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Mapping time use in clinical trials for vaccines against emerging infectious diseases

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Abstract

Background: Vaccines are potent tools to prevent outbreaks of emerging infectious diseases from becoming epidemics and need to be developed at an accelerated pace to have any impact on the course of an ongoing epidemic. The aim of this study was to describe time use in the execution of vaccine trials, to identify steps that could be accelerated to improve preparedness and planning for future emerging infectious diseases vaccine trials.

Methods: We used a mixed-methods approach to map time use and process steps that could be accelerated during vaccine trials. Trials for vaccines against infectious diseases registered in three global trial databases reported in the period 2011–2017 were eligible to join the survey. We invited sponsors to contribute data through a predefined structured questionnaire for clinical trial process metrics. Data were stratified by trial phase, disease type (i.e. emerging infectious diseases or not emerging infectious diseases), sponsor type, and continent. Qualitative interviews were conducted with purposively selected sponsors, and thematic analysis of the interview transcripts was performed.

Results: Based on data from 155 vaccine trials including 29,071 subjects, 52% were phase I, 23% phase II, and 25% phase III. We found that the regulatory approval, subject enrollment, study execution, and study close-out accounted for most of the cycle time of the vaccine trial process. Cycle times for the regulatory and ethical approvals, contract agreement, site initiation, and study execution were shorter in trials conducted during outbreaks. Qualitative interviews indicated that early engagement of the regulatory and independent ethical committee authorities in planning the vaccine trials was critical for saving time in trial approval. Furthermore, adapting the trial implementation to the reality of the study sites and active involvement of the local investigators during the planning of the trial and protocol writing were stated to be of paramount importance to successful completion of trials at an accelerated pace.

Conclusion: The regulatory approval, subject recruitment, study execution, and close-out cycle times accounted for most of the vaccine trial time use and are activities that could be accelerated during a vaccine trial planning and implementation. We encourage tracking of key cycle time metrics and facilitating sharing of knowledge across industry and academia, as this may serve to reduce the time from index case detection to access of a vaccine during emerging infectious diseases epidemics.

Keywords

Cycle time, metrics, accelerating vaccine trials, emerging infectious diseases

Introduction

Emerging infectious diseases (EID) pose a real and growing threat to global health security, and vaccines are our most powerful tools in the fight to mitigate or prevent epidemics.[1] Vaccines against EID should be developed in time to have any chance to avert or limit the impact of epidemics on affected populations, and both the clinical development and the challenges of manufacturing vaccines at large scale with a validated process must be overcome to enable timely and equitable access to these vaccines.[1]

Vaccine development is a complex, costly, lengthy, and highly regulated process. Traditionally, the entire process has taken 10–15 years from discovery, preclinical development, clinical development (phase I, II, III

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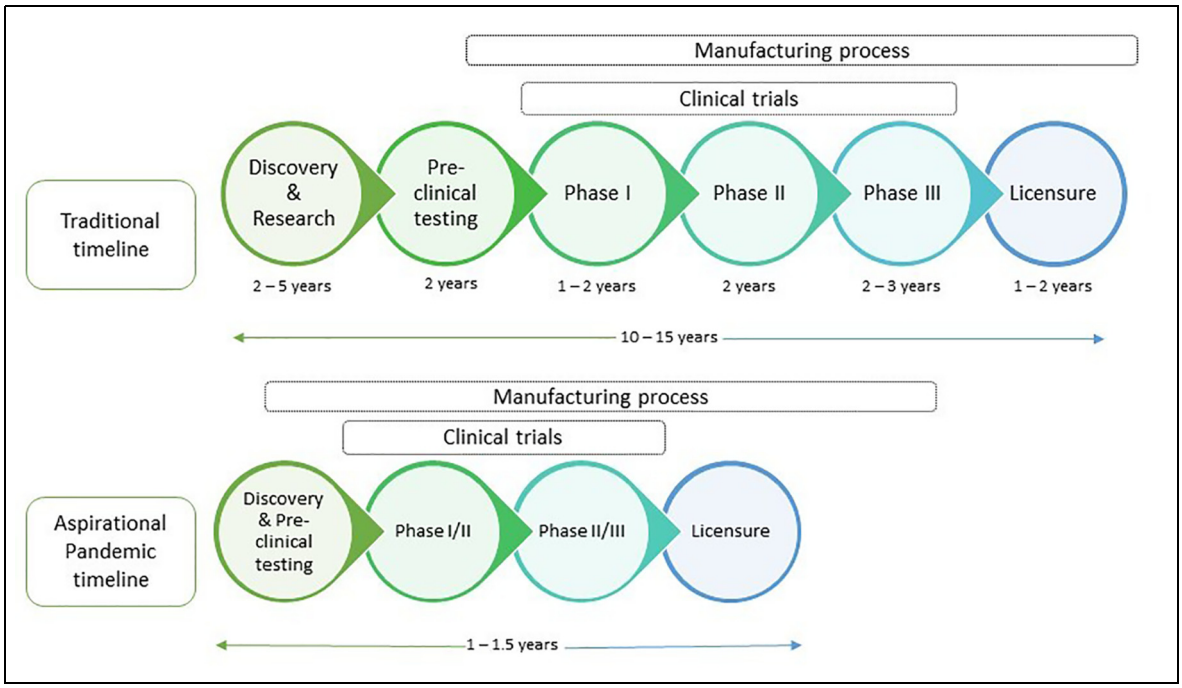

Figure 1. Accelerating vaccine development timelines.

clinical trials) to licensure.[2,3] The clinical trial phases constitute the longest duration of vaccine development timelines. In the case of outbreaks and public health emergencies like the COVID-19 pandemic, there is need for an accelerated vaccine development process to have any mitigating effect on the ongoing transmission and disease burden[4] (Figure 1). Vaccine development during outbreaks hence carries a high risk of failure, but a persistent endemic disease burden or recurrence of outbreaks may justify the investment. Implementing a clinical trial already bears a high risk for developers,[5] and additional complexity is seen if performed during outbreaks. Risk factors may include uncertainty about populations, interventions, comparators, effect size, heterogeneity of vaccine effect,[6] current technical capacities, acceptance or degree of community engagement, and poor stakeholder coordination.[7] Some of these affect the "lead-time" required to initiate and conduct clinical trials during an outbreak,[6] which presents a significant challenge to be overcome when there are expectations for rapid implementation to justify the investment compared to other potential interventions. Time is a decisive factor in the implementation of vaccine trials during epidemics; however, quality of trial data to enable regulatory submission and security of study staff as observed in the Ebola vaccine development.[8]

Current evidence shows that the expenditures, complexity, legal requirements, and documentation requirements related to the conduct of clinical trials have persistently increased at the global level.[9,10] The requirement for a rigorous clinical trial evaluation of new vaccines needs to be balanced against the earliest reasonable access during a pandemic.[11]

Regulators are, however, increasingly engaged about accelerating medical countermeasure development during epidemics. Previous studies have shown significant variability in time use in the implementation of clinical trials suggesting the need to devise mechanisms that enhance efficient implementation of vaccine trials for the timely development of vaccines for reactive or preventive use against EID.[8,12,13] To enable a full overview of time use in clinical evaluation, is essential to describe the cycle time of step involved in the entire vaccine trial process to serve as benchmarks for future planning and to identify the steps with the most potential for reducing overall time use. The aim of this study was to identify time use in the execution of individual clinical vaccine trials to identify steps that could be accelerated to improve preparedness and reduce clinical development time for vaccines against newly emerging pathogens.

Methods

We used a mixed-methods approach. Quantitative data was used to quantify time use and identify significant factors that could accelerate vaccine trials. In-depth interviews were applied to explore the perspectives of purposively selected sponsors on time use in vaccine trials.

Search strategy and selection criteria

We searched the global clinical trial registries of ClinicalTrials.gov, the WHO Clinical Trial Registry,

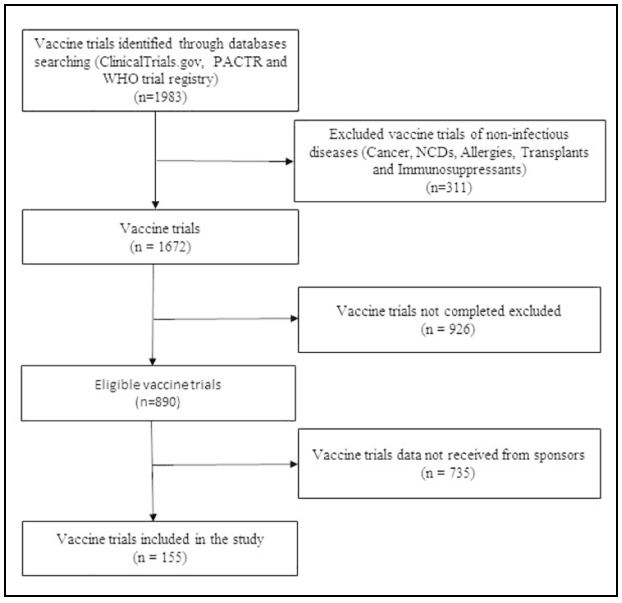

Figure 2. Flowchart of data collection for clinical trials subjected to study analysis.
NCDs: non-communicable diseases; WHO: World Health Organization; PACTR: Pan African Clinical Trial Registry.

and Pan African Clinical Trials Registry to identify eligible vaccine trials. We included vaccine trials that were in phases I, II, and III with enrollment between 1 January 2011 and 31 December 2017 that focused on human infectious diseases caused by viruses, bacteria, parasites, fungi, bacterial toxins, or unknown infectious agents (Figure 2).

Data collection on vaccine development metrics

After identifying eligible trials for the study, sponsors were invited to contribute data through a predefined structured questionnaire for clinical trial process metrics[12] (supplemental material—Online Appendix 1), adapted from Lamberti et al.[12] The data collected included types of activities in the trial process and dates from start to completion of each study cycle, including protocol approval, site selection, ethics, and regulatory review, study initiation, study enrollment, and completion.

Data analysis

Data were entered into Microsoft Excel and analyzed using Stata, version 11.0 (StataCorp, College Station, Texas) and Tableau Software version 2019.4. Cycle times were calculated by determining the number of days between relevant date fields (Table 1). Data were stratified by trial phase, disease type (i.e. EID or not EID), sponsor type, and continent. Descriptive cycle time metrics (medians and interquartile ranges) were calculated and compared by various subcategories using the Kruskal–Wallis one-way analysis of variance test for nonparametric data. We used Dunn's test overall threshold level of significance of $\leqslant 0.05$ for the statistical analysis. Missing observations were not included as a category for these analyses. When the results for the Kruskal–Wallis test were significant, post hoc multiple comparisons were run to help determine which groups were different while appropriately adjusting pairwise comparisons.

Understanding factors affecting time use in trials: qualitative interviews

In the qualitative interviews, purposefully chosen sponsors were asked to participate and were able to include in-depth explanations of the subject. An interview guide (supplemental material—Online Appendix 2) was developed based on a literature review on time use in clinical trials and designed to address the study objective of understanding factors affecting time use. The interview guide was pre-tested outside the study area and developed iteratively during the course of the interviews. The interview guide included questions about the interviewee's general perspectives of the vaccine trial performance, reasons for a delayed or expedited process, and lessons learned. Interview questions targeted experiences in specific vaccine trials that had delayed or accelerated vaccine trial processes. The interviews were conducted in English, done by videoconference or

Table 1. Key process cycle time metrics of vaccine trials.

Cycle time	Description
Site selection	Number of days from protocol approval to site selection
Contract agreement	Number of days from contract/budget sent to site to contract execution
Regulatory approval	Number of days from regulatory review submission to approval
Ethics approval	Number of days from ethics review submission to approval
Subject recruitment	Number of days for subject screening and enrollment
Site initiation	Number of days from the contract signed to site initiated
Study execution	Number of days from "First Subject In" to "Last Subject In"
Study close-out	Number of days from "Last Subject In" to Database Lock

Table 2. Cycle time metrics (weeks) for protocol approval to site selection, regulatory approval, ethical approval, and contract agreement.

By category	Protocol approval to site selection		Regulatory approval		Ethical approval		Contract agreement	
	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range
All data	7	2–22	10	7–19	7	3–15	8	4–28
Sponsor type	7	2–22	10	7–19	7	3–15	8	4–28
Product development partnerships	8	1–52	7	3–16	6	3–10	15	1–29
Academic	8	5–24	11	9–22	9	4–17	32	22–35
Industry	3	1–15	10	7–19	7	3–10	7	4–8
Phases	7	2–22	10	7–19	7	3–15	8	4–28
I	9	5–24	9	6–14	6	3–10	7	4–28
II	5	1–16	17	6–21	8	5–13	9	8–28
III	2	1–7	11	9–28	10	2–20	16	16–16
Disease type	7	2–22	10	7–19	7	3–15	8	4–28
EID	4	1–8	10	7–15	4	2–15	4	2–4
Non-EID	12	3–22	10	6–21	9	5–15	19	8–32
Continent	5	1–22	10	7–19	7	3–15	8	4–28
Africa	5	1–8	16	10–20	10	7–16	32	29–35
Americas	6	2–22	7	5–9	3	1–4	4	2–9
Asia-Pacific	4	1–22	18	10–25	10	5–18	22	16–28
Europe	5	15–15	9	6–14	9	3–15	7	4–8

EID: emerging infectious diseases.

telephone, lasted a maximum of 45 min and were recorded with interviewees' consent. Saturation was reached when little or no new information was raised. All interviews were transcribed verbatim. The coding was performed by a single coder, but the generated codes and quotes were thoroughly checked by the second co-author. Thematic analysis was performed to identify themes and sub-themes as per Braun and Clarke.[14,15]

Results

Mapping time use through process cycle time metrics in vaccine trials

The overall response rate of sponsors contributing to data was 10.5% (22/209) and represented 17.4% (155/890) of the eligible vaccine trials in the study period (Figure 2).

Out of 155 trials including 29,071 subjects, 52% were phase I, 23% phase II, and 25% phase III. Forty-two percent of the trials were conducted in the Americas, 35% in the Asia-Pacific, 14% in Africa, and 10% in Europe. Fifty-one percent of the trials were performed by academic institutions, 44% by industry, and 5% by product development partnerships. Fifty-five percent (85/155) of the trials involved EID heavily skewed toward Influenza (44%), Dengue (14%), and Ebola (9%).

The median time for the regulatory and ethical approval cycles was significantly higher in Africa and Asia-Pacific ($p < 0.05$) as compared to the Americas and Europe. The median time for the ethical approval cycle was significantly lower when using the national ethics committees ($p = 0.0351$) (Table 2).

Industry sites significantly had lower median times for site initiation cycle than academic institutions ($p = 0.0048$). The median times for subject recruitment, site initiation, and study execution were longest in trials conducted in Africa as compared to the Americas, Europe, and Asia-Pacific (Table 3).

We found that the regulatory approval, subject enrollment, study execution, and study close-out accounted for most of the cycle time of the vaccine trial process. Cycle times for the regulatory and ethical approvals, contract agreement, site initiation, and study execution were shorter in trials conducted during outbreaks (Figure 3).

Qualitative insights and themes —sponsors' perspectives on factors that could accelerate or slow down vaccine trials

Thirteen clinical research professionals participated in a total of seven interviews. Participants were mostly principal investigators and heads of vaccine trial centers.

Thematic analysis identified two major themes: (1) perception of the use of metrics in time use in clinical trials and (2) experiences of tracking cycle time metrics in running clinical trials (supplemental material—Online Appendix 3).

Table 3. Cycle time metrics (weeks) for site initiation, subject screening, subject enrollment, study execution, and study close-out.

By category	Site initiation		Subject screening		Subject enrollment		Study execution		Study close-out	
	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range
All data	8	4–25	8	3–13	14	7–34	21	9–67	44	18–63
Sponsor type	8	4–25	8	3–13	14	7–34	21	9–67	44	18–63
Product development partnerships	7	5–56	3	1–13	8	2–14	17	8–115	50	7–53
Academic	20	6–53	4	2–9	22	9–38	35	12–80	15	8–32
Industry	4	4–13	8	8–13	15	7–37	16	7–62	48	41–81
Phases	8	4–25	8	3–13	14	7–34	21	9–67	44	18–63
I	5	3–22	8	2–13	14	8–34	32	14–74	32	8–48
II	10	4–25	8	6–8	14	6–27	31	9–115	48	41–72
III	16	6–35	9	9–12	19	6–43	13	6–40	46	33–81
Disease type	8	4–25	8	3–13	14	7–34	21	9–67	44	18–63
EID	6	4–20	8	2–11	13	6–28	13	6–36	36	11–77
Non-EID	9	4–28	8	8-13	20	11–52	39	15–107	45	38–55
Continent	8	4–25	8	3–13	14	7–34	21	9–67	44	18–63
Africa	31	8–53	2	1–8	39	14–61	80	47–115	32	7–45
Americas	4	3–13	8	4–13	14	6–34	21	6–45	49	29–74
Asia-Pacific	9	5–22	8	3–9	9	6–24	13	7–38	43	11–81
Europe	3	1–6	13	8–13	14	12–20	51	15–86	48	38–53

EID: emerging infectious diseases.

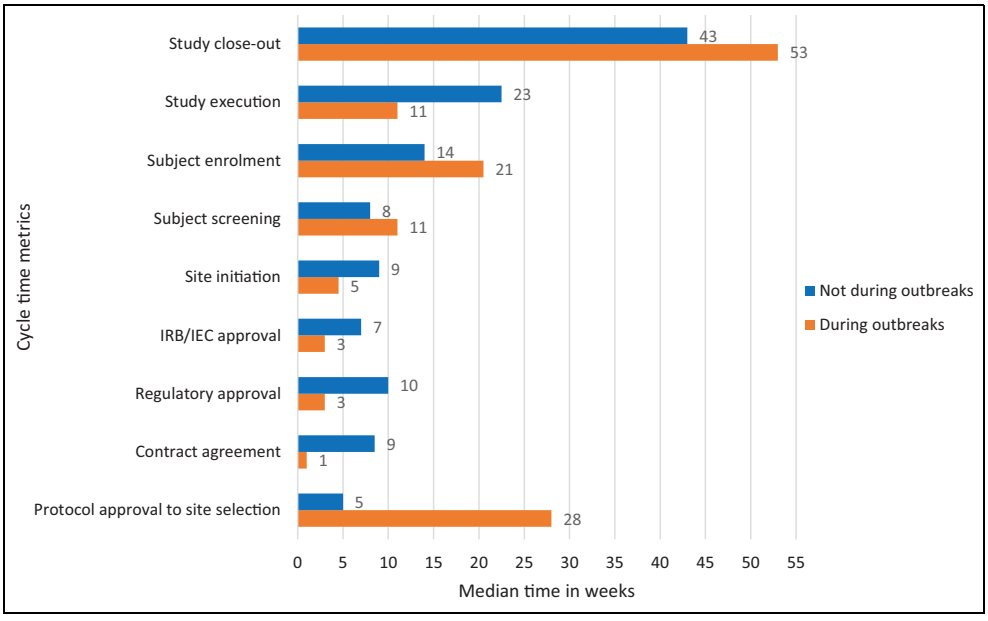

Figure 3. Vaccine trial process cycle time metrics during outbreaks or epidemics.
IRB: institutional review board; IEC: independent ethical committee.

Perception of the use of metrics in time use in clinical trials

The majority of the participants stated that they did not keep track of all the cycle time metrics, but widely concurred on the importance of monitoring such critical parameters for process improvement. When further probed, participants were neither negligent nor had a lack of knowledge to track process metrics. A reason mentioned to limit the tracking and focusing only on selected process metrics was to avoid increased workload burden on staff.

Experiences of tracking cycle time metrics in running clinical trials

Regulatory approval. Participants stressed the importance of early involvement of the regulatory and ethics authorities in the planning of the vaccine trials. The advice, guidance, and trust from regulatory and ethical authorities were vital to have a quick regulatory and ethical approval process. Parallel ethical and regulatory approval processes were essential to shorten the timelines. Vaccine trials involving multiple local ethics committees with varied approval processes led to a delay.

Subject recruitment. If the trial implementation required the use of several local languages needing translation per site, this slowed the informed consent process and eventually the subject recruitment. Several academic institutions had a large database of potential trial participants, and this led to shorter subject recruitment cycle time. At the site level in Africa, the lack of adequate regular Internet connectivity led to difficulties in conducting randomization using an interactive voice/web response system. Substantial media coverage of the Ebola virus disease with a high level of awareness during an outbreak led to a shorter study enrollment cycle time.

Study execution. At the site level, procurement processes, supply and logistics issues led to delays in initiating the study. Most interviewees stressed the importance of adapting the vaccine trial to the study participants' cultural environment as well as the health system, site-specific procedures, seasonal conditions, and the available human and infrastructural resources possible. Failure to do so during the planning and implementation of the vaccine trials led to significant delays.

Discussion

This study mapped time use in the entire vaccine trial process, rather than focusing on a subset of activities and cycle times as compared to prior studies.[8,12,13] A critical finding from this study was that most of the sponsors could not track every metric, rather they did track regularly a set of key clinical trial metrics; likely not because of lack of knowledge nor negligence but to avoid increased staff workload. Our findings can be compared to a survey by Metrics Champion Consortium that revealed that currently, on average, 83% of pharmaceutical and biotechnology companies use a set of key standardized performance metrics in clinical operations and data management.[16]

A significant finding from this study was that the contract agreement cycle time was significantly shorter for epidemic-prone EID trials, stipulating that this contracting process could be accelerated. Also, the contract agreement was longest when the trial was conducted in Africa, and this pinpoints a potential area for improvement. Our findings are similar to a case described by Trudie Lang et al. that identified agreeing on contracts as a significant delay in the implementation of clinical trials during the Ebola epidemic.[8] The literature reveals possible factors contributing to such delays, among other things, like inexperienced investigators, finalized budgets by financial institutions before agreement negotiations, and limited financial experts in resource-constrained settings.[10,17] We encourage future studies to elaborate on the mechanisms that could be implemented to shorten the contract agreement cycle time in EID vaccine trials especially in Africa.

This study revealed longer regulatory approval timelines for trials conducted in Asia-Pacific and Africa. Our findings are consistent with the knowledge that the regulatory approval process has been known as a possible delay as it abides by country-specific context-based rules with different levels of expertise and capacities.[10,17,18] A potential solution that emerged from the discussions with sponsors was early engagement with regulatory agencies to limit delays, which is consistent with the literature.[19] A recent paper stressed the need for more investments and collaboration from governmental bodies toward vaccine research in Africa.[20]

This study revealed that most ethical reviews were submitted for approval to the national as opposed to local ethics committees with shorter approval timelines. One critical delay was in countries with several local ethics committees with varied approval processes, timelines, and requirements. Longer approval times in Africa and Asia-Pacific stressed the need for capacity strengthening and further research.

In our study, there was no significant difference in the regulatory and ethical approval cycle times according to the type of disease (i.e. EID or not EID). This shows an area for improvement. We encourage future studies to provide evidence as to whether or not fast-tracking were implemented and if they did accelerate vaccine trials to make sure investigational products are available as early as possible during an outbreak to possibly affect the course of the epidemic. The US Food and Drug Administration and the European Medicines Agency have fast-track approval routes.[21,22] The African Union plans to set up a pan African Medicines Agency and encourages partnerships and collaborative approaches for fast-tracking approvals for clinical trials and registration of products in the affected countries.[23]

A significant finding is that industry sites used a shorter time to sign contracts and initiate a trial than academic sites. This is consistent with published literature.[12] The study initiation process involves several steps ranging from the prestudy visit, site selection, regulatory and ethical approval, contract agreement, and enrolling the "first subject in." Contributing factors to site initiation delays are contract and budgeting negotiations, regulatory and ethical approval timelines, and recruitment challenges.[24,25] Academic investigators revealed that reliable media coverage and awareness-raising activities to the general public (i.e. community engagement), as well as having a large pool of interested healthy volunteers, are contributing factors to accelerate site initiation and subject recruitment.

Our findings showed that the subject recruitment, site initiation, and study execution took the longest time in trials conducted in Africa. Conducting clinical trials in Africa often presents significant ethical, organizational, cultural, and infrastructural challenges to researchers, pharmaceutical companies, sponsors, and regulatory bodies.[26] A protracted trial is costly; however, the additional cost associated with performing trials in Africa also could be regarded as the time needed to do capacity development.[17,26] The long study initiation cycle time for the African continent could also serve as benchmark metrics relevant to planning. We encourage further studies to provide evidence as to how these processes could be accelerated.

In-depth interviews with sponsors on what may have contributed to a significant delay in study execution at the local level highlighted possible inefficiencies in the logistics supply. This warrants the need for efficient planning of logistics supply management ahead of the commencement and during the implementation of vaccine trials. Our findings showed that the study execution and subject recruitment went significantly faster for EID trials demonstrating the potential for acceleration. Further studies to identify mechanisms to accelerate trials during outbreaks are encouraged. Creative study designs such as a phase I/II randomized, multicenter study approach to determine efficacy, safety, and immunogenicity as well as early inclusion of target groups such as elderly are examples of innovative steps that can radically change overall development timelines.

Our findings showed that the close-out cycle time was the longest and academic institutions were significantly faster to close their sites than industries. This process entails ensuring that all documentation is complete and safe for long-term archiving including solving pending issues that may involve patient safety data reconciliation. One respondent cited that a pending self-limiting serious adverse event led to the extension

of the trial. Further studies are encouraged to elucidate why or why not academic institutions are faster to move to study closure and also how can this process be accelerated in EID vaccine trials.

One fundamental limitation of this study was a low response rate (155/890, 17%) from the sponsors, which may have affected the outcomes. We repeatedly made contacts to increase the number of participating sponsors, but to no avail due to restrictive data sharing policies practiced among a considerable number of sponsors and other unrevealed reasons. Missing data were due to missing or obsolete sponsors' data, wrong or invalid contact persons reported as responsible for the trial. Also, many companies shared their concerns that they do not track the metrics we were requesting. Others stated that the data would require a significant workload to retrieve and collate. Another possible limitation was recall bias, as this was a retrospective study. Despite this, this study is to our knowledge the largest to date on time use in vaccine trials, with a sufficiently high diversity of sponsors, diseases, and geographies included to draw conclusions that could be applicable for guiding future improvements.

Conclusion

The regulatory approval, subject recruitment, study execution, and close-out cycle times accounted for most of the vaccine trial time use and are key metrics that could be accelerated during a vaccine trial planning and implementation like in the case of COVID-19 vaccine development. Where possible, there is an advantage in agreeing in advance on the design of clinical trials, to run phase I/II trials in parallel, and to collaborate across borders to fast-track scientific assessment, regulatory approval, and roll-out. We encourage tracking of key cycle time metrics and facilitating sharing of knowledge across industry and academia, as well as the use of innovative, robust trial designs, as this may serve to reduce the time from index case to access of a vaccine during an EID epidemic.

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Author contributions

G.N. and S.A.Y. conceived protocol conception and designed the study. H.M., S.A.Y., and G.N. performed data collection and analysis. H.M., S.A.Y., and G.N. wrote the draft manuscript. H.M., S.A.Y., and G.N. edited and approved the final manuscript.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

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