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The Incidence and Occurrence of Mycoplasma Pneumoniae Pneumonia in Nagasaki City from 1968 to 1982

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The incidence and occurrence of *Mycoplasma pneumoniae* (=*M. pneu.*) pneumonia in patients who visited Nagasaki University Hospital were investigated during the 15-year period from 1968 to 1982.

A total of 2754 selected patients with acute respiratory tract infection, including clinically primary atypical pneumonia (=PAP) (642 cases) were studied. Of these, 241 cases (37.5%) had *M. pneu.* pneumonia as diagnosed on the basis of four-fold or greater rises in specific antibody titers against *M. pneu.* for a titer of 1:64.

Outbreaks occurred during 3-5 year periods including 1971-1972, 1975-1976, and 1980. Most cases were seen in April, May and August showing seasonal peaks in spring and early autumn.

This incidence and occurrence of *M. pneu.* pneumonia in Nagasaki City and surrounding suburbs were compared to those reported in Norway, Finland, Denmark, United Kingdom, the Netherlands and various cities in both the United States and Japan.

——Mycoplasma; Mycoplasma pneumoniae infection; Epidemiology.

INTRODUCTION

M. pneu. pneumonia occurs throughout the world. Longitudinal studies indicate that the disease occurs throughout the year, as do most respiratory disease that peak during the colder months. Although there has been seasonal outbreaks of *M. pneu.* pneumonia were reported in various parts of the world, the degree of communicability appears to be far less than that seen with common respiratory viruses.

Studies have shown that the degree of spread is directly related to the small community as well as military, dormitory facilities, schools and kindergartens. Studies have

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also that the presence of susceptible children is an important indicator in the transmission of disease throughout the family.

The incidence and occurrence of *M. pneu.* infection have been reported in Norway, Finland, Denmark, United Kingdom, the Netherlands and in various cities in Japan and the United States[2)3)6)-17)19)-33)]. Outbreaks generally occur in densely populated areas and under conditions in which subjects are confined to enclosed areas such as military and university housing.

Cyclic patterns of outbreaks general occur within 3-5 year periods.

The purpose of the present study to establish the incidence and occurrence of *M. pneu.* pneumonia in Nagasaki City and the surrounding areas, and to compare those findings with the incidence reported in other part of the world.

MATERIAL AND METHODS

Patients: Patients with acute respiratory disease including 642 cases with PAP were examined at the 2nd Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki Municipal Hospital and Fukui Hospital in Nagasaki City for the presence of *M. pneu.* infection. A total of 2754 patients were examined during a 15-year period from 1968 through 1982.

Diagnosis: The diagnosis of *M. pneu.* infection was made on the basis of microbiological (isolation of *M. pneu.*), serological methods (complement fixation test, cold hemoagglutinin test), clinical signs and symptoms and chest X-ray.

Mycoplasma cultural techniques: Nasopharyngeal swabs, nasopharyngeal washings or sputum specimens were inoculated directly onto PPLO agar and into PPLO broth media on the day of collection. One broth medium tube and two agar plates were used for each specimen. All cultures were incubated at 37°C. The agar plates were observed periodically for development of typical colonies. The identification of *M. pneu.* was determined by the paper disc diffusion method described by CLYDE[4)]. The broth cultures were subcultured to the agar plate following the first signs of growth and at weekly intervals for two to four weeks.

Complement-fixation test: Antigen was made with the FH strain of *M. pneu.*. The procedure used here was essentially that the same with the procedure reported by KENNY and co-worker's[18)]. Blood was obtained at the first visit and generally 2 weeks later for preparation of serum to determined CF antibody titers specific for *M. pneu.* infection. In addition, sera were tested for cold agglutinin titers. Evidence of *M. pneu.* pneumonia was based on specific CF antibody titers of 1:64, or a four-fold or greater rise in antibody titers between the acute and convalescent sera.

Clinical signs and symptoms: All patients were clinically examined for signs and symptoms of cough, sputum, sore throat, nasal discomfort, chest pain, headache, arthralgia, earache and also rales in chest.

Chest X ray: Front and lateral chest X-ray taken at the time of initial examination

were classified according to the location, area and characteristic of shadows by discussion with four specialists of the respiratory diseases.

RESULTS

Six hundread forty two patients with PAP were examined during a 15-year period. Of these, 241 cases (37.5%) were diagnosed as *M. pneu.* pneumonia.

1) **Age and sex (Table 1)**: Age ranged from 10 months to 84 years. Thirty-five cases (14.5%) were aged 9 years or less, 43 cases (17.8%) 10 to 19 years, 51 cases (21.2%) 20 to 29 years, and 55 cases (22.8%) 30 to 39 years. Approximately three-quarters of the patients (76.3%) were aged 40 years or less. The sex ratio was 1.1 male for every female.

2) **Occurrence of M. pneu. pneumonia**: In the number of cases of *M. pneu.* pneumonia and the percentage of *M. pneu.* pneumonia for total PAP during the period from 1968 to 1982 are shown in table 2. Periodic outbreaks of *M. pneu.* pneumonia were observed every three to four years. The first outbreak occurred from 1971 through 1972, the second from August through November in 1975, and in periods the spring of 1976, and the third in the spring of 1980. In these, the percentage of *M. pneu.* pneumonia for PAP showed 40% or more. Particulary, *M. pneu.* pneumonia was observed in 58.4% of all patients with PAP in 1980.

3) **Seasonal distribution**: The seasonal occurrence in the number of cases of *M. pneu.* pneumonia is shown in figure 1. The year was divided into four seasons (spring, summer, fall and winter). The peak of the number of cases was seen in 1972/73, 1975/76 and 1980.

4) **Monthly distribution (Table 3)**: Monthly distribution of the patients with 241 of *M. pneu.* pneumonia revealed that the highest incidences occurred in April (14.9%), May (12.9%) and August (12.0%), while the lowest incidences occurred in January (2.9

Table 1. Distribution of age and sex of M.pneumoniae pneumonia patients.

Age	Male	Female	Total
0····· 5	11	5	16
6····· 9	8	11	19
10·····15	15	4	19
16·····19	14	10	24
20·····29	22	29	51
30·····39	24	31	55
40·····49	19	11	30
50·····59	6	7	13
60·····69	5	4	9
70·····	2	3	5
Total	126	115	241

Table 2. The yearly occurrence in the number of cases of M.pneuminiae pneumonia and the percent of M. pneumoniae pneumonia against total primary atypical pneumonia during the periods from 1968 to 1982 in Nagasaki city and its suburbs.

Year	Primary atypical pneumonia	M.pneumoniae pneumonia	M.pneumoniae pneumonia / Primary atypical pneumonia
1968	8 cases	3 cases	37.5%
1969	15	4	26.7
1970	30	7	23.3
1971	22	10	45.5
1972	32	14	43.8
1973	57	15	26.3
1974	29	3	10.3
1975	81	36	44.4
1976	48	20	41.7
1977	55	9	16.4
1978	36	4	11.1
1979	30	10	33.3
1980	173	101	58.4
1981	11	3	27.3
1982	15	2	13.3
Total	642 cases	241 cases	

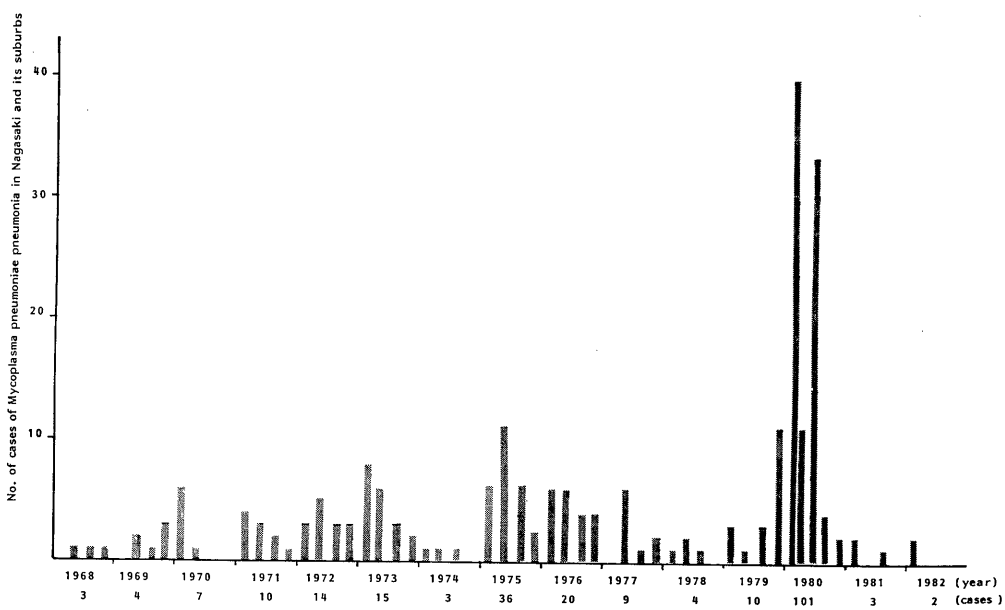

Figure 1. The seasonal occurrence in the number of cases of Mycoplasma pneumoniae pneumonia during the periods from 1968 to 1982. Each year was devided into four seasons: spring (March—May); summer (June—August); fall (September—November) and winter (December—February).

Table 3. Monthly occurrence of M. pneumoniae pneumonia during the periods from 1968 through 1982

	Jan.	Feb.	Mar.	Apr.	May.	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Total
1968						1				1		1	3
1969	1						1	1	1				4
1970				5	1			1					7
1971	1		2		2	2		1		1	1		10
1972		1	1	2		2	2	1			3	2	14
1973	1	1		5	2	2	1		1	2			15
1974								1		1		1	3
1975			3	2	1	1	1	9	6	5	5	3	36
1676	1	2		3	3	3	2	1		1	3	1	20
1977	2					2		4		1			9
1978					1			2	1				4
1979		1	1	1	1			1	2	1		2	10
1980	1	8	19	16	19	10	15	7	2		2	2	101
1981			1	1					1				3
1982				1	1								2
Total	7	13	27	36	31	23	22	29	14	13	14	12	241

%) and December (5.0%). A tendency for a low prevalence was observed in the witer season. As shown in Figue 2, a difference in patterns of seasonal incidence was observed between 1975 and 1980, showing that the peak was observed from late summer through fall in 1975, whereas it was observed in spring in 1980.

5) **CF titer in all patients with acute respiratory disease (Figure 3)**: The highest titer of the CF antibody in 2754 patients with acute respiratory diseases tested during a 15-year peroid revealed high values in 1971/72, 1975/76 and 1980, paralleling with high incidence of *M. pneu.* pneumonia.

6) **Isolation of M. pneumoniae**: Specimens taken from 154 patients with *M. pneu.* pneumonia were cultured from *M. pneu.* pneumonia. Of these, *M. pneu.* was isolated from upper respiratory tract in 80 cases (51.9%).

7) **Clinical manifestations**: The clinical signs and symptoms of patients with *M. pneu.* pneumonia at the initial examination are shown in table 4. All patients produced a characteristic cough, which was particularly severe at night and some patients had persisting cough for 3 to 4 weeks, even after the resolution of abnormal roentgenographic findings. Fever (≧37°C) was present 220 patients (93.6%); 32.8% of them had fever greater than 39°C, and 68.9% had fever of 38°C. Of the patients, sputum was ejected in 73.6% dry or moist rales were found in 60.4%, headache developed in 54.3%, and chest pain was present in 22.0%. Although myringitis has been reported to be aassociated with *M. pneu.* pneumonia in children, it was present in only 6 cases. Skin rash was a complicated in 5 patients. Thus, the salient features of *M. pneu.* pneumonia in the present study were persistent cough, sputum ejection, fever and headache, whereas symptoms such as nasal symptoms, chest discomfort and sore throat were relatively low incidence.

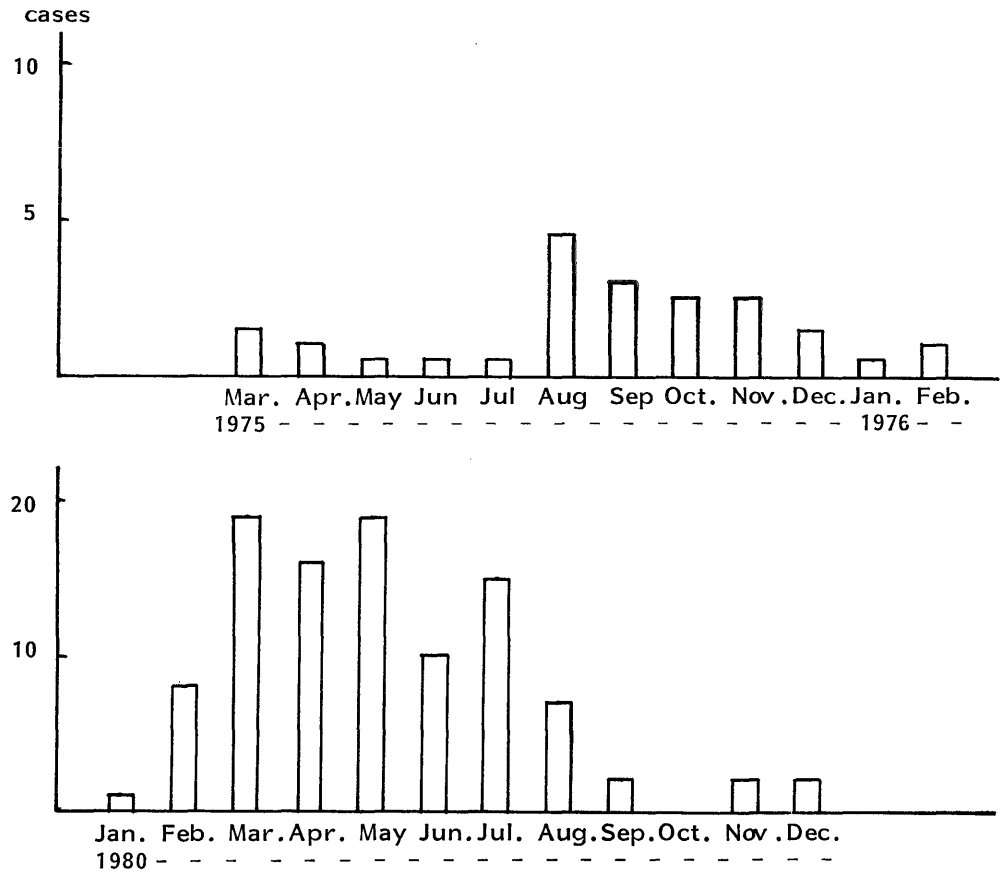

Figure 2. Monthly incidence of M. pneumoniae pneumonia in 1975 and 1980

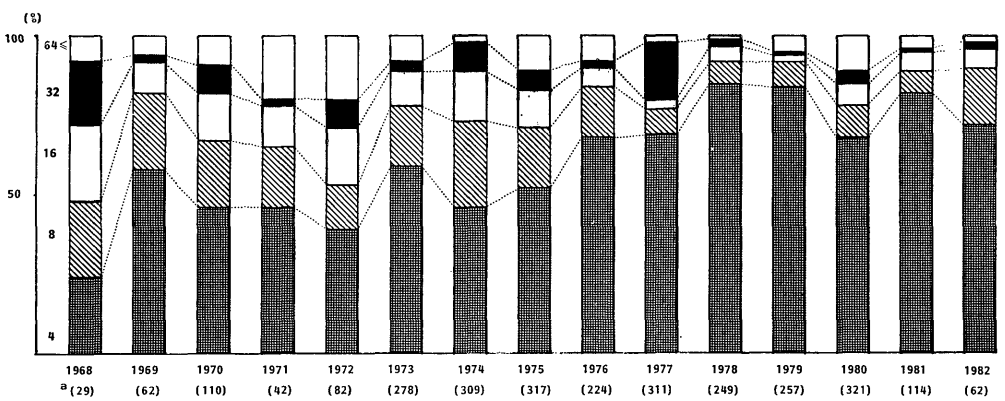

Figure 3. Percentage of CF antibodies titer against Mycoplasma pneumoniae of acute respiratory diseases patients in Nagasaki city and its suburbs.
a( ): the number of acute respiratory disease patients in each year.

8) **Laboratory findings**: Laboratory data revealed that leucocyte count remained within the normal limits in almost all cases, but some patients showed remarkable leucocytosis. Sedimentation rate increased moderately and C-reactive protein was positive in about 85% of all cases. The cold hemoagglutinin titers of 64 fold or more were detected in 53.6% of 224 cases of *M. pneu.* pneumonia, whereas in 43.0% of 249 cases with PAP (Table 5). Impairement of liver function was noted in 27 (20.6%) out of 131 patients examined.

Table 4. Clinical symptoms and findings in M. pneumoniae pneumonia patients.

	No. of patients investigated	positive cases	percent of positive cases
Cough	241	241	100.0
Sputum	231	170	73.6
Sore throat	238	78	32.8
Coryzal symptom	239	37	15.5
Chest pain	236	52	22.0
Fever	235	220	93.6
36.0···		15	6.4
37.0···		58	24.7
38.0···		85	36.2
39.0···		67	28.5
40.0···		10	4.3
Headache	232	126	54.3
Digestive disorder	125	16	12.8
Arthralgia	220	14	6.4
Skin rash	?	5	?
Otalgia	?	6	?
Rales	235	142	60.4
Liver function disorder	131	27	20.6

Table 5. Distribution of cold hemoagglutinin titers in M. pneumoniae pneumonia and primary atypical pneumonia at initial examination.

Cold hemoagglutinin titer	*M.pneumoniae positive*		*M.pneumoniae negative*	
	(cases)	(%)	(cases)	(%)
·····2048×	3	1.3	2	0.8
1024	10	4.5	4	1.6
512	29	12.9	10	4.0
256	23	10.3	22	8.8
128	34	15.2	39	15.7
64	21	9.4	30	12.0
32	21	9.4	27	10.8
16	14	6.3	18	7.2
8	15	6.7	33	13.3
4·····	54	24.1	64	25.7
Total	224 cases		249 cases	

9) **Roentgenographic findings**: The shadows were most commonly observed in the lower field, followed in order by the right lower field, the left lower field, and the middle lower field. Frontal and lateral chest X-ray revealed preferential occurrence of the lesion in the segments of S^4, S^5, S^8 and S^{10} of the right lung and mainly around in the segments of S^3, S^{10} of the left lung. Forty-three cases (17.8%) had bilateral abnormalities. The BROLIN's classification[1] of disease was used to evaluate the chest X-ray patterns in the present study group. Of patients studied at the first examination, 54% showed an alveolar pattern, 9% an interstitial pattern and 30% had a mixed alveolar an interstitial pattern of initial examination. Pleural effusion was developed in 11 patients (4.6%) and atelectatic changes was observed in 3 patients.

DISCUSSION

M. pneu. infections commonly occures in children and young adults[5]. *M. pneu.* pneumonia has been reported to account for 10 to 40% of all cases of PAP[20]. This wide deviation in the incidence of *M. pneu.* pneumonia is attributed to differences in age and life style of the patients surveyed and variations in prevalence.

In the present study, I examined 241 patients (37.5%) ranging in age from 10 months to 84 years with *M. pneu.* pneumonia among 642 cases of PAP encountered over the past 15 years. During this time periodic epidemic peaks were noted every 3 to 5 years. Each epidemic period continued for 6 to 8 months. These epidemic peaks were also noted by LIND[23)24)], PONKA[30)31)] and NIITSU[28)]. Seasonal prevalence was difference for each epidemic year with a slight tendency towards decrease in the months from October to February. As to age, a large proportion of the patients were less than 40 years old in the present study. On the other hand, the incidence was low in patients aged above 50 years. The youngest patient was a 10-month-old male and the oldest an 84-year-old female.

Various studies have been carried out on the occurrence of *M. pneu.* infections in Europe (Figure 4). LIND[22)23)24)] reported their results for a 17-years study from 1958 through 1974, by which sera were supplied by a central serological laboratory. All samples were examined for cold agglutinins and *M. pneu.* antibody titer. It was reported that four epidemics had occurred at regular four and a half year intervals. There were four epidemic peaks in 1958/59, 1962/63, 1967/68 and 1971/72.

In England, NOAH[29)] carried out a 9-year study, from 1967 through 1975, at the Epidemiological Research Laboratory of the Public Health Laboratory Service. They observed outbreaks of *M. pneu.* infections in 1971/72 and 1974/75. There was also moderate of a peak in 1967/68, indicating a probable epidemic. These epidemics occurred every 3 to 5 years.

In the Netherlands, HERS[15)] carried out a 6-year study from 1961 through 1966. He detected *M. pneu.* infections in 256 (41.2%) out of 622 patients with respiratory tract infections. The outbreaks occurred every 4 years, in 1961/62 and 1965/66.

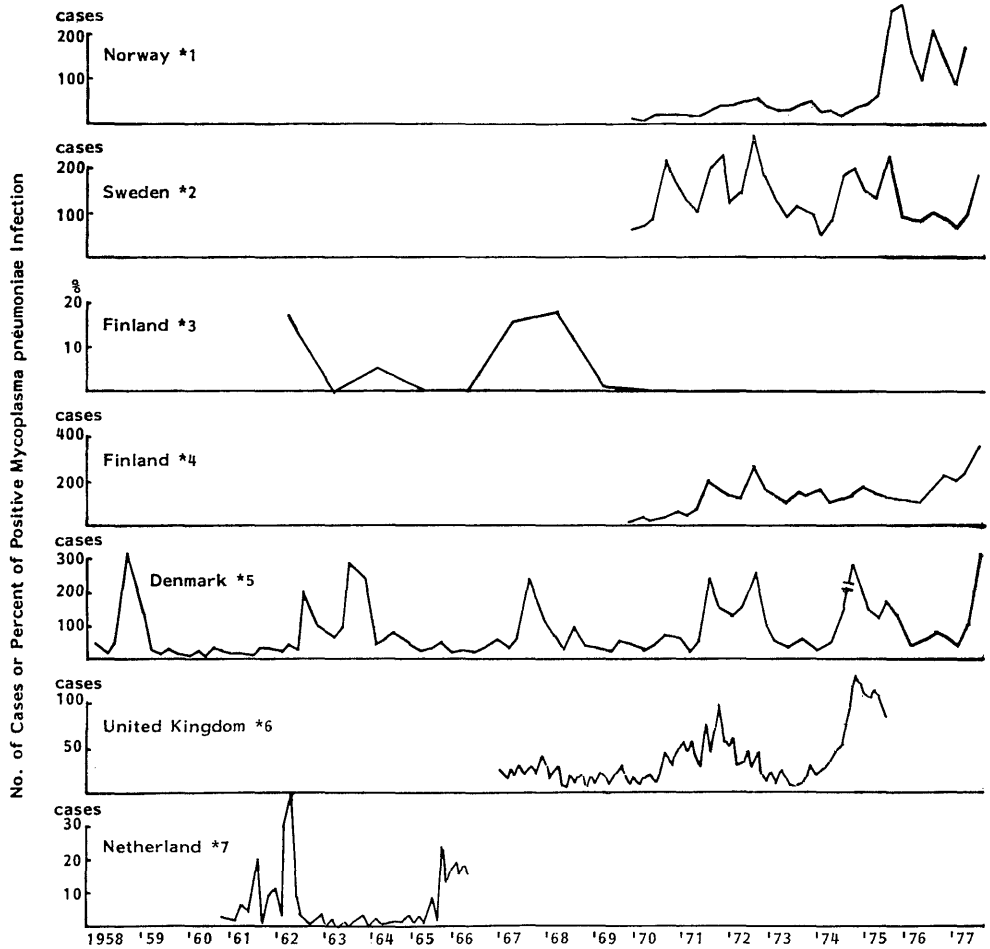

Figure 4. The data presented represents the number of cases of primary atypical pneumonia reported or the percent of cases with acute respiratory disease due to *M. pneumoniae*. Diagnosis was made primarily by serologic guidance. Data obtained from the following references: Norway No. 1 (30), Sweden No. 2 (30), Finland No. 3 (16), Finland No. 4 (30), Denmark No. 5 (24, 30), United Kingdom No. 6 (29) and The Netherlands No. 7 (15).

JANSSON[16] reported a 9-year study in Finland from 1962 through 1970, in which he had 146 cases of *M. pneu.* pneumonia. During this period, three epidemic waves had developed in 1962, 1963/64 and 1967/68. Also in Finland, PONKA[30] performed an 8-year study from 1970 through 1977, and identified 4114 cases of *M. pneu.* infection. There were two peak waves of outbreak during this period, in 1972/73 and in 1977. The interval between these two epidemics was about 5 years. Epidemics were seen in other Scandinavian countries 1971/72,1974/75 and 1977 in Sweden, 1974/75 and 1977 in Denmark and 1975/76 and 1977 in Norway.

According to these reports, there were some basic similarities in the patterns of the outbreaks of *M. pneu.* infections in these European countries. Longitudinal studies

on the occurrence of *M. pneu.* infections were carried out in both Denmark and Finland, and it was shown that there were simultaneous epidemics in 1962/63, 1967/68, 1971/72 and 1977. Sweden had peak waves in 1971/72 and 1974/75 and Norway had outbreaks in 1975/76 and 1977. Thus, the Scandinavian countries experienced epidemics in practically in the same years. In England and the Netherlands, as well, the peak incidences of *M. pneu.* infections occurred in almost the same years as in the Scandinavian countries.

With regard to the periodicity of the *M. pneu.* infection epidemics, LIND[22)23)24)] noted a four and a half year interval between the peaks of the waves, NOAH[29)] a 3-4 years interval, and JANSSON[16)] a 5-year interval.

Survey data are also available from the United States (Figure 5).

EVANS,[7)] carried out a 13-year study from 1953 to 1965 in Wisconsin. Evans studied 2549 students with acute lower respiratory tract infections of the incidence of *M. pneu.* infections. Three hundreds and seventy-eight were diagnosed to have *M. pneu.* infections, indicating that epidemics occurred in 1954/55, 1960/61 and 1964/65, showing to be 4-5 years. MONTO[26)] carried out a 6-year study of 3243 cases of respiratory in-

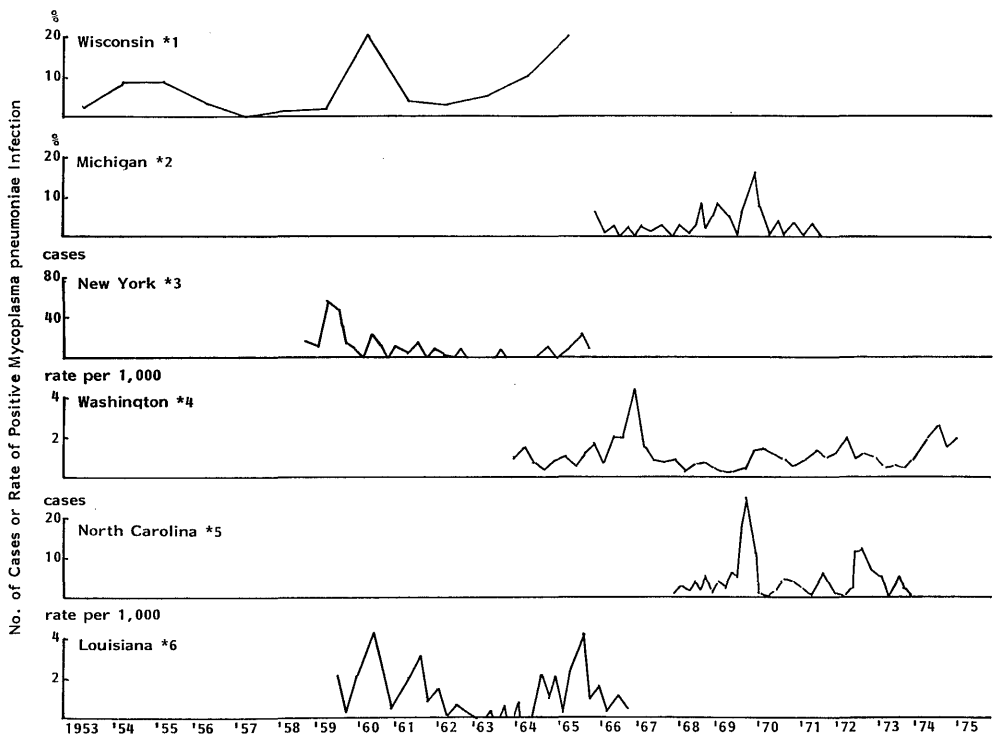

Figure 5. The data presented represents the number of cases of primary atypical pneumonia reported or the percent of cases with acute respiratory disease due to *M. pneumoniae*. Diagnosis was made primarily by serologic evidence. Data obained from the following references: Wisconsin No. 1 (7), Michigan No. 2(26), New York No. 3 (3), Washington State No. 4 (12), North Carolina No. 5 (8) and Louisiana No. 6 (27)

fections in Michigan between 1966 and 1971. *M. pneu.* infections were identified in 172 of these patients. Outbreaks of *M. pneu.* infections occurred in 1968/69 and 1970.

CHANOCK[3] studied the incidence of *M. pneu.* infections in Marine recruits durnig the 7-year-period from 1959 through 1965. The results indicated that 38% of 1369 cases of pneumonia were *M. pneu.* infections. Epidemics occurred in 1959/60 and 1965.

A epidemic survey of *M. pneu.* infections was carried out by FOY[12] in Washington State between 1963 and 1975. A total of 15,141 cases of pneumonia was investigated, and 13% of these were found to be positive for *M. pneu.* infection. During this period, two outbreaks occurred in 1967 and 1974.

MOGABGAB[27] carried out a 7-year survey from 1959 through 1966, of young airmen at a Mississippi Air Force base. This study revealed outbreaks in the years 1960/61 and 1965.

According to these data in the United States, it was suggested that *M. pneu.* infections were occurred with a intervals of 3 to 5 years for the period from 1953 through 1975.

In Japan, KITAMOTO [19,20] carried out a 6-year survey from 1963 through 1968 in Tokyo (Figure 6). A total of 235 cases of *M. pneu.* pneumonia were found among 639 cases of PAP showing an incidence of 37%, A comparison study of the incidences for each year revealed outbreaks of *M. pneu.* infections in 1964 and 1968 with the interval of 4 years.

NIITSU[28] made a 21-year survey in Sendai City, extending from 1960 through 1980. They carried out tests for *M. pneu.* infections which were diagnosed as having pneumonia based on the results of chest X-ray in mass medical examination of school children. The data revealed epidemics in the years of 1964, 1968, 1972, 1976 and 1980, which means that a peak of *M. pneu.* infection occurred at regular intervals of 4 years, showing beautiful cyclic patterns in Sendai.

The present study was carried out in Nagasaki City and its suburbs during the 15-year period from 1968 through 1982.

The results of the survey indicated that the percentage of patients found to be positive for CF antibody titer for *M. pneu.* and the number of patients diagnosed for *M. pneu.* pneumonia showed peaks in 1971/72, 1975/76 and 1980. Seasonal epidemic peaks occurred in 1972/73, 1975/76 and 1980.

Thus, *M. pneu.* infections showed a cyclic pattern of recurrence of about 3 to 5 years in Nagasaki area. A comparison among the three Japanese cities of Sendai, Tokyo and Nagasaki shows that both Sendai and Tokyo had epidemics in 1964 and 1968, whereas both Nagasaki and Sendai had outbreaks in 1972, 1976 and 1980.

M. pneu. infections have monthly been reported in fall and winter, but may also occur at other seasons[31]. In the present study, a comparison of the number of cases of *M. pneu.* infections and monthly occurrence shows that the greatest number of infections occurred in April and August, whereas the fewest were recored in the winter. However, different patterns were observed in monthly incidence among each epidemic year.

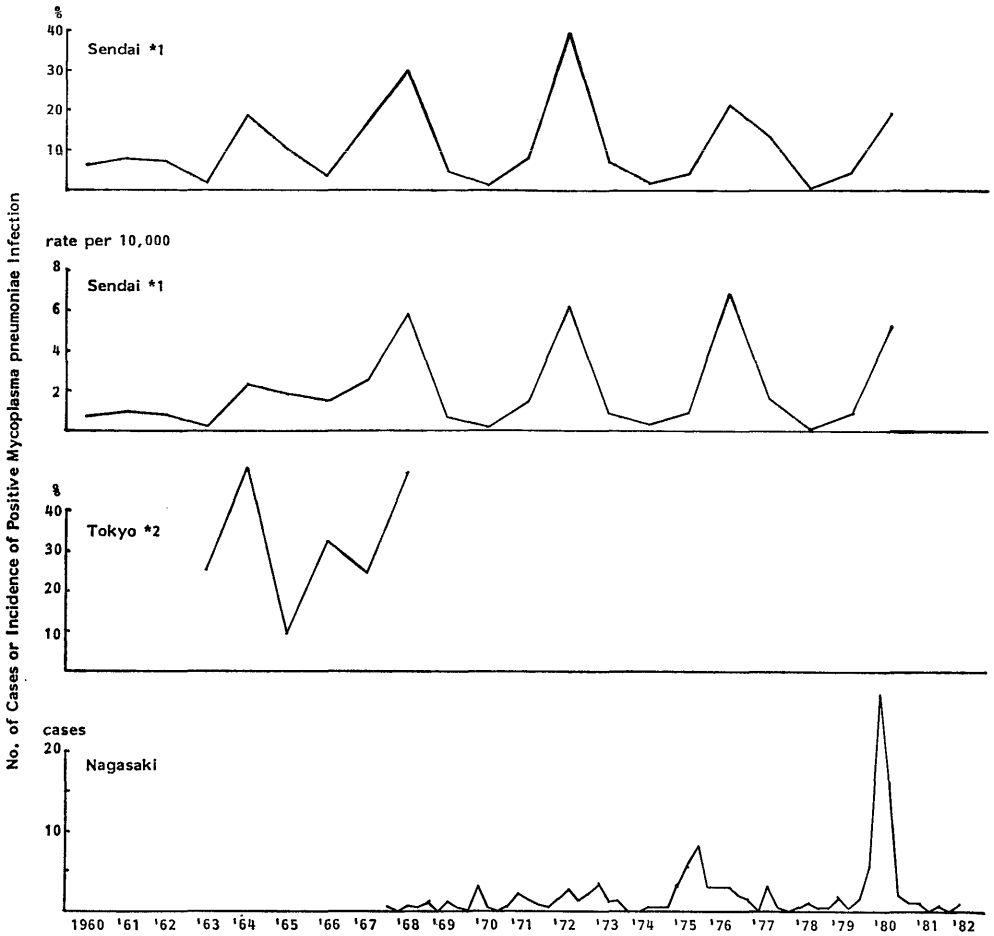

Figure 6. The data presented represents the number of cases of primary atypical pneumonia reported, the rate per 10,000 population or the percent of cases with acute respiratory disease due to *M. pneumoniae*. Data obtained from the following references: Sendai No. 1(28), Tokyo No. 2(20) and Nagasaki by author's.

The peaks of occurrence were observed in August, September and October in the epidemic year of 1975, but in March, April, May, June and July in 1980 (Figure 2).

On the other hand, POMKA[30)31)] found a large number of *M. pneu.* infections in the months of October, November and December, but few in June, July and August. EVANS[7)] detected peaks in September and October, and continuing into November and December.

EDWARDS[6)] reported that, as a result of averaging the data obtained for a 5-year period, the smallest number of cases of *M. pneu.* infections was seen in May, while peaks occurred in September and November.

LIND[22)] reported that outbreaks occurred in the three months of October, November and December.

GRAYSTON[14] reported that *M. pneu.* infections increased in the winter and spring, whereas FRANSEN[13] detected many cases from fall to winter.

FOY[12] and MONTO[26], on the other hand, reported no seasonal characteristics in the number of cases of *M. pneu.* infections.

With regard to extensive epidemics, *M. pneu.* infections are very prolonged, lasting for months at least a few months. My data also showed that the epidemics in 1975 and 1980 extended for 5 to 6 months. These prolonged epidemic is understandable in view of the long incubation period of the disease[15][21][29] and the prolonged carriage of *M. pneu.* in the infected patient.

As for regional defferences in *M. pneu.* infection epidemics, KRENCH[21] divided Switzerland into central, eastern and western sections, and investigated the changes in the population bearing antibodies against *M. pneu.*. He noted that an epidemic occurred in the central region in 1965, and in the eastern section in 1966. He thus found that there was a slight difference in the time of epidemics among the regions of Switzerland.

TAKESHITA[33] also reported that there were considerable differences of the distribution of CF antibodies titer for *M. pneu.* among the three areas of Nagasaki, Ohmura and Sasebo in Nagasaki Prefecture.

Therefore, differences are seen in timing of occurrence of *M. pneu.* epidemics, even among these closely-situated areas. These findings indicate that *M. pneu.* epidemics represent minor epidemics in small areas, rather than an epidemic rapidly spreading over wide regions at the same time. Also the outbreak of *M. pneu.* infections and the distributions of antibody titer in the population discloses that the waves of outbreaks of *M. pneu.* infections were not seen over the world at the same season. Furthermore, the individual sensitivity to *M. pneu.* and the presence of protective antibodies against *M. pneu.* appear to be important factors in the occurrence of *M. pneu.* epidemics and the development of disease.

According to STEINBERG[32], the environment of a military platoon is optimal for the development of an *M. pneu.* epidemic, and such a closed and small environment were seems to be a key to factor to support an epidemic. STEINBERG[32] also reported that the presence of antibodies for *M. pneu.* influenced the spread of the epidemic.

MACCORMICK[25] carried out a detailed study with regard to the relationship between *M. pneu.* epidemics and pre-existing *M. pneu.* antibodies in the military. The results showed a clear relationship between the presence of an antibody titer of 1:16 or more and the development of "mild infection" or "serious pneumonia".

The occurrence of an epidemic of *M. pneu.* infection is dependent on the presence of antibodies against *M. pneu.* in the general population. It is thought that the next outbreaks in some regions will be begin the year when the titer of acquired antibody from the last epidemic gradually decreased. The interval between the peak of the waves of *M. pneu.* infections shows cyclic variation. It has been posturated that the seasons for these long cyclic intervals is a long incubation period[9][11], or a low communicability in the infection of *M. pneu.*[24]. Most reports have shown an interval of 4 to 4.5 years,

but it would seem reasonable to assume an interval within the range of 3 to 5 years.

In the present study, 642 cases with PAP were examined over the past 15 years. The percentage of *M. pneu.* pneumonia for PAP is 37.5%. Three epidemic waves of *M. pneu.* infection were seen in Nagasaki city during and surrounding suburbs during 1968 to 1982.

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REFERENCES

1) BROLIN, I. and WERNSTEDT, L. (1978) Ragiographic appearance mycoplasma pneumonia. *Scand. J. Resp. Dis.* 59: 179–189.

2) CHANOCK, R. M. (1965) Mycoplasma infections of man. *N. Engl. J. Med.* 273: 1257–1264.

3) CHANOCK, R. M., FOX, H. H., JAMES, W. D. (1967) Epidemiology of Mycoplasma pneumoniae infection in military recruits. *Ann. N. Y. Acad. Sci.* 143: 484–496.

4) CLYDE, W. A. (1964) Mycoplasma species identification based upon growth inhibition by specific antisera. *J. Immunol.* 92: 958–965.

5) CLYDE, W. A. (1979) Mycoplasma pneumoniae infections of man. In: *THE MYCOPLASMAS* Vol. II, Academic Press, New York, p 275–306.

6) EDWARDS, E. A., CRAWFOD, Y. E., PIERCE, W. E., PECKINPAUGH, R.O. (1976) A longitudinal study of Mycoplasma pneumoniae infections in navy recruits by isolation and sero-epidemiology. *Amer. J. Epidemiol.* 104: 556–562.

7) EVANS, A. S., ALLEN, V., SUELTMANN, S. (1967) Mycoplasma pneumoniae infections in University of Wisconsin students. *Amer. Rev. Respir. Dis.* 96: 237–244.

8) FERNALD, G. W., COLLIER, A. M., CLYDE, W. A. (1975) Respiratory infections due to Mycoplasma pneumoniae in infants and children. *Pediatrics* 55: 327–335.

9) FOY, H. M., GEAYSTON, J. T., KENNY, G. E., ALEXANDER, E. R., MCMAHAN, R. (1966) Epidemiology of Mycoplasma pneumoniae infection in families. *J. A. M. A.* 197: 859–866.

10) FOY, H. M., KENNY, G. E., MCMAHAN, R., MANSY, A. M., GRAYSTON, J. T. (1970) Mycoplasma pneumoniae pneumonia in an urban area. *J. A. M. A.* 214: 1666–1672.

11) FOY, H. M., COONEY, M. K., MCMAHAN, R., GRAYSTON, T. (1973) Viral and Mycoplasma pneumoniae in aprepaid medical care group during an eight-year period. *Amer. J. Epidemiol.* 97: 93–102.

12) FOY, H. M., KENNY, G. E., COONEY, M. K., ALLAN, I. D. (1979) Long-term epidemiology of infections with Mycoplasma pneumoniae. *J. Infect. Dis.* 139: 681–687.

13) FRANSEN, H., FORSGREN, M., HEIGL, Z., TUNEVALL, G. (1969) Studies on Mycoplasma pneumoniae in patients hospitalized with acute respiratory illness. *Scand. J. Infet. Dis.* 1: 91−98.

14) GRAYSTON. J. T., KENNY, G. E., FOY, H. M., KRONNMAL, R. A., ALEXANDER, E. R. (1967) Epidemiological studies of Mycoplasma pneumoniae infections in civilians. *Ann. N. Y. Acad. Sci.* 143: 436−446.

15) HERS, J. F., MASUREL, N. (1967) Infection with Mycoplasma pneumoniae in civilians in the Netherlands. *Ann. N. Y. Acad. Sci.* 143: 447−460.

16) JANSSON, E., ROBERT, E., TUURI, S. (1971) Mycoplasma pneumoniae pneumonia in Helsinki 1962−1970. *Scand. J. Infect. Dis.* 3: 51−54.

17) JOOSTING, A. C. C., HARWIN, R. M., COPPIN, A., BATTAGLIA, P., HOEF, P. A. (1976) Serological investigation of Mycoplasma pneumoniae infection on the Witwaterland. *S. A. Med. J.* 50: 2134−2135.

18) KENNY, G. E. and GRAYSTON, J. T. (1965) Eaton pleuro-pneumonia-like organism (Mycoplasma pneumoniae) complement fixation antigen. *J. Immunol.* 95: 19.

19) KITAMOTO, O. (1970) Mycoplasma infection. *J. Jpn. Assoc. Infect. Dis.* 43: 251−255.

20) KITAMOTO, O. (1970) Mycoplasma common cold syndrome and Mycoplasmal pueumonia. *J. Jpn. Med. Assoc.* 63: 805−811.

21) KRENCH, U., PACCAUD, M. (1967) Comparative studies on the occurrence of Mycoplasma pneumoniae infections in Geneva and St Gallen. *Path. Microbiol.* 30: 1037−1040.

22) LIND, K. (1971) Incidence of Mycoplasma pneumoniae infection in Denmark from 1958−1969. *Acta Path. Microbiol. Scand.* Section B 79: 239−247.

23) LIND, K., BENTZON, M. W. (1976) The incidence of Mycoplasma pneumoniae infections in Denmark over the past seventeen years. *Infection* 4: 29−32.

24) LIND, K., BENTZON, M. W. (1976) Epidemics of Mycoplasma pneumoniae infections in Denmark from 1958 to 1974. *Int. J. Epidemiol.* 5: 267−277.

25) MACCORMICK, D. P., WENZEL, R. P., SENTERFIT, L. B., BEAM, W. E. (1974) Relationship of pre-existing antibody to subsequent infection by Mycoplasma pneumoniae in adults. *Infect. Immun.* 9: 53−59.

26) MONTO, A. S., BRYAN, E. R., RHODES, L. M. (1975) The Tecumseh study of respiratory illness. *Amer. J. Epidemiol.* 100: 458−468.

27) MOGABGAB, W.J. (1968) Mycoplasma pneumoniae and adenovirus respiratory illness in military and university personnel, 1959−1966. *Amer. Rev. Resp. Dis.* 97: 345−358.

28) NIITSÜ, V., SUZAKI, K., MIYAJI, T., HORIKAWA, M., KOMATSU, S., TERASAKI, M., SUETAKE, T. (1981) A very cyclic pattern of recurrence of every 4 years in Mycoplasma pneumoniae infection and susceptibility of clinical isolates of Mycoplasma pneumoniae to antibiotics. In: Proceeding of the VIII Annual Congress of the Japanese Society of Mycoplasmology, Tokyo, p163−168.

29) NOAH, N. D. (1976) Epidemiology of Mycoplasma pneumoniae infection in the United Kingdom. *Infection* 4: 25−28.

30) PONKA, A. (1980) Occurrence of serologically verified Mycoplasma pneumoniae infections in Finland and in Scandinavia in 1970−1977. *Scand. J. Infect. Dis.* 12:

27−31, 1980.

31) PONKA, A. (1979) The occurrence and clinical picture of serologically verified Mycoplasma pneumoniae infections with enphasis on central nervous system, cardiac and joint manifestations. *Ann. Clin. Res.* 11 Suppl 24: 1−60.

32) STEINBERG, P., WHITE, R. J., FULD, S. L., GUTEKUNST, R. R., CHANOCK, R. M. (1969) Ecology of Mycoplasma pneumoniae infections in marine recruits at Parris island. *Amer. J. Epidemiol.* 89: 62−73.

33) TAKESHITA, J. (1969) Study on carring state of antibodies against Mycoplama pneumoniae in civillian population. *Nagasaki Med. J.* 44: 226−244.