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Review

Pneumococcal conjugate vaccine use during humanitarian crises

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ABSTRACT

Streptococcus pneumoniae is a common human commensal that causes a sizeable part of the overall childhood mortality in low income settings. Populations affected by humanitarian crises are at especially high risk, because a multitude of risk factors that are enhanced during crises increase pneumococcal transmission and disease severity. Pneumococcal conjugate vaccines (PCVs) provide effective protection and have been introduced into the majority of routine childhood immunisation programmes globally, though several barriers have hitherto limited their uptake during humanitarian crises. When PCV coverage cannot be sustained during crises or when PCV has not been part of routine programmes, mass vaccination campaigns offer a quick acting and programmatically feasible bridging solution until services can be restored. However, we currently face a paucity of evidence on which to base the structure of such campaigns. We believe that, now that PCV can be procured at a substantially reduced price through the Humanitarian Mechanism, this lack of information is a remaining hurdle to PCV use in humanitarian crises. Considering the difficulties in conducting research in crises, we propose an evidence generation pathway consisting of primary data collection in combination with mathematical modelling followed by quasi-experimental evaluation of a PCV intervention, which can inform on optimal vaccination strategies that consider age targeting, dosing regimens and impact duration.

Contents

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1. Introduction

Approximately 68.5 million people, nearly 1% of the world's population, were forcibly displaced due to insecurity and war in 2017. In those who are refugees, more than half are under the age of 18, and 17% under the age of five [1,88]. In the same year, hundreds of millions were affected by armed conflicts [2,3], and almost 100 million were impacted by natural disasters [4]. Whether in the acute emergency or the protracted phase, crises substantially affect people's lives, and can dramatically increase premature mortality [5–7]. In most crises, excess deaths are often attributable to the indirect effects of crisis-emergent factors such as the breakdown of public health services, food insecurity, inadequate water and sanitation, and overcrowding; factors that increase both the incidence and severity of disease [8,9].

Infectious diseases are of particular concern, and require specific control measures that include, but are not limited to, vaccines. To date, only a small subset of licensed vaccines that are routinely used in most stable settings is commonly used in humanitarian crises. These usually include measles, polio, and (recently) cholera, with context-specific threats such as meningococcal disease or yellow fever infrequently addressed [10]. However, the prioritisation of pathogens targeted by these vaccines may not comprehensively address the local anticipated preventable disease burden. More recent additions to the vaccine portfolio, such as vaccines protecting against HPV (particularly in settings with high rates of sexual violence), rotavirus, and *Streptococcus pneumoniae*, have rarely been used in humanitarian settings. Using the example of *Streptococcus pneumoniae*, we here propose a framework to overcome some of the barriers for vaccine use in humanitarian settings, and to help prevent the likely substantial disease burden associated with respective pathogens in crises settings.

2. Streptococcus pneumoniae in crises

Streptococcus pneumoniae (the pneumococcus) is a human commensal that commonly resides in the nasopharynx, and occasionally causes disease (e.g. pneumonia, meningitis, and sepsis), especially in young children and people with weakened immune systems [11]. The pneumococcal disease burden in crises is largely unknown, but likely substantial. Outbreaks are thought to occur, but often go unnoticed due to non-existent or under resourced surveillance systems and the low specificity of symptoms [12]. Pneumococcal meningitis outbreaks have occasionally been reported in humanitarian settings [13,14], and pneumococcal pneumonia is a major concern. During crises, acute respiratory tract infections (ARI) and diarrhoeal disease make up the top two causes of morbidity in all age groups, with ARIs alone accounting for 20–35% of mortality in children younger than five years of age [15]. The exact aetiology of these ARIs remains unknown, but more than half of all ARI-related deaths worldwide were caused by pneumococci in the pre-pneumococcal conjugate vaccination era [16]. Risk factors that are commonly exacerbated in crises, such as malnutrition, indoor air pollution, and overcrowding, can increase pneumococcal carriage, transmission, disease, and mortality (Table 1). This likely amplifies this burden in crises. Many of these risk factors were also present in pneumococcal outbreaks that have been identified in stable settings [17]. In addition, the displacement and crowding of people from a range of different communities may expose them to a range of circulating serotypes that they have not seen before, increasing the risk of disease and probably extending the risk even more into older age groups.

3. Pneumococcal conjugate vaccines

Pneumococcal conjugate vaccines (PCVs) effectively protect against pneumococcal disease [11]. There are currently two PCV products available, protecting against 10 (PCV10) or 13 (PCV13) of more than 90 known pneumococcal serotypes, and PCVs with increased valency (PCV15 and PCV20) are currently in development [36,37]. In contrast to (unconjugated) pneumococcal polysaccharide vaccines [38], PCVs are recommended for use in children and, in addition to the direct protection against pneumococcal disease, also elicit indirect protection through interrupted transmission of vaccine-targeted serotypes (VT) [11]. Although their impact is dampened by replacement colonisation of the nasopharynx by non-vaccine serotypes, these serotypes are generally less likely to cause severe disease, resulting in a net benefit [39]. PCVs have now been introduced in the routine childhood immunisation programmes of the majority of countries [40]. In most places where PCVs are used at high coverage, the marked reduction in VT transmission has expanded the benefit beyond vaccinees alone [41–44].

4. Vaccination in crises

Vaccination strategies can be categorized into routine immunisation, which aims to reduce the disease burden by sustainable and

Table 1
Crisis-emergent risk factors that can plausibly affect the pneumococcal burden.

Risk factor	Increased transmission (carriage)	Increased probability that carriage leads to disease	Increased case-fatality ratio	Selected references
Acute malnutrition	++*	+++*	+++*	[18,19]
Measles outbreaks and other viral respiratory tract infections	++	++	++	[20–22]
Overcrowding and altered social contact patterns	+++*	–	–	[18,19,24,24]
Disrupted routine pneumococcal conjugate vaccine use	+[i]	+++	–	[25–27]
Low access to curative care	+[ii]	+	+++	[28–31]
Smoke inhalation	–	+	–	[32,33]
Inadequate water and sanitation	++	+	–	[34,35]

– no effect on outcome; + small effect on outcome; ++ medium effect on outcome; +++ large effect on outcome.
* Potential shift in the age-specific risk (younger average acquisition and increased carriage and disease among all age groups).
[i] Increase in carriage of vaccine-targeted serotypes, but not in overall carriage.
[ii] Increased transmission due to reduced bystander effect as a result of limited antibiotic usage in the community.

equitable vaccination of new birth cohorts [45], or mass vaccination campaigns, which aim for a quick but short lived (additional) reduction in disease burden. However, this distinction has become blurred with recent use of 'periodic intensification of routine immunisation' (PIRI) activities [46].

Routine immunisation is highly effective and cost-effective [47], but as a strategy faces a number of challenges during crises, including access to regular timely services, disruption of the cold chain, lack of personnel to deliver vaccines, safety of health care workers, and access of health workers to the affected population [48,49]. Consequently, in the acute phase of a crisis routine immunisation often breaks down and cannot ensure population immunity. Vaccination coverage may drop to levels too low to interrupt transmission in susceptible parts of the population. This is most pronounced in mass displacement scenarios; where overcrowding alone increases the transmission intensity of infections and, in combination with an accumulation of susceptible individuals, increases vaccination requirements to achieve herd immunity.

Accordingly, humanitarian actors including non-governmental organizations (NGOs) emphasise the role of mass vaccination campaigns. These campaigns are regularly used for outbreak control [50], but should in this instance not only aim to quickly control disease but also sustain impact for sufficient time until subsequent campaigns can be performed or routine immunisation can be resumed. The high number of vaccine doses given to extended age groups in a shorter time-frame usually make mass vaccination campaigns more feasible to execute and faster in reducing the disease burden.

Insufficient evidence on the causes underlying the disease burden during crises and limited guidance on vaccine priorities for humanitarian decision-makers may partly explain the hitherto narrow uptake of vaccine interventions. In an attempt to improve this situation the World Health Organization (WHO) introduced a Framework for Decision-Making on Vaccination in Humanitarian Emergencies in 2012, which was updated in 2017 [51]. This three-step framework aims to implement the most appropriate vaccination interventions in each crisis given the local epidemiology, vaccine characteristics, and other context-specific considerations. The framework emphasises expanding the range of vaccines offered to crisis-affected populations, but also recommends adapted vaccination strategies, including expanded age ranges and reduced-dose regimens.

5. PCV use in crises

Although the WHO Framework lists PCVs as one of the vaccines to be considered for use in crises [51], and despite a likely high preventable pneumococcal disease burden, they have rarely been used during crises [53–57]. The rationale for integrated PCV vaccination strategies in crises is clear: mass vaccination campaigns delivered as part of the initial package of interventions in the acute emergency phase of new crises could rapidly establish direct and indirect protection when vulnerability due to malnutrition, congestion of unplanned settlements, and lack of curative health services is likely to peak. These campaigns should ideally be multi-antigen interventions (e.g. bundling measles and cholera) or multi-interventional (e.g. bed nets or micronutrient supplementation).

A PCV-specific barrier to vaccination in crises has long been its price. If not supported by Gavi, lower and middle income countries (LMIC) spend about 20, 50, and 3 times as much for one complete regimen of PCV (50US$) compared to measles containing vaccine, oral polio vaccine, or rotavirus vaccine, which is indicative for prices paid by humanitarian actors until 2017 [57]. While PCVs have been prohibitively expensive, a "Humanitarian Mechanism" sponsored in 2017 by the WHO, Unicef, Médecins Sans Frontières and Save the Children now guarantees more affordable PCV procurement by humanitarian actors and affordable expedited delivery [58]. Although some 600,000 doses of PCV have been delivered through this mechanism to date [55], this only covers a small proportion of crises affected populations at risk. In addition, only multi-dose PCV vials are available through the humanitarian mechanism. Whereas this eases transportation and storage of the vaccine, it also increases wastage and may therefore decrease their cost-effectiveness, especially when used routinely in small populations.

A key barrier that has not yet been addressed is the insufficient evidence on optimal PCV deployment strategies via mass vaccination campaigns and their expected impact in crises [59,60]. In places where they have been used, they have been administered through different strategies targeted at different age groups [61–64]. The impact of those alternative approaches has not been assessed.

The WHO recently updated their recommendations on the use of PCVs in children [65]. These now include a recommendation to use PCV in children under one year of age and consider for children under five years of age during humanitarian crises and other emergencies. This is in line with the aforementioned WHO Framework [51]. However, in the absence of any evidence [66], no further guidance is given to the optimal age range to target in a campaign, the number of doses needed, and the frequency of campaigns.

There is no clear rationale to limit mass vaccination campaigns to those under one, two, or even five years of age. These are the age groups that usually bear the heaviest burden of pneumococcal pneumonia, but in crisis settings where high pneumococcal carriage prevalence likely extends to adulthood, targeting a larger proportion of the transmitting population is probably needed to control VT circulation. This would maximize herd protection, which is crucial in optimising vaccine use, as it protects unvaccinated children and adults. Such control is particularly needed if the effects of a campaign need to sustain protection for months or years until a subsequent campaign is feasible or routine immunisation can be restored. It is also key in settings where high prevalence of acute malnutrition may shift the age spectrum for pneumococcal disease towards older children [67]. Using an extended age range to 14 years of age for example, could be operationally convenient as it may allow co-administration with measles vaccine.

Multi-dose schedules are recommended in routine programmes [65] but may be unfeasible in crisis settings. If, for operational reasons, only a single dose of PCV can be administered, extended age ranges may partially compensate for a lack of optimal direct protection. Single dose strategies only provide moderate direct protection to infants if not followed by a booster dose [68], but this reduced direct protection may be offset by enhanced indirect protection from older age groups, provided that vaccine coverage levels are sufficiently high. Single-dose strategies are being intensively tested in stable settings [68–70], but their exact indirect effects remain unknown.

6. Evaluating optimal vaccination strategies

Vaccination strategies must consider both direct and indirect protection. The former will require estimation of age specific pneumonia burden, which is likely to vary considerably between crisis settings depending on malnutrition rates and other factors. The best evidence of vaccine impact comes from cluster-randomised controlled trials (cRCT). However, these are resource-intensive and exceptionally challenging to conduct during crises, with additional ethical concerns related to randomisation of vulnerable

populations to potentially less protected trial arms [71]. Moreover, only a small subset of many possible combinations of potentially viable dosing strategies and age ranges can be investigated.

We propose instead a sequential evidence generation pathway, consisting of primary data collection in combination with mathematical modelling followed by quasi-experimental evaluation of PCV intervention. Mathematical models are increasingly used to synthesize a multitude of evidence for vaccine decision making, particularly if indirect vaccine effects form a key part of the desired impact [72–74]. If adequately parameterised, these models are useful to simulate the pneumococcal epidemiology of a specific setting and predict PCV impact under various vaccination strategies, as has been done in stable settings such as Kenya [25,52] and Vietnam [75]. However, the use of modelling to inform and evaluate vaccine decision making in crises is limited. It has predominantly been used to assess reactive strategies for outbreaks [76–78], e.g. the potential of ring-vaccination strategies for Ebola control [79], but has for instance also been used for pre-emptive strategies for Hepatitis E in displaced populations [80].

PCV vaccination strategies have, to our knowledge, only been explored in stable settings. A limitation to the use of modelling to inform PCV use in crises-affected populations is the lack of context-specific data for model parameterisation. The key drivers of pneumococcal transmission are social contact behaviour (a proxy for disease transmission routes) and the pre-PCV prevalence of nasopharyngeal carriage that helps identifying pockets of the population driving pneumococcal transmission. Consequently studies have measured both in a multitude of settings [81,82], but few have been done in LMICs and evidence from crisis-affected populations is entirely absent. The main drivers of transmission are often children, due to the nature and frequency of their contacts in combination with high prevalence of pneumococcal carriage [83,84]. However, in displaced populations, both social contact patterns and pneumococcal carriage may be considerably altered from their pre-crisis baseline (see Table 1). As this may significantly affect the appropriate strategy, primary data is needed to construct meaningful models for hypothesis generation.

Specifically, we argue that a seemingly natural assessment of age targeting through PCV use in the age groups with highest incidence of pneumococcal disease is unlikely to make best use of PCV. Whereas this strategy would indeed provide direct protection to those at highest risk, it may lead to either under or over use of PCV. Without an assessment of transmission dynamics, such strategy could end up providing PCV to an age group that is too narrow so that no herd immunity is achieved. This would leave the rest of the population vulnerable, and upcoming generations who are at exceptionally high risk unprotected. Alternatively, the age group may be too broad, and many who would have been protected through herd effects will receive PCV without much added benefit.

Mathematical modelling can be used to study transmission dynamics, needed to predict vaccine impact. Specifically, it can formally integrate available evidence and their associated uncertainty into a prediction framework that can explore and propose vaccination strategies to potentially optimize impact, namely: (i) PCV target age groups for mass vaccination in crises; (ii) minimum vaccination coverage needed; (iii) single vs. multi-dose vaccination options; and (iv) the frequency with which campaigns should be implemented to sustain PCV effects until routine immunisation can be re-established. It can also be used to extrapolate to different crises settings such as overcrowded acute displacement camps or slow-onset food security crises in rural areas.

Although modelling can narrow down the range of potential strategies, pilot implementation of these strategies should be accompanied by impact measures. At a minimum this should include cross-sectional nasopharyngeal carriage studies in the target population before and after PCV use, though ideally extend to measures of impact on morbidity or even mortality. Quasi-experimental designs can be used to evaluate their impact with relatively low resources [85], as has been done in multiple post-licensure PCV studies where no or only a limited number of control sites is available [43,44,86,87]. In addition, such results can feed back into mathematical models [52], leading to more robust predictions of vaccine strategies and impact.

7. Conclusions

Vaccines that are most commonly used in humanitarian crises settings have not necessarily been prioritised based on the current or expected local preventable disease burden. More recent additions to the vaccine portfolio that could potentially prevent a disproportionally large burden, such as PCVs, are infrequently deployed. The high costs of PCVs are now largely mitigated by the availability of PCV through the Humanitarian Mechanism, but the lack of specific PCV usage recommendations is among the key factors that hinder uptake as a routine part of humanitarian responses. Evidence on practical, effective, and cost-effective ways to use PCV is critical for humanitarian actors to better evaluate the role of PCV in the vaccine portfolio for crises use.

Preventing a large proportion of the pneumococcal disease burden through PCV use would contribute to the overarching aim of humanitarian action: to save lives. We propose that a combination of targeted data collection in combination with mathematical modelling can be used to generate evidence-based hypotheses on optimal vaccination strategies for PCVs in crises, and ultimately pave the way for rational PCV use in crises. This evidence pathway could similarly be applied to other vaccine-preventable diseases, for which indirect effects are a key part of their overall effects, to eventually achieve an evidence based prioritisation strategy for optimal vaccine use in humanitarian crises.

Contributors

FC conceived the idea for the manuscript. KvZ wrote the first manuscript draft with support from SF and FC. All authors contributed to, and approved, the final draft. All authors attest they meet the ICMJE criteria for authorship.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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