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LETTERS TO THE EDITORS

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Comments on Takei et al.: Prenatal exposure to influenza epidemics and the risk of mental retardation

Comment by TJ Crow

This paper comes from a group of workers who are already convinced, in large part on the basis of their own work, that exposure to the influenza virus in the second trimester [or 5th month] of pregnancy increases the risk that the individual will later suffer from schizophrenia. They now present data which they claim establishes that in utero exposure to the influenza virus, in addition to being a cause of schizophrenia, makes an independent contribution to the causation of mental handicap. The type of data analysed and the statistical techniques employed are similar to those they have used in some, but not all, of their earlier studies of schizophrenia. Their case is that the strategy has proved its worth in the case of schizophrenia and the results can therefore be relied upon in the case of mental handicap. But, conversely, if there is a possibility that the authors have been misled by these methods in schizophrenia the findings and conclusions in mental handicap will be subject to the criticisms that have been applied in the field of schizophrenia.

In this paper, the authors cite six papers (Introduction p255 and the same list is repeated in the Discussion on p258) as suggesting that "prenatal exposure to influenza epidemics may affect fetal brain development in such a way as to increase the likelihood of subsequent schizophrenia" (p255) or "have linked prenatal exposure to influenza in the fourth to sixth month of gestation, with an increased risk of later developing schizophrenia" (p258). Since the authors do not raise any criticisms of these papers, beyond mentioning in passing in the Introduction that two studies do not suggest the same conclusions, the authors clearly regard their conclusions concerning the schizophrenogenic potential of prenatal exposure to influenza as established and expect the reader to do the same.

But there are serious problems with the conclusions of these papers. For example:

(i) The conclusions of Mednick et al. (1988) and O'Callaghan et al. (1991) are dependent upon their (somewhat idiosyncratic) methods of analysis. If Mednick et al. had examined *numbers* of patients with schizophrenia rather than *proportions* of admissions, or if O'Callaghan et al. had examined trimesters (as Mednick et al. had done) rather than months, the findings would not have been the same.

(ii) The positive conclusions of Mednick et al. (1988) and O'Callaghan et al. (1991) regarding the 1957 epidemic have not been supported in a study of similar design in Holland by Selten and Slaets (1994).

(iii) The findings of Barr et al. (1990) were not replicated by Adams et al. (1993) who applied *the same analyses to the same sample*.

(iv) There is a quantitative discrepancy between the conclusions of Mednick et al. (1988) and O'Callaghan et al. (1991) and those of Sham et al. (1992). The first two groups claimed an 87–88% increase in schizophrenia births in the Spring of 1958 as a consequence of the 1957 epidemic, but Sham et al. (1992) conclude that their results "indicate that 1–2% of all schizophrenic births can be explained by the number of influenza deaths in the preceding months". These claims are incompatible.

(v) The only study (Crow and Done, 1992) in which there is the possibility of identifying (in so far as this can be done) mothers who actually suffered from influenza, yielded no evidence of an increase in schizophrenia in the children.

(vi) The study of Torrey et al. (1991) has a sample size 26 times that of O'Callghan et al. but shows no evidence of an effect of the 1957 epidemic on schizophrenia birth rates.

There are a number of substantial discrepancies here that the authors are failing to address. Unless they are willing to do so, they cannot expect referees and editors to take their conclusions regarding influenza and schizophrenia as read. On the contrary, given the above discrepancies, there must be a serious suspicion that these authors (who quote six papers of their own with positive conclusions) have been misled by the methods they have adopted.

This must reflect on their conclusions regarding mental retardation. This paper has the same weaknesses of the papers by Sham et al. (1992) and Takei et al. (1993) – that a complex method of analysis is adopted in the course of

which a number of arbitrary assumptions are made, without an attempt being made to test whether the findings are robust in the face of variations in these assumptions. For example, in this paper, the authors use only female deaths from influenza and leave the seasonal term (which was not significant) in the analysis.

Would the results have been the same if they had used male deaths or omitted the seasonal term? It is also curious (p258 of the Discussion) that admissions to mental handicap hospitals were omitted. Why?

The authors are aware (p258) that they are making multiple tests of their hypothesis, i.e. they would have accepted evidence for associations other than in the third or fourth month as supporting the hypothesis. Strictly speaking, even if one accepts the limitations of their analysis, the findings are not significant.

Given the serious inconsistencies (Crow 1994) in the existing literature on prenatal exposure to influenza and schizophrenia, editors and referees should be under an obligation to ensure that, if the hypothesis that such exposure causes mental retardation is to be investigated, this should be done in a more cautious and critical manner. Perhaps it is not too late for the authors to assume some part of this responsibility.

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Comment by Evelyn Bromet

The paper by Takei et al. is offered as a test of the hypothesis that prenatal exposure to influenza increases the risk of mental retardation. While the hypothesis holds some appeal, the available data sets cannot begin to test the hypothesis, in part because of all of the reasons listed by the authors at the end of the paper. However, besides such crucial issues as incomplete and potentially biased samples, diagnostic inaccuracies, and crude data about exposure, there is another more fundamental problem. The authors propose an etiologic hypothesis, but they go about testing it with an ecological analysis. Since 1950, it has been pointed out repeatedly in epidemiology that ecological methods cannot be used to test causal hypotheses because of the inherent problem of "linkage failure" (Greenland and Robins 1994). That is, when the outcome event (in this case mental retardation cases discharged from mental institutions) is not directly linked to the individual exposure (influenza death rates), special biases can arise. Moreover, Brenner et al. (1992) showed that misclassification in exposure status can lead to overestimation of the exposure-outcome relationship rather than "masking a stronger association" (p. 9) as the authors imply.

Interpretations of correlations between two sets of aggregated data can only be made on a group level. Simply put, it is illogical to draw inferences about individuals from aggregated data. This is known as the "ecological fallacy." However, for practical reasons, ecological findings have been and will continue to be used to formulate hypotheses which will then need to be tested in studies of individuals. If the present findings were based on a sound ecological design, the next step would be a study of the relationship between documented maternal exposure to influenza and true incidence of mental retardation to test the hypothesis laid out by Takei et al. Even then, an ade-

quate study of these relationships would have to assess a representative sample, use unbiased measures, and control for potential confounders.

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Comment by Assen Jablensky

Given the chain of publications about a possible link between maternal influenza and schizophrenia in adult life and the inconclusive state of the evidence to date, it is surprising that the question about CNS sequelae of influenza epidemics, other than schizophrenia, had not been addressed before. For doing this, the report by Takei et al. is to be welcomed.

Prenatal infection (rubella, cytomegalovirus, toxoplasma) has a small (less than 2%) aetiological contribution to the incidence of intellectual handicap in the community (Wellesley et al. 1991). The CNS abnormalities so far attributed to influenza A_2 virus infection in the first gestational trimester involve severe defects such as anencephaly. A Helsinki survey of 6147 infants born after the 1957 pandemic (Hakosalo and Saxen 1971) found a weak positive correlation between possible exposure during the 5th–11th gestational week and CNS malformations. In a follow-up survey of 526 children in Dublin, born to mothers reporting "Asian flu" during pregnancy, Coffey and Jessop (1963) established an increased prevalence of anencephaly linked to first-trimester exposure; however out of the total of six cases of "mental deficiency" in their series, four were associated with second-trimester and two with third-trimester influenza. The only prospective study employing serological control of actual infection during the 1957 pandemic in Baltimore (Hardy et al. 1961) demonstrated an increased risk of congenital malformations associated with first-trimester infection, but the numbers were too small for identifying specific CNS sequelae.

The question about a wider spectrum of CNS morbidity associated with prenatal influenza therefore remains unanswered. It is now known that transplacental infection does occur (Yawn et al. 1971) and that there is a plausible mechanism linking the neurotropic influenza virus to the developing dopaminergic system (Rubinstein 1994). These are good reasons for exploring existing epidemiological databases for clues, prior to mounting hypothesis-testing studies. This is what apparently Takei et al. have done. Their results are suggestive of an association that merits further study but fall short of an adequate test of an hypothesis.

There are three factors which weaken the design of this study. First, the intellectually handicapped persons admitted to, and discharged from, psychiatric hospitals are a biased sample, selected for unspecified behavioural disturbances. Gross neurological and sensory defects were probably excluded in this group. What is needed in this type of study is the entire subgroup of individuals with intellectual handicap, "cause unknown" (about 20% of all mentally handicapped persons). Secondly, the exposure model used by the authors in this, as well as in several other analyses, relies on a rather remote "proxy" measure – the number of female deaths attributed to influenza. As the authors themselves point out, such deaths are usually reported in elderly women and their number is unlikely to be an accurate measure of the spread of the epidemic among the pregnant women in the community. Moreover, the Baltimore prospective study data indicate that adverse fetal outcomes were not related to the clinical severity of maternal infection. In a number of cases, fetal abnormalities occurred following subclinical infection which would have been missed in subjective reporting but was demonstrable serologically. Thirdly, the statistical model used in the data analysis (Poisson logistic regression) may be an overkill considering the uncertainties associated with both the independent and dependent variables.

Notwithstanding this, I agree with the authors that the limitations of their data are more likely to work against finding an association rather than necessarily exaggerate a spurious one. Although the 95% confidence intervals for the relative risks in Table 2 do not permit unassailable conclusions, this publication highlights an issue which is overdue on the research agenda.

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Reply to the comments on Takei et al.: Prenatal exposure to influenza epidemics and the risk of mental retardation

We are grateful to all three colleagues for their detailed comments. Professor Jablensky and Dr. Bromet focus on the present paper and make constructive criticisms with which we largely agree; we therefore reply to their comments together. In contrast, Dr. Crow takes the opportunity to attack not so much the present paper on mental handicap but rather our work on schizophrenia published elsewhere. We therefore reply to his criticism separately.

(Professor Jablensky's and Dr. Bromet's comments on mental retardation)

We agree that the evidence suggesting an association between prenatal exposure to influenza and risk of CNS abnormalities, in particular neural tube defects (NTD), has been controversial. This prerequisite for our hypothesis has, however, been further supported by a recent population-based case-control study in the USA, which shows a three-fold (95% CI 1.9–4.7) increased risk of NTD in infants of mothers who reported an episode of influenza in the first trimester of gestation (Lynberg et al. 1994).

It may be true that our sample was in some way selected, since we collected the data from the series of the Mental Health Enquiry discharges. Indeed, we discussed this limitation in the text. However, if, as Jablensky points out, subgroups with gross neurological and sensory defects were excluded from our data because of our sampling and these were related aetiologically to influenza, then our results would have been biased not towards an artifactural positive result but towards the null hypothesis.

The number of female deaths from influenza, of course, is a proxy measure. Antibody titres from mother's blood during pregnancy or immediately after birth are the ideal measure of quantifying the exposure level, but it is impractical to expect such information. The occurrences of influenza epidemics have a distinct pattern, usually forming an exponential increase in the number of cases after their inception. We assumed that the variations of the number of female deaths attributed to influenza reasonably reflect the extent to which pregnant women are affected with it. We cannot be sure, however, that the rates of subclinical infection precisely parallel fluctuations in the rates of severe cases. Nevertheless, this imprecision in measurement on exposure would lead to an underestimate of the relative risk but not to an overestimate. Therefore, again this would bias our results towards a negative finding.

Our measure of exposure (the number of deaths from influenza) cannot, of course, be an indicator of exposure level in each individual. Instead, we predicted that influenza-related cases of mental handicap increase with an increase in the prevalence of influenza during the susceptible period of gestation. However, influenza-related factors such as fever and/or use of medications could account for the association (Lynberg et al. 1994).

It is true that studies using a correlational approach face difficulty in interpreting results when potential confounding factors (i.e. covariates), which are not adequately taken into account, are postulated to explain the association. To allow the analysis of aggregate data to be analogous to analytical methods, – that is, allowing for the covariates in the analysis – statistical devices have been developed (Clayton and Schifflers 1987). We used a Poisson regression analysis in which population live births (as a denominator) were entered as an offset, and time-trends (polynomial terms) and seasonality (12 levels), of births of mental handicapped individuals were treated as covariates before the variable of interest, i.e. prenatal exposure to influenza, was examined.

This technique, Poisson regression analysis, has now appeared in other fields of medical research. Kuhn et al. (1994) applied this approach to evaluate the effect of a prevention programme on the changes over time in rates of child injury after allowing for both time-trends and seasonality factors as covariates, precisely as we did in our analysis. They clarify the usefulness by stating "Poisson regression provides a versatile analytical method for quantifying the time trends of relatively discrete outcomes". We think that this technique will soon be as familiar as logistic regression analysis, which used to be viewed as "a complex analysis".

Non-differential misclassification of exposure, as pointed out, could overestimate rather than underestimate the association under investigation. Even so, one anticipates that this ought to be pertinent equally to the gestational period examined but not especially to the postulated vulnerable period, i.e. around the late first or early second trimester of gestation. It is difficult to imagine how any random misclassification would produce results favouring our prediction, which involved a specific time period.

This is the first study to have shown an association between prenatal exposure to influenza and birth frequencies of mentally handicapped individuals. As an invariable rule, such findings have to be challenged and contrasted by the results from further observational studies (e.g. case-control and cohort studies) to confirm the causal relationship (Hill 1965).

(Dr. Crow's comments on schizophrenia)

We have updated the results of recently conducted studies concerning the relationship between prenatal exposure to influenza and risk of developing schizophrenia. Thirteen studies from various countries report a positive association (Mednick et al. 1988; Barr et al. 1990; O'Callaghan et al. 1991; Sham et al. 1992; Stöber et al. 1992; Adams et al. 1993; Fahy et al. 1993; Takei et al. 1994a, b; McGrath et al. 1994; Mednick et al. 1994; Kunugi et al. 1995; Wright et al. 1995). Three studies are equivocal [Kendell and Kemp 1989; Adams et al. 1993 (long-term examinations); Takei et al. 1995], and four studies did not find any association (Torrey et al. 1991; Crow and Done 1992; Susser et al. 1994; Selten and Slaets 1994). Some data examined by different investigators are not entirely independent; in particular, the last two studies were conducted using the same source of Dutch data. However, it is clear that the overall balance is in favour of the association.

We should learn lessons from the debate on the causal relationship between tobacco smoking and lung cancer. Surprisingly, it has taken decades to establish firmly the risk association even when a discernibly increased risk (10-fold increase) of lung cancer was noted from the early 1950s. Even the most prominent statistician of this century, R. A. Fisher, did not believe it initially. If the size of the "schizophrenogenic" effect of influenza is not as large as for the smoking-lung cancer relationship, then one would expect to encounter some failures in replicating the findings, and on this basis the postulated association might be disregarded. Any single study, however, cannot provide strong evidence for or against the hypothesis unless adequate statistical power for the study is ensured. To dismiss, with confidence, the association under study, power of at least 80% is required. The NCDS (the National Child Development Study) study by Crow and Done (1992), which has led them to conclude dogmatically that "prenatal influenza and schizophrenia are unrelated" (Crow and Done 1992), had only 30% power (Takei and Murray 1994c).

Table 1 Distribution of schizophrenic births by trimester in relation to exposure to 1957 pandemic

Male	Index[a]	Control[b]	OR†	*P*-value
2nd trimester	65	227	1.11	
1st and 3rd trimester	107	413	0.77–1.59	$P = 0.57$
Female	**Index**	**Control**	**OR**	***P*-value**
2nd trimester	38	106	1.60	
1st and 3rd trimester	53	237	0.97–2.65	$P = 0.05$

[a] Those were exposed to 1957 pandemic in utero
[b] Those were born in the 4 control years (see the paper by O'Callaghan et al. 1991)
† OR indicates odds ratio

To answer Crow's other specific questions:

(I) We have now analysed the data of our previous study (O'Callaghan et al. 1991) by trimester. The results were consistent; there was a birth excess in females but not in men in relation to the second trimester exposure to the 1957 pandemic (see Table 1).

(II) Findings similar to those by Mednick et al. (1989) and O'Callaghan et al. (1991) have now appeared in four other studies (Adams et al. 1993; Fahy et al. 1993; McGrath et al. 1994; Kunugi et al. 1995).

(III) The Danish sample that Barr et al. (1990) used is, strictly speaking, not the same as that used by Adams et al. (1993). The former examined 7,239 persons with a clinical diagnosis of schizophrenia born between 1911 and 1950, while for the latter 14,260 subjects with an ICD-schizophrenia born between 1911 and 1965 were examined. As for the sampling frame, patients for Barr et al.'s study were selected if they were treated as an inpatient or day patient over an 11-year period between April 1969 and August 1979, but Adams et al. chose subjects known to the register on 31 December 1991. Thus, the discrepancy in sample size between the two is due to both a sampling frame difference and the use of wider birth cohorts in the latter study. Age composition also differs; age range in Barr et al.'s and Adams et al.'s studies are 19–68 and 26–80 years, respectively. Thus, relatively young patients were not included in the study of Adams et al., which failed to detect the association. Furthermore, the Danish register for inpatients started in April 1969 and for day patients in April 1975; thereby a higher proportion of day patients with seemingly milder forms of the disorder were included in Adams et al.'s sample.

Dr. Crow alleges that the methods used by the two research groups (Barr et al. 1990; Adams et al. 1993) are the same. However, the underlying assumptions in their studies are quite different. Analysis of variance (ANOVA) assumes a normal distribution (Barr et al. 1990), whereas birth counts were assumed to have a Poisson distribution in Adams et al.'s analysis. Discrete rare events such as schizophrenic births are better approximated by a Poisson distribution (Kuhn et al. 1994), and thus, Adams et al.'s approach seems more appropriate. However, our own

study (Takei et al. 1994b) that examined Danish data using a Poisson regression analysis, replicated the results obtained by Barr et al.'s ANOVA analysis; in particular, narrowly defined schizophrenics showed the association in our study. Together with negative findings in Adams et al.'s study that seemed to have included a higher proportion of milder schizophrenics, this suggests that the effect of prenatal influenza may be relevant only to a subgroup, namely a severe type of schizophrenia.

(IV) Dr. Crow seems to have misunderstood the estimated percent increases reported by our different studies. The 88% increase in risk of developing schizophrenia in those exposed to the 1957 pandemic (O'Callaghan et al. 1991) is called the risk difference percent (RD%), namely the proportion of cases in the exposed group that were deemed to be caused by the exposure. In contrast, in the long-term studies, we calculated the population attributable risk fraction (PAF), which is a measure of the proportion of all cases in the study population (both exposed and unexposed) that may be attributed to the exposure; we obtained 1–2% for the estimate in the study of Sham et al. (1992) and similar proportion in a Danish sample (Takei et al. 1994b). To illustrate these differences, suppose that there was an 88% increase (22 extra cases; the expected number of births was 25) in births that occurred only in February 1958, which was related to the exposure, and no other increases were observed in the other 11 months of the year (constant births 25 in each month) because these months were not related to the exposure. In this example, RD% is 88% and PAF is obtained by $22/(25 \times 12)$, that is 7.3%. The latter estimate is higher that that found in our previous study (1–2%), but this is simply because a pandemic like the 1957 A2 pandemic is extremely uncommon, and therefore a greater effect would be expected in 1958.

(V) The negative findings from the NCDS study (Crow and Done 1992) were addressed earlier with respect to inadequate statistical power (also see Takei and Murray 1994c).

Although Dr. Crow is suspicious about the underlying assumptions made for our analysis, no systematic pattern was, however, found when the residuals obtained from the model were plotted against the fitted value, indicating that there were no serious violations against the assumptions. The relative robustness of this model was illustrated by Kuhn et al. (1994), who applied model-fitting techniques similar to ours to their data.

There is no reason to believe that the variation of frequencies of deaths from influenza differs between the two sexes. Therefore, we obtained only data on the female deaths attributable to influenza between 1952 and 1980. However, as the monthly number of male deaths between 1952 and 1969 (a total of 216 months) is also available to us, we have now computed the Pearson's correlation coefficient between male and female deaths over the period of 216 months. This was 0.9809 *(r)*, showing a high correlation between the two (95% CI of *r*: 0.9751–0.9854).

Seasonality term was retained in the model so as to be stringent for the test of any effect of influenza. However, even when the term was excluded from model, the effect of influenza 6 months before birth hardly changed (change in deviance, $\chi^2 = 5.24$, $df = 1$, $P = 0.022$), indicating that the effect of prenatal influenza was independent of season.

If multiple comparisons were made in a single study, one might be advised to choose a stringent criterion for "significance" such as a rule of Bonferroni correction. However, one needs to bear in mind that the reduction in risk of a type-I error is achieved only at the expense of an increase in a type-II error – that is, an increase in the number of false negatives. Further, the adjustment of *P*-value itself is disputable. The necessity has been questioned as Rothman (1986) states "Since no problem calling for any adjustments seems to exist unless the positive results from a large number of comparisons are reported without any information about the total number of comparisons, and since even then it appears that adjustments in the results only make them more difficult to interpret, the best course for the epidemiologist to take when making multiple comparisons is to ignore advice to make such adjustments in reported results". It should also be noted that there was a weighted prediction in our study on the susceptible period, i.e., the fourth–fifth month of gestation (see Text).

We quite agree with Dr. Crow on the point that one needs to be cautious and critical about new research findings. However, one also needs to be open to perspectives that may probably convey an important public health impact.

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