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Experiences with provider and parental attitudes and practices regarding the administration of multiple injections during infant vaccination visits: Lessons for vaccine introduction☆

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ABSTRACT

Introduction: An increasing proportion of childhood immunization visits include administration of multiple injections. Future introduction of vaccines to protect against multiple diseases will further increase the number of injections at routine immunization childhood visits, particularly in developing countries that are still scaling up introductions. Parental and healthcare provider attitudes toward multiple injections may affect acceptance of recommended vaccines, and understanding these attitudes may help to inform critical decisions about vaccine introduction.
Methods: We conducted a systematic review of the literature to examine factors underlying reported parental and healthcare provider concerns and practices related to administration of multiple injections during childhood vaccination visits.
Results: Forty-four articles were identified; 42 (95%) were from high income countries, including 27 (61%) from the USA. Providers and parents report concerns about multiple injections, which tend to increase with increasing numbers of injections. Common parental and provider concerns included apprehension about the pain experienced by the child, worry about potential side effects, and uncertainty about vaccine effectiveness. Multiple studies reported that a positive provider recommendation to the parent and a high level of concern about the severity of the target disease were significantly associated with parental acceptance of all injections. Providers often significantly overestimated parental concerns about multiple injections.
Discussion: Providers may play a critical role in the decision for a child to receive all recommended injections. Their overestimation of parental concerns may lead them to postpone recommended vaccinations, which may result in extra visits and delayed vaccination. More research is needed on interventions to overcome provider and parental concern about multiple injections, particularly in developing countries.
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1. Introduction

In 1974, when the World Health Organization (WHO) created the Expanded Program on Immunization, six antigens and up to eight vaccine doses (some vaccines require multiple doses) were included in the recommended childhood vaccination schedule. By 2012, the WHO recommendations had increased to 11 antigens administered as up to 21 vaccine doses [1]. The availability of funding for vaccine introduction for low- and middle-income countries through the GAVI Alliance and other mechanisms will soon enable more countries to introduce all WHO-recommended vaccines [2]. Introduction of pneumococcal conjugate vaccine (PCV) will reduce child mortality worldwide, and the introduction of inactivated poliovirus vaccine (IPV) in all countries is a critical component of the Global Polio Eradication Initiative endgame strategy [3]. These introductions will also increase the number of injections at vaccination visits in nearly all countries [2]. This trend will continue as vaccines currently being developed for malaria, tuberculosis and other diseases are licensed and introduced [2–4].

☆ *Disclaimer*: The findings and conclusions in this report are those of the authors and do not necessarily represent the official positions of the World Health Organization or the U.S. Centers for Disease Control and Prevention.

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An important consideration in the introduction of a new injectable vaccine is the increase in the number of recommended injections at a single vaccination visit. The universally endorsed practice of simultaneous administration of all recommended vaccines improves timeliness, ensures protection at the earliest possible age, and maximizes efficient use of finite health sector resources, which is particularly important in low- and middle-income countries [5,6]. However, since many of these countries have not yet introduced all WHO-recommended vaccines, little is systematically documented about healthcare provider and parental attitudes and practices toward vaccination visits with increased numbers of injections in these locations. Countries having well-documented provider and parental experiences with multiple injections may provide important information to help low- and middle-income countries prepare for an increase in the recommended number of injections given at a vaccination visit. To better understand the determinants of provider and parental attitudes about multiple injections, we conducted a systematic review of the literature. Our aim was to identify studies of parental and provider attitudes and practices regarding vaccination visits with multiple injections and factors associated with these attitudes and practices, and to consider strategies to increase acceptance.

2. Methods

2.1. Search strategy

We searched 29 databases for English, French and Spanish language articles (Table 1). Our search filters combined terms (and their derivatives) specific to vaccination, multiple injections (and synonyms), health care provider and parental (or other caregiver) practices, attitudes or beliefs. We identified gray literature reports and working papers related to multiple injections through discussions with immunization experts at UNICEF, WHO and the US Centers for Disease Control and Prevention (CDC), and examined references in identified articles to identify additional studies. We initially reviewed titles and abstracts of identified articles to determine if papers met the eligibility criteria. Articles that appeared to meet the eligibility criteria were fully read to ensure eligibility to be included in the systematic review process.

2.2. Eligibility criteria

We included papers that described findings from primary research in a setting of childhood vaccination services and assessed one or more of the following: (a) provider or parental attitudes or practices (or both) related to simultaneous administration of multiple injections; (b) provider or parental practices regarding administration or acceptance of multiple injections following recent addition of a new injectable vaccine to an existing vaccination visit; or (c) strategies for overcoming provider or parental concerns about administration of multiple injections. Studies could be from any country, published from January 1970 through January 2014. For the purposes of this analysis, we refer to all caregivers as parents.

2.3. Article review and analysis

We used a standardized data collection form to systematically abstract information from each article, including study rationale, country, vaccinations offered, sample size, data collection methods, and key findings and recommendations. We synthesized the abstracted information, identifying common areas of concern about multiple injections for providers and parents, and factors related to these concerns and their impact on vaccine coverage and delay; and summarized both tested and proposed interventions to overcome resistance to multiple injections.

Table 1
Keywords and data sources used for a systematic review of parental and health care provider attitudes and practices related to adding injections to childhood immunization schedules using literature from 1970 to 2014.

Keywords used singly or in combination	Literature databases used	Websites visited and organizations contacted
Acceptance	Access UN	www.basics.org
Added	AccessScience	www.searchbeta.bl.uk
Attitude[a]	AGRICOLA	www.care.org
Barrier[a]	Bioline International	www.fhi.org
Behavior[a]	BioMed Central	www.filariasis.org
Caregiver[a]	BIOSIS	www.gavialliance.org
Combination	CAB Abstracts	www.greynet.org
Compliance	CHID Online	www.hki.org
Concomitant	CINAHL	www.ifrc.org
Doctor[a]	Cochrane Library	www.msh.org
HBV	CSA-Illumina Databases	www.nyam.org/library/greylitorgs.shtml
Health worker[a]	Dissertation Abstracts	www.paho.org
HiB	EMBASE	www.path.org
Immunization[a]	Expanded Academic ASAP	www.pathfind.org
Infant	Global Health	www.psi.org
Injection[a]	IBSS	www.redcross.org
Vaccination[a]	IndMed	www.savethechildren.org
Multiple	LexisNexis Academic	www.savethechildren.org.uk
Simultaneous	LILACS	www.trachoma.org
Additional	MEDLINE	www.un.org
Pain	PAIS	www.undp.org
Parent[a]	POPLINE	www.who.int/library
Physician[a]	Population Index	Centers for Disease Control & Prevention
Pneumococcal	Proquest Research Library	UNICEF
IPV	PubMed	World Health Organization
Meningococcal	SIGLE	
Hepatitis B	UNDP Project Reports	
Practice	Web of Science	
Provider[a]	WHOLIS	
Schedule		
Vaccine[a]		
Sequential		
Combo		
Concern		

[a] Keyword search included singular and plural version of word.

3. Results

3.1. General characteristics of included publications

Among 218 articles identified by the initial review of abstracts and titles, 44 met the final inclusion criteria and were reviewed (Fig. 1). Forty-two (95%) of these were from peer-reviewed journals and 2 (5%) came from gray literature sources (Table 2). Only two (5%) studies were from low- or middle-income countries (Rwanda and Ukraine); whereas 27 (61%) were conducted in the United States, 6 (14%) in Canada and 6 (14%) in other high-income countries, including one seven-country survey (Table 2).

In four (9%) studies, investigators reviewed vaccination records, in 37 (84%) they conducted interviews (14 [32%] with providers only, 15 [34%] with parents only, and 8 [18%] with both), and in 4 (9%) they evaluated strategies to increase acceptance of multiple injections. Specific injectable vaccines were reported to have been recently introduced in 26 (59%) studies, including PCV ($n = 7$); IPV ($n = 4$); PCV and IPV ($n = 1$); PCV, influenza and varicella vaccines ($n = 1$); hepatitis B vaccine (HepB) ($n = 7$); meningococcal C vaccine (MenC) ($n = 3$); HepB and MenC ($n = 1$), *Haemophilus influenzae* type b vaccine (Hib) ($n = 1$) and a switch from whole-cell diphtheria–tetanus–pertussis (DTP) vaccine to acellular (DTaP)

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Table 2
Summary of studies analyzing provider and parental attitudes and practices regarding administration of multiple injectable vaccinations during a single routine infant vaccination visit, 1970–2014; by study type and year.

Ref.	Study year	Country	Study question	New vaccine(s)	Sample	Key findings
Healthcare provider-only studies						
[46]	1991	USA	Assess supply-side risk factors for non-vaccination	NA	175 HCPs	Identified reason for delayed vaccination was lack of simultaneous administration of multiple injectable vaccines
[11]	1992	USA	Assess provider attitudes for administering vaccinations	NA	1565 HCPs	HCPs who did not want to give all injections were concerned about infant pain, side effects, parental objections, overloading immune system
[15]	1992	USA	Post vaccine introduction assessment	HepB	476 HCPs	28–44% of physicians had not adopted new vaccine recommendation due to belief of too many injections in one visit
[16]	1992	USA	Assess provider attitudes and practices regarding new vaccination	HepB	368 HCPs	HCP belief in severity of disease determined likelihood of adding additional injection
[18]	1992	USA	Post vaccine introduction assessment	HepB	153 HCPs	37% of HCPs were opposed to infant receiving 3 injections in one visit
[7]	1993	USA	Assess provider attitudes and practices regarding vaccination	NA	62 HCPs	HCPs who did not want to give all injections were side effects, parental objections; private HCPs more concerned than public HCPs.
[20]	1994	USA	Assess provider attitudes and practices for administering vaccinations	NA	1241 HCPs	HCPs who did not want to give all injections were concerned about side effects, parental objections, overloading immune system
[17]	1998	USA	Post vaccine introduction assessment	IPV	263 HCPs	The choice of OPV versus IPV was significantly influenced by perceived risk of vaccine-associated paralytic paralysis from OPV and increased number of injections
[40]	1998	USA	Assess provider practices after introduction of a new injectable vaccine	IPV	673 HCPs; 8779 records	23% of HCPs almost always offered to defer a dose when 3 injections were due and 34% offered to defer a dose when 4 were due
[14]	2000	USA	Post vaccine introduction assessment	PCV	306 HCPs	20% of HCPs deferred PCV because of concern administering four injections in one visit
[12]	2000	USA	Assess HCP attitudes regarding MI in a single visit	PCV, IPV	232 HCPs	HCP factors related to adopting new PCV recommendations include comfort with 4 injections at one visit, low concern about any adverse events with 4 injections, belief in PCV effectiveness
[13]	2001	USA	Post vaccine introduction assessment	PCV	694 HCPs	95% of HCPs who adopted PCV recommendations within first year administer 4 or more injections at 2-month visit
[24]	2001	USA	Post vaccine introduction assessment	PCV	426 HCPs	After PCV introduction, 39% of HCPs deferred at least 1 injection to later visits and 15% added an additional new visit
[21]	2001	USA	Assess prevalence of injections being deferred based on number of injections due at a single visit	PCV	32 HCPs; 858 records	The rate of deferral of injections was associated with the number of injections due in a visit. Not deferring was the strongest predictor of up-to-date vaccination by 12 and 24 months of age
Parent-only studies						
[45]	1989	USA	Assess parental attitudes regarding vaccination and compare to vaccination status	NA	557 parents	Parental concern about safety of receiving ≥1 injection a single visit inversely related to child's vaccination status i.e. those not vaccinated had higher belief in multiple injections
[28]	1992	USA	Assess parental attitudes regarding MI in a single visit	NA	281 parents	91%, 51% and 41% of parents approved of 2, 3, and 4 injections, respectively, in a single visit
[37]	1995	USA	Assess parental willingness-to-pay values to allow MI in a single visit	NA	1059 parents	Vaccination delay by age 12 months occurred where health care providers (HCPs) offered to defer receiving ≥1 injection versus HCPs who did not offer to defer any injections
[10]	1996	USA	Assess parental attitudes regarding vaccination, including MI in a single visit	IPV, DTaP	227 parents	During introduction of IPV, majority of parents choose IPV over OPV because concern about more severe side effects of OPV was higher than concern about more injections with IPV
[37]	1997	USA	Assess parental preferences for outcomes associated with vaccination using willingness to pay values	NA	206 parents	Parents placed a higher value on avoiding severe fever, disease or pain from vaccination than on reducing the number of injections in a single visit
[47]	1998	Canada	Assess reasons for vaccination delay within context of multiple injection visits	NA	696 parents	Completely vaccinated infants by 24 months of age were significantly more likely to receive all injections simultaneously as recommended compared to incompletely vaccinated infants
[36]	1999	USA	Assess parental attitudes regarding MI in a single visit using a willingness to pay economic trade-off model	NA	294 parents	Strong parental preference to limit the number of injections per visit

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Table 2 (*Continued*)

Ref.	Study year	Country	Study question	New vaccine(s)	Sample	Key findings
[42]	1999	Canada	Post vaccine introduction assessment (Hepatitis B vaccine)	HepB	255 parents	After vaccine introduction, 9.5% of children did not receive the recommended multiple injections in a single visit but instead received them separately. Main factor why they were not received simultaneously was due to HCP concern about too many injections in a single visit
[29]	2002	USA	Assess parental perceptions regarding vaccine safety	NA	7810 parents	58% of parents preferred four injections in a single visit versus separate visits. There was no difference in infant vaccination status between parents who preferred one option over the other
[41]	2002	Canada	Post vaccine introduction assessment	HepB	487 parents	Parents who reported they received a positive HCP recommendation for all injections in a single visit were significantly more likely to have an infant vaccinated with HepB
[31]	2004	The Netherlands	Post vaccine introduction assessment	HepB, MenC	283 parents	If a visit had 3 or 4 injections in a single visit instead of 1–2, then 73% and 87%, respectively, of parents would not allow all injections to be given in one visit. Parents attitudes depended on the perception of the effectiveness of the vaccine
[32]	2004	Germany	Assess parental attitudes toward new vaccinations	NA	6025 parents	56% of parents would accept administration of >1 injection in a single visit. HCPs were the most important source of vaccine information for the parent
[33]	2004	United Kingdom	Assess parental attitudes regarding vaccination, including MI in a single visit	NA	859 parents	Parents who perceived high severity of disease were more likely to accept all recommended injections in one visit
[30]	2005	Belgium	Assess parental attitudes regarding MI after vaccine introduction	PCV, IPV	1347 infants; 1315 adolescents	10% of parents would allow 3 injections per visit, 51% of parents would allow 2 injections and 20% would allow only 1 injection per visit. 65% of parents who said they would only allow 1 injection had actually previously allowed their child two received 2 injections in one visit
[34]	2006	Canada	Assess parental attitudes and practices regarding MI before versus after multiple vaccine introductions	PCV, InfV, VarV	1347 infants; 1315 adolescents	Before introduction, 28% of the group of parents would allow 3 injections in one visit; after introduction, 36% would allow 3 injections
Integrated Healthcare provider and parent studies						
[9]	1992	USA	Assess parental and provider attitudes regarding MI in a single visit	NA	215 HCPs; 193 parents	HCPs were concerned about multiple injections due to perceived increased side effects, reduced immunogenicity and concern about parents returning for subsequent visits. Parents were concerned about infant pain response, increased vaccine side effects
[8]	1993	USA	Assess parental and provider attitudes regarding MI in a single visit	NA	88 HCPs, 342 parents	HCP and parental concern about various number of injections given in one visit was similar at around 50% of surveyed groups
[27]	1996	Canada	Assess parental and HCP preferences for DTP or DTaP resulting in more injections	DTaP	400 parents, 200 HCPs	HCPs significantly overestimated the proportion of parents who would want DTP and less injections versus DTaP and more multiple injections
[19]	1997	Australia	Assess parental and provider preference for pentavalent (combined) vaccine versus separate vaccines	NA	162 parents, 154 HCPs	HCP and parents were more concerned about the higher number of side effects from DTP vaccine versus DTaP vaccine. 54% of parents and 28% of HCPs preferred three injections in one visit
[35]	2009	Rwanda	Pre-vaccine introduction assessment	PCV	16 HCPs; 50 parents	Parents were concerned about additional pain from another injection but were more concerned about disease severity. All HCPs expressed concern that parents would refuse 2 injections in one visit
[23]	2008	Ukraine	Post vaccine introduction assessment (Hib vaccine)	Hib	19 HCPs	Both parents and HCPs cited refusal of the new, additional injection as a barrier to introduction of the new vaccine and reason why coverage for new vaccine was lower than for existing vaccines
[22]	2011	Australia, Canada, France, Germany, Spain, Sweden, United Kingdom	Assessment of parental and HCP concerns about multiple injections	NA	2460 parents725 HCPs	Factors governing parental decision-making include avoiding pain of child, ensure child receives all necessary vaccines and concern about severity of disease. Factors governing HCP decision include expectations of parental concern about child's discomfort and following recommended schedule

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Table 2 (*Continued*)

Ref.	Study year	Country	Study question	New vaccine(s)	Sample	Key findings
[26]	2013	USA	Assessment of parental and HCP concerns about multiple injections	NA	401 parents 105 HCPs	HCPs significantly overestimated the proportion of parents who would prefer other routes of vaccination over the injection route. Both HCPs and parents listed severity of disease as most important factor governing the decision to administer all injections in a single visit
Healthcare record review only studies						
[44]	1997	USA	Assess vaccination outcomes after introduction of a new injectable vaccine (inactivated polio vaccine) into an existing visit	IPV, DTaP	1134 records	90% of infants received 1 or 2 injections during the first two visits prior to introduction of the new injection and switch to DTaP. After introduction, 78% of infants received 3–4 injections. Coverage by 12 months of age was similar for pre and post-introduction cohorts
[39]	2002	Australia	Assess proportion of children who were administered all recommended injections at single visit	MenC	62,000 records	Infants who received all injections as recommended per visit averaged complete vaccination by 12 months of age versus 14 months of age for those who did not receive injections as recommended
[25]	2003	Australia	Assess proportion of children who were administered all recommended injections at single visit	MenC	751 records	83% of infants received 3 injections simultaneously after new vaccine introduction compared to earlier studies showing 54% of parents were concerned about 3 injections
Intervention studies						
[47]	1995	USA	Assess if differences in infant pain and parental preference exist between simultaneous versus sequential injections during vaccination	NA	46 infants	Infants who received sequential injections show no significant pain response difference compared to infants who received injections simultaneously
[50]	2004	USA	Assess analgesic properties of oral sucrose solution during infant vaccination	NA	83 infants	Infants who received oral sucrose solution between injections had significant pain reductions two minutes after solution administration compared to placebo
[51]	2008	Canada	Assess impact of providing feedback on reasons for vaccination delay	NA	10 clinics	In clinics where feedback was received that multiple injections was a challenge, the implementation of the feedback resulted in significant decreases in vaccination delay among infants
[49]	2012	United Kingdom	Assess if differences in infant pain and parental preference exist between simultaneous versus sequential injections during vaccination	NA	72 infants	Infants who received sequential injections show no significant pain response difference compared to infants who received injections simultaneously. Parents showed no difference in perception of infant distress

Definitions: HepB = hepatitis B vaccine; Hib = *Haemophilus influenzae* type-b vaccine; IPV = inactivated polio vaccine; MenC = meningococcal C vaccine; PCV = pneumococcal vaccine; DTaP = Diphtheria–tetanus–acellular pertussis vaccine; InfV = influenza vaccine; VarV = varicella vaccine; NA = not applicable; MI = multiple injections; HIC = high income country; LMIC = low or middle income country.

vaccine ($n = 1$). In 27 (61%) studies, the authors' primary objectives included assessment of provider or parental attitudes, practices, or both concerning multiple injections, whereas in the remaining 17 (39%) studies, the topic of multiple injections was a secondary component of a vaccination program assessment.

3.2. Provider attitudes and practices related to multiple injections

Six US studies from the 1990s suggested that providers were frequently reluctant to administer all recommended injections, and this reluctance was noted in six studies to increase with the number of recommended injections [7–12]. In one provider survey in the 1990s, when the US Advisory Committee on Immunization Practices (ACIP) first recommended up to 3 injections in a single visit (Fig. 2),[1] 86% of private providers believed all doses should be administered if 1–2 injections were due, whereas only 62% believed all injections should be given if more than 2 were due [7] (Table 3). Similar results were reported from other studies during the same time period: nearly all providers (86–95%) were comfortable providing 1–2 injections [7–10], 50–64% were comfortable providing 3 injections [8–10] but only 17–23% were comfortable administering 4 injections [9]. When different groups of US-based providers were surveyed in early 1990s, 80% of pediatricians and family practitioners in one study said they would administer 3 injections, but only 66% would administer four injections [11]. By 2002, when the ACIP recommended up to seven injections at a single visit (Fig. 2), a US survey found that 35–50% of providers approved of five injections but 75–80% approved of 3 injections and 70–72% approved of 4 injections [12].

Providers who were reluctant to give all recommended injections reported a variety of reasons for their reluctance. These included concern about giving too many injections [8,13–18] or perceived reactogenicity of multiple vaccines [8,10,19]; concern about possible adverse events [13,20] or previous earlier experiences with adverse events following vaccination [9,11,19]; worry about the child's experience of pain or distress when receiving multiple injections [8,9,11,13,21,22]; vaccine cost [13–15]; parental objections [20,22,23] or the possibility that the parent might not bring the child back for future vaccinations if multiple injections were given [9,22]; as well as questioning the necessity of the newly introduced vaccine [13–16,20,23]. Nine studies suggested provider concern varied by provider type; willingness to administer multiple injections was greater among pediatricians

[1] http://www.cdc.gov/vaccines/schedules/past.html

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Table 3
Summary of healthcare providers' attitudes and practices toward administration of multiple injectable childhood vaccines during a single immunization visit; studies published 1970–2014.

Study year	Attitudes and practices toward given number of injections recommended in single childhood immunization visit					Country	No. of HCPs[a]	Source
	1	2	3	4	5			
1991			80% would administer 3 recommended injections	66% would administer 4 recommended injections		USA	490	[11]
1992			72–77% reported some caregiver opposition to 3 injections in a single visit			USA	448	[15]
1992		86–100% would administer all injections if >1 are due	62–100% would administer all injections if >2 are due			USA	62	[5]
1992			60% had strong concerns about administering 3 recommended injections	80% had strong concerns about administering 4 recommended injections		USA	289	[9]
1992	8–12% believed that 1–2 injections were too many for a single visit		59–76% believed that 3 injections were too many for a single visit			USA	88	[8]
1996			11% would not administer 3 injections in a single visit			USA	1241	[20]
1998			76% usually would not offer to defer any doses when 3 injections due	52% usually would not offer to defer any doses when 4 injections due		USA	274–399	[40]
2002	95–97% would administer 1 recommended injection	97% would administer 2 recommended injections	96–97% would administer 3 recommended injections	89–90% would administer 4 recommended injections	59–69% would administer 5 recommended injections	USA	232	[12]

[a] Number of healthcare providers (HCPs) surveyed in study.

than family practitioners [14,15,18,20,31], public clinic providers than private providers [7], and younger or more recently trained providers than older providers [9,11,24].

Provider concern about multiple injections was found to delay vaccine introduction or cause providers to deviate from recommended vaccination practices [13–18,24]. For example, following the recommended switch from oral poliovirus vaccine (OPV) to IPV in the US, a survey of pediatricians and family practitioners reported that those who continued to administer OPV expressed greater concern about the number of injections than did those who switched to IPV [17]. In another US post IPV-introduction survey, 23% of providers often deferred 1 injection when three were due and 34% deferred 1 injection when four were due [32], suggesting that providers' likelihood of deferring recommended vaccines

Table 4
Summary of parents' attitudes toward administration of multiple injectable childhood vaccines during a single immunization visit; studies published 1970–2014.

Study year	Potential acceptability of given number of injections recommended in single childhood immunization visit					Country	No. of parents[a]	Source
	1	2	3	4	5			
1992			71% believed 3 injections were too many for a single visit			USA	342	[8]
1992	31% had strong concerns about a single injection		41% had strong concerns about 3 injections			USA	193	[9]
1992		91% approved of 2 injections	58% approved of 3 injections	42% approved of 4 injections		USA	281	[28]
1996		86% were comfortable with infant receiving 2 to 3 injections		26% were comfortable with 4 injections		USA	227	[10]
1996			54% approved of 3 injections			Australia	162	[19]
2001				58% were comfortable with 4 injections		USA	7810	[29]
2005	100% approved of 1 injection	82% approved of up to 2 injections	14% approved up to 3 injections	6% approved up to 4 injections	5% approved of unlimited injections	Belgium	1347	[30]
2006	34% preferred only 1 injection	91% preferred 2 or less injections	9% approved of 3 or more injections	2% approved of 4 or more		United Kingdom	796	[33]

[a] Number of parents surveyed in study.

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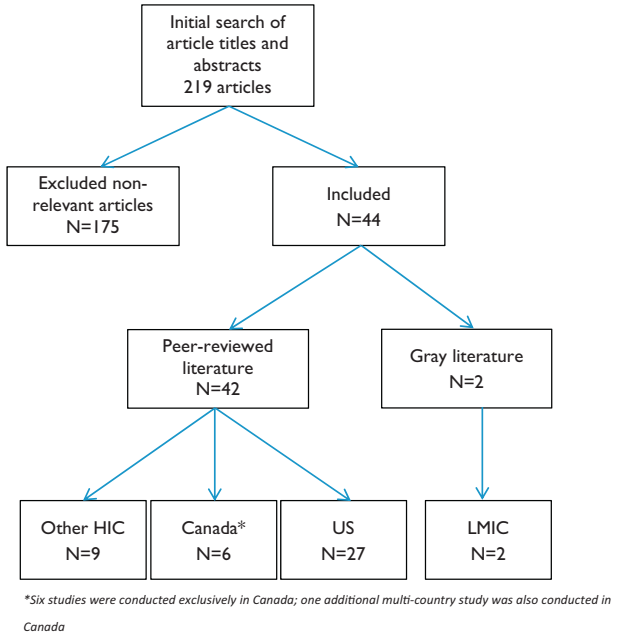

Fig. 1. Outcome of initial search and review of articles referencing provider or parental attitudes or practices regarding multiple injections. *Six studies were conducted exclusively in Canada; one additional multi-country study was also conducted in Canada

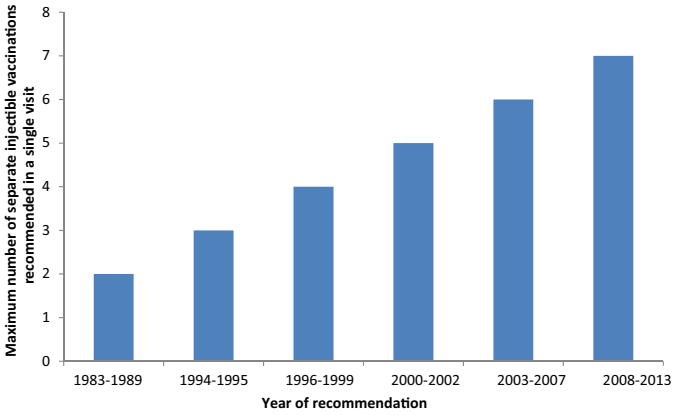

Fig. 2. Maximum number of injectable vaccinations recommended in a single pediatric visit in the United States, based on Advisory Committee on Immunization Practices (ACIP) recommendations, 1983–2013.

increased with the number of recommended injections. Providers who did not administer all recommended injections at one visit described a number of alternative delivery strategies, including deferral of one or more injections to later scheduled office visits [14,18,20,24], creation of an additional visit to administer deferred vaccinations [15,18,24,25], or increased use of combination vaccines [14].

Providers who complied with new vaccine introduction recommendations, on the other hand, were more likely than those who did not to believe the newly introduced vaccine was highly effective [13,26] and had a lower risk of side effects than previously recommended vaccines [17,27], and to believe that one visit was more convenient and less costly than two visits [8]. These providers were also more likely to be comfortable administering multiple injections [13,16]; to have personally cared for persons with the disease prevented by the vaccine [14]; to believe that the preventable disease was severe [16,22,27]; and to have received a positive endorsement to give all recommended injections at a single visit from their medical organization, medical colleagues, or both [17,24].

3.3. Parental attitudes and practices related to multiple injections

In 1992, when a maximum of 2 injections at one visit was recommended by the ACIP1 (Fig. 2), three US studies reported that parental acceptance of 3 injections ranged from 29% to 59% [8,9,28], with one study documenting a decline in parental acceptance as the number of injections increased, from 91% accepting two, 58% accepting three, and 42% accepting four injections [28] (Table 4). In 1996, when ACIP first recommended up to five injections at a visit, a US study found that 86% of surveyed parents approved of 2–3 injections, while 26% approved of four injections [10]. And in 2001, when ACIP routinely recommended four or more injectable vaccines for infants, and up to seven at age 15 months, a US survey [29] found that 58% of parents permitted their child to receive four injections at one visit, while 41% preferred to defer some doses.

In studies from multiple high-income countries [19,22,30–33], the maximum number of injections that the majority of interviewed parents were comfortable approving in a single visit corresponded to official country recommendations. For instance, in three European studies, 82% and 91% of parents in Belgium [30] and the UK [33], respectively, approved of one to 2 injections; in both countries, the maximum of injections in a single visit during the time of the survey was 2 injections. However, only 14% (Belgium), 9% (UK), and 13–27% (the Netherlands [31]) of parents approved of three or more injections, which was beyond existing recommendations during the time of the studies. Similarly, in a multi-country survey conducted in 2012 in Australia, Canada and five European countries [22], 70% of parents were most comfortable with either the officially recommended 2 injections in a visit or the number the provider recommended. Parental preferences were noted to change over time: one Canadian study found that the proportion of parents approving of ≥3 injections in a visit increased from 43% to 59% one year before compared with one year after introduction of two additional injections in a visit [34].

Reported reasons for parental concern about multiple injections included a child's potential pain [9–11,35,36], possible adverse events following multiple injections [8,10,32,34,37], and perceived stress to the immune system [27,32,34]. Parents who approved of multiple injections reportedly weighed multiple factors in the decision, including provider recommendations, perceptions of the disease severity, and vaccine effectiveness. In eight studies, parents reported that a strong provider endorsement was a key factor in their acceptance of all injections [10,22,25,37,39–42]. Six studies explored the interaction of parental perceptions of disease severity, preferences for vaccines with fewer side effects, and preferences for multiple injections [10,22,26,27,30,36]. Parental concern about disease severity and vaccine side effects outweighed parental concern about multiple injections as the parental concern about disease severity was associated with approval of all recommended injections. In one study [22], when parents were briefly educated that children were 8–25 times more likely to get the disease compared to older age groups, acceptance of the additional injection increased from 54% to 68%. In another US example [10], 92% of parents who were told about the recommended sequential IPV/OPV schedule chose IPV as the first polio vaccine for their child, and said that their concerns about OPV-associated paralytic poliomyelitis [43] outweighed their objection to an additional injection.

3.4. Comparison of provider and parental attitudes

One 1992 US study found that similar percentages of nurses (76%), physicians (59%) and parents (71%) were uncomfortable with a child receiving 3 injections [8]. However, five studies that directly

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compared provider and parental opinions about multiple injections found that their opinions often differed, and that providers frequently overestimated parental concern [9,19,22,26,27]. In one 1992 US study [9], for example, a higher proportion of providers (60%) than parents (41%) had "strong concerns" about 3–4 injections, and in a 1996 Canadian study [27], only 19% of providers predicted that mothers would willingly switch from whole-cell DTP vaccine to DTaP vaccine, if this resulted in an additional injection. However, 57% of mothers did choose DTaP because of its reduced reactogenicity compared with whole cell vaccine [44]. In a 2013 US study, 63% of providers estimated that parents would prefer a non-injectable vaccine, given the choice; however, 37% of parents stated a preference for the injection [26]. In this study, 80% of providers also predicted that parents would consider number of injections as the most important factor in approving all injections; however, 47% of parents instead cited disease prevention as the most important factor. In a 1996 Australian study, parents were more concerned about vaccine reactogenicity than multiple injections with the majority (58%) expressing a preference for DTaP alongside separate Hib and HepB vaccines (3 total injections) compared to whole-cell pentavalent vaccine (1 injection) [19]. However, provider concerns differed from the parents as 14% of providers preferred the 3 injections, including DTaP, over the pentavalent vaccine option.

3.5. Parental opinions and immunization behavior

Four studies that examined the association between parental opinions about and acceptance of multiple injections generally found little correlation [9,35,38,42]. Although all surveyed parents in two studies [9,35] said they would allow each recommended injection to be given, 31% of parents in a US study [9] and 41% of Rwandan parents [35] expressed concerns about multiple injections. In a 2002 Canadian study [42], parental concern about multiple injections was not statistically associated with children's HepB vaccination status, and a 1995 study in a US urban pediatric clinic found that 99% of children whose parents received a provider recommendation for simultaneous vaccination did receive all recommended vaccines – up to 5 injections – at the visit [38].

3.6. Multiple injections and vaccination timeliness and coverage

Two North American studies examined vaccination coverage after introduction of vaccines resulting in an increase in the number of injections [41,45]. Although a switch from OPV to IPV and introduction of DTaP increased the number of injections at two months of age from two to four, a US study [45] found no change in polio or DTP/DTaP vaccination coverage. Investigators in Canada who assessed HepB vaccination coverage six months after the vaccine was introduced at visits when DTaP–Hib–IPV combination vaccine was already given found similar DTaP and HepB coverage, and no significant correlation between multiple injections and delayed vaccination or non-vaccination [41]. Although a 2006 Canadian study found a difference in median age of vaccination among a cohort of children vaccinated after introduction of 3 injectable vaccines compared with a pre-introduction cohort, the difference (4 days) was not considered clinically significant [34].

Six studies found a correlation between concerns about multiple injections and vaccination delay [21,25,45–48]. Five reported that deferral of one or more vaccine doses because of concerns about multiple injections was associated with being incompletely vaccinated by 12, 18 or 24 months of age [14,21,25,45,48]. In a Canadian study, 85% of parents whose children were fully vaccinated by age 18 months favored 2 injections in one visit, compared with 60% of parents whose children were incompletely vaccinated [48].

3.7. Interventions to enhance acceptance of multiple injections

Four studies documented interventions aimed at increasing compliance with recommendations for simultaneous vaccination; three of these focused on efforts to reduce a child's pain in response to multiple injections [49–51]. Two trials conducted when compared parental acceptance of 2 injections administered either sequentially or by two providers administering the injections in different sites at the same time, and children's pain response [49,50]. In one trial [50], parents did not perceive a difference in child distress, while in the second [49], parents did perceive a difference and preferred the two-provider method. The independent observer measures of infant distress in both studies did not identify whether one method was better than the other. US researchers reported lower mean pain response scores following sequential injections given to children who received oral sucrose solution before vaccination compared with those who received sterile water, although pain response scores increased after each injection for both groups [51]. In the fourth study, the intervention focused on decreasing vaccination delay in Canadian clinics through use of supervisory feedback sessions with providers discussing reasons for vaccination delay [52]. In four clinics which identified multiple injections as a cause of vaccination delay, a significant decrease in vaccination delays among children was documented one year after the sessions.

3.8. Recommendations to reduce challenges with multiple injections

Development and wider use of combination vaccines was the most frequently proposed recommendation by researchers to overcome challenges associated with multiple injections [9,10,13,15,19,25,28,37,38]. Other suggested strategies for increasing provider compliance with recommendations included documenting understanding about the disease and vaccine and training to address concerns [16,25,28,38], improving provider knowledge about the safety of simultaneous vaccination [9,10,36], and ensuring articulation of a strong recommendation to the parent to vaccinate the child by the provider [9,13,19,25,27]. In one study, researchers briefly exposed parents to information about the severity of one disease, and acceptance of an additional injection increased from 54% to 68% [22].

4. Discussion

This review of the literature highlights some of the important challenges facing immunization programs in the implementation of recommendations for simultaneous administration of multiple injectable vaccines. In the United States and Canada, resistance to multiple injections among both providers and parents tended to increase as the number of recommended injections increased. However, as more immunizations were officially recommended, the maximum number acceptable to providers and parents also increased, possibly reflecting adjustment to a new "baseline" after the vaccine had been part of the routine schedule for some time. Parents weighed many factors in their decisions about accepting multiple injections, including fear of adverse reactions or impact on the immune system, pain and distress, and confidence in the vaccine, as well as the risk of acquiring the disease, and the relative benefits of some injectable vaccines (e.g., IPV vs OPV) and those with fewer antigens (e.g., DTaP vs DTP-Hib) in terms of potential side effects. Despite the influential role that providers can have in parents' decision-making process, many studies suggest

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that providers often overestimate parents' concerns about multiple injections, which may lead to delay in vaccination. Although we found little evidence that concerns about multiple injections heavily impacted vaccination coverage, studies indicated that some providers have responded to the increased number of injections by delaying and deferring infant vaccinations. Such practices may have implications for upcoming vaccine introductions in countries where vaccination timeliness may have important impacts on infant mortality and morbidity.

During the time many of the US studies in this review were conducted, introduction of several injectable vaccines nearly tripled the total number of vaccinations for children through 18 months, from seven in 1989 to 24 in 2014 [53], necessarily increasing in the number of injections administered at a single visit. However, no reviewed study examined individual-level changes in provider or parental opinions about multiple vaccine injections over time. Future longitudinal studies may help to explain how providers and parents come to accept a certain number of injections with time. Few studies directly examined interventions to overcome concerns about multiple injections, and there was little data on the effectiveness of those interventions, consistent with the general paucity of evidence regarding interventions to address vaccine hesitancy [54,55].

Parents expressed similar concerns as did providers about multiple injections; however, parental resistance was frequently overcome by their concern about the seriousness of disease itself, the inconvenience of having to return for additional injections, and most importantly, the provider's endorsement and reassurance. Parental and provider viewpoints on vaccination are known to be significantly associated [56], and surveyed parents often cite providers as a trusted source of information for decisions regarding childhood vaccination [54,56–58]. These findings, coupled with the findings that providers may overestimate the proportion of parents who will refuse multiple injections, point to the need to educate providers to explain the benefits of administration of multiple injections to parents who may initially appear reluctant, rather than offer to defer injections because of fear of parental resistance.

Apart from concern about parental refusal of multiple injections, providers cited similar reasons as parents for their own concerns, including worries about adverse reactions, discomfort and especially, questions about the need for a particular vaccine. Ensuring that providers understand the efficacy of the vaccines in question and receive education about disease severity, particularly if they have not had direct experience caring for patients with the disease, may help to overcome such challenges. In addition, providers should receive positive endorsements about multiple injections from their respective medical organizations. Specific strategies may need to be targeted toward providers who may be less likely to recommend multiple injections, including providers who have been practicing for many years.

This review had a number of limitations. Studies differed in sample size and location, and the absence of repeated measurements over time within the same population group limited the ability to measure attitude and behavior changes. A number of studies relied on convenience samples, which restricted our ability to compare findings from different studies. Additionally, many providers completed self-reporting questionnaires, which could have biased the results. Importantly, 95% of the studies were conducted in high-income countries, including 61% in the United States, which restricts our ability to generalize findings to low- and middle-income countries. Since many new vaccine introductions are or will be occurring in these countries, it is important to understand the attitudes and practices of providers and parents in these settings, so that appropriate and effective training can be developed, tested, and implemented. Other agencies who support national immunization programs but were not contacted, such as USAID, the Safe Injection Global Network or John Snow Inc., may also have unpublished literature which were not reviewed. Additional studies and publications of past experiences from low-and middle-income countries are warranted. Future studies should include parent and provider interviews, vaccination record reviews and immunization visit observations to determine both attitudes and practices related to the number of injections recommended in a single visit.

Immunizations are among the most cost-effective health interventions with estimates of an 18% rate of return by 2020 for investments to widely introduce new and under-utilized vaccines [59]. Since vaccine introductions will inevitably result in a growing number of injections and potential challenges among providers and parents, communication is needed to ensure these groups understand that administration of multiple injections has an extensive track record of both safety and acceptability [60] in multiple countries, including in developing countries where multiple injection visits have existed in the past, prior to introduction of pentavalent vaccine. Many reviewed studies identified the importance of the healthcare provider in ensuring high administration of all vaccinations during each visit. Using multiple opportunities to provide adequate preparation of healthcare providers on the topic of multiple injections may be needed, including incorporating education and role plays during pre-service and in-service trainings. Education should focus on the safety and acceptability of multiple injections as well as the potential downsides of not administering all recommended immunizations, including increased disease burden due to less timely immunization and increased costs to the health system due to increased unnecessary visits. VPD disease eradication initiatives and routine immunization funding agencies which have important roles in vaccine introduction should also be proactive in investing into research to develop and modify routine immunization education modules to incorporate information about multiple injections, including solutions which healthcare providers can use to alleviate any parental concerns. These same entities can also take a lead role in funding future research to study the magnitude and details of any issues with multiple injections in developing countries which will be useful in defining realistic solutions which can be implemented by program managers to ensure high administration and uptake of all recommended injections at each visit.

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