Acta virol. **32** : 235—242, 1988

CALCULATION OF THE FREQUENCY OF CONGENITAL RUBELLA SYNDROME IN POLAND

D. IMBS, D. SANDOW*, N. DENKMANN*, M. KAŃTOCH

Department of Virology, National Institute of Hygiene, 00791 Warsaw, Poland, and *Institute of Medical Microbiology of Martin Luther University, Halle, G.D.R.

Received March 26, 1987; revised September 29, 1987

Summary. — The annual number and incidence of congenital rubella syndrome (CRS) in Poland was evaluated by means of a methematical model and on the basis of serological studies. In its principles this model describes the infectious kinetics of rubella by the formula $y = 1 - e^{-at}$, where "y" is the rate of immune persons, "a" is a parameter representing the transfer of susceptibles to immunes and "t" is age. The calculated incidence of congenital rubella syndrome resulted in average values of 0.15 to 0.38 $^0/_{00}$, i.e. 15 to 38 CRS cases among 100 000 children born to mothers primarily infected by rubella virus during the first trimester of pregnancy.

Key words: congenital rubella; mathematical evaluation

Introduction

Rubella infections during pregnancy have been proved to cause a wide variety of congenital defects termed the congenital rubella syndrome (CRS). However, general data about the frequency of CRS are not available. The findings in the U.S.A. and various European countries cannot be generalized absolutely. The epidemiological situation concerning a country should only be evaluated by own representative investigations of the frequency of CRS. For this reason we tried to estimate the frequency of CRS in the country, especially because no mass rubella vaccination is performed up to now in Poland. A mathematical model on the basis of serological studies is described.

Materials and Methods

Serological surveys. The model is based on comprehensive seroepidemiological studies carried out in representatively selected areas of Poland (Imbs *et al.*, 1980; Imbs *et al.*, 1985). The calculation included 1629 sera collected from females in 1979 and 1211 sera taken from females and males in 1982. Year 1979 was preepidemic, year 1982 was postepidemic (Kańtoch and Imbs, 1986). With respect to the principles of the model the considered persons are aged from 1 to 60 years. Persons with haemagglutination inhibition (HI) antibody titres $\geq 1 : 10$ were regarded as seropositive.

The mathematical model. The mathematical calculation of the frequency of CRS and its premises were previously described (Berger, 1973; Sandow *et al.*, 1976). In brief, the model explains the kinetics of rubella virus infection in a population. The principle of the model can be described in the equation:

$$y = 1 - e^{-at} \tag{1}$$

where "y" is the proportion of immune persons, "t" is age of these persons and "a" is the time-independent parameter representing the transfer between the susceptible and infected state. The parameter "a" was calculated by its iterative variation till the total of square deviations between the age-dependent portions of immune persons really observed and estimated by equation (*1*) resulted in a minimum.

Following from the equation (*1*) the access "$\Delta\bar{y}_i$" of persons at a given age "t_i" and within a defined period "Δt" could be estimated thus:

$$\Delta\bar{y}_i = y\,(t_i + \Delta t) - y(t_i) = e^{-at_i}\,(1 - e^{-a\Delta t}) \tag{2}$$

In a further step we obtained the number "S_i" of primarily infected pregnant women by using the formula

$$S_i = \Delta\bar{y}_1 \,.\, N_i \tag{3}$$

where "N_i" is the annual number of registered live births of women at the age "t_i". The number of newborns was used because a register of pregnant women is not available.

Then the average risk of infection during the first trimester of pregnancy was taken as

$$f = \frac{1}{3} \cdot \frac{\sum_{i=1}^{n} S_1}{\sum_{j=1}^{n} N_j} \tag{4}$$

Finally we calculated the frequency of CRS

$$r = v \,.\, f$$

The symbol "v" means the reported portions of CRS in infants born to mothers infected with rubella during the first trimester of pregnancy.

Table 1. Observed and calculated rubella seropositivity in Poland according to serological studies in female population, 1979.

Age groups (years)	Middle of groups t_i	Number of persons N_i	Rate of immunity (%) observed $\bar{y}_i$	Rate of immunity (%) calculated[1] $\bar{y}_i$
1— 2	2.0	98	28.57	22.77
3— 4	4.0	97	43.30	40.35
5— 9	7.5	246	58.94	62.05
10—14	12.5	252	76.98	80.11
15—19	17.5	264	90.53	89.57
20—24	22.5	138	94.20	94.53
25—29	27.5	135	97.04	97.14
30—34	32.5	136	97.06	98.50
35—39	37.5	127	100.00	99.21
40—59	50.0	136	97.09	99.84
Total		N = 1629		

[1]) Calculation by $y = 1 - e^{-at}$; $a = 0.129$

Table 2. Observed and calculated rubella seropositivity in Poland according to serological studies in female and male population, 1982.

Age groups (years)	Middle of groups t_i	Number N_i	Female persons rate of immunity (%) observed $\overline{y}_i$	Female persons rate of immunity (%) calculated[1] $\overline{y}_i$	Number N_i	Male persons rate of immunity (%) observed $\overline{y}_i$	Male persons rate of immunity (%) calculated[1] $\overline{y}_i$
1— 2	2.0	38	42.10	28.19	48	29.17	24.04
3— 4	4.0	42	47.62	48.43	42	40.48	42.30
5— 9	7.5	105	63.81	71.11	121	64.46	64.34
10—14	12.5	119	89.08	87.37	110	81.82	82.06
15—19	17.5	116	92.24	94.48	111	93.69	90.98
20—24	22.5	70	92.85	97.59	52	88.46	95.46
25—29	27.5	71	97.18	98.95	53	96.23	97.72
30—34	32.5	57	100.00	99.54	56	100.00	98.85
Total		N = 618			N = 593		

[1] calculation by $y = 1 - e^{-at}$; $a_{female} = 0.166$; $a_{male} = 0.137$; $a_{total} = 0.150$

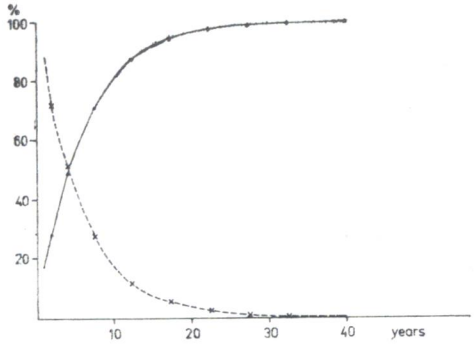

Fig. 1.
Calculated immunity and susceptibility against the rubella virus in female population of Poland
Calculation on the basis of a serological survey, 1982.
●——● immune persons
x— — — —x susceptible persons

Results

The Tables 1 and 2 show the age-dependent seropositivity observed by and calculated according to the serological surveys in 1979 and 1982. The calculated seropositivity and susceptibility resulting from the survey of female population in 1982 are illustrated in Figure 1. The female persons aged up to 20 years showed a faster increase of seropositivity in 1982 than 1979. Further, in 1982 a different seropositivity rate was found between female and male population. The females tested up to 20 years revealed HI antibodies 4 to 7 % more frequently than males in the same age group. The difference of this epidemiological situation was also expressed by various values of the parameter "a" (Table 3).

According to the further steps of our model the annually expected number and incidence of primarily infected pregnant women was computed (Table 3, Fig. 2). However, the birth register needed for the calculation contained only the annual number of infants born to mothers grouped in ages of 5 years. For this reason the number and incidence of primarily infected pregnant women per year were determined by forming the quotient ΣS_i (per 5 yrs) 5 (Table 3). Thus, on the basis of the survey in 1979 as incidence of primary infectious we calculated a value of 5.52 $^0/_{00}$ for all pregnant women, and the value of 1.84 $^0/_{00}$ for women in the first trimester of pregnancy. Considering the survey from 1982 these values amounted only 2.94 $^0/_{00}$ and 0.98 $^0/_{00}$, respectively.

In an equal manner, the annual age-dependent number "S" of primarily infected pregnant women (Fig. 2) was estimated by the quotients "$S_i/5$" formed for the given age-groups with intervals of 5 years. It showed a maximum in the group from 20 to 25 years old. The differences resulting from the calculations of the expected numbers on the various surveys are distinctly illustrated.

Finally, the annually expected number and incidence of CRS in Poland were computed. Table 4 summarizes the results related to various rates of CRS in infants born to mothers suffering from rubella during the first trimester of pregnancy. The rates of 10 to 25 % are representative statistical

Table 3. Calculated number and rate of primary rubella virus infections in pregnant women

List	Age of pregnant women (years)	Survey 1979[1]				Survey 1982[1]			
		Number of newborns	Calculated rate of infected persons (%)	Calculated access of infected persons (%)	Calculated number of primarily infected pregnant women	Number of newborns (%)	Calculated rate of infected persons (%)	Calculated access of infected persons (%)	Calculated number of primarily infected pregnant women
i	t_i	N_i[2]	y_i	$\Delta\bar{y}_i$	S_i	N_i[2]	y_i	$\Delta\bar{y}_i$	S_i
1	15—19	48125	85.60	6.85	3297.8	44126	91.65	4.70	2073.5
2	20—24	297466	92.45	3.59	10684.6	282591	96.35	2.05	5803.3
3	25—29	223733	96.04	1.88	4212.3	232485	98.41	0.90	2086.5
4	30—34	89326	97.93	0.99	881.5	109528	99.30	0.30	429.6
5	35—39	28904	98.91	0.52	149.5	22624	99.70	0.17	57.6
6	40—44	8716	99.43	0.27	23.6	8021	99.87	0.075	6.0
7	45—49	753	99.70	0.14	1.1	652	99.94	0.033	0.2
8	> 50	—	99.84	—	—	—	99.97	—	—
	Total S_i (incidence) in trimesters of pregnancy	I I—III	per 5 years		19250	per 5 years			10457
			per 1 year (5.52 ‰)		3850	per 1 year			2091 (2.94 ‰)
		I	per 1 year (1.84 ‰)		1283	per 1 year			679 (0.98 ‰)

1) serological studies in female population
2) register of Poland 1979, 1982.

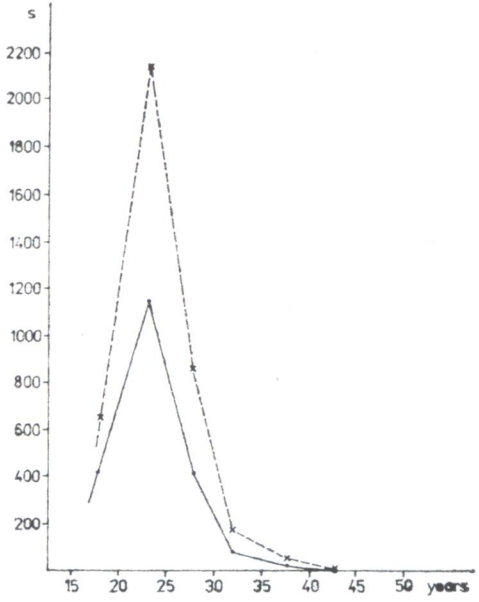

Fig. 2.
Annually expected number (S) of primary rubella infections in pregnant women — dependent on age
Calculation by survey in female population.
x— — — —x survey 1979
●————● survey 1982

reports (Enders-Ruckle 1970; Peckham 1985; Prevention of Rubella, 1973) compiled prospectively and empirically on the basis of primary infections in mothers and typical clinical syndrome in children.

The calculation by serological studies in 1979 results in a CRS incidence of 0.18 ‰ to 0.46 ‰. Accordingly, in the time following the year 1979 about 18 to 46 children with CRS per 100 000 live births could be expected. Related to the survey of 1982 the estimated incidence of CRS decreased to values of 0.10 to 0.25 ‰, i.e. 10 to 25 CRS for each 100 000 newborns.

Table 4. Calculation of the annually expected number and incidence of CRS in Poland

Reported rates of CRS[1)]	Number (incidence) of CRS Calculation by surveys 1979[2)]	1982[2)]	1979/1982[3)]
10 %	128 (0.18 ‰)	70 (0.10 ‰)	109 (0.15 ‰)
15 %	193 (0.28 ‰)	105 (0.15 ‰)	163 (0.23 ‰)
25 %	341 (0.46 ‰)	174 (0.25 ‰)	271 (0.38 ‰)

1) in infants born to mothers infected with rubella during the first trimester of pregnancy (Enders-Ruckle, 1970; Peckham, 1985; WHO Report, 1973)
2) surveys in female population, birth register 1979 and 1982 respectively
3) surveys in female and male population, birth register 1982.

On the basis of both of the serological surveys the incidence of CRS amounted to medium levels of 0.15 ‰ to 0.38 ‰.

Discussion

In Poland as well as in many other countries no comprehensive surveys of children with CRS exist. Only sporadic serological and clinical investigations were carried out and resulted in presumptions from which no general conclusions can be drawn. Because of this situation mathematical models were introduced to estimate the problem (Knox, 1980; Knox, 1985; Sandow *et al.*, 1976; Sandow *et al.*, 1983).

The incidence of CRS is influenced by a variety of factors, i.e. the maternal immune state, the effectivity of rubella contacts, the moment of primary rubella infection during pregnancy, the clinical or subclinical course of infection in the mother, and possibly the teratogenicity of circulating rubella strains. With exception of the last two mentioned factors the other conditions are regarded in the model (Sandow *et al.*, 1976).

An important premise of the calculation by the model is the percentage of CRS following rubella in pregnancy. Many prospective epidemiological studies were undertaken with follow-up beginning at the time of diagnosed maternal infection. The results of these investigations varied considerably However, it became evident that the rate of malformation was lower than had initially been supposed by retrospective studies. In general, the portion ranges from 10 % to 15 % to 25 % in children, whose mothers were infected in the first trimester (Enders-Ruckle, 1970; Peckham, 1985; WHO Report, 1973). These rates were increased up to 35 % if long-term observations of suspected children were carried out for detecting defects not recognizable on the birth or in the first lifetime (Enders-Ruckle, 1970).

Our calculation was based on these findings. The low but uncertain portions of congenital rubella after maternal infection during later stages of pregnancy were neglected. Neither were included the uncleared rates concerning spontaneous abortions or stillbirths. Furthermore, it should be mentioned that the calculated incidence of CRS possibly cannot be observed. Two factors play an important role. First, in cases of primary rubella infection during the first trimester the pregnancy will be mostly interrupted. Second, the exact monitoring of CRS is only feasible by a network of laboratories which confirm the suspected cases and exclude other causes of malformations. However, in majority of countries this requirement may be realized only in a few centres.

Summarizing the results of our model the correlation was proved between the calculated incidence of CRS and corresponding data published in the literature. On average, the incidence estimated for Poland was 0.15 ‰ to 0.38 ‰. These values are comparable to data of other countries which do not possess rubella vaccination programmes. Thus, the WHO (WHO Report, 1973) estimated for European countries a risk of CRS below 1 ‰, in a few states about 0.25 ‰. In the G.D.R. (Sandow *et al.*, 1983) the incidence calculated by the same model was 0.2 ‰ to 0.4 ‰. In the U.S.A. during

the prevaccine era an average incidence not higher than 1 0/00 was observed. In epidemic periods this value reached 1 ‰ to 4 ‰ (Grand and Wyll, 1973; Sever *et al.*, 1965).

However, our calculations carried out on the basis of serological studies (sera collected in 1979 and 1982) resulted in various risks of CRS. These differences can be explained by the epidemiological situation changed over this period. In Poland 1980—1981 a rubella epidemic was notified (Imbs *et al.*, 1985; Kańtoch and Imbs, 1986). Consequently, the estimates based on the sera of 1979 are valid and characteristic for non epidemic period, while the calculation based on survey carried on in 1982 is characteristic for post-epidemic period, for more immune female population.

From this comparison of our calculation with the estimate in the literature one can conclude that the rubella problem has the same significance in Poland as in other European countries with no mass vaccination programmes. Furthermore, the applied mathematical model was clearly proved as a method of a periodical assessing of maternal and congenital rubella.

References

Berger, J. (1973): Zur Infektionskinetik bei Toxoplasmose, Röteln, Mumps und Zytomegalie. *Zbl. Bakt. Orig. A.* **224**, 503—522.

Enders-Ruckle, G. (1970): Problems der Rötelnschutzimpfung. *Monschr. Kinderheilkd.*, **118**, 550—558.

Grand, M. G., and Wyll, S. A. (1973): Congenital rubella surveillance. A. Matter of priorities. *Clin. Pediatr.* **12**, 189—190.

Imbs, D., Rudnicka, H., and Prus, A. (1980): Występowanie przeciwcial dla wirusa różyczki u dziewcząt i kobiet w Poslce. *Przegl. Epid.* **34**, 241—247.

Imbs, D., Rudnicka, H., and Diuwe, A. (1985): Seroepidemiologiczne badania w kierunku różyczki wśród ludności w Polsce. *Przegl. Epid.* **39**, 193—198.

Kańtoch, M., and Imbs, D. (1986): Postinfection and postvaccination antirubella immunity. *Acta virol.* **30**, 381—389.

Knox, E. G. (1980): Strategy for rubella vaccination. *Int. J. Epidemiol.* **9**, 13—23.

Knox, E. G. (1985): Theoretical aspects of rubella vaccination strategies. *Rev. infect. Dis.* **7** (Suppl. 1), 194—197.

Peckham, C. (1985): Congenital rubella in the United Kingdom before 1970: The prevaccine sera. *Infect. Dis.* **7** (Suppl. 1), 11—16.

Sandow, D., Denkmann, N., and Starke, G. (1976): Hochrechnung zur Häufigkeit kongenitaler Röteln in der DDR. *J. Hyg. Epidemiol. Mikrobiol. Immunol.* **20**, 396—409.

Sandow, D., Dittmann, S., Arnold, U., and Pustowoit, B. (1983): Zur gegenwärtigen epidemiologischen Situation der Röteln bei Schwangeren in der DDR. *Zbl. Gynäkol.* **105**, 1062—1069.

Sever, J. L., Nelson, K. B., and Gilkeson, M. R. (1965): Rubella epidemic 1964. Effect on 6000 pregnances. I. Preliminary clinical and laboratory findings through the neonatal period: A Report from the collaborative study on cerebral palsy. *Amer. J. Dis. Child.* **110**, 395—407.

Prevention of Rubella. Report on a Working Group Convened by the Regional Office for Europe of the World Health Organization, Budapest 1972. Regional Office for Europe WHO, Copenhagen 1973.