SOME CRITICAL ISSUES IN THE EPIDEMIOLOGY OF HELP-B IN INDIA

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SUMMARY

1. Prevalence of carrier-rate of HB infection in India – The widely quoted figure of a carrier rate of 4.7% is highly exaggerated because positively rate for HBsAg – screening test has been confused with carrier rate, and averages have been calculated wrongly! Using the same scientifically, the carrier rate works out to be mere 1.42% of general adult population the carrier pool 12.75 million and not 42.5 million.

   The highly infectious HBeAg -positive pool in India is only 3.26 million.

2. To include HBV immunization as part of the National Health Program, we need to work out the following: -
   a. Systematic estimation of the public health importance of HBV – disease by estimating the morbidity and mortality burden due to acute and chronic HBV – disease and their sequelae in various age-groups. Systematic literature review by Lodha-Jain et. al shows that this burden is much less than what is generally believed by many doctors.
   b. Cost-efficacy of HBV-vaccination in terms of expenses per life year saved and per unit of infectious pool prevented. Systematic evaluation of different options in immunization stategies.
   c. Resource allocation for HBV immunization to be placed in the overall scenario of health and health care in India.

We are unaware of such exercise by I.A.P. before strongly recommending universal immunization of Indian children against HBV. Let this exercise be done.

It seems that most doctors are convinced about the overwhelming danger of hepatitis-B infection in India since experts have put forth-frightening figures. These experts have claimed that the carrier rate of hepatitis-B in India is 4.7% leading to a carrier population of 43 million (1); that "Liver disease due to HBV infection is considered to be the fourth or fifth important cause of mortality in the most productive period of life (15 to 45 years) – (2);" that "approximately 25 percent of these carriers will die of chronic sequelae of this infection-cirrhosis and primary hepatocellular carcinoma" (3).

We argue that such claims are highly exaggerated, unscientific & misleading. There is a need to scientifically assess the burden of morbidity, mortality and consequent loss of life-years due to Hep.B in India. In this brief note, we point out that a series of errors are being made in estimating the burden HBV – disease, and its significance. Secondly, there is a need to discuss in detail the various options for HB-Vaccination-strategy in India on the basis of cost effectiveness and logistical feasibility.

1) THE PREVALENCE - ISSUE

1.1 Positivity rate, true prevalence, carrier rate

1.11 Unscientific Method of Estimation of Prevalence of HBV carrier rate:

HBsAg Positivity is the cheapest of the serological markers of HBV infection and hence is used as mandatory screening test to detect HBsAg – infection amongst blood-donors.

The above-mentioned claim of HBV carrier rate of 4.7% in India is being widely quoted. This estimation by S.P. thyagarajan et al (see ref 1) in the widely read recent book – 'Hepatitis-B in India' is based on the results o 19 studies with 3rd generation serology as summerized in a table. (enclosed) this appears impressive. But this estimation suffers from 3 types of errors.

1. The studies in the table enclosed are all one time, cross-sectional studies of prevalence of HBsAg Positivity in mostly blood donors. This Positivity rate is quite a different indicator than carried rate. Carrier stage in HBV-infection is persistence of infection for six months or more. (4) Substituting Positivity rate of a screening test for carrier rate is a fundamental error and is inadmissible.

Most of these 19 studies report blood bank data of HBsAg Positivity – rate. The basic limitation of blood bank data are that they always report results of one point testing. Secondly some of the blood donors in some centers are Professional Blood Donors (PBDs) though they pose and are recorded as Voluntary Blood Donors (VBDs). Since the prevalence of HBV infection is higher in PBDs, such data do not represent the general population. Thirdly some VBDs donate blood repeatedly. Those who are HBsAg positive keep coming for repeat-donations since the result of the test is not communicated to the donor due to the policy of 'anonymous unlinked' blood donation. These BHsAg positives would be counted repeatedly in the blood bank date, and the Positivity rate thus reported would be higher than the Positivity rate in the general adult population.

2. The table contains 3 studies on professional blood donors and one from dental personnel. It is wrong to include such high-risk group in estimating prevalence in general population.
3. The average prevalence of 4.7% has been calculated by simply taking average of the averages of the individual studies! Scientific way would be to calculate the weighted average as has been done in table 2 (prevalence in pregnant women) in the next chapter of this book.

1.12 Corrected estimate of HBV carried-rate in India

A carrier of HBV infection is defined as any individual who has tow BHsAg positive tests six or more months apart. Hence the proper method to estimate the carrier is to use data in studies which have tested blood for BHsAg problem, 6 months after initial testing, and not to use blood bank data at all. Since such sequential data from large-scale studies from different centers in India are not available, we have to use available single test data by applying the necessary corrective factors. We have done this below in case of the data from the above referred table, presented by Thyagarajan et al. It would demonstrate the great change in results by using the same date scientifically.

We have excluded from the table, the studies on professional blood donors and detail personnel. Then we have calculated the weightage average of the HBsAg Positivity rate in different centers. In this process, we had to exclude studies, which have not

mentioned the number of persons tested. The weighted average of the remaining studies, was found to be 2.64%

This single test Positivity rate of 2.64% is not the point-prevalence. There are bound to be false positive results in this screening test. These false positives depend as much upon the actual prevalence of the disease as upon sensitivity and specificity of the test. The less the prevalence, the more the false-positives. To find out what proportion of the BHsAg positives would actually be infected with the HB-virus, we would have be apply the corrective factor of Positive Predicative Value.

The Positive Predictive Value (RPV) of the test, (the likelihood that a person with a positive test has the disease / infection / problem), is given by the formula (5)

$$\text{Positive Predictive Value} = \frac{\text{True Positive}}{\text{True Positive + false positives}} \times 100$$

HBsAg testing kits are marked by many companies in India. Most do not specify sensitivity and specificity of the kit in relation to a 'gold standard'. Some manufacturers have claimed that the test would be positive for HBsAg concentration as low as 0.5 to 2 ng/ml. This would mean almost 100% sensitivity. Specificity is generally not mentioned in quantitative terms or even not mentioned at all! (For example Reddy Laboratories 'Fast Forward HBsAg' Kit) 'Monozyme' a manufacturer, claims that the false positive results are no more than 1%. This means a specificity of 99%

TABLE: 1

POSITIVE PREDICTIVE VALUES OF A SCREENING TEST WITH A SENSITIVITY OF 100% & SPECIFICITY OF 99% WITH VARYING DEGREE OF PREVALENCE IN SUBSETS OF POPULATIONS OF 10,000 EACH

Prevalence	Infected Persons	Sensitivity 100%		Non-infected persons	Specificity 99%		RPV (c/c+g)x 100
		True (+) -tives	False (-tives -)		True (+) -tives	False (-) -tives	
(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)
1%	100	100	0	9900	9801	99	50%
2%	200	200	0	9800	9702	98	67%.1
3%	300	300	0	9700	9603	97	75%
4%	400	400	0	9600	9504	96	80%
5%	500	500	0	9500	9405	95	84%
6%	600	600	0	9400	9306	94	86.5%
7%	700	700	0	9300	9207	93	88.2%
8%	800	800	0	9200	9108	92	89.7%
9%	900	900	0	9100	9009	91	91%
10%	1000	1000	0	9000	8910	90	91.7%
25%	2500	2500	0	7500	7425	75	97%

As seen in table 1, the RPV of this screening test is 67.1% at the prevalence rate of 2%. The weighted average of single test Positivity of HBsAg in India is 2.64%. Hence let us assume, for a moment that the true prevalence of HBsAg Positivity in India is 2%. The true prevalence of HBsAg Positivity would thus be

$$\frac{2.64 \times 67.1}{100} = 1.77\%$$ 15.94 million in a population of 900 million

Studies, which have followed up, initial HBsAg positives for six months have found that about 75 to 80% of these positives continue to be positives and hence are carries (6,7,8). Extrapolating these findings to the above data of point-prevalence of HBsAg in India, HBsAg – carrier rate works out to be 1.77% x 0.80 = 1.42%. In a population of 900 million, there are 12.75 million HBV carries in India and not 42.5 million.

2) HEPATITIS – B AS A PUBLIC HEALTH PROBLEM

Whether a disease becomes a public health problem depends upon 3 factors – 1) The total burden of illhealth due to that disease premature deaths, and reduced efficiency and quality of life due to illness; relative importance of the disease in the overall health-scanario in the country 2) The threat of infection to the community in case of infectious disease 3) Burden on public exchequer for treating the patients.

In the above mentioned book, it has been claimed by B.N.T. Tandon (p.1) that "It is established beyond doubt that HBV infection is a public health problem in our country". This claim has not been backed up by scientific evidence on these three conts. We briefly point out below for wider consideration, a few facts about facts about public health importance of HBV infection in India on some of the aspects mentioned above.

2.1) Highly Infectious Carrier Pool

As is well known, not all HBsAg + ves are highly infectious. "HBsAg Positive containing HBsAg is more likely to be highly infectious. Persistence of HBsAg in serum beyond 3 months of acute infection may be predictive of the development of chronic infection and the presence of HBsAg during chronic hepatitis B is associated with ongoing viral replication, infectivity and inflammatory liver". (Harrison, 14th edi-1998, P. 1679)

What is the prevalence of this highly infectious carrier in India? Thyagarajan et al (op. cit) have summarised the blood-bank data on HBsAg Positivity rate in India, in a table on page 8 in the above mentioned book and have stated this rate to be 24.43% HBsAg positives, by taking simple average of averages from different studies.

We have excluded professional blood donor data and unpublished data from this table; have added data on pregnant women from this same book (p. 23) and have calculated the weighted average of all these 8 published studies. This works out to be HBsAg positives – (175/855).

This HBsAg Positivity rate would approach true prevalence, as at this high rate of prevalence of HBsAg positives amongst HBsAg positives, the Positive Predictive Value of this highly sensitive and specific test would approach 95%. However, the carrier rate of HBsAg positives would be less than this prevalence rate and needs further work.

We have seen earlier that there are 15.94 million HBsAg positives in India. Hence the pool of highly infectious HBsAg positives would be

$$\frac{15.94 \times 20.47}{100} = 3.26 \text{ million}$$

One of the important parameters of evaluating any immunisation strategy would be to estimate its cost effectiveness in reducing this pool of highly infectious HBV population in India. This point has been totally missed out by Aggarwal and Naik in their estimation of cost – efficacy of HBV immunisation strategy in India (9)

2.2) Life-years Lost Due to HBV Disease

Compared to hepatitis-A. Hep-B is feared because it can bead to chronically of infection and hence chronic sequalae. However, this danger is much less that what may doctors generally believe. Earlier it was thought that 5-10% of acute hep-B patients becomes chronic. However- **"More recent observations suggest that the rue rate of chronic infection after clinically apparent acute hepatitis-B is as low as 1% in normal, immunocompetent young adults."** (Harison, 1998, p.1689) Moreover even amongst these carriers, about 2% clear the virus every year.

To estimate this for HBV disease in India, we need appropriate data about prevalence of HBsAg Positivity, carrier rate in different age groups and data about prevalence of acute and chronic HBV disease with their sequalea in these age groups. Such data are not adequately available. Yet, based on available data some guess-estimate has to be made of the appropriate total burden of morbidity and mortality due to HBV disease in India. This burden of HBV disease has to be translated into number of Life years lost and compare these date with those of other diseases, especially vaccine preventable disease in India. This is a major exercise and we are not attempting it here. But we would like to point out some facts as seen from different studies. A team of pediatricians and two epidemiologists from AIIMS, N. Delhi have, with the help of internet, recently done a thorough literature review of published literature on HBV Epidemiology. (10). We merely quote below from their paper (sent for publication) on the quantitative aspects of sequalea of HBV-infection. The reference numbers in the bracket are those from their paper.

2.21) Sequelae of HBV Infection and Their Prevalence

2.211) Natural History of HBV infection

Liver histology of asymptomatic carriers with normal liver function tests [majority of whom were blood donors] reveal normal liver or minimal or nonspecific changes in 75-90% Chronic active hepatitis (CAH) was seen in only 1-5% of these individuals. The remaining had chronic persistent hepatitis (CPH) [50,51,55]

Popper et al (55) reviewed literature and observed that follow-up biopsies 2-7 years after initial examination in 364 persons revealed an unchanged liver histology appearance in 80.4%, improvement in 5.7% worsening in 12.6% and transition to cirrhosis in only 1.1% de Franchis et al (51) and Feinman et al (56) have also reported similar results. These studies had only adults as the subjects.

Chronic carriage of hepatitis B virus [HBV] is an important risk factor in the development of several serious diseases. Nearly three-fourths of the adult chronic carriers have normal liver function (50,53,54). Less than 5% of these have CAH on liver histopathology; the majority has normal histology or minimal changes (50,51,55). The liver histology is relatively stable over a period of time in these carriers (51,55,56).

In carriers with deranged liver function tests, nearly 85% had normal histology or nonspecific changes or CPH and about 15% had CAH with or without cirrhosis [50,53,56,60-65]. Even in these carries with deranged liver function, the vast majority has normal / minimal histologic changes or CPH (about 58%) (50, 53, 56, 60-65).

2.212) Outcome of Chronic Persistent Hepatitis

A number of studies in the literature report serial liver biopsies in-patients with HBsAg positive chronic persistent hepatitis (56,58,59,66-71). In most of these studies, only occasional cases progress to chronic active hepatitis or cirrhosis.

Weissberg et al [72] in their study estimated the 5 year survival in adults [mean age 35 ± 1 years] with chronic persistent hepatitis B to be 97%.

2.213) Outcome of Chronic Active Hepatitis

Available literature suggests that about 20% of individuals with chronic active hepatitis B progress to cirrhosis over a variable period of time (58,73-77). Weissberg et al (72) found that the estimated 5 years survival rates for patients with CAH alone was 86% [n-128] and for those with CAH and cirrhosis was 55% (n=130)

In a Korean study (79), 9% of the patients with chronic active hepatitis developed liver cirrhosis within 5 years. In a much larger study –n-684], Liaw et al [80] calculated the cumulative probability of developing cirrhosis in patients with chronic hepatitis [mean age at entry 32.2 ± 10 years; males 87.1%] at 5 years was 15% with the risk increasing with age of study subjects. However, the authors did to calculate the risk of developing cirrhosis separately in various categories of chronic hepatitis. The risk of developing cirrhosis is higher in-patients with HBeAg Positivity. The annual incidence of HCC in adults with chronic hepatitis has been reported to between 0.5% and 0.8% (80a, 80b).

In-patients with cirrhosis, the annual incidence of hepatocellular carcinoma ranges from 2% to 7% (79,81,82). Fattovich et al reported lower annual rates of 1.2% from Europe (82a). The estimated 5 year survival in-patients who have cirrhosis is reported to be about 50-80% (72,82b, 82c)' with the survival being more for compensated patients than for decompensated ones.

2.214) Overall Prognosis

On the basis of the available literature, the prognosis CPH in HBsAg carriers is excellent (56,58,59,66-71). However the number of subjects in all these studies is very small. The adult carriers with CAH have 9-20% risk of developing cirrhosis over a five year period (78-80). Two to seven percent of adult cirrhosis (associated with HBV infection) develops hepatocellular carcinoma every year (79,81,82). However, there is evidence to prove that the sequelae of chronic hepatitis B infection are less frequent and milder in females (48,52,72,89).

2.215) Studies in Children

Only a few studies have been reported in the pediatric age group regarding natural history. Lok and Lai (83) followed 51 asymptomatic carrier children (median age 10 years) for upto 4 years (median 2.5 years) clinically, biochemically and serologically. The authors concluded from the study that chronic HBV infection in asymptomatic Chinese children was associated with a mild and stable liver disease despite high levels of HBV replication; however, the histology was not studied.

2.3) Cost-Efficacy of Vaccination Strategies and Prioritization of Resource-Utilisation

Cost-efficacy of different immunization strategies have to be worked out for two parameters i) Expenses per life year saved due to immunization. ii) Expenses in reducing per unit of infectious pool.

The different immunization strategies could be

a. Test all pregnant women for HBsAg Positivity and give passive plus active immunization during first 24 hours after birth to babies of all these HBsAg positive mothers
b. Immunization of all new born
c. Immunization of all children and of all high-risk adults.

It is true that the U.S. abandoned selective, high-risk strategy of HB vaccination and instead, adopted universal immunization or adolescents and adults. The supporters of Universal Immunization in India quote this example and on that basis, outright reject a selective immunization strategy in India, without considering the vast different between the predominant mode of transmission and age-distribution of acquisition of Hep-B infection in India.

In United States "... the strategy of vaccinating persons in high risk group has not been effective ... fewer than 10 percent of all targeted persons in high-risk group have actually been vaccinated", (Harrison 1691, 14th edition)". In developed parts of world most infections occur among adults, sexual transmission in the source of the majority of HBV infection". (Maxy page 135). Perinatal transmission is uncommon in North America and Western Europe but occurs with great frequency and is the most important mode of HBV perpetuation in the Far East and developing countries (Harrison, P. 1685). In view of these differences, we should seriously consider that option of selective

immunization of newborns of HBsAg positive mothers or of all pregnant women. Logistically his is feasible, because unlike the high-risk groups in the U.S., this vulnerable group in India (newborns / infants) is anyway visited by the health-services for immunization work.

The strategy of TB-control Programme in India has been devised with detailed consideration of various aspects of control measures. The strategy of sputum examination of symptomatics rather than x-ray examination; of focussing on the sputum positives than the x-ray positives, though debatable, has been devised after a lot of detailed consideration. A strategy to immunize all children with HB-vaccine would involve, as indicated below, hundreds of crors of rupees annually. Hence as in the case of TB-control Programme, a detailed examination of various options is required before we embrace the prescription given by the WHO.

Lastly in allocating financial resources for vaccination Programme, the total expenses, the cost-efficacy and the contribution to the prevention of diseases in India has to be placed in the context of overall scenario of health programmes in India. For example, the cost vaccines of all the other 6 vaccine preventable diseases in the Expanded Programme of Immunization were Rs. 17 per child in 1992. (11). May be this has increased to Rs. 30/-. Compare this with the cost of Hep-B vaccine of say Rs. 100/- per child (if the cost is drastically reduced form the current cost of Rs. 210/-). At the rate Rs. 100/- per child, vaccine-cost alone of vaccinating only the newborns, would be Rs. 2500 million per year. Moreover, there are 110.4 and 196 million children in India in the 0 to 4 and 5 to 14 age group respectively. (12). The mere vaccine cost of

immunizing these children would be Rs. 11.040 million and Rs. 19,600 million respectively. Spread over say 3 years, the annual cost of immunizing children in these age groups would be o Rs. 3700 million and Rs. 6530 million respectively. Thus the total annual cost of the vaccine for this Programme in the first three years would, respectively, be Rs 6200 million to Rs, 12730 million, if 0-4 and 0-14 year age group is selected for immunization. Compare this with the current year's budget for malaria-control and TB control of Rs. 2240 and 1050 million respectively (13)

We have to also decide, at what level of cost-effectiveness, a vaccination programme should be introduced as part of the national health programme. Can we afford to introduce a vaccination strategy with a cost-efficacy of say Rs. 15,000 per of life-year saved, when our per-capita annual income is around Rs. 10,000/-? The drug industry would push such vaccination strategies and many experts wold oblige them. But shouldn't we form independent opinion?

The discussion about cost-efficacy is important, because newer, safe and effective vaccines are being gradually introduced into the Indian market. Eventually, there will be pressure to include these also into the National Health Programmes (NHPs). Hence a general approach, framework has to be worked out for including newer vaccines in the NHPs.

Lastly, are we going to relay only on vaccines for prevention of communicable diseases? What about public sanitation, sterilization of needless / syringes, safer sex and healthy socio-economic development?

We are unaware of any exercise by IAP which takes into consideration the issue outlined above, while strongly recommending Hep-B universal immunization in India. What is needed is to lobby for a much higher allocation for health-programmes, and suggest newer programmes as part of this effort. A focus on only a new programme may mean divergence by the government, of resources from say TB-control programme to the new programme.

Let there be more in-depth discussion on the various issues raised above.

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