© International Epidemiological Association 2000 Printed in Great Britain International Journal of Epidemiology 2000;**29**:596–601

Letters to the Editor

European stillbirth proportion and Chernobyl

From MARIA BLETTNER

Sir—Scherb *et al.*[1] reported results of a statistical analysis on still birth proportions in three European regions for the years 1980–1992 and explore whether the decreasing time trend in these proportions was distorted during or after the Chernobyl accident.

I have serious reservations about the scientific validity of the paper.

First, both the introduction and the discussion include much material that is not pertinent to the investigation that leads to a confused discussion. The major objective of the authors was to verify their hypothesis that the radiation exposure in Germany due to the Chernobyl accident led to an increase in stillbirth proportion. Using data from other 'Western' or 'Central' (for the very specific definition of 'Western' and 'Central' see Scherb *et al.*) European countries their hypothesis could not be confirmed. Additionally, in Table 7 'results' and 'conclusions' are listed that do not emerge from the analysis but are cited from former published and unpublished works of the authors.

Secondly, there are limitations in the statistical analysis:

a) The grouping of the 18 countries was based on geographic aspects. As can be seen from the values given in the legend of Figure 1 and even better in Table 1 of a paper by Dolk *et al.*[2] the radiation exposure levels vary substantially within the countries combined in each group. This classification is not a valid one based on radiation exposure after the Chernobyl accident. The group 'East' especially is questionable as countries with very different stillbirth proportions and different levels of radiation exposure are combined.

b) To avoid the difficulties caused by the classification and as national proportions were available, national proportions could have been used in an ungrouped form. At least they should have been plotted or presented for visual inspection. Such an analysis may also give a better appreciation of the relation between the stillbirth proportions and radiation exposure.

c) A result in Table 7 that is commented on, whether sex-ratio changed after the radiation exposure, is only mentioned in a short paragraph without data and without specific analysis. More importantly, it is stated that the classification used in the remainder of the paper was changed. For a statistical analysis this raises suspicions about its validity and leads to the impression that the change in the classification was used to obtain significant results.

d) Modelling the time trend should have been done in a uniform way for all three groups. As the analysis of the time trend is not of primary interest to the investigation (and could be considered as a confounder), it would be more logical to use the same time-trend model for all regions and to investigate the size and the significance of the added dummy variable(s).

In addition to the statistical analysis being questionable some details are not clear. Inspection of Figure 2 (and Table 6) shows a clear decrease with a small curvage for 'Central' and 'West'. There is no elevation in 1986 or 1987. The observation of the authors presented in previous papers that stillbirth proportion was increased in Germany in 1986 was not confirmed in this larger data set. Results for 'West' even show a significant decrease in 1987 and subsequent years, yet this group included countries (such as the northern part of the UK) where radiation exposure was higher than in Germany (see also Table 1 in Dolk *et al.*[2]). Figure 2 gives the impression that the decrease was accelerated slightly after 1986.

For 'East' the change of trend in 1986 is obvious. However, grouping countries is particularly questionable, as they are so disparate and as radiation exposure after Chernobyl varied widely within and between the grouped regions. Interestingly, as mentioned by the authors, data from the more contaminated Belarus and Ukraine do not confirm the observation of an elevation or change in trend during or after 1986.

The authors emphasize that causal inference can be drawn from this 'ecological' study, yet the discussion in Table 7 is centred around the 'radiation hypothesis'. Additionally, only parts of what is listed as 'results' in the table are presented in the paper. For example:

(1) The strong and significant deviation towards lower proportions from the decreasing trend in 1986 and 1987 in the region 'West' is neither mentioned nor commented on. This group includes some countries with a relatively high exposure (such as the northern UK).

(2) Belarus and Ukraine show no increase during or after 1986. These results do not fit the authors *a priori* hypothesis. It is incomprehensible that the authors specifically argue at this point about the general limitations in the data and the instability in the populations. The same argument holds for all results in similar ecological investigations and for other results in the paper.

(3) That perinatal death proportions do not show a clear increase in eastern countries is attributed to the instability in the perinatal data. No details of this analysis are given. The scientific validity of this is questionable as stated earlier.

(4) It is concluded from differences between perinatal death and stillbirth in 'East' (again, no details are presented in the paper), that 'radioactivity induces less neonatal deaths than stillbirth.' This is contradictory to the authors' statement that no causal conclusions can be drawn from the data and it does not take into account the results from the other regions.

An analysis of the highly aggregated data can neither prove nor disprove an effect between radiation exposure and stillbirth rates, especially in view of an exposure that is far below background radiation in most of the countries (maximum 0.7 mSv, most regions below 0.3–0.03 mSv, see Table 1 in *Dolk et al.*[2]) and that areas with very different exposures are combined for this ecological analysis. The authors state in the Abstract that 'Our results … contradict the present radiobiological knowledge'. Based on the data presented, I am unable to accept this conclusion.

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Authors' Response

From HAGEN SCHERB, EVELINE WEIGELT and IRENE BRÜSKE-HOHLFELD

Sir—Blettner disputes our results[1] on a number of points. We wished to investigate whether in other—especially eastern—European countries, the effects on stillbirth and perinatal death rates after the Chernobyl accident were similar to those observed in Germany.[2–5] We observed that, in Hungary, Poland and Sweden, the overall effect on the stillbirth rate was even stronger than in Germany.

The validity of our grouping into West, Central, and East countries (**a and b**) was questioned. This grouping served two purposes: to demonstrate and estimate a possible global spatial-temporal detrimental effect on European stillbirth rates after the Chernobyl accident and to ensure sufficient statistical power that could not be obtained using only single countries. No such coarse grouping was required if we had finely stratified data on contamination in Europe as we had for Bavaria and the former GDR,[3,4] but to our knowledge, such European data do not exist. Blettner's reference to Table 1 in the paper by Dolk *et al.* does not help, because the reported doses cover only a small proportion of the respective western and central European populations. For example, population coverage in the United Kingdom is only 61 710 births out of 759 041 births in 1986. No data at all are presented for eastern European countries. In view of the lack of detailed European exposure and perinatal data we decided to group the countries according to the obvious 'radial neighbourhood to Chernobyl' criterion into East, Central, and West strata. The difficulties we met in data availability, stability of stillbirth definition in the time periods studied and presumed exposure contrasts should be recognized.

We did not study the sex ratio as Blettner presumes (**c**). Because the sex ratio contains no direct information on stillbirths, we analysed the stillbirth odds ratio for gender: (male stillbirth/male live birth)/(female stillbirth/female live birth). This is an appropriate measure for the statistical analysis of the association between sex and stillbirth. For several countries we were unable to obtain gender specific stillbirth data and to apply the original West, Central, and East strata to the gender specific analysis. For example, for Poland, we did not obtain the gender specific stillbirth data according to the 28-week definition, instead, we were supplied with the gender specific stillbirth data according to a 600 g definition. Therefore, we investigated the time trend of the stillbirth odds ratio for gender in Denmark, Germany, Hungary, Norway and Sweden combined as well as in Poland on its own. The trend of the stillbirth odds ratio for gender including the change-point in ordinary linear weighted regression in 1987 and the trend of the sex ratio, for comparison, are shown in Figure 1 below. This effect can also be seen if countries are evaluated on their own or combined differently. It is interesting to note that stillbirth, unstratified by gender, in Denmark, Germany, Hungary, Norway, and Sweden combined shows essentially the same behaviour as in our original eastern group. Only the effect in 1986 is smaller and nonsignificant. It is not justified to imply that only certain combinations of the data would yield positive and significant results.

In contrast to Blettner (**d**), we do not consider that it is appropriate to use the same trend parameters for the three parts of Europe because the trends vary and differ highly significantly from each other. Moreover, applying a common trend model, i.e. only one intercept and only one slope, actually leads to a large overdispersion: Deviance/d.f. = 79.54. Using different intercepts and only one slope, improves the fit and renders the effects in the eastern part of Europe for 1986, 1987 and 1988–1992 positive and significant, similar to the result in our paper. Blettner ignored (**1**) our description of the relatively large and abrupt improvements in the stillbirth rates in western European countries in 1987 and 1988 (not 1986 and 1987 as Blettner assumed).

It was shown[2,4,5] that the perinatal death rate in 1987 is elevated in Germany. As far as we know, it has never been claimed that the stillbirth rate in 1986 was significantly elevated in Germany. On the contrary, in Table 7[1] we report that, as a rule, stillbirths are not significantly elevated in western and central countries in 1986 in contrast to some eastern countries. Assuming a size of effect and power, we acknowledge that an increase in stillbirth rate in Germany is not likely to be detected.

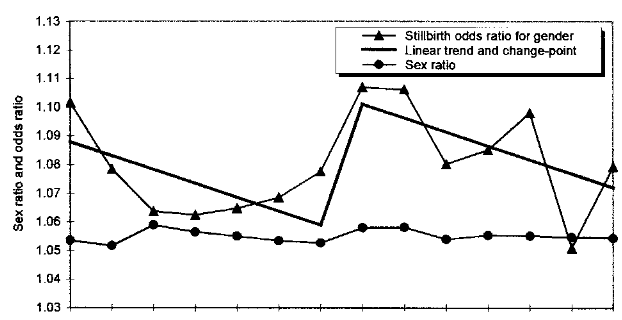

Figure 1 Sex ratio and stillbirth odds ratio for gender (male stillbirth/male live birth)/(female stillbirth/female live birth) with change-point in regression (*P*-value = 0.0095) for Denmark, Germany, Hungary, Norway, and Sweden combined

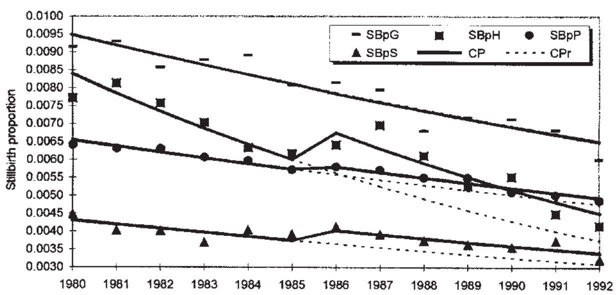

Figure 2 Stillbirth proportions (SBp) for Greece (G), Hungary (H), Poland (P), Sweden (S) 1980–1992, and linear logistic regression models with change-points (CP) in 1986 and reduced CP-models (CPr)

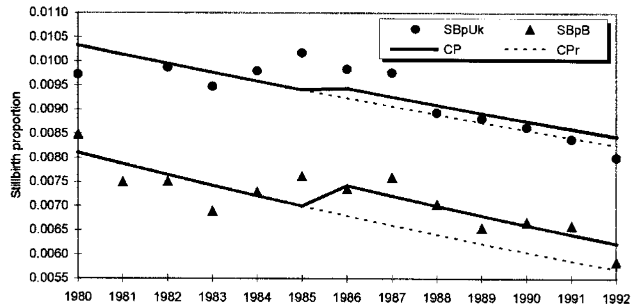

Figure 3 Stillbirth proportions (SBp) for Belarus (B) and Ukraine (U) 1980–1992, and linear logistic regression models with change-points (CP) in 1986 and reduced CP-models (CPr)

Limitations of space did not allow account of the 20 countries involved and only significant change-points in the trends of the stillbirth odds ratios for gender could be mentioned. Hopefully, our work will serve as a starting point for further analyses because it is impossible to exhaust the topic in one paper. Figure 2 shows the trends in our four eastern European countries. Blettner is correct in saying that these trends are different, but so are trends of sub-regions of single countries. In our view, the variability between and within these countries is not so high as to preclude an analysis of the combined trend (an exception is the highly overdispersed Ukrainian data, see Figure 3 and Table 1 below). In Figure 2 and Figure 3 we also included simple linear logistic change-point models with the change-point in 1986. This is a parsimonious and impartial approach. Table 1 contains quantitative information on these models. The change-point is non-significant for Greece, borderline (or one-sided significant) for Sweden, and significant for Poland and Hungary. The change-point is also significant for these four countries combined, which is in close agreement to the significant effects of the partial eastern model in our paper. Figure 3 shows the data for Belarus and Ukraine. Table 1 also contains information on the change-points for these data alone and combined with the other countries. Because of the highly variable Ukrainian data from 1980 to 1987 the change-point model does not fit the Ukrainian data alone or that of all six countries combined (Deviance/d.f. = 15.65 and 18.28, respectively). The less dispersed Belarus data reveal a one-sided borderline significant change-point in 1986 and combining this data with Greece, Poland, Sweden and Hungary yields a significant change-point in 1986, which also closely agrees with our original analysis. Thus, Blettner's statement (**2**): 'Belarus and Ukraine show no increase during or after 1986' is incorrect. We reiterate the lack of a definition of stillbirth in Belarus and Ukraine and all analyses involving these data are speculative. We interject here that we failed to point out in our paper, the highly significant effect in 1987 in the six eastern countries combined. We only mentioned the effect in 1986.

Perinatal death rates were significantly elevated in 1987 in eastern part of Europe. This supports the corresponding observation in Germany[2,5] and has been overlooked by Blettner (**3 and 4**). We hypothesize that radioactivity may induce more stillbirths than neonatal deaths based on the fact that the observed overall effect in our eastern Europe is weaker for perinatal death than for stillbirth alone. In addition, the spatial-temporal analysis in Bavaria[3,5] yields higher risk coefficients for stillbirth than for perinatal death. In many analyses we observed stronger overdispersion in early neonatal and perinatal data than in stillbirth data.

Blettner criticizes our interpretation in the abstract, which sounds somewhat contradictory to the simultaneously emphasized general limitations in our paper of results based on aggregated data. However, our statistical conclusion is conditional on the biological possibility that the observed spatial-temporal effects in Germany and Europe on small-scale and large-scale levels could be explained by radioactivity. Our position is strongly supported by the significant relative risks of stillbirth per 1 kBq/m^2 on a district level in Bavaria[3,5] (96 districts) and in the former GDR[4] (197 districts) in 1987/1988 of 1.0072 ($P = 0.002$) and 1.0264 ($P = 0.003$), respectively.

Table 1 Linear logistic change-point models (intercept, t, d_{86-92}) for stillbirth proportions of eastern European countries 1980–1992. Degrees of freedom (d.f.) = 10 for all models not containing the Ukraine.[a] CI and *P*-values corrected for overdispersion (Deviance/d.f. > 1) not corrected for underdispersion (Deviance/d.f. < 1)

Country	Odds ratio[b]	*P*-value	95% CI	Deviance/d.f.	Stillbirth	Live birth
Greece(G)	0.995	0.9320	(0.896, 1.106)	2.14	12 452	1 538 469
Poland(P)	1.038	0.0451	(1.001, 1.076)	0.94	47 326	8 167 116
Sweden(S)	1.102	0.0836	(0.987, 1.229)	0.86	5282	1 373 284
Hungary(H)	1.202	0.0117	(1.042, 1.387)	3.46	10 767	1 684 193
G+P+S+H	1.056	0.0085	(1.014, 1.099)	1.97	75 827	12 763 062
Belarus(B)	1.093	0.1204	(0.977, 1.222)	3.08	14 698	2 032 361
Ukraine(U)	1.022	0.6824	(0.922, 1.132)	15.65	82 238	8 723 263
G+P+S+H+B	1.065	0.0034	(1.021, 1.111)	2.61	90 525	14 795 423
G+P+S+H+B+U	1.054	0.1927	(0.974, 1.140)	18.28	164 387	22 304 183

[a] Missing data for Ukraine in 1981, d.f. = 9.[b] Odds ratio of the change-point variable d_{86-92}; $d_{86-92} = 0$ for 1980–1985 and $d_{86-92} = 1$ for 1986–1992.

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From ALFRED KÖRBLEIN

Sir—Scherb *et al.*[1] published stillbirth data for Belarus and Ukraine but excluded them from the analysis because the authors were not provided with the definition of stillbirths. But since these two countries suffered the highest fallout from Chernobyl, the data are of great interest and should be studied, even though there might be doubts about the definition. Therefore I analysed the data for Belarus plus Ukraine given in Table 2, but using a simple linear trend model. I only introduced one dummy variable for the year 1987, the year following the Chernobyl accident, since in an earlier investigation I had found an effect on German perinatal mortality for 1987 alone.[2] I also re-analysed the combined data for Poland, Sweden, Hungary and Greece, denoted East by Scherb *et al.* using the same model, and finally performed a combined regression of the two data sets to increase the test power.

Data

In conversations with physicians from a St Petersburg maternity hospital, I learned that the criterion for stillbirth was a birthweight greater than 1000 g in the former Soviet Union at this time. But I was warned against using official data before the time of Glasnost (1985), because of habitual underreporting then, so I used only the data for 1985–92 in my analysis for Belarus and Ukraine.

Method

I use a simple exponential trend model which is linear when the logarithm of stillbirth rates is used. For testing a possible deviation of the stillbirth rate in 1987 from the trend of the other years, a dummy variable d(87) is introduced. A one-sided t-test is used to find out whether the coefficient of d(87) is greater than zero.

Results

In spite of the reduced time span, the fit to the data from Belarus plus Ukraine shows a significant increase of stillbirth rate in 1987 ($P = 0.0245$). Also for the data East the increase in 1987 is significant ($P = 0.0134$). The time constants as well as the excess rates in 1987 agree for both data sets within the limits of error. Therefore a combined regression with individual parameters for the intercepts is performed, using a common time constant and a common coefficient for the excess rate in 1987. This model then reveals a highly significant increase in 1987 ($P = 0.0006$). The excess in 1987 translates to 614 extra stillbirths (95% confidence interval 361–867) in the eastern countries taken together, i.e. Poland, Sweden, Hungary, Greece, Belarus and Ukraine. The result of this analysis thus confirms the main result obtained by Scherb *et al.*

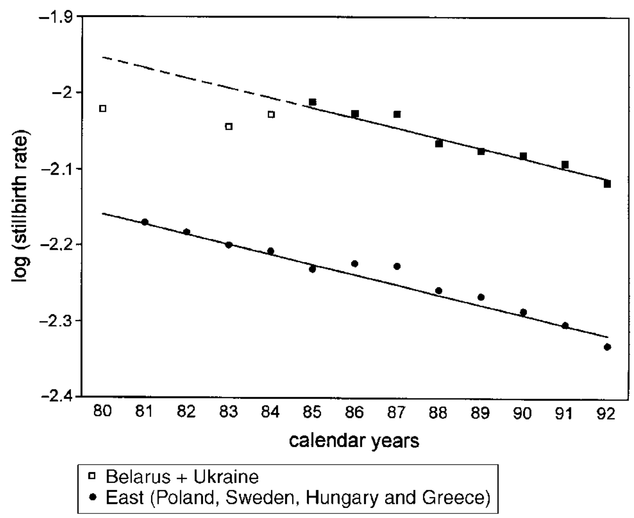

Figure 1 Stillbirth rates in Eastern Europe

In Figure 1, the logarithms of the stillbirth rates are plotted, because in a semi-logarithmic plot exponential functions appear as straight lines. The circles represent the stillbirth data East, the squares, the data for Belarus plus Ukraine. The two parallel lines show the result of the combined fit.

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Topical Antibiotic use and Circumcision-Associated Neonatal Tetanus: Protective Factor or Indicator of Good Wound Care?

From SÉRGIO DE A NISHIOKA

Sir—In their interesting study Bennett *et al.* demonstrated that circumcision is a risk factor for neonatal tetanus (NNT) in Punjab Province, Pakistan.[1] They also showed that the use of topical antibiotics on the circumcision wound decreased the risk of NNT to the same level observed in babies who were not circumcised. Based on these findings Bennett *et al.* suggest that topical antibiotics should be routinely applied to every circumcision wound, and add that topical application of other substances commonly used in the region should be avoided. I would like to comment on these recommendations.

One of Bradford-Hill's well-known criteria used for assessing a hypothesized causal relationship is biological plausibility.[2] When an association is plausible the hypothesis is usually more acceptable. In the assessment of the protective effect against NNT of topical antibiotics used in the circumcision wound it is important to know whether topical antibiotics inactivate *Clostridium tetani* spores or, more likely, vegetative forms, or if there are alternative mechanisms that explain why the use of such ointments would prevent this disease. Among the several topical antibiotics at least bacitracin is active against clostridia, and has also been shown to enhance epidermal healing of wounds.[3] This makes the observed protective effect of topical antibiotics on circumcision-associated NNT plausible, when the ointments used contained this antibiotic. However it is also possible that the use of topical antibiotics is just an indicator of good wound care. In such cases caregivers who used topical antibiotics in the circumcision wounds of their babies did it instead of using dung, ghee, urine etc, which explains why the babies did not get NNT.

Adjustment for use on the circumcision wound of the above-mentioned substances was apparently not done in the multivariate analysis. It would be interesting to know whether the use on the circumcision wound of dung and other substances likely to be contaminated with tetanus spores could have confounded the observed protective effect of local antibiotics in preventing NNT. I would not be surprised if these variables were highly negatively correlated to each other, i.e. those individuals who used topical antibiotics did not use dung in the circumcision wound, and vice-versa. Even if the correlation is not as high as I expect, analysis of a possible interaction between these variables would also be of interest. In which case my bet would be that those who used dung plus topical antibiotics had a higher risk of NNT than those who used only antibiotics.

If the use of topical antibiotics is only an indicator that wounds are kept clean and free of tetanus spores, what would be the best advice for health care workers involved in neonatal care in Punjab Province? Education of the population to not use substances that could contaminate the wound is an obvious solution that might not be easy to execute, at least in the short term. Dr Bennett *et al*. are familiar with the region and the local culture, so their recommendation to promote the topical use of antibiotics deserves respect. It may be the best short-term solution as it might decrease the use of dung and other substances rich in tetanus spores. On the other hand it would increase cost, create false expectations as to the effectiveness of antibiotic ointments, and increase the risk of side effects associated with the use of topical antibiotics.[3] Promoting the use of ointments containing only antiseptics is an alternative that deserves consideration.

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Authors' Response

From JOHN BENNETT, CATHERINE BREEN, JENNIFER MACIA, JOHN BORING

Sir—Dr Nishioka correctly surmises that there is a strong negative correlation between applying topical antibiotics and dirty substances to circumcision wounds. In fact, there were no reports of the combined use of both antibiotics and dirty substances in our study.[1] While it is possible that topical antibiotics are thus only markers signifying the absence of exposure to hazardous substances, other data suggest that this is not likely to provide a full explanation for the observed effects.

In a companion paper,[2] we demonstrated that applying nothing to umbilical wounds was significantly risky compared with topical antimicrobials. Small numbers prevent a confident evaluation of the magnitude of risk of dry care with circumcision wounds; only two cases and one control had dry care reported before the day of onset of NNT or onset date in a matched case, respectively. However, applying nothing is clearly not without risk.

We believe that failure to proactively protect both umbilical and circumcision wounds with antimicrobials will lead to increased risks of NNT in environments similar to our study areas,

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where animals and animal dung exist in close proximity to living areas, and frequent exposure of wounds to tetanus spores is likely. In addition, antimicrobials should also reduce risks of sepsis deriving from either of these frequently contaminated wounds.

Antiseptics were used too infrequently in our present study to assess their independent effects, although they have been shown to be protective against NNT from umbilical wounds in other studies.[2,3] We thus agree that topical antiseptics deserve careful consideration as alternatives to topical antibiotics.

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