To the Editor—In 2010, the World Health Organization (WHO) and the US Advisory Committee on Immunization Practices (ACIP) recommended the use of the 13-valent pneumococcal conjugate vaccine (PCV13) for children aged 6 weeks to 71 months in schedules of 3 primary infant doses (3+0), 3 doses with a booster after 1 year of age (3+1), or 2 primary infant doses with booster (2+1) [1,2].

In countries where PCV13 use has eliminated vaccine-type disease, experts question whether a 1- or 2-dose PCV13 schedule is sufficient to maintain indirect protection [3]. In immunogenicity studies, 81%–100% of children demonstrated sufficient antipolysaccharide immunoglobulin after 1 infant dose [4]. However, studies of clinical outcomes have been inconclusive. In a case-control study in the United States, low numbers of cases prevented investigators from calculating relative odds of invasive disease between partial dose groups [5]. Carriage studies can provide another marker of vaccine effectiveness, although comparisons of full and reduced PCV13 schedules and carriage have not been reported.

From 2008 through 2013, we conducted annual cross-sectional pneumococcal carriage surveys among Alaskan children aged <5 years [6]. In 2010, PCV13 replaced 7-valent pneumococcal conjugate vaccine (PCV7) in Alaska’s childhood immunization schedule. During this time, children who started the vaccination schedule with PCV7 completed it with PCV13. For example, infants who received 2 doses of PCV7 could receive a final primary and booster dose of PCV13, yielding a PCV13 schedule of 1+1. Children enrolled during this period provided the opportunity to compare carriage of the 6 additional PCV13 serotypes (ie, 1, 3, 5, 6A, 7F, or 19A) across partial PCV13 dose groups.

For each study participant, we obtained a nasopharyngeal swab specimen for pneumococcal identification and serotype determination [7]. Children were included if they received their first dose of PCV before 6 months of age. Primary doses were any dose before 12 months of age; booster doses were any dose after 12 months. Children receiving only PCV7 were included in the category of “no PCV13 doses.” We compared the prevalence of carriage of the 6 additional PCV13 serotypes between dose groups using generalized estimating equations. Models were adjusted for the year of study enrollment.

From 2010 to 2012, 2762 children were enrolled; 51% were colonized with pneumococcus. Receipt of any PCV13 vaccine increased from 8% to 94%, while carriage of the additional 6 PCV13 serotypes declined from 9% to 3% (Table 1). We did not detect any statistical differences in carriage of the additional PCV13 vaccine types comparing reduced- or full-dose groups to children who received no PCV13. The statistical power for these comparisons ranged from 4% to 25%.

Our results indicate that we had insufficient power to detect a difference between dose groups, despite a large sample size. To evaluate the effect

Table 1. Pneumococcal Carriage of Children Participating in Surveys, by Vaccination Group—Anchorage, Alaska, 2010–2012

<table>
<thead>
<tr>
<th>Year</th>
<th>No.</th>
<th>None</th>
<th>1 Dose</th>
<th>2 Doses</th>
<th>3 Doses</th>
<th>1 + 1 Doses</th>
<th>2 + 1 Doses</th>
<th>3 + 1 Doses</th>
<th>1 Dose</th>
<th>2 Doses</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>848</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>917</td>
</tr>
<tr>
<td>Any pneumococcus</td>
<td>428 (50%)</td>
<td>9 (60%)</td>
<td>3 (75%)</td>
<td>5 (71%)</td>
<td>2 (100%)</td>
<td>5 (100%)</td>
<td>1 (100%)</td>
<td>11 (41%)</td>
<td>5 (62%)</td>
<td>469 (51%)</td>
<td></td>
</tr>
<tr>
<td>Additional PCV13 typea</td>
<td>2 (13%)</td>
<td>0 (0%)</td>
<td>3 (43%)</td>
<td>1 (50%)</td>
<td>1 (20%)</td>
<td>1 (100%)</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
<td>8 (9%)</td>
<td>37 (8%)</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>142</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>925</td>
</tr>
<tr>
<td>Any pneumococcus</td>
<td>72 (51%)</td>
<td>30 (42%)</td>
<td>41 (45%)</td>
<td>39 (48%)</td>
<td>15 (41%)</td>
<td>17 (61%)</td>
<td>13 (62%)</td>
<td>239 (55%)</td>
<td>10 (67%)</td>
<td>476 (51%)</td>
<td></td>
</tr>
<tr>
<td>Additional PCV13 typea</td>
<td>8 (6%)</td>
<td>3 (4%)</td>
<td>5 (4%)</td>
<td>4 (5%)</td>
<td>1 (3%)</td>
<td>3 (11%)</td>
<td>0 (0%)</td>
<td>19 (4%)</td>
<td>0 (0%)</td>
<td>43 (5%)</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>59</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>921</td>
</tr>
<tr>
<td>Any pneumococcus</td>
<td>27 (46%)</td>
<td>24 (43%)</td>
<td>27 (48%)</td>
<td>59 (48%)</td>
<td>17 (57%)</td>
<td>44 (64%)</td>
<td>91 (54%)</td>
<td>164 (49%)</td>
<td>9 (50%)</td>
<td>462 (50%)</td>
<td></td>
</tr>
<tr>
<td>Additional PCV13 typea</td>
<td>2 (3%)</td>
<td>3 (5%)</td>
<td>2 (4%)</td>
<td>7 (5%)</td>
<td>1 (3%)</td>
<td>1 (1%)</td>
<td>3 (2%)</td>
<td>4 (1%)</td>
<td>0 (0%)</td>
<td>23 (3%)</td>
<td></td>
</tr>
<tr>
<td>All No.</td>
<td>1049</td>
<td>143</td>
<td>151</td>
<td>217</td>
<td>68</td>
<td>102</td>
<td>191</td>
<td>800</td>
<td>41</td>
<td>2762</td>
<td></td>
</tr>
<tr>
<td>Any pneumococcus</td>
<td>527 (50%)</td>
<td>63 (44%)</td>
<td>71 (47%)</td>
<td>103(47%)</td>
<td>34 (50%)</td>
<td>66 (65%)</td>
<td>105 (55%)</td>
<td>414 (52%)</td>
<td>24 (59%)</td>
<td>1407 (51%)</td>
<td></td>
</tr>
<tr>
<td>Additional PCV13 typea</td>
<td>86 (8%)</td>
<td>8 (6%)</td>
<td>7 (4%)</td>
<td>14 (6%)</td>
<td>3 (4%)</td>
<td>5 (5%)</td>
<td>4 (2%)</td>
<td>25 (3%)</td>
<td>0 (0%)</td>
<td>152 (6%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: PCV13, 13-valent pneumococcal conjugate vaccine.

aCarriage of 1, 2, 5, 6A, 7F or 19A.
of PCV dose schedule on carriage in observational studies, studies must be carried out with a very large sample size or a high prevalence of PCV13 serotype carriage. Meta-analyses of this and other carriage studies should be considered to enhance the power to evaluate this question [8, 9].

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the Agency for Toxic Substances and Disease Registry.

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Clinical Laboratory Values in Human Ebola Virus Disease Support the Relevance of the Intramuscular Ebola-Kikwit Rhesus Model

To the Editor—We read with interest the recent article in Clinical Infectious Diseases by Lanini et al, which focused on the relationship between human Ebola virus (EBOV) RNA and clinical chemistry values obtained during the West African outbreak in Goderich, Sierra Leone [1]. While many investigators have demonstrated that EBOV viremia is associated with survival [2–6], Lanini et al found that multilevel mixed-effects regression models demonstrated a significant correlation between EBOV viremia and aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine phosphokinas (CPK), lactate dehydrogenase (LDH), international normalized ratio (INR), and adjusted partial thromboplastin time (aPTT). This is important because these findings further support the possibility of using human clinical laboratory values as surrogate markers of EBOV viral load as Janvier et al suggested with regard to AST [7]. Moreover, we recently published that in a linear regression model at 5 days postinfection (dpi) in rhesus macaques exposed to 1000 plaque-forming units (PFU) of EBOV-Kikwit intramuscularly (IM), that platelet counts, prothrombin time (PT), AST, ALT, LDH, and CPK correlated significantly with time to death and with log_{10} viral RNA [8]. Similarly, we found in a linear regression model that at 7 dpi, LDH and CPK correlated significantly with time to death and with log_{10} viral RNA. These findings are not surprising given that Warren et al [9] showed that in the 1000 PFU IM EBOV-Kikwit rhesus macaque model, the course of EBOV viral load is mirrored by the clinical chemistry results in the setting of successful Ebola virus disease (EVD) treatment using GS-5734.

In the absence of another large-scale human EBOV outbreak, the path to licensure of an antiviral in the United States would most likely need to be via the US Food and Drug Administration (FDA) Animal Rule [10], with human data supplementing the animal data. We found that laboratory values in humans and in the IM EBOV-Kikwit rhesus model are strikingly similar, exhibiting changes consistent with systemic inflammatory response syndrome and multiorgan injury. Humans and rhesus nonhuman primates (NHPs) both exhibit thrombocytopenia, and alterations of serum AST, ALT, blood urea nitrogen, creatinine, albumin, C-reactive protein, LDH, PT, aPTT, and CPK. Both humans and rhesus NHPs exhibit high systemic viral load at the peak of disease and in the time leading to death.

We are encouraged that the laboratory values we observed in the IM EBOV-Kikwit NHP model recapitulate what has been reported by Lanini et al in human EVD. We plan to continue further characterizing this model at the US Army Medical Research Institute of Infectious Diseases. We believe that the model is a useful animal model for predicting response in human EVD and is well suited to be utilized to evaluate medical countermeasures under the FDA Animal Rule.

Notes

Disclaimer. The views expressed herein are those of the authors and do not reflect the official policy or position of the US Army Medical Research Institute of Infectious Diseases (USAMRIID), the US Army Medical Department, the US Army Office of the Surgeon General, the Department of the Army, the Department of Defense, or the US government.