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Reactogenicity of the 10-Valent Pneumococcal Conjugate Vaccine in Animal Models

Michael Walekhwa[1*], Teresa Ogeto[1], Fiona Maiyo[1], Filex Otieno[2] and Fred Kipsang[1]

[1]Department of Biomedical Sciences, School of Medicine and Health Sciences, Kabarak University

[2]Department of Pharmacology & Pharmacognosy, School of Pharmacy, Kabarak University

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ABSTRACT

Streptococcus pneumoniae poses significant global health challenges, particularly among vulnerable populations such as infants and the elderly. The 10-valent Pneumococcal Conjugate Vaccine (PCV-10) is a commonly utilized vaccination modality, necessitating a comprehensive understanding of its safety profile. This study evaluated the safety of PCV-10 through controlled in-vivo assessments, with a focus on adverse events including pain, swelling, heat, redness, and dizziness. The study employed an experimental design involving nine White New Zealand rabbits, divided into three cohorts. Each cohort consisted of two experimental and one control rabbit. PCV-10 vaccine administration replicated the infant vaccination schedule across the three cohorts, with each receiving three doses. Vaccine reactogenicity was assessed through adverse events recorded up to seven days post-administration, with parameters including redness, fever, drowsiness, appetite loss, swelling, irritability, fainting, and movement challenges. Data analysis was conducted using Microsoft Excel 2016. Results indicated that rabbits in cohort I generally exhibited mild to moderate pain and heat. Swelling and redness were mostly absent or mild after vaccine doses. Dizziness, absent after the first dose in cohort I, occurred with mild to moderate severity after subsequent doses. Rabbits in cohorts 2 and 3 experienced greater intensity of dizziness. Overall, adverse events were generally mild to moderate, varying across cohorts and doses. This study suggests a manageable reactogenicity profile for PCV-10 and recommends informing patients about possible adverse events, advising them to notify healthcare providers if such events persist.

Keywords: Pneumococcal Disease, Seroprotection, Pneumococcal Conjugate Vaccine, Reactogenicity

INTRODUCTION

The prevention of infectious diseases through vaccination remains a cornerstone of public health interventions worldwide. Among the myriad of vaccines available, the 10-Valent Pneumococcal Conjugate Vaccine (PCV-10) has emerged as a pivotal tool in combating pneumococcal infections, which are responsible for a significant global burden of morbidity and mortality, particularly among children under five years of age and the elderly population (Center for Disease Control and Prevention [CDC], 2022). Approximately, one million children are estimated to die annually from pneumococcal diseases across the world (World Health Organization [WHO], 2016). In Kenya, two children out of every 5 that visit public hospitals succumb to pneumococcal disease (O'Brien et al., 2018). Pneumococcal diseases encompass a range of illnesses, including pneumonia, meningitis, and sepsis, caused by the bacterium *Streptococcus pneumoniae* (S. pneumoniae). Given its prevalence and severity, the imperative for effective pneumococcal vaccination strategies cannot be overstated.

Pneumococcal Conjugate Vaccine is composed of polysaccharide antigens from ten distinct pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F) conjugated to a carrier protein (WHO, 2013), often CRM197, derived from *Corynebacterium diphtheria* (Whitney et al., 2006) or non-typable protein D from *Haemophilus influenza* (Odutola et al., 2015). This conjugation enhances the immunogenicity of the vaccine by eliciting a robust immune response, primarily mediated through the production of specific IgG antibodies (Whitney et al., 2006). The inclusion of these serotypes in PCV-10 is strategic, targeting the most prevalent and virulent strains responsible for invasive pneumococcal diseases, both globally and in Kenya (Lockhart, 2003). Consequently, PCV-10 has been instrumental in reducing the incidence of pneumococcal-related illnesses and mortality in vaccinated populations in Kenya.

While the efficacy of PCV-10 in conferring protection against pneumococcal diseases is well-established, understanding its reactogenicity profile is equally paramount. Reactogenicity refers to the inherent ability of a vaccine to induce adverse reactions, even though typically mild and transient, in vaccinated individuals. These reactions may manifest as local symptoms (e.g., pain, redness, swelling at the injection site) or systemic symptoms (e.g., fever, malaise) following vaccination. The reactogenicity profile of PCV-10, therefore, has significant implications for its safety, tolerability, and widespread acceptance.

A critical yet often understudied aspect influencing vaccine reactogenicity is storage time, encompassing the duration and conditions under which vaccines are stored before administration. Variations in storage time can potentially compromise the integrity and efficacy of vaccine components, including the polysaccharide antigens and carrier proteins. Such alterations may inadvertently amplify vaccine reactogenicity, posing challenges in maintaining a favorable benefit-risk profile. Kenya does not manufacture its own PCV-10 vaccines. Instead, the vaccine is imported from Germany and was introduced in 2011 as part of GAVI sponsorship and added to the National Expanded Program on Immunization (KEPI) due to the then high mortality rate of children under 5 years suffering from PD (Hammitt et al., 2014). It takes 8 weeks for the vaccine to be dispatched and cleared at the Kenyan port authorities. Throughout this period, the vaccine adjuvant molecules may settle risking vaccines losing the purity of their original constituents, potentially resulting in adverse reactions when administered to recipient. Consequently, elucidating the relationship between storage time and PCV-10 reactogenicity is imperative for optimizing vaccine storage protocols and enhancing vaccine safety profiles. Despite the pivotal role of PCV-10 in pneumococcal disease prevention, Existing literature provides fragmented insights, necessitating rigorous experimental studies to profile the reactogenicity of PCV-10. In light of the aforementioned considerations, this study aimed to investigate the reactogenicity of the 10-Valent Pneumococcal Conjugate Vaccine using White New Zealand.

METHODOLOGY

Study Design and Sample Population

Current study adopted a rigorous experimental framework as outlined by Fehrenbacher (2012). Nine sexually homogenous White New Zealand rabbits were procured and subsequently allocated into three distinct cohorts, each comprising three rabbits: two for experimental interventions and one as a control specimen.

Procurement and Husbandry of White New Zealand Rabbits

White New Zealand rabbits were sourced from the Institute of Primate Research (IPR) and were meticulously maintained in alignment with established ethical standards for animal research, as stipulated by Chave (2003). A systematic record encompassing procurement particulars, species classification, gender differentiation, nutritional protocols, and all pertinent medical or diagnostic interventions was consistently updated for all nine rabbits. Notably, experimental subjects within each cohort received a comprehensive dosage regimen of the PCV-10 vaccine, while control counterparts were administered a placebo. Housing facilities ensured segregation of experimental and control groups within designated compartments of the Biomedical Science Laboratories at Kabarak University, facilitating controlled environmental conditions.

Vaccine (Synflorix, GSK) Administration and Dosage Regimen

Vaccine vials of PCV-10 (Synflorix, GSK) with uniform production timestamps were sourced from the Unit of Vaccines & Immunization Services (UVIS) and stored within a temperature-controlled environment between 4°C and 8°C. Immunization protocols targeted the elicitation of T-cell independent, pneumococci-specific IgG within White New Zealand rabbits through the administration of PCV-10, comprising Diphtheria CRM 197 from GSK. The standard tri-dose vaccination schedule, originally designed for infant populations at weeks 6, 10, and 14 of age, was emulated across the following cohorts:

- **Cohort I**: Initiation of a 100 µL (0.34g) PCV-10 dosage was administered on day 0, paralleling the vaccine's procurement. Subsequent administrations occurred at 4-week intervals, culminating in doses at weeks 4, 8, and 12 post-commencements.
- **Cohort II**: Experimental subjects received their primary PCV-10 dose at week 4, synchronizing with the second dose of Cohort I. The subsequent regimen unfolded with dosages at weeks 8 and 12, mirroring the timeline established for Cohort I.
- **Cohort III**: The initiation of PCV-10 immunization for this cohort commenced at week 8, harmonizing with the third dose schedule of Cohort I. Consistent 4-week intervals characterized subsequent administrations at weeks 12 and 16 post-commencement.

Control rabbits across all cohorts were administered Phosphate Buffered Saline (PBS) to serve as comparative benchmarks.

Evaluation of Vaccine Reactogenicity

Assessment of vaccine reactogenicity post-administration was meticulously executed by observing and documenting immediate and up-to-seven-day post-inoculation adverse events. Comprehensive parameters encompassed manifestations such as erythema at the injection site, pyrexia, somnolence, anorexia, localized edema, agitation, syncope, mobility impairments, and any hypersensitivity reactions.

Data Analysis

Collected data were entered, cleaned, and analyzed using Microsoft excel 2016. A descriptive statistical approach was employed to characterize vaccine reactogenicity predicated on adverse event profiles, subsequently encapsulating findings within tabular representations for comprehensive interpretation and dissemination.

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RESULTS

Assessment of Reactogenicity Profile of PCV-10 Using Adverse Events

Table 1 below depicts the adverse events noted to have occurred amongst subjects before and after administration of PCV-10 and PBS. The parameters pain, swelling, heat, redness and dizziness were used to assess reactogenicity. Notably, there was absent of adverse events observed at baseline level for both experimental and control subjects; and for all control subjects after any of the three PBS doses. Pain and heat on average, were moderately recorded amongst subjects in any of the cohorts and after either of the three dose was administered. However, severity of both parameters amongst subjects in any of the cohorts and after administration of any of the doses range between mild to moderate. Swelling and redness was either absent or mild amongst experimental subjects after any of the vaccine dose was administered. Dizziness was absent after the 1st dose of vaccine amongst experimental subjects in cohort I but occurred after 2nd and 3rd doses in mild to moderate severity. Dizziness was however noted to occur with greater intensity amongst subject in cohort 2 and 3.

Table 1:
Adverse Events Experienced After Administration of Different Doses of 10vPnC Vaccine to Cohort 1, 2 & 3 of the Experimental Animals

10vPnC vaccine level	Adverse events	COHORT 1			COHORT 2			COHORT 3		
		EXP-I	EXP-II	CTRL-III	EXP-I	EXP-II	CTRL-III	EXP-I	EXP-II	CTRL-III
Baseline (Nil)	Pain	-	-	-	-	-	-	-	-	-
	Swelling	-	-	-	-	-	-	-	-	-
	Heat	-	-	-	-	-	-	-	-	-
	Redness	-	-	-	-	-	-	-	-	-
	Dizziness	-	-	-	-	-	-	-	-	-
Dose I (10vPnC)	Pain	++	+	-	++	+	-	++	+	-
	Swelling	+	+	-	+	+	-	+	+	-
	Heat	++	+	-	++	++	-	++	++	-
	Redness	-	+	-	-	+	-	-	+	-
	Dizziness	-	-	-	+++	++	-	+++	++	-
Dose II (10vPnC)	Pain	+	+	-	++	+	-	++	+	-
	Swelling	++	+	-	+	+	-	+	+	-
	Heat	+	-	-	++	++	-	++	++	-
	Redness	-	+	-	-	+	-	-	+	-
	Dizziness	+	++	-	+++	++	-	+++	++	-
Dose III (10vPnC)	Pain	+	++	-	++	+	-	++	+	-
	Swelling	-	+	-	+	+	-	+	+	-
	Heat	++	+	-	++	++	-	++	++	-
	Redness	+	++	-	-	+	-	-	+	-
	Dizziness	+	++	-	++	++	-	+++	++	-

Pain (degree of reaction to gentle hand palpation), Heat (temperature ≥40^{0}C)
-: refers to the absence of the parameter being measured
+: refers to the presence of the parameter being measured. The number of the + signs directly correlate with the degree of the parameter under evaluation.

DISCUSSION

The assessment of adverse events following the administration of the 10-Valent Pneumococcal Conjugate Vaccine (PCV-10) is critical for understanding its safety profile. In this study, parameters such as pain, swelling, heat, redness, and dizziness were rigorously evaluated to determine the vaccine's reactogenicity.

Pain

Pain emerged as a consistent but relatively mild adverse event across all cohorts following PCV-10 administration. The absence of baseline pain for both experimental and control subjects highlights the specificity of this reaction to the vaccine. Our findings resonate with other studies that have reported mild to moderate pain post-PCV-10 immunization (De Sévaux et al., 2020). The consistent presentation across cohorts arise from the fact that injections are usually painful, and the response noted is a pain reflex that is physiological.

Swelling

Swelling was predominantly mild, and in several instances, absent post-vaccination. This aligns with previous research highlighting the generally localized and benign nature of post-vaccination swelling associated with conjugate vaccines (Hammitt et al., 2018). Usually, the swelling subsides with time, but may persist in specific individuals who are sensitive to contents of the vaccine or who have been improperly injected. The absence of swelling in certain instances may also suggest that storage time might not significantly exacerbate this particular adverse event.

Heat

Elevated heat at the injection site was observed, with a spectrum ranging from mild to moderate across cohorts. This could indicate an inflammatory response, likely due to the body's immune reaction to the vaccine components. Similar observations have been noted in studies evaluating reactogenicity profiles of other conjugate vaccines, suggesting a commonality in the immunogenic response (Juergens et al., 2018).

Redness

Localized redness was predominantly mild, although its occurrence varied across cohorts. The mildness and sporadic nature of this adverse event corroborate findings from previous studies that emphasize the localized and transient nature of vaccine-induced erythema (Fortanier et al., 2019).

Dizziness

The manifestation of dizziness post-vaccination was variable across cohorts. Cohorts II and III demonstrated a heightened frequency and severity of dizziness compared to Cohort I, especially following subsequent doses. This variability underscores the potential cumulative effect of vaccine administration on neurological parameters. Previous research has explored vaccine-related dizziness, emphasizing its transient nature but also suggesting potential interactions with individual physiological responses (CDC, 2023).

CONCLUSION

In conclusion, current study elucidates a nuanced adverse event profile post-PCV-10 administration across distinct cohorts. While adverse events such as pain, swelling, heat, redness, and dizziness were predominantly mild to moderate in severity, their specific manifestation and intensity varied across cohorts.

RECOMMENDATIONS

The study findings and conclusions suggest a manageable reactogenicity profile for PCV-10 vaccine. Therefore, this study recommends that patients receiving the vaccination should be informed of the possible adverse events upon vaccination and be watchful notifying healthcare provider if they persist.

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Conflict of Interest

Authors declare no conflict of interest.

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