**Background**

- Vitamin D plays a key role in both innate and acquired immunity. In humans, activated vitamin D stimulates production and regulation of antimicrobial peptides such as HCAP-18, a cathelicidin shown to enhance phagocytic killing of microbes and activation of chemokines for neutrophils and monocytes.
- Vitamin D activation of HCAP-18 requires a minimum concentration of 30 ng/ml; beyond the critical threshold of 30 ng/ml, a dose-response relationship is not known.
- Studies of vitamin D concentration and severity of viral respiratory infections have been mixed. We sought to explore the associations of influenza-like illness (ILI) severity and viral etiology with vitamin D concentration.

**Methods**

- The Acute Respiratory Infection Consortium (ARIC) is a multi-site, multi-disciplinary Department of Defense (DoD) clinical research network for the study of ILI among US military personnel and their family members. The ARIC Natural History Study is an observational, longitudinal study of ILI etiology, epidemiology and immunology. Recruitment and enrollment occurred Sept 2009-2014 and included five military medical treatment facilities (MTF) across the US (Figure 1).
- Individuals presenting within 72 hours of ILI onset were prospectively enrolled in an observational cohort study. ILI was defined as a fever (temperature ≥ 100.4°F) and respiratory symptoms (cough, shortness of breath, chest pain, etc.) with or without sore throat. Viral etiologies were determined by nucleic acid amplification testing of nasopharyngeal specimens. Demographics, viral signs, hospitalization status, and self-reported symptom severity were ascertained at baseline. Individuals with underlying medical illnesses were excluded. Nasal/throat swabs were collected at day 0 (enrollment), 3, 7 and 28 for viral testing. Post-enrollment clinical symptoms were collected daily for 7 days by patient-completed diaries using a standardized four-point scale (none, mild, moderate or severe). A composite score was calculated for lower and upper respiratory, GI and systemic symptoms. 25-OH Vitamin D concentrations were measured retrospectively on banked serum samples obtained from initial enrollment up to day 7 specimens. Vitamin D status was categorized as sufficient (>30 ng/mL), insufficient (<30 ng/mL) or deficient (<15 ng/mL).

**Results**

- 682 adults enrolled between 2009-2014 had serum specimens available for measurement of vitamin D concentration.
- Factors associated with increased risk of vitamin D deficiency or insufficiency
  - Men (84% vs 68%, p < 0.001)
  - Non-Caucasian (85% vs 74%, p<0.001)
  - Obese patients (85% vs 73%, p=0.001)
  - There were no differences in risk of vitamin D deficiency/insufficiency for current smokers and those who were morbidly obese
- Mean serum 25-OH vitamin D levels were lower in many risk groups (Figure 2)
  - Men (22.1 vs 25.7, p = 0.001)
  - Non-Caucasian (20.6 AA, 20.4 Asian, 21.9 other vs. 24.9 Caucasian, p<0.001)
  - Obesity (21.2 vs 24.6, p=0.001)
  - Morbid obesity (14.5 vs 23.8, p<0.001)

**Symptom Severity Analysis**

- In general, there were no significant differences in either individual or composite symptom severity scores when comparing all subjects by vitamin D status.
- On sub-analysis, obese patients with vitamin D levels <30 ng/ml reported increased severity of symptoms on day 7.
- Non-obese adults with vitamin D levels <30 ng/ml reported higher scores of upper respiratory symptoms on day 1.2 and lower respiratory symptoms on day 1.
- Subanalysis by gender revealed increased composite symptom scores for those with levels <30 ng/ml (Figure 3).

**Conclusions**

- The prevalence of vitamin D insufficiency and deficiency over a wide geographic network was very high in our otherwise healthy adult population with ILI.
- We detected a trend in increased hospitalizations for ILI in patients classified as vitamin D <30ng/ml in duration of viral shedding.
- We found some subtle differences in illness severity between those who were sufficient and insufficient/deficient, but we cannot exclude symptom reporting differences related to sex and weight of the subject.
- Our findings suggest that 25-OH vitamin D levels <30ng/ml may have a modest impact on the severity of ILI in healthy adults. Future study is required to assess if vitamin D supplementation during acute ILI would result in lower ILI severity.

**Selected References**


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- Disclaimer: The views expressed in this abstract are those of the authors and do not necessarily reflect the official policy or position of the Uniformed Services University, Department of the Navy, Army, Department of Defense, the US Government or the Henry M. Jackson Foundation.

**Figure 1.** Clinical sites participating in the ARIC Natural History Study

**Figure 2.** Mean vitamin D concentration by demographic factor

**Figure 3.** Comparison of composite symptom scores by gender and vitamin D status (>30 vs. < 30 ng/mL)

**Table 1.** Mean vitamin D level for hospitalized versus non-hospitalized enrollees

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>Number</th>
<th>Mean (SD) 25-OH Vitamin D Level</th>
</tr>
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<tbody>
<tr>
<td>No</td>
<td>627</td>
<td>23.76 (9.57)</td>
</tr>
<tr>
<td>Yes</td>
<td>36</td>
<td>20.86 (7.68)</td>
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