Review of: "Sero-prevalence of Viral Hepatitis B and C infection and associated factors among Pregnant Women in Southeast Ethiopia: Community-based crossectional study"

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Potential competing interests: No potential competing interests to declare.

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The Reviewer rated it 4/5

Dr. Ingmar Wolffram

Declarations

Potential competing interests:

No potential competing interests to declare

Proposals and suggestions to consider

In my view this is a well-conducted study on an issue of world-wide importance and also a step towards the WHO- goal of eliminating HCV and HBV.

1.

Since there had been no systematic testing in Ethiopia (“no nation-wide survey”), it can be assumed, that most of the detected Hepatitis B and C (HBV- and HCV-) patients were previously undiagnosed.

So the study also shows the effectiveness of testing for HBV and HCV in this region of the country especially in pregnancy (not only the prevalence and an “intermediate endemicity”) and can encourage further comprehensive screening measures.

2.

Concerning the severity of the problem (“HBV and HCV … can lead to health problems some of which can be fatal”):

Consider to include (and correct) some Data which show the world-wide significance of the problem and the necessity of a comprehensive screening to reach the goal of eliminating HBV and HCV and to prevent serious complications.

(A comprehensive screening for hepatitis B and C as an effective means of cancer prevention and as a prerequisite for elimination of chronic viral hepatitis- Data and comment

on a discussion. DMW – Deutsche Medizinische Wochenschrift 2023 175-182 .10.1055/a-1972-4118.Ingmar Wolffram Georg Thieme Verlag)

a)

“According to estimates of the WHO there are 354 million people with chronic HBV infection and 58(3%) million people with chronic HCV infection.” Please correct: 58 Million are less than 3% of the global population.

b)

About 4.000 people world-wide die from HCV and HBV every day, with an upward trend (exceeding the number of deaths from Malaria, HIV or Tuberculosis!)

(Thomas DL. Global Elimination of Chronic Hepatitis. N Engl J Med 2019;

380: 2041–2050. doi:10.1056/NEJMra1810477)

c)

Most of the affected people are undiagnosed, since there are only unspecific symptoms for years or even decades. When diagnosed many of them have already life-threatening complications like cirrhosis or cancer of the liver and extrahepatic manifestations .

(Cacoub P, Gragnani L, Comarmond C et al. Extrahepatic manifestations of chronic HCV infection. Review Article. Digestiv and Liver Disease 2014; 46: 165–173)

Globally the rate of hepatitis B diagnosis is averaging 8% and of hepatitis C 18% (Thomas et. al)

d)

There are valid tests and effective therapies which can prevent the severe consequences of chronic viral hepatitis B and C. With anti-viral medicaments it is possible to reach a healing of chronic viral hepatitis C in nearly every case.

Early treatment without or with only mild fibrosis is necessary to reach a normal life-expectancy. (Kumada T, Toyoda H, Yasuda S et al. Long-term-outcome of viral eradication in patients with hepatitis C virus infection and mild hepatic fibrosis. Journal of Viral Hepatitis 2021; 28: 1293–1303;

Backus LI, Belpiero PS, Shahoumian TA et al. Direct-acting antiviral sustained virologic response: Impact on mortality in patients without advanced liver disease. Hepatology 2018; 68 (3): 827–838)

In case of HBV transmission and severe consequences like liver cancer can be prevented by early detection and usually life-long treatment .

e)

Therefore comprehensive screening is the prerequisite for the elimination of chronic viral hepatitis.

Although early detection of HBV and HCV like in the present study is essential, for ethical reasons there has to be access to therapy when testing persons for a serious disease.

f)

In 2016, 194 countries signed a declaration of the WHO to eliminate HBV and HCV as a threat to public health by 2030. 90% of the affected patients should be diagnosed at that time.

g)

Additionally for HBV an effective vaccination is available. The WHO also declared the aim of 90% HBV immunization coverage including HBV birth dose vaccine coverage.

However, this affords more efforts especially in regions like in Africa, where the current coverage of HBV birth dose vaccine is estimated at 11% or even lower. (Nayagam, S., Shimakawa, Y. & Lemoine, M. Mother-to-child transmission of hepatitis B: what more needs to be done to eliminate it around the world? J. Viral Hepat. 27, 342-349 2020) Note: All newborns should be vaccinated , irrespective of the serological status of their mothers!

3.

What kind of testing strategies are necessary?

Testing-strategies based on medical providers only asking patients about their risk behaviours have largely failed to identify the majority of the HCV- and HBV- infections.

(Centers for Disease Control and Prevention (CDC) - Locations and reasons for initial testing for Hepatitis C infection – chronic hepatitis cohort study united states, 2006-2010 M MWR Morb Mortal Wkly Rep 2013; 62: 645-8)

It should be emphasized that the" significant morbidity and mortality" of HBV and HBV is preventable by comprehensive screening, treatment and vaccination-not only by "universal precaution".

The study should be seen in the context of the "Change of Paradigma" towards universal screening and treatment for HCV and HBV and vaccination for HBV to reach the goal of elimination:

a)

Consider the great success of middle income countries like Georgia and Egypt and the Egyptian example showing that elimination of chronic viral Hepatitis C is feasible with universal screening and treatment: In 2019 in Egypt 59 Million people were screened for HCV!

(Waked I.et al. Screening and treatment program to eliminate hepatitis C in Egypt. N. Engl. J. Med. 384, 1166-1174 2020)

b)

Consider to mention the new CDC recommendations) for “universal” one-time screening combined with risk-based testing (HBV and HCV) and” universal” vaccination. (CDC Recommendation for Hepatitis C screening Among Adults – United States 2020. Recommendations and Reports 2020; 69 (2): 1–17. doi:10.15585/mmwr.rr6902a1;

Schillie S. et. al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisary Committee on Immunization Practices.M. MWR Recomm Rep 2018; 67 (NO, RR-1): 1-31)

4.

Note: Hepatitis A (HAV) causes acute but not a chronic Infection. So HAV is not relevant in the context of eliminating chronic viral hepatitis.

5.

Concerning “altering severity of HBV”, it should be mentioned, that the severity of the individual disease is depending mainly on the amount of HBV-DNA in the serum, which should be determined. For example , it was shown, that with a high viral load approx. 20% of patients develop a primary liver carcinoma within 13 years.

(Bruix J, Sherman M: Management of hepatocellular carcinoma: an Update. Hepatology 2011;53: 1020-1022.)

Transmission of HBV and severe concequences can be prevented by early anti-viral therapy.

Note: Globally the number of deaths from HBV and HCV and so the “severity” of these infections is increasing (Thomas et al)

Moreover there are valid tests for hepatitis D (HDV) too, which is a severe co-infection of HBV. HDV can only occur together with HBV. If every HBsAg- positive patient would be tested for HDV, it is possible to detect all HDV-positive patients too, so that transmission can be prevented(i.e. by precaution). However the feasibility of new HDV therapies has to be discussed. HDV-testing can be considered also in a next larger study).

6.

Please explain the background and reasons for “fragmented and non-existent response to hepatitis” (stigmatization? lacking financial support or funding?)

Note: Cost-effectiveness of an universal anti-HCV screening was proved by Eckman et al in 2018, if the prevalence is higher than 0,07%. This threshold was 0,3% in case of general HBV- screening.

(Eckman MH, Ward JW, Sherman KE. Cost Effectiveness of Universal Screening for Hepatitis C Virus Infection in the Era

of Direct-Acting, Pangenotypic Treatment Regimens. Clinl Gastroenterol and Hepatol 2019; 17: 930–939. doi:10.1016/j.cgh.2018.08.080; Eckman M, Kaiser TE, Sherman KE. The cost-effectiveness of Screening for chronic hepatitis B Infection in the United States. Clin Infect Dis 2011; 52 (11): 1294–1306. doi:10.1093/cid/cir199)

If the prices for diagnostic and therapy will be reduced, cost-effectiveness of universal screening is achievable also in case of even lower prevalence.

A reduction of the prices for the antiviral therapies can be reached by negotiations(like in Egypt) and is expected at the latest in 2026/2027, when the patents of important combinations of medicaments(Sofosbuvir/Velpatasvir and Glecaprevir/Pibrentasvir) expires. In case of HBV antiviral agents are available as generics since many years.

Thus it is possible after initial investment to save lives and money later. Initial support by governments and funding seems to be essential to reach the WHO goals.

7.

It might be emphasized, that the maternal complications and birth outcomes show the urgency of the problem of HCV and HBV in pregnancy as a priority in healthcare already.

In this context it would be helpful to explain the meaning of “fetal wastage” and to show the references concerning “19,2% maternal mortality” and ”42,6% fetal problems”

8.

Please explain the exact procedure in this community-level study:

Are all pregnant women in Ethiopia and especially in the selected communities usually registered? Were all registered pregnant women in the three communities invited to participate? Did you exclude only those who refused to provide the informed consent? How many refused? What is the participation rate?

9.

The relative small sample size is clearly a limitation of this study. A larger sample size seems to be necessary to reach more evidence concerning the associated risk factors especially for HCV. Consider also that especially risky behaviors could be underreported because of fear of stigmatization.

These are probably the main reasons for “variations of sero- prevalence” and for “expected risk factors not identified”.

10.

Importantly, anti-HCV has not been described to indicate active HCV-Infection!

To determine HCV-RNA (if anti-HCV is positive) is necessary to diagnose acute or chronic HCV-infections and for anti-viral treatment.

11.

Please explain: what is the best on-stage HCV test strip?

How was the sensitivity and the specificity of the tests applied?

12.

Are there informations about follow up concerning therapy of the mother and vaccination and immunization of the newborns? Will there be a further evaluation?

13.

Concerning risk factors, especially hospital admission seems to be a major problem:

Have there been further steps also concerning blood transfusion and dental extraction (like safety precaution in these settings)?

14.

In order not to underestimate an “intermediate endemicity” it should be considered, that even in countries with much lower prevalence HCV- and HBV-infections are regarded as a threat to public health, because of the severe consequences of an untreated chronic infection.

15.

Some of the “endless benefits” of this study and of comprehensive screening of all pregnant women could be mentioned:

a. to prevent transmission of HBV and HCV, especially mother to child transmission and
b. to prevent serious complications like cancer cirrhoses of the liver and extrahepatic manifestations for mother and child in the future , if there is access to therapy.
c. to reduce health disparities by eliminating the need for disclosure of potentially stigmatizing risk factors, when all pregnant women are included.
d. The study also shows the feasibility and effectivity of screening measures which should be extended to the whole population to achieve the aim of elimination and to prevent as many fatalities as possible.

Testing all pregnant women is urgent and cannot wait. It is also an important step towards the larger goal of eliminating chronic viral hepatitis B and C in the entire population. Additionally precaution measures are important to eliminate associated risk factors which can be evaluated and confirmed in larger studies.

Further questions and considerations:

16. Please, explain: What do you mean by “viral hepatitis interrupted infection”?

17. Please show the Data, if there is an increase of prevalence of HBsAg in Ethiopia?

18. Consider also a triple-panel-test for HBV (i.e. in a following larger study) as recommended by the CDC in the new Recommendations in March 2023. (HBsAg, total HBcAg and anti-HBc)

19. How was” liver disease of household members” diagnosed? (elevated ALT values?, Known HBV or HCV infections?)

20. Consider: mother-to-child transmission can only be prevented safely by screening all pregnant women before the 28th week of pregnancy, because it is necessary for them to receive antiviral therapy in time if the viral load is high.(In these cases injections of hepatitis B vaccine and immunoglobulin for the newborn are not sufficient)