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Review

Completeness and timeliness of diphtheria-tetanus-pertussis, measles-mumps-rubella, and polio vaccines in young children with chronic health conditions: A systematic review

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ABSTRACT

Objective: To systematically review literature on uptake and timeliness of diphtheria-tetanus-pertussis, measles-mumps-rubella, and/or polio-containing vaccines in infants who were born preterm, with a low birth weight, and/or with chronic health conditions that were diagnosed within the first 6 months of life.
Methods: Using a standardized search strategy developed by a medical librarian, records were extracted from MEDLINE, Embase, Database of Abstracts of Reviews of Effects, and CINAHL up to May 8, 2018.
Results: Out of the 1997 records that were screened, we identified 21 studies that met inclusion criteria. Eleven studies assessed vaccine coverage and/or timeliness in preterm infants, 6 in low birth weight infants, and 7 in children with chronic health conditions. Estimates of coverage in these populations were highly variable, ranging from 40% to 100% across the vaccines and population groups.
Conclusions: There is a lack of studies reporting coverage and timeliness of routine immunizations in special populations of children.
Policy implications: Our review suggests a need for improved surveillance of immunization status in special populations of infants, as well as a need for standardization of reporting practices.

Contents

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1. Introduction

Diphtheria-tetanus-pertussis (DTP), measles-mumps-rubella (MMR), and polio-containing vaccines (inactivated polio vaccine [IPV] and/or oral polio vaccine [OPV]) have been implemented into routine pediatric immunization programs worldwide for many years. According to the current World Health Organization (WHO) immunization guidelines, every child is expected to have received 3 doses and 2 boosters of DTP, 2 doses of MMR, and 3–4 doses of a polio-containing vaccine by 10 years of age [1]. With most immunizations being administered during the first 2 years of life, vaccines are an economical and effective health intervention for preventing childhood morbidity and mortality from communicable diseases, regardless of socioeconomic status. In addition to sustained individual immunity throughout childhood, routine pediatric immunizations may also confer indirect protection to the population when coverage levels are high. However, surpassing the critical threshold for an extremely contagious disease, such as measles, can require population-level vaccination rates of over 90% [2]. Moreover, delayed receipt of routine vaccines increases the period of vulnerability for infection and transmission of pathogens. Thus, to improve public health and reduce the burden of infectious diseases, it is pertinent to maintain high rates of coverage of routine childhood immunizations and ensure that their receipt is timely and according to schedule.

Infants who are born preterm (<37 weeks of gestation), with a low birth weight (<2500 g), and/or with chronic health conditions (a diagnosable disease or disorder with life-long health implications; e.g., cerebral palsy; congenital heart disease; cystic fibrosis) may be more susceptible to some communicable diseases and incur more severe manifestations of illness following infection [3,4]. The WHO recommends that all children, with few exceptions (e.g., those with certain immunodeficiencies, with severe allergies to vaccine components, or those who have had severe adverse reactions to vaccines in the past), receive vaccinations according to a country's immunization schedule [5]. Given the significance to public health, it is important to evaluate coverage and timeliness of routine childhood vaccinations in these special populations. This article presents a systematic review of the literature reporting on uptake and timeliness of DTP, MMR, and/or polio vaccines in populations of children under 5 years of age born at preterm gestation, with low birth weight, and/or having at least one chronic health condition that was diagnosed at birth or within the first 6 months of life.

2. Methods

We registered the protocol for this review on PROSPERO (CRD42017072075) and prepared this manuscript in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [6,7].

2.1. Search strategy and selection criteria

The search strategies were designed and conducted by a medical librarian experienced in systematic reviews, using a method designed to optimize term selection [8]. The following databases were searched: MEDLINE including Epub Ahead of Print, In-Process & Other Non-Indexed Citations (1946- May 8, 2018), Embase (1980- May 8, 2018), Database of Abstracts of Reviews of Effects - DARE (1st Quarter 2016 Issue) using the Ovid interface, and CINAHL (up to May 8, 2018). The SIGN methodological filter for observational studies was used for the Embase search, but no other language or study design limits were imposed [9]. Details of the search strategies are presented in Appendix S1.

Since the principal objective of this systematic review was to analyze coverage and timeliness of childhood vaccines in real-world settings, only observational studies were included. Studies had to provide coverage and/or timeliness data on at least 1 of the 3 vaccines under study (DTP, MMR, and IPV/OPV), either individually or as combination vaccines (e.g., DTP-IPV-Hib and MMRV). Since only two studies analyzed coverage of the 2nd dose of MMR, we made a post-hoc decision to limit the assessment of coverage to the 1st dose [10,11].

Although the WHO and most countries have guidelines on how to measure coverage and timeliness in the population, they often differ according to local context. To allow for expected heterogeneity in defining coverage and timeliness across the different study settings and time periods, we adopted broad definitions tailored to our review. We considered coverage to be the total proportion of infants who have received a vaccine at the time of measurement (which may be months to years after the recommended age of immunization) and timeliness as the proportion of infants who are considered to have received vaccines on-time according to local schedules (variably defined across settings, but commonly considered as receipt within a few weeks to 2 months after the recommended age for an immunization) [12]. The timing of vaccination differs depending on study setting due to differences in public health policies and immunization schedules, the specific types of vaccines being used, and the level of disease burden in a particular region (see Table S1 for examples of recommended schedules from the WHO, the United States, and Canada).

We required studies to have extractable numerator and denominator values — those that only presented data visually in graphs, thus requiring extrapolation, were not accepted due to the potential for miscalculation. The outcomes of interest had to have been recorded for children between the ages of 0–5 years, and the study population had to comprise children who had either been born at preterm gestation, born with low birth weight, and/or have at least one chronic health condition that was diagnosable at birth or within the first 6 months of life. Studies of patient populations with immunodeficiencies, whether primary or secondary in origin, were not included since some of these patients may have

contraindications to live vaccines (e.g., OPV, MMR) or may have required supplemental vaccine doses in addition to routine immunizations to achieve immunogenic levels of antibodies [4]. Furthermore, patients scheduled to undergo immunosuppressive treatments (e.g., organ transplant) may have been placed on an accelerated schedule to ensure an immunogenic response was achieved prior to treatment [13].

After initial online removal of duplicate records, those retrieved by the electronic search were downloaded and imported into a Reference Manager database, where any remaining duplicate references were removed. We then uploaded the records into Abstrackr for initial title and abstract screening by two independent reviewers (EJW and NI). Those studies remaining after this initial screening were subjected to full-text screening by both reviewers, and we searched the reference lists of all studies meeting inclusion criteria for any missed literature. Disagreements were resolved at the end of each round of screening; no further resolution was needed.

2.2. Data extraction and assessment of methodological quality

We extracted information from studies meeting inclusion criteria into an Excel spreadsheet. The data extracted included: author; date of publication; PubMed ID; duration and size of study; setting; age range of population; health condition(s) among children in the study; inclusion and exclusion criteria; immunizations received; coverage and timeliness estimates with 95% confidence intervals, where reported; and potential study limitations, including sources of bias. Numerator and denominator values for all estimates were extracted from the original studies. To standardize measurements, we reported timeliness as the proportion of infants who received vaccines on-time (as opposed to the proportion of infants that had delayed vaccine receipt) and extracted as much clarifying information from the study as possible, since we expected heterogeneity in these definitions owing to variation in local schedules. Additionally, we computed Fisher's exact (Clopper-Pearson) confidence intervals for coverage and timeliness estimates using numerator and denominator values reported in the studies. We conducted a bias assessment using a modified critical appraisal checklist for prevalence studies created by the Joanna Briggs Institute [14]. This checklist assessed four items: degree of relatedness between the true population and study subjects, description of the study population and setting, measurement of outcomes, and appropriateness of the statistical analyses and their reporting.

3. Results

3.1. Study selection

Database searching yielded 2066 records, of which 69 were duplicates. Two reviewers independently screened 1997 abstracts, identifying 67 records eligible for full-text review. Of the 67 papers, we excluded 44 for the following reasons: coverage estimates were not vaccine specific (n = 17), the chronic health condition(s) of the study population did not meet our inclusion criteria (n = 11), data elements were missing (n = 4), data were only visually presented in graphs (n = 1), and non-English/French or duplicate records (n = 11). We excluded an additional 3 studies during the data extraction stage due to: missing data in supplemental tables (n = 1), inappropriate study design (n = 1), and lack of numerator/denominator values (n = 1). Reference lists of the 20 studies eligible for qualitative synthesis were searched for records that had not been retrieved during database searching. This yielded 1 additional paper, providing a total of 21 papers included in the systematic review (Fig. 1). In total, this review includes immunization data from 201,751 infants.

3.2. Study characteristics

Of the 21 studies included in this review, 7 were cross-sectional [15–21], 7 were prospective cohort [22–28], 4 were case-control [10,11,29,30], and 3 were retrospective cohort studies [31–33]. Two of the prospective cohort studies were nested within randomized control trials analyzing vitamin A supplementation in neonates [23,28]. The majority of studies were conducted in high-income countries (n = 17), with the remaining studies being conducted in an upper-middle-income country (n = 1), lower-middle-income countries (n = 2), and a low-income country (n = 1). Country classifications were based on the World Bank's income thresholds for 2018, which does not necessarily represent the income-level at the time a study was conducted [34]. The main populations assessed by the studies meeting inclusion criteria were infants born at preterm gestation (n = 11) or at a low birth weight (n = 6; Table 1). In some studies, preterm and low birth weight groups were further stratified (e.g., extremely preterm, very low birth weight); however, the definitions used for these subgroups differed across studies. Neurologic defects (n = 2) [10,20] and inborn errors of metabolism (n = 2) [11,30] were the most commonly-studied chronic health conditions. Other conditions studied included sickle-cell disease (n = 1) [16], rare genetic diseases (n = 1) [35], and cystic fibrosis (n = 1) [26].

Criteria for on-time receipt and coverage varied by study; some studies analyzed coverage and timeliness at a specific age boundary, whereas others performed measurements at monthly intervals. The window for on-time vaccination also differed from two-weeks [15] to 70 days [31] after the recommended age of immunization, with there being a general convergence around 1 month. One study accounted for catch-up schedules so that if an infant received the first dose of a series late but followed the respective schedule thereafter, only the first dose would be considered delayed [15]. Additionally, one study allowed for earlier-than-recommended vaccinations in their timeliness analysis, considering those administered fewer than 5 days before the minimum recommended age to be on-time [32].

3.3. Diphtheria-tetanus-pertussis vaccination

Estimates of DTP coverage (n = 15) and timeliness (n = 5) were reported by 19 studies (Table 2), a majority of which assessed these metrics among infants born preterm (n = 10; Fig. S2). Coverage and timeliness estimates were highly variable, ranging from 44.8% to 100% and from 15.4% to 80.7%, respectively. A majority of papers (n = 11) reported the use of combination vaccines that included IPV (n = 10), *Haemophilus influenzae* type B vaccine (Hib; n = 9), and/or hepatitis B vaccine (HBV; n = 5).

3.4. Measles-mumps-rubella vaccination

A total of 12 papers analyzed coverage (n = 12) and timeliness (n = 2) of MMR, with coverage estimates ranging from 7.6% to 95.4% (Table 3). However, the study that reported a coverage estimate of 7.6% for the second dose of MMR is a clear outlier, which may be attributable to the fact that some of the study population was born in a time period when the second dose of MMR was not routinely recommended [10]. In the two studies with extractable data, timeliness for the first dose of a measles containing vaccine ranged from 56.6% to 58.6% [18,28]. Timing of immunization and number of doses received varied between studies depending

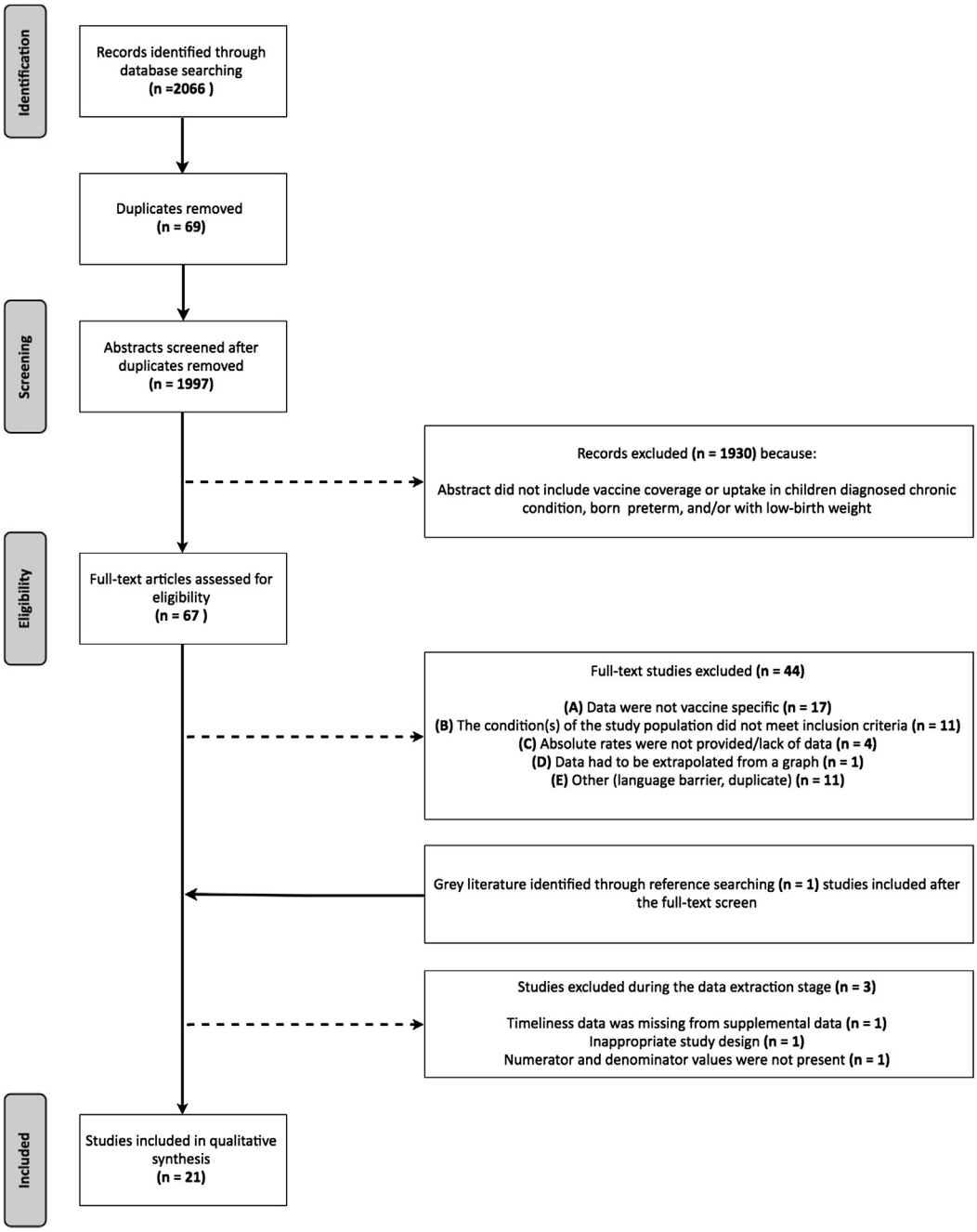

Fig. 1. PRISMA flowchart of database searching and study selection.

on the local schedule; generally, infants receive either 1 or 2 doses of MMR before 2 years of age. In one study, MMR was given in combination with varicella (MMRV); all others reported the use of MMR or a measles-only containing vaccine [30].

3.5. Polio vaccination

Out of the 21 studies, 20 provided coverage and/or timeliness data for polio vaccination (Table 4). Coverage and timeliness were reported by 16 and 6 studies respectively, with IPV being the most frequently-reported vaccine (n = 13). Overall coverage estimates ranged from 40.8% to 100% and timeliness from 11.5% to 80.7%. Combination vaccines (DTaP-IPV ± Hib ± HBV) were typically administered 4 times before the age of 2, whereas polio-only containing vaccines were typically administered 2–3 times within the same age range. Studies that exclusively reported OPV data (n = 3) either studied patients born before 2006 [15,18–20,30,33] or a population from a lower-income country [28].

3.6. Overall vaccination

One study provided an assessment of overall complete coverage among children with spina bifida at 2 years of age for 4 doses of DTP, 3 doses of OPV, and 1 dose of MMR [20]. Coverage was 58.3% for DTP4, MMR1 and OPV3 measured at 2 years of age. We included this study despite not having vaccine-specific estimates, since the overall estimate encompassed only the vaccines included in this review.

Table 1
Characteristics of studies included in the systematic review.

First author, year	Study location	Study design	Size of study	Study duration	Age of population	Chronic condition(s)	Inclusion criteria	DTP	MMR	Polio
Tillmann, 2005	University Children's Hospital, Basel, Switzerland	Case-control	n = 100	Infants born between March 1999 to April 2001	0–2 years	Chronic neurologic diseases (e.g., epilepsy, cerebral palsy, myopathies)	Patients diagnosed with congenital neurologic diseases at birth or within the first 6 months of life		✓	✓
Tillmann, 2001	University Children's Hospital, Basel, Switzerland	Case-control	n = 60	Infants were born between Jan 1994 to Dec 1995, with a study follow-up occurring in 1999	At the end of the observation period, 4–5 years	PTB (<37 weeks) and very LBW (<1500 g)	PTB infants who survived for at least 4 years, were born between 1994 and 1995, who had been admitted to the NICU and had follow-up information	✓	✓	✓
Tozzi, 2014	Italy, five regions:Friuli Venezia-Giulia, Tuscany, Marche, Lazio, and Calabria	Prospective cohort	n = 1091	Infants were born during 2003–2005, with a follow-up occurring at two years of age corrected for prematurity	0–2 years	Very PTB (22–31 weeks)	All very PTB infants enrolled in the ACTION cohort who survived until the end of the observation period	✓	✓	✓
Klein, 2011	Northern California Kaiser Permanente (NCKP), United States	Case-control	n = 77	Electronic medical records retrieved from 1990 to 2007	0–2 years	Inborn errors of metabolism (IEM) – subpopulations based on severity of disease	Infants diagnosed with an IEM who were insured at NCKP for the first two years of life	✓	✓	✓
Magoon, 1995	Aultman Hospital, Canton, United States	Cross-sectional	n = 111	Infants born between fall 1982 and spring 1991	0–2 years	High-risk PTB (<37 weeks)[a]	Infants that had at least one follow-up at the hospital's NICU and met high-risk criteria[a]	✓	✓	✓
Cerutti, 2015	Hôpital Necker-Enfants Malades, Paris, France	Case-control	n = 128	Study duration was Nov. 1st, 2013 to March 30th, 2014	0–2 years	IEM – subpopulations based on severity of disease	Patients with an IEM that had regular follow-ups at the study hospital during the period of investigation	✓	✓	✓
Pandolfi, 2012	Italy Specialty clinics in three Italian regions, unspecified	Cross-sectional	n = 187	Patients were surveyed in 2009	0–2 years	Cystic fibrosis, Down syndrome, and neurological diseases including epilepsy and/or neurological conditions impairing the respiratory function	Infants diagnosed with one of the chronic conditions who attended the specialty clinics during the study period	✓	✓	✓
Nacoulma, 2006	Yalgado Ouédraogo Hospital Center, Ouagadougou, Burkina Faso	Cross-sectional	n = 122	Patients were surveyed during Oct. 2005 to March 2006	0–6 months	Sickle cell disease	Sickle cell patients with a vaccination card that did not have any history of major hospitalizations	✓		✓
O'Leary, 2016	Kintampo Health Research Centre, Kintampo, Ghana	Prospective cohort (nested within RCT)	n = 3592	Newborns were recruited between Aug. 16th, 2010, and Nov. 7th, 2011	0–24 weeks	LBW infants (2000–2499 g), very LBW infants (1500–1999 g), and extremely LBW infants (<1500 g)	LBW infants that had taken part in a vitamin A trial	✓		
Denizot, 2010	Nantes University Hospital, Nantes, France	Prospective cohort	n = 602	Infants born between Jan. 2003 to July 2005	0–2 years	PTB (≤34 weeks)	All PTB infants that were discharged from the NICU and were a part of a follow-up network	✓		✓
Woestenberg, 2013	The Netherlands; nation-wide	Retrospective cohort	n = 111197	Infants born between Jan. 1st, 2006, to Dec. 31st, 2010	0–9 weeks	Extreme PTB (<32 weeks), PTB (32–36 weeks), extremely LBW (<1000 g), very LBW (1000–1499 g), and LBW (2000–2499 g) infants	All infants with a known birth weight, gestational age, and vaccination status	✓		✓

(*continued on next page*)

Table 1 (*continued*)

First author, year	Study location	Study design	Size of study	Study duration	Age of population	Chronic condition(s)	Inclusion criteria	DTP	MMR	Polio
Wilson, 2012	Ontario, Canada	Retrospective cohort	n = 65687	Infants born between April 1st, 2002 to March 31st, 2009	0–6 months	Near term (33–36 weeks), very PTB (28–32 weeks), and extremely PTB (<28 weeks)	Children who were present in a registered persons database and had provincial insurance up until 7 months	✓		✓
Pinquier, 2009	Normandy, France	Prospective cohort	n = 87	Infants were born in 2000, with a follow-up in 2003	0–2 years	PTB (>22 weeks, <33 weeks)	Infants of the HandiNord cohort that were born PT without karyotype abnormalities and/or congenital malformations	✓	✓	✓
Masson, 2015	Paris, France	Prospective cohort	n = 114	Patients were recruited from Nov. 2009 to Feb. 2010	0–2 years	Cystic fibrosis	Patients who participated in the MucoFlu study	✓	✓	✓
Batra, 2009	Southern California Kaiser Permanente (SCKP), United States	Retrospective cohort	n = 7785	Infants were born between Jan. 1st, 1997 to Dec. 31st, 2002	0–1 year	Extremely LBW (<1000 g), very LBW (1000–1499 g), and LBW (1500–2499 g)	Infants were enrolled in the SCKP health plan until at least one year of age	✓		✓
Esposito, 2016	University of Milan, Italy	Cross-sectional	n = 57	Patients were surveyed between Nov. 1st, 2014 to April 30th, 2015	0–15 months	Rubinstein-Taybi syndrome, Sotos syndrome, and Beckwith-Wiedemann syndrome	Infants with a history of follow-ups in the pediatric highly intensive care unit of the university	✓	✓	✓
Crawford, 2009	Melbourne, Australia	Cross-sectional	n = 100	Infants were born between July 2003 to June 2005	0–18 months	PTB (<32 weeks)	Patients were graduates from a level 3 neonatal unit in the Royal Children's Hospital and the Mercy Hospital for Women	✓	✓	✓
Cremer, 2002	Cologne Children's Hospital, Germany	Cross-sectional	n = 124	Infants born between Dec. 1993 to March 1996	0–6 months	PTB (<37 weeks) and LBW (<1500 g)	PTB infants with LBW whose parents provided vaccination information through a questionnaire			✓
Ochoa, 2014	Lima, Peru	Prospective cohort	n = 198	Infants were assessed for eligibility during March 2009–2010	0–1 year	PTB (<37 weeks) and very LBW (1000–1499 g) or extremely LBW (<1000 g)	PTB infants with a birth-weight under 1500 g who were born or transferred to the hospitals under study	✓		✓
Raddish, 1993	Boston Children's Hospital, United States	Cross-sectional	n = 120	Patients were recruited between Feb. to Aug. 1990	0–2 years	Spina bifida	All patients with spina bifida that visited the myelodysplasia clinic at the hospital under study	✓	✓	✓
Laforgia, 2018	Bari Policlinico University General Hospital, Italy	Cross-sectional	n = 159	Infants were born in 2013	0–2 years	PTB (<37 weeks)	All PTB infants that were discharged from the NICU in 2013	✓	✓	✓
Upadhyay, 2017	Haryana, India	Prospective cohort (nested within RCT)	n = 10 240	Newborns were recruited between June 24th, 2010, and July 1, 2012	0–1 year	LBW (<2500 g)	LBW infants that had taken part in a vitamin A trial	✓	✓	✓

LBW: low birth weight, PTB: preterm birth.

[a] In the study by Magoon et al., high risk preterm infants had at least one of the following: "a birth weight of <1750 g, need for mechanical ventilation for more than 1 day, diagnosis of significant asphyxia, meningitis, and intracranial hemorrhage."

4. Discussion

4.1. Main findings

Our systematic review has elucidated a paucity of published estimates of coverage and timeliness of routine pediatric immunizations in infants born preterm, at a low birth weight, and/or with chronic health conditions. A total of 21 studies, involving 201,751 infants, was identified for this review. Preterm infants were the most commonly-reported special population and polio and DTP were the most frequently-reported vaccines. We found that estimates of coverage and timeliness of routine childhood

Table 2
Summary of studies that analyzed coverage and/or timeliness of diphtheria-tetanus-pertussis vaccines.

First author, year of publication	Condition(s)	Vaccine type	Dose #: % coverage (95% CI)	Dose #: % on-time receipt (95% CI)
Tillmann, 2001 [27]	PTB (<37 weeks) and LBW (<1500 g)	DTaP	1: 98% (91.1–100) 4: 80% (67.7–89.2)	Not reported
Tozzi, 2014 [19]	Very PTB (22–31 weeks)	DTaP-IPV-HBV-Hib	1: 95.1% (93.6–96.3) 3: 92.1% (90.4–93.7)	Cannot extrapolate
Klein, 2011 [28]	Severe IEMs	DTwP and DTaP	4: 71.9% (53.3–86.3)	Not reported
	Chronic IEMs		4: 85.7% (42.1–99.6)	
	Stable IEMs		4: 73.7% (56.9–86.6)	
Magoon, 1995 [12]	High-risk PTB infants	DTP	Not reported	1: 15.6% (5.3–32.8)
	≤29 weeks			
	30–31 weeks			1: 15.4% (4.4–34.9)
	32–33 weeks			1: 27.0% (13.8–44.1)
	34–37 weeks			1: 44.1% (27.2–62.1)
Cerutti, 2015 [29]	Severe IEMs	DTaP-IPV-HBV-Hib	4: 86.6% (77.3–93.1)	Not reported
	Chronic IEMs		4: 80.0% (61.4–92.3)	
	Stable IEMs		4: 87.5% (61.7–98.5)	
Nacoulma, 2006 [13]	Sickle cell disease	DTaP-IPV	1: 98.4% (94.2–99.8) 2: 97.5% (93.0–99.5) 3: 97.5% (93.0–99.5)	Not reported
O'Leary, 2016 [20]	LBW (2000–2400 g)	DTP	1: 96.2% (95.5–96.9) 3: 95.2% (94.4–96.0)	Not reported
	Very LBW (1500–1999 g)		1: 86.9% (83.4–89.9) 3: 85.1% (81.5–88.3)	
	Extremely LBW (<1500 g)		1: 68.4% (59.1–76.7) 3: 66.7% (57.4–75.1)	
Denizot, 2011 [21]	PTB, <28 weeks	DTaP-IPV-Hib	Not reported	3: 51% (38–70) 4: 68% (54.5–79)
	PTB, 28–30 weeks			3: 40.5% (32–49) 4: 65% (57–73)
	PTB, 31–32 weeks			3: 37% (22–44.5) 4: 65% (57–72)
	PTB, 33–34 weeks			3: 37.5% (32–43) 4: 69% (63–74)
Woestenberg, 2014 [30]	Extreme PTB (<32 weeks)	DTaP-IPV	Not reported	1: 66% (64.9–67.1)
	PTB (32–36 weeks)			1: 76% (75.6–76.3)
	Extremely LBW (<1000 g)			1: 56.2% (53.7–58.6)
	Very LBW (1000–1499 g)			1: 66.6% (65.2–67.9)
	LBW (2000–2499 g)			1: 75.1% (74.7–75.5)
Wilson, 2012 [31]	Near term birth (33–36 weeks)	DTaP-IPV-Hib	Not reported	1: 80.7% (80.4–81.0) 2: 75.4% (75.1–75.8) 3: 71.1% (70.7–71.5)
	Very PTB (28–32 weeks)			1: 69.7% (68.7–70.6) 2: 77.1% (76.3–78.0) 3: 71.1% (71.2–73.1)
	Extremely PTB (<28 weeks)			1: 14.6% (13.1–16.1) 2: 65.5% (63.5–67.5) 3: 69.5% (67.5–71.5)
Pinquier, 2009 [22]	PTB (>22 weeks, <33 weeks)	DTaP-IPV-Hib	3: 44.8% (34.1–55.9) 4: 82.8% (73.2–90.0)	Not reported
Masson, 2015 [23]	Cystic fibrosis	DTaP-IPV-Hib	4: 86.0% (78.2–91.8)	Not reported
Batra, 2009 [32]	Extremely LBW (<1000 g)	DTwP and DTaP	1: 76.9% (73.0–80.5) 2: 64.6% (60.3–68.8) 3: 55.9% (51.5–60.3)	Not reported
	Very LBW (1000–1499 g)		1: 91.0% (88.8–92.9) 2: 78.7% (75.7–81.5) 3: 68.6% (65.3–71.9)	
	LBW (1500–2499 g)		1: 94.4% (93.8–95.0) 2: 84.8% (83.9–85.7) 3: 74.3% (73.2–75.4)	
Esposito, 2016 [34]	Rubinstein-Taybi syndrome	DTaP-IPV-HBV-Hib	3: 80.0% (51.9–95.7)	Not reported
	Sotos syndrome		3: 78.6% (49.2–95.3)	
	Beckwith-Wiedemann syndrome		3: 71.4% (51.3–86.8)	
Crawford, 2009 [15]	PTB (<32 weeks)	DTaP	1: 95.0% (88.7–98.4) 2: 95.0% (88.7–98.4) 3: 94.0% (87.4–97.8)	Not reported
Ochoa, 2015 [24]	PTB (<37 weeks) and very LBW (1000–1499 g)	DTaP-Hib-HBV	1: 100% (97.7–100) 2: 98.7% (95.5–99.9) 3: 96.8% (92.7–99.9)	Not reported
	PTB (<37 weeks) and extremely LBW (<1000 g)		1: 100% (91.4–100) 2: 92.7% (80.1–98.5) 3: 80.5% (65.1–91.2)	
Raddish, 1993 [17]	Spina bifida	DTP*	4: 58.3% (49.0–67.3)	Not reported
Laforgia, 2018 [18]	PTB (<37 weeks)	DTaP-IPV-HBV-Hib	1: 98.7% (95.5–99.9) 2: 91.2% (85.7–95.1) 3: 87.3% (81.1–92.1)	Not reported

(*continued on next page*)

Table 2 (*continued*)

First author, year of publication	Condition(s)	Vaccine type	Dose #: % coverage (95% CI)	Dose #: % on-time receipt (95% CI)
Upadhyay, 2017 [25]	LBW (<2500 g)	DTP	1: 74.1% (73.2–75.0) 2: 58.3% (57.3–59.3) 3: 45.4% (44.4–46.4)	1: 48.3% (47.2–49.4) 2: 32.2% (31.0–33.4) 3: 19.3% (18.2–20.5)

LBW: low birth weight, PTB: preterm birth.

Table 3
Summary of studies that analyzed coverage and/or timeliness of measles-mumps-rubella vaccines.

First author, year of publication	Condition(s)	Vaccine type	Dose #: % coverage (95% CI)	Dose #: % on-time receipt (95% CI)
Tillmann, 2005 [26]	Congenital neurological deficits	MMR	1: 69.7% (57.2–80.4) 2: 7.6% (2.5–16.8)	Not reported
Tillmann, 2001 [27]	PTB (<37 weeks) and LBW (<1500 g)	MMR	1: 80.0% (67.7–89.2)	Not reported
Tozzi, 2014 [19]	Very PTB (22–31 weeks)	MMR	1: 84.0% (81.8–86.2)	Cannot extrapolate
Klein, 2011 [28]	Severe IEMs Chronic IEMs Stable IEMs	MMR and MMRV	1: 81.3% (63.6–92.8) 1: 71.4% (29.0–96.3) 1: 78.9% (62.7–90.5)	Not reported
Cerutti, 2015 [29]	Severe IEMs Chronic IEMs Stable IEMs	MMR	2: 68.3% (57.1–78.1) 2: 63.3% (43.9–80.1) 2: 50.0% (24.7–75.4)	Not reported
Pinquier, 2009 [22]	PTB (>22 weeks, <33 weeks)	MMR	1: 95.4% (88.6–98.7)	Not reported
Masson, 2015 [23]	Cystic fibrosis	MMR	1: 87.7% (80.3–93.1)	Not reported
Esposito, 2016 [34]	Rubinstein-Taybi syndrome Sotos syndrome Beckwith-Wiedemann syndrome	MMR	1: 40.0% (16.3–67.7) 1: 50.0% (23.0–77.0) 1: 46.4% (27.5–66.1)	Not reported
Crawford, 2009 [15]	PTB (<32 weeks)	MMR	1: 92.0% (84.8–96.5)	1: 58.6% (48.0–68.9)
Raddish, 1993 [17]	Spina bifida	MMR	1: 58.3% (49.0–67.3)	Not reported
Laforgia, 2018 [18]	PTB (<37 weeks)	MMR	1: 76.4% (69.0–82.8)	Not reported
Upadhyay, 2017 [25]	LBW (<2500 g)	Measles-only containing vaccine	1: 35.6% (34.7–36.6)	1: 56.6% (55.6–57.6)

LBW: low birth weight, PTB: preterm birth.

vaccinations in these special populations were highly variable, ranging from 40% to 100% and 12% to 81%, respectively, across the vaccines and population groups. It is important to note that the studies included in our review originated from different geographic settings and time periods, limiting our ability for direct comparisons across studies, as immunization schedules and vaccines types have varied significantly over the past two decades and continue to vary regionally today. There were no apparent differences between estimates of vaccine coverage or timeliness across the different country income levels; however, only studies originating from high-income countries assessed MMR vaccine coverage and timeliness. Additionally, study populations from high-income countries (n = 17) greatly outnumbered those from lower income countries (n = 4), which limited our ability to discern differences in immunization practices by country income level. It is recommended that all children, with few exceptions, receive routine childhood immunizations according to local schedules [5]. Thus, the small number of studies and large range of coverage and timeliness estimates within these special pediatric populations signifies a need for future research to address gaps in immunization practice and surveillance.

The types of vaccines assessed by these studies differed depending on the year of publication and setting. Those that exclusively reported OPV data either studied patients born before 2006 or originated from a lower-income country. This finding was expected given the WHO's Polio Endgame Strategic Plan (1988 to present), which, among other objectives, aims to replace OPV with IPV globally [36]. The use of IPV as the sole vaccine for polio prevention has been in place in high-income, polio-eradicated countries for many years – for instance, in the United States, OPV has been contraindicated since 2000 [37].

4.2. Interpretation

Overall, measurements of coverage and timeliness, the types of vaccines administered, immunization schedules, and diagnostic criteria for the study populations in our review differed depending on the study setting, methodology, and year of study. We observed multiple sources of heterogeneity, which constrained the potential for direct comparisons across studies and precluded performing any meta-analyses. For instance, although preterm birth and low birth weight have internationally-accepted definitions [38,39], the weeks of gestation and birth weight cut-offs varied across studies, particularly when further stratified into smaller subgroups (e.g., extremely preterm, very low birth weight). However, the largest contributor to inter-study heterogeneity was the methodology used for capturing coverage and timeliness data. Coverage measurements varied from overall estimates at specific age boundaries to dose-specific measurements at monthly or yearly intervals. Moreover, the dose-specific estimates of coverage could be considered a measurement of timeliness in some studies, depending on the age at which estimation was conducted. In one study, for example, coverage was assessed for the 3rd dose of DTP at 6 months of age, despite local immunization guidelines recommending the 3rd dose be received by 4 months [25]. This could be considered a timeliness estimate if timeliness were defined as receipt within 2 months of the recommended period. In the included studies, definitions of timeliness ranged from a delay of two-weeks [15] to upwards of a 70-day [31] delay from the recommended age for the immunization. Overall, measurements of timeliness and coverage were not only study-specific but oftentimes were also ambiguously defined.

Table 4
Summary of studies that analyzed coverage and/or timeliness of polio-containing vaccines.

Authors, year of publication	Condition(s)	Vaccine type	Dose #: % coverage (95% CI)	Dose #: % on-time receipt (95% CI)
Tillmann, 2005 [26]	Congenital neurological deficits	Unspecified	1: 98.5% (91.8–100) 2: 97.0% (89.5–99.6) 3: 87.9% (89.5–99.6) 4: 69.7% (57.2–80.4)	Not reported
Tillmann, 2001 [27]	PTB (<37 weeks) and LBW (<1500 g)	Unspecified	1: 100% (94.0–100) 2: 100% (94.0–100) 3: 98.3% (91.1–100) 4: 81.7% (69.6–90.5)	Not reported
Tozzi, 2014 [19]	Very PTB (22–31 weeks)	DTaP-IPV-HBV-Hib	1: 95.1% (93.6–96.3) 3: 92.1% (90.4–93.7)	Cannot extrapolate
Klein, 2011 [28]	Severe IEMs Chronic IEMs Stable IEMs	OPV and IPV	3: 93.8% (79.2–99.2) 3: 85.7% (42.1–99.6) 3: 97.4% (86.2–99.9)	Not reported
Magoon, 1995 [12]	High-risk PTB ≤29 weeks 30–31 weeks 32–33 weeks 34–37 weeks	OPV and IPV	Not reported	1: 12.5% (3.5–29.0) 1: 11.5% (2.4–30.2) 1: 35.1% (20.2–52.5) 1: 50.0% (32.4–67.6)
Cerutti, 2015 [29]	Severe IEMs Chronic IEMs Stable IEMs	DTaP-IPV-HBV-Hib	4: 86.6% (77.3–93.1) 4: 80.0% (61.4–92.3) 4: 87.5% (61.7–98.5)	Not reported
Nacoulma, 2006 [13]	Sickle cell disease	DTaP-IPV	1: 98.4% (94.2–99.8) 2: 97.5% (93.0–99.5) 3: 97.5% (93.0–99.5)	Not reported
Denizot, 2011 [21]	PTB, <28 weeks PTB, 28–30 weeks PTB, 31–32 weeks PTB, 33–34 weeks	DTaP-IPV-Hib	Not reported	3: 51% (38–70) 4: 68% (54.5–79) 3: 40.5% (32–49) 4: 65% (57–73) 3: 37% (22–44.5) 4: 65% (57–72) 3: 37.5% (32–43) 4: 69% (63–74)
Woestenberg, 2014 [30]	Extreme PTB (<32 weeks) PTB (32–36 weeks) Extremely LBW (<1000 g) Very LBW (1000–1499 g) LBW (2000–2499 g)	DTaP-IPV	Not reported	1: 66% (64.9–67.1) 1: 76% (75.6–76.3) 1: 56.2% (53.7–58.6) 1: 66.6% (65.2–67.9) 1: 75.1% (74.7–75.5)
Wilson, 2012 [31]	Near term birth (33 to < 37 weeks) Very PTB (28–32 weeks) Extremely PTB (<28 weeks)	DTaP-IPV-Hib	Not reported	1: 80.7% (80.4–81.0) 2: 75.4% (75.1–75.8) 3: 71.1% (70.7–71.5) 1: 69.7% (68.7–70.6) 2: 77.1% (76.3–78.0) 3: 71.1% (71.2–73.1) 1: 14.6% (13.1–16.1) 2: 65.5% (63.5–67.5) 3: 69.5% (67.5–71.5)
Pinquier, 2009 [22]	PTB (23 to < 33 weeks)	DTaP-IPV-Hib	3: 44.8% (34.1–55.9) 4: 82.8% (73.2–90.0)	Not reported
Masson, 2015 [23]	Cystic fibrosis	DTaP-IPV-Hib	4: 86.0% (78.2–91.8)	Not reported
Batra, 2009 [32]	Extremely LBW (<1000 g) Very LBW (1000–1499 g) LBW (1500–2499 g)	OPV and IPV	1: 74.5% (70.5–78.3) 2: 63.8% (59.5–68.0) 1: 90.4% (88.1–92.3) 2: 78.6% (75.5–81.4) 1: 93.3% (92.7–93.9) 2: 83.4% (82.5–84.3)	Not reported
Esposito, 2016 [34]	Rubinstein-Taybi syndrome Sotos syndrome Beckwith-Wiedemann syndrome	DTaP-IPV-HBV-Hib	3: 80.0% (51.9–95.7) 3: 78.6% (49.2–95.3) 3: 71.4% (51.3–86.8)	Not reported
Crawford, 2009 [15]	PTB (<32 weeks)	OPV and IPV	1: 95.0% (88.7–98.4) 2: 95.0% (88.7–98.4) 3: 95.0% (88.7–98.4)	Not reported
Cremer, 2002 [16]	PTB (<37 weeks) with LBW (<1500 g)	OPV	2: 97.6% (93.1–99.5)	2: 37.1% (28.6–46.2)
Ochoa, 2015 [24]	PTB (<37 weeks) and very LBW (1000–1499 g) PTB (<37 weeks) and extremely LBW (<1000 g)	DTaP-Hib-HBV	1: 100% (97.7–100) 2: 98.7% (95.5–99.9) 3: 96.8% (92.7–99.9) 1: 100% (91.4–100) 2: 92.7% (80.1–98.5) 3: 80.5% (65.1–91.2)	Not reported
Raddish, 1993 [17]	Spina bifida	OPV	3: 58.3% (49.0–67.3)	Not reported
Laforgia, 2018 [18]	PTB (<37 weeks)	DTaP-IPV-HBV-Hib	1: 98.7% (95.5–99.9) 2: 91.2% (85.7–95.1) 3: 87.3% (81.1–92.1)	Not reported
Upadhyay, 2017 [25]	LBW (<2500 g)	OPV	1: 64.4% (63.5–65.3) 2: 51.5% (50.5–52.5) 3: 40.8% (39.8–41.8)	1: 51.9% (50.7–53.1) 2: 34.3% (33.0–35.6) 3: 19.3% (18.1–20.5)

LBW: low birth weight, PTB: preterm birth.

Immunization guidelines typically recommend either a minimum age for initial receipt or a minimum waiting period for administration of subsequent doses to ensure an optimal immunogenic response. In the United States, with few exceptions, an early immunization is only considered valid if administered fewer than 5 days before the minimum recommended age. Those administered earlier are often considered invalid and need to be repeated [40]. Only one study in this review allowed for earlier-than-recommended immunization in their assessment of timeliness by considering those administered fewer than 5 days earlier than recommended as being on-time [32]. Although the WHO and most countries have guidelines for the minimum age when starting an immunization series and minimum time interval between subsequent doses, there are no consistent guidelines for what is considered to be a meaningful delay [41–43]. For instance, the Advisory Committee on Immunization Practices (ACIP) has specified the earliest age for on-time immunization to be ≤ 4 days before the minimum recommended age, yet there is no specified maximum time period beyond which a vaccine would be considered delayed [44]. The variability in measuring delayed vaccine receipt is recognized within the WHO/UNICEF Joint Reporting Form for immunization, which indicates that the measurement depends on the member state's schedule and reporting practices [12]. Defining delayed-receipt is challenging since non-primary doses of DTP, MMR, or polio-containing vaccines received after the recommended time interval are still immunologically effective; however, delays nevertheless increase disease susceptibility due to sub-optimal protection during time periods of highest risk [45]. Some experts seem to have converged upon a pragmatic definition of timeliness for routine childhood immunizations, defined as vaccination within a 30-day window after the recommended age for administering the vaccine [45].

5. Strengths and limitations

Strengths of our review include comprehensive literature searching and double-screening of all abstracts and full-texts for eligibility. The small number of eligible studies and overwhelming heterogeneity across studies ultimately prevented us from conducting any meta-analysis of the coverage and timeliness estimates. Indeed, our strict eligibility criteria, which restricted the types of vaccines assessed and the types of pediatric chronic health conditions defining the study populations contributed, in part, to the small number of eligible studies. For instance, during the title and abstract screening phase, we noted a number of records that assessed immunization compliance not only for all routinely-recommended pediatric vaccines, but also other specific vaccines such as those targeting seasonal influenza, community-acquired pneumonia, and meningitis. However, we were specifically interested in DTP, MMR, and OPV/IPV as these vaccines have been widely incorporated into immunization schedules for decades [46]. A quarter of the studies on which we completed a full-text review were ultimately excluded because the study population had chronic health conditions that were not diagnosable within the first 6 months of life (e.g., type 1 diabetes) or included patients with immunodeficiencies (e.g., Di George syndrome, HIV). Nevertheless, we believe that broadening the scope of our review would have made synthesis across studies even more challenging based on the substantial amount of heterogeneity we already encountered using our more specific criteria. We were limited in our ability to directly compare across studies given that they were conducted across a range of settings and time periods during which immunization policies likely differed. Moreover, we were unable to assess how the coverage in each study compared with contemporaneous local recommendations for similar reasons.

6. Conclusions

This study has found that the definitions for coverage and timeliness of routine childhood vaccinations in special pediatric populations are inconsistently defined and evaluated, signifying a need for conventional reporting practices in immunization surveillance research. Moreover, there is a lack of studies reporting coverage and timeliness of routine immunizations in special populations of children with chronic health conditions. Future studies should address this public health evidence gap.

Author contributions

NE MacDonald and DB Fell developed the research question. EJ Walker and DB Fell planned the study and developed the systematic review protocol, including the analysis plan. EJ Walker and N Islam screened the abstracts and extracted the relevant data for included studies. EJ Walker analyzed the data under the supervision of DB Fell. EJ Walker drafted the initial article, and all of the authors helped critically revise the article throughout the development.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.02.031.

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