CAUSES OF FEVER IN ADULTS ON THE THAI-MYANMAR BORDER

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Armed Forces Research Institute for Medical Sciences (AFRIMS), Bangkok, Thailand; Kwai River Christian Hospital, Sangkhlaburi, Thailand; Brooke Army Medical Center and VETCOM Leptospirosis Reference Laboratory, Fort Sam Houston, Texas

Abstract. A hospital-based study was conducted along the Thai-Myanmar border to provide greater knowledge of the causes of febrile illness and to determine what zoonotic and vector-borne emerging infectious diseases might be present. A total of 613 adults were enrolled from June 1999 to March 2002. Cases were classified based on clinical findings and laboratory results. An etiologic diagnosis was made for 48% of subjects. Malaria was the most common diagnosis, accounting for 25% of subjects, with two-thirds Plasmodium falciparum. Serologic evidence for leptospirosis was found in 17% of subjects. Other etiologic diagnoses included rickettsial infections, dengue fever, and typhoid. The most frequent clinical diagnoses were nonspecific febrile illness, respiratory infections, and gastroenteritis. Clinical associations were generally not predictive of etiologic diagnosis. Apparent dual diagnoses were common, particularly for malaria and leptospirosis. Findings have been used to modify treatment of unspecified febrile illness in the area.

INTRODUCTION

For health care providers and public health officials, knowledge of local patterns of disease is critical for making informed treatment and prevention decisions. In many developing nations, prevalence and incidence of infectious disease is largely unknown, with estimates based on scanty or unreliable data.1 Diagnostic tools for infectious disease in particular require an investment in training, infrastructure, and technology that is beyond the reach of many developing nations.2 Presumptive treatment, even for a relatively easily diagnosed cause of fever such as malaria, remains the standard of care in many locales.3

One approach to improving knowledge of local patterns of infectious disease is to identify a sentinel site (typically a hospital) and to intensively study patients presenting with febrile illness at that site. Some of these hospital-based cohort studies have focused on bacterial infections, and others have included serologic testing as well as bacterial cultures.4–10 Results from these studies have been used to improve local empirical treatment decisions and to enhance the appropriate use of resources and to improve quality of diagnostic services.2 Three reports of studies of febrile illness in Thailand have been published: of bacterial infections in adults in Bangkok; of causes of fever in children during flooding in a provincial hospital; and of etiologies of acute pyrexia of unknown origin in children and adults at 10 community hospitals.5,10,11

The primary objectives of this study were, first, to provide greater knowledge of the causes of febrile illness among patients presenting for care at this community hospital, and second, to determine what zoonotic and vector-borne emerging infectious diseases might be prevalent at this sentinel site.

MATERIALS AND METHODS

Setting. Sangkhlaburi District is located in Kanchanaburi Province in western Thailand, on the border with Myanmar (Burma). Several ethnic groups are represented in the district, including Thai, Karen, Mon, and Burmese. The district is rural and mountainous and is a heavily traveled border crossing, with large numbers of people entering and leaving for trade and occasionally because of unrest inside Myanmar. Malaria is common, as is nonspecific febrile illness. Kwai River Christian Hospital (KRCH) is a 60-bed hospital and has served local residents as well as those who travel to the hospital seeking medical care since 1961. The Armed Forces Research Institute for Medical Science (AFRIMS) is a joint U.S.-Royal Thai Army tropical medicine research institute based in Bangkok. The AFRIMS/KRCH Clinical Center (AKCC) was established in 2000 and is a center for malaria and other infectious disease research at the hospital.

Subjects. Adult inpatients and outpatients presenting with temperature ≥ 38°C or history of fever over the previous 48 hours were admitted to the study and evaluated for cause of fever. Patients with fever longer than 48 hours were also eligible for enrollment, as long as the cause of fever was not yet known. Patients presenting for continuation of treatment of known cause of fever were excluded, as were those who were unable or unwilling to provide blood samples 2–4 weeks after enrollment. Clinical information and blood samples were obtained at enrollment and after approximately 3 weeks. Informed consent was obtained from each study subject before enrollment. Patients were enrolled under Walter Reed Army Institute of Research (WRAIR) protocol no. 745. The protocol was approved by the WRAIR Human Use Review Committee and by the Thai Ministry of Public Health’s Ethical Review Committee for Research in Human Subjects.

Laboratory and diagnostic techniques. Routine laboratory tests included complete blood count (CBC), and a standard biochemistry panel—alanine transferase (ALT), gamma glutamyl transferase (GGT), blood urea nitrogen (BUN), and creatinine. Other diagnostic tests, for example, chest x-ray, sputum studies, or rapid human immunodeficiency virus (HIV) testing, were done at the discretion of the attending physician. Cultures were not done. All reference diagnostic testing was performed at AFRIMS, with the exception of malaria blood smears, microscopic agglutination test (MAT), and immunofluorescent antibody (IFA) as discussed below.

Malaria. All subjects were screened for malaria at enrollment by thick and thin blood smear Giemsa microscopy performed by expert microscopists located at KRCH. If asexual
All subjects were screened by a commercially available IgM enzyme-linked immunosorbent assay (ELISA; PanBio, Inc., Baltimore, MD). All cases with a level of \( \geq 9 \) PanBio units on acute or convalescent samples were sent for confirmatory MAT, performed at the Veterinary Command (Fort Sam Houston, TX). Cases with an MAT titer of \( \geq 800 \) on a single sample or a \( \geq \) fourfold change between acute and convalescent titers were considered to be positive for leptospirosis. A panel of 24 serovars was used for MAT.

**Dengue fever and Japanese encephalitis.** All cases with paired samples available were tested for IgG and IgM antibodies for dengue and Japanese encephalitis by an in-house ELISA. Acute cases were defined as \( > 40 \) IgM antibody units with a rise in titer between the acute and convalescent specimens. The ratio of antibody to dengue versus Japanese encephalitis was used to differentiate the two infections, and the ratio of IgM/IgG was used to determine whether the infection was primary or secondary dengue infection. For specimens positive by ELISA, detection of dengue viral RNA was performed by reverse-transcription polymerase chain reaction using a modification of the primers used in the Lanciotti procedure.

**Rickettsioses.** Forty-six (46) cases selected by clinical criteria (rash or eschar, history of arthropod bites or jungle exposure) were evaluated for evidence of rickettsial infection (scrub typhus, murine typhus, and spotted fever group rickettsioses) at Unité des Rickettsies (Marseille, France). IFA techniques used for diagnosis have previously been described. IgG titers \( \geq 64 \) and/or IgM titers \( \geq 32 \) on acute or convalescent specimens were considered to be positive for acute infection.

**Typhoid.** Real-time PCR for *Salmonella enterica* serovar *typhi* (*S. typhi*) was done on a selected subset of 31 patients based on clinical criteria including nonlocalized rash or admitting or reviewing physician’s presumptive diagnosis of typhoid. DNA was extracted from reconstituted whole blood and sequences (DNA fragments) from the Vi antigen (ViaB gene) specific for *S. typhi* were amplified using the TaqMan PCR assay, with a lower detection limit of 1,000 cfu/mL of extract (Phasuk R, Sethabutr O, unpublished data). Patients with a clinical illness consistent with typhoid and with iliac perforation found on laparotomy were also counted as confirmed typhoid cases.

**Pulmonary TB and HIV/AIDS.** To be classified as pulmonary tuberculosis (PTB), subjects must have had a cavitory lesion on chest x-ray or admitting or reviewing physician’s presumptive diagnosis of TB. Malaria was diagnosed if parasites were seen on the smear, the patient was considered to have malaria.

**Leptospirosis.** All subjects were screened by a commercially available IgM enzyme-linked immunosorbent assay (ELISA; PanBio, Inc., Baltimore, MD). Cases with a level of \( \geq 9 \) PanBio units on acute or convalescent samples were sent for confirmatory MAT, performed at the Veterinary Command (Fort Sam Houston, TX). Cases with an MAT titer of \( \geq 800 \) on a single sample or a \( \geq \) fourfold change between acute and convalescent titers were considered to be positive for leptospirosis. A panel of 24 serovars was used for MAT.

**Meningitis.** An isolate obtained from bacterial meningitis was confirmed serotyped for serogroups A, C, W, and Y. Encephalitis was used to differentiate the two infections, and the ratio of antibody to dengue versus Japanese encephalitis was used to determine whether the infection was primary or secondary dengue infection. For specimens positive by ELISA, detection of dengue viral RNA was performed by reverse-transcription polymerase chain reaction using a modification of the primers used in the Lanciotti procedure.

Etiologic diagnoses. Table 2 shows combined etiologic and clinical diagnoses (\( N = 613 \)). A specific etiologic diagnosis was made for 294 (48%) of subjects. Malaria was the most frequent etiology, with 25.3% of subjects found to be positive for malaria parasites on enrollment. *Plasmodium falciparum* accounted for 61% of malaria cases. Leptospirosis was the next most frequent etiologic diagnosis, followed by rickettsial infection. All cases of dengue were diagnosed during an outbreak in 2001. Most of the dengue cases (8 of 9) were secondary infections. Seven of the nine cases were positive for dengue viral RNA by nested PCR, including one case also seropositive for leptospirosis. One case of Japanese encephalitis was diagnosed (included in “other” in Table 2). A diagnosis of typhoid fever was made in five cases, three by PCR and two on the basis of surgical

### RESULTS

Six hundred thirteen (613) subjects were enrolled into the study from June 1999 to March 2002. Demographic data are shown in Table 1. Follow-up specimens were obtained from 530 (86%) of subjects at a median of 21 days after enrollment. Nineteen percent of subjects were inpatients.

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Leptospirosis was the next most frequent etiologic diagnosis, followed by rickettsial infection. All cases of dengue were diagnosed during an outbreak in 2001. Most of the dengue cases (8 of 9) were secondary infections. Seven of the nine cases were positive for dengue viral RNA by nested PCR, including one case also seropositive for leptospirosis. One case of Japanese encephalitis was diagnosed (included in “other” in Table 2). A diagnosis of typhoid fever was made in five cases, three by PCR and two on the basis of surgical

#### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data (( N = 613 ))</td>
<td></td>
</tr>
<tr>
<td>Age (years), range</td>
<td>Median 38, 20–87</td>
</tr>
<tr>
<td>Male</td>
<td>325 (53)</td>
</tr>
<tr>
<td>Inpatient</td>
<td>118 (19)</td>
</tr>
<tr>
<td>Deaths</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Karen</td>
<td>320 (52)</td>
</tr>
<tr>
<td>Mon</td>
<td>120 (20)</td>
</tr>
<tr>
<td>Thai</td>
<td>112 (18)</td>
</tr>
<tr>
<td>Burmese</td>
<td>41 (7)</td>
</tr>
<tr>
<td>Other/not specified</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
</tr>
<tr>
<td>Farmer/forestry</td>
<td>224 (37)</td>
</tr>
<tr>
<td>Housewife/housekeeper</td>
<td>77 (13)</td>
</tr>
<tr>
<td>Hired worker not specified</td>
<td>79 (13)</td>
</tr>
<tr>
<td>Shop owner</td>
<td>34 (6)</td>
</tr>
<tr>
<td>Other</td>
<td>199 (33)</td>
</tr>
</tbody>
</table>
findings of iliac perforation. One of these cases was also seropositive for SFG rickettsiosis.

Of the 44 cases screened for serologic evidence of melioidosis by IgG ELISA, 7 had a rise in titer from negative (<9 PanBio units) to positive (>11 PanBio units). Six (6) cases were serofast positive. Of the 133 cases screened for serologic evidence of Q fever by IgM ELISA, 14 were positive (>11 PanBio units) on either an acute or convalescent specimen or both. One case showed a rise in titer from negative to positive, although 90 of these cases had convalescent titers only. These results were not felt to be convincing evidence of acute infection and were not included in the etiologic diagnoses.

**Clinical diagnoses.** For clinical diagnoses, fever not specified was most common, followed by respiratory infections, gastroenteritis, and urinary tract infections. Of the gastroenteritis cases, the most frequent presentation was diarrhea (12 of 16).

Of the eight deaths in the cohort, two were positive for typhoid by PCR, one was seropositive for leptospirosis, two had clinical end-stage acquired immune deficiency syndrome (AIDS), two were fever not specified, and one had clinical hepatitis with no etiology identified.

**Dual etiologic diagnoses.** Table 3 shows the numbers of cases with apparent dual diagnoses. Twenty-six (26%) of 155 (16.8%) smear-positive malaria cases had laboratory evidence of a second infection, most commonly leptospirosis. Twenty-eight (28) of 107 (26%) leptospirosis cases had evidence of a second infection, most commonly malaria. Evidence of dual infection was also seen for rickettsial infections (4 of 36, 11%) and for dengue (2 of 9, 22%).

**Clinical correlations for etiologic diagnoses.** Cases of malaria (grouped and *P. falciparum* only), leptospirosis, rickettsiosis (grouped), and dengue fever were compared with the remainder of the cohort to look for differences in age, sex, outpatient versus inpatient status, symptoms at presentation (documented fever, presence of rash, complaints of headache, myalgia, cough, and abdominal pain), and presence of leukopenia (white blood cells < 4.0 × 10^3/μL), anemia (hematocrit < 35%), thrombocytopenia (platelets < 150,000 × 10^3/μL), elevated BUN (>20 mg/dL), elevated creatinine (≥1.6 mg/dL), elevated ALT (>45 U/L), and elevated GGT (>76 U/L). Associations were examined including and excluding dual diagnosis cases. Results for all associations and for those significant after logistic regression are shown in Table 4.

For malaria overall, associations were seen for several hematologic and clinical variables. After regression, results remained significant for outpatient status, documented fever, and thrombocytopenia. Results were similar when *P. falciparum*–only cases were examined, but with fewer variables reaching statistical significance.

The only significant association for leptospirosis with the above variables was elevated ALT, which lost significance after regression was performed. For rickettsial diagnoses, significance was seen for age, with cases being slightly older than noncases, for the presence of rash, and for elevated GGT. However, the increased likelihood of rash is likely due to confounding as rash was one of the diagnostic criteria by which cases were chosen for serologic testing. No associations were seen for dengue fever, although the small number of cases (N = 9) makes statistical significance unlikely. For all diagnoses, results were similar when dual diagnosis cases were excluded (not shown).

**DISCUSSION**

As expected in this malaria-prevalent area, *Plasmodium* infection was the most common diagnosis among subjects, with *P. falciparum* being predominate. Malaria diagnosis was based on expert microscopy, and all patients enrolled were screened. Thus, the number of malaria diagnoses is likely to accurately reflect the true number of cases.

Leptospirosis was the next most frequent etiologic agent, accounting for 17.5% of cases overall. As with malaria, all subjects enrolled were screened, although subjects who did not follow up were less likely to be diagnosed due to lack of a convalescent specimen. Diagnosis of leptospirosis relied on serology. The MAT cutoffs used to define positive cases are the more stringent levels typically used in endemic regions (i.e., a titer of 800 rather than 200 for single sera). However, MAT titers can sometimes remain elevated for long periods after infection, so some proportion of the cases identified may be false positives. Conversely, treatment with antibiotics can blunt the immune response in leptospirosis, reducing the number of cases detectable by serology. As results of this study became available, clinicians at the hospital were more likely to treat for suspected leptospirosis, which had previ-

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**Table 2**

Diagnoses overall (N = 613)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of cases</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria total</td>
<td>155</td>
<td>25.3</td>
</tr>
<tr>
<td><em>P. falciparum</em></td>
<td>(95)</td>
<td>(15.5)</td>
</tr>
<tr>
<td><em>P. vivax</em></td>
<td>(48)</td>
<td>(7.8)</td>
</tr>
<tr>
<td>Mixed or other</td>
<td>(12)</td>
<td>(2.0)</td>
</tr>
<tr>
<td>Fever not specified</td>
<td>153</td>
<td>25.0</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>107</td>
<td>17.5</td>
</tr>
<tr>
<td>Lower respiratory infection</td>
<td>64</td>
<td>10.4</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>57</td>
<td>9.3</td>
</tr>
<tr>
<td>Rickettsiosis total</td>
<td>36</td>
<td>5.9</td>
</tr>
<tr>
<td>Spotted fever group (SFG) rickettsiosis</td>
<td>(20)</td>
<td>(3.3)</td>
</tr>
<tr>
<td>Murine typhus (<em>R. typhi</em>)</td>
<td>(9)</td>
<td>(1.5)</td>
</tr>
<tr>
<td>Scrub typhus (<em>O. tsutsugamushi</em>)</td>
<td>(7)</td>
<td>(1.1)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>16</td>
<td>2.6</td>
</tr>
<tr>
<td>Pyelonephritis/urinary tract infection</td>
<td>13</td>
<td>2.1</td>
</tr>
<tr>
<td>Dengue fever†</td>
<td>9</td>
<td>1.5</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>AIDS</td>
<td>7</td>
<td>1.1</td>
</tr>
<tr>
<td>Typhoid</td>
<td>5</td>
<td>0.8</td>
</tr>
<tr>
<td>Pulmonary tuberculosis (PTB)</td>
<td>7</td>
<td>1.1</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
<td>2.8</td>
</tr>
</tbody>
</table>

*Total is >100% due to dual diagnoses.

†All Dengue cases occurred between March and August 2001.

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**Table 3**

Apparent dual diagnoses

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria and leptospirosis</td>
<td>22</td>
</tr>
<tr>
<td>Malaria and rickettsiosis</td>
<td>2</td>
</tr>
<tr>
<td>Malaria and other (dengue, PTB)</td>
<td>2</td>
</tr>
<tr>
<td>Leptospirosis and rickettsiosis</td>
<td>4</td>
</tr>
<tr>
<td>Leptospirosis and other (dengue, PTB)</td>
<td>2</td>
</tr>
<tr>
<td>Rickettsiosis and other (typhoid, PTB)</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
</tr>
</tbody>
</table>

PTB, pulmonary tuberculosis.
As blood cultures were not done and diagnosis relied on sur-


teened area, confirmation of the presence of the disease is
critical, particularly as specific therapy with ceftazidime is
required for effective therapy, particularly for diabetic or
immunocompromised hosts.\textsuperscript{26} The serologic evidence for
the presence of Q fever is not as strong, as only one case was
shown to have a rise in titer. In general, interpretation of
serologic tests in a population where the prevalence of infec-
tion is unknown is problematic. Antibodies from previous
infection may persist, and cross-reactivity is common, particu-
larly for poorly characterized emerging infections.\textsuperscript{27,28}

Another important finding of the study is the high apparent
frequency of coinfection, particularly for malaria and lep-
tospirosis, both with each other and with other infectious
agents. Despite the use of reference laboratory standards and
strict criteria for diagnoses, 34 cases met criteria for two in-
fections. Details on seven likely malaria-leptospirosis coinfec-
tions from this study are reported elsewhere.\textsuperscript{29} However, in-
fec tion with malaria parasites often causes a polyclonal am-
plication of the immune response and may confound results of
serologic testing.\textsuperscript{30,31} Isolation of leptospires or rickettsial
agents in patients with a positive malaria smear would be
useful to confirm these findings. Possible coinfection between
leptospirosis and scrub typhus has also been reported in Thai-
land.\textsuperscript{32} A study of febrile illness in Nepal showed 5 out of 36

\begin{table}
\centering
\caption{CAUSES OF FEVER ON THAI-MYANMAR BORDER}
\begin{center}
\begin{tabular}{|l|l|l|l|}
\hline
\textbf{Diagnosis} & \textbf{Variable*} & \textbf{Cases vs. rest of cohort (\%)} & \textbf{Independent predictor} \\
& & & \textbf{P value} & \textbf{Odds ratio (95\% CI)} \\
\hline
Malaria all (\textit{N} = 155) & Outpatient & 86 vs. 79 & < 0.001 & 3.2 (1.7–6.0) \\
& Age & 36 vs. 39 & & \\
& Male sex & 61 vs. 50 & & \\
& Temp $\geq 38^\circ$C & 64 vs. 44 & 0.001 & 2.3 (1.4–3.8) \\
& WBC < 4.0 & 18 vs. 6 & & \\
& Platelets < 150,000 & 81 vs. 21 & < 0.001 & 17.2 (10.4–28.5) \\
& Creatinine > 1.6 & 2 vs. 7 & & \\
& Cough & 45 vs. 55 & & \\
& Headache & 95 vs. 86 & & \\
Malaria pf only (\textit{N} = 96) & Temp $\geq 38^\circ$C & 66 vs. 46 & 0.006 & 2.1 (1.2–3.5) \\
& Platelets < 150,000 & 80 vs. 29 & < 0.001 & 8.8 (5.1–15.5) \\
& Age & 35 vs. 39 & & \\
& WBC < 4.0 & 22 vs. 7 & & \\
& HCT $\leq 35$ & 35 vs. 24 & & \\
Leptospirosis (\textit{N} = 107) & ALT > 45 & 40 vs. 29 & & \\
Rickettsioses all (\textit{N} = 36) & Age & 42 vs. 38 & & \\
& Rash & 14 vs. 3 & & \\
& GGT > 76 & 36 vs. 19 & & \\
\hline
\end{tabular}
\end{center}
\end{table}

\textsuperscript{pt, \textit{Plasmodium falciparum}; Temp, temperature; WBC, white blood cell count; HCT, hematocrit; ALT, alanine transferase; GGT, gamma glutamyl transferase.}

\textsuperscript{*Variables listed were significant at the 0.05 level before regression. Variables with confidence intervals shown were also significant after regression. \textit{P} values are above.}
likely leptospirosis cases had positive blood cultures for S. typhi or S. paratyphi." Coinfection may be common, and the clinical assumption that only one etiologic agent is responsible for a given illness may not hold true in these settings. In an environment where exposure to multiple pathogens is common, patients not responding to treatment of a particular infection or those in whom the presentation is atypical or severe should be suspected of harboring a second infectious agent.

After logistic regression, significant clinical associations were seen for malaria only, partly because malaria was the most common diagnosis and numbers are large, reducing Type II error. Yet the number of leptospirosis cases is also large, and if clear clinical patterns were present, they should have been statistically significant. These results demonstrate the difficulty of making a clinical diagnosis of leptospirosis, which presents with nonspecific findings such as headache, cough, and myalgia. Clinical presentations of all of the infectious agents identified in this population overlap considerably.

Intensive surveillance to determine etiologic causes of febrile illness in underdeveloped regions with unique environments provides both public health and local community benefits. Study findings have been presented to the Sangkhlaburi community medical community and have been used to modify treatment practices in the area. For patients with nonspecific febrile illness who are malaria smear negative, doxycycline is now the antibiotic of choice for patients ill enough to require treatment, as it effectively treats leptospirosis, scrub and murine typhus, and spotted fever group rickettsiosis, as well as most community-acquired pneumonia. The drug is inexpensive and readily available. In addition, clinicians now have a heightened suspicion of the presence of dual infection in patients not responding to treatment.

Received June 2, 2005. Accepted for publication July 14, 2005.

Acknowledgments: This study was supported by the Global Emerging Infectious Disease Program (GEIS) of the U.S. Department of Defense. We would like to thank the field team of the Department of Immunology, AFRIMS, and the many nurses, technicians, and support staff at KRCH, AFRIMS, and elsewhere who contributed to this project. Presented in part at the International Conference of Emerging Infectious Diseases, Atlanta, Georgia, July 16–19, 2000.

Disclaimer: The opinions reflected herein reflect those of the authors and do not necessarily reflect the official views of the U.S. Army or the U.S. Department of Defense.

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