Influenza, Pregnancy, and Fetal Outcome

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THE EFFECT of virus infections on the outcome of pregnancy has been of interest to investigators since Gregg (*1*) demonstrated a relationship between congenital cataract and German measles in the mothers. Following Gregg's observation in 1941, several investigators have attempted to associate virus infections with congenital abnormalities, prematurity, fetal deaths, or maternal deaths. Swann (*2*) in 1943 implicated maternal mumps as a cause of fetal anomalies. Others (*3–15*) have since reported on the influence of virus infections on both the fetus and the mother, with contradictory findings as to the effect of influenza infection.

As a result of some of these investigations, pregnant women are generally considered to be a high-risk group with respect to influenza. Eickhoff and co-workers recommended that "immunologic protection through the routine use of influenza vaccine in such high-risk groups may be of great value in reducing the extent of influenza-associated excess mortality" (*15*). The importance of this recommendation emphasizes the need for critical evaluation and further studies.

From August 1957, when the A2 strain of influenza virus first appeared in New York City, through June 1961, we were able to identify six periods of increased activity of the A2 influenza virus in New York City. We thus were offered an unusual opportunity to study the relationship between influenza and complications of pregnancy including fetal outcome in a large population during several outbreaks. This paper reports findings pertaining to maternal deaths, prematurity, fetal deaths, and congenital anomalies.

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Material and Methods

Pneumonia-influenza mortality and other statistical data for New York City were obtained through the cooperation of the New York City Department of Health's bureau of records and statistics, Carl Erhardt, director, and Florence Eisinger and Louis Pincus, senior statisticians. It was not always possible to associate influenza with pneumonia deaths. However, during influenza outbreaks the death certificates implicated influenza in an overwhelming majority of the cases.

Paired prepartum and postpartum blood samples were obtained through the cooperation of Dr. Harold Jacobziner, assistant commissioner for maternal and child health of this department, and Dr. Louis Hellman and Dr. Schuyler Kohl of the State University of New York Downstate Medical Center and the Kings County Hospital, New York City. Prepartum samples were collected when pregnant women first appeared at the Kings County Hospital prenatal clinic, usually in the second or third trimester of pregnancy. Postpartum blood samples were taken immediately after delivery.

Periods of increased activity of the A2 influenza virus were determined by four types of observations: (*a*) mortality data, (*b*) frequency of influenza antibody (hemagglutination-inhibition technique) in various age groups of random samples of the population (50 serum samples from each age group tested each month), (*c*) virus isolations from throat washings and autopsy material in order to determine the presence and type of influenza virus in the

city during a given period, and (*d*) influenza antibody determinations on acute and convalescent serum samples submitted by clinicians as corroboration for the existence of A2 influenza infections.

The hemagglutination-inhibition test was performed as previously described (*16–18*).

Virus isolations were attempted from fetal specimens and curettage material obtained from patients in Mount Sinai Hospital and Kings County Hospital, by inoculating the material into eggs, HeLa cells, monkey kidney cells, and suckling mice.

For statistical evaluation of the data we used the exact formulas for the Poisson or binomial distribution, or the chi-square test with Yates' correction (*19*). Confidence limits for the frequency of independent events were calculated by using table $VIII_1$ in reference 19. This table gives expected values of different confidence levels for a fixed total number of events in two groups, for example, when we study a total of 26 influenza-associated deaths consisting of 12 deaths in pregnant women and 14 deaths in nonpregnant women. The theoretical background for the above binomial estimate is illustrated in examples 1, 2, and 4 of table $VIII_1$.

Calculations involving constants when applied to the above-discussed confidence limits result in values of identical confidence. This principle was used in determining the confidence limits for the 9.4 times increase in the susceptibility of pregnant women with regard to influenza mortality (see section, Maternal Deaths).

When the frequency of an event in single groups was considered, the Poisson-type confidence limits were also obtained from table $VIII_1$.

Confidence limits in figure 1 were calculated from Poisson distributions for the mean of the individual points in any one category; for example, malformations, fetal deaths, and so on.

Yates' correction was applied to the chi-square test for 2×2 contingency tables.

Results

Influenza profile. Periods of increased activity of A2 influenza virus in New York City were determined in order to establish a profile for comparison with possibly correlated events.

As seen in figure 1, there were six periods of increased pneumonia-influenza mortality for the total New York City population, which are identified as I_1 (October–November 1957), I_2 (January 15–March 15, 1958), I_3 (December 1958–January 1959), I_4 (March–April 1959), I_5 (February–March 1960), and I_6 (March 1961). Particularly pronounced were periods I_1, I_2, and I_4. I_1 and I_4 demonstrated similar sharp curves with approximately the same high peak. The I_2 curve was extended for a longer period, though the peak was lower than that of I_1 or I_4.

The association between rises in the serologic curve and rises in the mortality curve (I_1–I_4) has previously been discussed for a portion of these periods (*16–18*), and it is noted here for periods I_5 and I_6 in the 50–59 age group curve. It has also been noted previously that the younger age groups (15–19 years and 20–29 years) maintained their antibody level after the I_3 period (*18*). In figure 1 the serologic profile of the pertinent 20–29 year age group is compared with that of the 50–59 year age group. The younger group, in contrast to the older, retains the antibodies at a higher level between outbreaks. Thus, while for the older age group the curve fluctuates with the mortality profile in 1960 and 1961 as well as in the earlier years, the antibody level for the younger group remains at a peak of about 80 percent during these years.

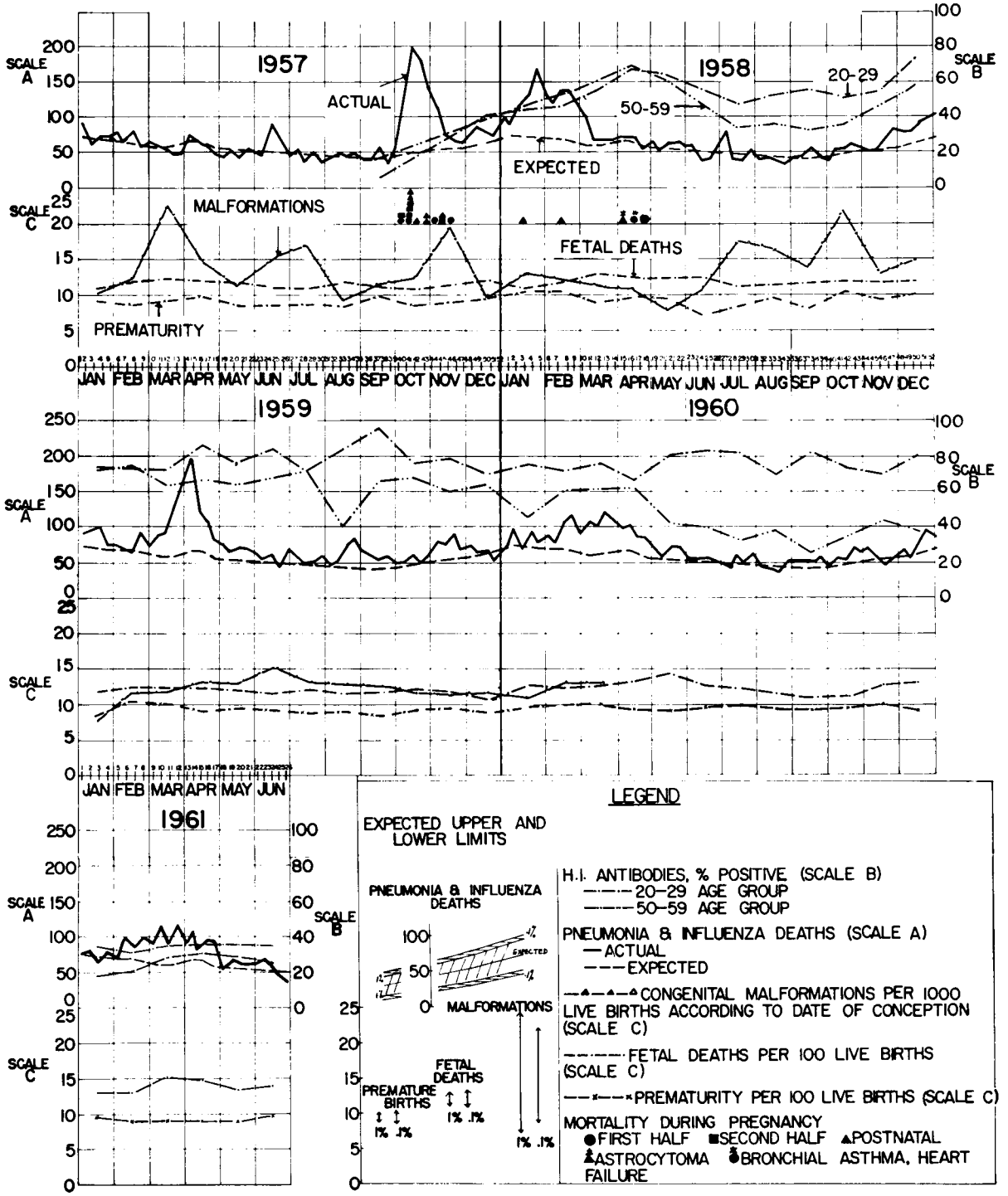
During the periods of increased mortality (I_1–I_6) clinicians reported higher incidence of influenza-like syndrome, and virus isolations and the testing of acute and convalescent serums from the patients established the activity of the A2 influenza virus in the city.

Maternal deaths. An attempt was made to select an age group for this study wide enough to include the large majority of pregnant women but sufficiently narrow to minimize "bias by trend" causing inhomogeneity of the pregnant and control groups.

The 20–29 year age group was selected to satisfy these requirements, since:

1. As seen in figure 2, curve II, the incidence of pregnancy reaches its maximum in the 20–29

Figure 1. Relationship between activity of A2 influenza virus, maternal deaths, and fetal outcome, New York City, January 1957–June 1961



year age group. It is calculated that in New York City during 1957–59, 15.4 percent of the women of this age group were pregnant at any given date. (9 mo./12 mo. × number of annual deliveries = incidence of pregnancy at any given date. The result excludes pregnant women whose pregnancies were terminated by abortion. However, our conclusions will be based on data for women in the second half of pregnancy, which is not affected by abortion.)

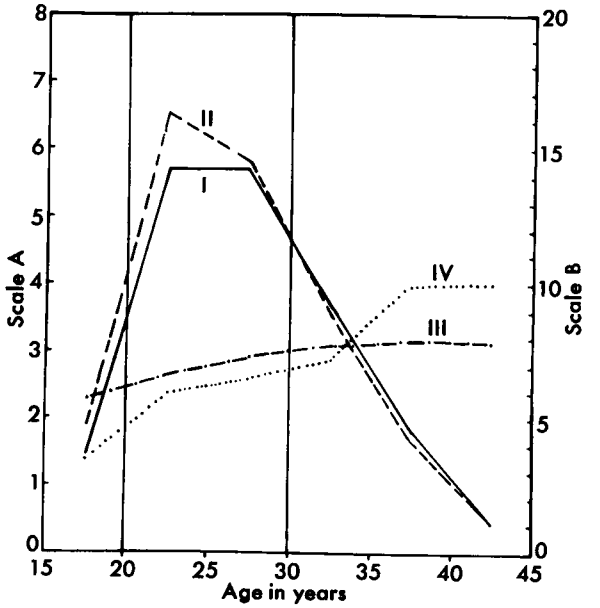
2. Deliveries in the age group 20–29 (114,602 yearly average for the 3-year period 1957–59) represent 60 percent of the total deliveries. This satisfies the requirement of selecting an age group of sufficient size.

3. The incidence of pregnancy (fig. 2, curves I and II) is fairly constant throughout the 20–29 year age group. Therefore, a bias by trend is negligible.

4. The age distribution within the 20–29 group is approximately uniform (fig. 2, curve III).

5. The pneumonia-influenza death rate (fig. 2, curve IV) is also fairly constant in this age group, thus minimizing bias by trend. The rates are considerably lower than among the older women and, therefore, extraneous factors which may contribute to the fluctuations in the death rate of older women are minimized.

Figure 2. Data on female population of New York City, by age group



Data were extracted from death certificates of the selected group of women for all deaths in which pneumonia-influenza was involved, during the period January 1957 through December 1960.

No deviation from stochastical independence was noted when the place of death (address or hospital) was analyzed. In both the pregnant and nonpregnant groups other serious conditions were frequently mentioned in addition to pneumonia-influenza as the cause of death.

An analysis of the total pneumonia-influenza deaths among women in the 20–29 year age group by pregnancy status is presented in table 1, and the deaths among pregnant women are shown in figure 1.

During the I_1 period there were two deaths in the 10–180 day postdelivery period (one at 6 weeks and one at 9 weeks). Since these two deaths are within the expected range based on the number among nonpregnant women, such mothers may be excluded from a high-risk group.

There were six deaths during the 9 days after delivery in the I_1 period, which equal the six deaths during the second half of pregnancy. We did not separate these two groups for statistical analysis since an overlapping of the two groups occurs when an infant is taken from a dying woman.

During 1957 all the pneumonia-influenza deaths in the pregnant women occurred during the months of October and November, influenza period I_1.

The pneumonia-influenza deaths in the pregnant group were a significantly higher proportion of the total pneumonia-influenza deaths in the 1957 period (15 out of 29) than in the 1958–59 periods (3 out of 54) ($P<0.1$ percent, using the chi-square test). However, the inclusion of deaths in the first half of pregnancy in the total mortality data may contribute toward a definite bias in view of the difficulty of determining early pregnancy in a woman who died of a respiratory disease. This may account for the relatively small number, 3

deaths, during the first 20 weeks of pregnancy compared with 12 deaths expected on the assumption that there were as many women in the first half of pregnancy as in the second half. To minimize this bias, only the data for the second half of pregnancy are used in the following analysis.

It was previously indicated that 15.4 percent of the New York City female population in the 20–29 year age group may be considered pregnant at any one time. It may be assumed then that 7.7 percent of this age group are in the second half of pregnancy, and 84.6 percent are nonpregnant. Since there were 14 deaths in the nonpregnant group in the I_1 outbreak (not excluding the possible erroneous classification of early pregnancy as nonpregnancy), the expected mortality in the pregnant group would be 1.27 deaths (7.7/84.6×14). There were, however, 12 deaths in women in the second half of pregnancy in the I_1 period, 9.4 times as many as expected (confidence limits, 4–22, P=95 percent; 3–29, P=99 percent (*19*), based on the binomial distribution of 12+14=26).

On the basis of similar calculations for 1958, 1959, and 1960, the expected number of deaths in the pregnant group would be 2.4 (7.7/84.6×27), 2.0 (7.7/84.6×22), and 2.0 respectively. The actual numbers were consistent with the expected: 3, 0, and 0 for 1958, 1959, and 1960 respectively.

It should be emphasized that the deaths in the nonpregnant group were not statistically different for 1957, 1958, and 1959 (P=15 percent, using chi-square test). The influenza-associated increase in mortality in pregnant women demonstrated in the I_1 period should therefore have been seen in the other periods since there were sufficient deaths in the nonpregnant group to be statistically significant. The observed mortality pattern, together with the serologic aspects, will be further evaluated in the discussion.

In summary, there was an increase in influenza mortality among pregnant women associated with the first appearance of the A2 influenza virus during October–November 1957. This was not true for any other period of increased influenza virus activity in 1958, 1959, and 1960.

Prematurity. Figure 1 shows the monthly fluctuations of premature (<2,500 gm.) births

Table 1. Number of pneumonia-influenza deaths among women aged 20–29 years, by pregnancy status, New York City, January 1957–December 1960

Period of death	Gestation		Postdelivery		Total during pregnancy (cols. A, B, and C) [1]	Total during second half of pregnancy (cols. B and C) [1]	Nonpregnant women and col. D	Total deaths (cols. E and G)
	0–19 weeks	20 weeks to delivery	0–9 days	10–180 days				
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)
October–November 1957 (I_1).	3	6	6	[2] 2	15 (10–20) (8–22)	12 (7–17) (6–19)	14	29
Rest of 1957	0	0	0	0	0 (0–3. 7) (0–4. 7)	0 (0–3. 7) (0–4. 7)	22	22
1958 (I_2, I_3)	2	0	3	0	[3] 5 (1. 7–11) (1. 1–12)	3 (0. 6–8) (0. 3–10)	27	32
1959 (I_3, I_4)	0	0	0	[4] 1	0 (0–3. 7) (0–4. 7)	0 (0–3. 7) (0–4. 7)	22	22
1960 (I_5)	0	0	0	0	0 (0–3. 7) (0–4. 7)	0 (0–3. 7) (0–4. 7)	22	22

[1] Figures in parentheses are confidence limits based on Poisson distribution: P=5 percent and P=1 percent.
[2] One 6 weeks and one 9 weeks after delivery.
[3] 2 during an influenza period; see fig. 1.
[4] 8 weeks after delivery.

in New York City per 100 live births. There were about 1,300 premature births per month in New York City during the period of study.

The variation in the rate of premature births does not exceed the expected variation as calculated on the assumption of Poisson's distribution (see arrows for confidence limits, fig. 1). Thus, no increase was noted in premature births associated with any period of increased activity of A2 influenza virus.

Fetal deaths. There were about 1,800 fetal deaths per month in New York City during the period of study. As seen in figure 1, the fluctuations of the monthly data are within the Poisson error (see arrows). Thus no relationship was noted between periods of increased activity of A2 influenza virus and fetal deaths in New York City.

Congenital malformations. Figure 1 shows the profile of congenital malformations for all age groups by month of conception. The actual monthly numbers ranged between 100 and 300. A 1-in-10 sample (10–30 actual cases) was selected randomly for 1957–58. The fluctuations, though large, are within the Poisson error (see arrows).

No influenza viruses were isolated from 50 fetal and 87 curettage tissue specimens. Further studies are in progress on these and other specimens in relation to isolation of viruses from currettage tissues.

The above data representing epidemiologic information for the New York City population were supplemented by data obtained for a sample population of the Kings County Hospital. The results of testing 1,264 paired prepartum and postpartum blood samples, together with the outcome of the pregnancies are presented in table 2. No significant differences could be determined in the frequency of stillbirths, neonatal deaths, premature births, or malformations between any of the three serologic categories (no increase, low titer; fourfold increase; or no increase, high titer).

Discussion

Positive relationships between infection by the A2 virus and pregnancy complications have been reported by a number of investigators but only for the initial outbreak. To extend the information on this question, we felt it important to study further this and subsequent influenza periods in New York City, for which substantial data were available.

A close association between excess pneumonia-influenza mortality and the serologic profile established six periods of increased activity of A2 influenza virus. These periods were, furthermore, coincidental with isolations of the A2 influenza virus and with clinical observations which were confirmed by increase in A2 antibody titer of convalescent serums.

Establishment of these influenza periods permitted a study of the various aspects of pregnancy in relation to Asian influenza infections.

Analysis of data found in the literature, in our opinion, must consider two factors: the

Table 2. Relationship between pregnancy outcome and results of HI antibody (A2) studies of paired prepartum and postpartum blood specimens, New York City, March 1960–April 1961 [1]

Comparison of titers of prepartum and postpartum paired specimens	Pregnancy outcome										Total	
	Normal birth		Stillbirth		Neonatal death		Premature birth		Malformation			
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
No increase, titer <1:64	594	88. 66	15	2. 24	5	0. 746	48	7. 164	19	2. 836	670	100
Fourfold increase	123	87. 85	4	2. 857	2	1. 43	10	7. 14	1	. 714	140	100
No increase, titer >1:64	502	89. 17	12	2. 131	11	1. 954	37	6. 57	13	2. 309	563	100

[1] 1,264 paired specimens and history of patients obtained from Kings County Hospital, New York City.

"unknown statistical background" and "bias by trend." Analysis of a phenomenon requires complete representation of all data studied, even if the findings are negative. Only in such instances do the statistical calculations become quantitatively meaningful. However, if a substantial number of related negative studies are not reported, then the reported positive findings decrease somewhat in significance (unknown statistical background).

The second point is the possibility that "bias by trend" may cause the test and control groups to become noncomparable. For example, the factor of age must be considered in comparing mortality data of pregnant and nonpregnant women since mortality in older age groups would normally be higher than in younger ones. If the nonpregnant group contains an excess of older women as compared with the pregnant group, then the mortality expectation would be higher in the control group (*20*). Such factors were considered in our analysis.

Higher influenza-associated mortality in pregnant than in nonpregnant women during the initial epidemic wave of the A2 virus was reported by Martin and others for Boston (*3*), by Polak for the Netherlands (*4*), and by Greenberg and others for New York City (*5*). Martin (*3*) reported 4 deaths in pregnant women out of 32 deaths analyzed (including 14 females), which in turn were obtained from an estimated 118 fatalities in the Boston area during the October 1957–April 1958 outbreak. He comments in his report that "major population groups particularly susceptible to severe disease (and therefore prime candidates for immunization) were pregnant women. . . ." The subjects Martin studied were selected from 11 Boston hospitals. It might be assumed that a pregnant woman would more readily be admitted to a hospital than a nonpregnant one with a similar influenza syndrome. This bias and the small number of deaths in pregnant women, as well as the lack of an estimate of the pregnant population in the age groups that were examined, raise a question as to the statistical significance of these findings.

Polak (*4*) reported from the Netherlands 11 influenza-associated deaths in pregnant women out of a total of 163 male and female deaths in the age group 20–49 years. He indicated that the death rate for pregnant women is, therefore, 8 per 100,000 population, compared with 3.8 for nonpregnant women, or a 2.1-fold increase. We may therefore assume that 5.2 would be the expected number of deaths in the pregnant women rather than the actual 11 reported. This result is significant only at the 5 percent level (chi-square test).

Greenberg and his co-workers (*5*) reported that during the first wave of influenza in New York City (I_1) there were 47 deaths among women aged 15–49 years, and that 22 of these women were pregnant. No statistical evaluation was presented.

In the present report we show that there was a ninefold increase in maternal deaths in the 20–29 year age group during the I_1 outbreak in New York City. No such increase was observed in the subsequent influenza periods (I_2–I_6). Actually, as seen in figure 1, only two deaths were established as influenza-associated during the I_2 period, and no deaths were recorded in the pregnant group in the subsequent four outbreaks. As previously observed, the annual pneumonia-influenza deaths in the nonpregnant 20–29 year age group did not decline to any extent in the period covered by this study. The continued susceptibility of this age group is further supported by unpublished data, which show that during the outbreaks subsequent to the I_1 period, pneumonia-influenza mortality increased in the 20–29 year age group.

As seen in figure 1, the percentage of the 20–29 year age group with minimal HI antibodies increased steadily. However, this antibody rise did not result in a decrease in mortality in the nonpregnant women similar to that observed in the pregnant group.

It would seem that although initially, when no HI antibodies against the A2 virus were present, pregnant women were less resistant than nonpregnant ones, this distinction disappeared concurrently with the apperance of the HI antibodies. We thus find that there was a greater increase in the resistance to the lethal effect of the virus in pregnant women than in nonpregnant women, concomitant with subsequent exposures to the A2 influenza virus (I_2–I_6).

This greater increased protection in pregnant

women may be explained by either of the following two hypotheses:

1. A higher titer of protective antibody due to a booster effect of pregnancy on antibody production, or to a more extensive immunization program. The immunization program in New York City was not well developed. Whether or not pregnancy has a booster effect on antibody production has not been reported for the influenza virus, and this aspect is being studied.

2. A decrease in nonspecific protective factors in pregnant women, for example, a decrease in the properidin level (*21*), resulting in a higher mortality in the initial influenza outbreak in the pregnant group than in the nonpregnant. It may be further hypothesized that if this is the explanation for the higher mortality during the initial outbreak, the decrease in the differential mortality in subsequent waves of A2 influenza may be attributed to development of the specific A2 protective factor, which is not decreased in pregnancy. This specific protective mechanism then assumes the major role of protection.

In view of these observations concerning the role of specific immunity in pregnant women, it may be appropriate to reevaluate our thinking with regard to use of the influenza vaccine for this so-called high-risk group. Immunization might be of value in protecting pregnant women if administered before the initial appearance of a new influenza strain in a given geographic area. We have no evidence, however, that immunization with heterologous influenza strains (for example, FM1) would protect pregnant women againt the lethal effect of a newly introduced virus (for example, A2). Before the appearance of the A2 influenza virus, more than 50 percent of the 20–29 year age group in New York City had demonstrable HI antibodies against the FM1 and PR8 strains, which were the previously dominant influenza strains. This did not prevent increased mortality among pregnant women, as apparently did exposure to the homologous A2 virus. Mortality in pregnant women disappeared concomitantly with the appearance of HI antibodies against A2 virus in about 50 percent of the 20–29 year age group. Eighty percent of this group have HI antibodies at the present time.

It would appear, therefore, that if an influenza vaccine is to be of value in preventing maternal deaths, such vaccine should be a homologous strain administered before exposure to the new virus. If such a program is contemplated, consideration should also be given to the lack of knowledge concerning the possible deleterious effect of sensitization of human mothers or fetus to egg products. This possibility must be weighed against the attempted elimination of 22 maternal deaths (15 in age group 20–29) in a city where there are about 140,000 pregnancies at any given date, with an additional 16,000 pregnancies monthly.

In general, publications concerning the relationship between influenza and fetal complications cover only pre-Asian outbreaks or the initial outbreak of A2 influenza in the community. Lande (*6*) reported on 16 cases of "post rubeola syndrome." One of these cases was influenza-associated and five cases were "cold-associated." The diagnosis of influenza and "cold" was based on questions asked the mothers. Lande concluded that influenza was a possible agent in this congenital abnormality. Campbell in 1950–51 (*7*) observed 989 pregnancies in 3 Belfast hospitals. One hundred and sixty-four of the mothers recalled an influenza infection during their pregnancy at the time of an A prime outbreak. There were 2.4 percent fetal deaths and 3.0 percent malformations in the offspring of mothers who recalled an influenza syndrome, compared with 1.5 percent fetal deaths and 1.5 percent malformations in the control group. His analysis indicates that this increase is not statistically significant.

Coffey and Jessop (*8*) in 1953 questioned 217 mothers of congenitally abnormal children (64 with anencephaly) after delivery. Influenza symptoms during their pregnancy were recalled by 40 (17 percent) of these mothers compared with 7 out of 192 (3.6 percent) mothers with normal children. The difference is statistically significant. However, bias in this type of retrospective study may be important, since a mother with an abnormal child may recall an illness during her pregnancy more readily than a mother with a normal child. In their later prospective study covering the initial phase of the A2 influenza outbreak in Dublin, Coffey and Jessop (*9*) questioned mothers prior to delivery

and reported that 3.6 percent of the 663 mothers with influenza had abnormal children (1.5 percent anencephaly) compared with 1.5 percent (0.45 percent anencephaly) in the randomly paired control group. The difference is significant at the 2 percent level (chi-square test). This evidence is supported by the higher incidence of malformations among the mothers who recalled an influenza infection during the earlier phases of pregnancy.

Abramowitz (*10*) studied 729 pregnant women in Cape Town hospitals during the first A2 influenza outbreak. There were 315 women in this group who were in bed with influenza symptoms for at least 1 day during the first half of pregnancy. The incidence of perinatal deaths, prematurity, and congenital malformations was 1.9 percent, 8.8 percent, and 0.95 percent, respectively. In comparison, there were 1.45 percent perinatal deaths, 9.5 percent premature births, and 1.2 percent malformations in the control group. This negative finding agrees with his observation that the monthly incidence of fetal complications did not increase during the outbreak in the total city population.

Similarly, Doll and others (*11*) reported no significant difference in congenital malformations and stillbirths between mothers who had had influenza and those who had not. They analyzed five cases of congenital malformation and one stillbirth.

In the Baltimore outbreak of A2 influenza, Frazier (*12*) found an increase in the fetal death ratio from 16.4 during the pre-Asian period to 20.8 during the influenza outbreak. This was followed by a 16.3 postinfluenza ratio. These findings are significant at the $P=1$ percent level (chi-square test). However, if all the data presented by him (including premature births, neonatal deaths, and congenital malformations, which did not show a similar increase) are analyzed, the level of significance becomes $P=3$ percent (chi-square test). Frazier's analysis of the average fetal death rates for the pre-Asian influenza years of 1955–57 suggested a similar seasonal increase, although he indicated that this increase was not significant.

While no similar increase in malformations was seen in Frazier's data, a similar type of grouping by Saxen (*13*) in connection with the 1957 epidemic in Finland did show an increase in malformations ($P=2$ percent, using chi-square test). However, no other years were studied for seasonal variation, and routine official data usually subject to various systematic errors were used by both Frazier and Saxen.

Hardy and others (*14*) reported on a prospective study of pregnant women who enrolled in a Baltimore prenatal clinic between October 14, 1957, and February 1958. The Asian influenza virus appeared in Baltimore in late September 1957 and by the end of October was widespread in the community. They stated that the influenza "infection seemed to adversely affect the outcome of pregnancy, especially if it occurred during the first trimester. The absence of comparative data from a true control group, however, precludes attaching too much significance to these findings."

The data on malformations, fetal death, and prematurity as related to influenza infections are usually of a low level of statistical significance. This low level of significance is further decreased by the "unknown statistical background" and "bias by trend" as discussed above. Nevertheless, the possibility of a positive correlation cannot be eliminated. Our own essentially negative findings indicate that even large outbreaks of Asian influenza (for example, I_1, I_2, I_4 periods) did not noticeably influence the frequency of prematurity, fetal deaths, or congenital malformations. However, this might indicate that causes other than A2 influenza infection are overwhelming in their significance, thus diluting any possible influence on the fetus by the influenza virus. Our prematurity and fetal death curves are based on such large numbers that the Poisson variations are small enough for the detection of considerable rises during the influenza outbreaks. The curve for the congenital malformations is less sensitive, since it is based on smaller numbers.

Positive correlations between influenza and fetal complications were usually determined by comparing pregnant women with and without influenza syndromes. There is no substantial evidence that the human embryo is infected with influenza virus, nor are there changes in the monthly profiles of the fetal complications concomitant with influenza outbreaks. Our evaluation of all available human data does not sup-

port a firm conclusion that influenza infection of the mother is responsible for fetal complications.

An alternative explanation may be that fetal complications and susceptibility to the influenza virus occurred coincidentally in women prone to both conditions. This hypothesis might explain the foregoing group of findings. Obviously, a correlation between two events (for example, influenza and malformations) does not prove a causative relation. The correlation may be coincidental because a third factor is causative for both. For example, if a drug or a nutritional factor causes both an increase in the incidence of malformations and an increased susceptibility to influenza, then a correlation as described by Coffey and Jessop may be coincidental. Immunization against influenza would not, in such instance, influence the incidence of malformations. We cannot exclude the above possibility. A consistent increase in malformations in connection with influenza outbreaks or a decrease in the number of malformations associated with influenza vaccination could substantiate a causative relationship between influenza and malformations. Further studies during influenza outbreaks are needed to provide such information.

Summary

Six outbreaks of Asian strain influenza, established by excess pneumonia-influenza mortality, a monthly serologic profile, and clinical reports and virus isolations, were observed in New York City from the initial appearance of the virus in August 1957 to the termination of this study in June 1961.

In the 20–29 year age group mortality among pregnant women was significantly higher (ninefold) than among nonpregnant women only during the first outbreak in October and November 1957. The mothers in the 10–180 day postdelivery period did not belong to this high-risk group. This distinction between pregnant and nonpregnant women disappeared in the later outbreaks, concomitantly with the appearance and retention of A2 influenza antibodies in the 20–29 year age group. One possible explanation for this finding is that pregnancy decreases nonspecific protective factors but not strain-specific immunity. This possibility and other considerations suggest that only administration of a homologous strain vaccine before exposure to a new virus would be effective in preventing excess maternal deaths.

No correlation could be found between maternal influenza infection and prematurity, fetal deaths, or congenital abnormalities when the monthly profiles of these events were analyzed. Isolated data from a single large hospital yielded similar findings. The correlation occasionally found in the literature cannot exclude the possibility of unknown factors causing increased susceptibility to both influenza and fetal malformations.

NOTE: Data extracted from death certificates for this study are available from the authors.

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Epidemiologic Note . . . Salmonellae in Easter Chicks

A pilot survey by the Ohio Department of Health to estimate the frequency of *Salmonella* infections in chicks offered to the public as pets for Easter resulted in three isolations of *Salmonella*. Cloacal swabs, fecal samples, and other specimens were collected 2 days before Easter, 1962, at the seven service stations, one clothing store, one dime store, and one pet shop in Columbus and Dayton, Ohio, that advertised the sale or free gift of chicks.

The specimens included cloacal swabs from 158 chicks, 5 ducks, and 2 parakeets, rectal swabs from 2 rabbits, 45 fecal samples from chick cages and 3 from duck cages, swabs of 12 chick waterers and 1 duck waterer, and 2 samples of chick feed. The chicks had come from five hatcheries, and almost all were 2 to 3 days old.

The isolations of *Salmonella* were all from specimens collected at the dime store. *Salmonella thompson* was isolated from 1 fecal sample and one chick waterer, and *Salmonella bareilly* was isolated from another waterer. None of the 23 cloacal swabs collected at the same store produced salmonellae. The cloacal swabs may have been poor indicators of infection, since it is difficult to obtain adequate fecal material on swabs of chicks only 2 or 3 days old.

Other gram-negative organisms recovered in the pilot survey were *Proteus mirabilis, Escherichia coli, Escherichia intermedius, Escherichia freundii, Aerobacter aerogenes, Alcaligenes faecalis,* and *Pseudomonas aeruginosa.*

Poultry and poultry products are well established as sources of *Salmonella* infections for man (*1*). At least one outbreak of salmonellosis has been attributed to Easter chicks (*2*). The fact that the birds are handled primarily by children, a susceptible population, heightens the potential seriousness of the problem. The pilot study in Ohio emphasizes the need for a more extensive study of Easter chicks as sources of human *Salmonella* infection.

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