

## Four-year study of WHO virus reports on enteroviruses other than poliovirus

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*In 1963 the World Health Organization established a system for collecting and distributing information on viruses. By 1970, 93 laboratories in 33 countries were participating. The present study is an analysis of the reports on coxsackieviruses A and B and echoviruses for the 4 years 1967-70. Among the coxsackieviruses A, type 9 was reported most frequently, and the most frequently reported coxsackievirus B was type 3. Among the echoviruses, types 9, 6, and 30 were common. In the northern hemisphere the season of highest incidence for each of the three groups was June-October; in the southern hemisphere it was November-February. Most of the infections were in children and the clinical manifestations usually included aseptic meningitis, respiratory disease, skin eruptions, undifferentiated febrile illnesses, and gastroenteritis. The relative frequency of an association of a virus with a clinical syndrome differed not only between the three groups of viruses under study, but in a number of instances between the types within a group. As is well known there were a number of instances in which a specific clinical syndrome was linked to certain specific viruses—e.g., hand, foot, and mouth disease to certain types of coxsackievirus A, and myalgia (Bornholm disease) and cardiac conditions to coxsackieviruses B. There was also an apparent relation between age and symptoms—e.g., those due to the coxsackievirus B associated with Bornholm disease in persons over 15 years of age.*

At the beginning of 1963 a system for collecting and distributing laboratory and epidemiological information on virus diseases was organized by WHO (World Health Organization, 1968). Under this system, the reference centres for enteric and respiratory viruses and suitable national virus laboratories complete standard record forms on infections diagnosed by virus isolation or serology. WHO then collates the forms and prepares quarterly and annual reports, which are distributed under confidential cover to the collaborating laboratories.

By 1970, 93 laboratories in 33 countries were participating in this scheme. In some instances the reports cover the virus laboratory work of a whole country—e.g., Canada and the United Kingdom (although the data for Scotland are analysed separately). In others they cover only parts of a country—e.g., reports from California, USA, and from Melbourne, Australia.

There are many difficulties in comparing data from different laboratories: variations in the level of technical performance or in the facilities for the laboratory work; interest limited to certain groups of viruses; delays in reporting and in completion of tests (mainly the final typing of viruses); the emphasis placed by public health authorities on the importance of certain virus diseases in comparison with others, and so on. Notwithstanding these limitations, a comparison of data from different laboratories can be useful and the results may give valid indications of time trends in viral infections on a global basis although a complete picture may not be defined. The present study is such an attempt and is limited to coxsackieviruses A and B and the echoviruses.

### METHODS

The study is restricted to the 4-year period for which the information has been stored on magnetic tape for computer analysis, 1967-70.

The viruses are discussed separately by type. So far as the individual virus types in the northern hemi-

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sphere are concerned, only laboratories providing more than 25 reports during any one of the reporting years under study are included. To provide a contrast with the northern hemisphere, laboratories from the southern hemisphere—namely, Melbourne and South Africa, which report regularly—are included, even though less than 25 isolations were reported. Viruses reported during special surveys or special studies are excluded.

#### FINDINGS

Restricting the study of each virus type to the reports from laboratories that provided at least 25 reports in at least one reporting year has reduced the number of laboratories included in the study to 50 (see Annex). For the same reason only coxsackievirus A types 2, 4, 5, 9, 10, and 16, coxsackievirus B types 1–5, and echoviruses types 1, 3, 4, 6, 7, 9, 11, 14, 17, 30, and 33 are included. The number of virus isolations varied from 2 233 for coxsackievirus A (ranging from 88 reports for coxsackievirus A10 to 1 016 reports for coxsackievirus A9) to 5 611 reports for coxsackievirus B (ranging from 650 for coxsackievirus B1 to 1 619 for coxsackievirus B3),

and to 8 621 reports for echovirus (ranging from 40 for echovirus 33 to 2 600 for echovirus 9).

The most frequently reported types were, for coxsackievirus A, types A9 and A16; for coxsackievirus B, types B3 and B2; and for echovirus, types 9, 6, and 30. With all virus types the number of reports fluctuated greatly from year to year. The yearly differences were more evident when considering individual countries or laboratories—e.g., of a total of 154 cases of coxsackievirus A5 reported by Japan, 146 were reported in 1967, 1 in 1968, 4 in 1969, and 3 in 1970. Similarly, of 308 cases of coxsackievirus A16, 14, 5, 55, and 234, respectively, occurred in the four years under study. England and Wales reported 425 cases of coxsackievirus B1, 375 (88% of which occurred in 1970), and the Federal Republic of Germany reported 282 cases of coxsackievirus B2, 253 (90%) of which occurred in 1968.

The reports of echoviruses were also unevenly distributed; for example, England and Wales reported 163 cases of echovirus 3, 112 (69%) of which occurred in 1967, and California, USA, reported 247 cases of echovirus 30, 217 (88%) of which occurred in 1968. In any one country, one or more virus types predominated during a given year and

Table 1. Number of reports of coxsackie and echoviruses by month of collection or month of receipt of specimen

Month	Coxsackievirus A <sup>a</sup>		Coxsackievirus B				Echovirus			
	Northern hemisphere		Northern hemisphere		Southern hemisphere		Northern hemisphere		Southern hemisphere	
	No.	%	No.	%	No.	%	No.	%	No.	%
January	26	1.5	49	1.3	36	15.2	112	1.8	36	9.8
February	35	2.0	28	0.7	27	11.4	103	1.7	36	9.8
March	39	2.2	43	1.1	22	9.3	62	1.0	30	8.2
April	34	1.9	60	1.6	12	5.1	61	1.0	30	8.2
May	132	7.5	151	3.9	7	3.0	224	3.6	27	7.4
June	285	16.1	326	8.3	6	2.5	483	7.8	12	3.3
July	368	20.8	636	16.5	8	3.4	1 046	16.9	9	2.5
August	291	16.4	999	26.0	8	3.4	1 646	26.6	12	3.3
September	192	10.8	683	17.8	9	3.8	1 162	18.8	9	2.5
October	155	8.8	532	13.8	16	6.8	827	13.4	40	10.9
November	152	8.6	228	5.9	40	16.9	339	5.5	80	21.9
December	62	3.5	108	2.8	46	19.4	118	1.9	45	12.3
Total	1 771	100.0	3 843	100.0	237	100.0	6 183	100.0	366	100.0

<sup>a</sup> There were only a few reports from the southern hemisphere and they have not, therefore, been included.

Table 2. Number of reports on coxsackieviruses included in the study according to age <sup>a</sup>

Age (years)	Coxsackievirus A, type:							Coxsackie B, type:							
	2	4	5	9	10	16	Total		1	2	3	4	5	Total	
							No.	%						No.	%
< 1	15	18	27	96	10	76	242	15.0	111	119	246	58	145	679	18.2
1-4	77	15	121	197	46	318	774	47.8	153	236	327	146	251	1 113	29.8
5-14	16	2	26	240	14	74	372	23.0	153	267	292	150	268	1 130	30.3
all children	108	35	174	533	70	468	1 388	85.8	417	622	865	354	664	2 922	78.3
15-24	0	0	2	67	0	14	83	5.1	42	68	80	24	83	297	8.0
25-59	3	3	1	96	11	28	142	8.8	64	86	169	57	112	488	13.1
≥60	0	0	0	5	0	0	5	0.3	7	4	10	0	5	26	0.7
all adults	3	3	3	168	11	42	230	14.2	113	158	259	81	200	811	21.8
total	111	38	177	701	81	510	1 618	100.0	530	780	1 124	435	864	3 733	100.0

<sup>a</sup> Cases of unknown age are excluded. No breakdown by age is available for England, Wales, and Northern Ireland for 1967 and 1968.

similar observations have been reported in the literature (*Brit. med. J.*, 1967; Keuth et al., 1970; Yamaoka, 1968).

There is apparently no regular yearly pattern for the recurrence of specific types, although England and Wales reported coxsackievirus A9 in large numbers in both 1969 and 1970 (212 and 204 cases, respectively) and in these two years it was reported to be epidemic in the United Kingdom (*Brit. med. J.*, 1970a, 1971a).

In the northern hemisphere, infections of all virus types were least common during the winter and spring months. They rose rapidly to peaks during the summer months and gradually declined each autumn (Table 1), although in the larger outbreaks cases sometimes continued into the winter. For example, in England and Wales an outbreak caused by coxsackievirus A16 occurred in 1969 and of the total of 112 cases reported 51 occurred in November and December. In the same areas in 1970 there was an outbreak caused by coxsackievirus A9 and the highest monthly number of cases was in November.<sup>1</sup>

The great majority of the specimens of coxsackievirus A came from children less than 5 years of age, except for type A9 where children less than 5 years of age accounted for less than 50% of the reports.

<sup>1</sup> The two epidemics have been reported in more detail (*Brit. med. J.*, 1970b, 1971a).

With coxsackievirus B, irrespective of type, most of the reports related to children less than 14 years of age, the age group 0-4 years accounting for about 50% or less (Table 2).

Most of the echoviruses were again isolated from children in the age group 0-14 years. The number of reports of cases of echovirus types 1, 3, 7, 11, 14, and 17 in the age group 0-4 years was greater than, or equal to, that for the age group 5-14 years. With the other types a larger number of isolations were obtained from children aged 5-14 years, by far exceeding the numbers for the 0-4-year age group for types 6 and 30 (Table 3).

Coxsackieviruses A were identified most frequently in cases of skin eruptions (in particular hand, foot, and mouth disease), aseptic meningitis, upper respiratory tract disease, undifferentiated febrile illness, and gastroenteritis (Table 4). Nearly 50% of the reported A9 infections were associated with disease of the central nervous system (CNS), mostly aseptic meningitis (see *Brit. med. J.*, 1970b, for the outbreak in England and Wales in 1970; and Shingu et al., 1970, for the outbreak in Japan in 1968).

Coxsackievirus B was most frequently associated with neurological conditions, mostly aseptic meningitis, respiratory illnesses, undifferentiated febrile disease, and gastroenteritis (Table 4), but a considerable proportion of the reports were associated with myalgia (Bornholm disease) and cardiac conditions

Table 3. Number of reports on echoviruses included in the study according to age <sup>a</sup>

Age (years)	Echovirus, type :											Total	
	1	3	4	6	7	9	11	14	17	30	33		
												No.	%
< 1	24	35	12	133	78	213	76	30	25	64	3	693	11.3
1- 4	14	33	22	344	157	536	77	30	56	103	1	1 373	22.4
5-14	15	64	84	712	96	976	126	14	68	472	16	2 643	43.1
all children	53	132	118	1 189	331	1 725	279	74	149	639	20	4 709	76.8
15-24	1	7	33	208	11	217	33	9	14	180	12	725	11.8
25-59	5	16	21	150	11	264	32	4	13	135	7	658	10.7
60 and over	1	0	0	14	1	14	6	1	1	1	0	39	0.6
all adults	7	23	54	372	23	495	71	14	28	316	19	1 422	23.2
total	60	155	172	1 561	354	2 220	350	88	177	955	39	6 131	100.0

<sup>a</sup> Cases of unknown age are excluded. No breakdown by age is available for England, Wales, and Northern Ireland for 1967 and 1968.

Table 4. Number of reports on coxsackieviruses included in the study according to the main clinical manifestation <sup>a</sup>

Main clinical signs or symptoms	Coxsackievirus A, type :							Coxsackievirus B, type :									
	2	4	5	9	10	16	Total		1	2	3	4	5	Total			
								No.	%								No.
total respiratory (lower respiratory)	27 (2)	20 (3)	16 (3)	126 (33)	32 (17)	19 (6)	240 (64)	11.8 (3.1)	113 (44)	255 (60)	281 (91)	153 (49)	164 (53)	966 (297)	19.1 (5.9)		
total CNS (paralytic CNS)	26 (0)	7 (1)	12 (1)	425 (8)	13 (3)	6 (0)	489 (13)	23.9 (0.6)	145 (4)	548 (8)	569 (13)	210 (9)	436 (12)	1 908 (46)	37.6 (0.9)		
cardiac	1	5	0	5	1	0	12	0.6	17	35	51	14	50	167	3.3		
muscular <sup>b</sup>	1	2	0	11	0	1	15	0.7	57	62	57	27	32	235	4.6		
gastrointestinal	16	12	20	87	7	3	145	7.1	57	181	204	98	68	608	12.0		
skin/mucous membrane <sup>c</sup>	45	11	151	61	18	543	829	40.6	24	25	68	22	26	165	3.3		
fever <sup>d</sup>	13	2	11	123	5	4	158	7.7	99	245	219	95	87	745	14.7		
others	1	0	1	42	0	3	47	2.3	23	56	54	34	20	187	3.7		
nil	7	32	7	29	11	21	107	5.2	3	30	38	14	4	89	1.8		
total	137	91	218	909	87	600	2 042	100.0	538	1 437	1 541	667	887	5 070	100.0		

<sup>a</sup> Cases with unknown clinical picture are excluded.

<sup>b</sup> Includes Bornholm myalgia.

<sup>c</sup> Includes exanthema and hand, foot, and mouth disease.

<sup>d</sup> With no other localizing signs or symptoms.

Table 5. Number of reports on echoviruses included in the study according to the main clinical manifestation <sup>a</sup>

Main clinical signs/symptoms	Echovirus, type :											Total	
	1	3	4	6	7	9	11	14	17	30	33	No.	%
	total respiratory (lower respiratory)	24 (8)	48 (11)	0 (0)	176 (65)	60 (11)	174 (63)	72 (22)	37 (11)	12 (2)	47 (12)	6 (3)	656 (208)
total CNS (paralytic CNS)	16 (1)	170 (1)	163 (2)	1 576 (8)	177 (3)	1 807 (13)	272 (3)	104 (5)	85 (1)	1 108 (2)	33 (0)	5 511 (39)	69.1 (0.5)
cardiac	2	0	1	17	1	11	7	0	3	7	0	49	0.6
muscular <sup>b</sup>	2	3	0	50	0	4	2	3	0	0	0	64	0.8
gastrointestinal	46	27	2	150	60	80	55	52	17	50	0	539	6.8
skin/mucous membrane <sup>c</sup>	0	6	2	31	40	109	14	9	3	6	0	220	2.8
fever <sup>d</sup>	9	23	2	144	93	160	61	20	42	52	0	606	7.6
others	2	13	0	43	9	43	10	16	0	7	0	143	1.8
nil	7	12	1	42	9	29	46	21	5	8	0	180	2.3
total	108	302	171	2 229	449	2 417	539	262	167	1 285	39	7 968	100.0

<sup>a</sup> Cases with unknown clinical picture are excluded.

<sup>b</sup> Includes Bornholm myalgia.

<sup>c</sup> Includes exanthema.

<sup>d</sup> With no other localizing signs or symptoms.

myocarditis and pericarditis).<sup>1</sup> The clinical picture showed only small differences among the five coxsackievirus B types under study (Table 4).

Table 5 shows that, with the exception of type 1, echovirus was identified most frequently from cases of CNS diseases, mostly aseptic meningitis.<sup>2</sup> Echovirus was also associated with cases of respiratory illness, non-localizing fever, and gastroenteritis. Skin rashes were noted in cases of echovirus 9, as has been found previously (*Brit. med. J.*, 1968). Irrespective of virus type, the largest number of cases of CNS disease were seen in children under 15 years of age (in particular in the age group 5–14 years), and the largest number of cases of respiratory illness in children under 5 years of age.

In coxsackievirus A infections, skin eruptions, including hand, foot, and mouth disease, were encountered mostly in children under 5 years of age.

In contrast, in coxsackievirus B infections, myalgia

was reported in disproportionately large numbers of adults, i.e., those over 15 years of age.

#### DISCUSSION

It is apparent that all types of enterovirus are worldwide in distribution, the limited number of virus types uncovered in individual studies being governed largely by the isolation technique used, by the number of types known at the time of study, and by the number of different typing sera available to, and by the interests of, the investigator.

Variations in the virus types recovered in a given area from year to year were noted early in the study, and their tendency to fluctuate in prevalence has been well demonstrated in later longitudinal studies involving healthy children, hospitalized patients, and the serial sampling of sewage (Gelfand, 1961; Gelfand et al., 1963; *Brit. med. J.*, 1971b).

In any one country, more than one type of enterovirus may become epidemic during the summer months. In some investigations (Gelfand, 1961; Moritsugu et al., 1970) the isolation of echovirus appeared to occur distinctly later than that of the coxsackieviruses. This was not apparent in the present study.

<sup>1</sup> Cocksackievirus infections in Britain in 1970 are reported in detail in *Brit. med. J.* (1970c, 1971b) and conform with the above observations.

<sup>2</sup> Some of the outbreaks reported to WHO have been described in greater detail in the literature—e.g., *Brit. med. J.* (1969a, 1969b, 1970d); National Communicable Disease Center (1969); Roggenkamp et al. (1970); Voorhoeve & Wilterdink (1969); Groh et al., (1971).

However, the results of the present study (Table 1) are in conformity with the observation made in temperate climates that infection goes on throughout the year, though at a much reduced rate in the winter.

The present study unfortunately does not give information on isolations in tropical countries and thus it is not possible to see if there is a contrast in seasonal pattern.

Studies on healthy subjects (Cole et al., 1951; Ramos-Alvarez & Sabin, 1956) indicate that young children constitute the most frequently infected group; older individuals are less frequently infected, primarily because they usually possess preexisting active immunity, but presumably also because of their more limited exposure to the virus. Investigations of patients with an enterovirus disease also show that the same inverse relationship exists between age and virus excretion. However, insufficient data are available in the literature to determine accurately age-specific coxsackievirus attack rates; this is particularly true for the infections caused by different types of coxsackievirus (Dalldorf & Melnick, 1965). In the case of echovirus, the literature shows a marked difference in the frequency of isolation of virus types by age (Wenner, 1962). It has to be remembered that both the age of the patients and the nature of their illness are likely to influence the submission of specimens. Also, in most cases enteroviruses are isolated from faeces and, since the enteroviruses can commonly be isolated from the faeces of healthy persons, the etiological significance of the

isolation in individual cases may be questionable. Notwithstanding these reservations, there is in this study, as has been found by others (Sabin et al., 1958; Johnsson, 1954; McNair Scott, 1961), an apparent age-associated variation in the clinical reaction to infection—e.g., Bornholm disease or myalgia was more frequently reported in adults whereas respiratory disease was mostly noted in younger children. No attempt is made in the present study to relate a clinical feature in certain age groups to the total number of persons investigated in this age group, since the clinical cases selected for laboratory examination were not necessarily representative of all infections with the virus. It is noted that while the majority of neurological cases were among children, in particular in the age group 5–14 years, none the less a disproportionately large number of neurological cases were reported in adults.

The present study demonstrates for temperate areas the importance of enteroviruses other than poliovirus in the production of disease. The study also shows that persistent paralysis is not a common feature, particularly in neurological conditions, although it does sometimes occur.

As the study was limited to 4 years no cyclic trends as have been reported, for example, in Britain (*Brit. med. J.*, 1970b, 1971b) could be included. However, a follow-up study is contemplated, which may not only illustrate cyclic patterns within any one country but may also provide information on the spread of infection across national frontiers.

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## RÉSUMÉ

### ÉTUDE, COUVRANT UNE PÉRIODE DE QUATRE ANS, DES RAPPORTS OMS RELATIFS AUX ENTÉROVIRUS AUTRES QUE LES POLIOVIRUS

En 1963, l'OMS a mis sur pied un système de rassemblement et de diffusion de renseignements sur les virus. Ce système a pris progressivement de l'extension et en 1970 93 laboratoires situés dans 33 pays y participaient et adressaient à l'OMS des rapports sur les infections virales diagnostiquées par isolement du virus ou examens sérologiques. La présente étude analyse les rapports reçus

de 1967 à 1970 concernant les entérovirus autres que les poliovirus, c'est-à-dire les coxsackievirus A et B et les échovirus. Elle ne mentionne un type donné de virus que si un laboratoire signale l'avoir isolé dans 25 au moins des rapports établis au cours d'une des quatre années considérées. De ce fait, le nombre des laboratoires inclus dans l'étude est réduit à 50 et l'analyse est limitée aux

coxsackievirus des types 2, 4, 9, 10 et 16, aux coxsackievirus B des types 1 à 5 et aux échovirus des types 1, 3, 4, 6, 7, 9, 11, 14, 17, 30 et 33.

Parmi les coxsackievirus A, les types les plus fréquemment signalés ont été les types A9 et A16; parmi les coxsackievirus B, les types B3 et B2, et parmi les échovirus, les types 9, 6 et 30. Quel que soit le type, le nombre de mentions dans les rapports envoyés par les laboratoires a varié considérablement d'une année à l'autre. La période de plus forte incidence, pour chacun des trois groupes, s'est étendue de juin à octobre dans l'hémisphère nord et de novembre à février dans l'hémisphère sud.

Les infections à coxsackievirus A ont atteint surtout les enfants de moins de 5 ans; seul le type A9 a été isolé avec une fréquence notable chez des sujets d'autres groupes d'âge. L'incidence des infections à coxsackievirus B a été particulièrement élevée parmi les enfants de moins de 15 ans et 50% environ d'entre elles ont été observées dans le groupe d'âge 0-4 ans. Quant aux échovirus des types 1, 3, 14 et 17, ils ont pour la plupart été isolés chez des enfants âgés de 0 à 4 ans, les autres types étant aussi fréquemment rencontrés dans d'autres groupes d'âge.

Les manifestations cliniques des infections à coxsackievirus et à échovirus ont consisté notamment en méningite aseptique, atteinte de l'appareil respiratoire, éruption cutanée, affection fébrile non différenciée et gastro-

entérite. Une association entre l'isolement d'un virus et un syndrome clinique a été observée avec une fréquence relative très variable selon le groupe de virus et aussi, souvent, au sein d'un même groupe, selon le type. On a relevé une association entre des manifestations cliniques et certains virus: syndrome main-pied-bouche dans l'infection à coxsackievirus A, myalgie (maladie de Bornholm) et affections cardiaques dans l'infection à coxsackievirus B.

Il semble exister une certaine relation entre l'âge et les manifestations cliniques. Quel que soit le type de virus en cause, les atteintes du système nerveux central sont les plus fréquentes chez les sujets de moins de 15 ans, et les maladies de l'appareil respiratoire chez les enfants de moins de 5 ans. Dans les infections à coxsackievirus A, les éruptions cutanées, et en particulier le syndrome main-pied-bouche, sont observées surtout chez les enfants de moins de 5 ans. En revanche, dans les infections à coxsackievirus B, ce sont essentiellement les adultes (sujets âgés de plus de 15 ans) qui présentent des atteintes de myalgie.

La présente étude montre le rôle pathogène important imparti aux entérovirus autres que les poliovirus dans les régions tempérées. Elle ne couvre qu'une période de quatre années, mais on envisage de la poursuivre afin de déceler d'éventuels aspects cycliques de ces infections et de recueillir des informations sur leur propagation d'un pays à d'autres.

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## Annex

## PLACES AND COUNTRIES INCLUDED IN THE STUDY \*

Melbourne, Australia

Sofia, Bulgaria

Belgium (6)

Canada

Copenhagen, Denmark

England, Wales & Northern Ireland

Federal Republic of Germany (21)

Helsinki, Finland

Lyon, France

Utrecht, Netherlands

Budapest, Hungary

Tokyo, Japan

Norway (5)

Bucharest, Romania

Stockholm, Sweden

South Africa

St Gall, Switzerland

California State, USA

New Haven, Conn., USA

New York, N.Y., USA

Atlanta, Ga., USA

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\* The figures in parentheses show the number of laboratories reporting separately.