*Epidemiol. Infect.* (2010), **138**, 1032–1035. © Cambridge University Press 2009
doi:10.1017/S0950268809991269

# SHORT REPORT
# Alternative risk factors of HCV infection in a rural community in China

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(*Accepted 5 November 2009; first published online 27 November 2009*)

## SUMMARY

A case-control study was conducted in Linxian, Henan Province in China to explore potential risk factors for hepatitis C virus (HCV) infection unassociated with injection drug use. One hundred and ninety-two persons (41·7% male, 95·8% aged >60 years) were recruited from an earlier cohort. Of these, 48 were HCV positive and 144 HCV negative. Residence in a plain region and 3–10 injections in a health setting per year were significantly associated with HCV in both univariate and multivariate analysis ($P<0·01$). In rural China, the geographic distribution of HCV infection was heterogeneous and associated with injections in a health setting, a pattern which differed from the epidemics in injection drug users in urban cities.

**Key words**: China, epidemiology, HCV, injection.

The prevalence of hepatitis C virus (HCV) infection is around 1–2% in most countries [1], while in some African countries (Egypt, Cameroon, Guinea), the prevalence exceeds 10% [2]. China is a country with an intermediate prevalence of this infection. According to a nationwide study in 1992 [3], HCV prevalence was reported to be 3·2% overall and 3·1% in some rural areas. Other smaller studies have reported a prevalence of 0–3% in rural populations from various Chinese provinces [4, 5]. Surprisingly, a study in a cohort in Linxian, Henan Province using blood samples collected in 2000 from people aged >55 years gave an HCV prevalence of 9·6% [6], a figure much higher than the national average. Despite the high HCV prevalence in Linxian, no human immunodeficiency virus (HIV) infection has yet been diagnosed, nor was there association with injection drug use, a factor contributing to both HIV and HCV infections in many countries, including China [7]. The discrepant observation raised our suspicions about any alternative risk factors related to HCV infection in rural China.

To test our hypothesis, we re-interviewed HCV-positive participants recruited in an earlier cohort and made comparisons with HCV-negative participants in a case-control study. This earlier cohort was established in 2000, comprising 500 participants from the Linxian Nutritional Intervention Trial (NIT) conducted for oesophageal and gastric cancer prevention in 1985. All of the 48 HCV-positive subjects detected in the 2000 cohort were recruited as cases in the current case-control study, with a 3:1 ratio of age-matched (Table 1*a*) HCV-negative subjects as controls. Their plasma samples were collected in 2000 and tested for HCV antibody by HCV enzyme immunoassay (EIA). A supplemental recombinant immunoblot assay (RIBA) was performed on positive

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Table 1*a*. *Characteristics of the study population in Linxian, Henan Province: demographics and residential location*

| | Total | | HCV+ | | HCV– | |
|---|---|---|---|---|---|---|
| Characteristics | *n* | (%) | *n* | (%) | *n* | (%) |
| Commune | | | | | | |
| Yaocun | 65 | (33·9) | 20 | (41·7) | 45 | (31·3) |
| Rencun | 36 | (18·8) | 14 | (29·2) | 22 | (15·3) |
| Donggang | 44 | (22·9) | 3 | (6·8) | 41 | (93·2) |
| Hengshui | 47 | (24·5) | 11 | (23·4) | 36 | (76·6) |
| Residential location | | | | | | |
| Plain area | 102 | (53·1) | 32 | (66·7) | 70 | (48·6) |
| Mountain area | 90 | (46·9) | 16 | (33·3) | 74 | (51·4) |
| Gender | | | | | | |
| Male | 80 | (41·7) | 19 | (39·6) | 61 | (42·4) |
| Female | 112 | (58·3) | 29 | (60·4) | 83 | (57·6) |
| Age (yr) | | | | | | |
| ⩽59 | 9 | (4·7) | 3 | (6·3) | 6 | (4·2) |
| 60–64 | 40 | (20·8) | 10 | (20·8) | 30 | (20·8) |
| 65–69 | 52 | (27·1) | 12 | (25·0) | 40 | (27·8) |
| 70–74 | 48 | (25·0) | 13 | (27·1) | 35 | (24·3) |
| ⩾75 | 43 | (22·4) | 10 | (20·8) | 33 | (22·9) |

samples [6]. A questionnaire survey was administered to inquire about the participants' behaviours between 1985 and 2000 through face-to-face interview. Apart from demographic information, the questionnaire explored potential risk factors for HCV infection, ranging from history of blood transfusion, blood/plasma donation, medical care procedures (including injection, surgical and dental operation), daily activities (including sexual activities and the sharing of razors) and household contacts. For those unavailable at the time of the interview, their spouses, siblings, or children responded to the questionnaire on their behalf. The study was approved by the Chinese University of Hong Kong Clinical Research Ethical Committee. All patients provided written informed consent for the survey, collection of samples and subsequent analysis. Data input was performed with EpiData and analysed by using SPSS version 13.0 (SPSS Inc., USA). The frequencies of demographic characteristics and risk factors between cases and controls were compared by $\chi^2$ analysis. Odds ratio (with 95% confidence intervals) measuring potential associations of risk factors with HCV infection was estimated by simple logistic regression analysis. Individual factors were tested as being significant before inclusion into multivariate analysis with the Enter method. Age and gender were adjusted because of their significance in previous studies. No interaction between subjects and services was considered on the assumption of an even distribution of healthcare services in both plain and mountain regions.

There were a total of 192 participants in our study, 48 of whom were HCV positive. None of the participants was an injection drug user. Participants resided in four communes of Linxian: Yaocun ($n=65$), Rencun ($n=36$), Donggang ($n=44$) and Hengshui ($n=47$) (Table 1*a*). Individual home address was recorded and participants were divided into two categories according to the main geographic characteristics: plain region and mountain region. Slightly more than half of the participants resided in the plain area. Over half of the participants were female and more than 90% were aged >60 years. One third of the participants had undergone at least one cytology procedure, a common diagnostic method for oesophagus cancer that was used in the NIT study. Regarding possible risk factors associated with HCV infection, more than 70% of participants reported having received injections in a local clinic or hospital 1–10 times per year. Forty percent had undergone intravenous blood sampling but only 5% reported ever having received a transfusion. However, 60% of the study population reported having undergone surgical operation, which included dental procedures. Current active HBV co-infection (defined as being positive for both HBsAg and HBcAb) was seen in only 6·4% of the study population, while past infection occurred in 54·6% of the population. The presence of both HBsAg- and HBcAb-positive results was used to indicate HBV co-infection in the subsequent statistical analyses.

Table 1*b* shows the results of univariate and multivariate analyses. Residence in plain region ($P<0·05$), having received injections 3–10 times per year ($P<0·01$) and skin piercing ($P<0·05$) were strongly associated with HCV infection. We included significant factors ($P<0·05$) obtained from univariate analyses for conducting the multivariate analysis. Age and gender were also adjusted in multivariate analyses since the previous study had shown their possible significance. Living in plain region (OR 2·9, 95% CI 1·4–6·1, $P<0·01$) and having received injections 3–10 times per year previously (OR 5·2, 95% CI 1·5–18·0, $P<0·01$) still remained significant in the multivariate analysis.

Overall, our study indicated that a high number of reported injections per year was specifically associated with a higher risk of acquiring HCV. Other studies have revealed that injection was related to HCV when

https://doi.org/10.1017/S0950268809991269 Published online by Cambridge University Press

Table 1*b*. *Characteristics of the study population in Linxian, Henan: risk factors associated with HCV infection*

| | HCV+ | | HCV– | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Characteristics | *n* | % | *n* | % | OR | *P* | 95% CI | aOR | 95% CI |
| Plain area | 32 | 66·7 | 70 | 48·6 | 2·114 | 0·032 | 1·068–4·187 | 2·868** | 1·357–6·065 |
| Male gender | 19 | 39·6 | 61 | 42·4 | 0·891 | >0·1 | 0·458–1·736 | 0·887 | 0·421–1·869 |
| 3–10 injections per year | 28 | 58·3 | 34 | 23·6 | 5·147 | 0·006 | 1·601–16·550 | 5·215** | 1·514–17·966 |
| Intravenous blood sampling | 20 | 41·7 | 63 | 43·8 | 0·918 | >0·1 | 0·474–1·780 | n.a. | n.a. |
| Surgery operation† | 28 | 58·3 | 91 | 63·2 | 0·815 | >0·1 | 0·419–1·588 | n.a. | n.a. |
| HBV co-infection | 1 | 3·2 | 10 | 12·7 | 0·230 | >0·1 | 0·028–1·878 | n.a. | n.a. |
| Transfusion | 3 | 6·3 | 7 | 4·9 | 0·766 | >0·1 | 0·190–3·089 | n.a. | n.a. |
| Skin piercing‡ | 48 | 100 | 133 | 92·4 | 1·361 | 0·068 | 1·247–1·485 | n.a. | n.a. |

n.a., Not available.

Odds ratio with 95% confidence interval and *P* value of $\chi^2$ test are reported in the table as OR, *P* and 95% CI. Odds ratio with 95% CI of multivariate logistic regression are reported as adjusted OR (aOR) and 95% CI in the table.

† Dental surgery is included.

‡ Skin piercing included: acupuncture, ear piercing, tattoo and other medical procedures involving a wound in skin or membrane such as venepuncture, haemodialysis, etc.

**$P<0·01$.

it was administered under poor hygienic conditions [8, 9]. Linxian, a county which is still relatively underdeveloped, relies on traditional agricultural activities to support the population's livelihood. Since the local medical care system is not well developed, injections were usually given in local village clinics, many of which lacked standard infection control procedures compared to city hospitals. Moreover, although disposable syringes were introduced into the community about 10 years ago, their widespread use is only just emerging in recent years. In an earlier study in Linxian [6], the authors speculated that the majority of infection had occurred between 1985 and 2000. It can be deduced that HCV infection might have resulted from the use of unclean syringes in local village clinics, before the use of disposable ones became standard practice.

The geographic distribution of participants in the study suggested that residence in a plain region was also significantly associated with HCV infection, an observation supporting the phenomenon of spatial variation of the infection across the four communes. In Linxian, the plain region is larger both in size and population, and is conveniently linked by transport to the city centre, while the mountain region is often small and isolated. The convenient location of the plain region implies that residents were better connected to each other, which might have accelerated the dissemination of infectious diseases, if there were any. The relatively isolated locations of the mountain region may mean a less mobile population. There was a lesser chance for infections to be introduced into these isolated localities, and a propensity for existing infections to be geographically confined without significant spread. It is possible therefore that endemic HCV infection has become established and widely disseminated in plain regions, which was possibly aggravated by the use of unclean syringes in health services.

In the last decade, there has been wide media coverage of the transmission of HIV through commercial blood donation. Such practice and its association with HCV infection had been reported in the adjacent province of Shanxi [10], and it is still the most important risk factor for blood-borne infections such as HCV and HIV in some rural parts of this province. The risk of blood-borne infections is high in commercial blood donation because of the use of contaminated equipment and the reinfusion of pooled red cells to donors. However, no similar practice of commercial blood donation had been reported in our study population, and therefore, unsurprisingly, HIV-1 co-infection had not been commonly diagnosed. These observations suggested that the HCV infection was less likely to be introduced to this population by commercial blood donation, and was more likely a result of poor hygiene as well as substandard infection control practice in local healthcare settings.

Our study carries a number of limitations. First, the study population was relatively old with a high proportion (95·8%) aged >60 years. Our questionnaire focused on the participants' recall of activities and

https://doi.org/10.1017/S0950268809991269 Published online by Cambridge University Press

behaviours occurring in the 6 years preceding the interview. Therefore, it might be difficult for respondents to remember specifically the details or the precise frequency of their risk activities. Furthermore, some questionnaires were completed with the assistance of family members of those unavailable for interview. As a result, this may undermine the accuracy of the answers, thereby affecting the determination of the correlation between risk factors and HCV prevalence. Similarly, sampling bias was an inherent problem as the patients had been recruited from the pool of 500 participants previously enrolled in a cohort in 2000, who were the surviving subjects of the NIT 1985 cohort. While patients in the original cohort might have been randomly drawn from the community, the 20-year lag period and the small size of the final sample could have led to potential bias. As a relatively isolated and less mobile community, the case-control study has enabled us to explore the presence of alternative risk factors for HCV in a rural setting, although these findings require further validation.

In conclusion, our study suggests that whereas needle-sharing in injection drug users was the main driving force of the global spread of HCV around the world, injection in healthcare settings could be a significant risk factor in some areas. HCV is common in residents of a rural Chinese community in Henan Province, China. The HCV prevalence varied in communes while injection in healthcare settings was a risk factor for the infection. The geographic variation further suggested that the endemicity of HCV infection could be associated with yet unknown factors, different from those for the epidemic in injection drug users.

## ACKNOWLEDGEMENTS

The authors thank Xiudi Sun, Yu Zhang, four interviewers and 102 village physicians for their assistance in the field study, the 192 study participants for their cooperation, staff at Stanley Ho Centre for Emerging Infectious Diseases, The Chinese University of Hong Kong for administrative support in the course of conducting the study. This study was supported by the Research Fund for the Control of Infectious Disease (RFCID), Food and Health Bureau, the Government of the Hong Kong SAR.

## DECLARATION OF INTEREST

None.

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