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Use of different combination diphtheria-tetanus-acellular pertussis vaccines does not increase risk of 30-day infant mortality. A population-based linkage cohort study using administrative data from the Australian Childhood Immunisation Register and the National Death Index.

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ABSTRACT

Objective: To determine whether differences in combination DTaP vaccine types at 2, 4 and 6 months of age were associated with mortality (all-cause or non-specific), within 30 days of vaccination.
Design: Observational nationwide cohort study.
Setting: Linked population data from the Australian Childhood Immunisation Register and National Death Index.
Participants: Australian infants administered a combination trivalent, quadrivalent or hexavalent DTaP vaccine (DTaP types) between January 1999 and December 2010 at 2, 4 and 6 months as part of the primary vaccination series. The study population included 2.9, 2.6, & 2.3 million children in the 2, 4 and 6 month vaccine cohorts, respectively.
Main outcome measures: Infants were evaluated for the primary outcome of all-cause mortality within 30 days. A secondary outcome was non-specific mortality (unknown cause of death) within 30 days of vaccination. Non-specific mortality was defined as underlying or other cause of death codes, R95 'Sudden infant death syndrome', R96 'Other sudden death, cause unknown', R98 'Unattended death', R99 'Other ill-defined and unspecified cause of mortality' or where no cause of death was recorded.
Results: The rate of 30 day all-cause mortality was low and declined from 127.4 to 59.3 deaths per 100,000 person-years between 2 and 6 month cohorts. When compared with trivalent DTaP vaccines, no elevated risk in all-cause or non-specific mortality was seen with any quadrivalent or hexavalent DTaP vaccines, for any cohort.
Conclusion: Use of routine DTaP combination vaccines with differing disease antigens administered during the first six months of life is not associated with infant mortality.

1. Introduction

Combination vaccines incorporating multiple vaccine-preventable disease (VPD) antigens in the same injection, have led to increased compliance in child vaccination schedules and improved vaccination coverage [1,2]. Some public uncertainty remains however, about inclusion of additional VPD antigens in combination vaccines and their effect on infant immune systems. Some parents may refuse to vaccinate their children or express hesitancy in accepting multivalent vaccines due to concerns increased VPD antigens may overload child immune systems [3–6].

An area of further debate discussed in the research literature, has been the effect of combination vaccines on morbidity and death in conditions other than the target diseases of the vaccine – described as non-specific vaccine effects [7,8]. One explanation postulated for these observed effects is that the disease-specific

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vaccine components either augment or diminish the innate immune response to other pathogens resulting in increased or decreased morbidity and mortality effects [9].

A 2016 systematic review investigating effects of vaccination on childhood mortality concluded receipt of diphtheria-tetanus-pertussis (DTP) vaccines may be associated with increased all-cause mortality, and recommended further assessment of DTP immunisation on mortality [10]. The findings however, related to studies conducted in low-income countries (predominately, West Africa and Southern Asia) with known higher child mortality compared to high-income nations [11]. Furthermore, the combination DTP vaccines described in these studies were restricted to three VPD antigen (trivalent) whole-cell DTP vaccines. Whole-cell DTP vaccines are recognised as having higher rates of systemic adverse reactions compared with the diphtheria-tetanus-acellular pertussis (DTaP) vaccines administered in most high-income nations [12–14]. Contemporary immunisation schedules also recommend use of combination DTaP vaccines containing additional VPD antigens (Hepatitis B, Haemophilus influenzae type b (Hib) and inactivated poliomyelitis (IVP)) as well as DTP, providing combined protection for up to six diseases. If non-specific effects were to contribute to all-cause mortality then increased mortality risk may be evident with administration of additional VPD antigens. The progression in current vaccine practice from whole-cell trivalent DTP vaccines to multivalent acellular DTP vaccines protecting against three to six diseases, raises the question of whether combination DTaP vaccines both individually or collectively, have non-specific effects and affect post-vaccination mortality.

Australia has varied its selection of combination DTaP-containing vaccines in the infant-based schedule both over time and between jurisdictions. The changing usage of different DTaP vaccines provides a natural experiment for studying the effect of combination DTaP vaccines on post-vaccination infant mortality. We sought to assess this using a linked population dataset comprising immunisation exposure data from the Australian Childhood Immunisation Register (ACIR) and mortality from the National Death Index (NDI). Our primary objective was to determine whether combination DTaP vaccines protecting against a differing number of diseases administered at 2, 4 and 6 months of age were associated with post-vaccination *all-cause mortality* within 30 days of vaccination. A secondary objective examined whether *non-specific mortality* within 30 days post-vaccination, differed across combination DTaP vaccines.

2. Methods

2.1. Setting, study design, data sources & data linkage

In Australia, routine vaccinations administered to children and adolescents are funded by the Australian Government as part of the National Immunisation Program (NIP). Since 1996, all childhood vaccines recommended in the NIP Schedule are recorded on ACIR, with records maintained until a child reaches seven years of age [15]. Recorded on ACIR are child demographic details, Aboriginality and immunisation history (date, vaccine brand name, dose and batch number of vaccine administered), together with provider contact information. The Register is a near complete representation of Australia's birth cohort, estimated to include 99% of infants by 12 months of age, [16] with children automatically included following enrolment with Australia's universal health scheme, Medicare.

Unlike Nordic nations, Australian administrative data lack a unique individual identifier which can be used to link datasets. Consequently, datasets are linked by probabilistically matching demographic, name and address information. The NDI is administered by the Australian Institute of Health and Welfare (AIHW) and collates death registrations from jurisdictional registers, primarily for use in epidemiological investigations. The NDI records demographic information, date of death, underlying and other cause of death information. Cause of death is classified by the Australian Bureau of Statistics according to the International Statistical Classification of Diseases and Related Health Problems tenth revision (ICD-10) with non-specific causes revised up to four years following death registration [17].

Probabilistic data linkage was undertaken by the AIHW. Children listed on ACIR were matched with NDI data using combinations of first, middle initial and last names, birthdate and gender. Three data files relating to individuals, administered vaccines and death information (occurrence, cause and date of death) were provided, integrated using a project-specific identifier. In selecting mortality events for analysis we delineated a minimum linkage weight threshold which included all presumed 'good' links (and excluded non-matches) for consideration in analyses. The threshold weight was based on examining the distribution of linkage weights described in the linkage statistics report. This report was generated following a clerical review process where a random sample of linked record pairs were selected from each batch of record pairs with a defined linkage weight. The sample of record pairs were then examined to determine the link status (link or non-link) for a record pair, providing a profile of incorrect or correct links within each batch of records.

Selecting a threshold weight represents a trade-off between excluding mortality records which fail to link (missed matches) and including incorrectly matched records (false matches). Our selected (minimum) threshold weight for all presumed goods links had a linkage accuracy of 89% which meant a proportion of linkage pairs were possible incorrect links (11%). By including all good matches we maximised the available sample for identifying any association between DTaP vaccines and mortality, a rare outcome. Harron et al. demonstrated that increasing threshold weights leads to inclusion of fewer linked records, thereby excluding potential matching records and decreasing the precision of effect estimates such that an exposure-outcome association seen with 'gold-standard' data may no longer be apparent [18]. Another concern with restricting linked records to a higher linkage weight is generalizability of study findings. Selection bias in the study sample may arise from elimination of uncertain links due to name misspellings, leading to exclusion of some ethnic groups [18,19].

2.2. Participants

Fig. 1 outlines the selection of study participants from the linked ACIR-NDI datasets. We received records for all immunisations (n = 50,813,769) including DTaP vaccines, administered to children up to 7 years of age (N = 4,601,963) between 1999 and 2010. Eligible children (N = 3,382,978) were aged up to one year at vaccination with a record of either a trivalent, quadrivalent or hexavalent DTaP vaccine administered between January 1999 and December 2010. Children with multiple DTaP-containing doses recorded on the same day (N = 2,111) or where age at vaccination could not be determined (N = 5,949) were not included. Children administered any of the pentavalent DTaP vaccines [Infanrix Penta DTaP-HepB-IPV and DTaP-Hib-IPV (Pediacel-PDCL or Poliacel-PLCL)] between 2001 and 2008 were also not included as use of these vaccines was limited to high disease risk populations in three selected jurisdictions (<0.6% of all 14,199,165 DTaP-containing vaccinations administered to 34,068 children). To minimise bias arising from misclassification of vaccine exposure, children were excluded where DTaP doses were administered before the product was formally funded on the NIP Schedule (N = 15,242). Duplication of DTaP vaccines and additional vaccine

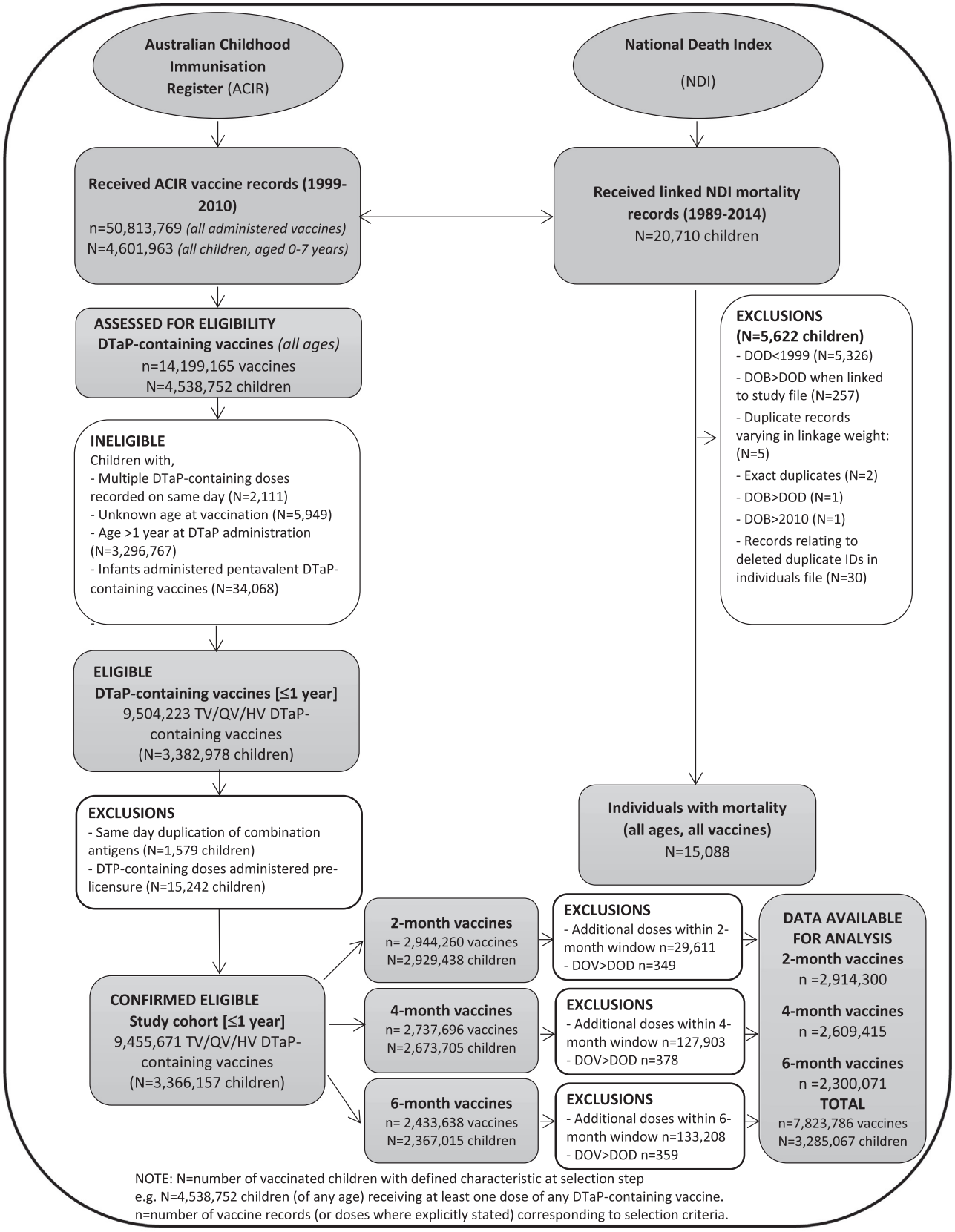

Fig. 1. Flow diagram detailing participant selection from contributing administrative datasets.

antigens of the same type observed on the same day were also excluded (N = 1,579). For example, a Hepatitis B antigen recorded as administered both as a separate and combination DTaP vaccine during the same vaccination encounter. This resulted in an initial study cohort of 3,366,157 children. Further exclusion of children recorded with subsequent doses during the same observation

window used to define an age cohort (see below) or vaccination encounters occurring after the mortality event yielded a final study cohort of 3,285,067 children administered 7,823,786 DTaP-containing vaccines.

2.3. Exposure

Four categorical combination vaccine exposure groups were created, representing both the number of vaccine-preventable diseases being protected against in the vaccine (TV = trivalent or three diseases, QV = quadrivalent or four diseases, HV = hexavalent or six diseases) and name of vaccine–preventable disease additional to DTaP, Hepatitis B (HepB), inactivated polio (IPV), *Haemophilus influenzae* type b (Hib). These were designated TV DTaP, QV DTaP-HepB, QV DTaP-IPV and HV DTaP-HepB-Hib-IPV vaccines where a '-' (dash) denotes additional VPD antigens combined with DTaP in the same vaccine. The publically-available vaccine codes representing the different combination DTaP vaccines are detailed in Appendix Table 1 [20].

2.4. Age-based cohorts

We constructed three cohorts corresponding to the recommended age of administration of three DTaP doses on the Australian Schedule [21]. Children immunised at 4–11 weeks of age were included in the 2 month cohort, 12–19 weeks in the 4 month cohort and 20–27 weeks in the 6 month cohort. The age specification for each cohort recognised similar delineations and timing of possible administration for each infant dose (also reflected by study data, Appendix Fig. 1) [21–23]. This included the 6 week minimum age for first vaccine administration [21].

2.5. Primary outcome

Our primary outcome was all-cause mortality within 30-days following DTaP vaccination. The 30-day risk period was selected as a biologically plausible interval following vaccination for occurrence of adverse effects including death [24,25].

2.6. Secondary outcome

Secondary analyses assessed non-specific cause mortality, 30-days post-vaccination. Non-specific mortality (or more accurately, unknown cause of death), was selected as a further measure of non-specific mortality effects. Non-specific cause was defined as underlying or other cause of death ICD-10 codes, R95 'Sudden infant death syndrome', R96 'Other sudden death, cause unknown', R98 'Unattended death', R99 'Other ill-defined and unspecified cause of mortality' or where no cause of death was recorded. Mortality records were available until December 2014, ensuring sufficient follow-up time for the study outcomes.

2.7. Statistical methods

With each age cohort, a Cox proportional hazards model was used to compare mortality risk within 30-days, for each DTaP vaccine group using the trivalent DTaP vaccines as the referent category. All analyses were performed for the combined data period (1999–2010). The proportional hazards assumption was evaluated using the Wald test and was satisfied in all Cox-specific analyses. Secular trends in mortality rates and use of different DTaP vaccines in each age cohort for the primary analysis (all-cause mortality), were examined using Kaplan-Meier method. The Log-rank test was used to compare survival distributions within 30 days following vaccination for the four vaccine exposures. In describing the cohort, a score establishing socioeconomic status was determined from postcodes mapped to the Index of Relative Socioeconomic Disadvantage (IRSD), a location-based measure of disadvantage [26–28]. Due to limitations in availability of child residential postcode restricted to latest address rather than address at time of vaccination, the immunisation provider postcode served as a proxy when creating the IRSD score. Analyses were conducted using SAS 9.4 (SAS Institute, Cary, North Carolina, USA).

2.8. Sensitivity analysis

A sensitivity analysis was conducted which involved increasing the linkage weight threshold to examine whether this impacted on direction and magnitude of point estimates. Conducted for all three age cohorts for the combined data period (1999–2010), primary and secondary outcomes, mortality events were included with a higher linkage weight threshold which corresponded to inclusion of 95% of presumed correct matches (previously 100% for the primary and secondary analyses). This 95% linkage rate also corresponded with improved linkage accuracy, 99.5% or higher (previously 89%), minimising false-positive matches to <0.05% (previously 11%). The increase in linkage weight did however, reduce the sample size of individuals with presumed correct and incorrect matches to 85% of the sample available for selection in the primary (and secondary) analyses.

2.9. Ethics approval

Ethical approval was granted by the University of Adelaide Human Research Ethics Committee (H-148-2008), the Commonwealth Department of Health and Ageing Ethics Committee (Project 2/2009) and the AIHW Ethics Committee (EC2010-3-35).

3. Results

3.1. Cohort description

Characteristics of the 2-, 4- and 6-month DTaP-containing cohorts are presented in Table 1. Around 35% of individuals in each age cohort used hexavalent DTaP-HepB-IPV-Hib vaccines, with 30% and 25% administered trivalent DTaP and quadrivalent DTaP-HepB vaccines, respectively (Table 1). Ten per cent of the cohort used quadrivalent DTaP-IPV vaccines. Use of combination DTaP vaccines by year are presented in Appendix Table 3. Between 1999 and 2004, two DTaP vaccines were used in the study cohort: trivalent DTaP vaccines and quadrivalent DTaP-Hep B vaccines, while between 2005 and 2010, all four study DTaP-containing vaccines were in use. Administration of quadrivalent DTaP-HepB vaccines in the 2-month cohort was highest between 2001 and 2004 and used in ~61% of the cohort declining to <0.5% of infants from 2006 onwards. The quadrivalent DTaP-IPV vaccines were used by half of the 2-month study cohort in 2006 and 2007, declining to <0.5% by 2010. The hexavalent DTaP vaccine first used in 2005 in 7.7% of infants, increasing to 45–46% of the 2-month cohort in 2006–2007, and 97% of infants in 2009 and 2010.

The proportion of Aboriginal and Torres Strait Islander (ATSI) infants aged 0–7 years using DTaP vaccines in the 2-month cohort varied from 2.9% to 4.5% (Table 1). Indigenous children were estimated to comprise 5.7% of all children aged 0–7 years in the 2011 Australian Census [29]. Therefore, all DTaP vaccine types appear to underestimate Indigenous status to varying extents. Appropriate re-distribution of ATSI status 'not recorded' would be required, but the marked difference in proportion 'unknown' for two vaccines administered early and late in the 12-year period

Table 1
Baseline characteristics of vaccinated children considered for the primary outcome (post-vaccination all-cause mortality within 30-days) by DTaP vaccine group and 2, 4 and 6-month cohorts.

2-month cohort					
	(TV) DTaP	(QV) DTaP-HepB	(QV) DTaP-IPV	(HV) DTaP-HepB-IPV-Hib	TOTAL
Persons with DTaP-containing vaccines	856,217 (29.4)	748,707 (25.7)	302,627 (10.4)	1,006,749 (34.6)	2,914,300 (100.0)
	N (%)	N (%)	N (%)	N (%)	N (%)
Gender					
Male	438,765 (51.2)	384,987 (51.4)	155,095 (51.3)	516,093 (51.3)	1,494,940 (51.3)
Female	417,452 (48.8)	363,720 (48.6)	147,532 (48.8)	490,656 (48.7)	1,419,360 (48.7)
ATSI status					
Non-Indigenous	522,852 (61.1)	530,738 (70.9)	277,752 (91.8)	929,531 (92.3)	2,260,873 (77.6)
Indigenous	24,643 (2.9)	33,397 (4.5)	10,150 (3.4)	38,134 (3.8)	106,324 (3.7)
Not recorded	308,772 (36.1)	184,572 (24.7)	14,725 (4.9)	39,084 (3.9)	547,103 (18.8)
Socioeconomic quartile[*]					
1 (Most disadvantaged)	182,745 (21.3)	201,405 (26.9)	56,883 (18.8)	201,415 (20.0)	642,448 (22.0)
2	164,563 (19.2)	201,652 (26.9)	69,648 (23.0)	245,557 (24.4)	681,420 (23.4)
3	168,602 (19.7)	148,838 (19.9)	78,074 (25.8)	232,624 (23.1)	628,138 (21.6)
4 (Least disadvantaged)	321,623 (37.6)	190,879 (25.5)	93,294 (30.8)	317,693 (31.6)	923,489 (31.7)
Missing	18,684 (2.2)	5933 (0.8)	4728 (1.6)	9460 (0.9)	38,805 (1.3)
4-month cohort					
	(TV) DTaP	(QV) DTaP-HepB	(QV) DTaP-IPV	(HV) DTaP-HepB-IPV-Hib	TOTAL
Persons with DTaP-containing vaccines	779,392 (29.9)	662,910 (25.4)	269,794 (10.3)	897,319 (34.4)	2,609,415 (100.0)
	N (%)	N (%)	N (%)	N (%)	N (%)
Gender					
Male	399,170 (51.2)	340,287 (51.3)	138,020 (51.2)	459,145 (51.2)	1,336,622 (51.2)
Female	380,222 (48.8)	322,623 (48.7)	131,774 (48.8)	438,174 (48.8)	1,272,793 (48.8)
ATSI status					
Non-Indigenous	464,305 (59.6)	467,877 (70.6)	246,282 (91.3)	828,858 (92.4)	2,007,322 (76.9)
Indigenous	22,976 (3.0)	28,534 (4.3)	8,783 (3.3)	32,008 (3.6)	92,301 (3.5)
Not recorded	292,111 (37.5)	166,499 (25.1)	14,729 (5.5)	36,453 (4.1)	509,792 (19.5)
Socioeconomic Quartile					
1 (Most disadvantaged)	168,324 (21.6)	177,376 (26.8)	50,799 (18.8)	179,308 (20.0)	575,807 (22.1)
2	151,086 (19.4)	178,948 (26.9)	61,371 (22.8)	218,198 (24.3)	609,603 (23.4)
3	154,412 (19.8)	130,418 (19.7)	70,874 (26.3)	207,651 (23.1)	563,355 (21.6)
4 (Least disadvantaged)	288,746 (37.1)	171,069 (25.8)	82,730 (30.7)	283,867 (31.6)	826,412 (31.7)
Missing	16,824 (2.2)	5099 (0.8)	4020 (1.5)	8295 (0.9)	34,238 (1.3)
6-month cohort					
	(TV) DTaP	(QV) DTaP-HepB	(QV) DTaP-IPV	(HV) DTaP-HepB-IPV-Hib	TOTAL
Persons with DTaP-containing vaccines	702,072 (30.5)	570,979 (24.8)	236,330 (10.3)	790,690 (34.4)	2,300,071 (100.0)
	N (%)	N (%)	N (%)	N (%)	N (%)
Gender					
Male	359,105 (51.2)	292,487 (51.2)	120,750 (51.1)	403,960 (51.1)	1,176,302 (51.1)
Female	342,967 (48.9)	278,492 (48.8)	115,580 (48.9)	790,690 (48.9)	1,123,769 (48.9)
ATSI status					
Non-Indigenous	406,270 (57.9)	400,348 (70.1)	214,162 (90.6)	728,462 (92.1)	1,749,242 (76.0)
Indigenous	21,807 (3.1)	25,297 (4.4)	7875 (3.3)	28,926 (3.7)	83,905 (3.7)
Not recorded	273,995 (39.0)	145,334 (25.6)	14,293 (6.1)	33,302 (4.2)	466,924 (20.3)
Socioeconomic Quartile					
1 (Most disadvantaged)	153,562 (21.9)	155,600 (27.3)	45,062 (19.1)	160,261 (20.3)	514,485 (22.4)
2	137,875 (19.6)	154,340 (27.0)	54,052 (22.9)	193,571 (24.5)	539,838 (23.5)
3	140,822 (20.1)	110,989 (19.4)	62,102 (26.3)	183,209 (23.2)	497,122 (21.6)
4 (Least disadvantaged)	255,117 (36.3)	145,709 (25.5)	71,661 (30.3)	246,613 (31.2)	719,100 (31.3)
Missing	14,696 (2.1)	4341 (0.8)	3453 (1.5)	7036 (0.9)	29,526 (1.3)

Abbreviations: TV DTaP = trivalent diphtheria-tetanus-acellular pertussis vaccine; QV DTaP-HepB = quadrivalent diphtheria-tetanus-acellular pertussis-hepatitis B vaccine; QV DTaP-IPV = quadrivalent diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine; HV DTaP-HepB-IPV-Hib = hexavalent diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis-*Haemophilus influenzae* type b vaccine.

[*] A score establishing socioeconomic status was determined from postcodes mapped to the Index of Relative Socioeconomic Disadvantage (IRSD), a location-based measure of disadvantage [26–28]. Due to limitations in availability of child residential postcode restricted to latest address rather than address at time of vaccination, the immunisation provider postcode served as a proxy when creating the IRSD score.

(36.1% for trivalent vaccine vs 3.8% for hexavalent vaccine), did not correlate with a markedly lower ATSI estimate (2.9% vs 3.8%, respectively).

3.2. Primary outcome (all-cause mortality within 30-days of vaccination)

Table 2 shows overall all-cause mortality within 30-days of vaccination in infants administered DTaP vaccines was low and declined with increasing age from 127.4, 90.5, to 59.3 deaths per 100,000 person-years in the 2, 4 and 6 month cohorts, respectively. Absolute number of deaths was low and variation in all-cause mortality rates was seen across DTaP vaccine types, particularly for the 2 and 4-month cohorts (Table 2). In the 2-month cohort for example, mortality rate was lowest with the hexavalent and trivalent DTaP vaccines (102.80 and 132.3 deaths per 100,000 person-years, respectively) increasing to 156.9 deaths per 100,000 person-years for the QV DTaP-IPV vaccines.

Table 2
Post-vaccination mortality rate and results of Cox proportional hazard models relating to primary (30-day all-cause mortality) and secondary outcomes (30-day non-specific cause mortality) by DTaP vaccine group and 2-month, 4-month or 6-month cohort.

Vaccine cohort DTaP vaccine group	Persons	ALL-CAUSE MORTALITY				NON-SPECIFIC CAUSE MORTALITY		
		Events	Person Years	Mortality rate*	Hazard Ratio (95% CI)	Events	Mortality rate*	Hazard Ratio (95% CI)
2-month cohort								
(TV) DTaP	856,217	93	70,322	132.25	1.0 (Referent)	50	71.10	1.0 (Referent)
(QV) DTaP-HepB	748,707	88	61,492	143.11	1.08 (0.81 – 1.45)	60	97.57	1.37 (0.94 – 2.00)
(QV) DTaP-IPV	302,627	39	24,855	156.91	1.19 (0.82 – 1.72)	15	60.35	0.85 (0.48 – 1.51)
(HV) DTaP-HepB-IPV-Hib	1,006,749	85	82,686	102.80	0.78 (0.58 – 1.04)	55	66.52	0.94 (0.64 – 1.37)
TOTAL	2,914,300	305	239,356	127.43		180	68.10	
4-month cohort								
(TV) DTaP	779,392	57	64,014	89.04	1.0 (Referent)	31	48.43	1.0 (Referent)
(QV) DTaP-HepB	662,910	56	54,446	102.85	1.16 (0.80 – 1.67)	27	49.59	1.02 (0.61 – 1.72)
(QV) DTaP-IPV	269,794	11	22,159	49.64	0.56 (0.29 – 1.06)	<5†	13.54	0.28 (0.09 – 0.91)
(HV) DTaP-HepB-IPV-Hib	897,319	70	73,699	94.98	1.07 (0.75 – 1.51)	32	43.42	0.90 (0.55 – 1.47)
TOTAL	2,609,415	194	214,318	90.52		93	43.39	
6-month cohort								
(TV) DTaP	702,072	36	57,664	62.43	1.0 (Referent)	14	24.28	1.0 (Referent)
(QV) DTaP-HepB	570,979	32	46,896	68.24	1.09 (0.68 – 1.76)	12	25.59	1.05 (0.49 – 2.28)
(QV) DTaP- IPV	236,330	13	19,411	66.97	1.07 (0.57 – 2.02)	<5†	20.61	0.85 (0.28 – 2.58)
(HV) DTaP-HepB-IPV-Hib	790,690	31	64,943	47.74	0.77 (0.47 – 1.24)	11	16.94	0.70 (0.32 – 1.54)
TOTAL	2,300,071	112	188,913	59.29		41	21.70	

Abbreviations: TV DTaP = trivalent diphtheria-tetanus-acellular pertussis vaccine; QV DTaP-HepB = quadrivalent diphtheria-tetanus-acellular pertussis-hepatitis B vaccine; QV DTaP-IPV = quadrivalent diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine; HV DTaP-HepB-IPV-Hib = hexavalent diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis-*Haemophilus influenzae* type b vaccine.

* Mortality rate represented as events per 100,000 person-years.

† Where cell sizes involve <5 events, actual number of events have been suppressed for that cell.

No difference was observed in 30-day all-cause mortality risk for any DTaP vaccine type when compared with trivalent DTaP vaccines in any of the age cohorts for the combined data period (Table 2). When stratified by calendar year, an elevated risk in all-cause mortality was observed for the 2-month dose cohort in 2003 (p = 0.003) (Appendix Table 4).

3.3. Secondary outcome (non-specific cause of death within 30-days)

When restricting deaths to non-specific causes, 30-day mortality rates declined with increasing age in the 2, 4 and 6-month cohorts (68.1, 43.4, to 21.7 deaths per 100,000 person-years, respectively). No difference in mortality was observed for DTaP vaccine types in either the 2-month and 6-month cohorts when compared with infants receiving trivalent DTaP vaccines. In the 4-month cohort, a reduction in non-specific cause mortality was seen with quadrivalent DTaP-IVP vaccines (HR 0.28 95% CI 0.09–0.91) compared with the trivalent DTaP vaccines (Table 2).

3.4. Sensitivity analysis

When limiting mortality record outcomes to higher linkage accuracy matches of 99.5%, 30-day all-cause and non-specific cause mortality results were similar to the primary analysis. In the 4-month cohort, a decreased risk in non-specific mortality was again seen with DTaP-IVP vaccines when compared with trivalent DTaP vaccines (HR 0.11 95% CI 0.02–0.79) and also for all-cause mortality (HR 0.42 95% CI 0.19–0.93) (Appendix Table 5).

4. Discussion

4.1. Principal findings

In this large vaccinated cohort, the absolute number of deaths in children following DTaP vaccination was low. No statistically significant difference in 30-day all-cause mortality risk was observed across different combination DTaP vaccines in the 2, 4 and 6-month cohorts, however, mortality rates for DTaP vaccine types varied. For example, in the 2-month cohort, all-cause mortality rates for the quadrivalent DTaP-HepB and DTaP-IVP vaccines were higher than for trivalent DTaP vaccines, while hexavalent DTaP vaccines showed lowest all-cause mortality. In the 4-month cohort, all-cause mortality rates were more similar across DTaP vaccines except for the quadrivalent DTaP-IVP where all-cause mortality rate was nearly 2-fold lower than other DTaP vaccines. Assessment of mortality risk across the different vaccines showed no markedly elevated all-cause or non-specific cause mortality risk for any single quadrivalent or hexavalent DTaP vaccine across the 12-year period of surveillance, at any age cohort. However, a decrease in non-specific mortality was observed for the quadrivalent DTaP-IPV vaccine in the 4-month cohort. The effect size estimates did not conform to any consistent pattern to indicate elevated all-cause mortality risk with combination multivalent vaccines.

When we stratified by calendar year, a difference in 30-day all-cause mortality between DTaP vaccine groups was seen with the 2-month dose cohort, in 2003. Inspection of this mortality difference identified a higher mortality rate for the quadrivalent DTaP-HepB vaccines compared to trivalent DTaP vaccines.

4.2. Interpretation

Quadrivalent and hexavalent DTaP vaccines did not have an elevated all-cause or non-specific mortality risk compared to trivalent DTaP at 30-days post-vaccination. These results suggest the co-administration of additional vaccines in combination with DTaP vaccines (i.e. combination multivalent vaccines) over time do not contribute to increased mortality, either all-cause or non-specific cause mortality. The variability observed in the mortality rates, effect estimates and moderately-wide confidence intervals for individual DTaP vaccines is attributable to the low child mortality in each age cohorts. It is plausible statistical differences between vaccine types may be observed with a larger sample size. For example, the hexavalent vaccine has the largest sample size, and all but one of the effect estimates (at 4-months) indicates a protective mortality effect, which requires a larger sample to confirm or refute.

The reduced non-specific mortality risk seen with the quadrivalent DTaP-IPV vaccines compared to trivalent DTaP at 4-months (and for all-cause mortality in the sensitivity analysis) reflected the few (<5) deaths and the smaller population size receiving quadrivalent DTaP-IPV vaccines in comparison with other vaccine types. This vaccine had limited usage in Australia, recommended for use in three smaller jurisdictions. It is possible that if administered to a larger population, a reduced mortality risk would no longer be evident.

The difference in all-cause mortality risk in the year 2003 (seen only with the 2-month cohort) is conceivably due to the multiple statistical testing undertaken, as no additional statistical differences in mortality between the two DTaP vaccines were seen in earlier years (1999–2002). Furthermore, the 5-fold difference in mortality rate for the quadrivalent DTaP-HepB vaccine is driven by the low number of deaths observed in the comparator trivalent DTaP vaccine, as mentioned above.

4.3. Strengths and limitations

As well as discriminating between different combination DTaP vaccine types, our study is the first to distinguish outcomes for both all-cause and non-specific mortality within 30-days following three different doses of primary childhood vaccines. Data for this study relate to a large infant cohort receiving universally-funded vaccines as part of Australia's National Immunisation Program and one of the largest populations studied. Vaccine receipt is recorded on ACIR with >90% of children receiving recommended vaccines by 12 months of age although lower amongst Indigenous children [30–32]. While infants analysed for the study were from a national register, children receiving pentavalent DTaP-HepB-polio or DTaP-Hib-polio vaccines were excluded from analyses. In Australia, the pentavalent vaccines were selectively administered to predominately Indigenous children in the Northern Territory (NT) and regional areas of Western Australia (WA). These children are known to have higher rates of illness including respiratory, infectious and parasitic disease, with Indigenous infants hospitalised for these conditions at three times the rate of non-Indigenous children [33]. Among infants aged up to 12 months, children administered pentavalent vaccines represented only a small proportion of all infants receiving DTaP vaccines (<1%), therefore their exclusion may reflect an under-representation of children in regional NT and WA in our results.

Due to the high rate of immunisation in Australia (>90%) and low absolute number of deaths, we were unable to reliably compare mortality with DTP-unvaccinated children. This limits understanding of mortality rate differences between vaccinated and non-vaccinated children.

A further possible study limitation was our construction of age-based cohorts as a proxy for dose number in the sequence of DTaP vaccines. Three cohorts were created using age at administration, ranging from a 6-week span (2-month cohort – representing dose 1) or 8-weeks for the 4 and 6-month cohorts rather than using the specified dose. Other studies [23,34] have also shown wide variation in timing of administration for scheduled vaccine doses, supporting our rationale for age limits as a basis to define cohorts rather than dose. We found the majority of vaccines in each age-based cohort reflected appropriate dose number for scheduled age, however, percentage of children receiving the scheduled dose declined as age increased. In the 2-month cohort 99.9% of children received Dose 1, in the 4-month cohort 93.4% received Dose 2 and in the 6-month cohort 78.7% received Dose 3. This selection of children based on age at immunisation is likely to minimise selection biases related to delayed (or early) vaccination [24] which could not be measured in our study.

Another study limitation arises from probabilistic linkage errors in matching immunisation exposure with mortality events. In our primary analysis we applied a linkage weight cut-off corresponding to a linkage weight which included all possible matches with moderately high accuracy (89%). We elected to include all available good linkage matches to maximise the size of the sample for identifying any association between vaccine and mortality [18]. However, some linked immunisation and mortality records representing false-positive links may have been included in cohorts. Conversely, missed links may have occurred due to name misspellings such as those arising with Indigenous children or other ethnic groups. Indigenous children represent 5.7% of the Australian population aged 0–7 years [29]. Hence, the proportion of Indigenous children is underestimated in this data linkage to varying extents for different DTaP vaccines (2.9–4.5%). With the pentavalent DTaP vaccines excluded from our analyses, there are no other instances over the 12-year period where one particular DTaP vaccine was administered only to Indigenous populations. Hence, it is likely the proportion of false-positive links is unrelated to combination DTaP vaccine type administered and therefore unlikely to bias our estimates of relative mortality between vaccine types.

Trivalent vaccines were predominately in use from 1999 to 2005, whereas hexavalent vaccines, introduced in 2005, incrementally increased in use to 97% in 2009 and 2010. Concerted efforts to improve Indigenous identification in ACIR has seen reporting of Indigenous status, compared with expected proportions, increase from 42% in 2002 to 95% in 2006 [32,35]. The differences in 'unknown' Indigenous identification between trivalent (36%) and hexavalent DTaP vaccines (4%) likely reflect the secular trends in usage of DTaP vaccines and improvements in reporting of Indigenous status in immunisation records over time.

To address potential for bias in linkage resulting from misclassification of mortality status, a sensitivity analysis was undertaken, restricting links to those with greater specificity. Results were similar to the primary and secondary analysis as previously described, except for the 4-month cohort where a statistically significantly reduced all-cause mortality risk was seen with DTaP-IVP vaccines compared with trivalent DTaP vaccines.

A further limitation of our study is that we only had access to immunisation data up to 2010. As current recommendations on the Australian immunisation schedule is for all jurisdictions to use the hexavalent DTaP vaccine, our results are likely to be consistent with current practice. Further research will be required to confirm these results.

4.4. Significance & future research

While variation in mortality rates was seen across combination DTaP vaccines we found no single DTaP vaccine had elevated mortality risk. This finding should provide policy-makers, immunisation providers and parents with confidence in the safety of these vaccines. Combination DTaP vaccines are the cornerstone of childhood immunisation programs and remain an important strategy for averting infectious diseases and their consequences, such as death and disability. This study also provides information for regulatory bodies on mortality rates in early infancy in a vaccinated population. This may serve a useful benchmark for any suspected mortality increases when new vaccines are introduced to the NIP [36].

We have demonstrated for the first time, the utility of national immunisation registry data for vaccine safety assessment in Australia when linked to the National Death Index. Priority should be given to linking immunisation data to other datasets such as hospital inpatient and emergency department datasets to enable monitoring for potential morbidity following vaccination. Large-scale, population-wide epidemiological studies that demonstrate

the safety of vaccinations are likely to increase confidence in immunisation receipt and enhance population uptake. Immunisation data for these analyses were made available only to 2010 and future investigations could include a program of ongoing study to monitor mortality risk in subsequent years. Other NIP vaccines could also be studied and proactive monitoring undertaken as new vaccine products are introduced.

5. Conclusion

In this large cohort of Australian children, there is no evidence to support exposure to different multivalent DTaP vaccines is associated with mortality. No increased mortality risk was observed with different types of combination DTaP vaccines administered in the first 6-months of life.

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Contributors

All authors attest they meet the ICMJE criteria for authorship. All authors contributed to study design and interpretation of data. KMD and MSG acquired the data. KMD undertook the statistical analysis, supported by NLP. All authors contributed to the interpretation of results. KMD wrote the first draft of the paper with all authors reviewing drafts and revising it critically for important intellectual content. All authors have approved the final manuscript. KMD is guarantor, with full data access and accepts responsibility for data integrity and accuracy of data analysis.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: KMD & MSG had grant support for the submitted work from the Australian Research Council and partner organisation support from the South Australian Department of Health & Ageing, NSW Ministry of Health, SAEFVic and APSU for undertaking the research. MSG is also the principal investigator and grant recipient of a non-related NHMRC Partnership Project which involves multiple partners including GSK. The study is not vaccine specific and GSK have provided a contribution towards the grant. GSK is the manufacturer of multivalent pertussis vaccines used in Australia.

Ethics approval

Ethical approval was granted by the University of Adelaide Human Research Ethics Committee (H-148-2008), the Commonwealth Department of Health and Ageing Ethics Committee (Project 2/2009) and the AIHW Ethics Committee (EC2010-3-35).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2018.11.025.

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