it can be easier to demonstrate a diagnostic rise in antibody than to isolate a virus from a single infected person. Only about one-third of respiratory specimens may yield virus, whereas 50-80% of paired sera usually exhibit a significant rise in antibody titers[172].

Providing that the non specific mucoprotein or protein inhibitors are eliminated from the sera to be tested, the hemagglutinin-inhibition (HI) is a very useful technique for serological diagnosis. Titration of neutralizing antibodies although useful in detecting a rise in titer is not widely used because it is expensive and time consuming. Although CF or HI tests can be run within a 24 hour period, there is a considerable time lag in making a serologic diagnosis since collection of acute and convalescent phase serum samples from the same individual takes 2 to 3 weeks. To minimize this time lag, serodiagnosis of an epidemic may be possible by comparing groups of acute and convalescent phase samples taken from different persons during the epidemic[173,174].

Detection of viral antigen in exfoliated cells obtained from nasopharyngeal secretions, nasal or throat washings, permits the rapid detection of influenza infection even when the patient has no clinical symptoms. The direct or indirect immunofluorescent technique used for this prupose allows diagnosis on more than 80% of the cases confirmed by viral isolation or serology[109].

Vaccines

Increased knowledge of the chemical and antigenic structure of influenza virus and application of up to date techniques of molecular biology has been especially useful in the development of more suitable influenza vaccines. The finding of chemicals able to release surface glycoproteins from the viral particle without affecting their antigenicity, the use of "high yield" influenza A reassortant viruses to produce seed strains for vaccine production and the obtaining of attenuated reassortants by genetic transfer are a few examples of how a more rational approach to vaccine development can be made.

Theoretically mass immunization against influenza would be able to prevent epidemics or at least decrease this spread. Until now attempts to obtain this goal have been incomplete. The existance of antigenic shift and drift in the influenza viruses made it necessary to immunize against those strains that are prevalent in the population. Vaccines in use are a mixture of several strains of A and B viruses in order to cover the known antigenic spectrum.

A reasonable aim would be to control epidemics through immunization of children[143,171]. This group of the population not only is an important link in the chain of transmission but has been shown to be more susceptible to influenza than previously thought[168].

There is much evidence indicating that a whole killed influenza virus vaccine administered by parental route is able to protect up to 70% of the innoculated population. However, as such vaccines can produce pyrogenic reactions with systemic symptoms (like mild influenza) as well as local reactions on the site of the innoculation, this vaccine has not been recommended for use in children. It has been given mainly to selected population groups, like the elderly or individuals suffering chronic or debilitating diseases, or other groups in which absenteeism may produce high financial losses or great disruption of critical public services[Rev.in 143,170,175].

Whole killed influenza vaccines are made from virus particles which can be disrupted by a treatment with detergents or organic solvents in order to produce a splitting of the particles without altering the HA or NS glycoprotein antigens. Split virus vaccines are less reactogenic than whole virus vaccines of similar antigenic content. However, they also are of lower antigenicity when innoculated in unprimed subjects. Further purification of the disrupted virus had led to the development of surface antigens vaccines that contain essentially the NA and HA antigens, almost free from non-immunogenic proteins and well tolerated in children[143,175].

Variants of influenza A virus used in inactivated vaccines are usually of a new genetic variant with an established strain in order to

ensure propagation of the newly emerged subtype to high titer. However, in some cases the wild type grows so well that making a genetic reassortant is not necessary. On the other hand methods for preparation of a high yield influenza B virus which often grows poorly has not been very successful.

Live attenuated vaccines are also used in order to prevent influenza infection. They are usually given by the intranasal route and are able to reproduce in the respiratory tract and to induce a local immune response. Obviously they may be eliminated into the environment and infect susceptible individuals. A potential problem may arise if the attenuated virus mutates and becomes virulent. To avoid this problem only genetically stable attenuated viruses of antigenic subtypes currently prevalent in the population should be used. Such vaccines have been proved to protect against influenza in interpandemic periods. However their possible use in a pandemic situation is not very clear. It would take up to one year to make enough vaccine and by this time the main pandemic wave would have passed.

Coxsackeviruses

Clinical and epidemiological features

A-B coxsackie viruses enter the host through the nose or mouth and local reproduction of the virus may induce symptoms in the upper respiratory tract (like the common). Certain group A viruses produce fever, sore throat, dysphagia and anorexia. At the beginning of symptoms

in these cases small papules are present in the throat but they become vesicles and ulcerate (Herpangina). Type specific antibodies may appear in the blood 7 days after infection, reach a peak in 3 or 4 weeks and decline thereafter. However, neutralizing antibodies can be detected for years. Resistance seems to be long lasting[176].

Serological surveys demonstrate that cocksackie viruses are widely distributed throughout the world. They spread by the respiratory route but fecal-oral spread also occurs. Epidemics usually occur in the summer and autumn. As the virus has high penetrability, up to 75% of the susceptible individuals may become infected in closed population. In different areas the prevalent types can be different, and moreover, the predominant type can vary every few years as the immunity in the population rises[176].

Laboratory diagnosis

To confirm the etiological diagnosis, viruses should be isolated from respiratory secretions by culture in human lung diploid fibroblasts and group identification is made by inoculation in suckling mice. Further identification of types is more cumbersome except for those types that agglutinate human red blood cells and can be identified by hemagglutination inhibition. To identify group A types, first neutralization titration can be carried out with pools of type specific sera, then individual type specific sera are used in order to make the final identification. Serological confirmation of infection can be carried out by neutralization, complement fixation, immunofluorescence or hemagglutination-inhibition titration[176].

Echoviruses

Clinical and epidemiological features

These viruses probably enter the respiratory tract by the oral route. They reproduce locally, inducing symptoms of the common cold. The types more commonly associated with ARI are 4,9,11 and 25[177].

Epidemiological features of the echovirus resemble those of the cocksakie viruses. Immunization does not seem to be a practical measure to prevent the infection because of the large numbers of serotypes involved[176].

Laboratory diagnosis

Throat secretions innoculated in rhesus monkey cells allow isolation of all serotypes. Some types grow also in kidney cells of patas monkeys. This is a valuable property that permits further identification of the isolated type. The hemagglutinin activity on human red blood cells of the different types can be also used for preliminary grouping, but neutralization titrations have the final word in the identification process[176].

Serology on paired samples can be used for detecting antibodies and certifying that an echovirus is responsible for the infection. However, this is expensive and time consuming as, at least theoretically, all the virus serotypes should be tested with the serum samples[176].

Rhinoviruses

Clinical and epidemiological features

These viruses enter humans, the natural host, through the respiratory tract mainly the nasal mucosa[176]. The infection is locally confined and is recognized as the single most important cause of the common cold, the most common viral respiratory disease in man[143]. From 3 to 8 days after onset of symptoms the virus can be isolated from the nasopharyngeal secretions[178]. Infections are able to stimulate production of serum neutralizing antibodies, but titers are low[179,180]. Although neutralizing antibodies may have a beneficial role, resistance to infection depends mainly on nasal secretory antibodies[181,182]. As immunity is type specific and many serotypes are available to infect man, multiple infections occur during a life time.

Rhinoviruses spread probably through infective aerosols and through fingers and hands[143,176,183]. The infection is geographically widely spread although the prevalent serotypes may differ in one area to another. Multiple types may circulate with no explanation to why they appear or reappear. Moreover in a given area, some types are endemic and others sporadic. Infections may occur continuously but seasonal peaks in the autumn and spring are common[143]. Rhinoviruses have high penetrability. The overall rate of infection in adults was shown to be up to 0.77 per person-year in different studies, and somewhat higher in infants and children[143,180,184].

Laboratory diagnosis

Isolation and identification of rhinovirus is not simple. Cell cultures of human embryonic nasal or tracheal cells are especially useful for primary isolation, but they are not very practical for routine diagnosis. Some strains multiply only in human cells (H strains) while others multiply also in monkey cells (M strains)[13, 17, 18]. However, isolation can be accomplished if primary embryonic human kidney cells, human lung diploid cells or a special line of Hela cells (H) are used at 33 C. Cytopathic effect in positive culture is slow to develop and is usually incomplete. Ether resistance and acid lability help to identify the isolates as rhinoviruses. However, neutralization- titrations should be used for type identification of the isolate. Because of the high numbers of serotypes, neutralizations can be made first with pools of sera containing antibodies against groups of serotypes. When the possibilities have been narrowed, further identification is also done by neutralization using standard sera against specific serotypes. Because of the existence of multiple serotypes, serological diagnosis is not very practical for routine work. Even using tissue culture and serology, up to 20% of the infections are not detected[180].

Serological surveys indicate higher contact with the virus with increasing age[143]. Studies on defined populations such as schools showed an attack rate up to 77 percent[143,185]. Moreover they suggest that infants and children play an important role as introducers of the infection into the family setting and in the spread of the virus in the community[143]. The acquired infections can be symptomatic or

inapparent[176]. Although the introducers health is an important factor in determining whether the infected contact will get clinical symptoms (70% of the infections acquired from all introducers were symptomatic versus 13% from unapparent cases)[180], the age, the serotype, genetic and environmental factors also play a role.

Vaccines

Early vaccination attempts with an inactivated type 13 vaccine on volunteers showed that some protection could be conferred with intranasal but not intramuscular innoculation[181,186]. It is possible that by using live attenuated vaccines by the former route, more protection can be obtained. However, rhinovirus strains may not completely lose their infectivity[187] and there is no guarantee that they will not increase it after human innoculation. The large number of serotypes that may cause the infection will necessitate the inclusion of several serotypes in the preparation although the existence of immunological cross-reactivity among strains may lessen this problem of strain representation[176]. However, there are indications that antigenic variation may occur[188]. Perhaps, as a result of dual infection that is fairly common, genetic reassortant variants may be originated. This finding may hamper the future development of vaccines.

Coronaviruses

Clinical and epidemiological features

These viruses are responsible for common cold like illness in children and adults. Studies in intranasally innoculated volunteers

indicate that the viruses multiply in the superficial cells of the respiratory tract and virus shed can be detected in the respiratory secretions. Symptoms are related to the upper respiratory tract (coryza, nasal congestion, sneezing and sore throat) and less commonly headache, fever and cough occur with or without muscular pain[189,191]. However, there are evidence that the clinical illness with which they could be associated is not restricted to upper respiratory infection[192]. The disease is self-limiting - about 7 days. Clinically the infection cannot be distinguished from that produced by rhinovirus, or with a mild infection by influenza virus. As a response to the infection neutralizing and complement fixing antibodies appear but the latter decline more rapidly from the circulation[190,191].

Coronaviruses are apparently transmitted through the respiratory route. They are probably responsible for about 20% of common cold-like illnesses. Inapparent illness may occur in 50% of those infected. Outbreaks tend to appear late in autumn, winter and early spring with a single immunologic type as the responsible etiological agent. Serological studies showed that 3% and 0.4% of colds in winter and autumn respectively were caused by this virus. The mean annual incidence ranges from7% to 15%. Antibody prevalence increases from 50% in three year old children up to 70% in adults.[143,190,191].

Laboratory diagnosis

Isolation of coronavirus is not within the scope of a routine diagnostic laboratory. Some strains, like the prototype 239E can be

isolated in human embryonic cell cultures and represent a characterized subgroup within these viruses. For isolation of the other subgroup of strains, organ cultures of human trachea or lung are needed(OC strains). Some of them have been further adapted to growth in monkey kidney and human cell. For serology the complement fixation test is a practical assay, while the neutralization test is difficult and very expensive .

Common bacterial aeteological agents responsible f~r ARI

Mycoplasma pneumoniae

Clinical and epidemiological features

This organism is the etiological agent of the majority of cases previously labelled primary atypical pneumonia. Besides that, it may produce inapparent infections, mild upper respiratory tract infections, bronchitis, bronchiolitis, bronchopneumonia and myringitis bullosa. Infection by M pneumoniae is infrequent in infants of less than 10 months. Symptoms of pneumonia are usually mild and do not correlate well with the signs found by physical examination. Illness is commonly confined to the respiratory tract and few fatal cases have been reported[114,193-196].

The infection gives rise to serum antibodies (IgM first and IgG later on) that can be detected by IFA complement fixation, growth inhibition or cell lysis in the presence of complement. Longitudinal studies open doubts whether these antibodies are or are not protective as

individuals with positive titers were able to develop pneumonia. However, early studies on vaccination in volunteers seem to demonstrate that protection is coincident with the presence of serum antibodies. On the other hand specific IgA in respiratory secretions seems to have a role in host resistance[196].

Anti-mycoplasma pneumoniae antibodies may appear in children 2-5 years of age while disease is usually seen in older children. It has been suggested that the pathogenesis of the disease originates in the host immune response sensitized by previous infection.

Serological surveys indicate that mycoplasma infections are fairly common. Its peak incidence is in older children and young adults and in this age group accounts for 15 to 50% of the pneumonias observed. In most areas the infection is endemic but it appears more commonly in late summer and autumn. The organisms spread by person to person contact, are mainly introduced into the household by school age children and have low transmission potential[193-196].

Laboratory diagnosis

Confirmation of a clinical diagnosis can be made by isolating the organism. For this purpose nasopharyngeal secretions are innoculated in Mycoplasma broth on top of agar. The broth should be subcultured at weekly intervals for a period of eight weeks in mycoplasma agar. The colonies are circular, partially imbedded in the medium, with a granular surface but without the peripheral zone observed with other mycoplasmas. Confirmation of the identity of the isolate is made by staining the

colony with fluorescent labelled antibodies[196]. This method is quick, specific and allows identification of different species that could have been present in the specimen. Although CIE has been used to detect Mycoplasma antigen in sputum as a rapid method for diagnosis, more experience is needed with this technique[197].

The complement fixation test is useful for serology. The infection is demonstrated when a fourfold rise in antibody titer titer is demonstrated during the convalescence. Detection of antibodies in one sample only is useless for diagnosis as high titers may persist for several months after primary infection[195-196]. Detection of cold agglutinins is not specific as the test can be also positive in several other pathological conditions. Moreover, some of the patients with proved M. pneumoniae infection are negative[114,196].

Vaccines

Results of field trials using inactivated M. pneumoniae vaccines have been encouraging[196,198] and these have been attempts to use attenuated mutants[187]. However, the finding that febrile illness accompanied by pneumonia occurred in recipients of vaccine which failed to produce detectable antibodies, as well as the possibility that lesions induced by M. pneumoniae in the lung result from an immune reaction, suggests that further work should proceed with caution[196,199].

Streptococcus pneumoniae

Clinical and epidemiological features

Although pneumococci are commonly found in the upper respiratory tract[200,201], pneumococcal pneumonia is not more common probably because of bacterial antagonism limiting the growth of pneumococci in the pharynx, difficulties encountered by the bacteria in overcoming the epiglottis, and the normal pulmonary defence mechanisms. However, pneumococci produce disease through their ability to multiply in the tissues plus several other predisposing factors such as a) the presence of viral respiratory infection, b) bronchial obstruction and atelectasia, c) alteration of the mucociliary function, d) pulmonary congestion, or e) splenectomy accidental or natural as occurs on sickle cell anemia. When the disease occurs, a fibrinous edema fluid is poured into the alveoli, followed by red cells and leukocytes. This results in the consolidation of the affected part of the lung. Mononuclear cells phagocytize the debris and the pneumococci, which are intracellularly digested. The fluid is then reabsorbed. A fatal outcome may occur when pneumonia is complicated with bacteriemia that is detected in 10 to 50% of the cases. The nature of the injury and physiological changes induced by the infection are not yet clearly understood, and the tissue lesion may not be reversed by anti-microbial therapy [202-205].

Since the introduction of sulphonamides and antibiotics, mortality produced by St. pneumoniae has sharply decreased. However there is a complete lack of evidence that morbidity has been reduced[203,204].

Penicillin is still the antibiotic of choice for treatment of pneumococcal infection[114]. However, these organisms have been shown to be resistant to tetracyclines, Erythromycin, Lincomycin and Clindamycin. Strains relatively insensitive or resistant to penicillin and chloramphenicol have been also recovered from infected patients. Furthermore multiple resistant strains have been detected. Spreading of resistance to a single multiple antibiotic would be a burden difficult to overcome and would lead to the necessity of routine testing of antibiotic sensitivity for the isolated strains[Rev.in 202].

About one week after infection anticapsular antibodies can be detected in the serum and they can account for the recovery that appears in 70% of untreated cases. They have a potent role as opsonins and activate complement by the alternate pathway setting in motion an early defensive mechanism of the host. Following recovery, antibodies can be detected for months. However, pneumococci continue to be carried for days or weeks and even chronically when the patient has persistent sinusitis. A new attack of pneumococcal disease, when it occurs, is due to a different type of pneumococci[200-203].

Pneumococcal pneumonia accounts for approximately 80% of all bacterial pneumonias. Development of disease is more related to the existance of the predisposing factors than to the exposure to the pneumococci. Even in the USA pneumococcal infections are still an important cause of community acquired pneumonia (0.5 million deaths per year), and a common etiological agent of otitis media affecting at least 25% of children up to 2 years of age (one million cases per year).

Pneumonia of this aetiology is a leading cause of hospital admissions in developing countries[201,203-205].

Laboratory diagnosis

Although a direct gram stain of the sputum can determine the presence of pneumococci, this finding can be difficult to evaluate because several organisms of the normal flora can resemble pneumococci. Despite the fact that it would be possible to identify the pneumococci because of the swelling of the capsule (quellung test), this does not answer the question of whether or not the bacteria is in the lung. Pneumococci can easily be found in normal individuals[200-205]. Conversely, a sputum culture that is negative for pneumococci does not rule out pneumococcal pneumonia[206].

To establish pneumococcal pneumonia by quantitative sputum culture is not a very reliable method either[207,208]. Previous antibiotic therapy, inadequate transport or overgrowth of commensals may be responsible for an unsuccessful isolation in the respiratory tract secretions even when there is bacteremia[204,206]. On the other hand although a positive hemoculture is diagnostic, bacteremia is only detected in a fraction of the cases[203,204,206]. Furthermore, detection of serum antibodies is not a practical method for diagnosis. The above is an indication of the different factors that may complicate the diagnosis of pneumococcal infections in individual cases and may underestimate the incidence of the disease in epidemiological studies. In recent years attempts to detect antigens in the sputum, nasopharyngeal

secretions, pleural fluid, blood and urine and lungs by CIE has been successfully accomplished[Rev. 206]. This method may differentiate between the carrier state and pneumonia and is positive in cases in which previous antibiotic chemotherapy made the sputum negative[206]. Moreover, COA and LA has been also used with success for detection of St pneumoniae antigens in body fluids[77].

Vaccines

Early attempts to induce protection in man against pneumococcal infection by innoculation with capsular polysaccharides were successful in preventing pneumonia. Protection coincided ith the appearance of type specific antibodies which may persist for several years. Although mild local and systemic reactions were observed after vaccination, further trials also confirmed the protective activity of the vaccine[Rev.205,209,210,211]. As immunity is type specific, the vaccines should have the most common types found in the area where it is going to be used. Results on vaccinated children older than 2 years with sickle cell anemia were encouraging[212]. Curiously, the poorest responses are to pneumococci of those types that most commonly infect children[209]. Therefore until further studies are made and increased immune response against certain serotypes is obtained, vaccination attempts in children should be restricted to those such as sicklers in whom previous pathological conditions predispose to pneumonia[211].

Streptococci

Clinical and epidemiological features

Streptococcus pyogenes in the upper respiratory tract is a common cause of acute pharyngitis with or without scarlet fever. Often this is complicated by supurative lesions on the surrounding area including cervical adenitis, otitis media, mastoiditis, peritonsillar abscesses and pneumonia. The invasiveness of this organism is related to the antiphagocytic properties of the M protein and hyaluronic acid capsule. Although antiboides against M. protein have been shown to be protective and may persist for 2 years or more, the number of different types precludes individuals from becoming immune to respiratory infections by group A streptococci.

Streptococci are transmitted from a person harboring these organisms usually through droplets from the respiratory tract. The incidence of pharyngeal and tonsile infections varies widely in different geographical areas being more frequent in temperate than in warm climates. They are most common among 6-12 year old children, and often appear during the late winter and early spring. Carriers are no more than 10% of the population. This percentage increases sharply before outbreaks[114,213].

Laboratory diagnosis

Diagnosis is made by isolation of the streptococci in culture. Alpha hemolytic streptococci are also usually found in throat culture, but they are associated with bacterial endocarditis instead of local

infection. On the other hand, strains belonging to groups C, F, H, K and O may be hemolytic and could be found in the upper respiratory tract with or without mild respiratory infections. Therefore, streptococci isolated from blood agar showing B hemolysis could be tentatively characterized as group A because of their sensitivity to bacitracin[213].

Group determination of the isolates is more appropriately made using specific antiserum. For this purpose the direct IFA test is very useful and shows results comparable to those obtained by the Lancefield precipitation test. Although the same technique can be used directly in specimens obtained from throat swabs, results have not been so reliable and it is not recommended. IFA for identification of isolates in culture is rapid and can be made in culture broth innoculated with the throat swabs. Results may be obtained from two to 24 hours after innoculation. Another technique available for grouping that also uses streptococci growth in culture broth is the CIE[214]. With this technique results are obtained within six hours after receiving and innoculating the swab. The COA also has been successfully used for grouping B hemolytic Streptococci on blood agar plates[215].

Detection of antibodies in the patient's serum is conveniently done by the antistreplolysin O test.

Bordetella pertussis

Clinical and epidemiological features

In nature these organisms are found only in man. They preferentially adhere to ciliated bronchial and tracheal epithelium where

they quickly multiply. Disintegrated organisms liberate their toxic products, injuring the cells lining the surface and causing catarrhal symptoms. Although B. Pertussis causes a surface infection and organisms below the mucosa are rarely seen, local subepithelial inflammation and necrosis occurs. This can be followed by peribronchial inflammation and intersticial pneumonia. Secondary bronchopneumonia produced by Staphylococcus or H. influenza is common[114,216].

The incubation period is about two weeks. At this stage symptoms are those of a benign nasopharyngeal infection. These are followed later on by the characteristic whooping cough indicating lower respiratory tract involvement. After the third week of infection antibodies against phase I B. Pertussis can be detected in serum by agglutination, precipitation or complement fixation test. Immunity is long lasting but not permanent. When reinfection occurs symptoms are usually mild[114,216,217].

Whooping cough is endemic all over the world. Epidemic outbreaks may also occur. Transmission is largely by aerosols. The source being a patient in the early catharral stage. Communicability is high with an attack rate as high as 90%. Children of less than five years of age are the most affected group and mortality is almost confined to children less than one year of age[216,217].

Laboratory diagnosis

Diagnosis is made by isolating the organism in Bordet Gengou media innoculated with material obtained through a nasopharyngeal swab.

Passing the swab through penicillin solution before streaking the agar prevents growth of other organisms without affecting B. Pertussis. After 2-3 days at 37 C the small, pearl-white, glistening colonies can be observed. Final identification is made by agglutination with specific antiserum or by IFA technique[216].

A rapid method for identification of B. Pertussis is the use of a direct IFA test on samples of nasopharyngeal smears[100-103].

Vaccines

A vaccine prepared by killed phase I organisms or a crude extract prepared from them is highly effective, although may produce undesirable reactions[218]. Vaccine failures are related to preparations of low potency or antigenic differences between the vaccine strains and those producing infection[216].

Hemophilus influenza

Clinical and epidemiological features

Naturally acquired disease by H. influenza seems to occur only in man. The infection begins with symptoms of nasopharyngitis that can be followed by sinusitis, otitis media, and sometimes pneumonia which could be complicated with empiema. If bacteriemia appears it could lead to development of meningitis. Uncommonly it is a cause of acute epiglotitis and laryngitis[114,216,219,220].

Susceptibility to H. influenza infection is inversely related to the existence of serum antibodies. Therefore neonates are well protected

by serum antibodies passively transferred from their mothers. Antibody titers in children begin to rise again when they are three years old, therefore the highest susceptible group are those aged three months to three years. Although antibodies and complement are able to lyse these bacteria, antibodies have another crucial role as they opsonize the bacteria and favor phagocytosis[216,221].

H. influenza type b, the most commonly found in the infections, is transmitted by person to person by the respiratory route. Epidemic outbreaks are rare. Although most children have acquired effective immunity at age 10, in children of less than three years it is still a problem[216,219-220].

Laboratory diagnosis

Confirmation of the diagnosis is made by isolation of the organisms in agar chocolate (in 5% CO_2 environment). Isolated organisms are submitted to a quellung test and for their requirements for X and V growth factors. Rapid tests by detection of antigens in secretions and body fluids have been successfully carried out by CIE, LA and ELISA[77,91].

Vaccines

Immunization with the polysaccharide antigen induces the same antibody response as the infection[221]. Antibodies can even be produced by E coli, which has a polysaccharide cross reacting antigen with H. influenza[222]. Although studies are being carried out on the

possibility of using it as a vaccine, young children who are the most susceptible group, do not elicit a good immune response[223]. Attempts are being made to increase the immunogenecity of the carbohydrate antigen by coupling it with proteins[223].

8. TREATMENT OF ACUTE RESPIRATORY INFECTIONS

There are some of the respiratory infections such as whooping cough and diphtheria which can be prevented by immunization and the possibility of preventing some forms of respiratory disease by vaccination has already been discusses. From the previous data shown on the environmental factors related to respiratory infection it is clear that some of them can be avoided or minimized e.g. parents can avoid smoking. This section however deals with the established respiratory infection and methods of managing it. Two basic approaches will be taken: - The perspective of the well defined clinical syndrome and the perspective of the site at which care is given: the persons and facilities available to give it.

Treatment of the established clinical syndromes

The assumption is made that there are competent well trained personnel and diagnostic facilities to allow the clinical syndrome to be defined. The classification followed is the same as that given in Section 5. No details of treatment regimes such as drug dosages are given since in most cases they are standard and well discussed in most good pediatric texts.

Acute nasopharyngitis

There is no specific therapy for the common cold which is the most frequent cause of nasopharyngitis. The basic aim is to keep the child comfortable and a series of general supportive measures are indicated especially in the young child under the age of one. Special attention should be paid to the following:

Nutrition:

There are three basic reasons for impaired feeding during episodes of nasopharyngitis. Acute nasal obstruction causes mouth breathing and especially in the child who is on the breast, this makes feeding very difficult. The second reason is the anorexia which is a normal accompaniment of infection at any age. Finally, in ithe older child, a sore throat per se may contribute to decreased intake. We have already mentioned the relationship between nutrition and infection and especially in situations in which food intake is marginal at best, special care must be taken to coax the child to feed.

Fluid intake:

Fluid requirements are increased during the acute phase, partly because of increased insensible loss resulting from tachypnoea and mouth breathing and also as a result of pyrexia. The child must be encouraged to take teas, juices or whatever appropriate fluid is available. Unfortunately, at this stage when there should be increased intake, the child is often reluctant to drink for the reasons mentioned above.

Fever:

This is important per se mainly because of the anorexia and increased catabolism which it induces.

Nasal drops can be recommended (phinylephrine 0.12%) to relieve obstruction but it is always stressed that these should be short acting. Some clinicians prefer to utilize mechanical suction rather than recommending nasal drops on the ground that the latter may cause infection to tract down to the lower respiratory tract. There is general agreement that antibiotics are not indicated but one study showed that as many as 37% of a group of family physicians would prescribe them for a child with rhinorrhorea and a low grade fever as the only abnormal features[224]. The misuse of antibiotics probably results from parental pressure as well as a genuine misconception that bacterial complications would supervene and can be prevented by early administration of antibiotics.

The most common complications of acute nasopharyngitis are otitis media and sinusitis. Although viruses cause otitis media in a number of cases, because it is impossible to distinguish clinically otitis media caused by viruses or bacteria, antibiotics are given as soon as the diagnosis is made. The initial antibiotic is usually ampicillin or amoxycillin and a ten day course is recommended. Most children get rapid relief of symptoms within 48 hours and failure to respond is sometimes due to bacterial antibiotic resistance. In a bacteriological study on samples taken at tympanocentesis from children who had otitis media unresponsive to initial antimicrobial therapy after 36 hours,

approximately 60% had sterile fluid, 20% had bacteria which were sensitive in vitro to the prescribed drugs and only 20% had resistant bacteria[225]. The authors point out that 36 hours is probably too short a period of therapy to guage efficacy: persistent symptoms and signs should lead the physician to consider tympanocentesis in order to arrive at the appropriate antimicrobal therapy. In practice however, it is probably more realistic to switch therapy to cotrimoxazole before proceeding to middle ear aspiration. Ampicillin or amoxycillin are also appropriate initial antimicrobial therapy for acute sinusitis along with a nasal decongestant to promote drainage from the affected sinus.

Acute Pharyngotonsillitis

Viral and bacterial causes cannot be distinguished easily. If there are systemic symptoms then oral penicillin V is usually given and the temperature and symptoms may show marked improvement in 36 hours. Some clinicians prescribe aspirin initially and would assume that failure to respond is indicative of a bacterial infection for which antibiotics should be prescribed. The major reason for urgency in treatment of acute tonsillitis is to prevent the sequelae of rheumatic fever in cases of streptococcal infection. Erythromycin or cotrimoxazole are alternatives to penicillin.

Acute laryngitis

The critical therapy in this situation is relief of respiratory obstruction. The inspiratory stridor and hoarseness, if mild, can be

treated initially with inhaling steam. However, any sign of increasing distress should prompt hospitalization, oxygen therapy and intubation if necessary. In several cases, especially when it is not clear if bacterial acute epiglottitis is present antibiotics are also given - most often ampicillin. Neither steroids nor alpha adenergic drugs have been shown to be of benefit[49,226]. Acute croup can be a medical emergency requiring treatment in an intensive care unit.

Acute bronchitis

Acute bronchitis is usually a viral infection and does not require anything but supportive therapy. Occassionally acute bronchospasm occurs and sympathomimetic amines may have to be used.

Brochiolitis

Because bronchiolitis, especially in infants less than one year, is most often viral, antibiotics are not indicated. Air trapping and hypoxaemia are the worst features of this entity[227] and oxygen is the mainstay of therapy. If there is progressive hypoxaemia then positive pressure ventilation is the therapy to be used[48].

Pneumonia

In addition to the supportive measures mentioned above, the mainstays of therapy are oxygen and the appropriate antibiotic. The appropriate initial antibiotic therapy can only be based on the epidemiology of pneumonia in the local setting. In North Carolina, for

example, the great majority of cases with pneumonia are due to viruses or mycoplasma pneumoniae. Unfortunately there are no clinical signs to indicate the aetiology on presentation and initial therapy is based on a best guess until specific microbiological data are available. On the contrary in New Guinea when there is lobar consolidation the child usually has infection with Streptococcus pneumoniae or H. influenzae and penicillin is the logical first line of therapy[1]. If there is no response, then Chloramphenicol is probably a good second choice.

Treatment taking account of site and facilities for care. Primary health care. In the majority of the countries in which ARI is a problem, the facilities and services are not available to allow the precise diagnosis to be made by highly trained professionals early in the course of the illness. In these countries, the following considerations are central to the development of any plan for managing ARI -

- the role of the family in recognition of and first line therapy for the disease syndromes

- the structure of the health services - what proportion of the care outside of the home environment is administered by what level of health care worker

- the fact that primary health care is the basic strategy for reaching all population groups

- the local ARI disease pattern in terms of the types of clinical syndromes which attack children of defined ages with specific seasonal variation.

The commonest approach to management strategies for ARI is the development of decision trees whereby various symptoms and signs are given as indicators of certain courses of action which need to be taken. It is not always clear from these decision trees what information should form critical decision points for families. It is recognized that many families bring ill children into the health care system far too late, thus some emphasis has to be placed on the information to be given to the family as to which are the critical symptoms which indicate that attention must be sought. Thus, family health education becomes the first important aspect of the management of ARI and we need more specific algorithms to take account of the steps to be followed by the family in the early stages of ARI.

We have mentioned the simple supportive measures to be taken for mild nasopharyngitis and in other syndromes. Some of them will have to be modified for use in homes, especially poor homes. It is dangerous to recommend the use of steam, and a humid atmosphere can be produced more safely by hanging wet towels around the bed or in the room.

It is not enough to place the burden of care on the mother. Appreciation of the importance of the symptoms of ARI should be a matter of common health education. In many countries, much of the care of younger children is in the hands of older siblings. Morley points out that programmes such as "child to child" may be used to give older children basic information about child care[228].

Figures 1-4 show algorithms devised by different groups as decision guides for management of ARI[1,229-231]. The tree developed

in Geneva (Fig. 2) gives a group of eight symptoms and it is indicated that a combination of these indicate respiratory infection. No indication is given of the relative importance of the various symptoms. The first critical point is the presence or absence of rapid breathing. In the scheme developed in New Guinea (Fig. 1) the important symptom for entry is cough with tachypnoea again being the first critical point. In the scheme from Brazil (Fig. 3), fever along with cough and dyspnoea represent the key symptoms for diagnosis of severe ARI. It immediately becomes apparent that every locale will of necessity have to modify a basic decision tree or develop its own.

There are minor differences in the cut off points for tachypnoea. Riley[1] proposed that a respiratory rate over 40/min was a cause for initiating therapy with antibiotics. It is not clear what was the real basis for a choice of 40/min. His criteria for a selection into the "severe" category were: a) a respiratory rate of 55 or more on admission in infants less than one year of age; a rate of 45 or more in children 1-4 years of age or a rate of 40 or more in children 5-9 years of age. b) in addition, one or more of the following signs: intercostal indrawing of soft tissues, flaring of the alae nasi, diminished percussion note, crepitations, rhonchi or bronchial breathing. In the Brazilian protocol to be used in peripheral health services, the important respiratory rates were over 40/min in children over one year and over 50/min in children under one year.

Thus in health services in which semi-professional personnel are the first point of contact with the supposedly ill child, less attention

has to be paid to the nature of the clinical diagnosis than to severity of illness[232]. It is of little interest at the primary care level if the child has bronchiolitis or lobar pneumonia. The only clinical diagnosis mentioned in the management scheme from New Guinea is heart failure and the basis on which that diagnosis is made is simple indeed.

It is common to all the decision trees that once a diagnosis of severe respiratory tract infection is made, penicillin is the drug of choice. This advice is given in ignorance of the prevalence of the various types of respiratory pathogens in the different parts of the world. In Papua New Guinea lung aspirates and blood cultures were taken from 70 children with pneumonia and H. influenzae and Streptococcus pneumoniae were the commonest pathogens[233]. On this basis, plus assumptions about patiant compliance, it was suggested that procaine penicillin for 3 days was an appropriate form of therapy. In a study from Egypt[234] in which lung puncture was also used, organisms were obtained in 79% of cases and the pneumococcus was only the fourth commonest cause of pneumonia, with H influenza first, and staphylococcus second. Analysis of 100 samples from Costa Rica showed that in those cases of pneumonia with pleural effusions staphylococci were as common as pneumococci. In the cases as a group, staphylococci were the commonest organisms in the first six months of life[235].

If children at the primary care level do not respond to penicillin as an outpatient - if there is stridor or cyanosis or indrawing of the chest then referral to a hospital is appropriate. In hospital, the appropriate clinical diagnosis would be made and therapy carried out

appropriately. Even in the hospital, the local epidemology of ARI is essential at least for the initial decisions about therapy.

Simple treatment programmes for ARI based on inservice training for auxiliary workers can be shown to reduce mortality from pneumonia[232]. It is essential however to establish the kind of procedures which make results readily available to be fed back to the workers and the community.

A group of experts met in Geneva in 1980 and discussed the use of flowcharts in the management of ARI and agreed that it was essential to observe the following procedure[230]:

1) Start using the chart under field conditions in a number of selected health institutions at different programme levels and in different parts of the country, in order to adapt the prototype chart to prevailing conditions. With the help of the flowchart it should be possible for health workers to identify the optimal management strategy: what care is required immediately, the place and type of treatment, and follow-up required according to the outcome of management (e.g. "successful, what next?", "new problem, what next?"). Management under sub-optimal conditions should be included: when referral is impossible, no drugs are available, certain skills are not available, or the management provided is not acceptable.

2) Monitor systematically the effect of managerial flowcharts.

3) Perform prospective studies in order to correlate clinical signs with the outcome of the management of various categories of illness. Wherever possible, the underlying etiology of severe acute

lower respiratory infections (SALRIs) should be investigated by means of bacteriological and virological examinations. Resistance to the most frequently used antibiotics should also be monitored.

4) Flowcharts for the management of SALRIs should be repeatedly reviewed. The management of SALRIs needs to take into account the practical experience gained by operating the programme in the field, as well as the results of systematic health service research, epidemiological and operational studies, and basic research such as controlled clinical trials that compare alternative drug regimens (in terms of therapeutic efficacy, toxicity, etc.). The conduct of basic research may be feasible only in certain countries where appropriate research facilities are available.

The group finally recommended that:

1) That WHO should continue with the development of technologies and approaches to aid appropriate decision-making in primary health care, with particular regard to ARI and its management, e.g. with the help of suitable flowcharts and action oriented records that fit the local situation in respect to epidemiology, health staff and other resources.

2) That model educational material be developed in the field of ARI and its management, for local adaptation;

3) That efforts be made to identify the risk factors in communities and individuals that influence the occurrence and clinical course of ARI;

4) That standard drug regimens be developed for the treatment of ARI and (especially) for SALRI, under various epidemiological and operational conditions.

Social factors involved

In discussions on the risk factors involved in ARI it was pointed out that social factors such as size of household and social class had a significant relationship with ARI. It has also been stated that, especially in developing countries, mothers often bring children for medical care late in the course of the illness. This must relate in part to the physical problems such as distance and transport available as well as to some psychosocial factors. We have been unable to trace literature which deals specifically with attitudes of mothers in relation to ARI especially in developing countries. It is well known that patients perception of abnormality , emotional response to symptoms, previous experience, guilt feelings may all influence their decision to seek medical care. It is possible for example that the apparent male predominance in some acute respiratory infections may not reflect a genuine sex differential in susceptibility but rather the attitude of the parent who is more attentive to the young male. Sociological variables such as the folklore importance attached to symptoms, and the mores of the particular culture will have an effect on sickness patterns and compliance with therapeutic regimes[236]. In both developing and developed societies these factors are critical. There are well documented studies on mothers compliance with therapies prescribed for their children and even in well developed countries this may be poor . In more and more medical and medicoenvironmental problems the importance of this kind of information is being realized.

In a classical longitudinal study carried out in Newcastle in England 35 years ago it was pointed out that the three main epidemiological features related to severe respiratory disease were a seasonal variation, a tendency to recur, and a striking association with unsatisfactoriy social circumstances[238]. Table (15) shows data taken from the study proving the relationship between social class and severe respiratory disease. It could also be shown that attacks of respiratory disease were more frequent in children living in houses with fewer rooms and in larger households (Tables 15 & 17).

9. SEQUELAE OF ARI

Persistent lung disease

When children have ARI, especially acute bronchiolitis, there are definite and expected abnormalities of lung function. There are increases of both inspiratory and expiratory resistances[239] and during the acute stage marked air trapping with thoracic gas volume increasing to approximately twice normal values[240]. These abnormalities disappear in a few weeks in the majority of children.

Colley et al studied 3,899 twenty-year olds and related the frequency of respiratory symptoms to lower respiratory tract illness under 2 years of age[241]. Although cigarette smoking was the major determinant of the prevalence of respiratory symptoms, a lower respiratory tract illness under age 2 was the next most important. In another population study, a history of pediatric respiratory illness was

Table 16

SEVERE RESPIRATORY DISEASE (BRONCHITIS AND PNEUMONIA) AND SOCIAL CLASS

	Social Class				
	I and II	III	IV	V and N.C.	TOTAL
Attacks	35	367	106	197	705
Children	84	452	121	190	847
Rate per child	0.417	0.812	0.876	1.037	0.832

VARIANCE ANALYSIS

	Sum of squares	Degrees of freedom	variance estimate
Between classes	22.9	3	7.63
Within classes	1,199.3	843	1.42
Total	1,222.2	846	1.44

$F = 5.37 \quad P \simeq 0.01$

Ref. 238

Table 17

RESPIRATORY DISEASE DISTRIBUTED BY NUMBER OF ROOMS IN DWELLING

Attacks	Rooms 1-2	3	4	5 and over	Total
0	9	11	7	7	34
1	19	22	17	13	71
2	34	39	40	27	140
3	36	35	39	23	133
4	25	44	18	16	103
5	22	42	37	19	120
6	20	18	20	11	69
7	25	23	14	7	69
8	8	7	12	8	35
9	8	6	10	5	29
10	3	0	5	0	8
11	3	8	3	1	15
12	3	1	1	1	6
13	2	1	2	0	5
14	3	0	1	0	4
15	1	1	0	0	2
16	0	0	2	0	2
18	1	1	0	0	2
Children at risk	222	259	228	138	847
Total attacks	1,036	1,116	1,042	542	3,736
Mean	4.67	4.31	4.56	3.93	..

$x^2 = 12.7$ n = 3 P = 0.02-0.01
i.e. significant

Ref. 238

correlated with signs and functional disturbance characteristics of chronic obstructive airways disease[242]. Table 18 shows data extracted from these findings in which age has been considered in making the comparison. There is a striking increase in symptoms in both age groups of those who had respiratory illnesses in childhood. Objective tests of respiratory functions also showed relative impairment of function in the group with a history of respiratory disease. However, there are several studies now which have examined pulmonary function at varying times after an attack of bronchiolitis and there is general agreement that persistence of respiratory abnormalities is found in a large number of children.

Sims et al[243] examined 35 eight year olds who had had bronchiolitis in infancy. No children had severe recurrent wheezing although the mean exercise bronchial lability was higher than in control children. In addition, there was very slight evidence of increased airways resistance. Other studies show more severe sequelae. Twenty three Canadian children who had had bronchiolitis were studied after 10 years and the majority had abnormal lung function tests[244]. The nature of the disturbances was such that it was impossible to be sure if there had been residual parenchymial or airways disease. It is possible that during the acute phase of bronchiolitis there is "obstructive damage or loss of recoid to some of the peripheral airways, causing ventilation perfusion abnormalities". Not only do children have abnormalities of lung function, but it has been shown that clinical evidence of bronchospasm is a real concern. In one study 12 months after the attack, 35% of the infants had coughing attacks and 50% had episodes of wheezing[245].

TABLE 19. Comparison of findings in those with and without childhood respiratory trouble (CRT) (Percent Prevalence).

	Age 20-44 (Years)			Age 45+ (Years)		
	With CRT (n-221)	Without CRT (n-822)	Significance	With CRT (n-194)	Without CRT (n-1,389)	Significance
Cough and sputum						
Any	36.2	24.2	P<0.01	49.0	35.6	P<0.01
Both chronic	16.3	10.0	P<0.02	26.3	15.3	P<0.001
Dyspnea						
Any	31.7	22.4	P<0.02	56.2	42.5	P<0.01
Grades 3 and 4	11.3	7.3	NS*	28.3	18.6	P<0.01
Chest illnesses						
>2, past 3 years	10.0	4.3	P<0.001	15.5	4.7	P<0.001
Attacks wheezing dyspnea						
Any	43.0	13.7	P<0.001	46.9	19.8	P<0.001
Known present asthma (physician-confirmed)	15.8	1.5	P<0.001	18.6	5.4	P<0.001
Wheezy chest						
Any	62.9	33.7	P<0.001	58.8	27.9	P<0.001
Most days	8.6	3.8	P<0.01	16.0	8.4	P<0.01
Chest roentgenographic history						
Liver abnormal	21.7	5.4	P<0.001	38.1	13.4	P<0.001
History of pneumonia						
Physician-confirmed diagnosis	43.9	14.6	P<0.001	66.5	27.2	P<0.001
Currently have emphysema	0.9	0.4	NS*	13.4	6.6	P<0.001
Currently have chronic bronchitis	5.0	1.7	P<0.01	21.7	7.8	P<0.001
Currently have chronic obstructive pulmonary disease°	5.9	1.9	P<0.01	30.9	11.9	P<0.001

*NS - Not significant.
°Physician-confirmed chronic bronchitis, emphysema, and/or bronchiectasis, still present.
Ref. 242

There have also been a few reports linking chronic lung disease with specific childhood infections. Twenty-seven children with type 7 adenovirus pneumonia were reassessed some 10 years after their illness . Twelve had abnormal chest X-rays and of these 6 had bronchiectasis. The majority of all the children had abnormal pulmonary function tests[246]. In a similar study from New Zealand[247] of 25 children with adenovirus type 12 pneumonia followed for 4 years, 60 percent had residual lung damage.

The conclusion is inescapable that acute respiratory infections lead to chronic lung disease in later life[248]. Kattan summarized the findings of 5 studies which involved epidemiologic follow up in a total of 18,478 children[249]. These studies not only showed that there was evidence of airway obstruction, but the rate of deterioration of function was exaggerated. The hypothesis was presented that the childhood respiratory diseases led to peripheral airway destruction with or without bronchial hyperreactivity, with the latter also being conditioned by genetic factors.

Another view is that childhood respiratory disease, especially bronchiolitis caused by respiratory syncytial virus is part of a continuum. There is first bronchiolitis, then wheezing bronchiolitis in the older child and finally asthma with the possibility that all three clinical states share a common pathogenetic mechanism[250,251].

Malnutrition

The relationship between nutrition and infection has been discussed above as regards the effect malnutrition had on the development

of respiratory infections. There is also a converse relationship and respiratory infections undoubtedly contribute to the development of malnutrition. In most cases we see the end result of the vicious cycle of infection-malnutrition-infection and it is difficult to know where it started (for review see 30).

The first and most striking effect of ARI is anorexia but the mechanism of this is not well understood. As mentioned above, nasal obstruction as well as pharyngitis lead to diminished food intake. In the acute stage of infection when there is fever there is increased tissue catabolism and in the well nourished individual it can be shown that acute febrile illnesses lead to an increased excretion of nitrogen and a negative nitrogen balance(252). Because of increased protein breakdown there may be a transitory increase in plasma aminoacids which is likely to be more marked in children because of the increased rate of turnover of their aminoacid pool(253). With chronic infections plasma aminoacids may fall. The loss of body protein which may be caused by severe respiratory infections in malnourised children can be as high as 12 percent(254). A fall in plasma albumen with recurrent infections is more closely related to the development of the florid clinical syndromes of malnutrition and in the children studied longitudinally in Uganda, the infections which led to this hypoalbuminaemia and kwashiorkor were predominantly respiratory(255). It has been suggested that the prime mechanism by which infection causes these metabolic changes is an increase in adrenocortical activity. The increased levels of plasma cortisol in malnutrition are probably a result of the nutritional deprivation rather than of infection(256).

Respiratory infections, like other infections which cause increased tissue catabolism cause increased electrolyte loss and this may be a contributing factor to the changes in electrolyte status which have been described in malnutrition[257]. Iron absorption will be decreased by any febrile illness and respiratory infections would be only one of the contributing factors to the development of anaemia in these children[258].

The development of clinical kwashiorkor may be linked not so much to the severity of the infection but to the frequency with which the child suffers from infection. It is normal after infections in children to have a period of "catch up growth". If infections recur in rapid succession, and food, especially energy intake, is marginal, then there will never be catch up growth. There will be steady nutritional deterioration itself contributing to the recurrence of new infections .

10. AREAS FOR FUTURE RESEARCH

The key areas for future research can be described under the following headings:

Epidemiological research

- Field
- Hospital or clinic based

Research on diagnostic methods

Research on control methods

- Prevention
  - -- Vaccine development
  - -- Health education
- Treatment
  - -- Appropriate treatment at primary care level using flowcharts, decision trees
  - -- New drugs and biologics

Health services research

- Systems of care for children
- Appropriateness of available technology

Sociological/behavioural research

- Attitudes and practices of mothers related to care of children in general and ARI in particular

Basic research

Epidemiological research

There are very few good data on the extent of the problem of ARI in developing countries: most of our information comes from figures of attendances at clinics or health centres or medical practitioners. The work of Mata is an outstanding example of a longitudinal field based study which assessed the true incidence of ARI in a defined population. It has been proposed that "sentinel" units is the answer to this. Countries should establish good centres serving a defined small

population and identify the critical epidemiological factors involved in the occurrence and sequelae of the acute attacks of respiratory infection. It should be possible to identify which groups are at risk and to participate in field studies on the application of new therapies. This epidemiological base is necessary before one can decide on the effectiveness and efficacy of vaccines.

The concept of the sentinel surveillance unit and its functioning in a developing country has been described fully by Riley and his colleagues in New Guinea[1]. They point out some basic requirements including a good data information system and a person or persons with experience in data collection and analysis. A good description of the functions of such a unit has been given by Douglas as follows[9]:

1) monitoring of mortality and morbidity attributable to ARD (acute respiratory disease) in defined populations;

2) definition of population groups and individuals at special risk of ARD;

3) monitoring of agents responsible for ARD and of their biological properties

4) description of the environmental conditions (including physical, cultural and social) that influence the incidence of ARD in defined populations;

5) description of host factors (including immunological, behavioral, nutritional and genetic) that determine susceptibility to ARD in the defined populations;

6) assembly, analysis, evaluation and dissemination of those data;

7) evaluation and monitoring of ARD control measures

8) training of personnel concerned with ARD surveillance and control;

9) research into methods of improving the effectiveness of control activities;

10) formulation of recommendations to administrative authorities authorities.

It is always pointed out that these units should as far as possible be part of the country's existing health services and serve to strengthen areas of deficiency. They should not be so specialized that they cannot be replicated in whole or in part in other parts of the health system or in other countries.

It is ideal to link field epidemiological studies with studies in a well equipped central facility. Decisions on appropriateness of initial therapy or decisions about the kind of therapy to be used in primary care settings may depend on accurate knowledge of the epidemiology of the infections seen. However, the separation between field and center based studies may be artificial, as they are essentially complementary. In order to gain good information about the incidence of respiratory infections it may not be necessary in all situations to utilize sentinel units, but to base prediction on cluster sampling of appropriate units for appropriate periods of time. In developing countries the accent has to be on clinical epidemiology. The information needed urgently relates to the knowledge of the types of clinical syndromes, their periodicity, severity, treatment and outcome.

The type of epidemiology needed and the reason for getting this information has been described clearly by Fox & Hall[259] in their introduction to their classic virus watch studies. They utilize the family as the basic unit for study and point out the kind of information which must be gathered. They state "while few would dispute the importance of knowing to the fullest extent possible the behavior of specific contagious agents in family groups, the reasons why such knowledge is important may not be fully appreciated. Almost without exception, the viruses of present concern are maintained exclusively in man by a chain of transmission formed by relatively short links, the lengths of which vary within the rather narrow limits set by the minimum incubation period and the sum of the maximum periods of incubation and communicability. Full description of the natural history of infections with specific agents requires many kinds of information. Mechanisms of transmission depend on how the virus invades and escapes from the host and how stable it is in the free state. The rate and extent of transmission are determined by the periods of incubation and communicability, the relative infectivity of the virus, and the number of susceptibles and their distribution in the population. Information relating to outcome of infection includes: knowledge of the pathogenicity (proportion of infections resulting in disease) and immunogenicityof the virus in man; how host response varies with age, sex, intercurrent illness, and level of prior immunity; and description of the spectrum of clinical manifestations. Finally, we need to know how virus spreads through the community and how the incidence of infection

(and disease) varies -over time; with season; with place; and among population groups defined by characteristics such as age, sex, ethnicity and culture, and socioeconomic status".

Clinico microbiological correlation

The hospital based studies should have the facilities of a good microbiological laboratory to allow the correlation between the clinical and radiological symptoms and the aetiological agent. It is only this close correlation which has allowed the group in Chapel Hill, N.C. to establish the aetiological basis for the clinical syndromes seen. For example, they have shown that in their practice the clinical picture of wheezing bronchitis below the age of five was most commonly associated with respiratory syncytial virus infection and mycoplasma pneumoniae was the most frequent isolate in older children[54]. It should be pointed out that other laboratories have shown that viruses - most commonly rhinoviruses were the main aetiological agent in wheezing bronchitis in children as a whole[260,261].

An adequate diagnostic approach to children with ARI has been described above and these kinds of approaches must be available in key hospitals especially in the developing countries. It must be possible to carry out the kind of research involving invasive techniques such as transtracheal aspiration and lung puncture. Serological tests on serum and culture of viruses in secretions from the respiratory tract are only presumptive evidence that these agents can cause the specific case of pneumonia.

The latter is not an innocuous proceedure, but has provided extremely useful information on the bacteriology of lung disease . There needs to be similar data for viral disease.

Follow up

Because of the probability that ARI lead to chronic irreversible lung damage[241-251], recovered children should be followed up with appropriate tests of lung function. This would have to be based on previous studies on the prevalence of chronic respiratory disease in the community and tests of function in normal children to allow comparisons to be made.

Clinicopathological correlation

Cases of pneumonia dying in hospital should have postmortems and the results recorded in a standardized format.

On occasion, the aetiology of the fatal infection may be clear after autopsy. Good histopathological data have not been given a great deal of attention in reports an studies on respiratory tract infections. One study presented recently[264] showed the importance of this kind of approach when feasible. In one hospital in South Africa it was found that out of 879 autopsies in children pneumonia was the chief cause of death -occurring in 31%. Of these pneumonias, 28% died within 28 days of measles, and the most impressive finding was bronchial and bronchiolar necrosis especially in children who had developed adenovirus or herpes virus infections after measles. Some of these childhood respiratory

infections go on to produce follicular bronchiectasis[265]. Apart from diagnosing these complications of measles, histopathology may pinpoint the classical measles pneumonia with the specific multinucleate giant cells with inclusions[266].

Thus, the hospital based research on ARI should have the following components or characteristics:

- Definition of the clinical syndromes
- Microbiological evaluation
- Clinico-microbiological correlation
- Epidemiological study of patterns of illness over a defined period of time
- Clinical evaluation of treatment regimens
  - antimicrobials
  - other drugs
  - other modes of therapy
- Host characterization
  - social indicators
  - environmental risk factors
- Follow up of recovered children
- If children die, autopsy according to a standard protocol

Research on diagnostic methods

Some of the tests mentioned in Item 6 like COA and CIE already have proved their capacity to contribute to the quick diagnosis of St. pneumoniae, H. influenza and streptococcal infections by antigen detection. The LA test is very promising, while ELISA and RIA have great potential but further studies are needed. It would be ideal if the different rapid methods and culture were tested together in secretions of the respiratory tract, induced cough swabs and nasopharyngeal aspirates so their advantages (or disadvantages) could be comparatively evaluated. Similarly, further development and evaluation of the ELISA test for detection of viral antigens in respiratory tract secretions would be especially advantageous. It is possible that production of monoclonal antibodies against the organisms responsible for ARI will produce specific antibodies in enough quantity to allow full advantage to be taken of the available techniques.

Research on Control Methods

Prevention

Vaccine development

In the last 30 years there have been successful vaccination programs in many parts of the world for the control of viral and bacterial diseases such as small pox, poliomyelitis, measles, mumps, tetanus, diphtheria and to a certain extent influenza. This has led to the belief that most if not all of the infectious diseases can be prevented by vaccination. However, with regard to the bacteria, viruses

and mycoplasma that could be responsible for ARI, progress has been slow because of lack of basic knowledge concerning the etiological agents and their interaction with the host.

For example, in the case of killed mycoplasma and RSV vaccines it was shown that use of vaccines may produce symptoms similar to those that the vaccine was supposed to prevent[199,133,134]. Therefore, more knowledge is needed about the immunological phenomena responsible for resistance and in certain circumstances for disease. If whole killed vaccines are not acceptable, it is possible that research on the antigenic composition of the virus will allow the separation of protective antigens from those responsible for pathogenesis or those that have a toxic effect. Methods for purification of killed influenza vaccines have permitted separation of the glycoprotein antigens associated with protection from the non protective antigens[175]. There is no reason to believe that similar techniques could not be applied to other viruses. Recent work done with an animal paramyxovirus may provide an approach to vaccination that may be both safe and effective[143,267].

It has been shown that SV5 virus can spread either by release of infective virus or through cell fusion, which results in direct cell-to-cell transfer. Dissemination of infection through release of viral particles is prevented by antibodies to the hemagglutinin and neuraminidase glycoproteins, but these antibodies do not have any effect on the spread of the infection by cell fusion. On the other hand, antibodies to viral fusion glycoprotein prevent the spread of infection

by both cell fusion and release of infectious viruses[268]. Therefore F pure glycoprotein might be an ideal immunogen for a paramyxovirus vaccine. Immunization in the lung by an aerosol with this immunogen could stimulate local secretory IgA without inducing the systemic immune response that could be responsible for tissue injury. Difficulties in raising enough IgA levels for sufficient time may be surpassed by giving an aggregated rather than a solubilized form of the antigen.[267] Alternatively, the F protein could be given with an adjuvant[267].

Eventually, all inactivated virus vaccines will be purified to such a degree that they will be very poor immunogens. Adjuvants can increase the immunogenic capacity of vaccines while lessening the amount of antigen and the number of doses required, thus making vaccination more economical and feasible[269]. Therefore, safer and more effective adjuvants must be developed and tested, not only for new antigenic preparations but in order to increase the immunogenic characteristics of older ones. Aluminum compounds have been used to increase the potency of diphtheria and tetanus and also of a subunit influenza vaccine[Rev.in 269]. Oil emulsions and synthetic adjuvants are more potent adjuvants than aluminum compounds and both types have been used with influenza virus. Furthermore, Hexons and fiber subunits of Adenovirus bound to liposomes, a synthetic adjuvant, elicited a higher immune response than when they were administered alone[269]. The possibility of combining non toxic synthetic immunoregulators of low molecular weight with antigens in order to stimulate a preselected part of the immunosystem is undoubtedly attractive. The major obstacle

limiting the use of adjuvants is the question of their safety and only further research will provide the answer to this[269].

Recent knowledge of the mucosal immune system, indicates that it may operate independently from the systemic immune response. One of its striking features is the existence of large quantities of secretory IgA. However, other Ig's and lymphocytes are also present. Furthermore, there is evidence indicating that antibodies that appear in the secretions are locally synthesized and that the cell mediated immune response can also be a local phenomena. Viruses like influenza, RSV and parainfluenza produce lesions at the site of initial replication in the mucosa. Moreover, local secretory (IgA) antibodies play a major role in protection. Thus, it is possible that locally applied live vaccines will induce a local immunity that would inhibit attachment and replication of the virus on the mucosal surface[270]. This will be a feasible approach to control of the disease at the primary portal of entry. For this purpose attempts have been made to develop attenuated mutants that can be used as a vaccine. Recent information on the structure and function of the genome of several viral pathogens make the manipulation of viral genes possible and allow a more rational approach toward development of specific mutations that attenuate the virus[Rev.in 270-272].

Although the progress in obtaining attenuated strains of influenza A-B by gene transfer has been impressive, identification of strains as suitable donors of genes associated with attenuation should be pursued

and more information is needed on the biology, genetic and biochemistry of potentially usable vaccine strains. Another approach could be by using chemical mutagenesis to produce a temperature sensitive, genetically stable RSV for intranasal administration(Rev.in 143, 271,272).

With some of the viruses responsible for ARI like the rhinoviruses and enteroviruses the multiplicity of serotypes will pose several practical problems for development of a vaccine. With rhinoviruses, one possible solution to the problem would be to identify certain immunotypes that might be more prevalent in certain areas and use them to prepare a vaccine to be used in this area. Another possibility is to exploit the antigenic relationships among the rhinoviruses. As both possibilities seem remote at this time, there is not much hope for development of a vaccine against this organism in the near future.

In the adenoviruses, although several serotypes exist, only certain ones cause disease. Therefore, a multivalent vaccine containing a few serotypes had been useful. Safety considerations have prevented the use of a vaccine with killed virus and have led to development of a live vaccine administered by the oral route in which the virus colonizes in the intestinal tract giving rise to specific antibodies. Therefore, the induced protection mirrors what happens in the natural infection. In children, the question has been raised whether immunization should be used to prevent a self-limiting infection, when potential oncogenic viruses are used in the vaccine and the possible intrafamiliar spread of virus from orally vaccinated children has been reported(Rev.in 143). However, in infants and young children, a vaccine containing types 1-7

will undoubtedly be useful in decreasing the morbidity from adenoviruses. Antigens from purified hexon and fiber capsid proteins, while stimulating neutralizing antibodies presumably may not have oncogenic danger and may therefore provide a suitable vaccine for use in children. This possibility has not been sufficiently explored.

Some of the problems encountered with viral vaccines are very similar to those found with vaccines against bacterial species responsible for ARI. In order to use pneumococcal vaccines in certain geographical areas, it would be necessary to establish which are the prevalent serotypes. Moreover, the immune response of children to polysaccharides is usually poor, and undesirable reactions may occur after vaccination[209-211]. In B. pertussis little is known of the local immune response of the respiratory tract in recovery from and resistance to infection; how existing vaccines protect and what is the role of vaccination in the host-parasite interaction in pertussis. Despite immunization, pertussis still persist in the community. It is envisaged that further attempts at isolation and characterization of cell components responsible for protection, development of genetic mutants devoid of toxicity and/or able to synthetize higher amount of protective antigens will facilitate the development of an effective vaccine with less reactogenicity[Rev.in 273].

Health education

There has been no research on the kind of health education necessary to prevent the occurrence or initiate treatment of ARI. There

already exists simple information on how to treat children with nasopharyngitis and how to recognize the severely ill child. It is possible to devise the kind of messages which can be put to mothers and evaluate their effectiveness. Already in the case of diarrhoeal diseases there is a considerable amount of research in this area, especially on the kinds of technologies which can be used to deliver this information. The United States Agency for International Development in association with the University of Stanford has been developing a programme in Honduras on the effect of various forms of communiction technology on improving the capacity of the mothers to preven_ and treat diarrhoeal diseases. Such a program of health education may make for more selective attendances at health facilities and perhaps reduce the actual numbers of children and allow more time for the severity ill children. This kinds of research also falls in the category of health services research -research to make more effective use of available resources.

Treatment

Appropriate treatment at primary care level using flowcharts, decision trees

It has been accepted that this must be based initially at the primary care level. In view of the absence of a single form of therapy analogous to oral rehydration salts in diarrhoeal diseases, it is essential that a set of guidelines be developed to allow primary care workers to make decisions based on sets of signs and symptons which are of proven local relevance. In many parts of the world primary care

workers are not used and mothers bring their ill children directly to a physician. In these circumstances it is still essential that we elaborate the essential signs and symptoms on which critical decisions should be based. There are several such flow charts or decision trees which have been proposed (see Figs. 1-4). Research is needed to develop charts best suited for a local environment and to assess the results of introducing such charts into the health services. This has to be on the basis of soundly constructed epidemiological surveys.

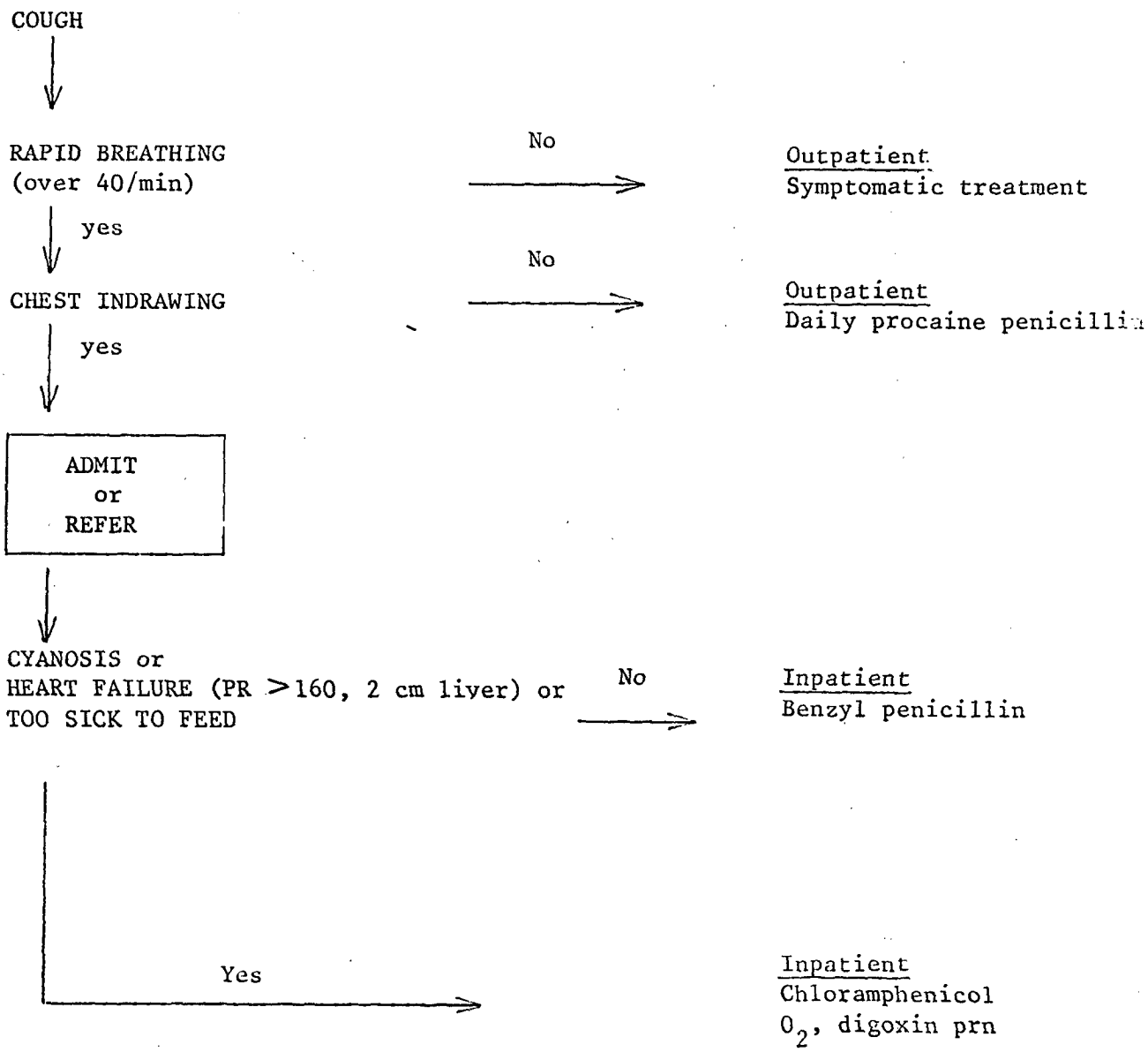
The mainstay of drug treatment is antibiotics and as has been pointed out, many flow charts advocate penicillin in the absence of local data on the most prevalent organisms and the resistance patterns of the bacteria present. The rapid spread of antibiotic resistance because of widespread sale of antibiotics without prescription and use of antibiotics in animal feeds is now a matter of serious concern in many parts of the world.

New drugs and biologics

As yet there is no antiviral agent available for use in children with ARI. Although increased mucus secretion may play a role in bronchiolar obstruction in ARI, there are no drugs available which can be used with safety to alter the rheological characteristics of respiratory mucous or increase mucociliary clearance in ARI. To our knowledge, there are no new drugs with the potential of increasing alveolar macrophage phagocytic activity or counteracting the effect of viral infections on cellular phagocytosing capacity. One of the difficulties in pointing to

Figure 1

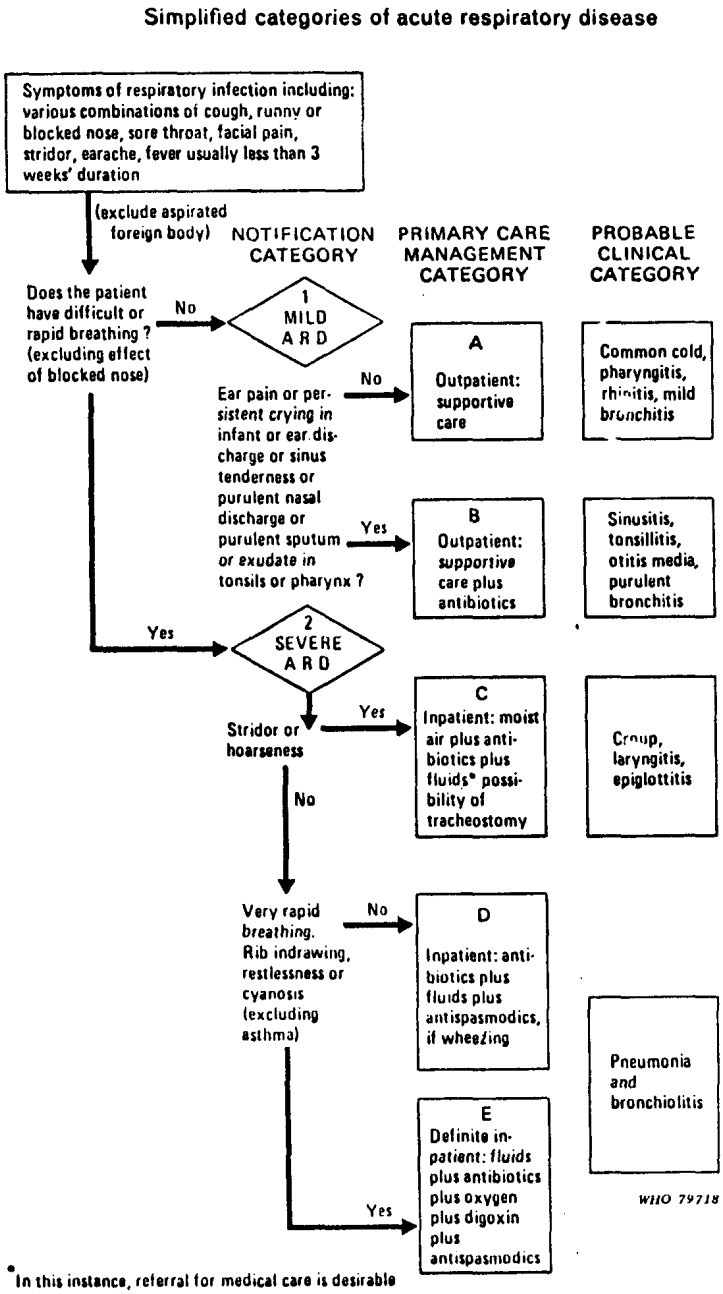
CLINICAL MANAGEMENT OF ARI IN CHILD < 5 IN PAPUA NEW GUINEA



Note: All children with fever are given antimalarials

Ref. 1

Figure 2



Ref. 229

Figure 3

Proposed flowchart for the diagnosis and treatment of pneumonia in peripheral health services (Level C^2), Sao Paulo, Brazil

(Health units staffed with health workers with minimal training
and having poor transport and communication with the upper level)

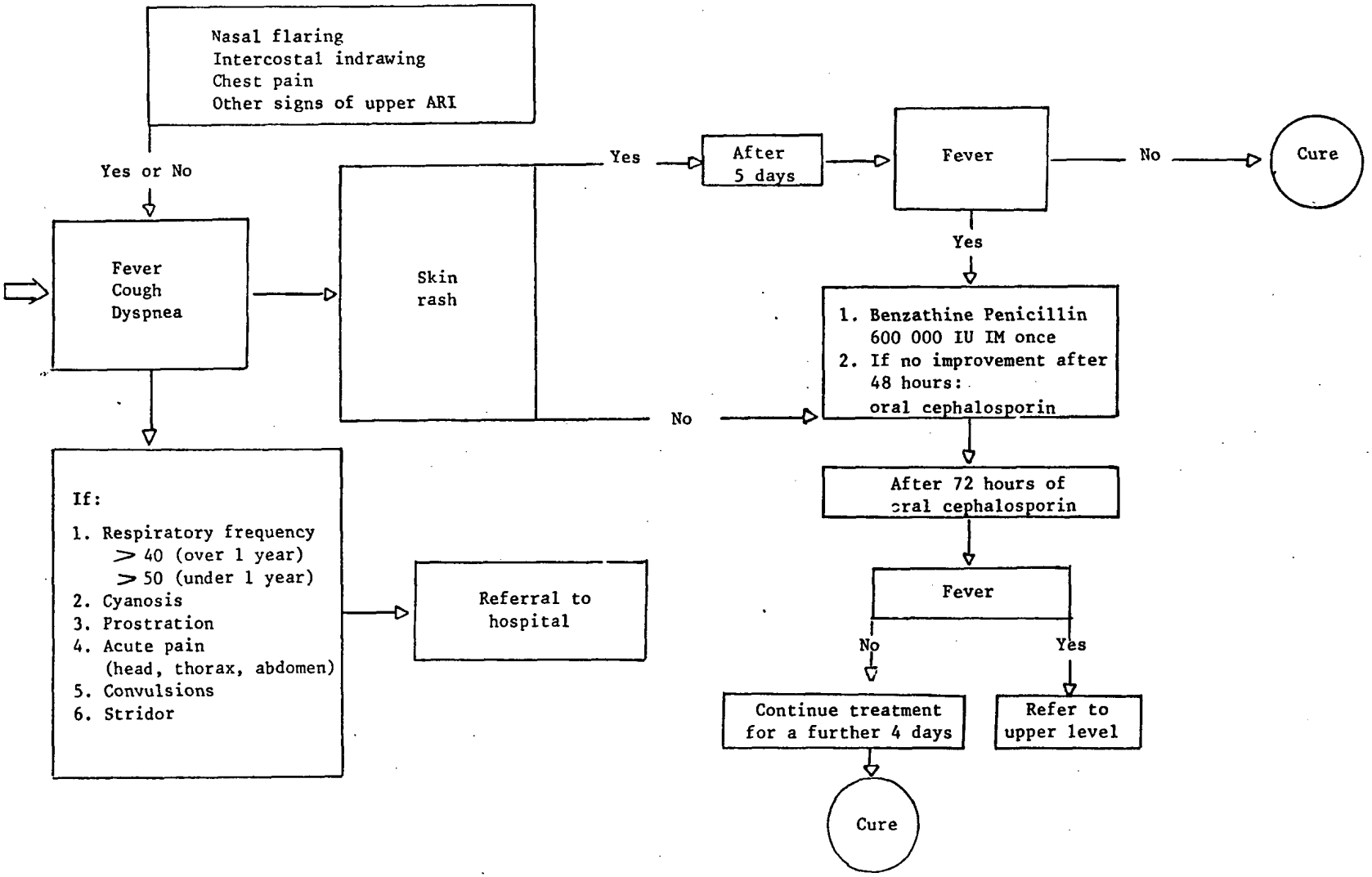
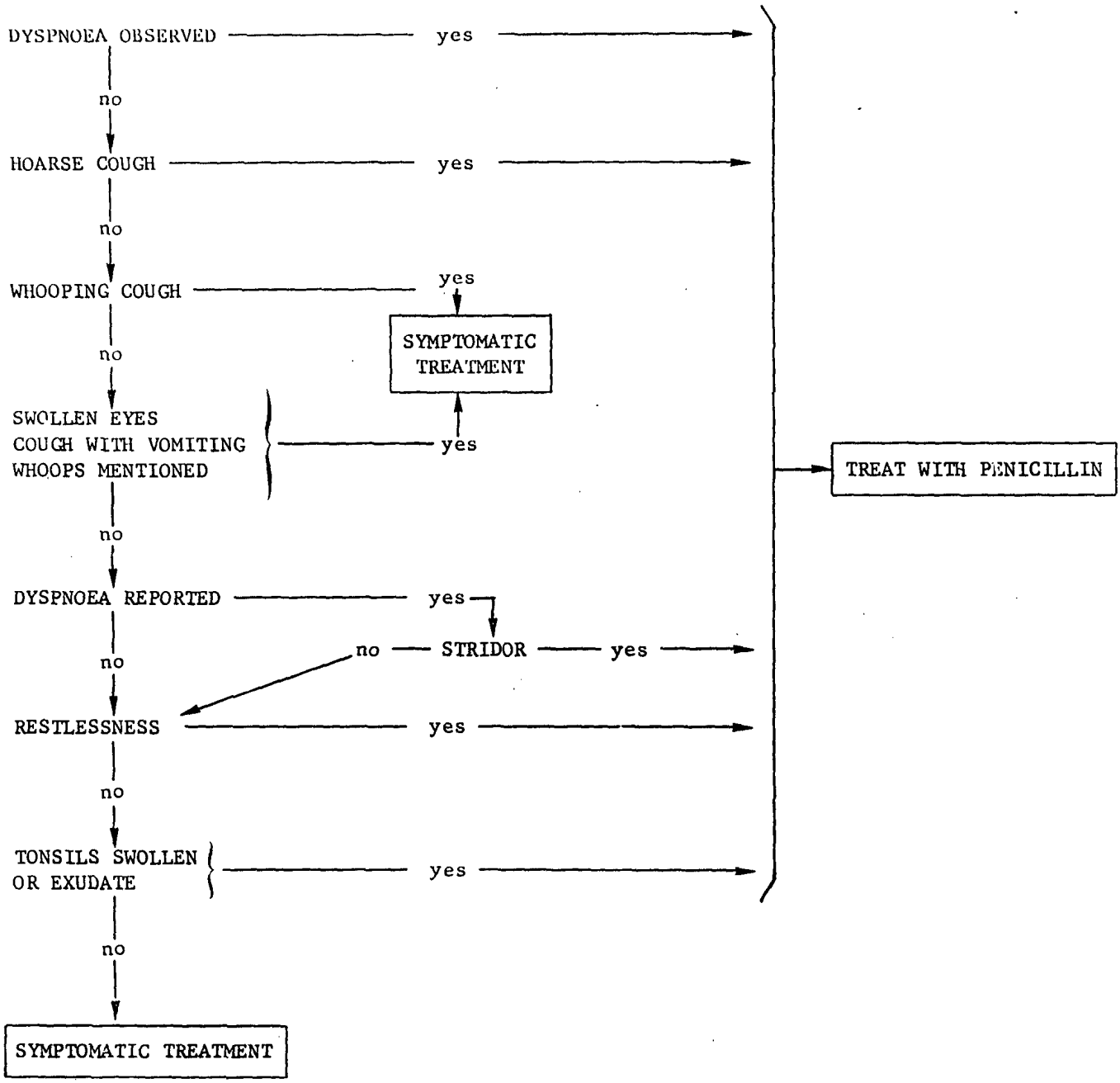


Figure 4

POSSIBLE DIAGNOSIS/TREATMENT SCHEME FOR CHILDREN PRESENTED WITH COUGH



Ref. 231

new development in drug therapy is the fact that pharmaceutical companies which are actively working in this area are naturally reluctant to divulge promising lines of research. However, the experience of the Special Programme for Research and Training in Tropical Diseases is that this industry will work with WHO under the appropriate conditioning.

Cough medicines are widely prescribed but there is no evidence that they are effective in children with different forms of ARI. The same can be said for antihistamines and decongestants.

Health Services Research

Accesibility to effective services is stated as the prime aim of any system of effective primary care. In developing and developed countries there is a need for studies on the ways by which delivery systems can be made more effective.

There is also need for research into the kinds of technology relevant to ARI in children. It is far fetched to relate cooking or heating stove design to ARI but if domestic smoke predisposes to ARI then it does become relevant to design appropriate cooking equipment and appropriate methods of ventilation for houses.

It is more critical, however, to develop research on simple systems to make oxygen available at peripheral clinics and health posts. At present, systems for storing and transporting this are bulky, expensive and appropriate only to large institutions. Availability of oxygen can be the difference between life and death in children with bronchiolitis.

There are other aspects of the early treatment of ARI which need to be studied in this regard. An increse in humidity is an important part of therapy and mothers are advised to hang wet towels in the room and around the bed. To our knowledge there are no data on the effectiveness of these kinds of simple methods on raising ambient humidity in specific locations of the world. It is not ideal or safe to recommend steam tents and a simple alternative would of real value.

Sociological/Behavioural Research

It was shown before that social variables play an important role in determining the incidence of ARI. Currently, many different questionnaires are being developed to assess the importance of these variables in the various settings. It is probably not appropriate at this stage to mount large studies on social variables which cannot be changed readily by intervention on our part. Attention could perhaps be focussed more sharply on those important social and environmental variables which are either amenable to change or which have to be considered when a programme of treatment or control is initiated. The definition of these variables calls for a program of research involving medical social scientists and medical anthropologists. There is a lack of knowledge of the attitudes, perceptions and practices of families in relation to ARI in children, information which should be vital in any control programme. Finally, it is necessary to obtain data on the social and economic burden caused by ARI. We have information in some instances on the numbers of children coming to the health services and the attack

rates of ARI with the average duration of these illnesses in certain places. There is no place-related study on the total economic drain this imposes. It has sometimes been argued that research in this area is not necessary, as health does not have to be justified in economic terms. However, allocation of resources within the health sector and between sectors often depends on the concept which planners have of the relative importance of various sectors and various problems within these sectors. Much of the lack of attention which has been paid to the development of research and management strategies for ARI may be due to this phenomenon.

Basic Research

There are two main lines of basic research which seem to be of immediate and direct relevance. First there is research into the organisms which cause respiratory infections. Much of this has already been covered in the sections dealing with epidemiology, the specific organisms and the potential for vaccine development. Other studies which will be needed are those which examine the immunology of host resistance and disease. There is need for much more knowledge of how viral infections affect the immune system and how the immune system reacts to viral illnesses. The immuno depression said to accompany measles may the cause for the appearance of the severe necrotizing viral pneumonias which supervene.

Research into the host is the other aspect of basic research needed. The section dealing with the anatomical factors predisposing to infection and the pulmonary defence mechanisms alluded to some of the

areas of deficiency. Only one example will be given. It was shown that malnutrition and respiratory diseases were closely linked, yet there is very little information on the mechanism by which malnutrition renders the respiratory tract susceptible to infection. Studies on mucociliary activity, mucus physiology and bronchial reactivity in experimental animals subjected to various kinds of nutritional deprivation should be correlated with studies done in children with and without malnutrition.

We are not aware of the whole range of research in pulmonary physiology and biochemistry which could be important for the development of a method of control for acute respiratory infections. However, we have already made reference to the fact that it was as a result of basic research on electrolyte transport in the intestine of the experimental animal that the oral rehydration solutions for treztment of diarrhea was developed.

11. TRAINING

The main focus of this paper has been research, but there will be a need for training in this field. Briefly, training will be needed in the following areas:

Clinical - All levels of health workers must be aware of the clinical presentations, basic epidemiology and appropriate therapy of ARI. Thus appropriate mterial has to be prepared for the various levels of these personnel. These include medical students, nurses and all auxiliary medical personnel treating children.

Laboratory - The research outlined above will require good laboratory support at some points. Therefore, efforts to develop and upgrade laboratory facilities should be an integral part of any programme. If it is possible to develop widespread interest in the diagnosis of agents responsible for ARI, this will enhance the national capabilities in the laboratory disciplines.

Epidemiology - Personnel in the areas of biostatistics, data management and analysis will be necessary in addition to good epidemiologists. The emphasis must not only be on clinical epidemiologists, but on having all levels of persons.

12 CONTROL

THERE SHOULD BE NO CONTROL PROGRAMME SPECIFICALLY FOR ACUTE RESPIRATORY DISEASES

It is a mistake to develop a vertical programme directed to the control of one cause, albeit an important cause, of infant mortality. The technologies available today (and in the future) for use in treating or preventing common diseases in children should be applied in horizontal programmes with one aspect strengthening and supporting the other. The oral rehydration solutions work dramaticlly for children with diarrhoea. Their use could be an entry point into the primary care system directed to all children. Any simple technology developed for respiratory diseases should be utilized in a similar manner.

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