Post-trial Access in Maternal Vaccine Trials

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Abstract

Provisions for post-trial access (PTA) of the experimental intervention are required before the start of a clinical trial. Although there has been ample attention for PTA in the context of preventive vaccine research, discussions on PTA barely include maternal vaccine trials in which mother–infant pairs are exposed to the intervention. In maternal vaccination trials, specific PTA arrangements are required because pregnancy is transient and PTA may apply to the next pregnancy or the child. In this article, we examine the application and adherence to PTA in the context of maternal vaccine trials. We focused on differences between publications before and after 2000 when international ethical guidance documents formalized PTA requirements. Randomized maternal vaccine trials were included after a systematic search for clinical trials in phases II and III with a maternal vaccine as intervention. We used PTA as defined at the time of publication in the World Medical Association's Declaration of Helsinki (DoH) or in the ethical guidelines of the Council for International Organizations of Medical Sciences (CIOMS). In addition, we investigated whether PTA was included in the trial design. Therefore, we contacted principal investigators (PI's) of the publications found in the review to fill out a questionnaire regarding provisions for PTA. Before and after 2000, no trial articles examined in the systematic review described PTA in their trial publication (0/7, 0% and 0/17, 0%, respectively). In addition, more than half of the PI's of the trials found were not familiar with PTA recommendations in international ethical guidelines. Most cases of PTA included making knowledge available by publishing the results of the trial. The revision of the DoH in 2002 and the CIOMS ethical guidelines in 2002 has not resulted in increased PTA provisions for maternal vaccination trials. PTA is a shared responsibility of various stakeholders including sponsors, Institutional Review Boards, regulators, political entities, and researchers. Inclusion of PTA provisions in trial protocols and publications on maternal vaccination trials is essential to increase transparency on the form and content of these provisions.

Keywords
- post-trial access
- maternal vaccination
- vaccine trials
- research
- ethical

Maternal vaccination is an intervention to protect newborns from life-threatening infectious disease in the first month of life. Maternal immunization can protect newborns via an immunoglobulin G (IgG) antibody response to an (in)activated micro-organism. IgG antibodies are transported actively across the placenta to the fetus and thereby provide passive immunity in the newborn which lasts for the first 6 months of life. After this period, the immune system of the

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child can generate active antibody responses via infant vaccination.[1] Maternal vaccines for several pathogens are already approved and recommended for pregnant women in various countries: influenza, tetanus, and pertussis, while meningo-/pneumococcus, group B *Streptococcus*, and *Haemophilus influenzae* type B are still in clinical development and not yet recommended. More vaccines are in the pipeline: cytomegalovirus, herpes simplex virus, and respiratory syncytial virus (RSV).[2,3] Despite maternal vaccination as a rapidly growing field, there is still hesitancy to vaccinate pregnant women.[4] However, various RSV trials are now moving forward from early to late phase clinical trials.[5] This development requires reflection on post-trial access (PTA) provisions.

International ethical guidelines for research involving human subjects support the value of PTA requirement for clinical trials. In 2000, PTA was added to the Declaration of Helsinki (DoH) paragraph 20. The DoH stated that "At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study." Various other international ethical frameworks, including the National Bioethics Advisory Commission, the Nuffield Council on Bioethics, and the Council for International Organizations of Medical Sciences (CIOMS) have adopted PTA requirements in their guidance documents (►**Fig. 1**).[6–9] Despite agreement about the importance of the requirement, there is extensive discussion about the underlying rationales for PTA, about its content, the length, and to whom it applies. In general, according to small interpretations fulfilling the PTA requirement implies making provisions for continued access to interventions identified as beneficial, but broader interpretations also include provisions for transitioning participants who continue to need care or preventive measures to appropriate health services when the study has ended. The responsibility to fulfill PTA requirements is typically shared among several stakeholders including sponsors, regulators, political entities, and researchers. The shared responsibility makes providing PTA a complex issue. Investigators of a study cannot provide PTA alone and are dependent on the government, pharmaceuticals, and sponsors.[10]

Although there is ample literature on PTA in the context of human immunodeficiency virus (HIV) prevention research, scholars have barely reported on PTA for maternal vaccination studies. Poor attention is remarkable since it is reasonable to assume that in the case of maternal vaccination, PTA could be conceived as access to the vaccine in future pregnancies not only for women receiving placebo.

To understand why PTA requirements receive limited attention in discussions about maternal vaccination studies, we performed an in-depth study whether and how PTA requirements as formulated in the CIOMS guidelines and the DoH are included in publications on late phase maternal vaccine trials and contacted principle investigators of these publications about provisions made. We compared PTA provisions made before and after 2000, when the guidelines were not in place yet. Furthermore, this study identifies best practices for implementation of PTA provisions.

Materials and Methods

Systematic Review

Randomized maternal vaccine trials were included after a systematic search (►**Supplementary Appendix A**, available in the online version) in PubMed for clinical trials in phases II and III with a maternal vaccine or prophylaxis as intervention. All articles were screened for eligibility by two people independently, using Rayyan.[11] The World Health Organization (WHO) clinical trial registry and ClinicalTrials.gov were searched for phase II/III maternal vaccine trials, using the same in- and exclusion criteria as for PubMed. Relevant completed or ongoing trials were included, and withdrawn trials were excluded. Trials with no article available were also excluded for the systematic review (►**Table 1**). Trials before 2000 and after 2000 were compared since PTA was first included in the ethical guidelines in 2000.

Guideline	Section	Obligation
CIOMS 2016	Guideline 6: Caring for participants' health needs	Addressing participants' health needs requires at least that researchers and sponsors make plans for: providing continued access to study interventions that have demonstrated significant benefit; and consulting with other relevant stakeholders, if any, to determine everyone's responsibilities and the conditions under which participants will receive continued access to a study intervention, such as an investigational drug, that has demonstrated significant benefit in the study.'
NBAC 2001	Section 4.1	'..make reasonable, good faith efforts before the initiation of a trial to secure, at its conclusion, continued access for all participants to needed experimental interventions that have been proven effective for the participants. ....research protocols should typically describe the duration, extent, and financing of such continued access. When no arrangements have been negotiated, the researcher should justify to the ethics review committee why this is the case.'
	Section 4.2	'Research proposals submitted to ethics review committees should include an explanation of how new interventions that are proven to be effective from the research will become available to some or all of the host country population beyond the research participants themselves…'
	Section 4.3	'Whenever possible, preceding the start of research, agreements should be negotiated by the relevant parties to make the effective intervention or other research benefits available to the host country after the study is completed.'
Nuffield Council on Bioethics Group report 2002	Section 9.48	'.. we recommend that the following issues are clearly considered by researchers, sponsors, national healthcare authorities, international agencies and research ethics committees as part of any research protocol before research relating to healthcare involving the testing of new interventions is undertaken:.....the possibility of providing participants with the intervention shown to be best (if they are still able to benefit from it), for an agreed period of time and the possibility of introducing and maintaining the availability to the wider community of treatment shown to be successful.'
DoH 2013	Guideline 22	'…In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.'
	Guideline 34	In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post- trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Fig. 1 Overview posttrial access in various ethical guidelines.[8–11]

Table 1 In- and exclusion criteria systematic review

Inclusion	Exclusion
Pregnant women	Women of childbearing age/ nonpregnant women
	Animals
Passive or active immunization	No vaccination
Maternal vaccine trials	HPV 16/18 trials (because goal of vaccination is not child protection)
	HIV PMTCT trials
Phases I/II, II, and III trials	Phases I and IV trials
Positive and negative outcomes	
Prospective randomized controlled trials	Editorial
Secondary analysis (NB: if duplicate, only primary article was included)	Review
	No PDF available
	No author information provided
	Language barrier
	Duplicates or secondary analysis while primary article was already included

Abbreviations: HIV, human immunodeficiency virus; HPV, human papillomavirus; PMTCT, prevention of mother-to-child transmission.

Definitions

A vaccine was defined according to the WHO's definition: an intervention that augments immunity to a particular disease, which contains an agent that resembles a disease-causing microorganism.[12] Human intravenous immunoglobulin (HIVIG) and intravenous immunoglobulin (IVIG) trials were included as relevant interventions. HIV prevention of mother-to-child transmission trials, HBV tenofovir trials, and antibiotic prophylaxis were not included since they do not enhance immunity or contain a part of a microbe, but only prevent mother-to-child transmission by reducing the viral load. Full-text articles were screened for description of PTA as defined at the time of publication in the DoH or CIOMS (►**Fig. 1**).

Data Collection

The principal investigator (PI) of each trial was contacted and asked to fill out a short questionnaire regarding provisions for PTA in the trial design. Contact with the PI was still attempted for trials that were excluded from the systematic review if there was no article available. All ongoing and completed trials from the WHO clinical trial registry and ClinicalTrials.gov were included. PI's were contacted first by telephone, then e-mail for a maximum of three times of follow-up. They were also asked to inform us if they were not willing to participate. The questionnaire was shared using Qualtrics software, version 2017. Where questionnaire data are factual, facts were verified against other sources such as trial protocols. The methods were modeled after the methodology of Haire and Jordens, *Developing World Bioethics*, 2015 in which PI's of phase IIB/III HIV efficacy trials were contacted in an empirical study of PTA.[12]

Results

Systematic Review

Twenty-four maternal vaccine trials were identified for this systematic review (►**Fig. 2**, ►**Table 2**). Before and after 2000, no trial articles examined in this systematic review described PTA in their trial report (0/7, 0% and 0/17, 0%, respectively); 6/17 (35.3%) trials mentioned that they were conducted in accordance with the DoH in their trial report but did not specify PTA provisions.

Questionnaires

Thirty trials were identified as the PI was contacted to collect data on PTA (►**Tables 2** and **3**). Thirty trials were eligible for the qualitative analyses. Out of 30 PI's, 17 responded to the questionnaire. One PI was not willing to participate, and 12 investigators did not respond after follow-up. Eighty-two per cent (14/17) of PI's from trials conducted after 2000 described provisions regarding PTA.

Awareness

The majority (59%, 10/17) of the PI's for maternal vaccine trials were not aware of post-trial recommendations in international ethical guidelines. In several cases, the PI was not aware of PTA, but the PI indicated that he or she had made provisions for PTA. Half of the PI's who were aware of posttrial provisions still did not describe them for their trial.

Best Practice

From the PTA provisions that have been made by investigators in phase II/III maternal vaccine trials, most of them included making knowledge available for the population and transition to care when the research is concluded (79% [11/14] and 64% [9/14]). Researchers who described PTA provisions shared their protocol. Some only described making knowledge available through publication of the article as PTA provision in their protocol. Researchers indicated that the best way to incorporate obligation of PTA in the future would be to state intentions to local Institutional Review Board and Research Ethics Committee. Several PI's indicated incorporating obligations in trial protocols and informed consent to be a best practice to conform to PTA obligations.

Challenges

Researchers reported different reasons to not address PTA. One reason was that PTA was felt to be the responsibility of the local government rather than that of the researcher. Other challenges included the lack of proven benefit, awaiting WHO recommendation or national approval, a delay caused by lack of funding, consulting with other relevant stakeholders, and determining the responsibilities of different stakeholders. Finally, the PI's indicated that there was no

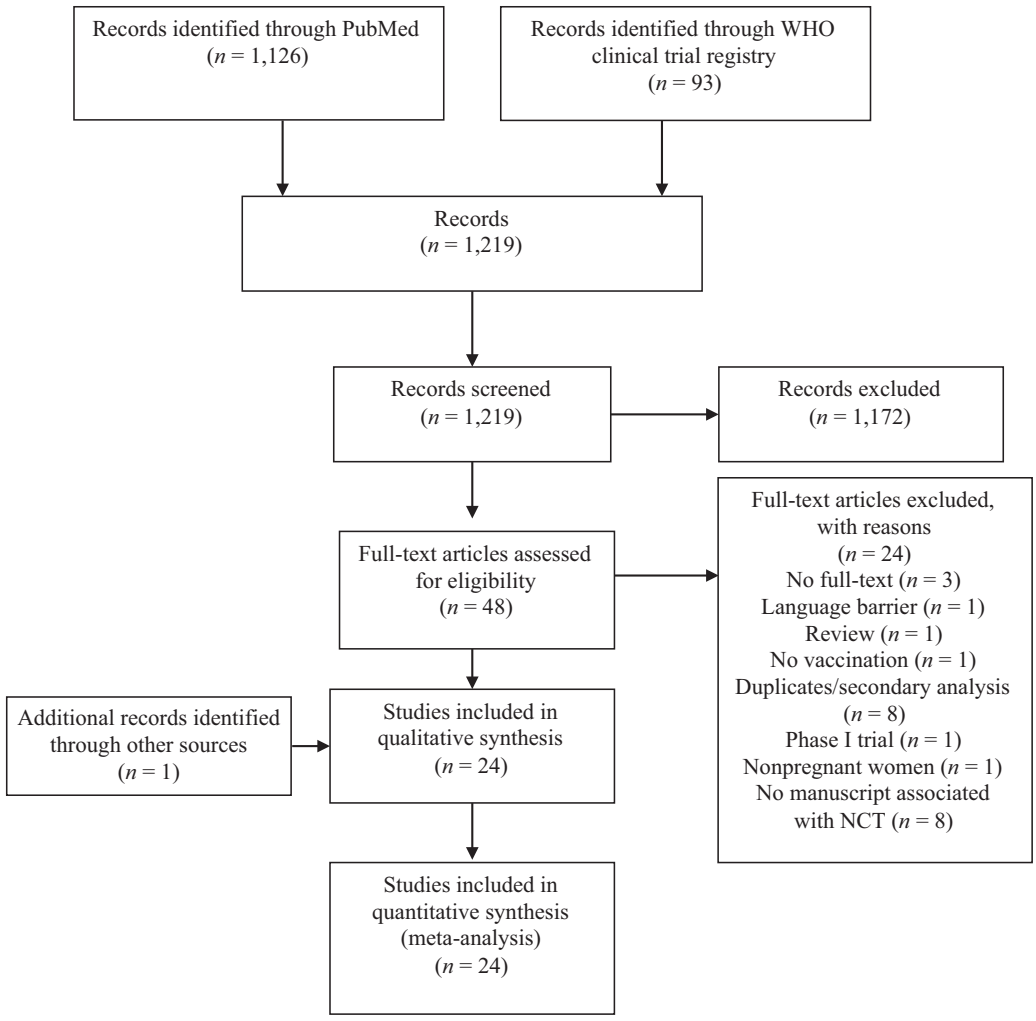

Fig. 2 Flow chart systematic review maternal vaccine trials.[13]

practical guidance available, or at least none that the investigators were aware of.

Discussion

No trial article, before and after 2000, examined in this systematic review described specifically PTA in their publication. However, 82% of the trials after 2000 described provisions regarding PTA elsewhere, for example, in trial protocols. Most of them included making knowledge available for the population. The percentage of 82% may be relatively high but should be critically examined. Several researchers published the article and did not address other aspects of PTA that are important for the community, such as providing continued access for study participants and making the vaccine available for the population.

The majority of the PI's was not aware of the concept of PTA. Remarkably, there were several cases in which the PI was not aware of PTA, but still indicated that he or she had made provisions for PTA. Lack of awareness of the concept PTA despite inclusion of provisions may indicate that provisions were included in the research without knowledge of the underlying concept of PTA such as publication of results without awareness of PTA obligations. Half of the PI's who were aware of posttrial provisions still did not describe them for their trial. This finding demonstrates a gap in implementation of PTA guidelines and not only awareness.

Best practices and obstacles in the process of PTA were identified. According to researchers, the best way to incorporate PTA obligations for trial planning in the future would be including PTA provisions in the protocol submitted to the ethical committees. Obstacles to including PTA in the trial planning were shared responsibilities, lack of funding, and awaiting proven benefit and recommendation. Lack of practical guidance available for PTA provisions in prevention trials remains an important obstacle and the creation of such guidance may also enhance awareness.

This study provides the first data on whether researchers implement provisions in the planning of published maternal vaccine trials. Thorough methodology was used including a systematic search with an extensive search term and careful examination of trials by two independent researchers. Furthermore, PI's of the trial were contacted to verify whether PTA provisions were included in the trial planning process. Where possible, facts have been verified against other sources, such as trial protocols. A limitation of this

Table 2 Maternal vaccine trials overview systematic review

	Pathogen	Article	Year	Country	Study size
Before 2000	Pneumococcal	Quiambao et al[14]	1994–1995	Philippines	160
		Munoz et al[15]	1995–1996	United States	60
	Meningococcal	Shahid et al[16]	1995–1998	Bangladesh	157
	Hib	Mulholland et al[17]	1993–1995	The Gambia	451
	Tetanus	Newell et al[18]	1961–1966	Colombia	1,618
	Varicella zoster	Koren et al[19]	1999–2000	United States	60
	RSV	Munoz et al[20]	1999–2002	United States	35
After 2000[b]	Influenza	Jackson et al[21]	2009	United States	120
		Tielsch et al[22]	2010–2018	Nepal	3,000[a]
		Omer et al[23]	2011–2013	Nepal	3,700
			2011–2013	Mali	4,193
			2012	South Africa	2,108
		Tsatsaris et al[24]	2009	France	107
		Abzug et al[25]	2009	United States	127
		Madhi et al[26]	2011–2012	South Africa	2,310
		Zaman et al[27]	2004–2005	Bangladesh	340
	Tetanus	Salama et al[28]	2002–2003	Egypt	131
	GBS	Donders et al[29]	2011–2013	Belgium Canada	86
		Madhi et al[30]	2010–2011	South Africa	417
		Heyderman et al[31]	2011–2012	Malawi South Africa	270
	Pneumococcal	Binks et al[32]	2006–2011	Australia	227
		Daly et al[33]	2000–2003	United States	153
		Lopes et al[34]	2005–2006	Brazil	139
	Tdap	Hoang et al[35]	2012–2014	Vietnam	103
		Villarreal Perez et al[36]	2011–2014	Mexico	204
		Munoz et al[37]	2009–2012	United States	80

Abbreviations: GBS, group B *Streptococcus*; Hib, *Haemophilus influenzae* type b; RSV, respiratory syncytial virus; Tdap, tetanus, diphtheria, pertussis.
[a]Ongoing trial.
[b]All trials after 2000 were included for contact with PI's.

Table 3 Additional trials contact PI's

Pathogen	NCT	Year	Country	Study size	Phase
Influenza	NCT00992719[38]	2009–2011	United States	84	II
	NCT01173211[39]	2010–2011	United States	183	II
	NCT00905125[40]	2009–2010	United States	102	II
	NCT01577316[41]	2012–2013	Mexico	240	II/III
	NCT01527825[42]	2012–2014	South Africa	800	III
GBS	NCT02046148[43]	2014–2016	United States	75	II
Pneumococcal	NCT02628886[44]	2016–2019[a]	Gambia	600	III
	NCT02717494[45]	2016–2019[a]	Brazil	345	II
RSV	NCT02624947[46]	2015–2020[a]	United States	8,618	III
	NCT02247726[47]	2014–2016	United States	50	II
Pertussis	NCT00553228[48]	2007–2016	Canada	440	II/III
Tdap	NCT02301702[49]	2016–2018[a]	Guatemala	376	II
HIV	NCT00000751[50]	2001–2007	United States	1,600	III

Abbreviations: GBS, group B *Streptococcus*; HIV, human immunodeficiency virus; PI, principal investigator; RSV, respiratory syncytial virus; Tdap, tetanus, diphtheria, pertussis.
[a]Ongoing trial.

study is the small group of maternal vaccine trials. Unfortunately, 12/30 investigators did not respond to our questionnaire. There may be selection bias. PI's who were aware of PTA and made provisions for PTA may have been more likely to respond to our questionnaire than PI's who did not make them. PI's with PTA provisions in place could be more likely to respond to our questionnaire, and therefore, the proportion of PTA provisions may be an overestimation of the actual provisions implemented.

In conclusion, the publication of international ethical guidelines in 2000 has not resulted in increased publication of ethical provisions in maternal vaccine trial literature. PTA provisions were described in trial protocols, but often the only PTA provision described was publication of the article to make knowledge available instead of providing continued access to interventions that have been proven significant benefit. Future studies should include PTA in their trial protocols, which will increase transparency on the form and content of these provisions. In theory, it can be stated that trials adhere to ethical guidelines and have PTA provisions in place, but in reality, studies do not incorporate all important aspects of PTA provisions into trial planning.

Conflict of Interest
None declared.

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