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Economic assessment of implementing Hexaxim® vaccine within the South African Expanded Programme on Immunisation (EPI-SA)

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Background: The South African Expanded Programme on Immunisation (EPI-SA) currently vaccinates against 10 childhood vaccine preventable diseases. Six injections are required for primary vaccination against diphtheria, tetanus, pertussis, polio, *Haemophilus influenza* type b and hepatitis B: three DTaP-IPV//Hib [Pentaxim®] doses and three monovalent Hep B vaccines to children under 12 months of age, with a seventh injection (Pentaxim® booster) at 18 months. Madhi et al (PIDJ 30:e68 2011) demonstrated no significant difference in the safety and efficacy between Pentaxim® plus monovalent Hep B and a new fully liquid hexavalent vaccine, Hexaxim® (DTaP-IPV-Hib-HepB). From a healthcare provider perspective, combination vaccines could reduce costs, simplify logistics and delivery infrastructure, and improve coverage with fewer injections. This study aimed to analyse the cost implications of a switch from the current combination of Pentaxim® plus monovalent Hep B injections, to a single Hexaxim® injection, from the public sector perspective.

Methods & Materials: Data were collected to derive direct costs, i.e. vaccines' prices (except Hexaxim®, no price yet available), transportation charges, cold chain storage, vaccine wastage rate, hazardous waste disposal and vaccine administration. All costs were calculated per dose, and expressed in South African Rand (R) (USD 1.00 = R10.19 per 2013 exchange rate). Indirect costs such as individual and societal benefits were excluded.

Results: Delivering one dose ofPentaxim® and Hep B costs R166.30. Reduced volumes result in cost reductions when using Hexaxim® for: cold storage; hazardous waste disposal; and vaccine administration, resulting in an estimated saving of R10.52 to R29.40 per dose, depending on utilisation of usable cold storage space.

Conclusion: Implementation of Hexaxim® within EPI-SA is highly recommended, because it reduces healthcare provider costs by simplifying logistics and delivery infrastructure. From a community perspective, such vaccines reduce clinic visits, vaccinators' errors, number of injections and side effects, which translate to better acceptability, convenience and increased compliance. As the use of Hexaxim® demonstrates direct and indirect cost savings, potential public sector introduction should be valued not only in terms of the price of Pentaxim® and Hep B.

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Efficacy and immunogenicity of inactivated influenza vaccine in pregnant women: A randomized, double-blind, placebo controlled trial

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Background: Pregnant women are at increased susceptibility to severe influenza-illness and are recommended by WHO to be a priority group for influenza vaccination. The aims of our study were to assess the immunogenicity of trivalent IIV (IIV3) in pregnant women vaccinated during their 2nd/3rd trimester and to calculate the vaccine efficacy (VE) to PCR-confirmed influenza illness (PCI).

Methods & Materials: A double-blind, randomized, placebo-controlled trial was undertaken in Soweto, South Africa in 2011 and 2012. 2116 confirmed HIV-uninfected pregnant women were randomized to receive either IIV3 or normal saline placebo intramuscularly. Immune responses to each vaccine-strain, using hemagglutination-inhibition (HAI) assays were measured pre-vaccination and one month post-vaccination. HAI titres of $\geq$1:40 were categorized as seroprotective and seroconversion was defined as at least a 4-fold increase in titres from pre- to post-vaccination. Participants were followed until six months post-partum for the presence of acute respiratory illness or hospitalization for acute cardio-pulmonary illness. When ILI was confirmed by a study physician oropharyngeal and nasopharyngeal swabs were collected for influenza virus testing by real-time PCR.

Results: One month post-vaccination, comparing IIV3 and placebo-recipients, the proportion of women who seroconverted were 72.5% vs. 8.1% to A/H1N1pdm09, 64.8% vs. 2.7% to H3N2, 92.3% vs. 2.0% to influenza-B strain (all comparisons $p < 0.001$). Post-vaccination, the proportion of women with seroprotective HAI titres were 93.7% vs. 48.0% for A/H1N1pdm09, 78.9% vs. 27.0% for H3N2 and 97.2% vs. 29.1% for influenza-B ($p < 0.001$ for all comparisons). The vaccine efficacy of IIV3 was 46.1% (95%CI: 6.4% to 69.0%) in protecting against PCI due to homotypic vaccine strains and 50.4% (95%CI: 14.5 to 71.2) when including the 3 non-vaccine influenza B-Yamagata cases that exclusively occurred among the placebo-recipients. The dominant strain of influenza virus identified was H3N2 which composed 22 (57.9%) cases in the placebo group and 10 (52.6%) in the vaccinees. 174 and 181 IIV-recipients and placebo-recipients, respectively, had at least one ILI medical visit. IIV3 was not associated with reduction of first episode of ILI (VE: 4.6%; 95%CI: -15.4% to 21.1%).

Conclusion: IIV3 vaccination of pregnant women induced good humoral immune responses likely to be associated with protection against influenza virus infection.

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DNA-launched sindbis virus based replicon encoding the yellow fever virus ED-lll protein

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Background: Yellow fever virus (YFV) is a positive sense single-stranded RNA virus that is transmitted by mosquitoes and is endemic in the tropical regions of Africa and South America. The World Health Organization has estimated the annual prevalence of yellow fever to be 200 000 cases, of which more than 90% is attributed to Africa. Although highly efficacious live attenuated vaccines are available, use of the vaccines in immunocompromised individuals are contra-indicated and, although rare, vaccine-associated viscerotropic adverse events have been reported. Hence development of a safer alternative that can complement the use of the live vaccines would have application. The aim of this study was to prepare a DNA-launched Sindbis based replicon encoding the ED-lll protein of YFV and to characterize the expression of the ED-lll protein in transfected cells prior to evaluation as a candidate vaccine in an animal model.

Methods & Materials: The gene encoding wild-type Asibi strain YFV ED-lll protein was codon optimized and synthesized by GenScript. The gene was cloned into a DNA based expression system carrying the Sindbis genome and designated pSinED-lll. The pSinED-lll replicon was purified and utilized for the transfection of BHK21 cells. A similarly constructed DNA launched Sindbis replicon expressing a reporter gene, green fluorescing protein, was used as a transfection control. Transfected BHK cells were assayed 24 hours post-transfection for the expression of the ED-lll protein using an indirect immunofluorescence assay (IFA). Anti-his_6 mouse monoclonal antibodies were used to detect the C-terminal histidine tag. In addition, sera obtained from mice immunized with bacterially expressed ED-lll, and shown to have an IgG antibody response to ED-lll, were used to detect ED-lll protein in transfected cells.

Results: The presence of the gene encoding the ED-lll protein in the construct was confirmed by PCR and sequencing using primers flanking the cloning site. The detection of the C-terminal histidine tag and the ED-lll protein in an indirect IFA confirmed the expression of YFV ED-lll protein in mammalian cells.

Conclusion: IFA confirmed the expression of ED-lll protein from pSinED-lll. Therefore the immunogenicity of the DNA-launched Sindbis virus based replicon will be evaluated using mice.

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A randomized, double-blind, controlled trial to evaluate the safety and immunogenicity of killed oral cholera vaccine (Shanchol®) in healthy individuals in Ethiopia

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Background: The WHO has prequalified a killed oral cholera vaccine (OCV) in 2011, which has been a key measure in facilitating its use as part of a comprehensive package including water and sanitation measures to cholera epidemic affected areas such as Guinea and Haiti. A recent phase 3 trial enrolling approximately 70,000 adults and children in India demonstrated a 65% cumulative protective efficacy over 5 years. This is the first trial to evaluate the safety and immunogenicity of a two dose OCV regimen in an African population. The vaccine has been evaluated in a large number of human subjects in India, Vietnam, and Bangladesh, where it has demonstrated safety, immunogenicity, and clinical protective efficacy. Though we do not expect the vaccine to act differently in the Ethiopian population, we aim to confirm our understanding of OCV use in healthy individuals aged 1 year and above in Africa.

Methods & Materials: This was an individually randomized, controlled, double blinded, placebo controlled trial in 216 subjects, equally divided among healthy children and adults. Participants received two doses of vaccine or placebo. Blood was drawn to measure vibriocidal antibody response before the first dose (day 0), before the second dose (day 14), and on day 28.

Results: Preliminary unblinded safety data suggests that the vaccine is safe, with only 8 adverse events (AE) for both vaccine and placebo groups. All AEs were mild, self resolved, and were not clustered following either dose. Full analysis is to be completed in March, 2014, at which time results comparing vaccine to placebo recipients for safety and vibriocidal response will be available. This serves as an important step towards a mass vaccination demonstration project, aimed to strengthen national cholera surveillance. These findings, alongside concurrent efforts in other high risk regions, can pave the way for the integration of OCV in both endemic and outbreak settings in Ethiopia, Africa and beyond.

Conclusion: Adverse reactions were observed with similar frequency among vaccine and placebo recipients in both age groups. Adverse events (AE) were reported within 28 days of any dose in 0% and 1.8% of vaccinees and 5.6% and 1.8% of placebo recipients in adults and children respectively. All AEs were mild and self resolving. A robust immune response against Vibrio cholerae O1 was observed, with an 81% and 77% seroconversion rate in adults and children. These findings, alongside concurrent efforts in other high risk regions, can pave the way for the integration of OCV in both endemic and outbreak settings in Ethiopia, Africa and beyond. As the WHO and partners work to create an international stockpile, safety and immunogenicity data outside of Asia will be support-