[6] Ohta A, Sekimoto M, Sato M, Koda T, Nishimura S, Iwakura Y, et al. Indispensable role for TNF-alpha and IFN-gamma at the effector phase of liver injury mediated by Th1 cells specific to hepatitis B virus surface antigen. J Immunol 2000;165:956–61.
[7] Kast RE, Altschuler EL. Remission of Crohn's disease on bupropion. Gastroenterology 2001;121:1260–1.
[8] Kast RE, Altschuler EL. Bupropion lowers TNF levels in congestive heart failure. Submitted for publication
[9] Spahr L, Rubbia-Brandt L, Frossard J-L, et al. Combination of steroids with infliximab or placebo in severe alcoholic hepatitis: a randomized controlled pilot study. J Hepatol 2002;37:448–55.

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# Computerised-hepatitis B-model is subject to processing axiom: garbage in, garbage out

*To the Editor*:

In their article on the cost-effectiveness of hepatitis B in India [1], Aggarwal and colleagues use sophisticated decision analysis software to construct a Markov model and conclude that 27.5% of hepatitis B carriers die of cirrhosis or hepatocellular carcinoma (HCC). This, they note, is similar to a 'widely quoted estimate of 20–27%' worked out by Miller and Kane [2].

The two groups use different methods of calculation and arrive at the same conclusion. Does this reiterate the point that the conclusion reached is correct? We can use different modes of transport, but we will reach the same point if we travel the same road, in the same direction. The reason that both sets of authors arrive at identical conclusions is both make their projections for India, based on similarly flawed data obtained from Taiwan and Europe [3–11].

A model is tested against reality. Dr Miller in his paper calculates that, as 27% carriers die of Hepatitis B, 261 000 deaths must be occurring in the country each year from this disease alone. However, using meticulously maintained population-based cancer-registries, the Indian Council of Medical Research has calculated that only 5000 people die of HCC due to hepatitis B in the country each year [12]. This figure is calculated yearly and has remained steady over the last 15 years. In a longitudinal study, McMohan et al. [13] has found, for 1.9 cases of HCC, 0.4 cases of decompensated cirrhosis occur per 1000 carrier years. In this proportion, when we add on deaths from cirrhosis to the Indian HCC figures, it adds up to 6000 deaths. This is less than 3% of the deaths projected by the computer simulation. Clearly the model does not fit reality [14].

Aggarwal et al., in their paper, briefly allude to population-based differences in mortality, when they quote McMohan's paper from Alaska [13] where the adverse events rate was 0.23%, which is about half the Taiwan rate. There is another widely cited study from Montreal [15], which showed that adverse events in Taiwan were at least 17 times the rate in Montreal. This Montreal study was not quoted in the paper by Aggarwal.

It is obvious that the projections from this computer generated model, using select mortality figures from overseas, are very different from the actual figures as counted and projected locally. Local figures must be used for projection of deaths for India.

Lokesh Tiwari, Raji Mathew Varghese, Jacob M. Puliyel*
*Department of Pediatrics, St. Stephens Hospital, Tis Hazari, Delhi 110054, India*

## References

[1] Aggarwal R, Ghoshal UC, Naik SR. Assessment of cost-effectiveness of universal hepatitis B immunization in a low-income country with intermediate endemicity using a Markov model. J Hepatol 2003;38:215–22.
[2] Miller MA, Kane M. Routine hepatitis B immunization in India: cost effectiveness assessment. Indian J Pediatr 2000;67:299–300.
[3] Beasley RP, Hwang LY. Epidemiology of hepatocellular carcinoma. In: Vyas GN, Dienstag JL, Hoofnagle JH, editors. Viral hepatitis and liver disease. Orlando, FL: Grune and Stratton; 1984. p. 209–24.
[4] Beasley RP. Hepatitis B virus: the major etiology of hepatocellular carcinoma. Cancer 1988;61:1942–56.
[5] Dusheiko GM, Roberts JA. Treatment of chronic type B and C hepatitis with interferon alfa: an economic appraisal. Hepatology 1995;22:1863–73.
[6] Wong JB, Koff RS, Tine F, Pauker SG. Cost-effectiveness of interferon-alfa2b for hepatitis B e antigen-positive chronic hepatitis B. Ann Intern Med 1995;122:664–75.
[7] Louis-Jacques O, Olson AD. Cost-benefit analysis of interferon therapy in children with chronic active hepatitis B. J Pediatr Gastroenterol Nutr 1997;24:25–32.
[8] Fattovich G, Giustina G, Schalm SW, Hadziyannis S, Sanchez-Tapias J, Almasio P, et al. Occurrence of hepatocellular carcinoma and decompensation in European patients with cirrhosis type B: the EUROHEP Study Group on hepatitis B virus and cirrhosis. Hepatology 1995;21:77–84.
[9] DeJongh FE, Janssen HLA, DeMan RA, Hop WCJ, Schalm SW, van Blankenstein M. Survival and prognostic indicators in hepatitis B surface antigen-positive cirrhosis of the liver. Gastroenterology 1992;103:1630–5.
[10] D'Amico G, Marabito A, Pagliaro L, Marubini E. Survival and prognostic indicators in compensated and decompensated cirrhosis. Dig Dis Sci 1985;31:468–75.
[11] Liaw Y-F, Lin D-Y, Chen T-J, Chu C-M. Natural course after the development of cirrhosis in patients with chronic type B hepatitis: a prospective study. Liver 1989;9:235–41.
[12] Dhir V, Mohandas KM. Epidemiology of digestive tract cancers in India III. Liver. Indian J Gastroenterol 1998;17:100–3.
[13] McMohan BJ, Holck P, Bulkow L, Snowball M. Serologic and

clinical outcomes of 1536 Alaska natives chronically infected with hepatitis B virus. Ann Intern Med 2001;135:759–68.
[14] Ojha RK, Abraham J, Khosla M, Puliyel JM. Vaccine promotion is circumventing market forces. Br Med J 2002;324:975.
[15] Villeneuve JP, Desrochers M, Infante-Rivard C, Willems B, Raymond G, Bourcier M, et al. A long term follow up study of asymptomatic hepatitis B surface antigen positive carriers in Montreal. Gastroenterology 1994;106:1000–5.

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# Cost-effectiveness of hepatitis B immunization: it is not 'garbage-in, garbage-out'

*To the Editor:*

We thank Dr Tiwari and colleagues for their interest in our paper [1]. Their primary argument is that Indian data should have been used in preference to those from other parts of the world for the natural history of chronic hepatitis B. Their point is perfectly valid and we would surely have used such data, if any were available. We are unaware of any long-term follow-up study of Indian patients with chronic hepatitis B and were unable to find any such published literature. In the absence of such data, we had no option but to take recourse to data from elsewhere.

Of the two papers [2,3] that Tiwari et al. have cited to support low rates of development of serious disease and of death among patients with chronic hepatitis B, we did take the one by McMahon et al. [2] into account in our analysis. We did not specifically refer to the other study [3] since it included a small number of patients and its results were similar to those of McMahon et al. The range of our sensitivity analysis well encompassed the disease progression rates observed by McMahon et al. We used a baseline estimate of development of liver cirrhosis among persons with chronic hepatitis B of 1% per year and included in our sensitivity analysis rates as low as one-tenth of this estimate. Thus, we studied the cost-effectiveness of universal hepatitis B immunization using the annual rate of development of liver cirrhosis as low as 1 per 1000. Using this estimate in our model, only 3.4% of persons with chronic hepatitis B would have died of consequences of hepatitis B virus infection (0.58% and 2.82% of hepatocellular carcinoma (HCC) and liver cirrhosis, respectively); this translates to a life time risk of adverse events among persons with chronic hepatitis B of 34.0 per 1000, which is even lower than the low risk observed by McMahon et al. (2.3 adverse events per 1000 carriers per year). Even with this low rate of development of adverse clinical events, our analysis found hepatitis B vaccination to be cost-effective.

Tiwari et al. also refer to the low rate of HCC recorded in the cancer registries in India. One must keep in mind that a large proportion of patients with hepatitis B related HCC have underlying liver cirrhosis and present clinically mainly as decompensation of liver cirrhosis. In the absence of advanced medical facilities, many of these patients are not diagnosed as having HCC. Thus, cancer registries in developing countries are likely to underestimate the rates of HCC. Second, the number of deaths calculated from registry data is not comparable to number of deaths calculated from Markov model analysis. Whereas, the registry data provide data on number of deaths that occur in a population during a calendar year, data from a Markov model, like ours, estimate the number of deaths in a single-year birth cohort, i.e. children born during a particular calendar year, over a life time. In a growing population like India's, the former estimate can be expected to be smaller than the latter estimate. Finally, our additional calculations using our Markov model at the lowest rate of disease progression show that in a single-year birth cohort of 25 million newborns, only 6,300 would be expected to die of HCC over their entire life span, a figure not much different from the registry data cited.

McMahon et al.'s study [2] in Alaska is one of the few studies where most deaths among HBV infected persons were due to HCC and only a few were due to cirrhosis. As all physicians looking after patients with chronic hepatitis B are aware, the number of deaths due to decompensated cirrhosis far outnumbers those due to HCC. Thus, the calculation by Tiwari et al. of hepatitis B-related cirrhosis deaths from HCC deaths using the relative frequencies of deaths due to these two diseases in the Alaskan study may not be appropriate.

One of the advantages of mathematical models is their ability to allow comparison of two alternative strategies even when real-life data are not available. Such models allow a wide range of 'what-if' analyses. If such analyses show that one strategy is favoured over a wide range of assumptions, one can be reasonably certain that this strategy should be followed. The only caveat is that the range of assumptions used must encompass the entire range of possibilities. We strongly believe that our analysis did so. We therefore reiterate that our finding of cost-effectiveness of universal hepatitis B vaccination over no vaccination in a low-income intermediate-endemic population is quite robust. This is not a case where the term 'garbage in, garbage out' applies.

Rakesh Aggarwal*, Uday C. Ghoshal
*Department of Gastroenterology,*
*Sanjay Gandhi Postgraduate Institute of Medical Sciences,*
*Raebareli Road,*
*Lucknow 226 014, India*