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Effect of multiple, simultaneous vaccines on polio seroresponse and associated health outcomes

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ABSTRACT

Background: Administration of multiple simultaneous vaccines to infants, children, and military recruits is not uncommon. However, little research exists to examine associated serological and health effects, especially in adults.
Method: We retrospectively examined 416 paired serum specimens from U.S. military subjects who had received the inactivated polio vaccine (IPV) alone or in combination with either 1 other vaccine (<3 group) or 4 other vaccines (>4 group). Each of the 2 groups was subdivided into 2 subgroups in which Tdap was present or absent.
Results: The >4 group was associated with a higher proportion of polio seroconversions than the <3 group (95% vs. 58%, respectively, $p < 0.01$). Analysis of the <3 subgroup that excluded Tdap vs. the >4 subgroup that excluded Tdap showed no difference between them ($p > 0.1$). However, the >4 subgroup that included Tdap had significantly more seroconversions than either the <3 subgroup that excluded Tdap or the >4 subgroup that excluded Tdap ($p < 0.01$). Overall, at least 98% of subjects were at or above the putative level of seroprotection both pre- and post-vaccination, yet at least 81% of subjects seroconverted. In an analysis of 400 of the subjects in which clinic in- and outpatient encounters were counted over the course of 1 year following vaccinations, there was no significant difference between the 2 groups ($p > 0.1$).
Conclusion: A combination of >4 vaccines including IPV appeared to have an immunopotentiation effect on polio seroconversion, and Tdap in particular was a strong candidate for an important role. The dose of IPV we studied in our subjects, who already had a high level of seroprotection, acted as a booster. In addition, there appear to be no negative health consequences from receiving few versus more multiple simultaneous vaccinations.

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1. Introduction

Recruits at all military basic training centers routinely receive three or more vaccinations within several days of arrival at the camp. Multiple simultaneous vaccinations are also very common in immunization schedules for children. Although practical in terms of time, cost, and compliance, the administration of multiple vaccinations raises questions regarding the immediate effect on the immune system, short- and long-term health concerns, and the effect of several simultaneous vaccines on the serological responses of the individual vaccines.

Strategies for study of multiple vaccinations include manipulation of timing of administration and number of vaccines given simultaneously. Pierce and Miller [1] studied Navy basic trainees, one group of which received the regular schedule of 6 vaccines in the first weeks of training and one which received only polio and influenza vaccines in the first 3 weeks and the others during weeks 5 through 9. The latter had significantly lower (approximately 20%) rates of febrile respiratory illness over the entire 10 weeks of training than the former. In this case, the number of vaccines given over the course of 9 weeks was the same but the timing affected the health outcomes. Timing was also investigated by Hotopf et al. [2], who found that receipt of multiple vaccines before deployment was associated with only 1 of the 6 adverse health outcomes that were monitored, while 5 of the 6 adverse

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outcomes were associated with receipt of the same vaccinations during deployment.

Investigating administration of multiple vaccinations with respect to the number and type of vaccines, various studies have found either diminished antibody responses [3–5], or poorer health outcomes [6] associated with various combinations of vaccines. A hypothesis for the latter of these effects in war veterans was proposed by Rook and Zumla [7], that a combination of multiple-vaccine schedules, stresses of war, and environmental exposures induced an exaggerated humoral immune response because the vaccines that had been used tend to drive a type 2 helper T cell (Th2) response, which, they argued, could contribute to chronic fatigue, mood change, and allergy. The hypothesis of the association of multiple vaccinations to Gulf War health concerns has been more recently cast in doubt [8–10], and a pediatric study showed no association of multiple vaccinations with increased illness [11].

Many studies have examined the tolerability and immune responses in children to various vaccine combinations, such as the five-component pertussis combination vaccine CPDT-IPV//PRP-T [12], or similar combinations with *Haemophilus influenzae* vaccines. Such combinations have been determined to be immunogenic and safe. A study of children receiving the recommended schedule of vaccines showed no adverse effects on neuropsychological outcomes. [13] Nevertheless, there is evidence of changes in immune response to particular vaccines when given along with others. Lower antibody titers were observed to type 3 polio virus when CPDT-IPV//PRP-T was given in the combined format [12]. Similarly, it was found, for example, that anti-polyribosylribitol phosphate (PRP) response was lower in children when DTaP-IPV-Hib (diphtheria-tetanus-acellular pertussis–inactivated polio vaccine –*H. influenzae* type b vaccine) was given with a conjugate meningococcal vaccine. [14] Likewise, PRP response was diminished when IPV rather than oral polio virus (OPV) was administered with DTaP/Hib [15].

Here we examine the effects of multiple simultaneous vaccinations on IPV-induced seroconversion and seroprotection and subsequent health outcomes in adults. We studied serological responses of individuals who received various combinations of vaccinations, all of which included IPV, and counts of a broad range of clinic encounters as defined by the *International Classification of Diseases, 9th Revision* (ICD-9). Because, as noted above, a form of tetanus/diphtheria/acellular pertussis (Tdap) has been included in many studies of multiple vaccines, we highlighted the inclusion of Tdap among the vaccine combinations.

2. Materials and methods

2.1. Ethics

The Naval Health Research Center Institutional Review Board approved the study protocol (NHRC.2011.0015), and the work was carried out in accordance with *The Code of Ethics of the World Medical Association (Declaration of Helsinki)* for experiments involving humans. The approved study protocol was also reviewed by the Centers for Disease Control and Prevention (CDC) human subjects office and was determined exempt. The subjects were pre-existing de-identified active-duty US military personnel who had provided serum at some time before entering training at a US military recruit center, had been vaccinated soon after arrival at the training center, and had provided serum after vaccination(s) in the time frames noted below, and whose relevant data had been stored the Defense Medical Epidemiological Database and made available by the Armed Forces Health Surveillance Center to the authors.

2.2. Sera

Pre-existing serum pairs were provided by the Department of Defense Serum Repository, stripped of all personally identifying information, and assigned a random identification number so that laboratory personnel were blinded to any study-related information. The Serum Repository regularly collects serum samples from all military personnel as part of its routine surveillance activities and stores them at −30 °C. The serum samples of 0.5 cc each were sent by overnight delivery from the Serum Repository to the Polio and Picornavirus Laboratory Branch, CDC, Atlanta, Georgia, for determination of neutralizing antibody titers.

2.3. Study design

Five study groups were planned, each including IPV. Group 1 was comprised of IPV alone, Group 2 of IPV and Tdap vaccine and any other single vaccine, Group 3 of IPV and any other 1 or 2 vaccines, Group 4 of IPV and 4 other vaccines including Tdap, and Group 5 of IPV and 4 other vaccines not including Tdap. Groups 1, 2, and 3 together were designated as the <3 group and Groups 4 and 5 together as the >4 group.

The subjects must have had 1 serum sample drawn before their vaccination(s) and 1 drawn after at one of three time points: 1–2 months, 3–5 months, or 6–12 months. The pre-vaccination serum sample must have been obtained less than 210 days before the vaccination(s). Data associated with each paired serum set included age, sex, race/ethnicity, military branch, and military grade, as well as outpatient and inpatient encounters in 14 ICD-9 code ranges occurring up to 1 year from the vaccination(s). The outpatient and inpatient encounters recorded under any one of these ICD-9 code ranges were summed for each subject over the course of 1 year from the vaccinations.

There were 416 subjects included in the serology analysis and 400 identified with data on outpatient and inpatient encounters (mean age 21 years, SD = 3.8).

2.4. Polio virus serotypes

Neutralizing antibody titers were determined for polio viruses types 1, 2, and 3, using the 3 Sabin vaccine strains. Stock viral cultures were maintained by passage in HEp-2C cells and frozen at −70 °C in small aliquots [16]. Laboratory personnel were blinded from any study group or patient identifier information.

2.5. Viral particle neutralization assay

Between 80 and 100 median cell culture infectious dose ($CCID_{50}$) of each poliovirus serotype and two-fold serial dilutions of serum (1:8 to 1:1024) were combined and preincubated at 37 °C for 3 h before the addition of HEp-2C cells. After incubation for 5 days at 37 °C and 5% CO_2, plates were stained with crystal violet, and cell viability was measured by optical density in a spectrophotometer. Each specimen was run in triplicate, with parallel specimens from one study subject tested in the same assay run, and the neutralization titers estimated by the Spearman–Karber method [17]. Each run contained multiple replicates of a standard antiserum starting at a 1:32 dilution to assess performance variation. The only serum titers examined were those of polio, not of other vaccines given simultaneously. A titer above the lower cutoff (1:8) was considered seroprotective, [18] a titer below 1:8 was considered negative, and the titer 1:1448 was the upper limit of the assay. Seroconversion was considered to be either a 4-fold rise in titer or a rise from any titer, other than 1:1448, to 1:1448.