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Association between prenatal exposure to indoor residual spraying insecticides and infection rates among South African children participating in the Venda Health Examination of Mothers, Babies and their Environment (VHEMBE)

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Abstract

In 2021, 53 countries conducted indoor residual spraying (IRS), the application of insecticides such as dichlorodiphenyl trichloroethane (DDT) or pyrethroids to the walls of homes to control malaria. Animal studies show that these insecticides can increase susceptibility to infections but only one human study was conducted in a population from an area where IRS is applied. The aim of the present study was thus to investigate whether maternal exposure to DDT, its breakdown product dichlorodiphenyl dichloroethylene (DDE) or pyrethroid insecticides is associated with symptoms of infection among children living in a region of South Africa were IRS is conducted annually. As part of the Venda Health Examination of Mothers, Babies and their Environment (VHEMBE) we measured maternal serum concentrations of DDT and DDE, and urinary concentrations of four pyrethroid metabolites in peripartum samples. Poisson regression models with robust variance estimates were used to investigate associations with the rates of infection symptoms between ages 3.5–5 years among 629 children as assessed based on

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Declaration of competing interest

The authors declare no competing interests.

CRediT authorship contribution statement

Brooklyn Davis: Methodology, Software, Validation, Formal analysis, Writing – original draft, Visualization. **Brenda Eskenazi:** Investigation, Writing – Review & Editing, Funding acquisition. **Riana Bornman**: Investigation, Writing – Review & Editing, Project administration. **Muvhulawa Obida:** Investigation, Project administration. **Joanne Kim**: Methodology, Software, Writing – Review & Editing. **Jonathan Chevrier:** Conceptualization, Methodology, Investigation, Writing – Review & Editing, Supervision, Project administration, Funding acquisition.

Appendix Supplementary data

Supplemental Tables and available in the Appendix.

caregiver interviews. Multiple pyrethroid metabolites were associated with infection symptoms. For instance, *cis*-DBCA was associated with increased rates of ear infection (Incidence Rate Ratio for a 10-fold increase (IRR_{10})=1.4; 95% Confidence Interval (CI)=1.0, 2.1) and persistent diarrhea (IRR_{10}=2.1; 95% CI=1.2, 3.9), *trans*-DCCA was associated with increased rates of colds in children (IRR_{10}=1.3; 95% CI=1.0, 1.6) and persistent fever (IRS_{10}=1.4; 95% CI=1.0, 2.0), and 3-PBA was associated with increased rates of persistent fever (IRR_{10}=1.8; 95% CI=1.0, 3.0). We found limited evidence of association between maternal DDE and DDT serum concentrations and infection symptoms. Results suggest that prenatal exposure to pyrethroid insecticides may be associated with childhood infections among children from an area where IRS is conducted.

Keywords

DDT/DDE; Pyrethroids; Diarrhea; Fever; Infections; Respiratory symptoms

1. Introduction

According to the World Health Organization (WHO), in 2021, 53 countries used indoor residual spraying (IRS), the application of insecticides to the interior walls of homes to control malaria vectors (1). There are an estimated 247 million new cases of malaria annually, with 95% occurring in Africa (1). Malaria is of particular importance on the continent of Africa where 5.3% of the population at risk is protected by IRS (1). Globally, IRS is the second most widely implemented vector control intervention by malaria programmes (1). However, IRS results in high exposure to insecticides for 80 million people in low- and middle-income countries (LMICs), most of whom are Africans (1). The insecticide dichlorodiphenyltrichloroethane (DDT) has been banned for decades in Western countries but is still part of IRS policy in 8 countries, including South Africa (1). Pyrethroids are one the main classes of insecticides utilized for IRS globally, with deltamethrin and cypermethrin being primarily used in South Africa (1-3). Although IRS is effective in controlling malaria, there is limited research regarding its potential side effects.

In laboratory animals, exposure to DDT and pyrethroids alters immune function and increases viral load and mortality following infection (4-7). For instance, a study conducted by Banerjee et al. found that mice who were fed DDT were more susceptible to human leprosy bacilli infections relative to controls (4). Rehman et al. (7) infected mice with *Candida albicans*, a common pathogenic yeast, alone and in combination with deltamethrin and found significantly more colony-forming units (a measure of the extent of infection) in the liver and spleen of deltamethrin-treated mice relative to controls. In another study, mice orally exposed to deltamethrin had an inhibited immune response to malaria infection leading to a more rapid increase in parasitemia that peaked earlier relative to controls (5). These finding are of potential concern because most countries that apply DDT and pyrethroids as part of their IRS programs also experience high rates of infectious diseases. Indeed, the WHO reports that infectious diseases account for more than a third of deaths among children under the age of 5 in LMICs (8) with children from Sub-Saharan Africa being disproportionately affected (9).

Although DDT and pyrethroids cross the placental barrier, few studies have investigated the association between prenatal exposure to these insecticides and infections among children. A study conducted in Mexico found no association between maternal serum concentrations of *p,p′*-DDT during pregnancy and rates of lower respiratory tract infections (LRTIs) in 1–2 year old boys (11). Similarly, in the only study that investigated associations between prenatal exposure to DDT and childhood infections in a population located in an area where IRS is practiced, we found no association between maternal *p,p′*-DDT serum concentrations and respiratory infection symptoms, fever or ear infections in 1–2 year old South African children participating in the Venda Health Examination of Mothers, Babies and their Environment (VHEMBE) (10).

The literature is more mixed for dichlorodiphenyl dichloroethylene (DDE), DDT's breakdown product. In the Mexican cohort mentioned above, researchers observed no association between maternal *p,p′*-DDE concentrations and LRTI incidence rates in 2-year olds (11). In contrast, prenatal exposure to *p,p′*-DDE was associated with a higher relative risk of recurrent LRTI among Spanish children ages 12–14 months (12). Evidence also suggested that maternal *p,p'*-DDE serum concentrations were associated with higher incidence rates of LRTIs and upper respiratory tract infections (URTIs) as well as ear and gastrointestinal infections among Inuit children at age 12 months (13-15). However, indications of exposure-response relations were limited. Finally, in the VHEMBE study, maternal *p,p'*-DDE serum concentrations during pregnancy were associated with higher incidence rates of persistent fever among 1–2 year old children (10).

To our knowledge, the VHEMBE study conducted the only investigation of associations between prenatal pyrethroid exposure and childhood infections; limited evidence was found for higher rates of fever and sore throat among children aged 1–2 years when stratifying for maternal urine collection timing (10). As we are not aware of any study investigating associations between prenatal exposure to IRS insecticides and child infections beyond age 2, it is not clear whether associations with DDE persist at older ages or if relations with pyrethroids and DDT may emerge later on in childhood.

The aim of the current study was thus to determine whether prenatal exposure to DDT, DDE and pyrethroids was associated with elevated rates of symptoms of infection among South African children aged between 3.5 and 5 years living in a region where IRS is conducted.

2. Material and methods

2.1 Study participants and recruitment

This study is based on data from VHEMBE, a birth cohort study located in the Vhembe district of Limpopo Province in South Africa. In this area, IRS is conducted by the Limpopo Malaria Control Programme whose staff spray the interior walls and eaves of residences with DDT or pyrethroids annually. The study area presents a natural experiment where variations in altitude influence temperature, mosquito vector survival and malaria transmission, and thus includes both sprayed and unsprayed regions.

Women were recruited into the study between August 2012 and December 2013, when they presented for delivery at Tshilidzini Hospital in the town of Thohoyandou. Eligibility criteria for the study included: being at least 18 years of age, speaking Tshivenda at home as the main language, living within 20 km of Tshilidzini Hospital and planning to remain in the area for the next 2 years, not contracting malaria during the index pregnancy, having contractions at least 5 minutes apart (to ensure that participants were capable of giving consent) and giving birth to a viable singleton child. Of the 1,648 mothers screened by the study staff, 920 met the eligibility criteria. Of those, 752 (82%) completed a baseline questionnaire and provided blood samples at delivery for DDT and DDE exposure quantification. Follow-up assessments occurred at 1 week, as well as 1, 2, 3.5 and 5 years postpartum. A total of 640 children were followed to age 5 years (88% retention, excluding 25 child deaths), 629 of whom were accompanied by a primary caregiver who completed a questionnaire on infection symptoms. This included mothers (n=537), fathers (n=7) and others (n=85), most of whom were grandmothers. Of the 629 children followed up to age 5 years, 620 of their mothers provided a sufficient urine sample at the time of delivery for pyrethroid metabolite quantification. Additionally, a single urine sample did not meet quality control standards for the measurement of the pyrethroid metabolite 3-phenoxybenzoic acid (3-PBA) and was excluded from analyses.

Informed consent was obtained from all participants prior to data collection and the study was approved by the Institutional Review Boards of McGill University, the University of California, Berkeley, the University of Pretoria, the Limpopo Department of Health and Social Development, and Tshilidzini Hospital.

2.2 Data collection and measurement

Delivery Visit.—Questionnaire-based interviews were administered by bilingual study staff in Tshivenda, the most commonly spoken language in the Vhembe district. Mothers were first interviewed prior to discharge from the hospital to collect information on demographics, socioeconomic status, pregnancy history, health, nutrition and personal habits. We defined poverty as having a household income below the South African mid-2013-year food poverty level of 386 Rand/month/person (16). Maternal energy intake was estimated by a South African nutritionist based on a validated quantitative questionnaire (FoodFinder3 software, South Africa Medical Research Council/WAMTechnology, Stellenbosch, South Africa) (17). Low energy intake was defined based on U.S. Institute of Medicine guidelines for pregnant women (18) as described by Huang et al. (10).

Infant birthweight, gestational age at birth and method of delivery were obtained from maternal and child medical records by two Registered Nurses who were blind to participants' exposure status. Child birthweight was measured by hospital staff at delivery using a Tanita BD-815U neonatal scale (Tanita Corporation of America, Inc., Arlington Heights, Illinois). Gestational age at birth was determined based on the date of last menstrual period, as described in Chevrier et al. (3). Maternal HIV status was ascertained from self-report or from use of anti-viral drugs ascertained from medical records abstracted by Registered Nurses. Duration of non-exclusive breastfeeding was determined based on data from the 1-, 2- and 3.5-year visit questionnaires.

5-year Visit.—At the 5-year visit, a questionnaire was administered to the child's primary caregiver to collect data on the number of occurrences of infection symptoms since the prior study visit. Prior visits occurred at age 3.5 years for 626 children and at age 2 years for 3 children who did not complete a 3.5-year visit. Infection symptoms included episodes of persistent fever lasting 4 or more days, diarrhea, persistent diarrhea lasting 4 or more days, ear infections, colds and severe sore throats. Potential determinants of infections were extracted from the 5-year questionnaire, including crowding (household size and the number of individuals sleeping in the same room as the child) and exposure to indoor smoking. Additionally, information was collected on whether the primary caregiver had lived with the child all the time since the last study visit and on interviewers' perception of the quality of the answers provided by the caregivers. These reliability ratings were categorized as "high quality," "generally reliable" and "questionable".

Serum DDT/E Measurements.—Maternal blood samples collected at delivery were immediately processed and stored at −80°C until shipment on dry ice to analytical laboratories. Emory University's Environmental Health Laboratory (Atlanta, Georgia) measured p,p′-DDT, p,p′-DDE, o,p′-DDT, and o,p′-DDE in serum via gas chromatography–tandem mass spectrometry (GC-MS/MS) with isotope dilution quantification (19). Limits of detection (LODs) were 0.01 ng/mL (o,p′-DDE, o,p′-DDT, and p,p′-DDT) and 0.03 ng/mL (p,p′-DDE). The corresponding limits of quantification (LOQs) were 0.05 ng/mL and 0.15 ng/mL. As o,p′-DDE was only quantified in 16% (n=102) of samples, it was excluded from further analyses. DDT and DDE were lipid-corrected and expressed in ng/g lipid. Total lipid concentrations were estimated based on triglycerides and total cholesterol serum levels (Roche Chemicals, Indianapolis, Indiana) (20).

Urinary Pyrethroid Metabolite Measurements.—The maternal urine samples collected at the time of delivery were immediately processed and stored at −80°C. Samples were shipped on dry ice to the Centre de Toxicologie du Québec of the Institut National de Santé Publique du Québec (Québec City, Québec, Canada), where the following five pyrethroid metabolites were measured via gas chromatography-mass spectrometry (19): 4-fluoro-3-phenoxybenzoic acid (4-F-3-PBA), *cis*-3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropane carboxylic acid (*cis*-DBCA), *cis*-3-(2,2,-dicholorvinyl)-2,2-dimethyl-cyclopropane carboxylic acid (*cis*-DCCA), *trans*-3-(2,2,-dicholorvinyl)-2,2-dimethyl-cyclopropane carboxylic acid (*trans*-DCCA) and 3-PBA. *cis*-DBCA is a metabolite of the pyrethroid insecticide deltamethrin, while *cis*-DCCA, *trans*-DCCA, and 3-PBA are nonspecific metabolites of several pyrethroid pesticides, including permethrin, cypermethrin, and cyfluthrin (21). LODs were 0.005μg/L (4-F-3-PBA), 0.0025μg/L (*cis*-DBCA), 0.0045μg/L (*cis*-DCCA), 0.0038 μg/L (*trans*-DCCA), and 0.0047μg/L (3-PBA). Corresponding LOQs were 0.011μg/L, 0.0082 μg/L, 0.015 μg/L, 0.013 μg/L and 0.016 μg/L, respectively. Concentrations of 4-F-3-PBA were only quantified in 8% (n=50) of samples and were thus excluded from analyses. Pyrethroid metabolite concentrations (expressed in μg/L) were corrected for urine dilution based on specific gravity, which was measured using an Atago PAL-10S (Atago, Tokyo, Japan) refractometer.

2.3 Statistical analysis

For all analytes, we used machine-read values for concentrations between the LOD and the LOQ. We imputed values below the LOD at random based on a log-normal probability distribution whose parameters were estimated via maximum likelihood methods (22). To reduce the influence of outliers, analyte concentrations were log-10 transformed. We used one-way analysis of variance (ANOVA) to examine bivariate associations between categorical variables and analyte concentrations and Fisher's Exact Test to examine bivariate associations between categorical variables and infection symptoms. We determined associations between analyte concentrations and rates of infection symptoms using Poisson regression models with robust (Huber-White) variance estimates. We categorized outcomes based on the number of episodes of persistent fever (0, 1, ≥2 events), diarrhea (0, 1, 2, ≥3 events), persistent diarrhea (no, yes), ear infection (0, 1, 2, ≥3 events), cold (≤2, 3–5, ≥6 events) and severe sore throat (0, 1, ≥2 events). Although we aimed to administer questionnaires at specific ages, the exact ages varied between children. An offset was included in the Poisson models to account for the different follow up times.

We identified potential confounders using directed acyclic graphs. These included maternal age (<25 years, 25–35 years, >35 years), education level (<grade 12, grade 12, >grade 12), married or living as married (no, yes), parity (0, 1, ≥2 children), HIV status (negative, positive), maternal smoking (no, yes), alcohol consumption (no, yes), energy intake during pregnancy (insufficient, sufficient); household food poverty level (below, above); child sex (male, female), breastfeeding duration (≤18 months, >18 months) and exposure to tobacco smoke (no, yes); and crowding as represented by the number of people living with the child (household size) (1–4, 5–8, 9–12, ≥13 people) and the number of people who shared sleeping quarters with the child (≤2, 3–5, 6–8, ≥9 people). Given the large number of potential confounders, we included in final models variables that were moderately associated ($P < 0.20$) with at least one of the exposures and one of the outcomes. Final models included maternal age, education, married or living as married, HIV status, energy intake during pregnancy, child sex, and breastfeeding duration. Because breastfeeding duration may either be on an open non-causal path if residual confounding by socio-economic status (SES) remained or an intermediate between exposures and outcomes, we conducted sensitivity analysis by re-running models without adjusting for breastfeeding.

Variables with missing data (no more than 2%) were imputed at random based on observed probability distributions. We assessed effect measure modification by child sex, household food poverty and maternal energy intake during pregnancy by including cross-product terms. These variables were selected based on prior studies in the VHEMBE cohort and other populations that suggested that poverty and malnutrition may augment the adverse effect of environmental exposures (10-12) and evidence that DDT/E and pyrethroids may have sexually dimorphic effects (3, 23, 24). In sensitivity analyses, we used zero-inflated Poisson models to account for the possibility that caregivers who did not live continuously with the child may have missed episodes of infection. Zero-inflated models included as independent variables whether respondents continuously lived with the child, child household size and the reliability score described above. Data analysis was conducted using RStudio version

1.6.1 (RStudio, PBC, Boston, Massachusetts) and Stata version 16.1 (StataCorp, College Station, Texas).

3. Results

3.1 Participant characteristics

Table 1 shows the characteristics of participants included in this analysis. All participants were black/of African origin. At childbirth, most women were under the age of 25 years (51%), did not have a high school-level education (57%), were unmarried (54%) and were parous (58%). The majority of mothers did not drink alcohol (94%), were not around others who smoked (62%) and all but one did not smoke during pregnancy. Poverty and malnutrition were common, with 61% of participants being classified below the South African food poverty level and 69% of mothers having insufficient energy intake during pregnancy. Overall, 12% of mothers were HIV positive at delivery, though few children (1%) sero-converted. Half of the children were male (51%), about 4 in 10 breastfed for greater than 18 months (41%) and 24% were born via caesarean section. Additionally, 98% of the children attended either daycare or school. The mean follow-up time between the 3.5- and 5-year questionnaires was 580 days.

3.2 Peripartum serum DDT/E and urinary pyrethroid metabolite concentrations

Table 2 summarizes the distribution of the maternal peripartum analyte concentrations, as well as detection and quantification frequencies. The geometric means of *p,p'*-DDE, *o,p'*-DDT and *p,p'*-DDT serum concentrations were 296.4, 9.3 and 72.0 ng/g lipid respectively. These values were 0.3, 0.5, 0.5 and 1.1 ug/L for *cis*-DBCA, *cis*-DCCA, *trans*-DCCA and 3-PBA respectively. With the exception of o,p'-DDT (91% detection) and p,p'-DDT (98% detection), the concentrations of all analytes for all participants included in the present analysis were above the LOD. DDT/E (r=0.69–0.85, $P < 0.05$) and pyrethroids (r=0.33–0.87, $P < 0.05$) were highly inter-correlated within but not between (r=0.03–0.07, $P > 0.05$) insecticide classes. Higher *p,p'*-DDE as well as all pyrethroid metabolite concentrations, except *cis*-DBCA, were associated with higher parity (Supplemental Tables 1.1 and 1.2). *o,p'*-DDT and *cis*-DCCA were also associated with the mother being married or living as married, *cis*-DCCA and 3-PBA were associated with older maternal age at delivery, and 3-PBA was associated with HIV positive status. Female children, compared to males, were exposed prenatally to higher levels of *o,p'*-DDT and *p,p'*-DDT but not *p,p'*-DDE and maternal concentrations of *trans*-DCCA were higher among children breastfed for more than 18 months.

3.3 Childhood Infection Symptoms

Infection symptoms determined over an average of 1.6 years (standard deviation=0.2), for a total of 999 child-years. Incidence rates (IR) were highest for colds, with 1.4 (95% Confidence Interval (CI)=1.3, 1.5) episodes per child-year, followed by diarrhea, ear infection, severe sore throat, and persistent fever with 0.3 (95% CI=0.3, 0.3), 0.2 (95% CI=0.1, 0.2), 0.1 (95% CI=0.1, 0.1) and 0.1 (95% CI=0.1, 0.1) events per child-year, respectively (Table 3). Persistent diarrhea was the least common. Greater maternal education was positively associated with number of colds and diarrhea, being married or living as

married was associated with persistent fever, persistent diarrhea and diarrhea, as well as greater parity being associated with persistent diarrhea (Supplemental Table 2.1 and 2.2). Children who breastfed for ≤18 months were more likely to have experienced persistent diarrhea and had a greater number of cold episodes. Being born prematurely was also associated with more frequent diarrhea. The number of people who smoked inside the child's home was associated with greater president fever and severe sore throat. Finally, children who slept in the same room as others experienced more episodes of persistent fever.

3.4 Associations between maternal peripartum DDT/E and pyrethroid concentrations and infection symptoms

As shown in Table 4, we found limited evidence of associations between DDT or DDE and symptoms of infection. For the pyrethroid metabolites, a 10-fold increase in maternal urinary concentration of *cis*-DBCA was associated with a doubling in the rates of persistent diarrhea (IRR_{10}=2.1; CI=1.2, 3.9) and a 40% increase (IRR_{10}=1.4; 95% CI=1.0, 2.1) in the rates of ear infections. Persistent fevers were also positively associated with concentrations of 3-PBA (IRR_{10}=1.8; 95% CI=1.0, 3.0). In addition, a 10-fold increase in concentrations of *trans*-DCCA was associated with a 40% increase in rates of persistent fevers (IRR_{10}=1.4; 95% CI=1.0, 2.0) and a 30% increase in rates of colds (IRR_{10}=1.3; 95% CI=1.0, 1.6). Results from the adjusted Poisson models without breastfeeding duration as a confounder were similar to those that included the variable (Supplemental Table 3.1 and 3.2). Results from the zero-inflated Poisson models were also similar to those from standard Poisson models (Supplemental Table 4.1 and 4.2).

When investigating effect modification, we found positive associations between *p,p'*-DDT and rates of persistent diarrhea in female children (IRR_{10}=1.6; 95% CI=1.0, 2.6); interaction p-value (P_{int})=0.01) compared with male children (IRR_{10}=0.6; 95% CI=0.3, 1.1) and between *p,p'*-DDE and severe sore throats in male children (IRR_{10}=1.7; 95% CI=1.1, 2.7; P_{int}=0.04) compared to female children (IRR_{10}=0.9; 95% CI=0.6, 1.4) (Supplemental Table 5). Similarly, we found some evidence of effect modification by food poverty in that *p,p'*-DDT and rates of severe sore throats were positively associated only among children from households that were below the food poverty level (IRR_{10}=1.4; 95% CI=1.0, 2.1; P_{int}=0.05) compared with those above (IRR_{10}=0.9; 95% CI=0.6, 1.2). In addition, we found association between maternal urine 3-PBA concentrations and rates of severe sore throats only among children whose mothers had sufficient energy intake during pregnancy (IRR_{10}=1.6; 95% CI=1.0, 2.9; P_{int}=0.06) compared to those who did not (IRR_{10}=0.5; 95% CI=0.2, 1.2). Though we observed the individual associations described above, we found no consistent patterns across strata for any of the three potential effect modifiers.

4. Discussion

We found that maternal peripartum urine concentrations of multiple pyrethroid metabolites were associated with several symptoms of childhood infections; prenatal exposure to the pyrethroid metabolite *cis*-DBCA was associated with increased rates of ear infections and persistent diarrhea, *trans*-DCCA was associated with increased rates of persistent fevers and colds, and 3-PBA was associated with elevated rates of persistent fevers. These findings

differ from those of Huang et al., the only other study to investigate prenatal exposure to pyrethroids and childhood infections, which found no evidence of associations between maternal urinary concentrations of pyrethroid metabolites and rates of childhood infection symptoms in VHEMBE children at 2 years of age (10). However, our results are in line with animal studies which found that exposure to deltamethrin increased susceptibility to certain infections (5, 7). *cis*-DBCA and 3PBA both devolve from deltamethrin with cis-DBCA being a metabolite specific to deltamethrin.

We also found some evidence of an association between maternal *p,p'*-DDE serum concentrations and rates of persistent fever in children. These results are consistent with prior research on DDE that has reported associations between *p,p'*-DDE and LRTIs, URTIs, persistent fevers, and ear infections in children 2 years of age and younger (10, 12-15). In particular, Huang et al. found that a 10-fold increase in maternal *p,p'*-DDE was associated with an IRR_{10} of 1.2 (95% CI=1.0, 1.5) for persistent fever in 1–2 year old VHEMBE children (10), a point estimate that is identical to the one we report here among children aged 3.5-5 years (IRR_{10}=1.2; 95% CI=0.9, 1.6). The slightly wider confidence interval in the present study is likely due to the smaller rate of persistent fever between 3.5 and 5 years relative to age 1 to 2 years. Indeed, in the present study, children experienced 0.1 (95% CI=0.1, 0.1) episodes of persistent fevers per child-year (n=91 episodes) whereas Huang et al. reported 0.3 (95% CI=0.2, 0.3) episodes per child-year (n=269 episodes). This trend, which was also observed for other infection symptoms such as diarrhea, persistent diarrhea and colds, was expected given that younger children are generally more susceptible to infections. However, we found no associations between maternal DDT serum concentrations and infection symptoms in children, which is consistent with prior research conducted by Huang et al. (15) as well as by Cupul-Uicab et al. in a study of 1–2 year old boys from Chiapas, Mexico (11).

This study has several strengths. To our knowledge, it is the first investigation of associations between prenatal exposure to DDT/E and pyrethroids and infection symptoms in children aged above age 2, and the second study conducted in a population residing in an area where IRS is used. In the study by Cupul-Uicab et al. conducted in Mexico, DDT had not been used for IRS after 2000 (25). In contrast, other studies were conducted in populations that banned DDT use in the 1970s (26, 27). While prior research has almost exclusively focused on respiratory infections, the current study is also one of the few to have investigated associations between DDT/E or pyrethroid exposure and gastrointestinal infections (i.e. diarrhea and persistent diarrhea). Investigating these outcomes is of particular importance in LMICs since gastrointestinal infections are a leading causes of infectious disease-related death among young children, with diarrheal diseases alone accounting for 9% of deaths among children below age 5 years (8). In addition, analytes were measured by experienced laboratories using state-of-the-art methods and equipment, resulting in low limits of detection; we also had a high retention rate, with more than 85% of children still alive being followed from birth through age 5 years; and we had detailed and nearly complete information on multiple potential confounders including maternal demographics, lifestyle and nutrition, household income and crowding as well as child characteristics and environmental tobacco smoke exposure.

This study also has some limitations. For instance, the fact that data on child infection symptoms were based on caregiver reports may have introduced measurement error. However, any misclassification would be expected to be non-differential due to study participants being blinded to their analyte concentrations and to the specific research questions investigated here. This generally results in a bias towards the null and would thus not be expected to explain the associations reported in this study. Nonetheless, we attempted several strategies in order to mitigate the potential impact of misclassification. First, we only included in our study children whose respondents were primary caregivers. Respondents who did not identify as such were excluded even if they regularly lived with children. In addition, in order to account for possible underreporting, we ran zero-inflated Poisson models in sensitivity analyses and included potential markers of caregiver's recollection as independent variables. We also note that several of the symptoms that we considered, such as persistent fevers, persistent diarrhea, ear infections and severe sore throat, represent more severe symptoms that may be more likely to be accurately remembered and may thus be less prone to misclassification. The fact that we primarily found associations with these more memorable outcomes may supports this hypothesis. In addition, the short elimination half-life of pyrethroids (approximately 5-13 hours) may present challenges for exposure assessment (28, 29). However, the intraclass correlation coefficients for repeated spot urine measurements of pyrethroid metabolites have been shown to vary greatly (from 0.21 to 0.85) between populations (30, 31), suggesting that the reliability of a single measurement may differ according to the exposure setting. In the VHEMBE population, storage of pesticide containers and self-reported use of pesticides, which are indicators of regular pesticide use, were both associated with greater maternal pyrethroid metabolite concentrations, suggesting that a single measurement may represent longer-term exposure in this population (32). The unique setting, in which IRS insecticides are purposefully used so that residues remain inside homes for an extended period of time may contribute to this observation. Finally, due to financial constraints, we could not account for postnatal exposure, which may also be associated with childhood infections. However, previous results from the VHEMBE cohort indicated that maternal serum concentrations of *p,p'*-DDT and *p,p'*-DDE were highly correlated with those of children at 1 and 2 years (r=0.87–0.98) (33), suggesting that teasing out the effects of prenatal and postnatal exposure may be difficult in this population. In addition, weak to moderate correlations (r = 0.06–0.25) have been reported between pyrethroid metabolite concentrations during pregnancy relative to those measured among 5 year old children (34) suggesting that confounding by postnatal exposure may be unlikely for this insecticide class. This said, we cannot exclude the possibility that our findings may be due to uncontrolled confounding or chance. Additional studies should be conducted to confirm our findings.

5. Conclusion

In conclusion, we found that prenatal exposure to DDE and pyrethroids may be associated with higher rates of childhood infection symptoms among South African children 3.5 to 5 years old from an area where IRS is conducted. Our study helps to fill an important research gap given the limited information available on the relation between exposure to IRS insecticides and immune function in children. These results have important public health

implications, given the high burden of morbidity and mortality caused by communicable diseases in South Africa and other IRS areas. Results may thus help inform global and national policy makers in defining and implementing sustainable malaria control interventions. Given the widespread use of pyrethroids in agriculture and retail products available to the public both in low- and high-income countries, findings may also have implications beyond the use of IRS. Similar research in other populations is thus warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Access to data and computing code may be discussed by contacting the corresponding author.

Abbreviations

3-PBA	3-phenoxybenzoic acid
4-F-3-PBA	4-fluoro-3-phenoxybenzoic acid
ANOVA	Analysis of variance
CI	Confidence interval
***cis*-DBCA**	cis-3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropane carboxylic acid
***cis*-DCCA**	cis-3-(2,2,-dicholorvinyl)-2,2-dimethyl-cyclopropane carboxylic acid
DAG	Direct acyclic graph
DDD	Dichlorodiphenyldichloroethane
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
DDT/E	Dichlorodiphenyltrichloroethane and dichlorodiphenyldichloroethylene

GM	Geometric mean
GC-MS/MS	gas chromatography–tandem mass spectrometry
GSD	Geometric standard deviation
HIV	human immunodeficiency virus
IARC	International Agency for Research on Cancer
IR	Incidence rate
IRR	Incidence rate ratio
IRR_{10}	Incidence rate ratio for a 10-fold increase
IRS	Indoor residual spraying
ITN	Insecticide-treated bed net
IVM	Integrated vector management
LLIN	Long-lasting insecticidal net
LMIC	Low- and middle-income country
LOD	Limit of detection
LOQ	Limit of quantification
LRTI	Lower respiratory tract infection
P_{int}	P-value for interaction
POP	Persistent organic pollutant
RR	Relative risk
SES	Socio-economic status
***trans*-DCCA**	trans-3-(2,2,-dicholorvinyl)-2,2-dimethyl-cyclopropane carboxylic acid
URTI	Upper respiratory tract infection
VHEMBE	Venda Health Examination of Mothers, Babies and their Environment
WHO	World Health Organization

References

1. World Health Organization. World malaria report 2022. Geneva, Switzerland: World Health Organization; 2022.
2. Vector Biology and Control Unit, Division of Healthy Environments and Sustainable Development. Implementation of Indoor Residual Spraying of Insecticides for Malaria Control in the WHO

African Region Report. Brazzaville, Republic of Congo: World Health Organization Regional Office for Africa; 2007.

3. Chevrier J, Rauch S, Obida M, Crause M, Bornman R, Eskenazi B,. Sex and poverty modify associations between maternal peripartum concentrations of DDT/E and pyrethroid metabolites and thyroid hormone levels in neonates participating in the VHEMBE study, South Africa. Environ Int. 2019;131.
4. Banerjee BD, Koner BC, Pasha ST. Influence of DDT Exposure on Susceptibility to Human Leprosy Bacilli in Mice. Int J Lepr Other Mycobact Dis. 1997;65(1):97–9. [PubMed: 9207760]
5. Suwanchaichinda C, Khamkong P, Worasuttayangkurn L, Satayavivad J. Deltamethrin exposure affects host resistance to Plasmodium infection in mice. Environ Toxicol Pharmacol. 2005;20(1):77–82. [PubMed: 21783571]
6. Brander SM, Gabler MK, Fowler NL, Connon RE, Schlenk D. Pyrethroid pesticides as endocrine disruptors: molecular mechanisms in vertebrates with a focus on fishes. Environ Sci Technol. 2016;50(17):8977–92. [PubMed: 27464030]
7. Rehman H, Mohan A, Tabassum H, Ahmea F, Rahman S, Parvez S, Raisuddin S. Deltamethrin Increases Candida albicans Infection Susceptibility in Mice. Scandinavian Journal of Immunology. 2011;73(5):459–64. [PubMed: 21272049]
8. Number of deaths in children aged <5, by cause [Internet]. World Health Organization. 2018. Available from: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/number-of-deaths.
9. Unicef. Childhood diseases: unicef; [Available from: https://www.unicef.org/health/childhood-diseases.
10. Huang J, Eskenazi B, Bornman R, Rauch S, Chevrier J. Maternal Peripartum Serum DDT/E and Urinary Pyrethroid Metabolite Concentrations and Child Infections at 2 Years in the VHEMBE Birth Cohort. Environmental Health Perspectives. 2018;126(6):067006. [PubMed: 29906263]
11. Cupul-Uicab LA, Terrazas-Medina EA, Hernández-Ávila M, Longnecker MP. Prenatal exposure to p,p'-DDE and p,p'-DDT in relation to lower respiratory tract infections in boys from a highly exposed area of Mexico. Environ Res. 2014;132:19–23. [PubMed: 24742723]
12. Gascon M, Vrijheid M, Martínez D, Ballester f, Basterrechea m, Blarduni e, Esplugues A, Vizcaino E, Grimalt JO, Morales E, Sunyer J Pre-natal exposure to dichlorodiphenyldichloroethylene and infant lower respiratory tract infections and wheeze. European Respiratory Journal. 2012;39:1188–96. [PubMed: 22075485]
13. Dallaire F, Dewailly E, Muckle G, Vezina C, Jacobson SW, Jacobson JL, Ayotte P. Acute Infections and Environmental Exposure to Organochlorines in Inuit Infants from Nunavik. Environmental Health Perspectives. 2004;112:14.
14. Dallaire F, Dewailly E, Vezina C, Muckle G, Weber J-P, Bruneau S. Effect of prenatal exposure to polychlorinated biphenyls on incidence of acute respiratory infections in preschool Inuit children. Environ Health Perspect. 2006;114(8):1301–4. [PubMed: 16882544]
15. Dewailly E, Bruneau S, Gingras S, Belles-Isles M, Roy R. Susceptibility to infections and immune status in Inuit infants exposed to organochlorines. Environmental Health Perspectives. 2000;108(3):205–11. [PubMed: 10706525]
16. Statistics South Africa. Poverty trends in South Africa: An examination of absolute poverty between 2006 and 2011. Statistics South Africa; 2014.
17. MacIntyre UE, Venter CS, Vorster HH. A culture-sensitive quantitative food frequency questionnaire used in an African population: 2. Relative validation by 7-day weighted records and biomarkers. Public Health Nutr. 2001;4(1):63–71. [PubMed: 11315682]
18. IOM (Institute of Medicine), NRC (National Research Council). Appendix B: Supplementary information on nutritional intake. In: Weight Gain during Pregnancy: Re-examining the Guidelines. Washington, DC: National Academies Press; 2009.
19. Barr JR, Maggio VL, Barr DB, Turner WE, Sjödin A, Sandau CD, Pirkle JL, Needham LL, Patterson DG Jr. New high-resolution mass spectrometric approach for the measurement of polychlorinated biphenyls and organochlorine pesticides in human serum. Chromatogr B Analyt Technol Biomed Life Sci. 2003;25(794):137–48.

20. Phillips DL, Pirkle JL, Burse VW, Bernert JT Jr, Henderson LO, Needham LL. Chlorinated hydrocarbon levels in human serum: effects of fasting and feeding. Arch Environ Contam Toxicol. 1989;18(4):495–500. [PubMed: 2505694]
21. Barr BD, Olsson AO, Wong L-Y, Udunka S, Baker SE, Whitehead RD, Magsumbol MS, Williams BL, Needham LL. Urinary concentrations of metabolites of pyrethroid insecticides in the general US population: National Health and Nutrition Examination Survey 1999-2002. Environmental Health Perspectives. 2010;118(6):742–8. [PubMed: 20129874]
22. Lubin JH, Colt JS, Camann D, Davis S, Cerhan JR, Severson RK, Bernstein L, Hartge P. Epidemiologic Evaluation of Measurement Data in the Presence of Detection Limits. Environ Health Perspect. 2004;112(17):1691–6. [PubMed: 15579415]
23. Chevrier J, Ruach S, Crause M, Obida M, Gaspar F, Bornman R, Eskenazi B. Associations of Maternal Exposure to Dichlorodiphenyltrichloroethane and Pyrethroids With Birth Outcomes Among Participants in the Venda Health Examination of Mothers, Babies and Their Environment Residing in an Area Sprayed for Malaria Control. Am J Epidemiol. 2019;188(1):130–40. [PubMed: 29992330]
24. Coker E, Chevrier J, Rauch S, Bradman A, Obida M, Crause M, Bornman R, Eskenazi B. Association between prenatal exposure to multiple insecticides and child body weight and body composition in the VHEMBE South African birth cohort. Environ Int. 2018;113:122–32. [PubMed: 29421401]
25. Yanez L, Ortiz-Perez D, Batres LE, Borja-Aburto VH, Diaz-Barriga F. Levels of Dichlorodiphenyltrichloroethane and Deltamethrin in Humans and Environmental Samples in Malarious Areas of Mexico. Environmental Research Section A. 2002;88(174–181).
26. Zumbado M, Goethals M, Álvarez-León EE, Luzardo OP, Cabrera F, Serra-Majem L, Domínguez-Boada L. Inadvertent exposure to organochlorine pesticides DDT and derivatives in people from the Canary Islands (Spain). Science of The Total Environment. 2005;339(1-3):49–62. [PubMed: 15740757]
27. Government of Canada. Toxic substances list: DDT: Government of Canada; 2013 [Available from: https://www.canada.ca/en/environment-climate-change/services/management-toxic-substances/list-canadian-environmental-protection-act/dichlorodiphenyltrichloroethane.html.
28. Ratelle M, Coté J, Bouchard M. Time profiles and toxicokinetic parameters of key biomarkers of exposure to cypermethrin in orally exposed volunteers compared with previously available kinetic data following permethrin exposure. J Appl Toxicol. 2015;35(12):1586–93. [PubMed: 25772368]
29. International Programme on Chemical Safety. Deltamethrin. (Environmental health criteria 97). Geneva, Switzerland; 1990.
30. Morgan MK, Sobus JR, Barr DB, Croghan CW, Chen F-L, Walker R, Alston L, Andersen E, Clifton MS. Temporal variability of pyrethroid metabolite levels in bedtime, morning, and 24-h urine samples for 50 adults in North Carolina. Environ Res. 2016(144):81–91.
31. Wielgoms B. Variability of urinary excretion of pyrethroid metabolites in seven persons over seven consecutive days--implications for observational studies. Toxicol Lett. 2013;221(1):15–22. [PubMed: 23711692]
32. Rauch S, Bradman A, Coker E, Chevrier J, An S, Bornman R, Eskenazi B. Determinants of Exposure to Pyrethroid Insecticides in the VHEMBE Cohort, South Africa. Environ Sci Technol. 2018;6(21):12108–21.
33. Verner M-A, Chevrier J, Ngueta G, Rauch S, Bornman R, Eskenazid B. Early-life exposure to p,p′-DDT and p,p′-DDE in South African children participating in the VHEMBE study: An assessment using repeated serum measurements and pharmacokinetic modeling. Environ Int. 2018;119:478–84. [PubMed: 30036731]
34. Islam JY, Hoppin J, Mora AM, Soto-Martinez ME, Cordoba Gamboa L, Ernesto J, Castaneda P, Reich B, Lindh C, van Wendel de Joode B Respiratory and allergic outcomes among 5-year-old children exposed to pesticides Thorax, 78 (2023), pp. 41–49. [PubMed: 35210357]

Table 1 –

Maternal peripartum concentrations of DDT/E and pyrethroids by participant characteristics, Venda Health Examination of Mothers, Babies and their Environment (VHEMBE), Limpopo, South Africa

Characteristics	n[a]	%[b]
Maternal characteristics during pregnancy		
Age (years)		
< 25	319	51
25–35	237	38
> 35	73	12
Education		
< Grade 12	361	57
Grade 12	183	29
> Grade 12	85	14
Married or living as married		
No	338	54
Yes	291	46
Parity (prior to birth of index child)		
0	268	43
1	173	28
≥ 2	188	30
HIV status		
Negative	552	88
Positive	77	12
Energy intake during pregnancy[c]		
Insufficient	431	69
Sufficient	198	31
Household poverty[d]		
No	246	39
Yes	383	61
Smoking during pregnancy		
No	628	100
Yes	1	0
Around smokers during pregnancy		
No	391	62
Yes	238	38
Alcohol during pregnancy		
No	592	94
Yes	37	6
Child household characteristics		
Household size		
1–4	159	25
5–8	323	51

Characteristics	n[a]	%[b]
9–12	115	18
≥ 13	32	5
Number of people sleeping in same room as child		
≤ 2	151	24
3–5	344	55
6–8	112	18
≥ 9	22	3
Number of people who smoke inside child's home		
0	572	91
≥ 1	57	9
Child characteristics		
Sex		
Male	322	51
Female	307	49
Birthweight (g)		
< 2500	47	7
≥ 2500	582	93
Premature birth (< 37-week gestation)		
No	552	88
Yes	77	12
Method of delivery		
Vaginal	481	76
C-section	148	24
Breastfeeding (months)		
≤ 18	363	58
> 18	260	41

Notes:

[a] Totals may not add to 629 due to missing data.

[b] Percentages may not add to 100% due to rounding.

[c] Energy intake was defined based on U.S. Institute of Medicine guidelines for pregnant women (18) as described by Huang et al. (10)

[d] Household income below the South African mid-2013-year food poverty level of 386 Rand/month/person

Table 2 –

Descriptive statistics of maternal peripartum serum DDT/E and urinary pyrethroid metabolite concentrations among participants in the Venda Health Examination of Mothers, Babies and their Environment (VHEMBE), Limpopo, South Africa

Analyte	n	Detection frequency (%)[a]	Quantification frequency (%)[b]	GM	GSD	Min	25th %ile	Median	75th %ile	Max
Serum DDT/E (ng/g lipids)										
p,p'-DDE	629	100	97.5	296.4	4.7	4.0	94.8	259.4	874.4	22613.4
o,p'-DDT	629	90.6	45.1	9.3	4.6	< LOD	3.6	7.7	23.3	2029.3
p,p'-DDT	629	98.1	90.8	72.0	6.6	< LOD	20.2	61.2	402.8	15027.6
Urinary pyrethroid metabolites specific gravity corrected (ug/L)										
cis-DBCA	620	100	99.5	0.3	3.1	0.02	0.2	0.3	0.7	13.4
cis-DCCA	620	100	99.8	0.5	2.5	0.05	0.3	0.5	0.8	209.5
trans-DCCA	620	100	99.7	0.5	3.0	0.03	0.3	0.5	1.0	268.9
3-PBA	619	100	100	1.1	2.4	0.1	0.7	1.0	1.8	88.2

Notes:

DDT = dichlorodiphenyltrichloroethane; DDE = dichlorodiphenyldichloroethylene; *cis*-DBCA = *cis*-3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropanecarboxylicacid; *cis*-DCCA = *cis*-3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane carboxylicacid; *trans*-DCCA = *trans*-3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane carboxylicacid PBA = phenoxybenzoic acid; GM = geometric mean; GSD = geometric standard deviation; Max = maximum; Min = minimum; LOD = limit of detection.

Geometric means and geometric standard deviations for DDT/E only include values above the LOD.

[a] Limits of detection: 0.03 ng/mL (*p,p'*-DDE); 0.01 ng/mL (*o,p'*-DDT and *p,p'*-DDT); 0.0025 µg/L (*cis*-DBCA); 0.0045 µg/L (*cis*-DCCA); 0.0038 µg/L (*trans*-DCCA); 0.0047 µg/L (3-PBA).

[b] Limits of quantification: 0.05 ng/mL (*o,p'*-DDT, and *p,p'*-DDT); 0.15 ng/mL (*p,p'*-DDE); 0.0082 µg/L (*cis*-DBCA); 0.015 µg/L (*cis*-DCCA); 0.013 µg/L (*trans*-DCCA); 0.016 µg/L (3-PBA).

Table 3 –

Rates of infection symptoms by age among children participating in the Venda Health Examination of Mothers, Babies and their Environment (VHEMBE), Limpopo, South Africa (n=629)

Infection outcomes	IR[a] [95% CI[b]] (per child-year)		
	1–2 years	2–3.5 years	3.5–5 years
Ear infection	0.2 [0.2, 0.3]	0.2 [0.2, 0.3]	0.2 [0.1, 0.2]
Diarrhea	1.0 [0.9, 1.1]	1.6 [1.5, 1.7]	0.3 [0.3, 0.3]
Persistent diarrhea	0.1 [0.1, 0.2]	0.1 [0.1, 0.2]	0.0 [0.0, 0.0]
Persistent fever	0.3 [0.2, 0.3]	0.7 [0.7, 0.8]	0.1 [0.1, 0.1]
Cold	2.6 [2.5, 2.7]	3.2 [3.1, 3.3]	1.4 [1.3, 1.5]
Severe sore throat	0.2 [0.1, 0.2]	0.7 [0.6, 0.7]	0.1 [0.1, 0.1]

Notes:

Infection occurrences were included only for children in this study (n = 629)

[a] Incidence rate

[b] Confidence interval

Table 4 –

Associations between maternal peripartum serum DDT/E and urinary pyrethroid metabolite concentrations and infection rates among children participating in the Venda Health Examination of Mothers, Babies and their Environment (VHEMBE), Limpopo, South Africa

		Adjusted IRR[b] [95% CI[c]]					
Exposure[a]	**n**	**Persistent fever**	**Diarrhea**	**Persistent diarrhea**	**Ear infection**	**Cold**	**Severe sore throat**
DDT/E							
p,p'-DDE	629	1.2 [0.9, 1.6]	1.1 [0.9, 1.3]	0.9 [0.5, 1.6]	1.0 [0.7, 1.3]	1.0 [0.9, 1.2]	1.1 [0.8, 1.5]
o,p'-DDT	629	1.3 [0.9, 1.7]	1.2 [0.9, 1.4]	1.1 [0.7, 1.8]	1.1 [0.8, 1.5]	1.0 [0.9, 1.2]	0.9 [0.7, 1.2]
p,p'-DDT	629	1.1 [0.8, 1.5]	1.1 [0.9, 1.3]	1.0 [0.7, 1.6]	1.0 [0.8, 1.3]	1.0 [0.9, 1.1]	0.9 [0.7, 1.2]
Pyrethroid metabolites							
cis-DBCA	620	1.3 [0.8, 2.0]	1.0 [0.8, 1.3]	2.1 [1.2, 3.9]	1.4 [1.0, 2.1]	0.9 [0.7, 1.1]	0.8 [0.6, 1.3]
cis-DCCA	620	1.1 [0.7, 1.6]	1.0 [0.7, 1.4]	1.8 [0.9, 4.0]	1.1 [0.7, 1.8]	1.2 [0.9, 1.5]	1.2 [0.8, 1.9]
trans-DCCA	620	1.4 [1.0, 2.0]	1.0 [0.8, 1.4]	1.9 [0.9, 3.9]	1.0 [0.7, 1.6]	1.3 [1.0, 1.6]	1.1 [0.7, 1.7]
3-PBA	619	1.8 [1.0, 3.0]	1.1 [0.7, 1.5]	1.4 [0.6, 4.0]	1.2 [0.7, 2.0]	1.2 [0.9, 1.6]	1.3 [0.8, 2.2]

Notes:

Models adjusted for maternal age, education, marital status, energy intake and HIV status as well as child sex and breastfeeding duration.

[a] Exposures are log-10 transformed

[b] IRR = incidence rate ratio

[c] CI = confidence interval