Published in final edited form as:

Infect Dis Clin Pract (Baltim Md). 2018 July ; 26(4): 240–241. doi:10.1097/IPC.0000000000000659.

Comments on “Screening US Vietnam Veterans for Liver Fluke Exposure 5 Decades After the End of the War”

Theodore E Nash, MD¹, David Sullivan, MD², Edward Mitre, MD³, Eric Garges, MD, MPH MTMandH (LTC, MC)⁴, Victoria J. Davey, PhD, MPH⁵, Gary Roselle, MD⁶, Stephen J. Davies, BVSc, Ph.D⁷, and Peter D. Rumm, MD, MPH⁸

¹Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland ²Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD ³Department of Microbiology and Immunology, Uniformed Services University of the Health Sciences (USUHS), Bethesda, MD ⁴Division of Tropical Public Health, Department of Preventive Medicine, USUHS, Bethesda, MD ⁵Office of Research and Development, Department of Veteran Affairs (VA), Washington, DC ⁶National Infectious Diseases Service, VA, Cincinnati, OH ⁷Department of Microbiology and Immunology, Uniformed Services University of the Health Sciences (USUHS), Bethesda, MD ⁸Post Deployment Health Services, VA, Washington, DC

We have read with great interest the article by Psevdos et al.¹ on screening U.S. Veterans of the Vietnam War for exposure to liver flukes, an endemic public health issue in Southeast Asia. We commend the authors for undertaking this investigation of an important knowledge gap concerning the risk of these types of infections in both veterans and, potentially, in active duty military serving in endemic areas. However, the authors concluded that their study “provides evidence of exposure to the liver fluke parasites in U.S. soldiers during their service in the Vietnam War”. This conclusion may potentially overstate the strength of their findings.

Foremost, the method description in the present paper contains no details beyond that a “multihelminth antigen assay” (not FDA approved) includes a crude whole worm *Clonorchis* antigen preparation was used to detect antibodies to *Opisthorchis* (the likely parasite that these Veterans were exposed to in Vietnam). In the cited multihelminthic study² there were no stated positive or negative controls and present, past and cross reactive antibodies could not be determined. In this and another study³ the authors rely on the potential cross reactivity with *Clonorchis* to detect the presence of *Opisthorchis* antibodies, but the extent to which this actually occurs with this particular test is not described. Also, as noted by Psevdos et al, there may be significant cross reactivity between other helminths with this assay. We believe that use of appropriate positive and negative controls would have better clarified the meaning of detected antibodies. Without these controls, it is difficult to

Corresponding author is Dr. Peter Rumm at peter.rumm@va.gov or 810 Vermont Avenue, Department of Veteran Affairs, (10P4Q) Post-Deployment Health Service, Washington, DC 20420.

The authors have no conflicts of interest to disclose.

conclude whether the positive results are more likely to represent true prior infections or false positives.

While it is very possible that some Veterans were exposed to hepatobiliary flukes in the Vietnam War Theater, determining whether such exposures resulted in long term health consequences or are adversely affecting the health of Vietnam veterans today will be challenging. Hepatobiliary flukes have been documented to live for 20-30 years.⁴ Since it has been five decades since the Vietnam War veterans are unlikely to still harbor active infections, and indeed none were found in the study by Psevdos et al. Furthermore, the risk of complications, such as cholangiocarcinoma, is likely related to the intensity of the fluke infection, which in infected veterans may have been low compared to endemic populations who may regularly consume undercooked or raw fish.⁵ Even in infected immigrant populations diagnosed in the U.S., cholangiocarcinoma is rare.⁶

The authors' state: "Based on our pilot findings, we recommend an epidemiological study using a larger patient sample for serological testing using a specific *O. viverrini* antigen". We fully agree with the need for more studies to determine whether these flukes pose a threat to current or past military personnel. There are several types of epidemiological studies that could be done in the near future in Vietnam Veterans; such as studying incidence of or mortality from cholangiocarcinoma (recognizing there are other risk factors), or conducting a case control study, as this is a very rare cancer with an incidence rate of about 2/100,000.⁷ Possible future development of more sensitive and specific assays for these infections, including nucleic acid-based tests on stool samples and/or serological studies specific for each species of fluke (potentially with recombinant antigens) might also enhance our ability to measure the past and current risk of these parasites to veterans and active military personnel. However, these are not currently in existence and would have to be developed and rigorously tested for clinical validity before any potential usage in any large scale research.

Finally, the findings from this pilot study by Psevdos et al., while important in acknowledging a health concern of Vietnam Veterans, are not sufficient to change clinical practice at this time. Instead, we encourage clinicians to educate concerned patients as to their low risk of cholangiocarcinoma and also discuss other more common causes of liver cancer including the viruses, hepatitis B or C. We encourage interested clinicians and Veterans to access the following VA website at: <https://www.publichealth.va.gov/exposures/infectious-diseases/cholangiocarcinoma.asp> that is linked to a number of recently updated Centers for Disease Control and Prevention (CDC) websites on these topics that are reachable through: https://www.cdc.gov/parasites/liver_flukes/. As far as clinical management, the CDC states: "*Serologic testing for Opisthorchis is not useful for patient management and is not available in the United States*" https://www.cdc.gov/parasites/opisthorchis/health_professionals/index.html. At present, we agree with that assessment, and thank you for letting us comment on this research paper and the importance of this topic in general.

Acknowledgments

(Dr. Nash is supported by intramural NIAID) The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs, the National Institutes of Health/Department of Health and Human Services, or the Department of Defense.

References

1. Psevdos G, Ford FM, Hong ST. Screening US Vietnam veterans for liver fluke exposure 5 decades after the end of the war. *Inf Dis in Clin Pract*.
2. WarJin Y, Kim EM, Choi MH, et al. Significance of serology by multi-antigen ELISA for tissue helminthiasis in Korea. *J Korean Med Sci*. 2017; 32:1118–1123. [PubMed: 28581268]
3. Choi MH, Ryu JS, Lee M, Li S, Chung BS, Chai JY, Sithithaworn P, Tesana S, Hong ST. Specific and common antigens of *Clonorchis sinensis* and *Opisthorchis viverrini* (Opisthorchiidae, Trematoda). *Korean J Parasitol*. 2003 Sep; 41(3):155–63. [PubMed: 12972729]
4. Lim JH. Liver Flukes: the malady neglected. *Korean J Radiol*. 2011 May-Jun;12(3):269–279. [PubMed: 21603286]
5. Haswell-Elkins MR, Mairiang E, Mairiang P, Chaiyakum J, Chamadol N, Loapaiboon V, Sithithaworn P, Elkins DB. Specific and common antigens of *Clonorchis sinensis* and *Opisthorchis viverrini* (Opisthorchiidae, Trematoda). *Int J Cancer*. 1994 Nov 15; 59(4):505–9. [PubMed: 7960220]
6. Stauffer WM, Sellman JS, Walker PF. Biliary liver flukes (Opisthorchiasis and Clonorchiasis) in immigrants in the United States: often subtle and diagnosed years after arrival. *J Travel Med*. 2004 May-Jun;11(3):157–9. [PubMed: 15710057]
7. Saha SK, Zhu AX, Fuchs CS, Brooks GA. Forty-Year Trends in Cholangiocarcinoma Incidence in the U.S.: Intrahepatic Disease on the Rise. *Oncologist*. 2016 May; 21(5):594–9. [PubMed: 27000463]