Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic

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The birth dates of schizophrenic inpatients in eight health regions in England and Wales were reviewed for any effect of the 1957 A2 influenza epidemic. 5 months after the peak infection prevalence, the number of births of individuals who later developed schizophrenia was 88% higher than the average number of such births in the corresponding periods of the 2 previous and the next 2 years. This finding is in accordance with a study from Helsinki and with clinical and neuropathological evidence of aberrant fetal brain development in the pathogenesis of schizophrenia.

Lancet 1991; **337**: 1248–50.

Introduction

Individuals born in late winter and early spring are more likely to develop schizophrenia than those born at other times of the year,[1] a reproducible and widely observed seasonal effect that is most striking among those without a family history of the disorder.[2,3] Is there some season-dependent environmental factor which causes neurodevelopmental damage in the prenatal or perinatal period that in turn increases the risk of later schizophrenia? Maternal influenza is one of many possible candidates. Influenza epidemics occur frequently in autumn and winter months, and psychotic states were reported after the 1919 pandemic.[4] Mednick et al[5] have reported an increased risk of schizophrenia among those who were in their second trimester of fetal life when Helsinki was subject to the 1957 pandemic of A2 influenza, but studies in Scotland[6] and the USA[7] did not show a relation between prenatal exposure to influenza and risk of schizophrenia. We set out to investigate whether the 1957 pandemic of A2 influenza in England and Wales was followed by an increase in the births of individuals who have subsequently been diagnosed as schizophrenic.

Methods

A2 influenza arrived in the UK in the summer of 1957; from serological data gathered during the epidemic,[8] the peak incidence of new infections occurred from mid-September to mid-October (fig 1). Reported claims for sickness benefit[9] are consistent with this interpretation, because they refer to claims for illness during the week before the claim was made; although there was some geographical variation, the total number of claims nationwide increased rapidly from about Sept 15, reached a peak during the first week of October, and fell considerably by the end of that month (fig 1).

Data were analysed for 12 consecutive months; to follow the sampling methods of two earlier studies,[5,8] and to allow estimation of the time in pregnancy when exposure most probably occurred, these periods ran from the fifteenth day of one month to the fourteenth day of the next. The first period therefore included all those born on Aug 15, 1957, to Sept 14, 1957, and so on to period 12 (July 15, 1958, to Aug 14, 1958). If the epidemic was indeed at its peak from Sept 15 to Oct 14, 1957, people born in the first period were most likely to have been exposed to influenza in the second month after birth, those born in period 7 would most probably have been exposed to the infection in the fifth month in utero, and those born in period 12 would not have been exposed at all.

Data from the Mental Health Enquiry for first discharges from hospital between 1976 and 1986 were sought for all individuals born in the United Kingdom between Aug 15, 1957, and Aug 14, 1958, who had a primary discharge diagnosis of schizophrenia (International classification of disease [ICD] 8 or 9). Similarly diagnosed schizophrenic patients born in the corresponding periods (1–12) of the previous two and the next two years (from Aug 15 1955, 1956, 1958, and 1959) were taken for comparison and to control for the known season-of-birth effect for schizophrenia. Data were obtained from the following regional health authorities in England and Wales: North-west Thames (1976–1984), Oxford (1979–1986), Wales (1976–1980), South West (1978–1987), North West (1976–1986), Mersey (1976–1981), Trent (1979–1986), and Yorkshire (1976, 1978, and 1980–1984).

Results

339 schizophrenic patients in these health regions were born during the index year and 1331 in the 4 control years. The number of index and control patients were compared for each of the twelve periods (see table).

DISTRIBUTION OF AFFECTED BIRTHS IN AUG 15, 1957–AUG 14, 1958, COMPARED WITH AVERAGE FOR CONTROL YEARS (AUG 15, 1955–AUG 14, 1957, AND AUG 15, 1958–AUG 14, 1960)

	All		Men		Women	
Period*	Control†	1957/58	Control†	1957/58	Control†	1957/58
1	24	24	15·25	13	8·75	11
2	34	31	22·75	23	11·25	8
3 (9)	23·75	29	17	17	6·75	12
4 (8)	25·5	35	15	25	10·5	10
5 (7)	27·25	24	17	16	10·25	8
6 (6)	27	23	19·75	17	7·25	6
7 (5)	25·5	48	16·25	26	9·25	22
8 (4)	30·75	32	20·75	22	10	10
9 (3)	26·75	17	17·75	8	9	9
10 (2)	28·75	29	19	21	9·75	8
11 (1)	30·5	26	17·5	20	13	6
12	29	21	17·25	17	11·75	4

*Numbers in parentheses indicate month of gestation (for index year) during peak of 1957 A2 influenza epidemic.
†Multiply by 4 for total births in the 4 control years studied.

There is a significant difference in the distributions of schizophrenic births in 1957/58 compared with the control years ($\chi^2 = 23{\cdot}22$; $p = 0{\cdot}016$). The most striking difference was seen in period 7 (February/March, 1958) of the index year: individuals born in this period were in their fifth month of fetal development when the influenza epidemic was at its peak. Fig 2 shows the ratio of affected births in the index year compared with average numbers over the 4 control years: there is an 88% excess of such births in period 7. On the null hypothesis that the number of births of

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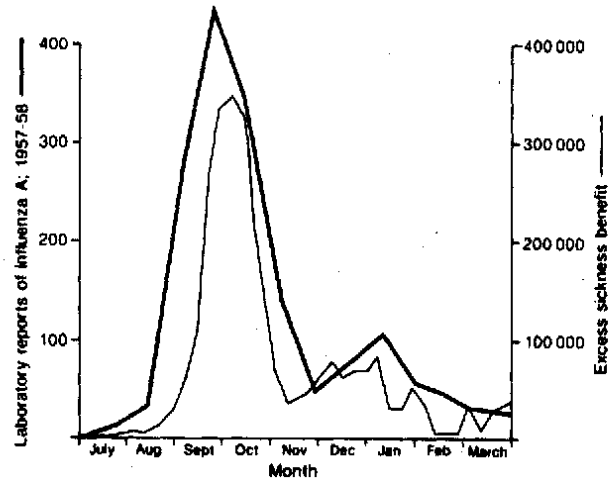


Fig 1—Monthly laboratory reports of influenza A, 1957/58, and excess claims for sickness benefit (1957/58 – 1953/54).

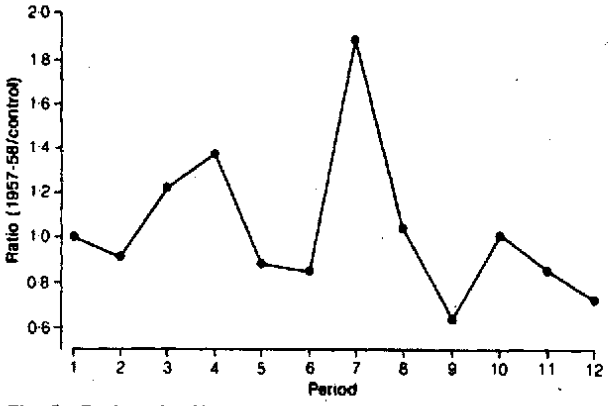


Fig 2—Ratio of affected births (study period/average for previous 2 and next 2 years).

patients with later schizophrenia in period 7 of the index year reflects a Poisson variable with a mean equal to the average number of such births during the corresponding periods in the control years (25·5), the observed number of 48 is 4 SD above the mean and represents a highly improbable event ($p < 0·0001$). This result is unlikely to be caused by fluctuations in the general population birth rate, because the number of births in England and Wales in February and March, 1958 (126 959), is very similar to the average for the same months in the control years (126 327). When the results were considered separately for men and women, the difference between the index and control years was significant for women ($p = 0·011$) but not for men ($p = 0·227$; see table).

Discussion

Our findings support Mednick et al's report[5] that exposure to the A2 influenza virus during the second trimester increases the risk of later schizophrenia. Our data do not cover the whole of England and Wales, and several years of discharge records are missing from several regional health authorities, but we think it unlikely that a sampling artifact beyond our control might have biased the results towards an excess of future schizophrenia in those exposed to influenza at the time predicted in the original report. We also have no direct evidence that the mothers of the individuals who developed schizophrenia were infected with the virus, and it is not certain whether the virus crosses the placenta. Nevertheless, maternal influenza during pregnancy is associated with an increase in congenital abnormalities of the central nervous system, particularly anencephaly,[10] and mothers infected with influenza in the autumn of 1957 had twice as many children with congenital malformations as did uninfected controls.[11] Female fetuses appear to have a greater risk of abnormalities in the central nervous system as a result of such infections,[11] but it is unclear whether this is due to greater susceptibility, or because affected male fetuses have a greater risk of spontaneous abortion. Although a test for interaction by sex on our data did not reach significance, both our data and those of Kendell and Kemp[6,12] show a more obvious schizophrenogenic effect on female than on male fetuses. Schizophrenia usually presents earlier in men than in women, and in a young sample such as ours one might expect many more affected men than women—despite an overall male:female ratio of 1·97:1 in the index year, the ratio fell to 1·18:1 for period 7.

How should these findings be interpreted in the light of our current knowledge about schizophrenia? There is now compelling evidence that many schizophrenic patients have evidence of a neurodevelopmental disorder:[13] schizophrenics have more minor physical anomalies, obstetric complications, and minor neurological signs, and have poorer childhood psychosocial adjustment than controls.[13-16] Computed tomography and magnetic resonance imaging indicate increased cerebral ventricular size and a reduced volume of medial temporal lobe structures in some schizophrenic patients,[17,18] and these structural abnormalities appear to originate in fetal or neonatal life; some studies indicate that patients born in the late winter and early spring are especially likely to have enlarged ventricles.[19,20] Neuropathological studies have confirmed these observations and also report misplaced pre-alpha cells in the entorhinal cortex.[21,22] Jacob and Beckman[22] suggest that these misplaced pre-alpha cells result from "disturbed migration in the entorhinal region toward the end of the fifth month", which corresponds with the time at which maternal influenza appears to increase the risk of later schizophrenia.

We thank the regional health authorities that provided the data and the Wellcome Trust, Generation Trust, and Leverhulme Trust for financial support.

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