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Costs and Consequences: Hepatitis C Seroprevalence in the Military and Its Impact on Potential Screening Strategies

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Knowledge of the contemporary epidemiology of hepatitis C viral (HCV) infection among military personnel can inform potential Department of Defense screening policy. HCV infection status at the time of accession and following deployment was determined by evaluating reposed serum from 10,000 service members recently deployed to combat operations in Iraq and Afghanistan in the period 2007-2010. A cost model was developed from the perspective of the Department of Defense for a military applicant screening program. Return on investment was based on comparison between screening program costs and potential treatment costs avoided. The prevalence of HCV antibody-positive and chronic HCV infection at accession among younger recently deployed military personnel born after 1965 was 0.98/1000 (95% confidence interval 0.45-1.85) and 0.43/1000 (95% confidence interval 0.12-1.11), respectively. Among these, service-related incidence was low; 64% of infections were present at the time of accession. With no screening, the cost to the Department of Defense of treating the estimated 93 cases of chronic HCV cases from a single year's accession cohort was $9.3 million. Screening with the HCV antibody test followed by the nucleic acid test for confirmation yielded a net annual savings and a $3.1 million dollar advantage over not screening. *Conclusions:* Applicant screening will reduce chronic HCV infection in the force, result in a small system costs savings, and decrease the threat of transfusion-transmitted HCV infection in the battlefield blood supply and may lead to earlier diagnosis and linkage to care; initiation of an applicant screening program will require ongoing evaluation that considers changes in the treatment cost and practice landscape, screening options, and the epidemiology of HCV in the applicant/accession and overall force populations. (HEPATOLOGY 2016;63:398-407)

Emergent whole blood transfusion has been an important feature of combat casualty resuscitative care in conflicts in Iraq and Afghanistan.[1] More than 10,000 units of whole blood were used in exigent circumstances with modified precautions not meeting Food and Drug Administration (FDA) guidelines. The rate of viral transmitted disease among recipients of these non-FDA-approved blood products was assessed in a retrospective study.[2] It identified a single case of transfusion-transmitted hepatitis C among 475 transfusion recipients

Abbreviations: DoD, Department of Defense; EIA, enzyme immunoassay; FDA, Food and Drug Administration; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NAT, nucleic acid testing; RIBA, recombinant immunoblot assay.

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tested for blood-borne viral pathogens. In a separate study, three of 2831 donated whole blood units were hepatitis C virus (HCV)-infected.[3] In a later study of transfusion recipients in this combat theater, seven individuals had deployed while already infected with HCV.[4]

More broadly, prevalence of hepatitis C infection in military service members was last determined systematically in a serologic study of specimens from the 1990s, yielding evidence of HCV infection in approximately five per 1000 active duty service members.[5] In the intervening years, awareness of viral hepatitis and its sequelae has increased. The Centers for Disease Control published a recent guideline expanding hepatitis C testing to include anyone born from 1945 to 1965 regardless of other risk status.[6] Meanwhile, the US Preventive Services Task Force assessed hepatitis C screening and found that risk factor-based screening misses patients and that further research was needed.[7]

We undertook a contemporary assessment of hepatitis C in recently deployed military forces in order to inform potential strategies to screen military personnel with the aims of decreasing the burden of HCV in military personnel, decreasing the threat posed by HCV-infected personnel deployed to combat operations who may enter the emergent non-FDA blood supply, and improving health outcomes for individuals through earlier diagnosis and linkage to care.

Materials and Methods

This was an Armed Services Blood Program Office-endorsed, Joint Staff Surgeon-tasked investigation of the seroepidemiology of viral hepatitis (hepatitis B [HBV] and HCV) in the deployed force. HBV and its issues are being addressed separately. The tasking was service-concurred and directed at the US Army Public Center (Provisional) (formerly US Army Public Health Command) with technical support from the Military HIV Research Program and service counterparts, the Navy Bloodborne Infection Management Center, and the US Air Force HIV Medical Evaluation Unit at San Antonio Military Medical Center. The Walter Reed Army Institute of Research Institutional Review Board reviewed the investigation protocol and affirmed it as a public health activity (no. 1822).

Seroepidemiology. A random sample of 10,000 Army, Navy, Air Force, and Marine Corps service members (active and reserve components, National Guard) who ended their most recent deployment to combat operations in Iraq and Afghanistan in the period from October 2007 through October 2010 was identified. Additional inclusion criteria included (1) presence of at least one reposed sample collected after accession in the Department of Defense (DoD) Serum Repository,[8] Armed Forces Health Surveillance Center (Silver Spring MD). The most recently collected sample was preferentially selected and, (2) at least one "accession sample" reposed in the DoD Serum Repository obtained prior to entering military service from screening through a Military Entrance Processing Station or obtained within 180 days of initially entering military service of sufficient volume.

This sample size was selected to maximize the precision of the HCV seroprevalence estimate for the full random sample. Assuming that the observed overall prevalence would be equal to or less than that observed in the study by Hyams et al., the upper limit of the 95% confidence interval for the point estimate of the overall prevalence would not likely exceed 1%, which was deemed to be sufficiently precise to inform DoD policy.[5]

For each included service member reposed serum from the DoD Serum Repository and relevant archived deidentified personnel, deployment, and health data from the Defense Medical Surveillance System[8] were obtained.

Case Definitions. The following definitions of HCV infection were employed for entry into the cost model. (1) *HCV antibody-positive:* HCV antibody screen

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enzyme immunoassay (EIA)-positive and confirmed by supplemental confirmatory antibody test. These patients may have past or current HCV infection. (2) *Chronic HCV infection:* HCV antibody screen (EIA)-positive and confirmed by positive HCV nucleic acid testing (NAT).

Laboratory Measures. Assessment of HCV infection status was initiated with evaluation of the most recently collected reposed serum. These samples were tested by EIA, followed by recombinant immunoblot assay (RIBA) confirmation. When confirmed positive, an accession reposed sample was tested under the same algorithm. Due to discontinuation of RIBA by the manufacturer during the course of this investigation, all accession samples that were EIA-positive were confirmed by INNO-LIA HCV Score (Fujirebio US, Inc.). HCV infection status was determined using the following laboratory HCV diagnostic algorithm: initial screen was with the Ortho HCV, version 3.0, enzyme-linked immunosorbent assay (Ortho-Clinical Diagnostics, Inc.); reactive samples were repeated in duplicate. Repeat reactive samples were reflexed to supplemental confirmatory testing using the CHIRON RIBA HCV 3.0 SIA (Novartis Diagnostics) or the INNO-LIA HCV Score. Samples that were HCV EIA repeat reactive and RIBA-positive or INNO-LIA-positive were considered positive for HCV infection and reflexed to HCV NAT to distinguish chronic infection from resolved infection. Samples that were HCV EIA repeat reactive and RIBA-negative or INNO-LIA-negative or indeterminate were reflexed to HCV NAT to resolve indeterminate and suspected window period specimens.

Statistical Methods. Prevalence rates were assessed for significance by constructing 95% confidence intervals. Data for service members born after 1965 were analyzed separately from those for members born before 1966. Characteristics among service members across the services and components were compared using the chi-squared test at an alpha of 0.05. Data sets were managed and analyzed with Statistical Analysis Software, version 9.2 (SAS Institute, Cary, NC).

Cost Modeling. We developed a decision tree reflecting three possibilities: (1) no screening of applicants for military service, (2) screening using an EIA test only, and (3) screening using an EIA test with an NAT follow-up. The following assumptions impacted the construction of the cost model.

- With no applicant screening, accessions with chronic HCV infection will enter military service each year and their treatment will generate health care costs to the military health care system.
- With either of the testing strategies, the number of accessions with chronic HCV infection who enter military service will be smaller than the number with no testing.
- Some HCV-uninfected applicants will be misclassified as HCV-infected and not be allowed to enter military service as the screening test(s) is not 100% specific.
- Some applicants with chronic HCV infection will be allowed to enter military service with either testing strategy because the screening test(s) is not 100% sensitive.
- In the setting of NAT following EIA, in contrast to EIA testing alone, an increase in specificity with slight loss in sensitivity due to testing performed in series will result in more HCV-uninfected applicants entering military service and slightly more applicants with chronic HCV infection entering military service.

Specific assumptions and inputs to the cost model were derived employing the results from the seroprevalence data in this study as well as various costs and relevant statistics drawn from within the DoD and the peer-reviewed scientific literature (Table 1).[9] We assumed that the test performance of both EIA and NAT is uniform across the candidate population of potential accessions, including in the case of NAT for the subpopulation that already has screened positive by EIA. And we assumed that the prevalence among all applicants, including those who apply but do not enter military service, would be the same as the prevalence observed among our study population of recently deployed service members who, by definition, were applicants who successfully entered military service. The model addressed HCV infection as a risk among otherwise qualified accessions, so other exclusion criteria were not included.

We assumed that all applicants undergo screening with HCV EIA prior to accession; all applicants with a positive screening test receive the NAT. Based on review of historical data and incorporating usual attrition, the applicant pool size was assumed to be the sum of 232,000 accessions and 95,000 nonaccessions.[10]

We also assumed that all accessions who have chronic HCV infection at accession would be identified during their period of military service and treated while serving in the armed forces. We assumed all would be genotype 1 and treated with a sofosbuvir-based regimen or equivalent according to current guidelines[11] and that treatment cost would be $100,000.00.

Last, we assumed that all otherwise fully qualified individuals who are identified with chronic HCV by an applicant screening program and not permitted to

Table 1. Model Inputs

Parameter	Base Case Estimate (95% Confidence Interval); Alternate Values Considered	Source, Reference
Prevalence of HCV antibodies detected by repeatedly reactive EIA (HCV antibody repeat reactive)	0.16% (0.80-2.40)	Observed*
Prevalence of HCV detected by HCV seropositivity confirmed by supplemental confirmatory antibody test†	0.08% (0.02, 1.30)	Observed
Prevalence of chronic HCV infection detected by HCV NAT	0.04% (0.00-0.90); 0.06% and 0.068%	Observed Derived**
HCV screening antibody (EIA) sensitivity	98.1% (92.6-99.7)	Abdel-Hamid, 2002[9]
HCV screening antibody (EIA) specificity	99.8% (99.2-99.9)	Abdel-Hamid, 2002[9]
HCV NAT sensitivity	99.6% (98.9-99.9)	APTIMA/TMA HCV kit insert
HCV NAT specificity	99.6% (n/a)	APTIMA/TMA HCV kit insert
HCV EIA test cost/test	$10.84	S.A. Peel, unpublished data
HCV NAT test cost/test	$70.00	S.A. Peel, unpublished data
Annual number of applicants who apply and accession into military service	232,000	Accession Medical Standards Analysis & Research Activity[10]
Annual number of applicants who apply but do not accession	95,000	Accession Medical Standards Analysis & Research Activity[10]
Cost to treat one case of chronic HCV infection	$100,000.00; $83,319.00	Chhatwal et al.,[19] Najafzadeh et al.,[21] Rein et al.,[13]
Recruitment cost per accession	$22,898.00	J. Thomas, unpublished data

*Observed: observed among 9997 recently deployed US military personnel.
**Derived from 0.75-0.85 of observed confirmed HCV seropositivity.
†HCV EIA repeat reactive samples confirmed with INNO-LIA.

accede would have to be replaced with another fully qualified individual and that this would incur a burden in rerecruitment costs of nearly $23,000 per individual with chronic HCV infection barred from accession (J. Thomas, unpublished data).

The net cost of screening was determined by the cost of screening, the savings from avoiding treatment of those who are HCV-infected who are prevented from entering military service, and the costs of rerecruiting applicants with positive HCV screening test results who are not allowed to enter.

We also conducted a threshold sensitivity analysis to calculate the minimum proportion of cases that are prevalent at accession that must be treated while in the armed forces for the cost of medical care averted to offset the cost of screening. This proportion was compared to historical rates and counts of diagnoses of chronic HCV among active-duty service members.[12]

Other sensitivity analyses performed included lowering the model input for cost of treatment to the lowest published rate, $83,319.00, for current standard of care therapeutic regimens[13] and considering plausible rates of chronic HCV infection that could be present among future applicants that are higher than observed.

Results

Burden of HCV. Of the 10,000 randomly selected service members, 9997 met the inclusion criteria and had complete HCV test results generated from evaluation of reposed serum; two service members had insufficient reposed sera, and one was in the Coast Guard. Most were less than 25 years old (83%), white (74%), and male (89%) and were in the active component (74%) and in the Army (56%).

This sample was representative of the deployed force and the applicant population. Age distribution reflects that these deployed service members are slightly younger than the overall force. After excluding those recently deployed service members born before 1966, the demographics of the younger cohort (those born after 1965) are similar to those of the overall population of service members and to the applicant population.[14] This sample is also representative of the applicant population. Most current applicants for military service are 18-25 years old (92%), male (82%), and white (75%),[10] which is consistent with the demographics of this study sample.

Of these service members, 9224 were born after 1965 and 773 before 1966. These birth cohorts were separated in subsequent analyses regarding HCV prevalences and their risk associations. Those results are shown in Table 2.

There were a total of 23 chronic HCV cases present among service members tested at the most recent time point. Among those, 18 (78%) already were infected at accession. All incident, service-related HCV infections occurred among younger service members.

Among the older birth cohort, there were nine chronic HCV cases present at the most recent sample collection time point. Most cases were male, all were

Table 2. Prevalence of HCV Antibody Positivity at Accession and Postdeployment Time Points Among Recently Deployed US Military Personnel (n = 9997*)

	Birth Before 1966				Birth After 1965						
		Accession/Postdeployment				Accession			Postdeployment		
	No. Tested	HCV +	Prevalence/ 1000	(95% Confidence Interval)	No. Tested	HCV+	Prevalence/ 1000	(95% Confidence Interval)	HCV+	Prevalence/ 1000	(95% Confidence Interval)
All	773	9	11.64	(5.34-21.99)	9224	9	0.98	(0.45-1.85)	14	1.52	(0.83-2.55)
Sex											
Male	692	7	10.12	(4.08-20.73)	8196	7	0.85	(0.34-1.76)	13	1.59	(0.84-2.71)
Female	81	2	24.69	(3.00-86.36)	1028	2	1.95	(0.24-7.01)	1	0.97	(0.02-5.41)
Race											
White	583	5	8.58	(2.79-19.90)	6782	8	1.18	(0.51-2.32)	12	1.77	(0.91-3.09)
Black	128	3	23.44	(4.86-66.97)	1398	0	0.00	(0.00-2.64)	1	0.72	(0.02-3.98)
Other/unknown	62	1	16.13	(0.41-86.62)	1044	1	0.96	(0.02-5.33)	1	0.96	(0.02-5.33)
Service											
Army	452	9	19.91	(9.14-37.46)	5112	6	1.17	(0.43-2.55)	10	1.96	(0.94-3.59)
Air Force	214	0	0.00	(0.00-17.09)	1636	0	0.00	(0.00-2.25)	1	0.61	(0.02-3.40)
Marine Corps	14	0	0.00	(0.00-231.64)	1085	1	0.92	(0.02-5.12)	1	0.92	(0.02-5.12)
Navy	93	0	0.00	(0.00-38.89)	1391	2	1.44	(0.17-5.18)	2	1.44	(0.17-5.18)
Component											
Active duty	337	0	0.00	(0.00-10.89)	7093	7	0.99	(0.40-2.03)	9	1.27	(0.58-2.41)
National Guard	264	5	18.94	(6.18-43.64)	1390	1	0.72	(0.02-4.00)	3	2.16	(0.45-6.29)
Reserve	172	4	23.26	(6.37-58.47)	741	1	1.35	(0.03-7.50)	2	2.70	(0.33-9.72)
Foreign-born											
Yes	30	1	33.33	(0.84-172.17)	737	1	1.36	(0.03-7.54)	1	1.36	(0.03-7.54)
No	222	5	22.52	(7.35-51.77)	7610	8	1.05	(0.45-2.07)	13	1.71	(0.91-2.92)
Unknown†	521	3	5.76	(1.19-16.73)	877	0	0.00	(0.00-4.20)	0	0.00	(0.00-4.20)
Health worker											
Yes	72	2	27.78	(3.38-96.77)	530	1	1.89	(0.05-10.47)	1	1.89	(0.05-10.47)
No	701	7	9.99	(4.02-20.47)	8694	8	0.92	(0.40-1.81)	13	1.50	(0.80-2.56)

*HCV antibody positive means HCV antibody repeat reactive + HCV antibody confirmation with supplemental confirmatory antibody test. Excluded: one Coast Guard service member and two individuals who were not tested for HCV postdeployment.

†Birth country unknown or missing.

present among Army soldiers in the National Guard or Reserve component, and prevalence rates were highest among those who were foreign-born or health workers. However, case counts were low and the confidence intervals wide. All nine (100%) infections were present at the time of accession.

Among the younger cohort, there were 14 chronic HCV cases present at the most recent sample collection time point. Prevalence rates were much lower and the risks associated with subgroups less clear. Most cases were male and were present among Army soldiers in the active component. Unlike the older birth cohort, prevalence rates were higher among US-born service members and were not significantly higher among health workers. Nine of 14 (64%) past or current infections were present at the time of accession, and nearly one-third (5/14) of the infections in the younger cohort were incident infections during service (Table 3). Service members who were HCV-infected at accession were significantly older (n = 9, median 29 years) than those who were not (median 24 years) ($P < 0.05$).

Costs. With no screening, the cost to the armed forces of treating the estimated 93 cases of chronic HCV cases from a single year's accession cohort of 232,000 was $9.3 million. The cost of screening all 327,000 applicants, regardless of whether or not they acceded, with HCV EIA alone is $3.5 million. Screening with HCV EIA alone would identify 91 of the 93 cases of chronic HCV infection among the applicant population who acceded, which would result in a treatment cost avoided of $9.1 million. Thus, the total cost of treatment is reduced from $9.3 million to $0.2 million by a screening program consisting of HCV EIA alone that costs $3.5 million. However, the additional recruiting costs required to replace these 91 applicants who do not accede offsets these savings by $2.1 million. Employing EIA alone, though, has another consequence: the exclusion of 554 individuals who do not have chronic HCV infection, 89 with past or resolved HCV infection, and an additional 464 HCV-uninfected applicants with false-positive HCV EIA screening test results. Replacement of these applicants results in an additional $12.7 million cost or a net cost over not screening of $7.2 million.

In contrast, the combination of EIA testing followed by NAT for EIA^+ samples adds only a small incremental cost of $0.045 million because the NAT-inclusive

Table 3. Prevalence Estimates of HCV Antibody Positivity and Chronic HCV Infection at Accession per 1000 Personnel Among Recently Deployed US Military Personnel Born After 1965

	Sample n	n	Prevalence/ 1000	95% Confidence Interval
HCV antibody screen-positive*	9224	14	1.52	(0.86-2.49)
HCV antibody-positive†	9224	9	0.98	(0.45-1.85)
Chronic HCV‡	9224	4	0.43	(0.12-1.11)

*HCV antibody screen-positive = HCV antibody repeat reactive.
†HCV antibody-positive = HCV antibody repeat reactive + HCV antibody confirmation with supplemental confirmatory antibody test.
‡Chronic HCV = HCV antibody repeat reactive + HCV nucleic acid test-positive.

screening strategy is only administered to the small number of applicants with EIA^+ screening test results. With the addition of NAT, two HCV-infected applicants who would have been excluded from accessioning under the EIA test-only scenario are allowed to enlist and their treatment costs contribute to the total cost to the armed forces. However, the addition of HCV NAT permits the accessioning of 552 of the 554 applicants who do not have chronic HCV infection and who would not have been permitted to accede based on positive HCV EIA screening test results alone. This results in saving most of the $12.6 million of replacement recruitment costs. Together, the testing strategy employing an EIA test followed by NAT for positive samples yielded a net savings and a $3.1 million advantage over not screening. This screening strategy results in the lowest overall cost to the armed forces, a net savings over not screening, and shifts a much higher cost associated with treating service members with chronic HCV infection to lower costs primarily associated with screening applicants for military service (Fig. 1).

A threshold sensitivity analysis was applied to the performance of the more cost-effective of the two screening strategies—EIA test followed by NAT. In terms of cost of test and treatment alone, among the 93 cases of accessions with chronic HCV infection, 42.0% (n = 39) of the service members who had HCV infection at the time of accession from the no screening scenario would have to receive care within the military health system during their period of service in order for the screening strategy cost to offset the treatment costs avoided. With incorporation of rerecruitment costs this percentage reached 57.4% (n = 53). These numbers were less than the average of more than 200 new cases of chronic HCV identified each year among active duty service members in the periods 2000-2010[12] and 2006- 2013 (A. Cost, personal communication).

Assuming only a lower cost of treatment ($83,319) than the base case, screening with HCV EIA and NAT yields a net savings and a $1.4 million advantage over not screening. The break-even point for screening cost based upon the number of chronic HCV-infected patients treated is where 72.2% of the 93 HCV-infected accessions (n = 67) would have to receive care within the military health system during their period of service in order for the screening strategy cost to offset the treatment costs avoided.

Assuming a higher accession prevalence rate of chronic HCV infection where 75% of the observed rate in this study population with confirmed HCV seropositivity have chronic HCV infection (0.75 × 0.08% = 0.06%), screening with HCV EIA and NAT yields a net savings and a $6.2 million advantage over not screening. The break-even point is where 39.9% (n = 69) of the 139 HCV-infected accessions would have to receive care within the military health system during their period of service in order for the screening strategy cost to offset the treatment costs avoided. And assuming a chronic HCV rate of 85% of the observed rate of HCV seropositivity further increases the net savings to $7.5 million with a break-even point of 36% (n = 56) of the 158 cases of chronic HCV cases being identified and treated during their period of service.

Last, assuming both a lower cost of treatment ($83,319) and a higher than observed rate of chronic HCV (0.06%) increased the net savings to $4.0 million with a break-even point of 50% (n = 70) of the 139 cases of chronic HCV being identified and treated during their period of service.

Discussion

Screening for chronic HCV infection by EIA test followed by confirmation with NAT minimizes accessions of HCV-infected applicants while reducing inappropriate

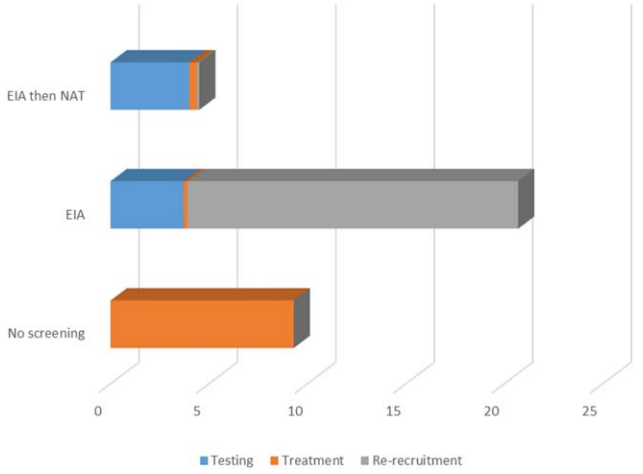

Fig. 1. Screening strategy. Bars show the total cost in millions of U.S. dollars of each of the three policy options for HCV screening. Each bar is color coded as identified above for the contributions of testing, re-recruitment and treatment to the total cost.

exclusion of fully qualified applicants. The use of confirmatory testing is important in stratifying risk and treatment decisions in individual patients, as discussed in clinical guidelines.[11,15] An EIA-only arm was important to explore in this model as population screening aims that refer individuals to other mechanisms for patient evaluation and care may differ from usual clinical test use. Systematic inclusion of NAT could require new investments. Because the majority of all HCV infections among US military personnel were present at accession, an applicant screening program is likely to be the most effective way to decrease the burden of HCV infection among US military personnel, will decrease the threat deployed service members with chronic HCV infection pose to the emergency battlefield non-FDA blood supply, and will likely result in opportunities for earlier diagnosis and linkage to care for those identified with chronic HCV infection. Accession screening is predicted to markedly reduce the burden of HCV infection in the deployable force, but given the low level of service-related incidence of HCV infection, it will not entirely eliminate HCV infection. Accession screening is predicted by this model to result in a small system net cost savings due to treatment costs avoided while also decreasing armed services prevalence of HCV.

The sample studied was representative of both the accession population and the deployed force. All members of the deployed force were, by definition, accessions who at one time were successful applicants for military service. The accession population and the deployed force do not necessarily reflect the entire applicant population, which includes both applicants who successfully acceded and all those who did not. It is possible that the applicant population that does not accede could differ significantly from those applicants who do accede and that the prevalence of HCV infection in these two groups could differ. But these differences would have only minimal impact on this model and would not significantly alter the findings.

HCV screening among more than 200,000 sailors and Marines tested on accession as part of a pilot program at initial training depots in the period 2011-2013 yielded similar HCV prevalence rates as this study (0.6/1000 and 0.4/1,000 person tested for HCV antibody-positive and chronic HCV infection, respectively; C.G. Beckett, unpublished data). This study had rates similar to those of Hyams et al.[5] for younger service members but a three-fold higher prevalence among older service members (born before 1966). And, overall, these results are consistent with evidence driving current Centers for Disease Control recommendations on hepatitis C screening in the general population and those of the US Preventive Medicine Task Force.[6,16]

All service-related HCV incidence occurred among the younger birth cohort. All occurred among US-born males in non-health care worker occupations, and most occurred among white males in the Army. Behavioral and personal exposure histories were not obtained as part of this investigation, and given the small numbers of infections, risk factors for incident infection cannot be identified. Further study and a larger sample are required to make any additional determination and recommendations regarding the potential utility and costs associated with periodic screening of the force following accession screening.

Emergent whole blood transfusion has been an important feature of combat casualty resuscitative care in the conflicts in Iraq and Afghanistan. The US military uses freshly collected blood products for life-threatening injuries when available stored blood components in theater have been exhausted or when these components are unsuccessful for resuscitation. Countermeasures in place to reduce the risk of transfusion-transmitted infections associated with use of these freshly collected products include periodic and combat theater entrance screening for human immunodeficiency virus (HIV), universal HBV vaccination, use of prescreened blood donor pools, a donor screening questionnaire, and point of collection rapid diagnostic tests. DoD policy has included universal HBV vaccination during initial entry training since 2001, and all personnel who entered military service prior to 2001 who have not been vaccinated are required to initiate vaccination prior to entry into the combat theater of operations. Volunteers at deployed facilities with blood donation capacity are initially screened for HIV, HBV, HCV, human T lymphotropic viruses I and II, West Nile virus, and syphilis and rescreened each time they donate and every 90 days after admission. And at the time of donation, donated units are tested for HIV, HBV, and HCV with rapid diagnostic tests. There are situations, such as mass casualty or combat casualty care scenarios in smaller military treatment facilities, where prepositioned FDA-compliant blood component supplies are exhausted and only limited screening of emergency blood donors is possible. To date, one transfusion-transmitted HCV infection has been documented, and this occurred in an austere setting where no countermeasures were in place.[2] Because most HCV infections among service members who deploy were present at accession, an accession screening program will markedly reduce the number of deployed service members with HCV infection who may enter the battlefield blood. However, given the small service-related incidence of chronic HCV infection,

accession screening will markedly reduce but not entirely eliminate this potential threat.

Test performance can have a marked impact on observed prevalence and cost model outcomes. The sensitivity and specificity of the EIA test and NAT employed in this cost model were based on the product labels. HCV antigen tests have become increasingly available. Their test sensitivity against NAT as a gold standard may range from 50% to 90%.[17] As these and other assays become available, different screening strategies may be possible and subsequent cost models will need to be developed to reevaluate the status quo.

The cost model presented was developed from the perspective of the DoD, and the return on investment was based on a comparison between the costs associated with initiating a screening program of applicants and the potential treatment costs avoided by identifying applicants with HCV infection and barring them from entry into military service. It is not possible to know prospectively how many HCV-infected applicants identified through an accession screening program would have been identified as infected and would have required treatment during the course of their military service if there was no accession or periodic force screening program. It is also unknown how those active duty service members who are identified, more than 200/year on average, every year with chronic HCV infection came to be identified; and no data are available regarding whether or not those trends and rates of case identification would persist in the future. This model was based on the assumption that case finding would occur at similar rates and that the case identification among active duty personnel in recent years was stable. If trends resulting in case identification significantly changed prospectively, this model would have to be adjusted accordingly.

The HCV treatment landscape is rapidly evolving. Difficult treatment decisions, such as when to initiate therapy, are strongly influenced by the high cost of treatment. Newer antiviral agents with activity against HCV already have been incorporated into clinical practice guidelines.[11] Current treatment guidelines discourage the use of older line treatments because they are inferior to recommended treatment regimens and because most of the interferon-containing regimens are associated with higher rates of serious adverse events and have many features that compromise compliance and completion of therapy including longer treatment duration, numerous drug-drug interactions, and more frequent dosing.[11] The $100,000 cost of treating an HCV-infected accession used in this model was based upon treatment using the new highly effective HCV treatment including sofosbuvir. Newer drugs are very costly. As the range of therapeutic options grows (such as with the licensure of the all-oral regimen of ledipasvir and sofosbuvir), more experience is gained in the operationalized clinical performance of newer therapies, and market pressures evolve pricing, the relative importance of excluding versus accepting and treating HCV-infected candidates may change. The value of screening may change from excluding candidates to the importance of early identification for treatment initiation and lower long-term system costs. For now, the cost of treatment remains high.

Clinical and exposure data for cases identified in this investigation, including risk factors for infection, duration of infection, and fibrosis score, were not obtained. This model assumed that all cases of chronic HCV infection identified would be treated. Offering therapy is the standard of care. Delays in therapy for some patients because of resource or other issues could impact the cost model and conclusions from the perspectives of both the DoD and other government agencies such as the Veterans Administration which could experience cost shifting.

This cost model was developed from the perspective of the DoD. However, a screening program that resulted in earlier identification of individuals with chronic HCV infection could lead to earlier diagnosis, linkage to care, and treatment which could both benefit individual health and improve public health. From the perspective of the infected individual and society's willingness to pay, one analysis of switching to all-oral therapy identified a cost of approximately $80,000 per quality-adjusted life year.[18] In more recent analyses considering sofosbuvir, costs ranged widely, from less than $10,000 to nearly $300,000 per quality-adjusted life year depending on patient and virus factors.[13,19,20] Incorporation of other novel agents drove costs up to six times higher.[21] Many of these analyses have incremental cost-effectiveness ratios per quality-adjusted life year that far exceed the generally accepted threshold of US society's willingness to pay of $100,000.00.[20] It is unclear at this time, however, when and how these individual benefits might be realized in the setting of a DoD applicant screening program. Many of the applicants identified with chronic HCV infection and barred from entry into the armed forces may have early HCV infection given their relative youth and may lack the resources necessary or may not qualify for programs that provide care and treatment.

The impact on diversity of the force of an HCV applicant screening program is likely minimal. The impact of HCV-infected applicant exclusion on diversity is difficult to quantify, though the total number of applicant

exclusions across the more than 200,000 accessions would be very low, so presumably the impact would be minimal. A new assessment of national HCV incidence highlighted white nonurban young adults as a growing pool of infected persons.[22] This same report identified a 150% increase in HCV case reporting between 2010 and 2013, highlighting the potential importance of screening initiatives. Like any large-scale screening initiative, prospective operational public health research would be necessary in order to enable comprehensive monitoring, assessment, and intervention of program performance as well as identifying health improvement opportunities.

While contemporary hepatitis C seroprevalence rates are lower than among those born before 1966, in the setting of the deploying military force, costs associated with infection are nontrivial. Screening strategies here provided small absolute cost benefits when modeled. There also are implied value benefits regarding safety of the walking blood bank in the deployed setting through less chance of HCV infection among personnel in the field.

This study employed reposed sera from the DoD Serum Repository. This repository has a long history of successful use with serologic testing, but performance related to NAT is less clear. This may have resulted in underestimation of chronic HCV infection when NAT was employed for confirmation. However, this potential limitation is mitigated by the fact that a higher than observed prevalence of chronic HCV infection prospectively among the applicant population would make applicant screening even more favorable. Other potential limitations include the fact that differences exist among the total force between those who deploy and those who do not deploy, that performance and costs of diagnostic assays and therapies are evolving, and that attention to HCV genotype was not given. Missing data were also problematic, particularly with regard to birth location. And direct comparison with similar studies of cost in civilian settings is limited by the fact that they do not incorporate the additional occupational costs and consequences incurred by the military with any health condition. Cost modeling here for HCV treatment in active duty military personnel sought to minimize the presence of personnel with permissive chronic viremia, in the setting where most HCV cases identified in this study had been infected for at least several years. It assumed immediate treatment of disease in a setting where clinical care is well resourced. This cost model obtains savings through exclusion of HCV-infected applicants. In the future, as cost of treatment approaches rerecruitment cost (Table 1), this strategy could be reassessed.

In conclusion, despite decreased hepatitis C seroprevalence in deployed service members born after 1965, screening by EIA test followed by confirmation with NAT will minimize accession of HCV-infected applicants while reducing inappropriate exclusion of applicants. An applicant screening program will also markedly reduce the burden of chronic HCV infection in the overall force, will result in a small system costs savings of approximately $3 million per year due to decreases in treatment costs to the military health care system, will decrease the threat of transfusion-transmitted HCV infection in the emergent battlefield non-FDA blood supply posed by HCV-infected personnel, and may provide an opportunity for individuals with chronic HCV infection to obtain earlier diagnosis and linkage to care and treatment. Initiation of an applicant screening program will require ongoing evaluation that considers changes in the treatment cost and practice landscape, screening options, and the epidemiology of HCV in the applicant/accession and overall force populations. Future study to more fully characterize the epidemiology of incident, service-related chronic HCV infection is also recommended; and those findings will inform policy regarding population-based screening and contribute to countermeasures intended to ensure the safety of the battlefield blood supply.

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