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A controversial necrotizing enterocolitis outbreak in a neonatal unit

To the Editor:

In a recent article Faustini et al. [1] reported an outbreak of neonatal necrotizing enterocolitis (NEC), which occurred in 1999 in the Teaching Hospital Umberto I in Rome, Italy. The authors claimed that 18 cases of NEC occurred 5–7 days after two clusters of diarrhoea (14 cases) and an infective origin for the outbreak.

Our account of the outbreak, published in 1999 [2], was not referenced by Faustini et al. In our investigation, over the 5-week period NEC was initially diagnosed in 10 neonates as stage II (definite) and in four as stage I (suspect). Only the first two cases (stage II) underwent surgery (NEC histological diagnosis) [3]. Because of the unusual factors in the outbreak, which included no mortality, a majority of full-term babies, few recognized risk factors, and no microorganism isolated, a clinical revision of cases, according to the definition proposed by Bell et al. [4] was undertaken.

A panel of experts, working double blind, reviewed the clinical features and checked the radiographs for NEC confirmatory hallmarks [5], which are essential for diagnosis [6, 7]. The final result confirmed NEC stage II diagnosis in three newborns (including the two who underwent surgery) and stage I in one. This finding confirmed there had been an epidemic but less serious than at first feared [2].

In their conclusions Faustini et al. appear to have misjudged several aspects.

First the authors admit explicitly to having included as NEC cases neonates not conforming to Bell's case definition [4], justifying this decision by quoting other studies [8–13]. However in these

studies babies without clear signs of *pneumatoxis intestinalis* on X-ray were included on the basis of a common isolated aetiological infective agent [8–10] which was not the case in the outbreak under review. They also refer to a study showing that among 136 patients with strictly documented NEC, 19 had never demonstrated *pneumatoxis intestinalis*. However 15 out of these 19 (79%) patients died of NEC complications and the remaining four had NEC confirmed from surgically resected tissue [11]. Another study [12] made a clear distinction between definite and suspected cases on the basis of radiographic criteria. The final article described an important multicentre study carried out in 1976 by Ryder et al. [13] before Bell's case definition had been adopted.

Second, the absence of mortality was explained by stating that the NEC outbreak was consistent with a less severe form of the disorder which occurred in healthy, full-term infants. However, this does not explain why the only two neonates who underwent surgery for their critical conditions, were not the smallest ones (weight >2500 g).

Third, no microorganism was isolated. NEC aetiology is multifactorial and includes both infective and non-infective factors [14, 15]. The authors appear committed to the 'infective hypothesis' in spite of the time elapsed between the first case on 6 June and the others, and the absence of gastrointestinal symptoms in the full-term babies. Furthermore to support the 'infective hypothesis' they quote 'the interruption of NEC clustering by the use of antibiotics and by control measures'. However, they omitted to mention that newborn admissions were stopped on 6 July 1999, and could have avoided overestimating NEC by doing so.

Fourth, NEC onset age was very low at 1.3 days (0–6 days). In a recent review of 17 epidemics [14] a mean age of 9.5 days (range 6.6–29 days) was found. Faustini et al. cited a study by Wiswell et al. [16], showing a median onset of 2 days. However, it should

be stressed that all their cases fulfilled Bell's case definition [5], especially regarding the radiological signs.

In conclusion it appears that by ignoring the preceding clinical revision of cases [2, 5] and misjudging the unusual conditions occurring in the outbreak the authors seriously overestimated the size of the epidemic [1].

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The authors reply:

Professors Orsi and Fara question the case definitions we used in the investigation of an outbreak of mild necrotizing enterocolitis (NEC) in 1999 at the Umberto I Teaching Hospital, Rome [1]; the size of that epidemic; and the infective hypothesis we postulated. However, neither in the letter they published in 1999 [2], nor in the comments above, do they cast doubt on the occurrence of an epidemic or on the diagnosis of NEC.

The correspondents commented that we did not reference their 1999 account of the outbreak [2]. In fact, their account of the NEC outbreak was based on our official Italian report [3] and served as a starting point to discuss the 'errors in radiology and pathology'. The point was well taken as during the outbreak more than one revision of NEC cases was performed by two expert panels (the former commissioned by the Umberto I Teaching hospital, the latter charged by the judge) and the internal Committee on Nosocomial Infections in which the correspondents took part. None of these unpublished revisions was blind with regard to the disease status of the newborns, as only the suspected NEC cases were considered. However, a revision of NEC cases involved in the epidemic was published in a study on reliability of radiological diagnosis carried out after the outbreak [4]. The study considered 297 X-rays from 57 high-risk infants, with and without a diagnosis of NEC, which were examined blind by three independent experts in paediatric radiology. In our report [1], we took into account the results of this

study as the methods and the findings were part of the available literature.

For the *case definition* of NEC, we included both stage II (confirmed) and stage I (suspected) NEC cases in our analysis, according to Bell's criteria. Although we discussed the possibility that stage I cases may not be NEC cases, as Bell himself underlined, we preferred to adopt a more sensitive case definition; in fact, by using both radiological and clinical evaluations we reduced the false-negative errors. The study of the reliability of radiological diagnosis [4] came to the same conclusion: the reliability was 'low for NEC diagnosis and individual radiological signs among the three expert radiologists' as 'the level of agreement beyond chance for radiographic diagnosis suspected/confirmed was 0.31 ($P < 0.01$)'. These authors concluded 'clinical information and the presence of more than one radiological sign can reduce the margin of observer's error that inevitably exists when dealing with a diagnosis as difficult as NEC'. In our study, the clinical radiologists diagnosed 10 pneumatoses (stage II of NEC) and six loop distensions (stage I of NEC) (the radiological diagnosis for two children was not reported in the chart). Despite the poor reliability of radiology for this condition, the independent and blind revision of 13 NEC cases in our study confirmed (based on the agreement between two radiologists) three cases as NEC stage II, and eight cases as NEC stage I; the radiographs of two children were classified as negative. We did overestimate the epidemic, for two cases, as we tried to be as sensitive as possible in describing an epidemic for a disease characterized by low sensitivity of diagnosis.

The isolation of an infective agent is not included at all among Bell's criteria for confirmed NEC, because of the multi-factorial nature of the disease and because no single bacterial agent or virus has been consistently identified as a cause of NEC. There is general agreement, however, that NEC does not occur without bacterial colonization of the gastrointestinal tract.

We hypothesized an infective nature of the epidemic based on three observations: (a) the time-space clustering of cases, (b) the clinical characteristics of the NEC cases (higher birth weights, fewer perinatal complications, lower case fatality rate than usually reported in sporadic cases), (c) the sequence diarrhoea – NEC, as reported in at least seven papers previously. The characteristics of a disease in populations or groups have allowed epidemiologists to hypothesize the nature and even the aetiology of an emerging

disease or an epidemic, even those not yet confirmed microbiologically. This contribution to public health is very important, as occurred with Burkitt's lymphoma, AIDS, and SARS.

The detection of an infective agent did not confirm the diagnosis of NEC for single patients, but in many other epidemics referenced in our paper, it allowed the authors to conclude that when a cluster of NEC occurs, the infective hypothesis is highly probable. In this case, it is legitimate to include even stage I cases in analysing the epidemic, because infective cases generally had mild symptoms, and were not in critical condition. Obviously, if a microorganism had been isolated from NEC cases in this outbreak, we could have confirmed the nature of the epidemic, instead of only making a hypothesis. Unfortunately, the stools of the children involved in the outbreak were tested only for *Salmonella* and *Shigella* before antibiotic therapy, and no blood cultures were done. That was an obvious mistake. The only conclusion that can be made is that microorganisms were not tested adequately. We cannot conclude that no microorganisms were isolated. This mistake surprised us, because a laboratory surveillance of diarrhoea was active in the region (including Rome) during the outbreak, testing any bloody stool samples for *Escherichia coli*, one of the bacteria frequently implicated in NEC epidemics.

The infective hypothesis seems to be the only possible explanation of the two confirmed stage II cases, which underwent surgical intervention. They were not the smallest (weight > 2500), nor were they in critical condition. They underwent surgery because of the serious lesions in their abdomen, and not because of their overall poor condition. What possible explanation besides infection can the commentators suggest for these two cases of confirmed NEC?

Professors Orsi and Fara did not present alternative hypotheses which we would have liked to discuss. Their criticisms do not provide additional evidence to alter our conclusions.

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Tattoos, incarceration and hepatitis B and C among street-recruited injection drug users in New Mexico, USA: update

To the Editor:

In a previous report [1], we described significant risks for hepatitis B (HBV) and hepatitis C (HCV) positivity associated with receipt of tattoos, particularly while incarcerated, among a street-recruited population of injection drug users (IDUs) in New Mexico, United States from 1995 to 1997. Another recent report in this Journal, based on a study conducted on prisoners in Australia, found tattooing in prison to be an independent risk for HCV [2]. Another report also described a strong association between tattoos and HCV, but found the strongest association to be with commercial tattooing venues [3]. That study found the risk associated with receipt of tattoos in prison elevated, but not statistically significant. That same report reviewed other articles and found a significant risk for HCV infection associated with tattoos in six out of eight studies that had data available. Further, a recent U.S. Centers for Disease Control and Prevention (CDC) document summarized the literature on risks for hepatitis infections in correctional settings and developed extensive control guidelines [4].

We noted in our previous report that the observed association between HBV/HCV and tattoos received while incarcerated may have been confounded by

history of incarceration. Many studies have described elevated rates of HBV and HCV in prison settings [4], including HBV in the penitentiary of New Mexico prior to identification of the HCV virus [5]. Therefore, in an attempt to independently assess the effect of tattoos, incarceration, and receipt of tattoos while incarcerated, we added items to our 1998 IDU outreach programme asking specifically about lifetime history of incarceration.

A total of 469 IDUs participated in the 1998 programme, which was conducted in Bernalillo County, New Mexico (where Albuquerque, the largest city in New Mexico, is located). The demographic and behavioural characteristics of these participants were similar to the characteristics previously described [1]. Notably, these participants were primarily male (70·2%) and Hispanic (70·1%). Of these participants, 1·3% (6/469) were HIV antibody positive, 64·5% (285 out of 442 tested) were HBV antibody (anti-HBc) positive, and 86·7% (386 out of 445 tested) were HCV antibody positive. Twenty-four participants not tested for HBV or HCV were excluded from further analyses. The associations between most of the demographic (e.g. gender, race/ethnicity) and behavioural (e.g. sharing injection equipment, years of injection, and tattoo) characteristics with HBV and HCV were similar to our previous report. In particular, Hispanics were more likely to be HBV and HCV positive than were non-Hispanic whites. One exception to our previous report was that even in the youngest age groups, a large proportion of participants were already HCV positive [e.g. 86·4% of 15- to 24-year-olds ($n=22$); compared to 45·5% ($n=112$) previously, $P<0\cdot001$].

Overall, 9·0% of project participants reported never having been in jail or prison, 49·2% reported having been in jail only, 2·9% reported having been in prison only, and 38·9% reported have been in both jail and prison. Because prison generally involves a much longer period of incarceration than jail, and because the number of participants that had been in prison only was small, for this analysis ‘prison only’ and ‘jail and prison’ were combined into ‘any prison’. Table 1 shows that participants who had been in prison were significantly more likely to be positive for both HBV (78%) and HCV (94%) than were participants who had not been incarcerated (43% and 75% respectively). Participants who had been in jail only were also more likely than those never incarcerated to test positive for both HBV (57%) and HCV (83%), but these differences were not statistically

Table 1. Incarceration, tattooing history and years of injections and the univariate association with HBV and HCV seropositivity among injection drug users, New Mexico, 1998

	No.	%	Hepatitis B ^a		Hepatitis C	
			% pos.	<i>P</i> value	% pos.	<i>P</i> value
Incarceration history						
Never incarcerated	40	9.0	42.5	<0.0001	75.0	0.0006
Jail only	219	49.2	56.9		83.1	
Any prison	186	41.8	78.0		93.6	
Tattoo/tattoo venue ^b						
No	127	28.7	57.5		78.0	
Yes	316	71.3	67.4	0.06	90.2	0.001
Yes, none in prison/jail ^b	201	45.4	60.3	0.0004	87.6	0.002
Yes, some in prison/jail	23	5.2	69.6		95.7	
Yes, all in prison/jail	90	20.3	83.2		94.4	
Years of injection ^b						
0–4	70	22.5	24.3	<0.0001 ^c	61.4	<0.0001 ^c
5–9	72	23.2	40.9		83.3	
10–14	64	20.6	62.5		89.1	
15–24	48	15.4	78.4		93.3	
25+	57	18.3	89.8		95.3	

^a *n* = 3 not tested for HBV.

^b Numbers do not sum to total because of missing data.

^c χ^2 trend test.

Table 2. Multivariate logistic regression assessment of the independent association of tattooing with HBV and HCV seropositivity among injection drug users, New Mexico, 1998

	Hepatitis B			Hepatitis C		
	OR	95% CI	<i>P</i> value	OR	95% CI	<i>P</i> value
Model 1 – dichotomous tattoo variable						
Any tattoo	1.9	1.1–3.3	0.01	2.0	1.0–3.9	0.04
	[age (<i>P</i> = 0.002) and years of injection (<i>P</i> < 0.0001) also significant]			[race (<i>P</i> = 0.005), sharing injection equipment (<i>P</i> = 0.04), and years of injection (<i>P</i> < 0.0001) also significant]		
Model 2 – multilevel tattoo variable						
None			0.02	n.s.		
Tattoo, none in prison/jail***	1.8	1.0–3.2				
Tattoo, some in prison/jail	0.9	0.3–2.7				
Tattoo, all in prison/jail	3.2	1.4–7.1				
	[age (<i>P</i> = 0.002) and years of injection (<i>P</i> < 0.0001) also significant]			[race (<i>P</i> = 0.0009) and years of injection (<i>P</i> < 0.0001) only significant variables]		

OR, odds ratio; CI, confidence interval; n.s., not significant.

significant. The statistical power for these comparisons is limited because only 40 participants reported never having been incarcerated. Table 1 shows that participants with tattoos were significantly more likely to be HCV positive (90%) than participants

without tattoos (78%). The same pattern is seen for HBV seropositivity but this difference did not reach statistical significance (*P* = 0.06). Table 1 also shows the very strong association between increasing years of injection and both HBV and HCV seropositivity.

Because of strong interrelationships between these key variables and potential confounding, multivariate logistic regression using SAS version 8 (SAS Institute, Cary, NC, USA) was used to assess independent associations of these characteristics with HBV and HCV positivity. We used standard stepwise procedures to determine the final models, and reassessed these models by forcing certain variables into or out of the models. Because 'tattoo' and 'venue of tattoo' could not be included in the same model due to complete collinearity, we ran separate models that included a dichotomous 'yes/no' tattoo variable, and a four-level 'no tattoo, tattoo-none in prison/jail, tattoo-some in prison/jail, tattoo-all in prison/jail' variable. For HBV, tattoo (both dichotomous and four level), age, and years of injection were retained in the final models, and tattoos in prison/jail appeared to be associated with positivity more strongly than tattoos not in prison/jail (Table 2). For HCV, similar associations were seen, but age was not retained; and sharing contaminated equipment and race/ethnicity were retained. Importantly, the incarceration variable was not significant in *any* final model, and appears to be significant in the univariate analysis only because of the strong confounding effect of years of injection. Data not shown indicate a very strong association of incarceration with years of injection – they indicate, not surprisingly, that the longer people have been injecting, the more likely they are to be in jail and then in prison. Length of time in prison was assessed for persons who had been in prison, and it was also found to be associated with HBV and HCV in univariate but not multivariate analyses. The incarceration variables were only significant in multivariate models if the years of injection variable was forced out of the models.

These 1998 outreach project data found a strong association in univariate analysis of having been in prison, compared to never having been incarcerated, for both HBV and HCV. Univariate analysis also found a strong association of tattooing and HCV and a marginal association with HBV. However, multivariate analysis indicates that the observed association between prison and HCV and HBV positivity is due to confounding by years of injection. In final analyses, an independent association of tattooing with both HBV and HCV remained significant, and for HBV tattoos received in prison appear to be particularly risky. These findings suggest that the previously reported association of HBV and HCV

with having received a tattoo in prison is more from the tattooing risk than any other prison risk.

Hepatitis prevention activities should include education about risks associated with tattooing and should support efforts to emphasize sanitary tattooing practices in all settings. Because of previously described unsanitary tattooing practices in prisons [1, 6], public health action needs to be taken to prevent bloodborne pathogen transmission in prisons, including consideration of making sterile tattooing equipment available.

Declaration of Interest

None.

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