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Research article

Vaccination reaction rate is unaltered by ambient temperature on the day

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ABSTRACT

Minor reactions are often experienced following the human papillomavirus (HPV) vaccination and negative vaccination experiences may discourage individuals from seeking future vaccinations. Ambient temperature is suggested to be linked to reaction rates. Optimising immunisation programs requires understanding associations of temperature and reactions. To investigate a potential association between temperature and reactions, logistic regressions were performed on data obtained for a two-year period from a vaccine safety monitoring system for children (ages 10–15 years) who received the HPV vaccination ($n = 20466$) and from publicly available meteorological records in Australia. Reaction rate was 8.3% overall and higher with concomitant vaccination versus HPV alone (9.3% vs 7.8%, p=<0.001). Logistic regression found no relationship between reactions and maximal temperature on the day of vaccination ($p = 0.581$); controlling for concomitant vaccination, age and gender did not alter the temperature-reaction relationship ($p = 0.851$) but did identify concomitant vaccination as a significant predictor. Our results suggest immunisation programs must weigh the advantages of improved vaccination coverage resulting from concomitant vaccination against an increase in reaction rates and, importantly, can be safely administered across a range of temperatures.

1. Introduction

Fear of a negative vaccination experience is one reason cited as a cause for hesitation to receive a vaccination [1] and reduced vaccination uptake following media reports of purported adverse events following human papillomavirus (HPV) vaccination has been documented [2]. Therefore, improving rates of positive vaccination experience is imperative for individual and herd immunity through vaccination uptake.

Children in Australia may receive free HPV vaccinations through the Australian National Immunisation Program which, since 2018, has employed the nine-valent vaccine with a 2-dose schedule [3]. Adverse reactions to HPV vaccinations commonly include soreness (89.3% and 71.5% in boys and girls, respectively, ages 9–15 years) and swelling (47.8% and 20.2%, respectively) at the site of injection [4]. While such reactions are short-term and not serious events, reducing such reactions is desirable to improve the vaccination experience and reduce barriers to optimal vaccination uptake.

Patterns of ill health and mortality variations with weather extremes are found in the literature. For example, temperature, humidity and seasonality have been related to infections with cardiac implantable electronic devices [5] and influenza mortality [6]. Antibody levels in response to a variety of vaccinations may also vary with season [7]. Further, there is some suggestion that reaction rates in young men following influenza vaccinations may be higher in colder winter temperatures compared to mild weather [8, 9] and anecdotal evidence from immunisation nurses [10] suggests an increased incidence of adverse reaction on hotter days. We found only one report in the literature related to this conjecture: a 2014 letter reported increases in both ambient maximum and minimum temperatures increased risk for adverse reactions to pertussis vaccine among children but acknowledged that improper vaccine storage may have contributed to the reaction rate [11]. Were there an association between ambient temperature and risk of reaction to vaccination, there could be ramifications for delivery of immunisation programs, particularly in countries where recorded temperature extremes vary wildly, such as Australia with its recorded

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extremes of -23.0 to 50.7C [12]. Therefore, this study investigates whether there are associations with reactions in young persons to the anti-HPV vaccination and ambient temperature.

HPV was selected as the vaccine of interest for two reasons. First, the HPV vaccine has the aforementioned high rate of local adverse events and has been the subject of media attention for adverse events. Secondly, the experience of an adverse reaction may be particularly harmful in a young and potentially vulnerable cohort as it may then negatively influence their medical interactions for life.

Using data obtained from SmartVax, a vaccine safety monitoring system in Australia, and public meteorological recordings, we have investigated the relationship between ambient temperature and adverse reactions to the HPV vaccine. We hypothesized that warmer ambient temperatures would be associated with adverse reactions.

2. Methods

2.1. Data source and treatment

This study was deemed of negligible risk and exempt from ethical review by the University of Sydney Ethics Office.

Deidentified HPV vaccination reaction data was obtained from SmartVax, an automated text message-based system to monitor vaccination reactions. In immunisation clinics and general practices that register with SmartVax, the system automatically records patient details (gender, age, contact phone number, vaccine type and batch). SmartVax began also auto-recording clinic postcode in October 2019 and programmed the database to retroactively add postcodes. Three days following vaccination, patients or their guardian received a text message to which they could voluntarily report presence or absence of adverse events. Specifically, respondents were asked if they experienced any of the following: fever/temperature, swelling or redness at injection site, pain at injection site, feeling tired/fatigued, feeling irritable, sleep pattern change, rash, headache, vomiting, diarrhoea, convulsions/seizures, rigors, non-responsiveness/loss of consciousness or other symptom. (See supplement for reported frequency of symptoms.)

SmartVax data for HPV patients ages 10–15 were obtained for the period 1 February 2018–31 December 2019. In total, 75142 records were retrieved. Vaccine type was recorded dichotomously as HPV only or HPV administered concomitantly with another vaccine (e.g., for pertussis). Responses were dichotomously coded as symptom present or absent.

Records with no postcode or weather data were removed (n = 39633) as were records without recorded reaction responses to the text message within 14 days (n = 15043), leaving 20466 records. (A supplement contains a description of the full data set as well as analyses comparing the subset used for addressing the research question to the full set.)

Postcode coordinates were obtained from Corra.com [13]. The coordinates were manually entered into the Bureau of Meteorology website [14] to find weather stations within 50km that recorded maximum daily temperature. The nearest station which was operable and reported to be $\geq$ 90% complete during the study period was selected. Some of the 235 postcodes mapped to the same station, one did not have a station within 50 km and a second postcode had no station with useable data, resulting in data from 115 unique stations.

2.2. Data analysis

The data sets were joined and analysed, with alpha set at 0.05, using R packages [15, 16, 17]; the final set included 20466 persons with known ambient temperature and vaccination reaction, as shown in Figure 1. The chi-square, student t-test, and Mann-Whitney test were used for descriptive analysis. Binary logistic regression was employed to test whether the rate of reactions differed by maximal daily ambient temperature.

3. Results

Among the 20466 text-responders studied, there was an 8.3% reaction rate (see Table 1). There was no difference by gender, with reaction rate slightly higher among females than males (8.6% vs 8.0%, $p = 0.109$). On average, patients reporting reactions were younger by 21.9 days ($p = 0.003$) than those reporting no reaction. About one third of the sample vaccinations (n = 6972, 34.1%) received concomitant vaccinations; reactions were reported for a higher proportion of these children (9.3%) than for those only receiving the HPV vaccination (7.8%, $p < 0.001$).

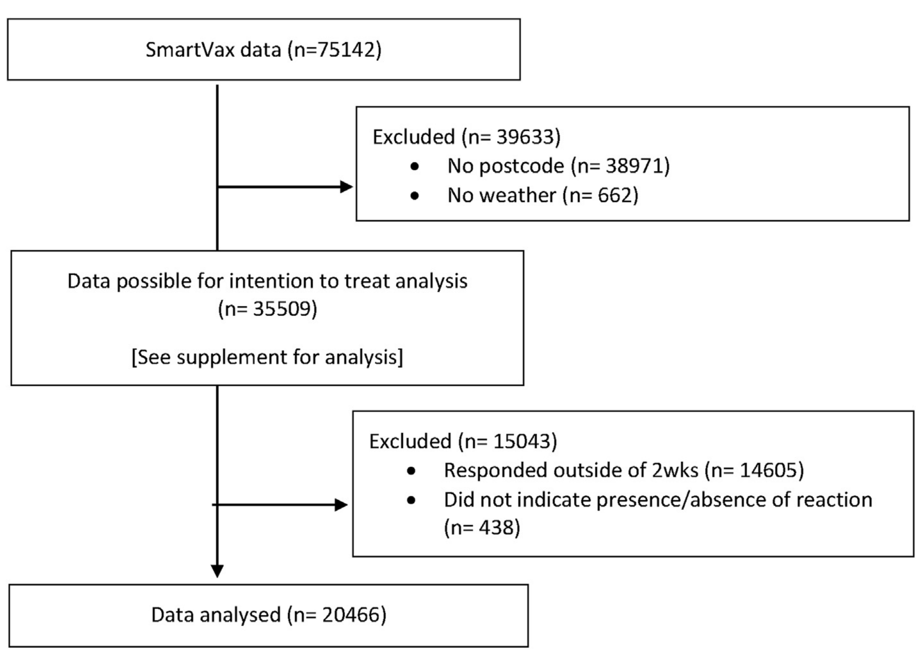

Figure 1. Data set flowchart.

Table 1. Sample characteristics, by reaction status.

Characteristic	No reaction	Reaction	p value
Total (n, % of total)	18771, 91.7%	1695, 8.3%	
Female (n, % of column)	9393, 50.0%	883, 52.1%	0.109
Age in years (mean ± sd)	12.8 ± 0.77	12.8 ± 0.77	0.003
Concomitant vaccination (n, % of column)	6323, 33.7%	649, 38.3%	<0.001
Maximum temperature on day in Celsius (median, IQR; range)	22.6, 19.3–26.1; 5.6–45.7	23.1, 19.4–26.2; 11.6–41.5	0.278

Table 2. Binary logistic regression analysis for prediction of experiencing HPV vaccination reaction.

Predictors in model (comparator)	B	SE B	Z value	df	p	Odds ratio (OR) and 95% confidence interval (95%CI)		
						OR	Lower 95%CI	Upper 95%CI
Maximum temperature (1C)	0.0026	0.0048	0.552	20465	0.581	1.00	0.993	1.012
(Intercept)	-2.4661	0.1144	-21.554		<0.001	0.08	0.068	0.106
Maximum temperature (1C)	-0.0009	0.0049	-0.188	20461	0.851	1.00	0.989	1.008
Age (1 year)	-0.0654	0.0347	-1.885		0.059	0.94	0.875	1.002
Concomitant vaccination (only HPV)	0.1696	0.0557	3.044		0.002	1.18	1.062	1.321
Sex (male)	-0.0761	0.0508	-1.497		0.134	0.93	0.839	1.024
(Intercept)	-1.5702	0.4673	-3.36		<0.001	0.21	0.083	0.521

Binary logistic regression revealed the occurrence of a reaction did not depend on maximal ambient temperature on the day of vaccination: for every increase in degree Celsius, the odds of a reaction increased by 1.00 (95%CI: 0.993, 1.012; p = 0.581). This relationship remained insignificant (OR 1.00, 95%CI: 0.989, 1.009; p = 0.851) when adjusted for other potential predictors; however, concomitant vaccination significantly predicted vaccination reaction (OR 1.18, 95%CI: 1.062, 1.321; p = 0.002). Table 2 presents the regression equations while Figure 2 depicts the ambient maximal temperature of the geographic location on the day of vaccination and reaction presence (or absence).

We further calculated both change and absolute change in maximal temperature from the day before the day of vaccination in order to determine if rapid fluctuations in temperature might influence reaction rates. Similarly, there was not a difference in the predictive value of change in temperature from the previous day (OR 1.00, 95%CI: 0.989, 1.018; p = 0.638 and OR 1.01, 95%CI: 0.991, 1.020; p = 0.453, adjusted) or with absolute change in temperature (OR 1.00, 95%CI: 0.981, 1.022; p = 0.889 and OR 1.00, 95%CI: 0.980, 1.021; p = 0.970, respectively) on vaccination reaction and in each case concomitant vaccination remained predictive (respectively, OR 1.19, 95%CI: 1.064, 1.322; p = 0.002; and OR 1.18, 95%CI: 1.062, 1.319; p = 0.002).

4. Discussion

This study explored reactions to HPV vaccinations over a two-year period among 10-15-year-olds in relation to ambient temperature. We found no relationship between maximum daily temperature and presence of reactions. This is a positive finding for public health as it suggests that vaccination administration need not be weather-dependent. The observed predictive nature of concomitant vaccination for reactions does suggest the benefits of improved vaccination coverage must be weighed against risks associated with reactions.

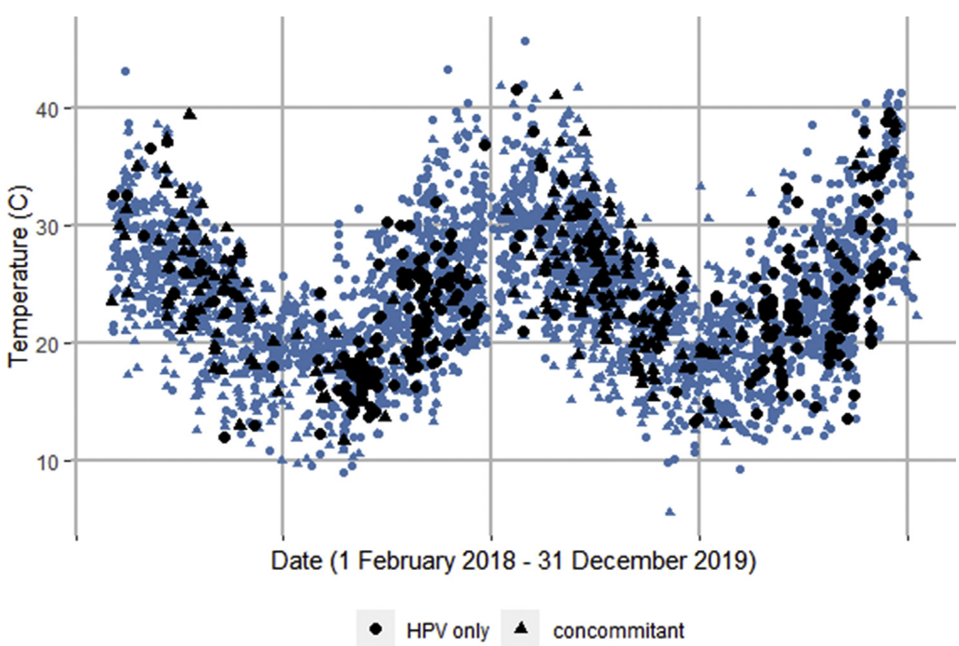

Figure 2. Maximal ambient temperature and HPV vaccination reaction incidence from 2018-19. Type of vaccination is shown by shape (circle = HPV only vaccination) and response is shown by color (black = reaction).

From a public health perspective, it is imperative to lessen barriers to immunisations and vaccinations so as to improve herd immunity. The observed reaction rate was higher in those receiving concomitant vaccinations compared to HPV alone (9.3% vs 7.8%, $p < 0.001$) and concomitant vaccination was a significant predictor in all models. A large majority (95.7%) of those receiving concomitant vaccination received a diptheria-tetanus-pertussis (DTP) vaccine as the Australian vaccination schedule includes an adolescent DTP booster with HPV vaccination, but there was with no difference ($p = 0.887$) in reaction rates between those also receiving DTP-type versus non-DTP-type vaccines. A recent metanalysis of randomized controlled trials in HPV vaccinations administered to 9-25 year-olds also documented increases in the relative risks for minor and systemic reaction rates (RR = 1.31, 95%CI: 1.17–1.47 and RR = 2.09, 95% CI: 1.69–2.59, respectively) with concomitant vaccination for multivalent HPV vaccines but not for the bivalent vaccine [18]. The national immunisation program adopted the quadrivalent vaccine in 2018; thus, it is likely our data included primarily the quadrivalent vaccine but we cannot be certain as vaccine specification was not part of the dataset. As the adverse reactions observed here and in the meta-analysis were overwhelmingly minor, transient events, the benefits afforded to the individual and population through improved vaccination coverage resulting from concomitant vaccination may outweigh any increase in reaction rates.

A second public health consideration is the immune response to vaccinations. While measuring such was outside the scope of this study, we note that there is some suggestion in the literature that efficacy for other vaccines may vary with seasonal variation [7]. To date, the potential for weather-related variations in efficacy has not been investigated in regards to the HPV vaccination, but similar efficacy has been found with concomitant and solitary HPV vaccination [18].

Our analysis has some limitations, predominantly that the experienced ambient temperature may differ from recorded climate data, thus placing a different level of thermal stress on an individual [19]. This limitation could be overcome in future investigations through use of personal monitoring devices. Secondly, the reaction data analysed here encompasses many reaction types but is self- or parent-reported. Thirdly, because the data is cross-sectional and the vaccine is given as a two-dose schedule, it is possible some observations capture the same person at dose 1 and dose 2. To address this possibility, we analysed separately each six-month period and still found no effect between reaction and temperature (results not reported). However, as a first study exploring the relationship between climate and vaccination reactions, our study holds several strengths. Notably, our sample size comprised two years of population data across a temperature range of over forty degrees Celsius.

Conclusion: Vaccination reaction rates do not appear to vary with ambient temperature, suggesting that immunisation programs can be administered across a range of climates without increased risk of negative vaccination experience. Future studies measuring participant-experienced thermal stress or, at the minimum, recording presence of climate control systems may be warranted to confirm these findings.

Author contribution statement

E. Goldbaum: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

L. Ross, A. Leeb and I. Peters: Contributed reagents, materials, analysis tools or data.

R. Booy: Conceived and designed the experiment.

K.M. Edwards: Conceived and designed the experiments; Analyzed and interpreted the data.

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Declaration of interests statement

The authors declare a potential competing interest for authors Leeb and Peters through their affiliation with the organisation providing the vaccination-related data; Leeb and Peters involvement was limited to data collection and provision and comment on methods and synthesis. No other authors have known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Additional information

Supplementary content related to this article has been published online at https://doi.org/10.1016/j.heliyon.2020.e05527.

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