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Review article

Vaccine dose fractionation in Africa: A systematic review

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ABSTRACT

Background: The major challenges of vaccination programs are notably coverage in the target population, vaccine hesitancy and cost-effectiveness. **Aim:** This study aimed to review the literature on administering fractional vaccine doses in Africa. **Methods:** A systematic search of PubMed and Google Scholar was conducted to identify articles published up till March 31, 2024. Keywords used for the search were “fractional dosing”, “Vaccines”, and “Africa”. **Results:** Findings from eleven eligible studies were analyzed. Studies were from the Democratic Republic of the Congo, Gambia, Ghana, Kenya, South Africa, and Uganda. They covered five vaccines including the yellow fever vaccine (n=3; 27.3%), inactivated poliovirus vaccine (n=3; 27.3%), meningococcal A/C/Y/W135 vaccine (n=2; 18.2%), *Haemophilus influenzae* type b vaccine (n=2; 18.2%), and malaria vaccine (n=1; 9.1%). Fractionated doses used most often consist of one-fifth of the standard dose (n=8; 72.7%). Regarding immunogenicity/efficacy, eight of ten studies that addressed immunogenicity suggest that immune responses to the fractional dose vaccines were comparable to that of the standard dose vaccines and resulted in higher antibody titers. Regarding safety, all of the eight studies that addressed the safety of fractional doses in Africa, suggest that safety and tolerability data of fractional dosing were favorable compared to full dose regimen. **Conclusion:** Fractional dosing may be considered to address the availability and acceptability of certain vaccines while maintaining protection. **Contribution:** Although efforts are currently underway to increase the possibility of vaccine manufacturing on the African continent, fractional dosing strategies may also be needed in the future and potentially offer other benefits.

Introduction

Vaccination is acknowledged as the most effective and cost-effective means of preventing and reducing the severity of infections [1,2]. Vaccination may further reduce the magnitude of epidemics and their consequences on hospital capacity by reducing caseloads thereby preserving

the capacity of healthcare institutions to manage all acute and chronic pathologies [3,4]. According to the World Health Organization (WHO), vaccination could prevent 3.5 to 5 million deaths each year worldwide [5]. These numbers could increase by 1.5 million if global immunization coverage improves in all countries [5]. The expected effect of the

implementation of a vaccination campaign is to obtain vaccination coverage allowing for the reduction in the circulation of the identified infectious agent in the population while protecting individuals [6,7]. To achieve these goals, and derive maximum benefit, vaccination coverage must reach certain critical levels for different pathogens if herd immunity is a goal of the vaccination program [8].

According to WHO, reluctance or refusal to vaccinate is complex and does not depend on a simple set of individual factors [9]. Understanding these concerns and developing strategies to facilitate the acceptance of vaccination programs is important. In addition to the problem of vaccine refusal, some countries will face vaccine stock shortages with the global outbreak of epidemics straining the global vaccine supply [10,11]. Today, 99% of Africa's vaccine supply is imported, and African countries consume nearly 25% of the globally produced vaccine [12]. Many countries depend on donations or donor initiatives to provide vaccines. African countries are taking steps to achieve vaccine sovereignty in 2024 by producing 60% of the vaccines they need. Before this ambitious goal can be achieved, alternative solutions including fractional dosing must be used to improve vaccination coverage in Africa.

Fractional dosing is a dose-saving approach under consideration to address vaccine stockouts [13]. For example, in yellow fever, fractional dosing relies on the fact that the minimum amount of virus required to achieve a protective titer of neutralizing antibody is 1000 IU [14]. In contrast, the standard vaccine dose typically contains $\geq 10,000$ IU of the virus. Fractional doses contain one-third, one-fifth, one-tenth, or one-fifth of the standard dose. In practice, when a full-dose vaccine vial is used to deliver fractional doses, the number of doses in the vial is increased threefold, fivefold, or tenfold: e.g., a vial containing 5 or 10 full doses becomes a vial of 25 or 50 fractional doses, respectively. According to the authors, fractional dosing can help reduce dependence on donor programs and create resilient vaccine supply chains, resulting in improved public health systems and reduced morbidity and mortality.

The objective of this review was to analyze the literature on the strategy of administering fractional doses of vaccines in Africa, focusing on efficacy, immunogenicity, and safety.

Materials and Methods

Literature search

We searched PubMed and Google Scholar to identify articles related to fractional doses of vaccines in humans in Africa. Google Scholar was used through publish or perish software (<https://harzing.com/resources/publish-or-perish>). Two authors (AY and BS) independently performed the literature search. Keywords used for the search were “fractional doses” “fractional dosing”, “Vaccines”, “Africa”, and specific names of all African countries. The detailed search strategy can be found in the Supplementary file. A manual search for additional studies was performed using references cited in original study articles and reviews. Additionally, studies were retrieved by searches of the WHO vaccines and immunization Infobase. To avoid the inclusion of duplicate studies, publications were cross-referenced considering the place and period of reported studies.

Study selection

Publications identified were considered up to March 31, 2024. Literature published either in English or French was considered. Studies identified in the initial search were first screened by title and abstract and retained if they met the predefined inclusion criteria, as follows: (i) original article published in a peer-reviewed journal, (ii) studies that described the use of fractional doses of vaccines, and (iii) studies conducted in any of the 54 Africa countries. Expert opinions, review articles, modeling studies, animal models, and protocols were excluded. Publications were reviewed by two independent researchers (A.Y. and S.B.) to determine whether they met inclusion/exclusion criteria and if disagreement was arbitrated by L.MM.

Data extraction

Information extraction was done using Microsoft Excel 2013 on a predesigned database, developed for the purposes of this review.

Data extracted included article information (first author, year of publication, and country), study design (type of study, sample size, age group), vaccines used, type of fractionated doses, and main findings. Additionally, to address the immunogenicity of fractional doses of vaccines, a complementary information including seroconversion percentage and geometric mean concentrations (GMC) were extracted.

Data synthesis and analysis

A literature synthesis was performed based on the information gathered from the analyzed publications. Qualitative data were presented as effective and frequencies. Statistical analyses and visualization were performed using R-software version 4.0.4. Summary figures describing the main findings were made using the Biorender application (<https://app.biorender.com>).

Results

Literature search

A total of 740 non duplicates potentially relevant articles on fractional dose vaccine strategy in Africa were identified in the initial electronic search. The titles and/or abstracts of 740 studies were screened for relevance. Of the 740 studies screened, 709 studies were excluded and the remaining 31 studies were retrieved for full text review. Ultimately, 11 studies were included in this review (**Figure 1**).

Data and study characteristics

Of the 11 studies included, two (18.2 %) were from the Democratic Republic of the Congo [15,16], two (18.2 %) were from Gambia [17,18], two (18.2 %) were from South Africa [19,20], three (20.0 %) from Uganda [21–23], including one (9.1 %) performed in two countries, Uganda and Kenya [23] (Supplementary Figure 1a).

Vaccines fractionated in Africa were mostly yellow fever vaccine [15,16,23], (n=3; 27.3%) and inactivated poliovirus vaccine [17,18,24], (n=3; 27.3%), followed by meningococcal A/C/Y/W135 vaccine [21,22], (n=2; 18.2%) (**Table 1**).

Fractionated doses used in Africa consist most often of one-fifth (1/5) of standard dose (n=8; 72.7%) [15–18,21–23,25]. Other dilutions used as fractional doses included 1/10 [20–22] and half (1/2) [24] of the full dose (**Table 2**). The result of distribution by time indicates that the literature on fractional dosing strategy in Africa was first published in 2002 in South Africa [20] (Supplementary Figure 1b). Studies consisted of randomized and controlled trials [16–25] (n=10; 90.9%) and community-based pharmacovigilance [15] (n=1; 9.1%). Of the randomized trial, half (5/10) were non-inferiority trials (**Table 2**).

Advantages of fractional doses strategy

Evidence synthesis on the advantages of fractional dosing strategy highlighted that in addition to the reduction of vaccine antigen overload, reduction of vaccine cost, reduction of stock-outs, and long-term durable protection, fractional doses retain their immunogenicity and have good safety and efficacy profiles (**Figure 2**).

Immunogenicity and efficiency of fractional dosing strategy

Ten of eleven studies [16–25] addressed the immunogenicity of fractional doses strategy in Africa. Of the ten, two studies [17,24] did not establish non-inferiority of the fractional dose strategy compared with a full dose (**Table 2**). In one study [25], authors reported that 1/5 of the full dose was as effective as the standard dose of the malaria vaccine (**Table 2**). Evidence from eight studies [16,18–23] suggests that the fractional dosing strategy could yield high immune responses, comparable to those for standard doses of the same vaccine (**Table 2**). For example, in the case of fractional doses of yellow fever vaccines, the authors found a seroconversion rate of 98% (95%CI: 96 to 99)[16] to 100% (95%CI: 96.8 to 100.0) [23] on days 28 and 30, with a geometric mean concentration (GMC) of 1340 lg/ml (95%CI: 1117 to 1607) [16] to 5874 lg/ml (95%CI: 4162 to 8289) [23] in patients who were seronegative for neutralizing antibodies against yellow fever at baseline. In one year, the seroconversion rate in these patients was 96 % (95%CI: 94 to 98) with a GMC of 143 lg/ml (95%CI: 123 to 166) [16]. In another study on yellow fever vaccine, the absolute difference in seroconversion between fractional and standard doses of the vaccine was 1.82% (–2.75 to 5.39) to –0.90% (–4.24 to 3.13). Fractional doses from all yellow fever vaccines met the noninferiority criterion of a less than 10% decrease in seroconversion in fractionated doses compared with standard dose groups, 28 days after vaccination.

Safety of fractional dosing strategy

Eight of eleven (72.7%) studies [15,17–21,23,25] addressed the safety of fractional doses strategy in Africa. All of them suggest that the safety and tolerability data of fractional dosing were favorable compared to the full dose regimen. In fractional doses yellow fever vaccine, the most common adverse events up to day 28 after vaccination were headache, fatigue, myalgia, and self-reported fever. Headache was observed in 17.5% to 25.0% and

18.3% to 25.0% of split-dose and standard-dose yellow fever vaccine recipients, respectively [23]. In another study on a malaria vaccine, related serious adverse events within 30 days were reported in 3 (1%), and 0 cases in “standard schedule; full doses only”, and “fractional third dose [month 2] and early fractional fourth dose [month 14]”, respectively

[25]. Moreover, no clinically significant changes in the two groups were observed in hematology or biochemistry parameters [25].

Table 1. Vaccines fractionated in Africa

vaccines	Number	Percentage
<i>Haemophilus influenzae</i> type b vaccine	2	18.2
Inactivated Poliovirus vaccine	3	27.3
Malaria vaccine	1	09.1
Meningococcal A/C/Y/W135 vaccine	2	18.2
Yellow fever vaccine	3	27.3
Total	11	100.0

Table 2. Mains findings related to fractional doses vaccination in Africa.

Reference	Country	Vaccines	Type of study	Participants number	Intervention	Immunogenicity			Long term protection	Safety
						Seroconversion, % (CI 95%)	Geometric mean concentrations (GMC) in lg/ml (CI 95%)	Findings		
Casey et al. 2019 [16]	Democratic Republic of the Congo	Yellow fever	randomized controlled trial	764	1/5 of standard dose	In one month: 98 % [96–99]; In one year: 96 % [94–98]	In one month: 1340 (1117–1607); In one year: 143 (123–166)	The immunologic response to a fractional dose of the 17DD yellow fever vaccine was appropriate for a response to a yellow fever outbreak among children 2 years of age or older and among nonpregnant adults	Not reported	Not reported
Barnes et al. 2011 [22]	Uganda	<u>Menomunefrom Sanofi Pasteur, a tetravalent A/C/Y/W135 polysaccharide vaccine</u>	randomized controlled trial	115	1/5 and 1/10 of full dose	Not reported	1 month after the first dose: 1/10 of full dose 43.3 (36.5–51.4) 1/5 of full dose 44.6 (38.4–51.8)	Fractional doses can elicit antibodies of as good avidity against serogroup A polysaccharide as a full dose	Not reported	Not reported
Bashorun et al. 2022 [18]	Gambia	Inactivated poliovirus vaccine	pragmatic, open-label, non-inferiority trial	3170	1/5 of full dose	Poliovirus 1: 88.3% (80.6–93.1) Poliovirus 2: 100.0% (93.1–100.0) Poliovirus 3: 81.9% (76.5–86.1)	Poliovirus 1: ≥1448 (1448–1448) Poliovirus 2: ≥1448 (1448–1448) Poliovirus 3: ≥1448 (1448–1448)	Non-inferiority was demonstrated between the full dose and fractional doses when administered with a BCG needle and syringe, a disposable syringe jet injector, and an intradermal adaptor	Not reported	Safety and tolerability data were favorable
Clarke et al. 2016 [17]	Gambia	Inactivated poliovirus vaccine	randomized, non-inferiority trial	182	1/5 of full dose (0.1 ml)	Polyovirus 1: 86.4% (66.7–95.3) Polyovirus 2: 100.0% (67.6–100.0) Polyovirus 3: 90.4% (79.4–95.8) Measle:	Not reported	fractional doses did not achieve non-inferiority compared with the full dose	Not reported	Safety and tolerability data were favorable
Guerin et al. 2008 [21]	Uganda	A/C/Y/W135 polysaccharide meningococcal vaccine	Randomized Non-Inferiority Controlled Trial	750	1/10, 1/5 of full dose	PerProtocol (PP) population 1/5 of full dose Serogroup A : 77.5 (72.0–83.0) Serogroup W135 : 94.6 (91.6–97.6) Serogroup C : 80.4 (75.2–85.6) Serogroup Y : 82.4 (77.4–87.4) 1/10 of full dose Serogroup A : 69.4 (63.5–75.3) Serogroup	PerProtocol (PP) population 1/5 of full dose Serogroup A : 2054.4 (1612.2–2618.0) Serogroup W135 : 2041.6 (1582.2–2634.5) Serogroup C : 467.3 (328.0–665.8) Serogroup Y : 768.3 (524.4–1125.6) 1/10 of full dose Serogroup A : 1369.3 (1083.3–1730.7) Serogroup W135 : 2426.3	Non-inferiority was demonstrated between the full dose and fractional doses against serogroups W135, Y and A. Fractional doses did not achieve non-inferiority compared with full dose for serogroup C.	Not reported	Safety and tolerability data were favorable

						up W135 : 95.6 (93.0–98.2) Serogroup C : 76.6 (71.1–82.1) Serogroup Y : 83.9 (79.2–88.6)	(1979.7–2973.7) Serogroup C : 396.3 (274.6–572.0) Serogroup Y : 816.8 565.1–1180.8			
de Deus et al. 2020 [24]	Mozambique	monovalent type 2 oral poliovirus vaccine (mOPV2)	randomized, controlled, open-label, noninferiority trial	378	½ of the full dose	53.6% (44.9%–62.1%)	Not reported	Fractional doses did not achieve non-inferiority compared with full dose	Not reported	Not reported
Huebner et al. 2004 [19]	South Africa	Haemophilus influenzae type b vaccine conjugated either to diphtheria CRM197 (Chiron, Sienna, Italy) or tetanus toxoid (Berna Biotech Ltd., Berne, Switzerland)	randomized trial	168	1/16; 1/8; 1/4; 1/2 of full dose	1/8 of full dose 100 % (95–100)	1/8 of full dose 6.33 (4.21–9.50)	vaccines of ≥1.25 µg (1/8 of full dose) may be sufficient to stimulate an immune response that offers both short and longer-term protection from invasive Hib disease	Offer longer-term protection from invasive Hib disease	Safety and tolerability data were favorable
Nicol et al. 2002 [20]	South Africa	Haemophilus influenzae type b polysaccharide-tetanus toxoid conjugate (PRP-T) vaccine	randomized trial	168	1/10 of full dose	94%	Not reported	The 1/10 dose of PRP-T was as immunogenic as the full dose.	Not reported	Safety and tolerability data were favorable
Juan-Giner et al. 2021 [23]	Kenya and Uganda	Yellow fever: 17DD Bio-Manguinhos-Fiocruz, 17D-213 Chumakov Institute of Poliomyelitis and Viral Encephalitis, 17D-204 Institut Pasteur Dakar, 17D-204 Sanofi Pasteur	randomized, double-blind, non-inferiority trial	960	1/5 of full dose	Day 28 17DD Bio-Manguinhos-Fiocruz: 100·0 % (96·7 to 100·0); 17D-213 Chumakov Institute of Poliomyelitis and Viral Encephalitis: 99·1 % (95·1 to 100·0); 17D-204 Institut Pasteur Dakar: 100·0 % (96·8 to 100·0); 17D-204 Sanofi Pasteur: 100·0 % (96·8 to 100·0)	Day 28 17DD Bio-Manguinhos-Fiocruz: 3939 (2812, 5516); 17D-213 Chumakov Institute of Poliomyelitis and Viral Encephalitis: 5874 (4162 to 8289); 17D-204 Institut Pasteur Dakar: 4279 (3182 to 5753); 17D-204 Sanofi Pasteur: 5545 (4106, 7488)	non-inferior to the standard dose in inducing seroconversion 28 days after vaccination	Not reported	Safety and tolerability data were favorable
Samuels et al. 2022 [25]	Ghana	Malaria vaccine	randomized controlled trial	2157	1/5 of full dose	Not reported	Not reported	1/5 of full dose regimen does not affect protective efficacy over	Not reported	Safety and tolerability data were favorable
Nzolo et al. 2018 [15]	Democratic Republic of the Congo	17DD Yellow Fever Vaccine	Community-based pharmacovigilance	4020	1/5 of full dose	Not reported	Not reported	Not reported	Not reported	Safety and tolerability data were favorable

Figure 1. Flow diagram of the selection process of the included studies.

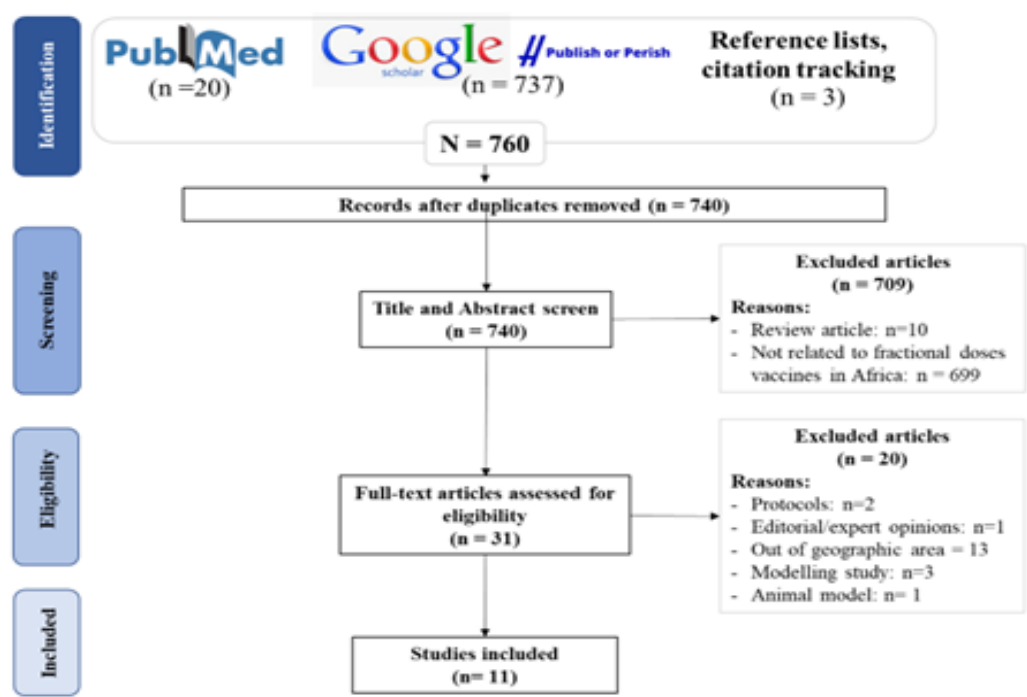


Figure 2. Advantages of vaccination using fractional dosing strategy.

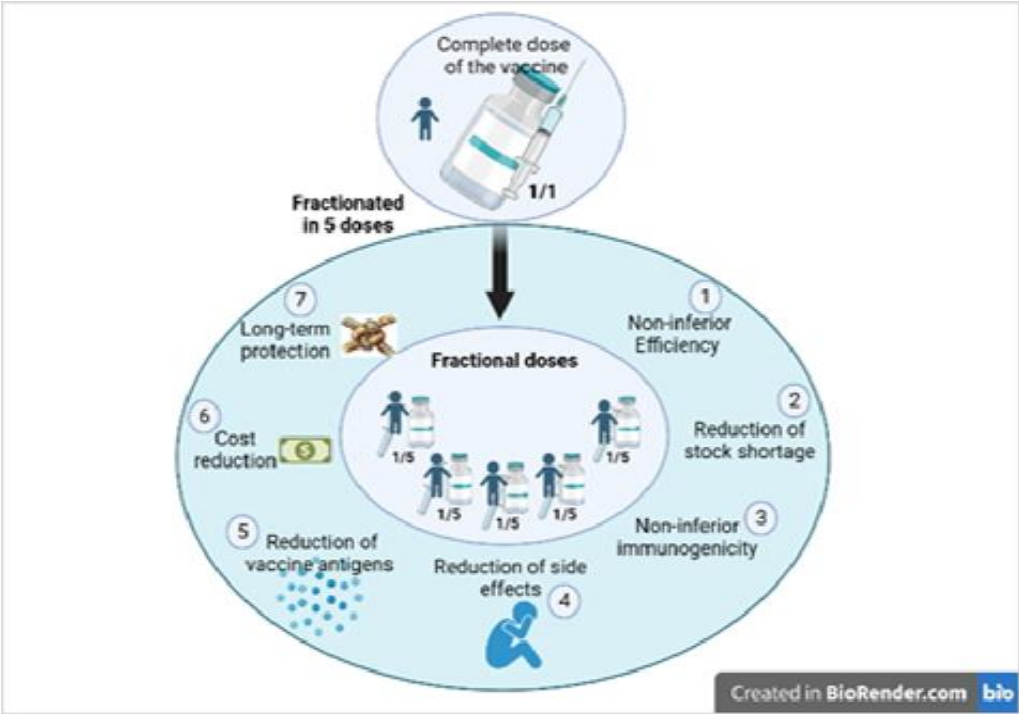
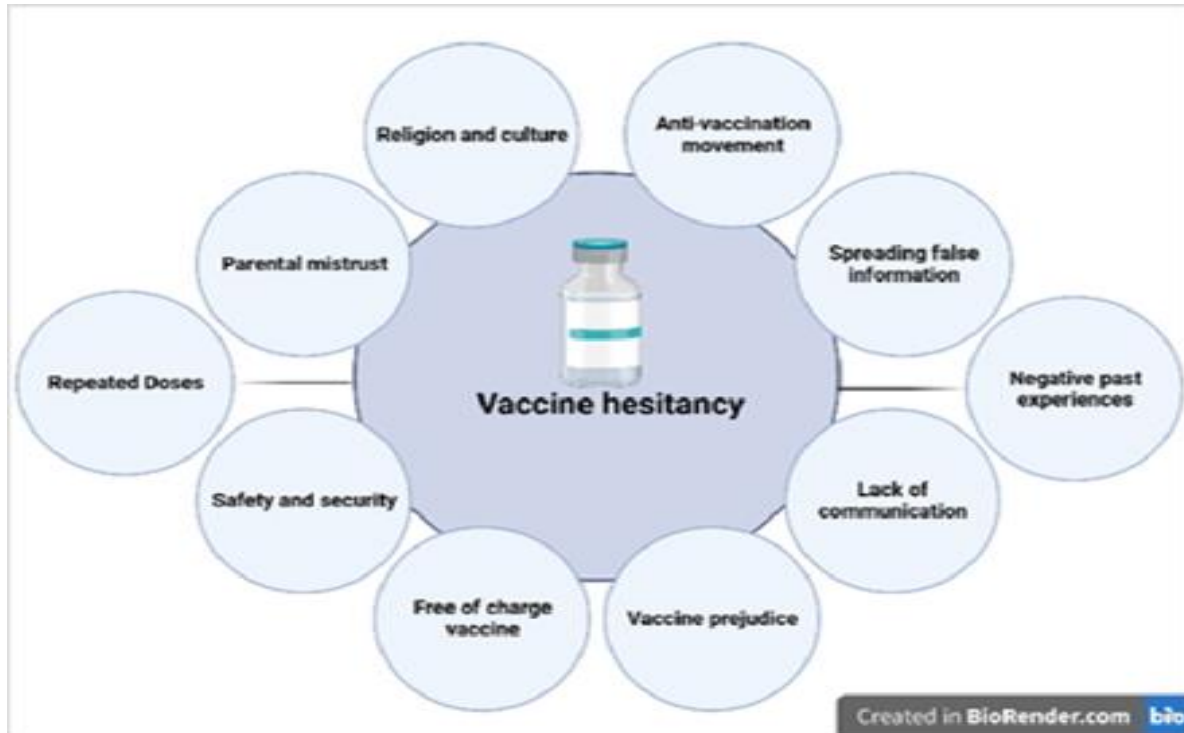


Figure 3. Main factors behind vaccine hesitancy.

Discussion

The use of a fractional dosing strategy is a well-known strategy [13,26,27]. Our study demonstrated that a fractional dosing strategy may be as sufficient to stimulate an immune as a standard dose of vaccine. This means that, for yellow fever, inactivated poliovirus, A/C/Y/W135 polysaccharide meningococcal, and *Haemophilus influenzae type b* vaccines, immunogenicity data suggest that 1/5 or 1/10 doses could be almost as efficacious as the standard dose used of the same vaccines. Authors reported that the 1/5 of standard dose of the 17DD Yellow fever vaccines was effective at inducing seroconversion in 98% of the participants who were seronegative at baseline, which is similar between genders [16]. In a recent study, seroconversion rates at four to five weeks following vaccination were similar between participants who received standard doses and participants who received fractional doses containing one-third, one-fifth, one-tenth, and one-fifth of the standard dose [13]. Concerning long-term protection, in a study published in 2018, the authors demonstrated that 40 healthy adults who had received a fractionated dose of 0.1 ml intradermally 10 years previously had similar levels of virus-neutralizing antibodies to 35 people who had received the standard 0.5 ml intradermal dose during the same period [28]. Among the immunological

mechanisms proposed to explain this phenomenon, one can cite the fact that dose fractionation favors the persistence of antigen-specific B lymphocytes [29]. The increase in somatic hypermutation and antibody avidity [30,31] has high responses to immunoglobulin G class 4 [32] and higher neutralizing antibody titers [33]. Additionally, fractional doses may also have less side effects [34], vaccine antigen overload, cost, and stock-outs [35,36,16] than standard dose. Vaccine shortages and stockouts during outbreaks happen frequently in underdeveloped countries, and occasionally in developed countries [37–40]. In a country, the shortage/stockout events can occur at the national and at subnational level. The most frequently reported causes vaccine shortages/stockouts in Africa include global shortage, disease outbreaks, poor stock management, poor supply chain structure, delays in deliveries, lack of trained health personnel, and lack of resources to purchase vaccines [41,42]. Typically, to address vaccine shortages/stockouts, actions undertaken by African countries were to purchase additional doses of the vaccine from other suppliers/manufacturers, use available stockpiles of vaccine, redistribute stock doses among regions and facilities, to import vaccine from other countries, or to contact WHO (or other institutions) for technical assistance. On top of that, using lower doses of vaccine is one such action [16]. Currently, the fractional-dose strategy is

emerging as an alternative option for urgently stretching restricted vaccine supplies [10,11,35]. WHO supports the use of a fractional doses strategy for yellow fever as part of an emergency response to an epidemic if the shortage of full doses exceeds the capacity of the global stockpile [36]. Many countries in developed and underdeveloped countries have experimented with the use of fractional doses to address vaccine shortages [10,11,35].

Studies showed that one of the most serious concerns influencing vaccination acceptance are about side effects [43,44]. Individuals or parents were concerned about the potential side effects of vaccines [45]. According to **Saied et al.** [43] in Egypt, 96.8% of the participants of their study had concerns regarding the vaccine's adverse effects [43]. In a community-based-pharmacovigilance, fractional dosing of 17DD Yellow fever vaccine has a good tolerability and safety profile, which is almost similar between females and males [15]. Fractional doses of the same vaccine may be superior if they offer comparable efficacy with fewer side effects. If efficacy is comparable to that of standard doses, and side effects are lesser, fractional doses might be superior to current doses in terms of individual benefit-risk profile.

Fractional doses strategy to address vaccination coverage in Africa

Childhood vaccination is one of the fundamental strategies for achieving goal three of the Sustainable Development Goals (SDGs), which is to reduce under-five mortality to less than 25/1000 live births by 2030 [46]. In Africa, vaccination coverage is lagging behind the 90% target set in the regional strategic plan for vaccination 2014-2020 [47]. As an example, vaccination coverage remained low in 2017 for DTP3 (72%), PCV3 (68%), Hib3 (72%), MCV1 (70%), and RCV1 (26%) [48]. Many barriers exist to achieving good vaccination coverage in Africa, including factors associated with vaccine hesitancy.

Fractional doses strategy to address vaccine hesitancy

There are several possible reasons for vaccine refusal (**Figure 3**). The main factors are religion, parental distrust, dissemination of misinformation, and anti-vaccine movements. According to WHO, vaccine hesitancy or refusal is the 8th most prevalent health threat after pollution and climate, non-communicable diseases, pandemic influenza, vulnerable countries, antimicrobial resistance, Ebola and high-risk pathogens, and

primary health care [49]. Vaccination denial dates back to the first vaccine administered in humans, the smallpox vaccine [50].

Parents' decisions about whether or not to vaccinate their children are complex and multidimensional. However, the main parent-specific factor most often involved in their experience with vaccination (side effects) [51–53]. In addition to keeping parents away from the vaccine, the presence of side effects could amplify the spread of misinformation about the vaccine anti-vaccine movements. Fractional dose strategies may resolve this issue by reducing the side effects of the vaccines compared to full doses [13,23,54–57].

The rise of well-organized anti-vaccine movements is currently a serious threat to vaccination programs in both developed and developing countries. The main concerns put forward by the anti-vaccine community were antigenic overload [58], and autoimmunity [59,60]. By reducing vaccine antigen overload compared to full dose regimen, fractionated doses strategy may address this issue.

Cost-effectiveness analyses are critical to planning vaccination campaign financing decisions. It is a measure of the amount of money needed to fund a vaccination project and achieve the previously defined goal. Fractional doses vaccines could be an economically viable vaccination strategy compared to full-dose vaccination or no vaccination [61]. Additionally, the fractional doses vaccine strategy could save a large number of lives, and mitigate the public health costs of resurgences after vaccination [62].

However, fractional dosing may further exacerbate vaccine reluctance, leading to confusion and conspiracy theories such as the rapid roll-out of COVID-19 vaccines has already generated [63]. For this reason, fractional dosing should be considered in the context of community acceptance.

Strengths and Limitations

To the best of our knowledge, this study is the first to review the vaccination strategy with fractional doses strategy in Africa, a topic with a potentially significant public health impact. However, it is limited by the relatively few publications on fractional dosing strategy in Africa that may impact generalizability. Another flaw in the current systematic review that may impact generalizability is that the majority of the studies are from Southern Africa. There is, therefore a need for

a continuous update, especially on the impact of fractional dosing strategy on vaccine hesitancy, as new evidence emerges. Another shortcoming is that meta-analysis is not performed, which might impact the power to study the factors associated to the fractional dose strategy. Even then, this study synthesized the current state and should help inform policy decision-making and research needs for fractional dosing strategy in Africa.

Conclusion

In Africa, despite the progress made in recent years in the various immunization programs, vaccination coverage is far from reaching the 90% target. Various complex factors are at the origin of vaccine hesitancy. The use of a fractional doses vaccine strategy could be a solution to improve the availability and acceptability of vaccines while saving costs, reducing side effects, and maintaining efficacy, immunogenicity, and long-term protection. This strategy could have a potential significant public health impact, especially in low- and middle-income countries.

Author contributions

Conceptualization, A.Y. and S.B.; methodology, A.Y., S.B., L.MM.; software, A.Y. and A.I.; validation, S.B., M.D., R.G.; formal analysis, A.Y. and A.I.; investigation, A.Y., S.B., L.MM.; resources, S.M., E.A., R.G.; data curation, A.Y. and S.B.; writing—original draft preparation, A.Y., S.B., M.D.; writing—review and editing, A-K.A, A.I., L.MM., D.A., M.D., O.G., I.S., ME.G, S.M.; visualization, A.Y.; supervision, E.A. and R.G.; project administration, R.G. All authors have read and agreed to the published version of the manuscript.

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Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

Data availability statement

The datasets generated and analyzed during this current study are available from the corresponding author upon reasonable request.

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Conflicts of interest

The authors declare no conflict of interest.

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